Organic Syntheses

Synthesis of *N*-Boc-*N*-Hydroxymethyl-L-phenylalaninal

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Checked by Zhaobin Han and Kuiling Ding
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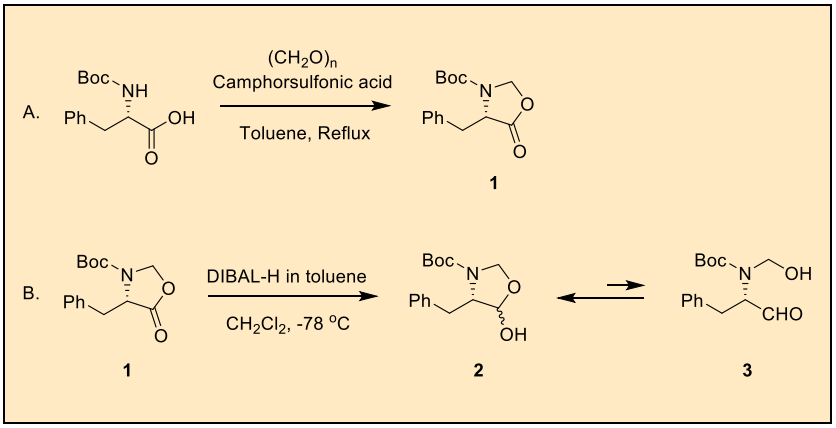


Procedure (Note 1)

A. *(4S)-4-Benzyl-3-[(1,1-dimethylethoxy)carbonyl]-5-oxazolidinone* (**1**). A 500-mL, single-necked, round-bottomed flask equipped with a Teflon-coated, oval magnetic stir bar (30 x 15 mm) is charged with *N*-Boc-L-phenylalanine (11.94 g, 45.0 mmol, 1.00 equiv) (Note 2), paraformaldehyde (13.51 g, 450.0 mmol, 10.0 equiv) (Note 3), (1*S*)-(+)-10-camphorsulfonic acid (314 mg, 1.4 mmol, 0.03 equiv) (Note 4), and toluene (225 mL) (Note 5). The flask is then fitted with a Dean-Stark trap topped with a water-cooled condenser, which is open to the atmosphere. The reaction mixture is placed in a pre-heated oil bath set at 130 °C and heated with stirring for 40 min (Note 6) (Figure 1). The reaction mixture is allowed to cool to room temperature and filtered through a Büchner funnel (with a 25–50 μm frit, 70 mm diameter) with 10 g of Celite pad and washed with toluene (20 mL)

to remove insoluble solid. The volume of the filtrate is reduced to approximately 35 mL (Note 7) on a rotary evaporator under reduced pressure (40 °C, 25 mmHg), and the concentrated solution is purified by silica gel column chromatography (hexane:EtOAc 19:1 (v/v) and hexane:EtOAc 9:1 (v/v)) (Note 8) to afford 10.88 g (87%) of compound **1** (Notes 9 and 10).

Figure 1. Apparatus assembly for Step A – provided by checker

B. *N-[(1,1-Dimethylethoxy)carbonyl]-N-hydroxymethyl-L-phenylalaninal* (**2**). A 500-mL, single-necked, round-bottomed flask equipped with a Teflon-coated, oval magnetic stir bar (30 x 15 mm), a 100 mL pressure-equalizing addition funnel capped with a rubber septum, and inert gas inlet via a

needle (Note 11) is charged with (4*S*)-4-benzyl-3-[(1,1-dimethylethoxy)carbonyl]-5-oxazolidinone (**1**) (10.54 g, 38.0 mmol, 1.00 equiv) and anhydrous dichloromethane (200 mL) (Note 12), and the flask is cooled in a dry ice-acetone bath to –78 °C (Figure 2). A solution of DIBAL-H (49.4 mL, 1.0 M in toluene, 1.30 equiv) (Note 13) is added via an addition funnel over a 3 h period (Note 14). After completion of the addition, the reaction mixture is stirred at –78 °C for

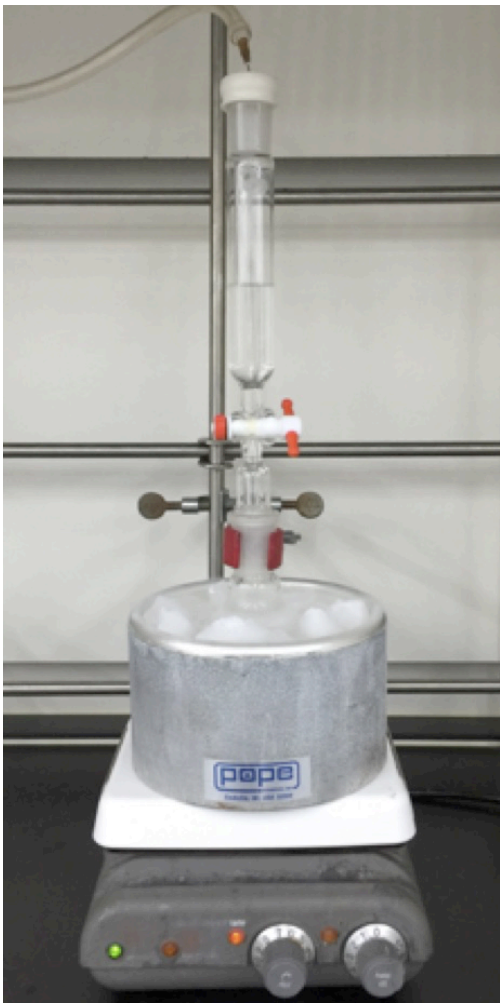


Figure 2. Apparatus assembly for Step B

30 min and then quenched by addition of MeOH (7.5 mL) (Note 15). After 5 min at –78 °C, the cold solution is transferred to a 1-L beaker equipped with a large magnetic stir bar (70 x 12 mm) containing a saturated aqueous solution of Rochelle salt (150 mL) (Note 16) and water (150 mL). The resulting mixture is vigorously stirred for 30 min and transferred to a 1-L separatory funnel. The aqueous layer is separated and further extracted with dichloromethane (2 x 200 mL). The combined organic layers are dried over $MgSO_4$ (45 g), filtered, and concentrated on a rotary evaporator under reduced pressure (25 °C, 25 mmHg). The resulting crude oil is purified by silica gel column chromatography (hexane:EtOAc 9:1 (v/v) and hexane:EtOAc 5:1 (v/v)) (Note 17) to afford 7.80 g (73%) of compound **2** (Notes 18 and 19).

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 *N*-Boc-L-phenylalanine, paraformaldehyde, (1*S*)-(+)-10-camphorsulfonic acid, toluene, hexane, ethyl acetate, dichloromethane, dry ice, acetone, methanol, Rochelle salt, and magnesium sulfate.
2. *N*-Boc-L-phenylalanine (>99%) was purchased from Aldrich Chemical Company, Inc. and used without further purification.

3. Paraformaldehyde (>96%) was purchased from Acros Organics and used without further purification. The use of excess reagent is necessary for the complete conversion in a short time.
4. (*1S*)-(+)-10-Camphorsulfonic acid (>99%) was purchased from Aldrich Chemical Company, Inc. and used without further purification. The use of other acid catalysts, such as benzenesulfonic acid, *p*-toluenesulfonic acid monohydrate, and sulfuric acid shows lower yields than that of (*1S*)-(+)-10-camphorsulfonic acid because of the more facile deprotection of the Boc or *N,O*-acetal group. (±)-10-Camphorsulfonic acid monohydrate can be used instead of (*1S*)-(+)-10-camphorsulfonic acid to give the similar results.
5. Toluene (ACS reagent grade, >99.5%) was purchased from Acros Organics and used without further purification. The reaction in benzene shows slightly better yields than that in toluene, but the reaction is done in toluene because of the toxicity associated with benzene.
6. The yields tend to decrease slightly as the reaction time increases. The arm of a Dean-Stark trap is wrapped with a layer of cotton, which is wrapped with a layer of aluminum foil. The submitters report that both the round-bottomed flask and the hot plate were covered with aluminum foil to facilitate heating and reduce the reaction time.
7. Because residual paraformaldehyde remains in the crude product, a more concentrated filtrate (less than 35 mL) usually solidifies when it is loaded onto the silica gel column, which inhibits purification by column chromatography. Thus, the crude product is usually concentrated until about 35 mL of the reaction solvent remains.
8. The column chromatography is performed using a 7.0-cm wide, 50-cm high column of 180 g of Merck silica gel (60 mesh, 0.063–0.200 mm) packed by slurring silica gel with an eluent of hexane:EtOAc 19:1 (v/v). The concentrated solution of the crude product **1** is loaded onto the column. After 300 mL of initial elution of the eluent hexane:EtOAc 19:1 (v/v), the eluent is changed to a more polar eluent hexane:EtOAc 9:1 (v/v). Then, 30 mL of fractions are collected and checked by TLC (R_f of **1** = 0.69, hexane:EtOAc 2:1 (v/v), silica gel 60 F254 obtained from Merck, UV and visualization with *p*-anisaldehyde stain). The fractions 15-67 (approximately 1.5 L) containing the desired product are collected and concentrated by rotary evaporation (25 °C, 25 mmHg).
9. A second reaction on identical scale provided 10.96 g (88%) of the product **1**. The physical and spectroscopic properties of **1** are as follows: white powder; mp 79–81 °C; $[\alpha]_D^{28}$ = +189.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR

($CDCl_3$, 600 MHz, 50 °C) δ: 1.50 (s, 9H), 3.15 (dd, *J* = 3.0 Hz, 13.8 Hz, 1H), 3.35 (s, 1H), 4.28 (s, 1H), 4.47 (s, 1H), 5.21 (s, 1H), 7.16 (d, *J* = 7.2 Hz, 2H), 7.24-7.30 (m, 3H) ppm (Better resolution on the ^{1}H NMR spectrum is obtained at higher temperature (50 °C) due to the slow conformational equilibrium of the oxazolidinone ring); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 27.9, 34.8, 35.9, 55.8, 56.3, 77.7, 81.4, 127.1, 128.4, 129.4, 134.7, 151.5, 171.9 ppm; IR (film) cm^{-1}: 2981, 1792, 1681, 1408, 1153, 1040, 700 cm^{-1}; HRMS (ESI, $[M+H]^+$) *m*/*z* calcd for $C_{15}H_{20}NO_4$: 278.1387, Found: 278.1385; Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05, found: C, 65.08; H, 6.83; N, 4.98.

10. The submitters report that the purity of **1** (>97%) was determined by quantitative HPLC analysis based on the standard (purity >99%) and calibration curve. The standard was prepared by further recrystallization of product **1** with Et_2O-hexane in about 70% yield as follows. 7.0 g of product **1** is dissolved in Et_2O (10 mL), and hexane (100 mL) is slowly added. The solution is then placed in a freezer (–20 °C). The resulting white precipitate is collected on sintered-glass funnel and rinsed with cold hexane (10 mL). Reverse phase HPLC analyses of the standard and the sample are performed with an Mightysil RP-18 GP, 5 μm, 4.6 × 250 mm column (25 °C) at a flow rate of 1.0 mL/min of 60:40 MeCN:H_2O (v/v) and observed at 203 nm, giving a retention time of 10.80 min. The calibration curve is generated by analyzing the standard at three concentrations (about 250, 500, 1000 ppm).
11. All glassware and needles are dried in an oven at 120 °C and kept in desiccator overnight prior to use. All reactions are performed under nitrogen or argon atmosphere.
12. Dichloromethane (>99.8%) was purchased from Aldrich Chemical Company, Inc. and dried over calcium hydride.
13. DIBAL-H (1.0 M in toluene) was purchased from Acros Organics. The submitters used DIBAL-H (1.0 M in dichloromethane) purchased from Aldrich Chemical Company, Inc. The submitters report that a solution of DIBAL-H in dichloromethane provides better yields than a solution comprised of different solvents, such as THF or cyclohexane.
14. Control of the addition rate of DIBAL-H is critical to the yield of compound **2**. The yields are decreased when adding the DIBAL-H solution faster because of difficulties in controlling the reaction temperature. The addition with a syringe pump can be also used instead of an addition funnel.

15. Methanol (>99%) was purchased from Aldrich Chemical Company, Inc. and added via an addition funnel over a 10-min period.
16. Rochelle salt (potassium sodium tartrate tetrahydrate) was purchased from Aldrich Chemical Company, Inc. The use of 2-3 mL of the saturated solution per 1.0 mmol of DIBAL-H was found to be optimal. Use of less salt results in incomplete complexation. The submitters report that stirring times longer than 30 min after the addition of the aqueous solution of Rochelle salt can result in a slight decrease of yield.
17. The column chromatography is performed immediately after the concentration using a 7.0-cm wide, 50-cm high column of 180 g of Merck silica gel 60 mesh (0.063–0.200 mm) packed by slurring silica gel with an eluent of hexane:EtOAc 9:1 (v/v). The crude oil is loaded onto the column. After 600 mL of initial elution of the eluent hexane:EtOAc 9:1 (v/v), the eluent is changed to a more polar eluent hexane:EtOAc 5:1 (v/v). Then, 30 mL of fractions are collected and checked by TLC (R_f of **2** = 0.38, hexane:EtOAc 2:1 (v/v), silica gel 60 F254 obtained from Merck, UV and visualization with *p*-anisaldehyde stain). The fractions 17-85 (approximately 2.0 L) containing the desired product are collected and concentrated by rotary evaporation (25 °C, 25 mmHg).
18. A second reaction on identical scale provided 7.81 g (73%) of the product **2**. The physical and spectroscopic properties of **2** are as follows: colorless oil; $[\alpha]_D^{28}$ –44.6 (*c* 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz, 50 °C) δ: 1.45 (s, 9H), 2.67 (dd, *J* = 9.6 Hz, 13.8 Hz, 1H), 2.67 (br s, 1H), 2.97–3.10 (m, 1H), 4.02–4.10 (m, 1H), 4.86–4.92 (m, 1H), 5.12 (s, 1H), 5.33 (d, *J* = 3.6 Hz, 1H), 7.17–7.33 (m, 5H) ppm (The better resolution on the NMR spectra is obtained at higher temperature due to the slow conformational equilibrium of the oxazolidine ring); ^{13}C NMR ($CDCl_3$, 100 MHz, a mixture of diastereomers) δ: 28.1, 33.4, 37.0, 37.7, 61.1, 63.1, 63.6, 77.5, 80.4, 96.6, 98.7, 99.3, 125.9, 126.3, 128.0, 128.4, 129.1, 129.4, 137.2, 138.5, 152.7, 153.7 ppm; IR (film) cm^{-1}: 3390, 2974, 1671, 1397, 1133, 1028, 699 cm^{-1}; HRMS (ESI, $[M+H]^+$) *m*/*z* calcd for $C_{15}H_{22}NO_4$: 280.1543, Found: 280.1544. The checkers determined the purity of **2** to be 97% based on quantitative ^{1}H NMR with ethylene carbonate as the internal reference.
19. The submitters report that the purity of **2** (>97%) was determined by quantitative HPLC analysis based on the standard (purity >99%) and calibration curve. The standard was prepared by another column chromatography of the column-purified product **2**. Reverse phase HPLC analyses of the standard and the sample are performed with an

Mightysil RP-18 GP, 5 μm, 4.6 × 250 mm column (25 °C) at a flow rate of 1.0 mL/min of 50:50 MeCN:H_2O (v/v) and observed at 203 nm, giving a retention time of 10.99 min. The calibration curve is generated by analyzing the standard at three concentrations (about 200, 400, 800 ppm).

Working with Hazardous Chemicals

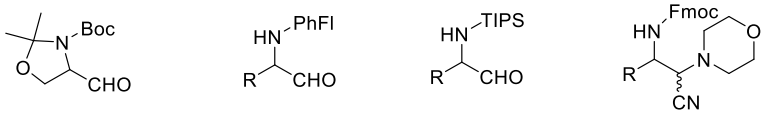
The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The 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

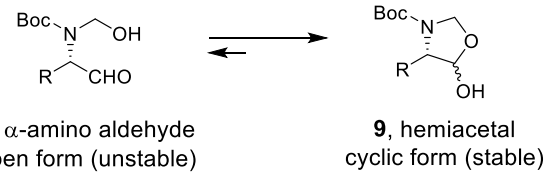
α-Amino aldehydes are widely used as chiral synthons in asymmetric synthesis of nitrogen-containing natural and synthetic products.[2] However, α-amino aldehydes have been known to be both chemically and configurationally labile because of the rather acidic proton positioned at the α-carbon to the carbonyl group.[2a,3] Therefore, relatively configurationally stable α-amino aldehydes have been investigated as an attractive target. Although some useful relatively configurationally stable α-amino aldehydes for asymmetric syntheses have been reported as shown in Figure 3,[4] they also have some limitations. For example, Garner's aldehyde **4**, one of the most cited chiral building blocks in recent times, is only applicable to a limited number of α-amino acids containing a hydroxyl group such as serine. In the case of *N*-PhFl protected amino aldehyde **5**, the *N*-PhFl protection requires stoichiometric amount of the environmentally unfriendly reagent, and its removal requires harsh conditions.



4 **5** **6** **7**

Figure 3. Reported configurationally stable α-amino aldehydes

We have found that the *N*-hydroxymethyl group of α-amino aldehydes could stabilize the labile stereogenic α-carbon by shifting the equilibrium from **8** to **9** (Figure 4).[5] Interestingly, the hemiacetal of *N*-Boc-*N*-hydroxymethyl serinal (R = CH_2OR', Figure 4) showed less amount of racemization (<1%) during its preparation and storage than Garner's aldehyde **4**.[5b]



8, α-amino aldehyde open form (unstable)

9, hemiacetal cyclic form (stable)

Figure 4. Stabilization of α-amino aldehydes by the *N*-hydroxymethyl group

The enantiomeric purity of **2** could be determined by the formation of a Mosher amide of **11** because a Mosher ester of **11** did not give a good separation on the NMR spectra as shown in Figure 5.[5a] It was reported that almost no racemization occurred for a month of storage at –22 °C as well as during the preparation. Nevertheless, we recommend that α-amino aldehyde **2** be used immediately after preparation or kept at –78 °C and used within a week or so in order to reduce a small possibility of racemization.

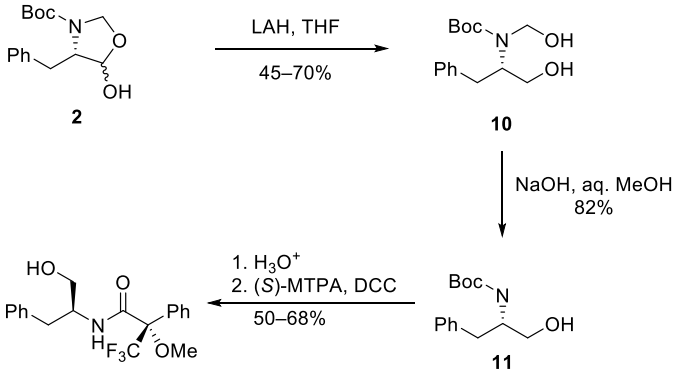


Figure 5. Determination of the enantiomeric purity of 2

The advantages of the *N*-hydroxymethyl group are that it can be easily introduced to various amino acids in good yields and removed under mild conditions.

Moreover, the *N*-hydroxymethyl group attached to α-amino aldehydes could be also used as an internal nucleophile for the stereoselective syntheses of several γ–amino-β-hydroxy acids,[6] β,γ–diamino acids,[7] γ–amino-α,β-dihydroxy acids,[8] and β–amino-α-hydroxy acids (Figure 6).[9] They are the important moieties frequently found in various biologically active and pharmaceutically important compounds such as anti-hypertensive (-)-statine and its unnatural but more potent analog (-)-aminodeoxystatine, potential anti-cancer *N*-Boc-(3*R*,4*S*)-AHPPA (4-amino-3-hydroxy-5-phenylpentanoic acid) and its diastereomer *threo*-AHPPA, selective glutamate receptor agonists or antagonists, (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid and *threo*-β -hydroxy-L-glutamic acids.

Finally, we hope that other α-amino aldehydes with the *N*-hydroxymethyl group would be useful synthons for asymmetric synthesis of various biologically important products.

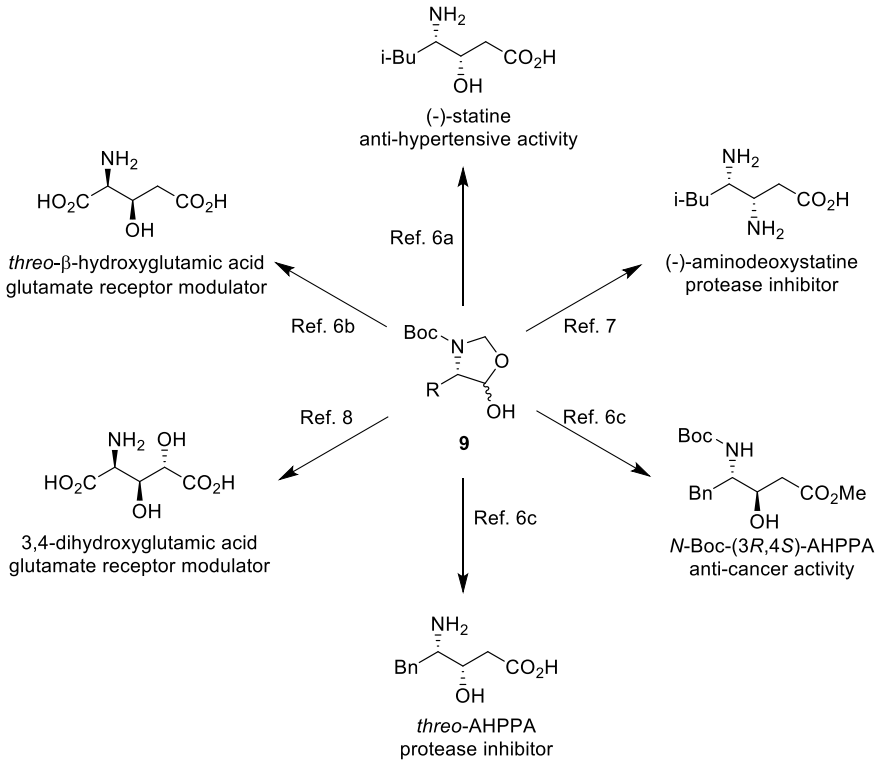


Figure 6. Applications of the α-amino aldehydes with the *N*-hydroxymethyl group to biologically active compounds

References

1. Department of Chemical and Biological Engineering, Seoul National University, Seoul 151-744, Republic of Korea. Email: ygkim@snu.ac.kr. We thank the BK-21 Plus Program and the Fundamental R&D Program for Core Technology of Materials funded by the Ministry of Knowledge Economy for financial support. Y. Seo especially thanks the Global Ph.D. Fellowship that the National Research Foundation of Korea had conducted from 2011 to 2014.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

N-Boc-L-phenylalanine: L-Phenylalanine, *N*-[(1,1-dimethylethoxy)-carbonyl]-; (13734-34-4)
Paraformaldehyde: Paraformaldehyde; (30525-89-4)
(1*S*)-(+)-10-camphorsulfonic acid: Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (1*S*,4*R*)-; (3144-16-9)
DIBAL-H: Aluminum, hydrobis(2-methylpropyl)-; (1191-15-7)
Rochelle salt (Potassium sodium tartrate tetrahydrate): Butanedioic acid, 2,3-dihydroxy-(2*R*,3*R*)-, monopotassium monosodium salt; (304-59-6)

Young Gyu Kim received his undergraduate education at Seoul National University in Korea. He received his Ph.D. at Vanderbilt University in 1991 under supervision of Dr. Jin K. Cha. Dr. Kim is Professor of the Department of Chemical and Biological Engineering at Seoul National University, where his research focuses on the development of new synthetic methodologies and processes, and their applications for the synthesis of biologically or industrially important compounds.

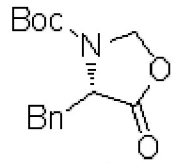
Jae Won Yoo received his B.S. and M.S. degrees from Seoul National University in 1997 and 1999, respectively. He is currently pursuing a Ph.D. degree at Seoul National University in the research group of Professor Young Gyu Kim and working for Amorepacific corporation.

Youngran Seo received her B.S. degree from Dankook University in 2007, and she received her M.S. and Ph.D. degrees from Seoul National University in 2011 and 2015. She is now a postdoctoral associate in the research group of Professor Young Gyu Kim at Seoul National University.

Dongwon Yoo received his B.S., M.S., and Ph.D. degrees from Seoul National University in 1998, 2000, and 2004, respectively. He was a postdoctoral associate and a staff research associate at the University of California, Los Angeles. He is currently an Assistant Professor at the Institute for Basic Science (IBS) in Yonsei University.

Dr. Zhaobin Han received his B.S. degree in chemistry from Nanjing University in 2003. He received his Ph.D. degree from Shanghai Institute of Organic Chemistry under the supervision of Prof. Kuiling Ding and Prof. Xumu Zhang in 2009, working on development of novel chiral ligands for asymmetric catalysis. Now he is an associate professor in the same institute and his current research interests focus on the development of efficient catalytic methods based on homogeneous catalysis.

(4*S*)-4-Benzyl-3-[(1,1-dimethylethoxy)carbonyl]-5-oxazolidinone



1

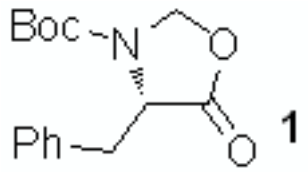
^{1}H NMR (600 MHz, $CDCl_3$, 50 °C)

7.291 7.280 7.267 7.264 7.251 7.240 7.168 7.156 5.208 4.472 4.280 3.351 3.166 3.161 3.143 3.138 1.607 1.504 1.396 0.000

2.94 1.74 0.90 0.89 0.92 0.93 1.00 9.31

f1 (ppm)

(4*S*)-4-Benzyl-3-[(1,1-dimethylethoxy)carbonyl]-5-oxazolidinone



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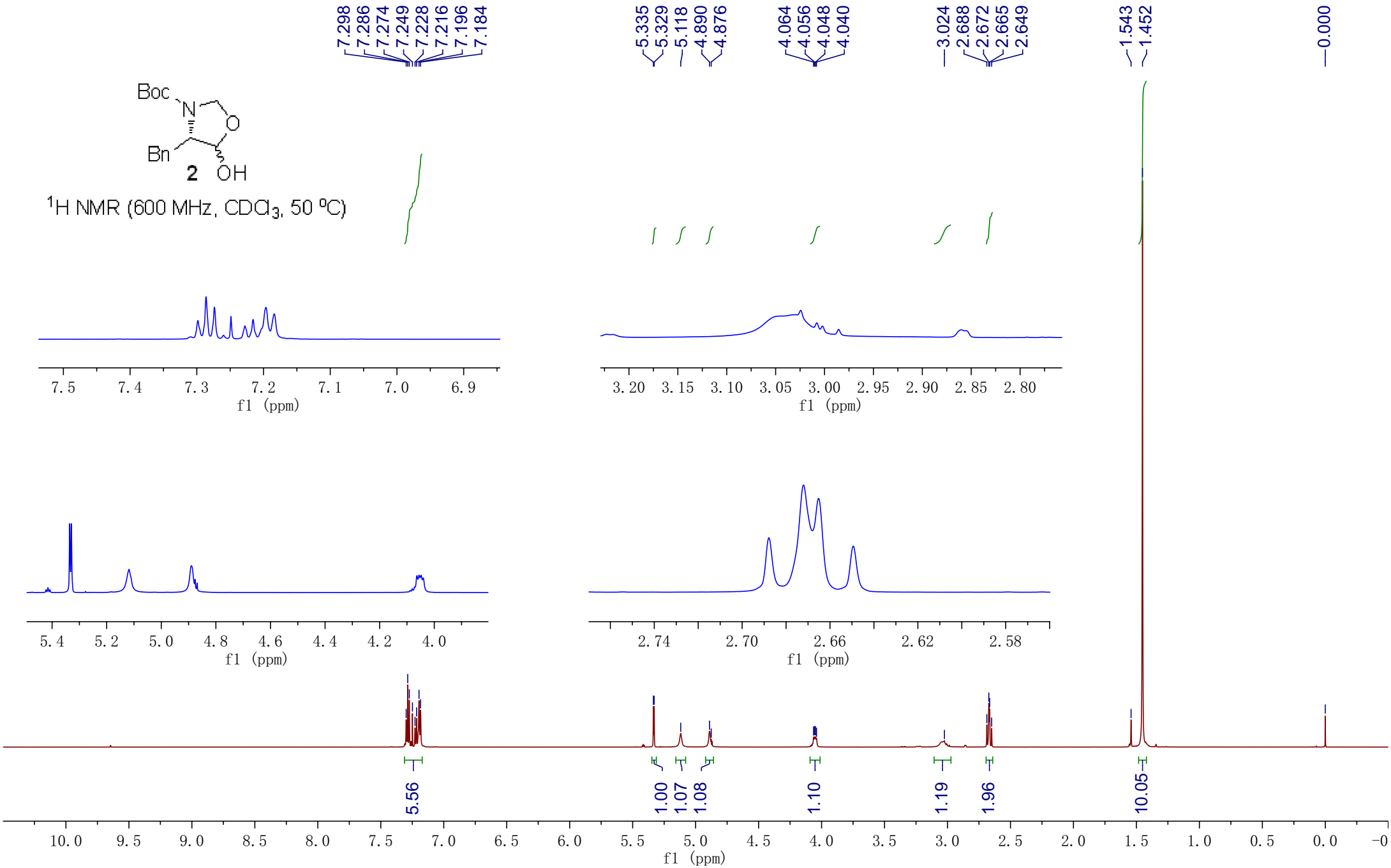
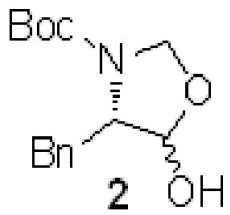
^{13}C NMR (100 MHz, $CDCl_3$)

N-[(1,1-Dimethylethoxy)carbonyl]-*N*-hydroxymethyl-*L*-phenylalaninal



N-[(1,1-Dimethylethoxy)carbonyl]-*N*-hydroxymethyl-*L*-phenylalaninal

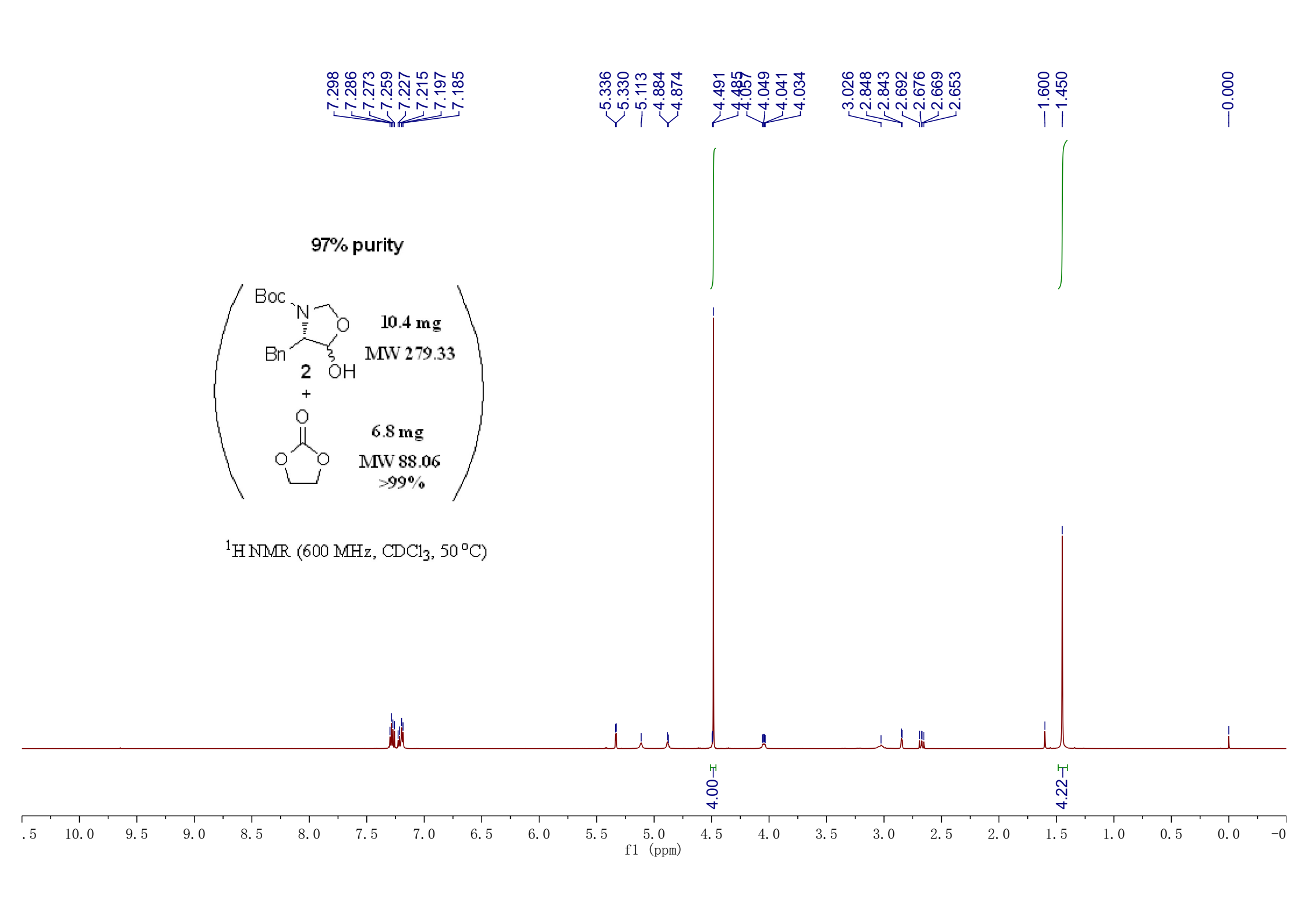


2

^{13}C NMR (100 MHz, $CDCl_3$)

153.70
152.68
138.48
137.16
129.42
129.05
128.35
128.00
126.34
125.91
99.29
98.70
96.61
80.44
77.53
77.32
77.00
76.68
63.55
63.08
61.12
37.69
36.98
33.36
28.08

f1 (ppm)


7.298
7.286
7.273
7.259
7.227
7.215
7.197
7.185
5.336
5.330
5.113
4.884
4.874
4.491
4.485
4.057
4.049
4.041
4.034
3.026
2.848
2.843
2.692
2.676
2.669
2.653
1.600
1.450
0.000
97% purity
Boc
N
O
Bn
2
OH
+
10.4 mg
MW 279.33
6.8 mg
MW 88.06
>99%
1H NMR (600 MHz, CDCl3, 50 °C)
4.00
4.22
f1 (ppm)