Organic Syntheses

Synthesis of Methyl *trans*-Oxazolidine-5-carboxylate, a Chiral Synthon for *threo*-β-Amino-α-hydroxy Acid

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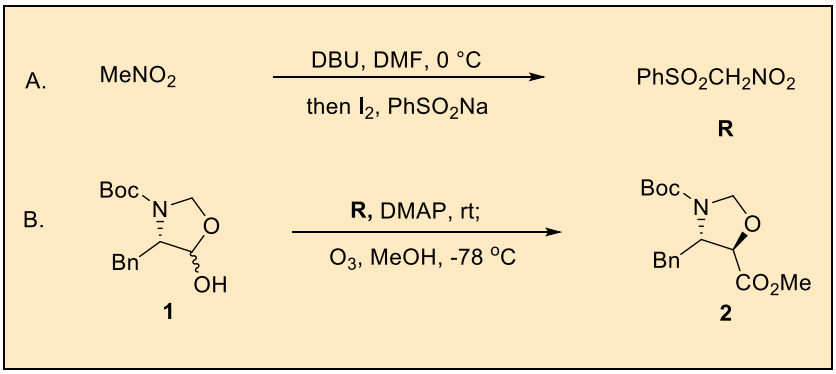


Procedure (Note 1)

A. *Phenylsulfonylnitromethane* (***R***).[2] A 1-L, single-necked, round-bottomed flask equipped with a Teflon-coated, oval magnetic stir bar (40 × 20 mm) is charged with nitromethane (9.0 mL, 165.1 mmol, 1.00 equiv) (Note 2) and *N*,*N*-dimethylformamide (DMF, 180 mL) (Note 3). After the reaction mixture is stirred while open to the air for 10 min at 0 °C in an ice bath, 1,8-diazabicycloundec-7-ene (DBU, 27.4 mL, 181.7 mmol, 1.10 equiv) (Note 4) is added by syringe within 5 min. After further stirring for 20 min at 0 °C, benzenesulfinic acid sodium salt ($C_6H_5SO_2Na$, 22.50 g, 137.1 mmol, 0.83 equiv) (Note 5) and iodine (31.85 g, 125.5 mmol, 0.76 equiv) (Note 6) are added to the flask and the mixture is stirred for another 5 min at 0 °C. Then,

the reaction mixture is warmed to room temperature and stirred for one hour. The reaction mixture is cooled to 0 °C in an ice bath, and diluted with water (150 mL). A saturated aqueous solution of Na_2SO_3 (*ca*. 100 mL) (Note 6) is added to the reaction flask until the mixture turns from dark brown to bright yellow. The mixture is then slowly acidified over the course of 10 min to *ca*. pH 1 at 0 °C with a *conc*. aqueous solution of HCl (*ca*. 45 mL) (Note 7). The acidified mixture is transferred to a 2-L separatory funnel and the reaction flask is rinsed with Et_2O (2 x 50 mL). The aqueous layer is extracted with additional Et_2O (4 x 300 mL). The combined organic layers are washed with an aqueous solution of HCl (0.1 M, 2 x 500 mL), dried over $MgSO_4$ (30 g), filtered, and concentrated under reduced pressure (25 °C, 25 mmHg). The resulting crude product is purified by silica gel column chromatography (Note 8) to afford 10.00 g (36%) (Note 9) as white powder (Notes 10 and 11).

B. *3-tert-Butyl 5-methyl (4S,5R)-4-benzyloxazolidine-3,5-dicarboxylate* (**2**). A 250-mL, single-necked, round-bottomed flask equipped with a Teflon-coated, oval magnetic stir bar (30 × 15 mm) is charged with *N*-Boc-*N*-hydroxymethyl-L-phenylalaninal (**1**)[3] (7.38 g, 26.41 mmol, 1.00 equiv) (Note 12) and THF (50 mL) (Note 13) and sealed with a rubber septum. The reaction mixture is stirred at 0 °C for 10 min, and after the removal of the rubber septum, phenylsulfonylnitromethane (**R**) (6.91 g, 34.3 mmol, 1.30 equiv) and 4-dimethylaminopyridine (DMAP, 4.19 g, 34.3 mmol, 1.30 equiv) (Note 14) are added through the open neck at 0 °C and then the flask is resealed with a rubber septum. After the mixture is vigorously stirred at 0 °C for 30 min, the reaction continues at room temperature for 72 h with vigorous stirring (Note 15) (Figure 1). The resulting solution is concentrated using a rotary evaporator (25 °C, 25 mmHg) until about half of the solution remains (Note 16). After the addition of methanol (60 mL) to the concentrated mixture, the mixture is cooled to 0 °C in an ice bath. To the cold reaction mixture, 1,8-diazabicycloundec-7-ene (DBU, 11.9 mL, 79.2 mmol, 3.00 equiv) (Note 4) is added over the course of 2 min, and the resulting mixture is stirred for an additional 30 min in the ice bath. After the ice bath is replaced with a Dewar bath containing dry ice/acetone, a glass tube is connected via Teflon tubing to an ozone (O_3) generator. The glass tube is inserted into the reaction solution through the open neck of the flask, and ozone is bubbled through the reaction mixture for 2 h at –78 °C (Note 17) (Figure 2). After the ozonolysis is completed, the reaction mixture is purged sequentially with oxygen for 5 min and then with argon for another 5 min in order to remove excess ozone from

the reaction mixture. Then, dimethyl sulfide (2.52 mL, 34.3 mmol, 1.30 equiv) (Notes 18 and 19) is added to the reaction mixture at –78 ºC to quench any peroxides present and the solution is allowed to warm up to room temperature and stirred for 1 hr. The reaction mixture is concentrated using a rotary evaporator (25 ºC, 25 mmHg), and the residue is transferred to a 250-mL separatory funnel, while rinsing the flask with EtOAc (2 x 20 mL) (Note 20). An additional portion of EtOAc (60 mL) and saturated aqueous solution of NH_4Cl (60 mL) are added to the separatory funnel. The aqueous layer is separated and extracted with EtOAc (2 x 60 mL). The combined organic layers are dried over $MgSO_4$ (30 g) filtered, and concentrated with a rotary evaporator (25 ºC, 25 mmHg). The resulting crude oil is purified by silica gel column chromatography hexane:EtOAc 8:1 (v/v) (Note 21) to afford 2.73 g (32%) of pure **2** (Notes 22 and 23).

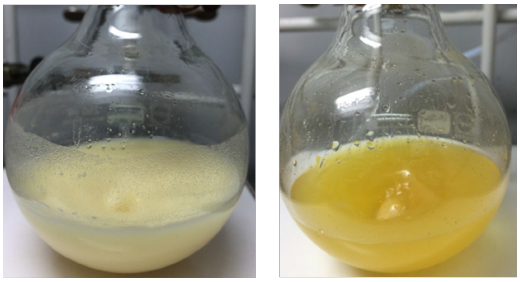
Notes

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 nitromethane, *N*,*N*-dimethylformamide (DMF), 1,8-diazabicycloundec-7-ene (DBU), benzenesulfinic acid sodium salt, iodine, sodium sulfite, hydrochloric acid, diethyl ether, magnesium sulfate, silica gel, hexanes, ethyl acetate,

N-Boc-*N*-hydroxymethyl-L-phenylalaninal, tetrahydrofuran (THF), 4-dimethylaminopyridine (DMAP), methanol, ozone, dimethyl sulfide, and ammonium chloride, as well as the proper procedures for ozonolysis, *Ozone is extremely toxic and can react explosively with certain oxidizable substances. Ozone also reacts with some compounds to form explosive and shock-sensitive products. Ozone should only be handled by individuals trained in its proper and safe use and all operations should be carried out in a well-ventilated fume hood behind a protective safety shield.*

2. Nitromethane (>99%) was purchased from Acros Organics and used without further purification.
3. *N*,*N*-Dimethylformamide (DMF, 99.5%) was purchased from Daejung Chemical & Metals and stored with molecular sieves (3 Å, bead, 4~8 mesh). The checkers purchased *N*,*N*-Dimethylformamide (DMF, 99.8%, SuperDry) from Acros Organics and used it as received.
4. 1,8-Diazabicycloundec-7-ene (DBU, 98%) was purchased from Tokyo Chemical Industry and used without further purification.
5. Benzenesulfinic acid sodium salt (97%) was purchased from Acros Organics and used without further purification.
6. Iodine (99%) was purchased from Daejung Chemical & Metals and used without further purification. The checkers purchased iodine (99%) from Acros Organics and used it as received. Sodium sulfite (Na_2SO_3, ACS reagent grade, 98%) was purchased from Acros Organics and used without further purification.
7. Aqueous hydrochloric acid (35%) was purchased from Daejung Chemical & Metals and used without further purification. The checkers used aqueous hydrochloric acid (35%) from Acros Organics as received.
8. Column chromatography is performed using a 7.0-cm wide, 50-cm high column with 250 g of Merck silica gel (60 mesh, 0.063–0.200 mm) packed by slurring the silica gel with 800 mL of hexane:EtOAc 9:1 (v/v). The crude product of **R** is loaded onto the column with CH_2Cl_2 (15 mL). After 750 mL of initial elution with hexane:EtOAc 9:1 (v/v), the eluent is changed to a more polar eluent hexane:EtOAc 4:1 (v/v). At this time, fractions of 35 mL are collected and checked by TLC (R_f of **R** = 0.45, hexane:EtOAc 2:1 (v/v), silica gel 60 F254 obtained from Merck, visualization by UV and with ninhydrin stain). Fractions 13-96 (approximately 3.0 L) containing the desired product are collected and concentrated by rotary evaporation (25 °C, 25 mmHg).

9. The yields are calculated based on the amount of benzenesulfinic acid sodium salt (22.50 g, 137.1 mmol). A second reaction on identical scale provided 10.16 g (37%) of the product **R**.
10. The submitters report that if **R** is not obtained as white powder after the column purification, further purification procedure can be conducted as follows. First, the column purified product is diluted with Et_2O (50 mL). Then, the diluted solution is transferred to a 250 mL separatory funnel and the flask is rinsed with Et_2O (10 mL × 2). The organic layer is washed with an aqueous solution of HCl (0.1 M, 2 x 100 mL). The washed organic layer is dried over 10 g of $MgSO_4$ (10 g) filtered, and concentrated under reduced pressure (25 °C, 25 mmHg).
11. The purity of **R** is confirmed by melting point, spectroscopic and elemental analyses: white powder; mp 80–81 °C (lit.[2] mp 78 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.61 (s, 2H), 7.66 (t, J = 7.6 Hz, 2H), 7.80 (t, J = 7.2 Hz, 1H), 7.96–8.00 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 90.2, 129.2, 129.7, 135.5, 135.6 ppm; IR (film): 3017, 2950, 1549, 1316, 1150, 739, 586, 521 cm^{-1}; HRMS (EI, $[M]^+$) m/z calcd for $C_7H_7NO_4S$: 201.0096. Found: 201.0098; Anal. Calcd for $C_7H_7NO_4S$: C, 41.79; H, 3.51; N, 6.96, Found: C, 42.02; H, 3.66; N, 7.02.
12. Colorless *N*-Boc-*N*-hydroxymethyl-L-phenylalaninal (**1**) is synthesized as described in the preceding procedure.[3] It is recommended to use the synthesized α-amino aldehyde **1** immediately in order to minimize its racemization. If the α-amino aldehyde **1** is not used immediately, it should be kept in a deep freezer (–78 °C) and used within a week.
13. THF (99.5%) was purchased from OCI Company and used without further purification. The checkers used THF (99.5%) purchased from Acros Organics without further purification.
14. 4-Dimethylaminopyridine (DMAP, 99%) was purchased from Alfa Aesar and used without further purification.
15. As shown below in Figure 1, the color of the reaction mixture changes from pale yellow to orange over the reaction time.



after 24 h after 48 h

Figure 1. Appearance of the reaction mixture after each reaction time

16. The partial removal of THF after the reaction between α-amino aldehyde **1** and $PhSO_2CH_2NO_2$ is helpful for high conversion in the following in situ ozonolysis reaction.
17. Ozone is bubbled through a glass tube (diameter: 5.38 mm, length: 11 cm) with an ozone generator. A thinner tube could be clogged during the ozonolysis. The optimal pressure on the generator is adjusted to 0.5 kgf/cm^2, and the O_2 flow rate is set to 500 Ncm^3/min at 20 °C. After the ozonolysis is completed, the reaction mixture is purged sequentially with oxygen for 5 min and then with argon for another 5 min in order to remove excess ozone from the reaction mixture.

Figure 2. Apparatus assembly for the O_3 bubbling

18. Dimethyl sulfide (>99%) was purchased from Aldrich Chemical Company and used without further purification. All manipulations involving dimethyl sulfide-contained solutions are performed in a well-ventilated fume hood.
19. Potassium iodide-starch paper was purchased from Johnson Test Papers, and the iodide-starch paper is used to detect any residual peroxides.[4a] The iodide-starch paper test was negative for peroxides before the work-up of the ozonolysis, but the additional reductive work-up procedure using dimethyl sulfide was performed to ensure the reaction mixture was completely peroxide-free.[4b,4c]
20. During the concentration of the reaction mixture, any intermittent bumping should be carefully controlled by adjusting the rotating speed or the pressure.
21. Column chromatography is performed using a 4.0-cm wide, 30-cm high column with 95 g of Merck silica gel (60 mesh, 0.063–0.200 mm) packed by slurring the silica gel with 400 mL of hexane:EtOAc 8:1 (v/v). The crude product of **2** is loaded onto the column with a small amount of CH_2Cl_2 (less than 5 mL), and the elution was continued with 1.8 L of the eluent. Fractions of 35 mL are collected and checked by TLC (R_f of **2** = 0.55, hexane:EtOAc 2:1 (v/v), silica gel 60 F254 obtained from Merck, visualization by UV and with ninhydrin stain). Fractions 11-49 (approximately 1.33 L), which contain the desired product, are collected and concentrated by rotary evaporation (25 °C, 25 mmHg).
    Figure 3 shows the TLC plates with spots of the starting material **1**, the product **2**, the conjugate addition intermediate adduct **IV** (R^1=Bn, see Scheme 2) and the reagent ($PhSO_2CH_2NO_2$, represented as **R** on TLC plates). Each spot is visualized with a ninhydrin solution (left) and UV light (254 nm) (right). The following R_f values are calculated with the stained spots by ninhydrin (hexane:EtOAc 2:1 (v/v)): R_f of **1** = 0.39; R_f of **2** = 0.55; R_f of **IV** (R^1=Bn) = 0.42; R_f of **R** = 0.45.

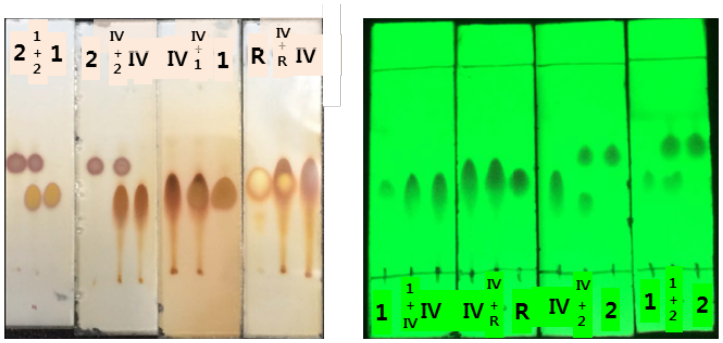


Figure 3. Images of the TLC analysis (UV (right), ninhydrin stain (left))

22. The yields of **2** are influenced by the concentration of the reactant. In a large scale, an efficient and consistent stirring is difficult at high concentration due to the increased viscosity of the solution. A lower concentration of the reaction increases the reaction time and decreases the yield. For example, when the reaction between **1** and **R** is performed in a smaller scale at higher concentration of **1** (82 mg~374 mg, 0.3~2.3 mmol, 2 M solution of THF) for a shorter reaction time (48 h), **2** was obtained in higher yields (66~72%).
23. A second reaction on half scale provided 1.40 g (32%) of the product **2**. The purity of **2** is confirmed by spectroscopic and elemental analyses: colorless oil; $[\alpha]_D^{28}$ –30.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz, 50 °C)[5] δ: 1.44 (s, 9H), 2.88 (dd, *J* = 7.8 Hz, 13.2 Hz, 1H), 3.06 (s, 1H), 3.68 (s, 3H), 4.37 (s, 1H), 4.39–4.41 (m, 1H), 4.73 (s, 1H), 5.19 (s, 1H), 7.18–7.32 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.8, 37.7, 38.5, 51.8, 59.4, 77.7, 78.9, 80.2, 126.3, 128.1, 129.1, 136.4, 151.9, 170.4 ppm; IR (film): 2976, 1750, 1699, 1454, 1164, 700 cm^{-1}; HRMS (EI, $[M]^+$) *m/z* calcd for $C_{17}H_{23}NO_5$: 321.1576, Found: 321.1563; Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36, found: C, 63.43; H, 7.25; N, 4.18.

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.

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Discussion

Stereoselective syntheses of vicinal amino hydroxy acids have been studied by many research groups[6] because various non-proteinogenic amino acids are found in a number of biologically active natural products, such as a potent anti-hypertensive (-)-statine,[7] an anti-cancer paclitaxel,[8] excitatory neurotransmitters hydroxyglutamic acids,[9] and an anti-leukemia bestatin (Figure 4).[10] Some amino hydroxy acids have been also used as chiral synthons or auxiliaries.[11]

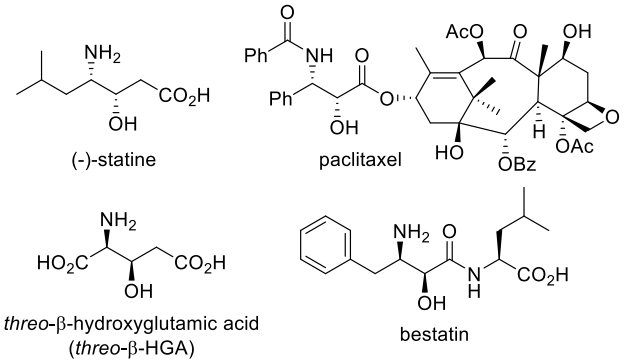
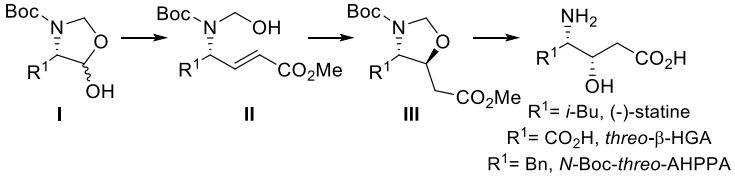


Figure 4. Vicinal amino hydroxy acids in bioactive compounds

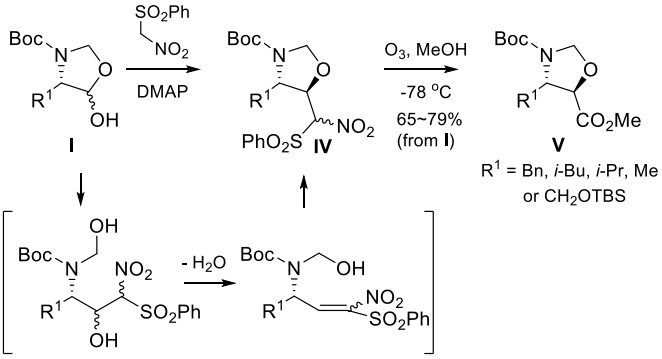
We had previously reported the stereoselective intramolecular conjugate addition of the *N*-hydroxymethyl group bound to the amino group of γ-amino-α,β-unsaturated esters **II**, derived from the corresponding configurationally stable α-amino aldehydes **I**,[3] to produce several bioactive γ-amino-β-hydroxy acids and their analogs (Scheme 1).[7c,9e,12]



Scheme 1. Reported stereoselective syntheses of γ-amino-β-hydroxy acids

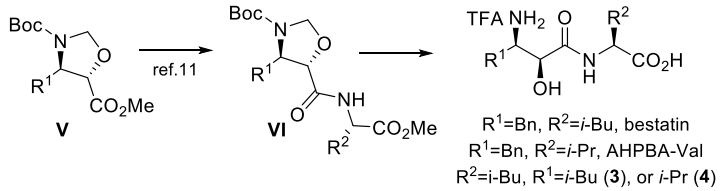
For the synthesis of more abundant β-amino-α-hydroxy acids than γ-amino-β-hydroxy acids in nature, we extended the utility of the *N*-hydroxymethyl group by reacting **I** with phenylsulfonylnitromethane ($PhSO_2CH_2NO_2$) (Scheme 2).[13] We have found that the treatment of **I** with $PhSO_2CH_2NO_2$ under the mild reaction conditions produced the *trans*-oxazolidines **IV** as a result of three sequential reactions, i.e., the nitro-aldol addition, the dehydration, and the intramolecular conjugate addition reactions (Scheme 2). The phenylsulfonylnitromethyl group in **IV** was effectively oxidized to the desired carboxylate group to yield several β-amino-α-hydroxy acid derivatives **V** with high stereoselectivity (dr. ≥

20:1).[13] We could develop the one-pot procedure to produce five analogs of **V** in 65-79% yields from **I** on a smaller scale.



Scheme 2. Stereoselective syntheses of methyl *trans*-oxazolidine-5-carboxylates V from I with $PhSO_2CH_2NO_2$

The analogs of **V** were also utilized as the suitably protected chiral synthons in the synthesis of some aminopeptidase inhibitors as presented in Scheme 3. After the efficient basic hydrolysis of the ester group of **V**, a simple peptide coupling followed by the global deprotection steps gave a natural bioactive dipeptides, bestatin and AHPBA-Val, and its unnatural analogs (Scheme 3).[13,14] The unnatural alkyl substituted analogs of bestatin, **3** and **4**, were successfully synthesized via the same procedure as that for bestatin, starting from the two analogs of **V**, which were derived from *N*-Boc-D-Leu-OH or *N*-Boc-D-Val-OH, respectively.



Scheme 3. Applications of V for the peptide syntheses

In summary, the properly protected methyl *trans*-oxazolidine-5-carboxylates **V** have been shown to be effective and versatile synthons for the synthesis of various peptides as well as β-amino-α-hydroxy acids. We hope that the chiral synthons **V** would be utilized for the synthesis of biologically important natural or unnatural analogs.

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 generous 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)

Phenylsulfonylnitromethane: Benzene, [(nitromethyl)sulfonyl]- (21272-85-5)
Nitromethane (75-52-5)
1,8-Diazabicycloundec-7-ene: Pyrimido[1,2-*a*]azepine, 2,3,4,6,7,8,9,10-octahydro- (6674-22-2)
Sodium benzenesulfinate: Benzenefulfinic acid, sodium salt (1:1) (873-55-2)
Iodine (7553-56-2)
4-Dimethylaminopyridine: 4-Pyridinamine, *N*,*N*-dimethyl- (1122-58-3)

Young Gyu Kim received his B.E. degree at Seoul National University in Korea. He earned his Ph.D. at Vanderbilt University in 1991 under supervision of Dr. J. 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.

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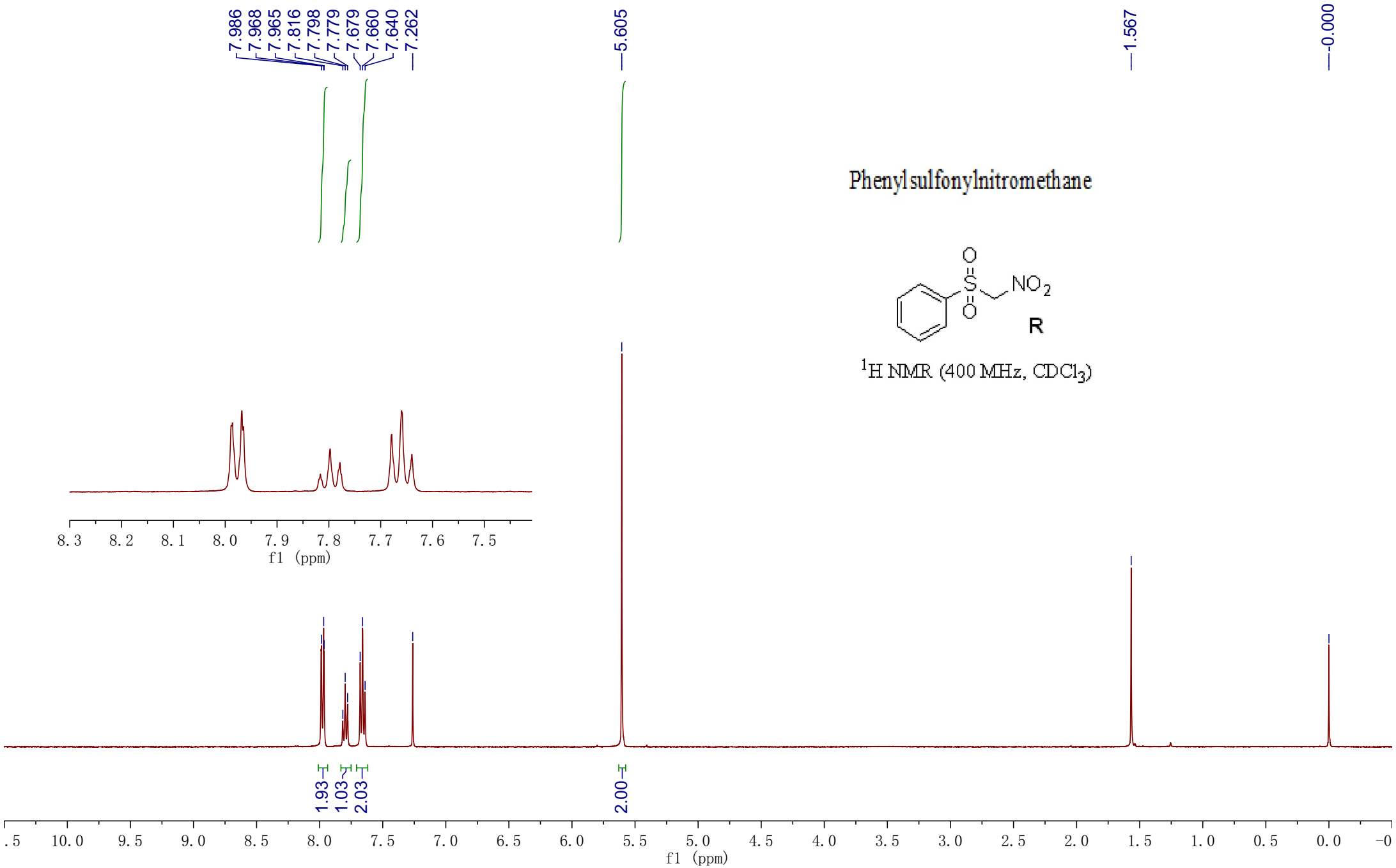
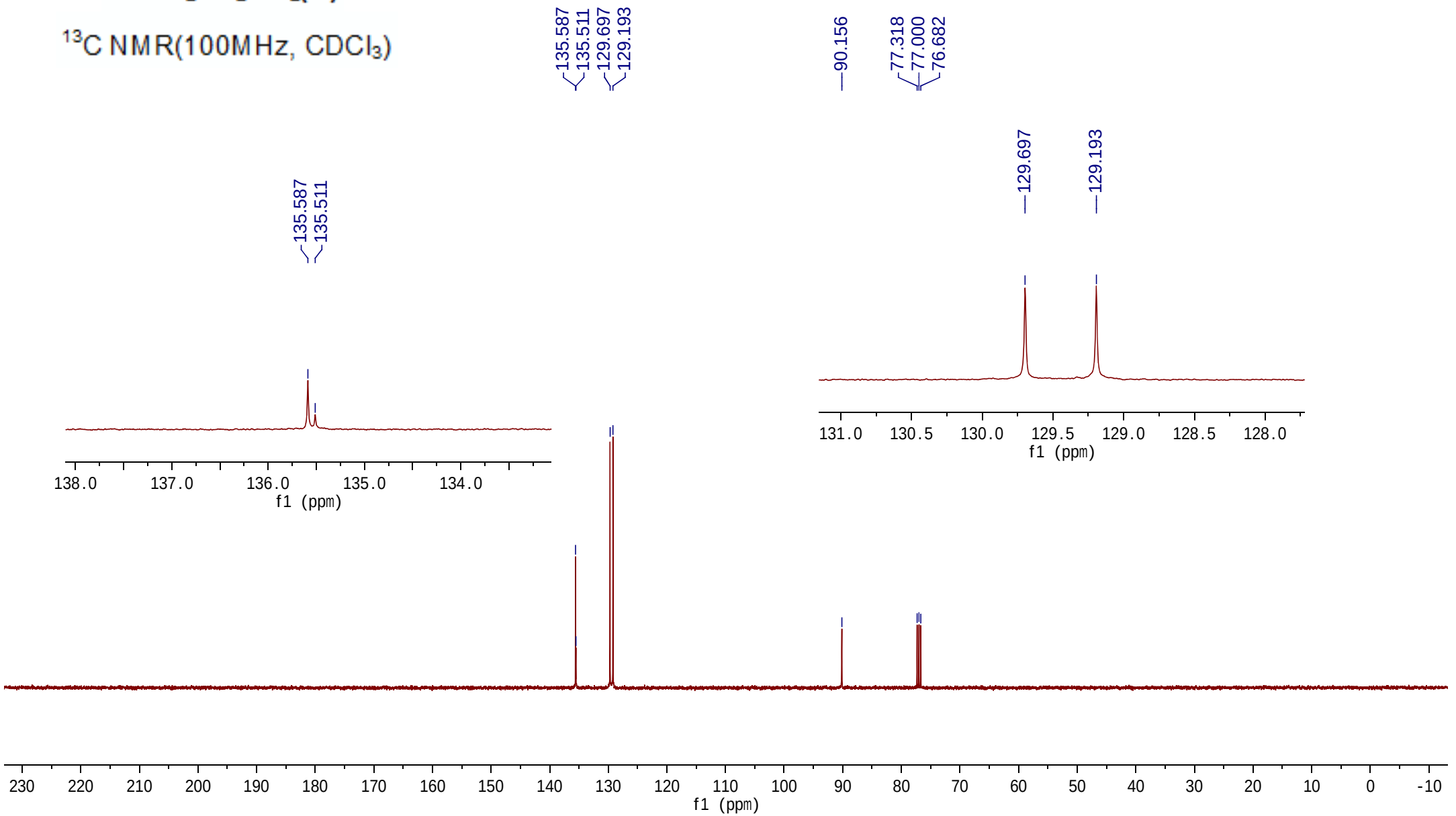

7.986
7.968
7.965
7.816
7.798
7.779
7.679
7.660
7.640
7.262
5.605
1.567
0.000
Phenylsulfonylnitromethane
O
S
O
NO2
R
1H NMR (400 MHz, CDCl3)
8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5
f1 (ppm)
1.93
1.03
2.03
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

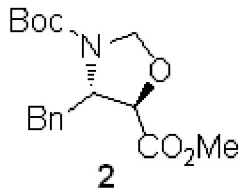
Phenylsulfonylnitromethane

$PhSO_2CH_2NO_2$(R)

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



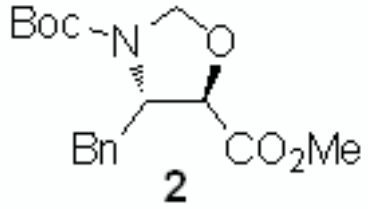
3-*tert*-Butyl 5-methyl (4*S*,5*R*)-4-benzyloxazolidine-3,5-dicarboxylate



2

^{1}H NMR (600 MHz, $CDCl_3$, 50 °C)

3-*tert*-Butyl 5-methyl (4*S*,5*R*)-4-benzyloxazolidine-3,5-dicarboxylate



2

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

170.383
151.931
136.388
129.060
128.144
126.343
80.200
78.896
77.684
77.321
77.000
76.680
59.424
51.781
38.502
37.700
27.793