Organic Syntheses

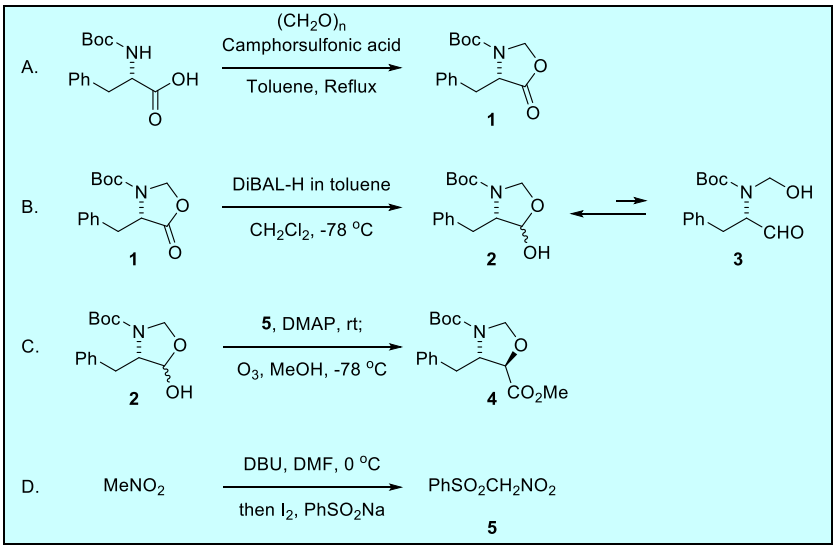
Discussion Addendum for:

Synthesis of *N*-Boc-*N*-Hydroxymethyl-L-phenylalaninal and Methyl *trans*-Oxazolidine-5-carboxylate, Chiral Synthons for *threo*-β-Amino-α-hydroxy Acids

Youngran Seo, Jae Won Yoo, Dongwon Yoo, Yoonjae Lee, and Young Gyu Kim*[1]

Department of Chemical and Biological Engineering, Seoul National University, Seoul 08826, Republic of Korea

Original Articles: Yoo, J.W.; Seo, Y.; Yoo, D. and Kim, Y.G. Org. Synth. ***2017****, 94, 358–371; Seo, Y.; Yoo, J.W.; Lee, Y.; Lee, B.; Kim, B. and Kim, Y.G. Org. Synth.* ***2017****, 94, 372–387.*



N-Boc-*N*-Hydroxymethyl α-amino aldehyde **3** is a configurationally stable α-amino aldehyde,[2] which was successfully converted to *trans*-oxazolidine methyl ester **4**, a chiral synthon for β-amino-α-hydroxy acids.[3] The *N*-hydroxymethyl group on **3** shifts the equilibration to the five-

DOI: 10.15227/orgsyn.99.0274

membered cyclic hemiacetal **2**, which ensures the high stability of the corresponding α-amino aldehyde and enables an intramolecular conjugate addition for highly diastereoselective introduction of an α-hydroxyl group. As a result, *trans*-oxazolidine methyl ester **4** was obtained from **2** as a chiral synthon for *syn*-β-amino-α-hydroxy acids.[3] Other γ-amino-β-hydroxy acids, β-deoxy-β,γ-diamino acid, and α-amino-β-hydroxy acid have been synthesized from *N*-Boc-*N*-hydroxymethyl α-amino aldehydes.[2,4–6] In addition, phenylsulfonylnitromethane (**5**) has been used for a two-way homologation of aliphatic aldehydes, which was applied to synthesize precursors for histone deacetylase (HDAC) inhibitors.[7]

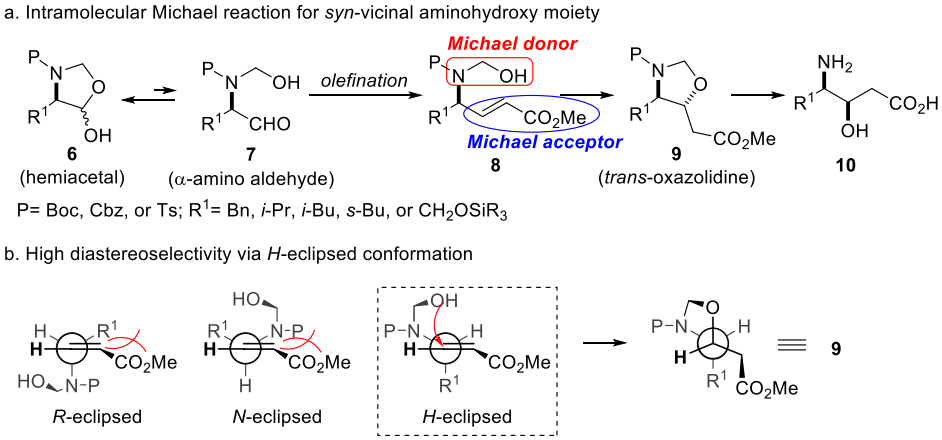
Configurationally Stable α-Amino Aldehyde

The preparation of configurationally stable α-amino aldehyde for the applications as chiral synthons or auxiliaries has been an important topic in asymmetric synthesis because of the rather acidic α-proton adjacent to the carbonyl group.[8,9] Even Garner's aldehyde,[10] one of the most cited stable α-amino aldehydes, not only suffers from 3~5% racemization during the preparation and storage,[8] but it is also only applicable to certain α-amino acids containing a hydroxyl group such as serine.

We have proposed *N*-hydroxymethyl α-amino aldehydes **7** as a suitable candidate for the configurationally stable α-amino aldehyde and undertaken investigations to demonstrate their diverse applications (Scheme 1). Various *N*-protected amino acids (*i.e.*, phenylalanine, valine, serine, leucine and isoleucine) were successfully converted to the corresponding *N*-hydroxymethyl α-amino aldehydes **7**, whose *N*-protecting group could be varied with a Boc, Cbz, or Ts group. As expected, *N*-protected *N*-hydroxymethyl α-amino aldehydes **7** showed remarkable configurational stability due to the shift of equilibrium to the five-membered cyclic hemiacetal **6** (Scheme 1a).[2,11] For example, phenylalaninal **2** showed 1~1.5% racemization during the preparation, and no racemization during the storage at room temperature for a month. *N*-Boc-*N*-hydroxymethyl serinal (**7**, R^1 = CH_2OSiR_3), an alternative for Garner's aldehyde, also showed less than 1% racemization during the preparation, and no racemization during storage at room temperature for 15 days. In addition, the aldehydes successfully reacted with various nucleophiles via the aldol reaction,[11,12] the nitroaldol reaction,[3,7] and the Wittig reaction.[4-6, 13-16]

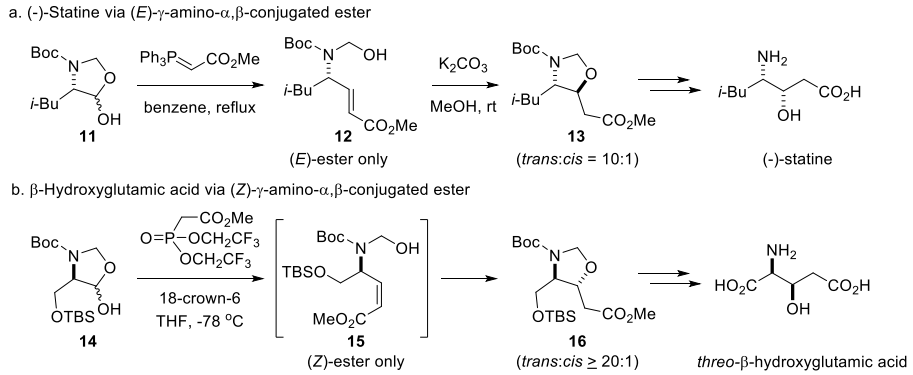
γ-Amino-β-hydroxy Acids from *N*-Hydroxymethyl α-Amino Aldehydes

One of the most useful applications of *N*-hydroxymethyl α-amino aldehydes **7** was the stereoselective synthesis of a series of γ-amino-β-hydroxy acids **10** (Scheme 1a). The intramolecular conjugate addition of the *N*-hydroxymethyl group, which was introduced to enhance the stability of α-amino aldehyde, onto γ-amino-α,β-unsaturated esters **8** provided *trans*-oxazolidines **9** with high diastereoselectivity, presumably through a favored *H*-eclipsed conformation due to the allylic strain (Scheme 1b).



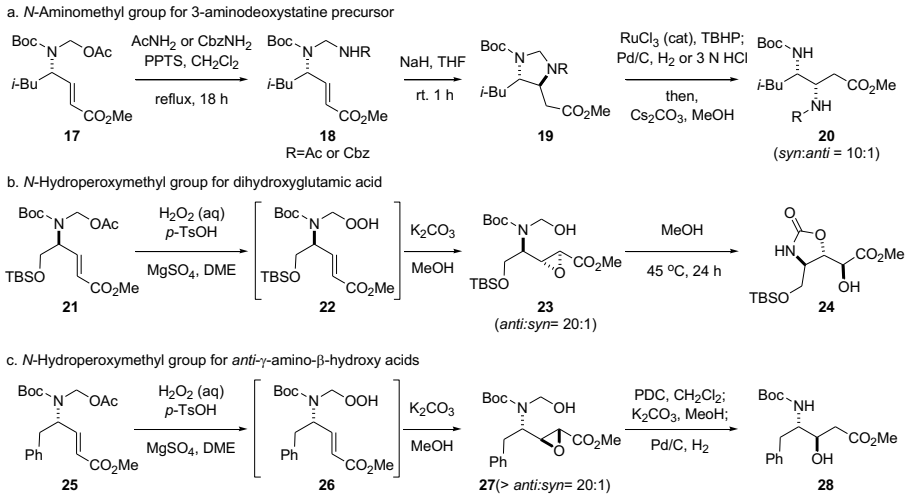
Scheme 1. Intramolecular conjugate addition with *N*-Boc-*N*-hydroxymethyl α-amino aldehydes

This synthetic strategy was first applied to the synthesis of (-)-statine, a key component of a natural antibiotic (Scheme 2a).[4] The intramolecular conjugate addition onto (*E*)-α,β-unsaturated methyl ester **12**, prepared from *N*-Boc-*N*-hydroxymethyl-L-leucinal via a Wittig reaction with methyl(triphenylphosphoranylidene)acetate, afforded *trans*-oxazolidine **13** (up to *trans*:*cis* = 10:1). The change in R^1 group in Scheme 1 from a bulky isobutyl group (R^1=-$CH_2CH(CH_3)_2$, Scheme 2a) to a smaller group (R^1=CH_2OTBS, Scheme 2b) resulted in a decreased diastereoselectivity of *trans*-oxazolidine (*trans*:*cis* = 5:1).[5] However, the reaction onto (*Z*)-α,β-unsaturated methyl ester **15**[17] afforded much higher diastereoselectivity of *trans*-oxazolidine **16** (*trans*:*cis* ≥ 20:1), which was converted to a glutamate receptor modulator *threo*-β-hydroxyglutamic acid (Scheme 2b).[5]



Scheme 2. Synthesis of γ-amino-β-hydroxy acids

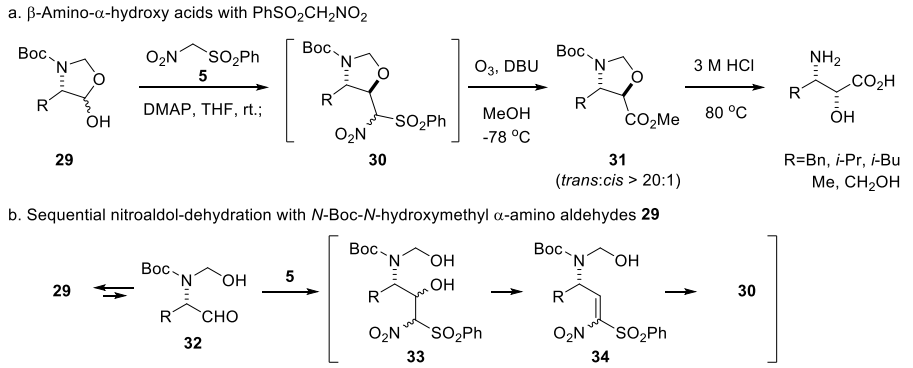
Other internal nucleophiles such as an *N*-aminomethyl group or *N*-hydroperoxymethyl group could be introduced by simple modification of the *N*-hydroxymethyl group in γ-amino-α,β-unsaturated ester (Scheme 3).[6,14–16] The intramolecular conjugate addition with the *N*-aminomethyl group enabled the diastereoselective synthesis of a 3-aminodeoxystatine derivative **20**. The intramolecular nucleophilic epoxidation of γ-amino-α,β-unsaturated ester **22** afforded *anti*-epoxide **23** with more than 20:1 diastereoselectivity, which was converted to *trans*-oxazolidinone **24**, a precursor for a glutamate receptor modulator 3,4-dihydroxyglutamic acid, via 5-*exo* cyclization with the *N*-Boc group.[15,18] Interestingly, a complementary *anti*-isomer of γ-amino-β-hydroxy acid could be obtained by the modification of synthetic procedures. The regioselective reduction by Pd-catalyzed hydrogenation of *anti*-epoxide **27** gave *anti*-γ-amino-β-hydroxy acid (Scheme 3c),[16] whereas the intramolecular conjugate addition of the *N*-hyroxymethyl group onto γ-amino-α,β-unsaturated esters gave *syn*-γ-amino-β-hydroxy acid (Scheme 2).



Scheme 3. Modification of *N*-hydroxymethyl for γ-amino-β-hydroxy acid analogs

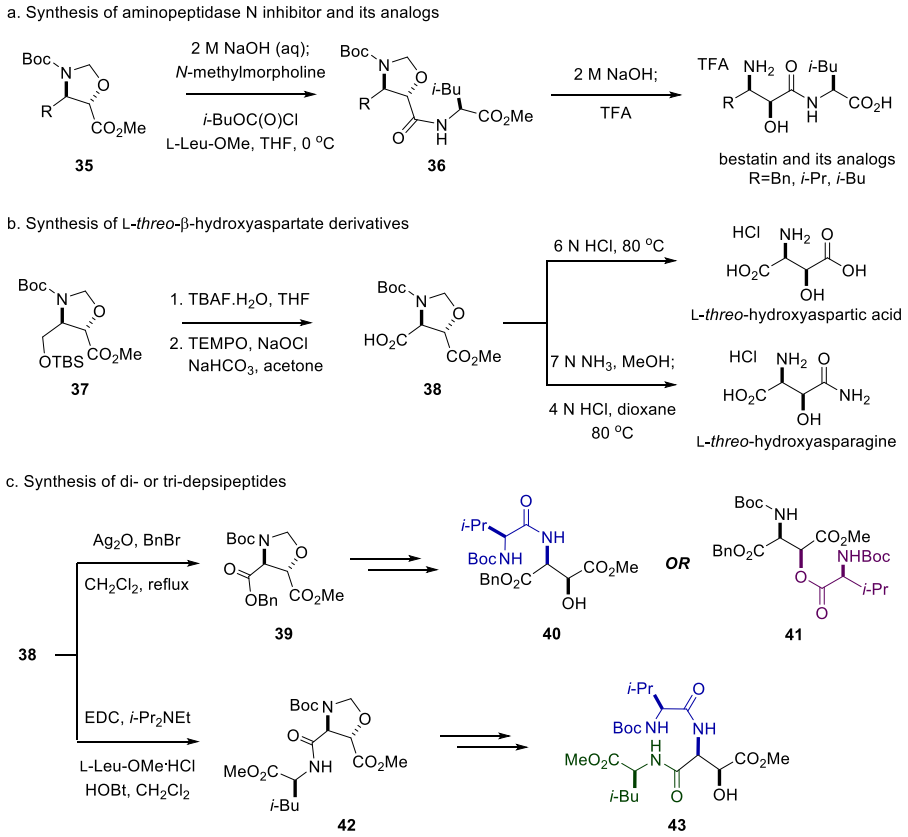
β-Amino-α-hydroxy Acids from *N*-Hydroxymethyl α-Amino Aldehydes

Next, the synthesis of one-carbon lower homologs of γ-amino-β-hydroxy acids, β-amino-α-hydroxy acids, from *N*-Boc-*N*-hydroxymethyl α-amino aldehydes **29** was explored (Scheme 4a).[3] While γ-amino-α,β-unsaturated esters were used as a Michael acceptor for the synthesis of γ-amino-β-hydroxy acids, nitroolefin derivatives such as **34** prepared with activated nitromethanes (*i.e.*, $PhSO_2CH_2NO_2$ (**5**)) was chosen as a one-carbon lower Michael acceptor for the synthesis of β-amino-α-hydroxy acids because *N*-Boc-*trans*-oxazolidine methyl esters **31** could be conveniently obtained by sequential nitroaldol, dehydration, and stereoselective intramolecular conjugate addition reactions under mild basic conditions (**29**→**33**→**34**→**30** in Scheme 4b), followed by one-pot ozonolysis. These sequential one-pot reactions could afford chiral synthons *trans*-oxazolidne methyl esters **31** in 65~79% yields with more than 20:1 diastereoselectivity from the corresponding *N*-Boc-*N*-hydroxymethyl α-amino aldehydes **29**, which were readily prepared from α-amino acids (*i.e.*, phenylalanine, leucine, valine, alanine and serine).



Scheme 4. Synthesis of β-amino-α-hydroxy acids

N-Boc-*trans*-Oxazolidine methyl esters **35**, a properly protected form of β-amino-α-hydroxy acids, were useful synthons to synthesize derivatives of β-amino-α-hydroxy acid. Basic hydrolysis of **35** followed by the peptide coupling with L-Leu-OMe or L-Val-OMe produced anti-leukemia dipeptide bestatin and its analogs without additional amino- or hydroxy-protecting steps (Scheme 5a).[3,19] Furthermore, *trans*-oxazolidine methyl ester **37** derived from D-serine was efficiently converted to L-*threo*-hydroxyaspartic acid and L-*threo*-hydroxyasparagine after an oxidation of the hydroxymethyl group from deprotection of **37** to the carboxylic acid group of **38** (Scheme 5b).[20] In addition, the orthogonal protecting groups on chiral intermediate **38** made the chemoselective peptide bond formation possible either at the α-amino group (**38**→**39**→**40**), β-hydroxyl group (**38**→**39**→**41**), α-carboxylic acid group (**38**→**42**), or β-carboxylic acid group (Scheme 5c).[20] Therefore, *trans*-oxazolidine dicarboxylate **38** would be useful for the synthesis of bioactive peptides containing an L-*threo*-β-hydroxy aspartate moiety, such as WAP-8294A$_2$, ramoplanin, dolastatins, kahalalide F and neurotoxin antillatoxin.

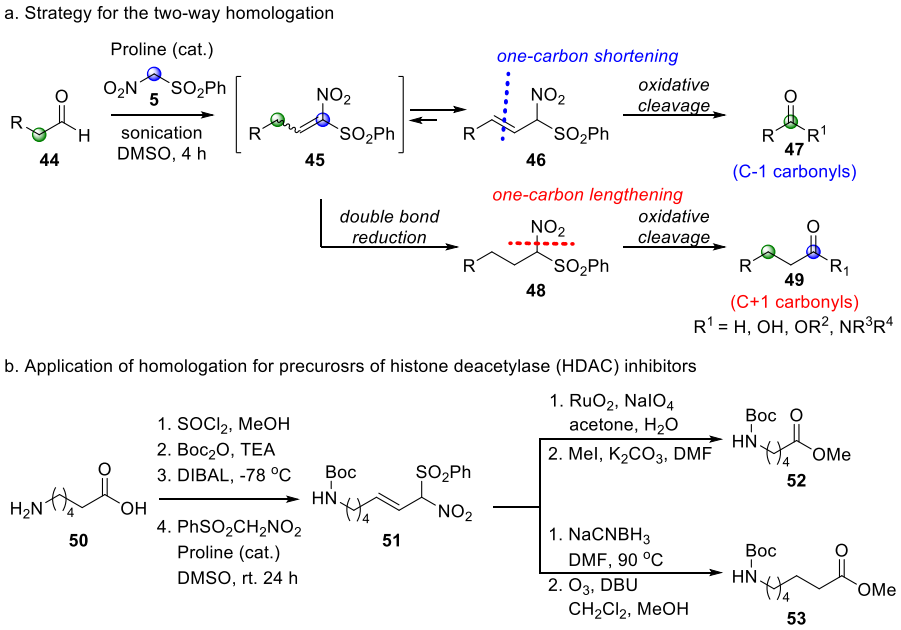


Scheme 5. Application of *trans*-oxazolidine methyl esters

$PhSO_2CH_2NO_2$ (5) for One-carbon Homologation

Based on the reaction results between *N*-Boc-*N*-hydroxymethyl α-amino aldehyde **2** and phenylsulfonylnitromethane ($PhSO_2CH_2NO_2$ (**5**)) as a one-carbon carboxylate synthon, we investigated a new one-carbon homologation of aliphatic aldehydes using $PhSO_2CH_2NO_2$ (**5**). Unlike its reaction with *N*-Boc-*N*-hydroxymethyl α-amino aldehyde **2**,[3,19] the reaction of **5** with aliphatic aldehydes was not successful under similar basic conditions. After enormous attempts, aliphatic aldehydes were successfully converted to β,γ-unsaturated α-nitrosulfone **46** under proline-catalyzed conditions (Scheme 6a).[7] The nitroaldol reactions of **5** with aliphatic aldehydes followed by a dehydration

reaction of the nitroaldol intermediate initially yielded α,β-unsaturated α-nitrosulfone **45**, which was isomerized to favored β,γ-unsaturated α-nitrosulfone **46**[21] in the absence of an internal nucleophile. The reaction time was dramatically shortened to 4 h under ultrasound irradiation conditions from 2~3 days with stirring at room temperature.



Scheme 6. Applications of $PhSO_2CH_2NO_2$ (5) for one-carbon homologation

The preference of β,γ-unsaturated α-nitrosulfone **46** over α,β-unsaturated α-nitrosulfone **45** enabled a novel approach toward a two-way homologation of aliphatic aldehydes from the same intermediate β,γ-unsaturated α-nitrosulfone. First, carbonyl compounds (**47**) with one fewer carbon in the chain were obtained by the ozonolysis of β,γ-unsaturated α-nitrosulfone **46**. Four different one-carbon lower carbonyl homologs, dimethyl acetal, aldehyde, carboxylic acid, or primary alcohol, were obtained by quenching ozonides with trimethyl orthoformate and dimethyl sulfide, dimethyl sulfide, hydrogen peroxide, or sodium borohydride, respectively. Next, one-carbon higher carbonyl homologs **49** were obtained by the chemoselective double bond reduction of β,γ-unsaturated α-nitrosulfone **46** followed by the

oxidation of phenylsulfonylnitromethyl group to the carbonyl group. The selective reduction was smoothly conducted probably by a conjugate addition of sodium cyanoborohydride onto α,β-unsaturated α-nitrosulfone **45**, which was generated after in-situ isomerization of β,γ-unsaturated α-nitrosulfone **46** in DMF at 90 °C (**46**→**45**→**48** in Scheme 6a). The divergent homologation developed was further applied for the synthesis of the two precursors for biologically active histone deacetylase inhibitors from the common C_6-amino acid **50**, a C_5-amino acid derivative **52** and a C_7-amino acid derivative **53** (Scheme 6b).

References

1. Department of Chemical and Biological Engineering, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul, 08826, Republic of Korea. Email: ygkim@snu.ac.kr. (ORCID: 0000-0001-7437-5110).
2. Hyun, S. I; Kim, Y. G. *Tetrahedron Lett.* **1998**, *39*, 4299–4302. https://doi.org/10.1016/S0040-4039(98)00715-1.
3. Seo, Y.; Kim, H.; Chae, D. W.; Kim, Y. G. *Tetrahedron Asymm.* **2014**, *25*, 625–631. https://doi.org/10.1016/j.tetasy.2014.03.012.
4. Yoo, D.; Oh, J. S.; Kim, Y. G. *Org. Lett.* **2002**, *4*, 1213–1215. https://doi.org/10.1021/ol025653u.
5. Kim, H.; Yoo, D.; Kwon, S.; Kim, Y. G. *Tetrahedron Asymm.* **2009**, *20*, 2715–2719. https://doi.org/10.1016/j.tetasy.2009.11.023.
6. Yoo, D.; Kwon, S.; Kim, Y. G. *Tetrahedron Asymm.* **2005**, *16*, 3762–3766. https://doi.org/10.1016/j.tetasy.2005.10.018.
7. Yoo, J. W.; Seo, Y.; Park, J. B.; Kim, Y. G. *Tetrahedron* **2020**, *76*, 130883. https://doi.org/10.1016/j.tet.2019.130883.
8. Bera, S.; Mondal, D.; Singh, M.; Kale, R. K. *Tetrahedron* **2013**, *69*, 969–1011. https://doi.org/10.1016/j.tet.2012.11.054.
9. Gryko, D.; Chałko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514–541. https://doi.org/10.1002/chir.10243.
10. Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64–77. https://doi.org/10.15227/orgsyn.077.0064.
11. Yoo, D.; Oh, J. S.; Lee, D.-W.; Kim, Y. G. *J. Org. Chem.* **2003**, *68*, 2979–2982. https://doi.org/10.1021/jo026653a.
12. Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **1999**, *40*, 2653–2656. https://doi.org/10.1016/S0040-4039(99)00265-8.

13. Reddy, G. V.; Rao, G. V.; Sreevani, V.; Iyengar, D. S. *Tetrahedron Lett.* **2000**, *41*, 953–954. https://doi.org/10.1016/S0040-4039(99)02106-1.
14. Yoo, D.; Song, J.; Kang, M. S.; Kang, E.-S.; Kim, Y. G. *Tetrahedron Asymm.* **2011**, *22*, 1700–1704. https://doi.org/10.1016/j.tetasy.2011.09.021.
15. Yoo, D.; Kim, H.; Kim, Y. G. *Synlett* **2005**, 1707–1710. https://doi.org/10.1055/s-2005-871558.
16. Kim, H.; Yoo, D.; Choi, S. Y.; Chung, Y. K.; Kim, Y. G. *Tetrahedron Asymm.* **2008**, *19*, 1965–1969. https://doi.org/10.1016/j.tetasy.2008.07.036.
17. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408. https://doi.org/10.1016/S0040-4039(00)85909-2.
18. Seo, W. D.; Curtis-Long, M. J.; Jeong, S. H.; Jun, T. H.; Yang, M. S.; Park, K. H. *Synthesis* **2007**, 209–214. https://doi.org/10.1055/s-2006-958956.
19. Seo, Y.; Lee, S. B.; Kim, Y. G. *Appl. Chem. Eng.* **2015**, *26*, 111–115. https://doi.org/10.14478/ace.2014.1134.
20. Lee, Y.; Seo, Y.; Lee, B.; Kwon, H.; Chung, K.; Kim, Y. G. *Amino Acids* **2022**. https://doi.org/10.1007/s00726-022-03196-8.
21. Wade, P. A.; Murray, J. K.; Shah-Patel, S.; Palfey, B. A.; Carroll, P. J. *J. Org. Chem.* **2000**, *65*, 7723–7730. https://doi.org/10.1021/jo0000170.

Young Gyu Kim received his B.S. 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.

Youngran Seo received her B.S. degree from Dankook University in 2007, and she received M.S. and Ph.D. degree from Seoul National University in 2011 and 2015.

Jae Won Yoo received his B.S., M.S., and Ph.D. degrees from Seoul National University in 1997, 1999, and 2020, respectively. He is currently working for Amorepacific corporation.

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. Dr. Yoo is Assistant Professor of the Department of Chemical and Biological Engineering at Seoul National University.

Yoonjae Lee received his B.S. degrees from Yonsei University in 2014, and M.S. and Ph.D. degrees from Seoul National University in 2016 and 2022.