# Synthesis of Alkyl Bridged-Tris- $\alpha$-Amino Acids as $\mathrm{C}_{3}$-Symmetric and Linear Linkers 

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Abstract: Although bis- $\alpha$-amino acids have been used to synthesize dimer models of aggregative peptides involved in neurodegenerative diseases, tris- $\alpha$-amino acids are employed to a lesser extent for trimer models. The reported tris- $\alpha$-amino acids substituted on the 1,3,5positions of an aromatic ring are not suitable for mimicking trimers due to their low flexibility and high planarity. Here, we design and synthesize two new alkyl bridged-tris- $\alpha$-amino acids with Fmoc protecting groups as new flexible linkers for trimer models.

## Introduction

Accumulated evidence suggests that misfolded protein aggregates contribute to the pathogenesis of intractable diseases such as Alzheimer's (AD), Parkinson's, and prion diseases. ${ }^{[1]}$ Elucidation of the toxicity mechanism of the corresponding misfolded protein aggregates, including oligomers or fibrils should improve the understanding of such intractable diseases at the molecular level. Currently, the structures of these oligomers or fibrils remain elusive due to their labile or quasi-stable properties and the presence of various strains. ${ }^{[2]}$ Thus, the development of dimer and trimer models as the minimum units of these oligomers and fibrils should reveal the important structure for biological activity.

Regarding amyloid $\beta(A \beta)$ peptides involved in $A D,{ }^{[3]}$ dimer models have extensively been developed to examine their contribution to the onset of AD. ${ }^{[4]}$ Among them, bis- $\alpha$-amino acids, L,L-2,6-diaminopimelic acid (DAP) and L,L-2,8-diaminoazelaic acid (DAZ), have been used to synthesize chemically and metabolically stable full-length $A \beta$ dimers to compare intermolecular disulfide bond formation. ${ }^{[5,6]}$ Some of these dimers exhibit potent neurotoxicity in vitro. Although trimers may also contribute to the pathogenesis of AD, the lack of flexible linkers similar to DAP and DAZ has limited the synthesis of the trimer models of full-length $A \beta$. ${ }^{[7]}$

Tris- $\alpha$-amino acids would be useful to tether trimers. Aromatic $\mathrm{C}_{3}$-symmetric tris- $\alpha$-amino acid derivatives have been synthesized using the Horner-Wadsworth-Emmons (HWE) reaction followed by asymmetric hydrogenation, ${ }^{[8]}$ cross-coupling
reactions, ${ }^{[9]}$ or alkylation of a glycine equivalent (Fig. 1). ${ }^{[10]}$ These derivatives have been utilized as building blocks of synthetic peptides. For example, Kotha and Todeti reported the synthesis of $\mathrm{C}_{3}$-symmetric dipeptide trimers. ${ }^{[9 \mathrm{e}]}$ Frejd and Ritzén prepared chiral peptide dendrimers, which contain 1,3,5-phenyltris-Lalanine (PtA) ${ }^{[8]}$ as the central core unit. ${ }^{[11]}$ However, the application of such amino acids to biologically important peptides has yet to be reported. Recently, Irie and colleagues incorporated PtA into the C-terminal region of $A \beta 40$ proteins to synthesize quasi-stable trimer models. ${ }^{[12]}$ However, the neurotoxicity of these trimer models did not exceed that of the corresponding monomer or the dimer model, ${ }^{[6 b]}$ suggesting that the low flexibility, high planarity, or hydrophobicity of the aromatic ring may inhibit the optimal conformation that shows neurotoxicity.

aryl spacer with $C_{3}$-symmetric

This work



Fmoc-( $S, S, S$ )-tert-butyltris-L-alanine (1) Fmoc-( $S, S$ )-a, $\alpha$-di-L-homonorleucyl-L-glycine (2)
alkyl spacer with $C_{3}$-symmetric
alkyl spacer with linear
Figure 1. Tris- $\alpha$-amino acid derivatives previously reported and those synthesized in this study. Boc $=$ tert-butoxycarbonyl, Fmoc $=9$ fluorenylmethyloxycarbonyl.

The above issue may be addressed by replacement of a benzene ring that binds three $\alpha$-amino acid moieties with a flexible alkyl chain. In this paper, we report the synthesis of two new types
of tris- $\alpha$-amino acid derivatives connected with alkyl spacers. One is $\mathrm{C}_{3}$-symmetric tert-butyltris-L-alanine (tButA), and the other is linear tris- $\alpha$-amino acid, which was named $\alpha, \alpha$-di-L-homonorleucyl-L-glycine (di-hNor-Gly), along with their 9fluorenylmethyloxycarbonyl (Fmoc)-protected derivatives (1 and 2, respectively, Fig. 1). These linkers should lead to various types of trimer models of pathogenic aggregative peptides such as $\mathrm{C}_{3}$ symmetric trimers and those forming intermolecular parallel $\beta$ sheets.

## Results and Discussion

## Synthesis of Fmoc-(S,S,S)-tert-butyltris-L-alanine (Fmoc tButA, 1)

Two paths were envisioned to synthesize 1, whose amino acid moieties would be installed via the HWE reaction and subsequent asymmetric hydrogenation (Scheme 1). ${ }^{[13,14]}$ In a three-directional approach, 1 would be obtained by asymmetric hydrogenation of tris-dehydroamino acid 3 (route A). Although a trialdehyde may be a precursor of 3 , it would be labile and unsuitable for the synthesis. Thus, a stepwise introduction was planned to access compound $\mathbf{3}$ by the HWE reaction from dialdehyde 5 or $\mathbf{6}$ through compound 4. Compound $\mathbf{5}$ or $\mathbf{6}$ could be derived from carboxylic acid 7.


Scheme 1. Retrosynthetic analysis of Fmoc-(S,S,S)-tert-butyltris-L-alanine (1). Fmoc-OSu = $N$-(9-fluorenylmethoxycarbonyloxy)succinimide, $\mathrm{Cbz}=$ benzyloxycarbonyl, TBS = tert-butyldimethylsilyl.

On the other hand, a stepwise asymmetric hydrogenation would realize compound 1 (route B). Compound 1 would be synthesized from compound 8, which would be produced from alcohol 9 . Compound 9 would be derived via an asymmetric hydrogenation of compound 4. A stepwise introduction of amino
acid moieties would produce orthogonally protected amino acids to synthesize psuedo $\mathrm{C}_{2}$-symmetric trimers. Additionally, route B could be used to synthesize tButA stereoisomers, where each stereocenter has a different configuration, namely, ( $S, S, R$ )- and $(S, R, R)$-tButA. However, both routes A and B would be suitable to synthesize $(S, S, S)$ - and ( $R, R, R$ )-tButA.

The synthesis began with ozonolysis of the double bond of silyl ether 10, which was readily prepared from carboxylic acid $\mathbf{7}$ by a known procedure (Scheme 2). ${ }^{[15]}$ The resultant dialdehyde was immediately converted to protected bis-dehydroamino acid 12 by the HWE reaction using commercially available glycine phosphonate 11 in $31 \%$ yield from 10. The tert-butyldimethylsilyl (TBS) group of $\mathbf{1 2}$ was removed under acidic conditions to give alcohol 13 in $85 \%$ yield. Oxidation of the primary alcohol of 13 using 2-azaadamantane-2-ol (AZADOL) ${ }^{[16]}$ was attempted to produce hemiaminal 14. However, the reaction gave a complex mixture, including a bicyclic compound, which did not react under the Wittig reaction conditions for a one-carbon elongation.


Scheme 2. Attempted synthesis of Fmoc-(S,S,S)-tert-butyltris-L-alanine via bisdehydroamino acid 13. DBN $=1,5$-diazabicyclo[4.3.0]non-5-ene, $\mathrm{CSA}=( \pm)$-10camphorsulfonic acid, AZADOL $=2$-azaadamantane-2-ol.

To avoid the production of stable six-membered bicyclic compounds, the bis-dehydroamino acid unit was introduced after the one carbon elongation (Scheme 3). Carboxylic acid 7 was converted to known alcohol 16 in four steps, including the ArndtEistert synthesis and a $\mathrm{LiAlH}_{4}$ reduction. ${ }^{[17]}$ After silylation of compound 16, the olefin of 17 was cleaved by oxidation with ozone. Reductive treatment with triphenylphosphine produced better results than the use of dimethyl sulfide and yielded the dialdehyde upon stirring at room temperature for 20 minutes. The dialdehyde was immediately subjected to the HWE reaction to give protected bis-dehydroamino acid 18 in $61 \%$ yield from compound 17.

Next, the third dehydroamino acid unit was introduced (route A). Removal of the TBS group of 18 and subsequent oxidation of resultant primary alcohol 4 using AZADOL gave aldehyde 15. The HWE reaction of $\mathbf{1 5}$ gave protected tris-dehydroamino acid $\mathbf{3}$ in $73 \%$ yield. Asymmetric hydrogenation of 3 with (S,S)-2,3-bis(tert-butylmethylphosphino)-quinoxaline-Rh $\quad((S, S) \text {-QuinoxP*-Rh })^{[18]}$
catalyst gave protected tButA 20 in $84 \%$ yield. The enantiomeric excess and diastereomeric ratio of $\mathbf{2 0}$ were $>99 \%$ ee and $>97 \%$ de, respectively.


Scheme 3. Synthesis of Fmoc-(S,S,S)-tert-butyltris-L-alanine (1). (S,S)-QuinoxP*-Rh $=$ (S,S)-2,3-Bis(tert-butylmethylphosphino)quinoxaline(1,5cyclooctadiene)rhodium(I)hexafluoroantimonate or (S,S)-2,3-Bis(tert-butylmethylphosphino)quinoxaline(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate.

We also investigated stepwise route $B$. The two alkene functionalities of 18 were hydrogenated asymmetrically under the same conditions as route A using a ( $S, S$ )-QuinoxP*-Rh catalyst to produce protected bis- $\alpha$-amino acid 9 in $85 \%$ yield ( $>99 \%$ ee and $>98 \%$ de). The TBS group of 18 was removed during hydrogenation, which may be because methanol, which served as the solvent, also acted as a nucleophile. After AZADO oxidation of the primary alcohol of 9 , the HWE reaction of 19 gave compound 8 in $64 \%$ overall yield. Asymmetric hydrogenation of 8 using ( $S, S$ )-QuinoxP*-Rh catalyst gave protected tButA 20 in 91\% yield (>98\%de).

With protected tButA (20) in hand, the protecting group manipulation was performed to access Fmoc-protected $t B u t A(1)$, which can be used in solid-phase peptide synthesis. Hydrolysis of 20 under basic conditions and subsequent removal of the benzyloxycarbonyl (Cbz) groups, gave tButA 21. Although the hydrophilic property of the three free amino acid moieties prevented extraction of 21 from water, the ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra $\left(\mathrm{D}_{2} \mathrm{O}\right)$ confirmed its structure. Fmoc groups were introduced to the primary amino groups of 21 to produce 1 in $54 \%$ yield from 20. Since both ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR analyses showed that the corresponding signals of each homoalanine (-
$\mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{CHNHR}^{2}\left(\mathrm{CO}_{2} \mathrm{R}^{1}\right)$ ) moiety of $\mathbf{2 0}$ and $\mathbf{2 1}$ were equivalent, the $\mathrm{C}_{3}$-symmetric structure of the product was confirmed.

## Synthesis of Fmoc-(S,S)-a, a-di-L-homonorleucyl-L-glycine

 (Fmoc-di-hNor-Gly, 2)We then focused on the synthesis of Fmoc-di-hNor-Gly (2), which is a linear tris- $\alpha$-amino acid for trimer peptide models. Scheme 4 depicts our envisioned retrosynthesis. The terminal amino acid moieties of Fmoc-di-hNor-Gly (2) would be introduced via the HWE reaction of dialdehyde 23 and subsequent asymmetric hydrogenation of 22 . Compound 23 would be derived from bisolefin 24, which would be prepared from isocyanide 25 .


Scheme 4. Retrosynthetic analysis of Fmoc-(S,S)-a, a-di-L-homonorleucyl-Lglycine (2).

Compound 25 was dialkylated by following Schöllkopf and Hoppe's procedure ${ }^{[19]}$ to give isocyanide 26 in $84 \%$ yield (Scheme 5). Hydrolysis of the isocyanide group of 26 and subsequent treatment of CbzCl and $\mathrm{Na}_{2} \mathrm{CO}_{3}$ in toluene at $80^{\circ} \mathrm{C}$ produced $\mathrm{Cbz}-$ protected amino acid $\mathbf{2 4}$ in $\mathbf{7 3 \%}$ yield. The terminal olefins of $\mathbf{2 4}$ were cleaved by ozonolysis and then treated with triphenylphosphine. The resultant dialdehyde was immediately converted to compound 22 by the HWE reaction. Asymmetric hydrogenation of 22 using the ( $S, S$ )-Quinox $P^{*}$-Rh catalyst gave protected di-hNor-Gly (27) in 98\% yield. The enantiomeric excess and diastereomeric ratio of 27 were $>99 \%$ ee and $>96 \%$ de, respectively.


Scheme 5. Synthesis of Fmoc-(S,S)-a, a-di-L-homonorleucyl-L-glycine (2). DMSO = dimethyl sulfoxide, TFA = trifluoroacetic acid.

Acidic hydrolysis of the tert-butyl ester, alkaline hydrolysis of the methyl ester, and subsequent hydrogenolysis of the Cbz groups gave di-hNor-Gly (28). Finally, the Fmoc groups were
introduced to the primary amino groups of $\mathbf{2 8}$ to produce $\mathbf{2}$ in 55\% yield from 27. Although the tetrasubstituted carbons of 27,28 , and 2 have the same two side chains, these compounds are chiral because the side chains contain a chiral center (namely, pseudo $\sigma$-symmetry). Hence, the two chains are not equivalent. As expected, the signals derived from each carbon in ${ }^{13} \mathrm{C}$ NMR spectra were observed independently.

## Conclusion

Here, we established an enantioselective synthetic route toward two new $\mathrm{C}_{3}$-symmetric and linear tris- $\alpha$-amino acids containing alkyl spacers, $(S, S, S)$-tButA (21) and ( $S, S$ )-di-hNor-Gly (28). Both compounds were converted into the corresponding Fmocprotected amino acids. These synthetic routes should allow the syntheses of various derivatives with modified protecting groups and configurations. They should realize powerful tools to synthesize various cross-linked trimer models of pathogenic aggregative peptides using a solid-phase Fmoc strategy, as exemplified in the synthesis of the trimer models of Aß40. ${ }^{[12]}$ Currently we are trying to synthesize these trimer models, including $\mathrm{C}_{3}$-symmetric and $\beta$-sheet peptides. These results, which consider the structure-activity relationships, will be reported in due course.

## Experimental Section

General: All non-aqueous reactions, except hydrogenation reactions, were carried out under a nitrogen or argon atmosphere in dried glassware. Analytical thin-layer chromatography was performed with TLC Silica gel 60 F254 (Merck, Darmstadt, Germany). Silica gel column chromatography was performed with Wakogel C-200 (Wako Pure Chemical Industries, Osaka, Japan) or Chromatorex BW-300 (Fuji Silica Chemical, Aichi, Japan). Flash column chromatography was performed with a Model 800E with a Model prep UV-10V UV detector (Yamazen, Osaka, Japan), and YMC*GEL ODS-A (YMC, Kyoto, Japan) was used as the carrier. HPLC was performed with Model 600E with a Model 2487 UV detector (Waters, Milford, MA, USA). Proton nuclear magnetic resonance ( ${ }^{1} \mathrm{H}$ NMR) spectra were recorded on an AVANCE III 400 (Bruker, Germany) at 400 MHz or an AVANCE III 500 (Bruker, Germany) at 500 MHz . Chemical shifts were reported relative to $\mathrm{Me}_{4} \mathrm{Si}(\delta 0.0)$ in $\mathrm{CDCl}_{3}$, and residual solvent of $\mathrm{CD}_{3} \mathrm{OD}$ ( $\delta 3.31$ ) and $\mathrm{D}_{2} \mathrm{O}$ ( $\delta 4.79$ ). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance ( ${ }^{13} \mathrm{C}$ NMR) spectra were recorded on an AVANCE III 400 (Bruker, Germany) at 101 MHz or an AVANCE III 500 (Bruker, Germany) at 126 MHz . Chemical shifts were reported relative to $\mathrm{CDCl}_{3}(\delta 77.0)$ and $\mathrm{CD}_{3} \mathrm{OD}(\delta 49.0)$. Infrared spectra were recorded on a FT/IR-470 Plus Fourier-transform infrared spectrometer (Jasco, Tokyo, Japan). Specific rotations were recorded on a P-2200 digital polarimeter (Jasco, Tokyo, Japan). Low- and highresolution mass spectra were recorded on a JMS700 mass spectrometer (JEOL, Tokyo, Japan) for FAB-MS (matrix, m-nitrobenzyl-alcohol) or timsTOF (Bruker, Germany) for ESI-MS and APCI-MS.
Compound 12: A solution of 10 ( $605 \mathrm{mg}, 2.85 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(30 \mathrm{~mL})$ was cooled to $-78^{\circ} \mathrm{C}$. The solution was bubbled with $\mathrm{O}_{3}$ until it turned blue. Excess $\mathrm{O}_{3}$ was removed from the reaction mixture by purging with $\mathrm{O}_{2}$. To the mixture was added $\mathrm{Me}_{2} \mathrm{~S}(3 \mathrm{~mL})$ at $-78^{\circ} \mathrm{C}$, and the reaction mixture was stirred for 25 minutes. Then the reaction mixture was washed with water, and the aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The organic layers were washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. Filtration and concentration afforded a crude dialdehyde. To a solution of (Z)- $\alpha$-phosphonoglycine trimethyl ester ( $1.98 \mathrm{~g}, 5.99 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$ was added DBN $(0.750 \mathrm{~g}, 6.04 \mathrm{mmol})$. The mixture was
stirred at $0^{\circ} \mathrm{C}$ for 15 minutes. The dialdehyde in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$ was added slowly at $0^{\circ} \mathrm{C}$. The reaction mixture was gradually warmed to room temperature while stirring overnight. The reaction mixture was washed with 1 M aqueous HCl solution. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $3 / 7$ ) to afford 12 ( $577 \mathrm{mg}, 31 \%$ for 2 steps) as colorless oil. $\mathrm{R}_{\mathrm{f}}=0.62$ (hexane/ethyl acetate $=1 / 1$ ); ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.36-7.28(\mathrm{~m}$, $10 \mathrm{H}), 6.55(\mathrm{t}, J=7.6 \mathrm{~Hz}, 2 \mathrm{H}), 6.50(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 5.12(\mathrm{~s}, 4 \mathrm{H}), 3.74(\mathrm{~s}, 6 \mathrm{H})$, $3.48(\mathrm{~d}, \mathrm{~J}=5.4 \mathrm{~Hz}, 2 \mathrm{H}), 2.31-2.18(\mathrm{~m}, 4 \mathrm{H}), 1.95-1.85(\mathrm{~m}, 1 \mathrm{H}), 0.86(\mathrm{~s}, 9 \mathrm{H})$, $0.03 \mathrm{ppm}(\mathrm{s}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 164.8$ (2C), 154.1 (2C), 136.0 (2C), 134.2 (2C), 128.5 (4C), 128.24 (2C), 128.21 (4C), 127.0 (2C), 67.4 (2C), 65.2, 52.4 (2C), 40.0, 29.8 (2C), 25.9 (3C), 18.3, -5.4 ppm (2C); IR (neat on KBr plate): ũ 3316, 3033, 2952, 2856, 1725, 1659, 1500, 1226, 1049, 837, 777, $698 \mathrm{~cm}^{-1}$; HRMS (FAB): m/z calcd for $\mathrm{C}_{34} \mathrm{H}_{47} \mathrm{~N}_{2} \mathrm{O}_{9} \mathrm{Si}$ : $655.3051[\mathrm{M}+\mathrm{H}]^{+}$; found: 655.3054.
Compound 13: To a solution of $12(44.7 \mathrm{mg}, 68.3 \mu \mathrm{~mol})$ in $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ $(1.5 \mathrm{~mL} / 1.5 \mathrm{~mL})$ was added ( $\pm$ )-10-camphorsulfonic Acid (CSA, 3.2 mg , $13.8 \mu \mathrm{~mol})$ at room temperature. The reaction mixture was stirred overnight at room temperature and then was added triethylamine (9.10 mL ). The mixture was evaporated and purified by silica gel column chromatography (hexane/ethyl acetate, $1 / 1$ to $1 / 4$ ) to afford $13(31.4 \mathrm{~g}$, $85 \%$ ) as colorless oil. $\mathrm{R}_{\mathrm{f}}=0.30$ (hexane/ethyl acetate $=3 / 7$ ); ${ }^{1} \mathrm{H}$ NMR (400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 7.38-7.29(\mathrm{~m}, 10 \mathrm{H}), 6.71(\mathrm{brs}, 2 \mathrm{H}), 6.56(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 2 \mathrm{H})$, $5.14(\mathrm{~s}, 4 \mathrm{H}), 3.74(\mathrm{~s}, 6 \mathrm{H}), 3.50-3.48(\mathrm{~m}, 2 \mathrm{H}), 3.05(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 2.42-2.34(\mathrm{~m}$, $2 \mathrm{H}), 2.22-2.15(\mathrm{~m}, 2 \mathrm{H}), 1.94-1.85 \mathrm{ppm}(\mathrm{m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz , $\mathrm{CDCl}_{3}$ ): $\delta 164.9$ (2C), 154.4 (2C), 135.9 (2C), 134.7 (2C), 128.5 (4C), 128.3 (2C), 128.2 (4C), 127.0 (2C), 67.5 (2C), 63.3, 52.4 (2C), 39.8, 30.1 ppm (2C); IR (neat on KBr plate): ũ 3307, 3032, 2952, 1717, 1655, 1508, 1238, 1054, 753, $698 \mathrm{~cm}^{-1}$; HRMS (FAB): m/z calcd for $\mathrm{C}_{28} \mathrm{H}_{33} \mathrm{~N}_{2} \mathrm{O}_{9}$ : $541.2186[\mathrm{M}+\mathrm{H}]^{+}$; found: 541.2191.
Compound 17: A solution of $16(722 \mathrm{mg}, 6.43 \mathrm{mmol})$ in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20$ mL ) was cooled to $0^{\circ} \mathrm{C}$ under a nitrogen atmosphere. To this solution were added $\operatorname{TBSCI}(1.13 \mathrm{~g}, 7.51 \mathrm{mmol})$ and imidazole ( $861 \mathrm{mg}, 12.6 \mathrm{mmol}$ ). The reaction mixture was warmed to room temperature and stirred overnight. Water ( 10 mL ) was then added, and the two layers were separated. The aqueous layer was further extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2} 3$ times, and the organic layers were washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $9 / 1$ ) to afford $17(1.21 \mathrm{~g}, 83 \%)$ as colorless oil. $\mathrm{R}_{\mathrm{f}}=0.21$ (hexane/ethyl acetate $=$ $1 / 0$ ); ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.69-5.64(\mathrm{~m}, 2 \mathrm{H}), 3.63(\mathrm{t}, J=6.7 \mathrm{~Hz}$, $2 \mathrm{H}), 2.52-2.44(\mathrm{~m}, 2 \mathrm{H}), 2.37-2.28(\mathrm{~m}, 1 \mathrm{H}), 2.02-1.95(\mathrm{~m}, 2 \mathrm{H}), 1.64(\mathrm{dd}, \mathrm{J}$ $=13.9,6.9 \mathrm{~Hz}, 2 \mathrm{H}), 0.90(\mathrm{~s}, 9 \mathrm{H}), 0.05 \mathrm{ppm}(\mathrm{s}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 126 MHz , $\mathrm{CDCl}_{3}$ ): $\delta 129.9$ (2C), 62.3, 39.6, 38.9 (2C), 34.2, 26.0 (3C), 18.3, -5.3 ppm (2C); IR (neat on KBr plate): ũ 3055, 2928, 2857, 1472, 1255, 1102, $835,775 \mathrm{~cm}^{-1}$; HRMS (APCI): m/z calcd for $\mathrm{C}_{13} \mathrm{H}_{27} \mathrm{OSi}$ : $227.1826[\mathrm{M}+\mathrm{H}]^{+}$; found: 227.1824.
Compound 18: A solution of 17 ( $688 \mathrm{mg}, 3.04 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(30 \mathrm{~mL})$ was cooled to $-78{ }^{\circ} \mathrm{C}$. The solution was bubbled with $\mathrm{O}_{3}$ until the color of it turned blue ( 6 minutes). Excess $\mathrm{O}_{3}$ was removed from the reaction mixture by purging with $\mathrm{O}_{2}$ for 3 minutes. To the mixture was added $\mathrm{Ph}_{3} \mathrm{P}$ $(4.08 \mathrm{~g}, 15.6 \mathrm{mmol})$ at $-78^{\circ} \mathrm{C}$, and the reaction mixture was stirred at $-78{ }^{\circ} \mathrm{C}$ for 10 minutes and warmed to room temperature with stirring for an additional 20 minutes. Then the reaction mixture was washed with water, and the aqueous layer was extracted with ethyl acetate twice. The organic layers were washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $3 / 7$ ) to afford the dialdehyde as colorless oil. To a solution of $(Z)-\alpha-$ phosphonoglycine trimethyl ester ( $2.18 \mathrm{~g}, 6.59 \mathrm{mmol}$ ) in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20$ $\mathrm{mL})$ was added DBN $(0.800 \mathrm{~g}, 6.44 \mathrm{mmol})$ under a nitrogen atmosphere. The mixture was stirred at $0{ }^{\circ} \mathrm{C}$ and allowed to gradually warm to room temperature with stirring for 2.5 h . The dialdehyde in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(4 \mathrm{~mL})$ was added slowly by cannula at $0^{\circ} \mathrm{C}$. The reaction mixture was gradually warmed to room temperature while stirring overnight. The reaction mixture was washed with 1 M aqueous HCl solution. The aqueous layer was further extracted with ethyl acetate twice. The organic layers were washed
with water, saturated aqueous $\mathrm{NaHCO}_{3}$ solution, and brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 1$ ) to afford $18(1.25 \mathrm{~g}, 61 \%$ for 2 steps) as colorless oil. $R_{f}=0.26$ (hexane/ethyl acetate $=7 / 3$ ); ${ }^{1} \mathrm{H} \mathrm{NMR}(500 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right): ~ \delta 7.38-7.30(\mathrm{~m}, 10 \mathrm{H}), 6.63(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 6.32(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 5.14$ ( $\mathrm{s}, 4 \mathrm{H}$ ), $3.74(\mathrm{~s}, 6 \mathrm{H}), 3.64(\mathrm{t}, J=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 2.29-2.18(\mathrm{~m}, 4 \mathrm{H}), 2.01-1.94$ $(\mathrm{m}, 1 \mathrm{H}), 1.55-1.51(\mathrm{~m}, 2 \mathrm{H}), 0.89(\mathrm{~s}, 9 \mathrm{H}), 0.04 \mathrm{ppm}(\mathrm{s}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (126 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right): ~ \delta 164.8$ (2C), 154.1 (2C), 136.0 (2C), 135.9 (2C), 128.5 (4C), 128.2 (2C), 128.1 (4C), 126.5 (2C), 67.4 (2C), 60.7, 52.3 (2C), 37.0, 34.2, 32.8 (2C), 25.9 (3C), 18.3, $-5.4 \mathrm{ppm}(2 \mathrm{C})$; IR (neat on KBr plate): ũ 3321, 3033, 2952, 2856, 1726, 1658, 1502, 1256, 1051, 837, 776, $698 \mathrm{~cm}^{-1}$; HRMS (FAB): m/z calcd for $\mathrm{C}_{35} \mathrm{H}_{49} \mathrm{~N}_{2} \mathrm{O}_{9} \mathrm{Si}: 669.3207[\mathrm{M}+\mathrm{H}]^{+}$; found: 669.3217.

Compound 4: To a solution of $18(51.8 \mathrm{mg}, 77.4 \mu \mathrm{~mol})$ in $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ $(0.5 \mathrm{~mL} / 0.5 \mathrm{~mL})$ was added CSA $(2.0 \mathrm{mg}, 8.6 \mu \mathrm{~mol})$ at room temperature. The reaction mixture was stirred at room temperature for 70 minutes and then was added triethylamine ( 1.50 mL ). The mixture was evaporated and purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $3 / 7$ ) to afford $4(29.7 \mathrm{~g}, 70 \%)$ as colorless oil. $\mathrm{R}_{\mathrm{f}}=0.25$ (hexane/ethyl acetate $=3 / 7$ ); ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ : $\delta 7.38-7.28(\mathrm{~m}, 10 \mathrm{H}), 6.61(\mathrm{t}$, $J=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 6.54(\mathrm{~s}, 2 \mathrm{H}), 5.13(\mathrm{~s}, 4 \mathrm{H}), 3.73(\mathrm{~s}, 6 \mathrm{H}), 3.64-3.61(\mathrm{~m}, 2 \mathrm{H})$, 2.32-2.16 (m, 4H), 2.05 (br s, 1H), 2.00-1,94 (m, 1H), 1.55-1.51 ppm (m, 2H); ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 164.9$ (2C), 154.3 (2C), 135.9 (2C), 135.4 (2C), 128.5 (4C), 128.2 (2C), 128.1 (4C), 126.6 (2C), 67.4 (2C), 60.2, 52.4 (2C), 36.3, 34.3, 32.6 ppm (2C); IR (neat on KBr plate): ũ 3310, 3033, 2952, 1714, 1658, 1505, 1240, 1053, 754, $699 \mathrm{~cm}^{-1}$; HRMS (ESI): m/z calcd for $\mathrm{C}_{29} \mathrm{H}_{33} \mathrm{~N}_{2} \mathrm{O}_{9}$ : $553.2192[\mathrm{M}-\mathrm{H}]^{-}$; found: 553.2191.
Compound 15: To a solution of $4(63.8 \mathrm{mg}, 115 \mu \mathrm{~mol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$ were added $\mathrm{Phl}(\mathrm{OAc})_{2}(52.9 \mathrm{mg}, 184 \mu \mathrm{~mol})$ and AZADOL $(2.6 \mathrm{mg}, 17$ $\mu \mathrm{mol})$. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water, extracted with ethyl acetate ( 3 times), and washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 1$ ) to afford $15(38.7 \mathrm{mg}$, $61 \%$ ) as colorless oil. $\mathrm{R}_{\mathrm{f}}=0.30$ (hexane/ethyl acetate $=2 / 3$ ); ${ }^{1} \mathrm{H}$ NMR (400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 9.69(\mathrm{~s}, 1 \mathrm{H}), 7.37-7.28(\mathrm{~m}, 10 \mathrm{H}), 6.56(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 2 \mathrm{H})$, 6.43 (br s, 2H), $5.13(\mathrm{~s}, 4 \mathrm{H}), 3.74(\mathrm{~s}, 6 \mathrm{H}), 2.45-2.34(\mathrm{~m}, 3 \mathrm{H}), 2.27-2.24$ ppm (m, 4H); ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 201.4,164.6$ (2C), 154.1 (2C), 135.8 (2C), 134.1 (2C), 128.5 (4C), 128.3 (2C), 128.1 (4C), 127.0 (2C), 67.4 (2C), $52.5(2 \mathrm{C}), 47.9,32.7$ (2C), 32.1 ppm ; IR (neat on KBr plate): $\tilde{\mathrm{u}}$ 3312, 3033, 2952, 2732, 1721, 1659, 1500, 1233, 1049, 754, $699 \mathrm{~cm}^{-1}$; HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{29} \mathrm{H}_{32} \mathrm{~N}_{2} \mathrm{O}_{9} \mathrm{Na}: 575.2000[\mathrm{M}+\mathrm{Na}]^{+}$; found: 575.1990.

Compound 3: To a solution of ( $Z$ )- $\alpha$-phosphonoglycine trimethyl ester ( $25.5 \mathrm{mg}, 77.0 \mu \mathrm{~mol}$ ) in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(1 \mathrm{~mL})$ was added DBN ( $10.6 \mathrm{mg}, 85.4$ $\mu \mathrm{mol})$ under an argon atmosphere. The mixture was stirred at $0^{\circ} \mathrm{C}$ for 15 minutes. A solution of $15(33.8 \mathrm{mg}, 61.2 \mu \mathrm{~mol})$ in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(4 \mathrm{~mL})$ was then added slowly by cannula at $0^{\circ} \mathrm{C}$. The reaction mixture was gradually warmed to room temperature with stirring overnight. The reaction mixture was washed with 1 M aqueous HCl solution. The aqueous layer was further extracted with ethyl acetate twice. The organic layers were washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 1$ ) to afford $3(33.7 \mathrm{mg}$, $73 \%$ ) as colorless oil. $\mathrm{R}_{\mathrm{f}}=0.34$ (hexane/ethyl acetate $=2 / 3$ ); ${ }^{1} \mathrm{H}$ NMR ( 400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ : $\delta 7.36-7.27(\mathrm{~m}, 15 \mathrm{H}), 6.58(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 3 \mathrm{H}), 6.40(\mathrm{brs}, 3 \mathrm{H})$, $5.12(\mathrm{~s}, 6 \mathrm{H}), 3.71(\mathrm{~s}, 9 \mathrm{H}), 2.24-2.21(\mathrm{~m}, 6 \mathrm{H}), 2.05-2.00 \mathrm{ppm}(\mathrm{m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 164.7$ (3C), 154.2 (3C), 135.9 (3C), 135.2 (3C), 128.6 (6C), 128.3 (3C), 128.2 (6C), 126.6 (3C), 67.5 (3C), 52.4 (3C), 37.4, $33.1 \mathrm{ppm}(3 \mathrm{C})$; IR (neat on KBr plate): ũ 3311, 3032, 2952, 1724, 1659, 1504, 1235, 1053, $755,699 \mathrm{~cm}^{-1}$; HRMS (APCI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{40} \mathrm{H}_{44} \mathrm{~N}_{3} \mathrm{O}_{12}$ : $758.2920[\mathrm{M}+\mathrm{H}]^{+}$; found: 758.2925 .
Compound 9: Compound 18 (933 mg, 1.40 mmol$)$ and $[\mathrm{Rh}((S, S)-$ QuinoxP*)(cod)]SbF6 ( $21.6 \mathrm{mg}, 27.6 \mu \mathrm{~mol}$ ) were charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, degassed $\mathrm{MeOH}(3 \mathrm{~mL})$ was added. The hydrogen pressure was adjusted to 4 atm , and the mixture was stirred
vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 4$ ) to afford $9(665 \mathrm{mg}$, $85 \%$ ) as orange oil. Ee and de were determined by HPLC (Daicel CHIRAL CEL OX-RH, $\lambda=254 \mathrm{~nm}, \mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=9 / 11,0.5 \mathrm{~mL} /$ minutes, $>99 \%$ ee, $>98 \% \mathrm{de}$ ). $\mathrm{R}_{\mathrm{f}}=0.12$ (hexane/ethyl acetate $=3 / 7$ ); $[\alpha]_{\mathrm{D}}{ }^{27}=+13.4$ ( $c=1.64$ in $\mathrm{CHCl}_{3}$ ); ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.37-7.29(\mathrm{~m}, 10 \mathrm{H}), 5.41(\mathrm{~d}, \mathrm{~J}=$ $8.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.37(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.10(\mathrm{~s}, 4 \mathrm{H}), 4.37-4.33(\mathrm{~m}, 2 \mathrm{H}), 3.74$ $(\mathrm{s}, 3 \mathrm{H}), 3.73(\mathrm{~s}, 3 \mathrm{H}), 3.60-3.58(\mathrm{~m}, 2 \mathrm{H}), 1.86-1.20 \mathrm{ppm}(\mathrm{m}, 11 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 172.8$ (2C), 156.0, 155.9, 136.29, 136.26, 128.5 (4C), 128.2 (2C), 128.1 (4C), 67.1, 67.0, 60.4, 54.0, 53.7, 52.3 (2C), 36.2, 33.0, 29.8, 29.4, 28.7, 28.6 ppm ; $\mathbb{R}$ (neat on KBr plate): ũ 3335, 3033, 2952, 1714, 1531, 1455, 1215, 1051, 742, $698 \mathrm{~cm}^{-1}$; HRMS (FAB): m/z calcd for $\mathrm{C}_{29} \mathrm{H}_{39} \mathrm{~N}_{2} \mathrm{O}_{9}$ : $559.2656[\mathrm{M}+\mathrm{H}]^{+}$; found: 559.2662 .
Compound 19: To a solution of $9(515 \mathrm{mg}, 922 \mu \mathrm{~mol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$ were added $\mathrm{Phl}(\mathrm{OAc})_{2}(444 \mathrm{mg}, 1.38 \mathrm{mmol})$ and AZADOL ( $14.2 \mathrm{mg}, 92.7$ $\mu \mathrm{mol})$. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 1$ ) to afford $19(342 \mathrm{mg}$, $67 \%$ ) as pale yellow oil. $R_{f}=0.23$ (hexane/ethyl acetate $=1 / 1$ ); $[\alpha]_{D^{27}}=$ $+17.5\left(\mathrm{c}=1.20\right.$ in $\left.\mathrm{CHCl}_{3}\right)$; ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.71(\mathrm{~s}, 1 \mathrm{H}), 7.37-$ $7.29(\mathrm{~m}, 10 \mathrm{H}), 5.37(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.33(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.10(\mathrm{~s}$, $4 \mathrm{H}), 4.37-4.33(\mathrm{~m}, 2 \mathrm{H}), 3.74(\mathrm{~s}, 6 \mathrm{H}), 2.34(\mathrm{~d}, \mathrm{~J}=5.4 \mathrm{~Hz}, 2 \mathrm{H}), 2.03-1.96$ (m, 1H), 1.85-1.77 (m, 2H), 1.67-1.57 (m, 2H), 1.44-1.24 ppm (m, 4H); ${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): ठ $201.5,172.5$ (2C), 155.8 (2C), 136.2 (2C), 128.5 (4C), 128.2 (2C), 128.1 (4C), 67.1 (2C), 53.8 (2C), 52.4 (2C), 48.0, 31.8, 29.8, 29.6, 29.2, 29.1 ppm ; IR (neat on KBr plate): ũ 3342, 3033, 2953, 1729, 1714, 1531, 1455, 1215, 1047, 753, $699 \mathrm{~cm}^{-1}$; HRMS (FAB): m/z calcd for $\mathrm{C}_{29} \mathrm{H}_{3} \mathrm{~N}_{2} \mathrm{O}_{9}$ : $557.2499[\mathrm{M}+\mathrm{H}]^{+}$; found: 557.2506.
Compound 8: To a solution of $(Z)$-a-phosphonoglycine trimethyl ester $(86.6 \mathrm{mg}, 261 \mu \mathrm{~mol})$ in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \mathrm{~mL})$ was added DBN $(36.0 \mathrm{mg}, 290$ $\mu \mathrm{mol})$ under a nitrogen atmosphere. The mixture was stirred at $0^{\circ} \mathrm{C}$ for 15 minutes. A solution of $19(126.7 \mathrm{mg}, 228 \mu \mathrm{~mol})$ in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \mathrm{~mL})$ was then added slowly by cannula at $0^{\circ} \mathrm{C}$. The reaction mixture was gradually warmed to room temperature with stirring for 5.5 h . The reaction mixture was washed with 1 M aqueous HCl solution. The aqueous layer was further extracted with ethyl acetate twice. The organic layers were washed with water, saturated aqueous $\mathrm{NaHCO}_{3}$ solution, and brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $2 / 3$ ) to afford $8(166 \mathrm{mg}, 96 \%)$ as colorless oil. $R_{f}=0.36$ (hexane/ethyl acetate $=1 / 1$ ); $[\alpha]_{D^{27}}=+15.5(c=1.24$ in $\left.\mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 7.36-7.28(\mathrm{~m}, 15 \mathrm{H}), 6.60(\mathrm{t}, \mathrm{J}=6.7$ $\mathrm{Hz}, 1 \mathrm{H}), 6.36(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.46-5.42(\mathrm{~m}, 2 \mathrm{H}), 5.13-5.05(\mathrm{~m}, 6 \mathrm{H}), 4.33-4.29$ $(\mathrm{m}, 2 \mathrm{H}), 3.72(\mathrm{~s}, 9 \mathrm{H}), 2.18-2.15(\mathrm{~m}, 2 \mathrm{H}), 1.83-1.74(\mathrm{~m}, 2 \mathrm{H}), 1.67-1.52(\mathrm{~m}$, 3H), 1.38-1.21 ppm ( $\mathrm{m}, 4 \mathrm{H}$ ); ${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 172.6$ (2C), 164.7, 155.9 (2C), 154.2, 136.23 (2C), 136.18, 136.0, 128.48 (2C), 128.47 (4C), 128.2 (2C), 128.1 (4C), 128.05 (2C), 127.96, 126.6, 67.4, 67.0 (2C), 53.9 (2C), 52.3 (3C), 36.4, 31.8, 29.51, 29.48, 29.0, 28.8 ppm ; IR (neat on KBr plate): ũ 3334, 3033, 2952, 1714, 1519, 1455, 1218, 1052, 753, 699 $\mathrm{cm}^{-1}$; HRMS (FAB): m/z calcd for $\mathrm{C}_{40} \mathrm{H}_{48} \mathrm{~N}_{3} \mathrm{O}_{12}: 762.3238[\mathrm{M}+\mathrm{H}]^{+}$; found: 762.3229 .

Compound 20: Method A: A solution of $\left[R h(c o d)_{2}\right] \mathrm{BF}_{4}(2.4 \mathrm{mg}, 5.9 \mu \mathrm{~mol})$ and $(S, S)$-QuinoxP* $(2.6 \mathrm{mg}, 7.8 \mu \mathrm{~mol})$ in degassed $\mathrm{MeOH}(0.5 \mathrm{~mL})$ was stirred vigorously at room temperature under nitrogen atmosphere. After 45 minutes, additional degassed $\mathrm{MeOH}(0.5 \mathrm{~mL})$ was added to the mixture. Compound 3 ( $25.8 \mathrm{mg}, 34.0 \mu \mathrm{~mol}$ ) was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm, and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 1$ ) to afford 20 ( $21.9 \mathrm{mg}, 84 \%$ ) as pale yellow oil. Ee and de were determined by HPLC (Daicel CHIRAL CEL OX-RH, $\lambda=254 \mathrm{~nm}, \mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=3 / 2,0.5$ $\mathrm{mL} /$ minutes, $>99 \%$ ee, $>97 \%$ de). Method B: Compound 8 ( $193 \mathrm{mg}, 254$ $\mu \mathrm{mol})$ and $\left[\operatorname{Rh}((S, S)\right.$-QuinoxP*) $(\operatorname{cod})] \mathrm{SbF}_{6}(2.0 \mathrm{mg}, 2.6 \mu \mathrm{~mol})$ were charged in a hydrogenation bottle. After the bottle was evacuated and filled
with hydrogen several times, degassed $\mathrm{MeOH}(1 \mathrm{~mL})$ was added. The hydrogen pressure was adjusted to 4 atm , and the mixture was stirred vigorously overnight at room temperature. The suspended reaction mixture was dissolved in $\mathrm{CHCl}_{3}$ and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 1$ ) to afford 20 ( $177 \mathrm{mg}, 91 \%$ ) as colorless oil. De was determined by HPLC (Daicel CHIRAL CEL OJ-RH, $\lambda=254 \mathrm{~nm}, \mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=1 / 1,0.5$ $\mathrm{mL} /$ minutes, $>98 \%$ de). $\mathrm{R}_{\mathrm{f}}=0.24$ (hexane/ethyl acetate $=1 / 1$ ); $[\alpha]{ }_{\mathrm{D}}{ }^{27}=$ +22.3 ( $\mathrm{c}=1.35 \mathrm{in} \mathrm{CHCl}_{3}$ ); ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.37-7.28$ ( m , $15 \mathrm{H}), 5.39(\mathrm{~d}, \mathrm{~J}=6.9 \mathrm{~Hz}, 3 \mathrm{H}), 5.13-5.06(\mathrm{~m}, 6 \mathrm{H}), 4.34-4.29(\mathrm{~m}, 3 \mathrm{H}), 3.73$ (s, 9H), 1.79-1.68 (m, 3H), 1.64-1.53 (m, 3H), 1.37-1.17 ppm (m, 7H); ${ }^{13} \mathrm{C}$ NMR (101 MHz, CDCl3): ס 172.8 (3C), 155.9 (3C), 136.2 (3C), 128.5 (6C), 128.22 (3C), 128.16 (6C), 67.1 (3C), 53.9 (3C), 52.4 (3C), 36.1, 29.5 (3C), $28.4 \mathrm{ppm}(3 \mathrm{C})$; IR (neat on KBr plate): ũ 3340, 3033, 2952, 1714, 1531, 1455, 1215, 1050, 753, $698 \mathrm{~cm}^{-1}$; HRMS (FAB): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{40} \mathrm{H}_{50} \mathrm{~N}_{3} \mathrm{O}_{12}$ $764.3394[\mathrm{M}+\mathrm{H}]^{+}$; found: 764.3401 .
Compound 1: To a solution of $20(147 \mathrm{mg}, 193 \mu \mathrm{~mol})$ in $\mathrm{MeOH}(8 \mathrm{~mL})$ was added 2 M aqueous NaOH solution ( 1.49 mL ). The reaction mixture was stirred at room temperature for 75 minutes. The volatile in the reaction mixture was removed under reduced pressure. The residual water layer was adjusted to pH 2 using 1 M aqueous HCl solution and extracted with ethyl acetate 3 times. The organic layers were washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. Filtration and concentration afforded a crude tricarboxylic acid. To a solution of the tricarboxylic acid in deoxygenated $\mathrm{MeOH}(5 \mathrm{~mL})$ was added $\mathrm{Pd} / \mathrm{C}(10 \mathrm{wt} \%$, 35.6 mg ), and the reaction mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction mixture was filtered through celite and washed with $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(1 / 1$ to $0 / 1)$ to afford triamino acid 21 as a white solid: ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{D}_{2} \mathrm{O}$ ): $\delta 3.75(\mathrm{t}, \mathrm{J}=5.9 \mathrm{~Hz}$, 3H), 1.93-1.79 (m, 6H), 1.56-1.30 ppm (m, 7H); ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{D}_{2} \mathrm{O}$ ): б 174.7 (3C), 54.9 (3C), 35.9, 27.32 (3C), 27.28 ppm (3C).
To a suspension of the $\mathbf{2 1}$ in $\mathrm{H}_{2} \mathrm{O} /$ acetone ( $3 \mathrm{~mL} / 3 \mathrm{~mL}$ ) were added Fmoc$\mathrm{OSu}(214 \mathrm{mg}, 636 \mu \mathrm{~mol})$ and $\mathrm{Na}_{2} \mathrm{CO}_{3}(137 \mathrm{mg}, 1.29 \mathrm{mmol})$. The reaction mixture was stirred at room temperature for 4 days. The reaction mixture was adjusted to pH 2 using 1 M aqueous HCl solution and extracted with ethyl acetate 9 times. The organic layers were washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 4,1 \%$ acetic acid), ODS flash column chromatography $\left(\mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=3 / 7\right.$ to $7 / 3,0.1 \%$ TFA $)$, and HPLC (YMC Pack ODS-A No. $2015000608, \lambda=254 \mathrm{~nm}, \mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=7 / 3$, $0.1 \%$ TFA, $8.0 \mathrm{~mL} /$ minutes, retention time 19.0 minutes) to afford 1 (103 $\mathrm{mg}, 54 \%$ ) as a white solid. $\mathrm{R}_{\mathrm{f}}=0.04$ (hexane/ethyl acetate $=0 / 1,1 \%$ $\mathrm{AcOH}) ;[\alpha]_{\mathrm{D}}{ }^{27}=+26.6\left(\mathrm{c}=1.31\right.$ in $\left.\mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}, 313\right.$ $\mathrm{K}): ~ \delta 7.63(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 6 \mathrm{H}), 7.58-7.34(\mathrm{~m}, 6 \mathrm{H}), 7.27(\mathrm{t}, J=7.5 \mathrm{~Hz}, 6 \mathrm{H})$, $7.18(\mathrm{t}, J=7.3 \mathrm{~Hz}, 6 \mathrm{H}), 6.79(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.81(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 4.83-3.87(\mathrm{~m}, 12$ H), 2.00-1.44 (m, 6H), 1.44-0.97 ppm (m, 7H); ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$, 313 K): $\delta 176.4$ (3C), 156.5 (3C), 143.6 (6C), 141.3 (6C), 127.7 (6C), 127.1 (6C), 125.0 (6C), 112.0 (6C), 67.4 (3C), 53.8 (3C), 47.0 (3C), 35.8, 29.1 (3C), 28.2 ppm (3C) (The signals derived from a minor conformation were also observed); IR (neat on KBr plate): ũ 3321, 3066, 2952, 2869, 2603, 1715, 1520, 1450, 1219, 1050, $741 \mathrm{~cm}^{-1}$; HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{58} \mathrm{H}_{55} \mathrm{~N}_{3} \mathrm{O}_{12} \mathrm{Na}: 1008.3678$ [M+Na] ${ }^{+}$; found: 1008.3677.
Compound 26: To a suspension of $\mathrm{NaH}(60 \%)(1.30 \mathrm{~g}, 32.4 \mathrm{mmol})$ in dry $\mathrm{Et}_{2} \mathrm{O} / \mathrm{dry}$ DMSO ( $100 \mathrm{~mL} / 5 \mathrm{~mL}$ ) was added $25(1.53 \mathrm{~g}, 10.8 \mathrm{mmol})$ dropwise under a nitrogen atmosphere at room temperature. The mixture was stirred for 30 minutes. 6-Bromo-1-hexene ( $5.14 \mathrm{~g}, 31.5 \mathrm{mmol}$ ) was added and the reaction mixture was stirred at room temperature for 1 h . 10 mL of $\mathrm{H}_{2} \mathrm{O}$ was added dropwise to the reaction mixture at room temperature. The two layers were separated, and the aqueous layer was extracted with $\mathrm{Et}_{2} \mathrm{O} 3$ times. The organic layers were washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to 19/1) to afford $26(2.78 \mathrm{~g}$, $84 \%$ ) as colorless oil. $\mathrm{R}_{\mathrm{f}}=0.44$ (hexane/ethyl acetate $=9 / 1$ ); ${ }^{1} \mathrm{H}$ NMR (400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 5.83-5.73(\mathrm{~m}, 2 \mathrm{H}), 5.04-4.94(\mathrm{~m}, 4 \mathrm{H}), 2.10-2.04(\mathrm{~m}, 4 \mathrm{H})$, 1.91-1.83 (m, 2H), 1.76-1.68 (m, 2H), 1.65-1.54 (m, 2H), $1.49(\mathrm{~s}, 9 \mathrm{H}), 1.46$ 1.37 (m, 4H), 1.34-1.23 ppm (m, 2H); ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 167.8$ 158.2, 138.2 (2C), 114.8 (2C), 83.4, 68.9, 39.1 (2C), 33.3 (2C), 28.4 (2C),
27.8 (3C), 23.4 ppm (2C); IR (neat on KBr plate): ũ 3077, 2933, 2863, 2137, 1748, 1641, 1370, 1254, 1153, 911, $844 \mathrm{~cm}^{-1}$; HRMS (APCI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{19} \mathrm{H}_{32} \mathrm{NO}_{2}: 306.2428[\mathrm{M}+\mathrm{H}]^{+}$; found: 306.2427.
Compound 24: Isocyanide 26 ( $2.77 \mathrm{~g}, 9.08 \mathrm{mmol}$ ) was dissolved in EtOH $(10 \mathrm{~mL})$ containing 12 M aqueous HCl solution $(398 \mu \mathrm{~L})$ and the resulting mixture was stirred overnight at room temperature. Additional 12 M aqueous HCl solution ( $390 \mu \mathrm{~L}$ ) was added and the mixture was stirred for 40 minutes. The solvent was removed under reduced pressure and the remaining oil was taken up in toluene ( 100 mL ). The mixture was cooled to $0^{\circ} \mathrm{C}$, and $\mathrm{CbzCl}(1.80 \mathrm{~g}, 10.6 \mathrm{mmol})$ and 1 M aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}$ solution $(18.5 \mathrm{~mL})$ were added. The reaction mixture was stirred at room temperature for 2 h and at $80^{\circ} \mathrm{C}$ for 1.5 h . Additional $\mathrm{CbzCl}(1.52 \mathrm{~g}, 8.93$ mmol ) and 1 M aqueous $\mathrm{Na}_{2} \mathrm{CO}_{3}$ solution ( 18.2 mL ) were added and the mixture was stirred at $80^{\circ} \mathrm{C}$ for 35 minutes. The two layers were separated, and the aqueous layer was extracted with ethyl acetate twice. The organic layers were washed with 0.1 M aqueous HCl solution and saturated aqueous $\mathrm{NaHCO}_{3}$ solution. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ $\mathrm{Et}_{2} \mathrm{O}=1 / 0$ to 49/1) to afford 24 (2.84 $\mathrm{g}, 73 \%$ for 2 steps) as colorless oil. $\mathrm{R}_{\mathrm{f}}=0.30$ (hexane/Et $\mathrm{t}_{2} \mathrm{O}=9 / 1$ ); ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.40-7.28(\mathrm{~m}, 5 \mathrm{H}), 5.88(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.80-5.70(\mathrm{~m}, 2 \mathrm{H})$, $5.06(\mathrm{~s}, 2 \mathrm{H}), 5.00-4.90(\mathrm{~m}, 4 \mathrm{H}), 2.34-2.27(\mathrm{~m}, 2 \mathrm{H}), 2.02-1.97(\mathrm{~m}, 4 \mathrm{H}), 1.71-$ $1.63(\mathrm{~m}, 2 \mathrm{H}), 1.45(\mathrm{~s}, 9 \mathrm{H}), 1.41-1.22(\mathrm{~m}, 6 \mathrm{H}), 1.06-0.94 \mathrm{ppm}(\mathrm{m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, CDCl3): $\delta 172.9,153.9,138.7$ (2C), 136.9, 128.4 (2C), 127.9, 127.8 (2C), 114.4 (2C), 82.2, 66.0, 64.1, 35.5 (2C), 33.5 (2C), 28.7 (2C), 27.9 (3C), $23.4 \mathrm{ppm}(2 \mathrm{C})$; IR (neat on KBr plate): ũ 3418, 3075, 2928, 2859, 1717, 1640, 1496, 1253, 1158, 1067, 911, $697 \mathrm{~cm}^{-1}$; HRMS (FAB): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{26} \mathrm{H}_{40} \mathrm{NO}_{4}: 430.2957$ [M+H] ${ }^{+}$; found: 430.2963 .
Compound 23: A solution of $24(685 \mathrm{mg}, 1.60 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(15 \mathrm{~mL})$ was cooled to $-78^{\circ} \mathrm{C}$. The solution was bubbled with $\mathrm{O}_{3}$ until the color of it turned blue ( 10 minutes). Excess $\mathrm{O}_{3}$ was removed from the reaction mixture by purging with $\mathrm{O}_{2}$ for 2 minutes. To the mixture was added $\mathrm{Ph}_{3} \mathrm{P}$ $(1.64 \mathrm{~g}, 6.26 \mathrm{mmol})$ at $-78{ }^{\circ} \mathrm{C}$, and the reaction mixture was stirred at $-78{ }^{\circ} \mathrm{C}$ for 10 minutes and warmed to room temperature with stirring for an additional 30 minutes. Then the reaction mixture was washed with water, and the aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2} 3$ times. The organic layers were washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=4 / 1$ to $3 / 2$ ) to afford $23(672 \mathrm{mg}, 97 \%)$ as colorless oil. $\mathrm{R}_{\mathrm{f}}=0.38$ (hexane/ethyl acetate $=3 / 2$ ); ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ : $\delta 9.71(\mathrm{t}, \mathrm{J}=1.6 \mathrm{~Hz}, 2 \mathrm{H}), 7.38-$ $7.28(\mathrm{~m}, 5 \mathrm{H}), 5.88(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 5.06(\mathrm{~s}, 2 \mathrm{H}), 2.43-2.29(\mathrm{~m}, 6 \mathrm{H}), 1.72-1.65(\mathrm{~m}$, $2 \mathrm{H}), 1.62-1.54(\mathrm{~m}, 4 \mathrm{H}), 1.46(\mathrm{~s}, 9 \mathrm{H}), 1.33-1.21(\mathrm{~m}, 2 \mathrm{H}), 1.09-1.98 \mathrm{ppm}(\mathrm{m}$, $2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, CDCl 3 ): ס 202.2 (2C), 172.5, 153.9, 136.8, 128.5 (2C), 128.0, 127.9 (2C), 82.7, 66.1, 63.8, 43.6 (2C), 35.3 (2C), 27.9 (3C), 23.5 (2C), $21.8 \mathrm{ppm}(2 \mathrm{C})$; IR (neat on KBr plate): ũ 3416, 3033, 2938, 2865, 2721, 1718, 1497, 1252, 1157, 1070, 847, 742, $698 \mathrm{~cm}^{-1}$.
Compound 22: To a solution of $(Z)$ - $\alpha$-phosphonoglycine trimethyl ester ( $712 \mathrm{mg}, 2.15 \mathrm{mmol}$ ) in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(4 \mathrm{~mL})$ was added DBN ( $280 \mathrm{mg}, 2.25$ mmol ) under an argon atmosphere. The mixture was stirred at $0^{\circ} \mathrm{C}$ for 20 minutes. A solution of $23(443 \mathrm{mg}, 1.02 \mathrm{mmol})$ in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(6 \mathrm{~mL})$ was then added slowly by cannula at $0^{\circ} \mathrm{C}$. The reaction mixture was gradually warmed to room temperature with stirring overnight. The reaction mixture was washed with 1 M aqueous HCl solution. The aqueous layer was further extracted with ethyl acetate twice. The organic layers were washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $3 / 2$ ) to afford $22(552 \mathrm{mg}$, $64 \%$ ) as colorless oil. $\mathrm{R}_{\mathrm{f}}=0.35$ (hexane/ethyl acetate $=1 / 1$ ); ${ }^{1} \mathrm{H}$ NMR (400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 7.38-7.28(\mathrm{~m}, 15 \mathrm{H}), 6.57(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 6.31(\mathrm{brs}, 2 \mathrm{H})$, $5.88(\mathrm{~s}, 1 \mathrm{H}), 5.14(\mathrm{~s}, 4 \mathrm{H}), 5.04(\mathrm{~s}, 2 \mathrm{H}), 3.72(\mathrm{~s}, 6 \mathrm{H}), 2.34-2.27(\mathrm{~m}, 2 \mathrm{H})$, 2.23-2.12 ( $\mathrm{m}, 4 \mathrm{H}$ ), 1.68-1.60 (m, 2H), 1.44-1.39 (m, 13H), 1.31-1.20 (m, 2H), 1.06-0.95 ppm (m, 2H); ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 172.6,165.0$ (2C), 154.2 (2C), 154.0, 138.1 (2C), 136.7, 136.1 (2C), 128.5 (4C), 128.4 (2C), 128.2 (2C), 128.1 (4C), 128.0, 127.8 (2C), 125.5 (2C), 82.5, 67.3 (2C), 66.2, 64.0, 52.3 (2C), 35.2 (2C), 27.93 (2C), 27.88 (2C), 27.8 (3C), $23.5 \mathrm{ppm}(2 \mathrm{C})$; IR (neat on KBr plate): ũ 3410, 3326, 3033, 2951, 2861, 1714, 1659, 1504, 1227, 1063, 754, $698 \mathrm{~cm}^{-1}$; HRMS (FAB): m/z calcd for $\mathrm{C}_{46} \mathrm{H}_{57} \mathrm{~N}_{3} \mathrm{O}_{12} \mathrm{Na}$ : $866.3840[\mathrm{M}+\mathrm{Na}]^{+}$; found: 866.3838 .

Compound 27: A solution of $\left.[R h(c o d))_{2}\right] \mathrm{BF}_{4}(3.9 \mathrm{mg}, 9.6 \mu \mathrm{~mol})$ and $(S, S)$ QuinoxP* ( $4.1 \mathrm{mg}, 12.3 \mu \mathrm{~mol}$ ) in degassed $\mathrm{MeOH}(0.5 \mathrm{~mL})$ was stirred vigorously at room temperature under nitrogen atmosphere. After 50 minutes, additional degassed $\mathrm{MeOH}(1.5 \mathrm{~mL})$ was added to the mixture. Compound 22 ( $421 \mathrm{mg}, 499 \mu \mathrm{~mol}$ ) was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 1$ ) to afford 27 ( $412 \mathrm{mg}, 98 \%$ ) as colorless oil. Ee and de were determined by HPLC (Daicel CHIRAL CEL OX-RH, $\lambda=254 \mathrm{~nm}, \mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=7 / 3,0.5$ $\mathrm{mL} /$ minutes, $>99 \% e \mathrm{e},>96 \% \mathrm{de}$ ). $\mathrm{R}_{\mathrm{f}}=0.39$ (hexane/ethyl acetate $=1 / 1$ ); $[\alpha]{ }^{27}=+8.67\left(c=0.92\right.$ in $\left.\mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.36-7.27$ (m, 15H), 5.87 (s, 1H), $5.34(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.26(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H})$, $5.12(\mathrm{~s}, 2 \mathrm{H}), 5.10(\mathrm{~s}, 2 \mathrm{H}), 5.06(\mathrm{~s}, 2 \mathrm{H}), 4.37-4.30(\mathrm{~m}, 2 \mathrm{H}), 3.73(\mathrm{~s}, 3 \mathrm{H})$, $3.72(\mathrm{~s}, 3 \mathrm{H}), 2.30-2.23(\mathrm{~m}, 2 \mathrm{H}), 1.78-1.72(\mathrm{~m}, 2 \mathrm{H}), 1.67-1.54(\mathrm{~m}, 4 \mathrm{H}), 1.44$ (s, 9H), 1.32-1.19 (m, 10H), 1.00-1.91 ppm (m, 2H); ${ }^{13} \mathrm{C}$ NMR ( 101 MHz , $\mathrm{CDCl}_{3}$ ): $\delta 173.0,172.9,172.7,155.9,155.8,153.9,136.8,136.25,136.20$, 128.5 (4C), 128.4 (2C), 128.14, 128.11, 128.07 (2C), 128.0 (2C), 127.9, 127.8 (2C), 82.3, 66.9 (2C), 66.0, 64.0, 53.81, 53.77, 52.3 (2C), 35.5, 35.3, $32.5,32.3,29.0,28.8,27.9$ (3C), 25.0, 24.8, 23.7, 23.4 ppm . IR (neat on KBr plate): ũ 3412, 3353, 3033, 2950, 2861, 1716, 1499, 1214, 1066, 698 $\mathrm{cm}^{-1}$; HRMS (FAB): m/z calcd for $\mathrm{C}_{46} \mathrm{H}_{61} \mathrm{~N}_{3} \mathrm{O}_{12} \mathrm{Na}: 870.4153[\mathrm{M}+\mathrm{Na}]^{+} ;$ found: 870.4154.
Compound 2: To a solution of 27 ( $285 \mathrm{mg}, 336 \mu \mathrm{~mol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$ was added TFA $(5 \mathrm{~mL})$ at room temperature. The mixture was stirred for 1.5 h . The volatile in the reaction mixture was removed under reduced pressure. The residue was reconstituted in $\mathrm{Et}_{2} \mathrm{O}(30 \mathrm{~mL})$ and washed with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ solution 3 times. The organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. Residual solvent was removed by azeotropic drying with pentane to afford monocarboxylic acid as colorless oil. To a solution of the monocarboxylic acid in $\mathrm{MeOH}(7 \mathrm{~mL})$ was added 2 M aqueous NaOH solution ( 1.65 mL ). The reaction mixture was stirred at room temperature for 1 h . The volatile in the reaction mixture was removed under reduced pressure. The residual water layer was adjusted to pH 1 using 1 M aqueous HCl solution and extracted with ethyl acetate 3 times. The organic layers were washed with and brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. Filtration and concentration afforded a crude tricarboxylic acid as a white solid. 5 mL of MeOH was added to the tricarboxylic acid and $\mathrm{Pd} / \mathrm{C}(10 \mathrm{wt} \%, 62.0 \mathrm{mg})$. The reaction mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction mixture was filtered through celite and washed with $\mathrm{H}_{2} \mathrm{O}$ to afford triamino acid 28 as a white solid: ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{D}_{2} \mathrm{O}\right)$ : $\delta 3.79-3.76(\mathrm{~m}$, $2 \mathrm{H}), 1.91-1.73(\mathrm{~m}, 8 \mathrm{H}), 1.48-1.33(\mathrm{~m}, 10 \mathrm{H}), 1.29-1.19 \mathrm{ppm}(\mathrm{m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{D}_{2} \mathrm{O}$ ): $\delta 175.9,174.5$ (2C), 65.1, 54.5 (2C), 35.8, 35.9, 30.1, 30.0, 28.23, 28.18, 23.9, 23.7, 22.6, 22.5 ppm.

To a suspension of the 28 in $\mathrm{H}_{2} \mathrm{O} /$ acetone ( $3 \mathrm{~mL} / 3 \mathrm{~mL}$ ) were added Fmoc$\mathrm{OSu}(349 \mathrm{mg}, 1.04 \mathrm{mmol})$ and $\mathrm{Na}_{2} \mathrm{CO}_{3}(209 \mathrm{mg}, 1.97 \mathrm{mmol})$ at $0^{\circ} \mathrm{C}$. The reaction mixture was gradually warmed to room temperature with stirring 1.5 days. The reaction mixture was adjusted to pH 1 using 1 M aqueous HCl solution and extracted with ethyl acetate 3 times. The organic layers were washed with brine. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $0 / 1,1 \%$ acetic acid) and HPLC (YMC Pack ODS-A No.2015000608, $\lambda=254 \mathrm{~nm}$, $\mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=7 / 3,0.1 \%$ TFA, $8.0 \mathrm{~mL} /$ minutes, retention time 26.9 minutes) to afford 2 ( $186 \mathrm{mg}, 55 \%$ for 4 steps) as a white solid. $\mathrm{R}_{\mathrm{f}}=0.37$ (hexane/ethyl acetate $=0 / 1,1 \%$ acetic acid); $[\alpha]^{27}=+1.58$ (c $=0.92$ in MeOH ); ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ): $\delta 7.74-7.71$ ( $\mathrm{m}, 6 \mathrm{H}$ ), 7.64-7.58 (m, $6 \mathrm{H}), 7.36-7.24(\mathrm{~m}, 12 \mathrm{H}), 4.43-4.25(\mathrm{~m}, 6 \mathrm{H}), 4.20-4.10(\mathrm{~m}, 5 \mathrm{H}), 2.17-2.04$ $(\mathrm{m}, 2 \mathrm{H}), 1.83-1.69(\mathrm{~m}, 4 \mathrm{H}), 1.68-1.56(\mathrm{~m}, 2 \mathrm{H}), 1.47-1.11(\mathrm{~m}, 10 \mathrm{H})$, , 0.97$0.71 \mathrm{ppm}(\mathrm{m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ): $\delta 176.9,176.1$ (2C), 158.6 (2C), 156.1, 145.33 (2C), 145.27, 145.24, 145.16 (2C), 142.6 (6C), 128.8 (6C), 128.1 (6C), 126.3 (4C), 126.1 (2C), 120.9 (6C), 67.9 (2C), 67.2, 64.4, 55.3 (2C), 48.4 (3C), 36.0, 35.9, 32.6, 32.5, 30.1, 30.0, 26.7, 26.6, 24.8, 24.6 ppm; IR (neat on KBr plate): $\mathbf{~ U} 3405,3066,2940,2861,2604,1693$, 1514, 1449, 1207, $740 \mathrm{~cm}^{-1}$; HRMS (ESI): m/z calcd for $\mathrm{C}_{61} \mathrm{H}_{61} \mathrm{~N}_{3} \mathrm{O}_{12} \mathrm{Na}$ : $1050.4147[\mathrm{M}+\mathrm{Na}]^{+}$; found: 1050.4146 .

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## Entry for the Table of Contents



The lack of suitable trivalent linkers has limited trimer peptide models. This study designed and synthesized two new alkyl bridged-tris- $\alpha$-amino acids with Fmoc protecting groups as flexible linkers, which are characterized by $\mathrm{C}_{3}$-symmetric and linear structures, respectively.


Contents
I. Copy of NMR spectra of new compounds
II. Experimental procedure of synthesis of stereoisomers of $\mathbf{9 , 2 0}$, and $\mathbf{2 7}$
III. Copy of HPLC chart of compounds $\mathbf{9}, \mathbf{2 0}$, and 27

## I. NMR spectra of new compounds





13
( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )





( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


17
( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


17
( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )
210


( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )


[^0]
4
( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )









20
(400 MHz, $\mathrm{CDCl}_{3}$ )












2
$\int_{1}^{3} \frac{4}{5}$

21
( $101 \mathrm{MHz}, \mathrm{D}_{2} \mathrm{O}$ )
3




1
( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}, 313 \mathrm{~K}$ )


$$
\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)
$$


$t \mathrm{BuO}_{2} \mathrm{C} N \mathrm{NC}$
$\mathrm{CH}_{4}$
26
( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

24
(400 MHz, $\mathrm{CDCl}_{3}$ )

(BuO2C)
24
( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )
$\begin{array}{lllllllllllllllllllllllll}210 & 200 & 190 & 180 & 170 & 160 & 150 & 140 & 130 & 120 & 110 & 100 & 90 & 80 & 70 & 60 & 50 & 40 & 30 & 20 & 10 & 0 & -10 & \mathrm{ppm}\end{array}$
$t \mathrm{BuO}_{2} \mathrm{C} \mathrm{NHCbz}$
$\mathrm{OHC}_{\underset{4}{ } \mathrm{Y}_{4}}^{\mathrm{YH}_{4} \mathrm{CHO}}$
23
( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

$\xrightarrow{\mathrm{OHCO}_{2} \mathrm{BH}_{4}} \mathrm{HH}_{4}^{\mathrm{CHO}}$
23
( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )







27
( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )

[^1]
28
(400 MHz, $\mathrm{D}_{2} \mathrm{O}$ )


28
$\left(101 \mathrm{MHz}, \mathrm{D}_{2} \mathrm{O}\right)$
8
8






## II. Experimental procedure of synthesis of stereoisomers of 9, 20, and 27



A solution of $\left[\mathrm{Rh}(\operatorname{cod})_{2}\right] \mathrm{BF}_{4}(4.0 \mathrm{mg}, 9.9 \mu \mathrm{~mol}),(S, S)$-QuinoxP* $(2.2 \mathrm{mg}, 6.6 \mu \mathrm{~mol})$ and $(R, R)$-QuinoxP* $(2.2 \mathrm{mg}, 6.6 \mu \mathrm{~mol})$ in degassed $\mathrm{MeOH}(0.5 \mathrm{~mL})$ was stirred vigorously at room temperature under nitrogen atmosphere. After 40 minutes, additional degassed $\mathrm{MeOH}(2.5 \mathrm{~mL})$ was added to the mixture. Compound $18(97.5 \mathrm{mg}, 146 \mu \mathrm{~mol})$ was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm , and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 9)$ to afford a mixture of $(2 S, 8 S)-,(2 S, 5 S, 8 R)-,(2 S, 5 R, 8 R)-,(2 R, 8 R)-9(19.5 \mathrm{mg}, 24 \%)$ and a mixture of $(2 S, 8 S)-,(2 S, 5 S, 8 R)-,(2 S, 5 R, 8 R)-,(2 R, 8 R)$-S1 (63.2 mg, $64 \%)$ as colorless oil. ( $(2 S, 8 S)$ $\mathbf{9}:(2 S, 5 S, 8 R)-\mathbf{9}$ and $(2 S, 5 R, 8 R)-\mathbf{9}:(2 R, 8 R)-\mathbf{9}=1.0: 2.3: 1.3)$


A solution of $\left[\mathrm{Rh}(\operatorname{cod})_{2}\right] \mathrm{BF}_{4}(1.9 \mathrm{mg}, 4.7 \mu \mathrm{~mol}),(S, S)$-QuinoxP* $(1.4 \mathrm{mg}, 4.2 \mu \mathrm{~mol})$ and $(R, R)$-QuinoxP* $(1.4 \mathrm{mg}, 4.2 \mu \mathrm{~mol})$ in degassed $\mathrm{MeOH}(0.5 \mathrm{~mL})$ was stirred vigorously at room temperature under nitrogen atmosphere. After 4 h , additional degassed $\mathrm{MeOH}(1.5 \mathrm{~mL})$ was added to the mixture. Compound 3 (6.5 $\mathrm{mg}, 8.6 \mu \mathrm{~mol})$ was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm , and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $3 / 7$ ) to afford a mixture of $(2 S, 8 S, 11 S)-,(2 S, 8 S, 11 R)-,(2 S, 8 R, 11 R)-,(2 R, 8 R, 11 R)-\mathbf{2 0}(5.4 \mathrm{mg}, 82 \%)$ as colorless oil. $((2 S, 8 S, 11 S)-\mathbf{2 0}:(2 S, 8 S, 11 R)-\mathbf{2 0}$ and $(2 S, 8 R, 11 R)-\mathbf{2 0}:(2 R, 8 R, 11 R)-\mathbf{2 0}=1.0: 3.8: 0.4)$


A solution of $\left[\mathrm{Rh}(\operatorname{cod})_{2}\right] \mathrm{SbF}_{6}(2.7 \mathrm{mg}, 4.9 \mu \mathrm{~mol})$ and $(R, R)$-QuinoxP* $(2.9 \mathrm{mg}, 8.7 \mu \mathrm{~mol})$ in degassed $\mathrm{MeOH}(0.7 \mathrm{~mL})$ was stirred vigorously at room temperature under nitrogen atmosphere. After 50 minutes, additional degassed $\mathrm{MeOH}(1.3 \mathrm{~mL})$ was added to the mixture. Compound $\mathbf{8}(97.5 \mathrm{mg}, 146 \mu \mathrm{~mol})$ was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm, and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $2 / 3$ ) to afford a mixture of starting material $\mathbf{8}$ and the product. The mixture was hydrogenated by the same procedure as above using $\left[\mathrm{Rh}(\mathrm{cod})_{2}\right] \mathrm{SbF}_{6}(3.5 \mathrm{mg}, 6.3 \mu \mathrm{~mol})$ and $(R, R)$-QuinoxP* $(3.2 \mathrm{mg}, 9.6 \mu \mathrm{~mol})$. After completion of the reaction, the reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $2 / 3)$ to afford $(2 S, 8 S, 11 R)-\mathbf{2 0}(44.4 \mathrm{mg}, 54 \%)$ as colorless oil.


A solution of $\left[\mathrm{Rh}(\operatorname{cod})_{2}\right] \mathrm{BF}_{4}(2.2 \mathrm{mg}, 5.4 \mu \mathrm{~mol}),(S, S)$-QuinoxP* $(1.3 \mathrm{mg}, 3.9 \mu \mathrm{~mol})$ and $(R, R)$-QuinoxP* $(1.3 \mathrm{mg}, 3.9 \mu \mathrm{~mol})$ in degassed $\mathrm{MeOH}(0.5 \mathrm{~mL})$ was stirred vigorously at room temperature under nitrogen atmosphere. After 60 minutes, additional degassed $\mathrm{MeOH}(0.5 \mathrm{~mL})$ was added to the mixture. Compound $22(43.0 \mathrm{mg}, 50.9 \mu \mathrm{~mol})$ was charged in a hydrogenation bottle. After the bottle was evacuated and filled with hydrogen several times, the catalyst solution was added. The hydrogen pressure was adjusted to 4 atm , and the mixture was stirred vigorously overnight at room temperature. The reaction mixture was concentrated, and the crude product was purified by silica gel column chromatography (hexane/ethyl acetate $=1 / 0$ to $1 / 1)$ to afford a mixture of $\left(8 S, 8^{\prime} S\right)-,\left(8 S, 2 S, 8^{\prime} R\right)-,\left(8 S, 2 R, 8^{\prime} R\right)-,\left(8 R, 8^{\prime} R\right)-\mathbf{2 7}(36.0 \mathrm{mg}$, $83 \%)$ as colorless oil. (( $\left.8 S, 8^{\prime} S\right) \mathbf{- 2 7}:\left(8 S, 2 S, 8^{\prime} R\right) \mathbf{- 2 7}$ and $\left.\left(8 S, 2 R, 8^{\prime} R\right) \mathbf{- 2 7}:\left(8 R, 8^{\prime} R\right)-\mathbf{2 7}=1.0: 2.7: 1.7\right)$

## III. Copy of HPLC chart of compounds 9,20 , and 27



Ee and de were calculated from the peak area of each stereoisomer in HPLC (Daicel CHIRAL CEL OX$\mathrm{RH}, \lambda=254 \mathrm{~nm}, \mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=9 / 11,0.5 \mathrm{~mL} /$ minutes) by weighing each peak.


|  |  |  |  |
| :---: | :---: | :---: | :---: |
| peak <br> No. | ret. time <br> (min) | wight of paper (mg) | wight of paper (\%) |
| 1 | 23.5 | 39.7 | 21.8 |
| 2, 3 | 24.6, 25.8 | 90.3 | 49.5 |
| 4 | 28.0 | 52.3 | 28.7 |




Enantiomer was not detected.


Ee and de were calculated from the peak area of each stereoisomer in HPLC (Daicel CHIRAL CEL OX$\mathrm{RH}, \lambda=254 \mathrm{~nm}, \mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=3 / 2,0.5 \mathrm{~mL} /$ minutes) by weighing each peak.



| peak <br> No. | ret. time <br> $(\mathrm{min})$ | wight of <br> paper $(\mathrm{mg})$ | wight of |
| ---: | ---: | ---: | ---: |
| 1 | 16.6 | 13.6 | 19.3 |
| 2,3 | $19.3,22.4$ | 51.3 | 72.8 |
| 4 | 25.8 | 5.6 | 7.9 |




| Peak | ret. time | wight of | wight of |
| ---: | ---: | ---: | :--- |
| No. | $(\mathrm{min})$ | paper (mg) | paper (\%) |
| 1 | 16.7 | 87.9 | 98.8 |
| 2 | 19.6 | 1.1 | 1.2 |

A diastereomer (peak 3 in the above chart) and enantiomer were not detected.


De was calculated from the peak area of each stereoisomer in HPLC (Daicel CHIRAL CEL OJ-RH, $\lambda=$ $254 \mathrm{~nm}, \mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=1 / 1,0.5 \mathrm{~mL} /$ minutes) by weighing each peak.


(2S, $8 S, 11 S$ )-, ( $2 S, 8 S, 11 R$ )-20

| peak | ret. time | wight of | wight of |
| ---: | :--- | ---: | :--- |
| No. | (min) | paper (mg) | paper (\%) |
| 1 | 23.6 | 13.2 | 35.8 |
| 2 | 28.2 | 23.7 | 64.2 |



|  |  |  |  |
| :---: | :---: | :---: | :---: |
| peak <br> No. | ret. time <br> (min) | wight of paper (mg) | wight of paper (\%) |
| 1 | 24.2 | 0.7 | 0.6 |
| 2 | 29.0 | 124.3 | 99.4 |



Ee and de were calculated from the peak area of each stereoisomer in HPLC (Daicel CHIRAL CEL OX$\mathrm{RH}, \lambda=254 \mathrm{~nm}, \mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}=7 / 3,0.5 \mathrm{~mL} /$ minutes ) by weighing each peak.


(8S, $\left.8^{\prime} S\right)-,\left(8 S, 2 S, 8^{\prime} R\right)-$, ( $8 S, 2 R, 8^{\prime} R$ )-, ( $8 R, 8^{\prime} R$ )-27

| peak | ret. time <br> No. | wight of <br> $(\mathrm{min})$ | wight of |
| ---: | ---: | ---: | :--- |
| 1 | 16.7 | 21.3 | 18.6 |
| 2,3 | $18.9,19.6$ | 56.8 | 49.7 |
| 4 | 22.6 | 36.2 | 31.7 |



|  |  |  |  |
| :---: | :---: | :---: | :---: |
|  |  |  |  |
| peak | ret. time | wight of | wight of |
| No. | (min) | paper (mg) | paper (\%) |
| 1 | 16.6 | 75.4 | 98.2 |
| 2 | 19.6 | 1.4 | 1.8 |

Enantiomer was not detected.


[^0]:    $\begin{array}{llllllllllllllllllllllll}210 & 200 & 190 & 180 & 170 & 160 & 150 & 140 & 130 & 120 & 110 & 100 & 90 & 80 & 70 & 60 & 50 & 40 & 30 & 20 & 10 & 0 & -10 & \mathrm{ppm}\end{array}$

[^1]:    $170 \quad 1$
    100

