JOC The Journal of Organic Chemistry

Article

Total synthesis of plusbacin A3 and its dideoxy derivative using a solvent-dependent diastereodivergent Joullié–Ugi three-component reaction

Akira Katsuyama, Fumika Yakushiji, and Satoshi Ichikawa

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00038 • Publication Date (Web): 19 Feb 2018

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Total synthesis of plusbacin A_3 and its dideoxy derivative using a solvent-dependent diastereodivergent Joullié–Ugi three-component reaction

Akira Katsuyama[†], *Fumika Yakushiji*[†,‡], *and Satoshi Ichikawa**[†, ‡]

AUTHOR ADDRESS

[†]*Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan.*

[‡]*Center for Research and Education on Drug Discovery, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan.*

AUTHOR EMAIL ADDRESS

ichikawa@pharm.hokudai.ac.jp

RECEIVED DATE

CORRESPONDING AUTHOR FOOTNOTE

[†]*Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan.*

[‡]*Center for Research and Education on Drug Discovery, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan.*

ABSTRACT: Full details of our synthetic studies toward plusbacin A_3 (**1**), which is a depsipeptide with antibacterial activity, and its dideoxy derivative are described. To establish an efficient synthetic route of **1**, a solvent-dependent diastereodivergent Joullié−Ugi three-component reaction (JU-3CR) was used to construct *trans*-Pro(3-OH) in a small number of steps. Two strategies were investigated toward the total synthesis. In the first synthetic strategy, the key steps were the *trans*-selective JU-3CR and a macrolactonization at the final stage of the synthesis. The JU-3CR using alkyl isocyanides in 1,1,1,3,3,3-hexafluoroisopropanol provided the *trans* products, and the coupling of the fragments to prepare the macrocyclization precursor proceeded smoothly. However, attempts toward the macrolactonization did not provide the desired product. Then, the second strategy that included esterification in an initial stage was investigated. Methods for constructing *trans*-Pro(3-OH) were examined using a convertible isocyanide, which could be converted to a carboxylic acid required for the following amidation. Ester bond formation was achieved through an intermolecular coupling using a hydroxyl-Asp derivative and the corresponding alcohol, and the amidation afforded a linear depsipeptide. The macrolactamization of the linear peptide gave the cyclic depsipeptide, then the global deprotection accomplished the total synthesis of **1** and its dideoxy derivative.

INTRODUCTION

Bacteria have cell walls that protect them from harmful environments, such as increases in turgor pressure or drug penetration. In particular, peptidoglycan is a main component of the bacterial cell wall, and its disruption through the inhibition of its biosynthesis is an established strategy for developing antimicrobial agents. β-Lactams inhibit the transpeptidase that polymerize lipid II, a precursor of peptidoglycan,[1] and vancomycin inhibits lipid II polymerization by binding to the D-Ala-D-Ala moiety of lipid II.[2] Both classes of antibacterial drugs are frequently used in clinics; however, multiple drug-resistant bacteria that are resistant to these drugs have been reported.[3] Therefore, developing drug candidates that can control outbreaks of resistant pathogens via different mechanisms of actions is very important. It is also important to develop antibacterial agents that are less susceptible to these drug

resistances. Some natural products that bind to non-protein peptidoglycan precursors including lipid II, such as vancomycin, ramoplanin and teixobactin, are currently known to be less susceptible to the generation of drug resistance.[4] Hence, this series of compounds that inhibit peptidoglycan biosynthesis via binding to its precursors can be promising antibacterial leads.

Plusbacin A_3 (**1**, Figure 1) was isolated from *Pseudomonas sp.* PB-6250 in 1992 as a potential antimicrobial agent against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococci* (VRE).[5] It has been reported that **1** inhibits lipid II polymerization, although the details of the mechanism of action remain to be elucidated.[6] Hence, the development of efficient synthetic route and an investigation of the mechanism of action of **1** are significant challenges in developing new antibacterial candidates.

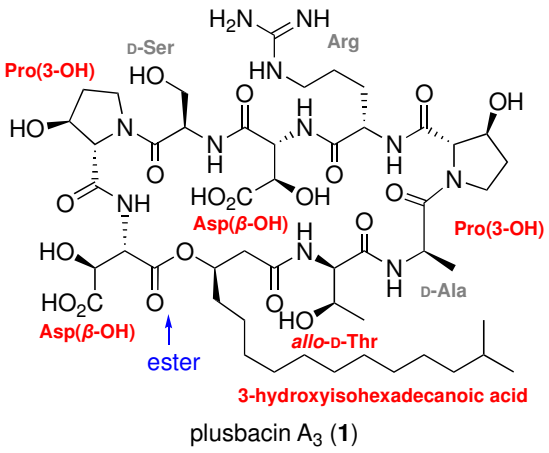
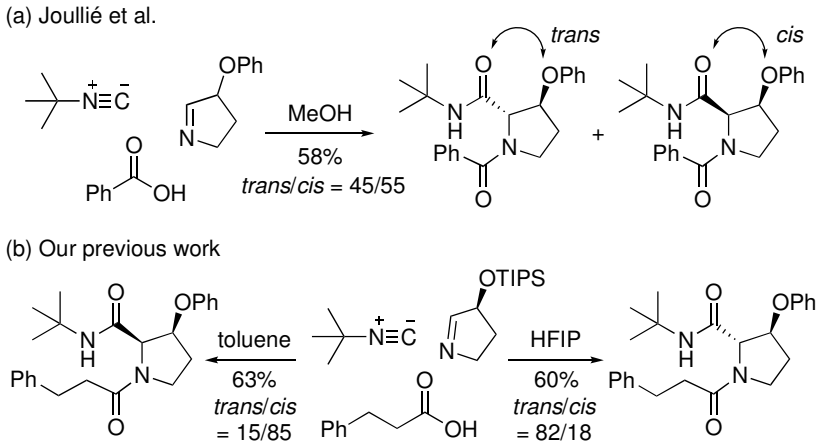


Figure 1. Chemical structure of plusbacin A_3 (**1**).

Plusbacin A_3 is a cyclic depsipeptide that contains two *trans*-3-hydroxyl L-prolines [Pro(3-OH)], L- and D-β-hydroxy-aspartic acids [Asp(β-OH)], and 3-hydroxyisohexadecanoic acid in its 28-membered cyclic peptide core skeleton. To achieve an efficient total synthesis of **1**, the construction of Pro(3-OH) is a key step. Park and co-workers reported that D-gluconolactone could be converted to Pro(3-OH) via an allylglycine derivative in 14 steps.[7] The conversion from but-3-yn-1-ol to Pro(3-OH) via a Sharpless asymmetric epoxidation in 15 steps was described by Chandrasekhar's group.[8] These methodologies are

well-designed; however, diastereoselective transformation in short steps is required for the synthesis of **1**. Since the Pro(3-OH) is also included in some peptide-based natural products,[9] it is important to develop an efficient synthetic methodology for constructing the Pro(3-OH). As a result, a Joullié–Ugi three-component reaction (JU-3CR),[10] which enables the construction of Pro(3-OH) in one step, was selected for efficiency. The JU-3CR was first reported in 1982 as a three-component coupling reaction using the combination of an isocyanide, a cyclic imine and a carboxylic acid (Scheme 1(a)).[10a] This reaction has the advantage that it can synthesize Pro(3-OH) with simultaneous amide bond formation at both the *C*- and *N*-termini. In our previous work, a diastereodivergent JU-3CR that can regulate the *trans*/*cis* selectivity through the selection of the proper solvent was developed.[11] Non-polar solvents, such as toluene, provided *cis* products, while polar 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) afforded predominantly *trans* products with the same combination of substrates (Scheme 1(b)). This newly developed solvent-dependent diastereodivergent JU-3CR was thought to be effective for the rapid construction of the two Pro(3-OH) moieties of **1**.

Scheme 1. Joullié–Ugi three-component reaction.



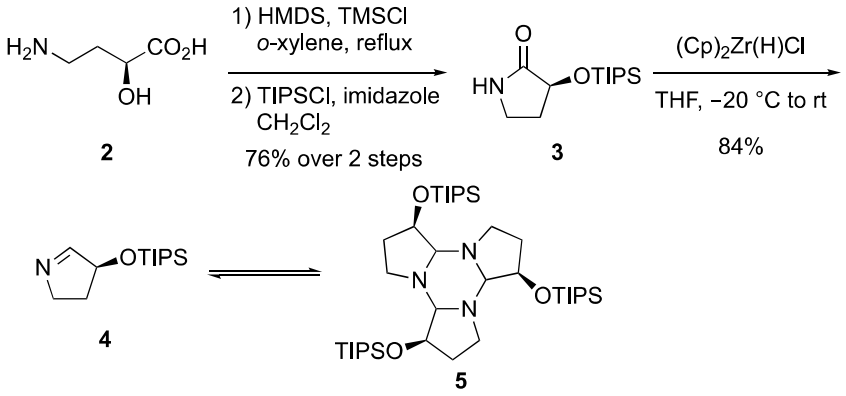
To date, total syntheses of plusbacin A_3 (**1**) have been reported by VanNieuwenhze and co-workers in 2007,[12] and by our group in 2017.[13] We describe herein the full details of our effort to accomplish the

total synthesis of **1** via the solvent-dependent diastereodivergent JU-3CR.[11] During this study, a dideoxy derivative was also synthesized.

RESULTS AND DISCUSSION

Upon utilizing the JU-3CR for the total synthesis of **1**, the cyclic imine **4** was prepared as shown in Scheme 2. (*S*)-4-Amino-2-hydroxybutanoic acid (**2**) was treated with hexamethyldisilazane (HMDS) and a catalytic amount of TMSCl to obtain a lactam,[14] and its secondary alcohol was protected as a triisopropylsilyl ether to give **3** in 76% yield over two steps. Lactam **3** was cleanly converted to cyclic imine **4** (84% yield) using the hydrozirconium reagent reported by Schwartz.[15] Imine **4** existed in equilibrium with trimer **5** in several organic solvents.

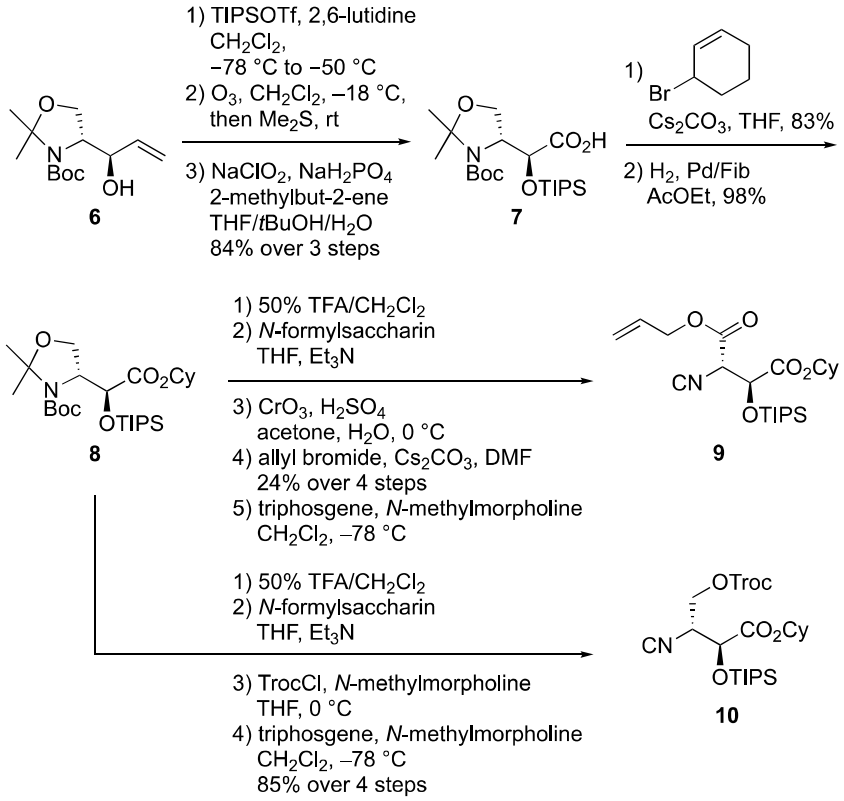
Scheme 2. Synthesis of cyclic imine **4**.



Isocyanide **9**, which is composed of the Asp(β-OH) residue at the *C*-terminal of one of the Pro(3-OH) moieties, was prepared as shown in Scheme 3. Known alcohol **6**[16] was protected with a triisopropyl silyl group, and ozonolysis of the olefin followed by oxidation gave carboxylic acid **7** in 84% yield over three steps. As a β-hydroxy carboxylic acid protecting group, a cyclohexyl ester was selected to avoid an intramolecular cyclization. The condensation reaction between **7** and cyclohexanol using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and DMAP and a Mitsunobu reaction

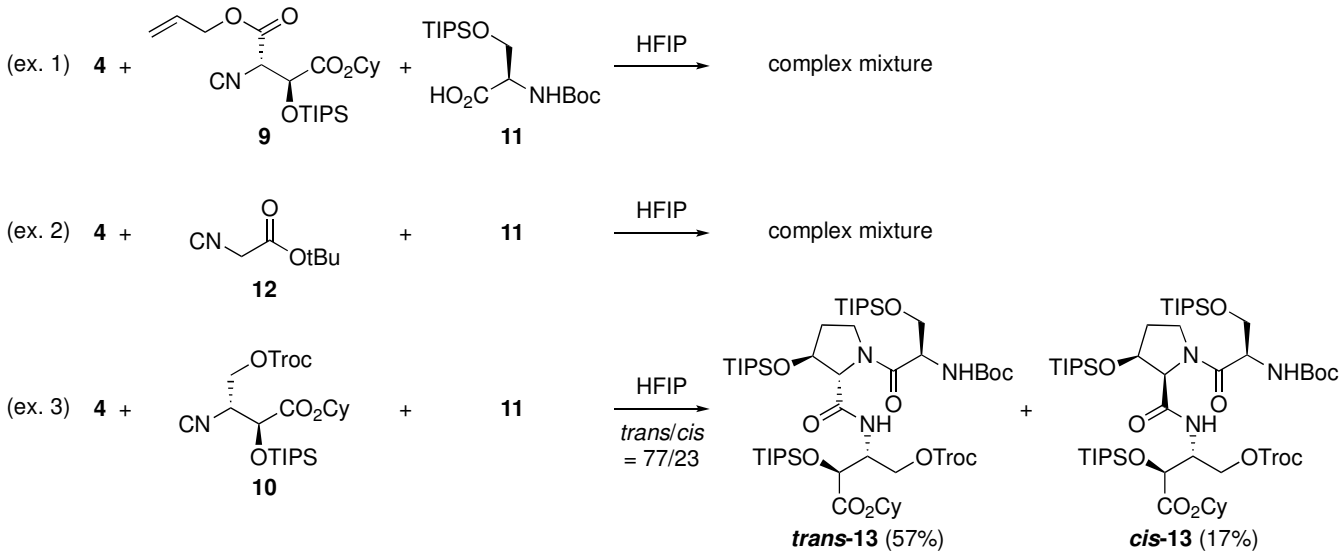
using DEAD and PPh_3 were initially examined; however, only a moderate amount of **8** was obtained. Therefore, a stepwise construction of **8** was investigated by using 3-bromocyclohex-1-ene as the coupling partner. Alkylation of **7** with 3-bromocyclohex-1-ene under basic conditions and hydrogenation of the resulting cyclohexenyl ester using H_2 and the Pd/Fibroin complex (Pd/Fib)[17] provided cyclohexyl ester **8** in excellent yield (83% and 98% yield for the two steps, respectively). The Boc protecting group of **8** was removed under acidic conditions, and the liberated amine was formylated using *N*-formylsaccharin.[18] The remaining primary alcohol was oxidized to the carboxylic acid, which was allylated (24% yield over four steps), and the corresponding allyl ester was then treated with triphosgene to provide isocyanide **9**. In addition, 2,2,2-trichloroethoxycarbonyl (Troc)-protected isocyanide **10** was synthesized in four steps from **8**.

Scheme 3. Synthesis of isocyanides **9** and **10**.

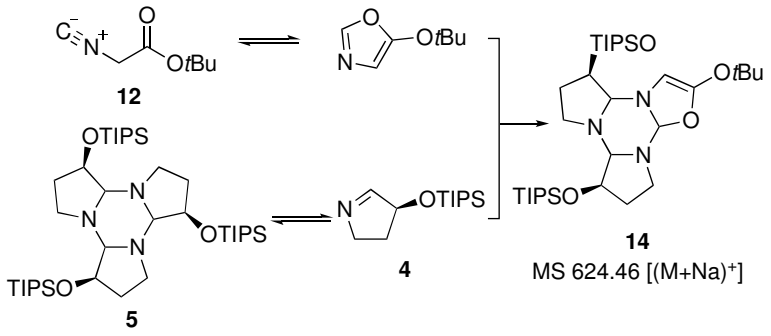


In our initial exploration of the JU-3CR for the total synthesis of **1**, the scope and limitations of the isocyanides were investigated (Scheme 4). Considering a direct conversion, the combination of cyclic imine **4**, isocyanide **9** and protected Ser **11** was examined in HFIP. However, this reaction provided a complex mixture (ex. 1). Because steric hindrance was thought to be the reason why the reaction did not proceed, simple isocyanide **12** containing a β carbonyl moiety was used instead of **9**, but this combination also provided a complex mixture of products (ex. 2). Zhu and coworkers reported that α-isocyanocarboxamide can be converted to an oxazoline by an intramolecular cyclization.[19] In the analysis of the reaction mixture with mass spectrometry, a peak at 624.46 [$(M+Na)^+$] corresponding to complex **14**, which is composed of oxazoline and **4**, was detected. Oxazoline was incorporated into the equilibrium of the trimer formation, and generated complex **14** could interfere in the progression of the reaction (Scheme 5). In the case of Troc-protected alkyl isocyanide **10**, which lacks the carbonyl group and thereby cannot form a trimer such as **14**, desired ***trans*-13** was obtained in 57% yield as the major product over ***cis*-13** (17%) (ex. 3). These investigations suggested that the carbonyl on the β position of the isocyano group should be avoided in the JU-3CR.

Scheme 4. Initial scope and limitations of isocyanides for the JU-3CR.

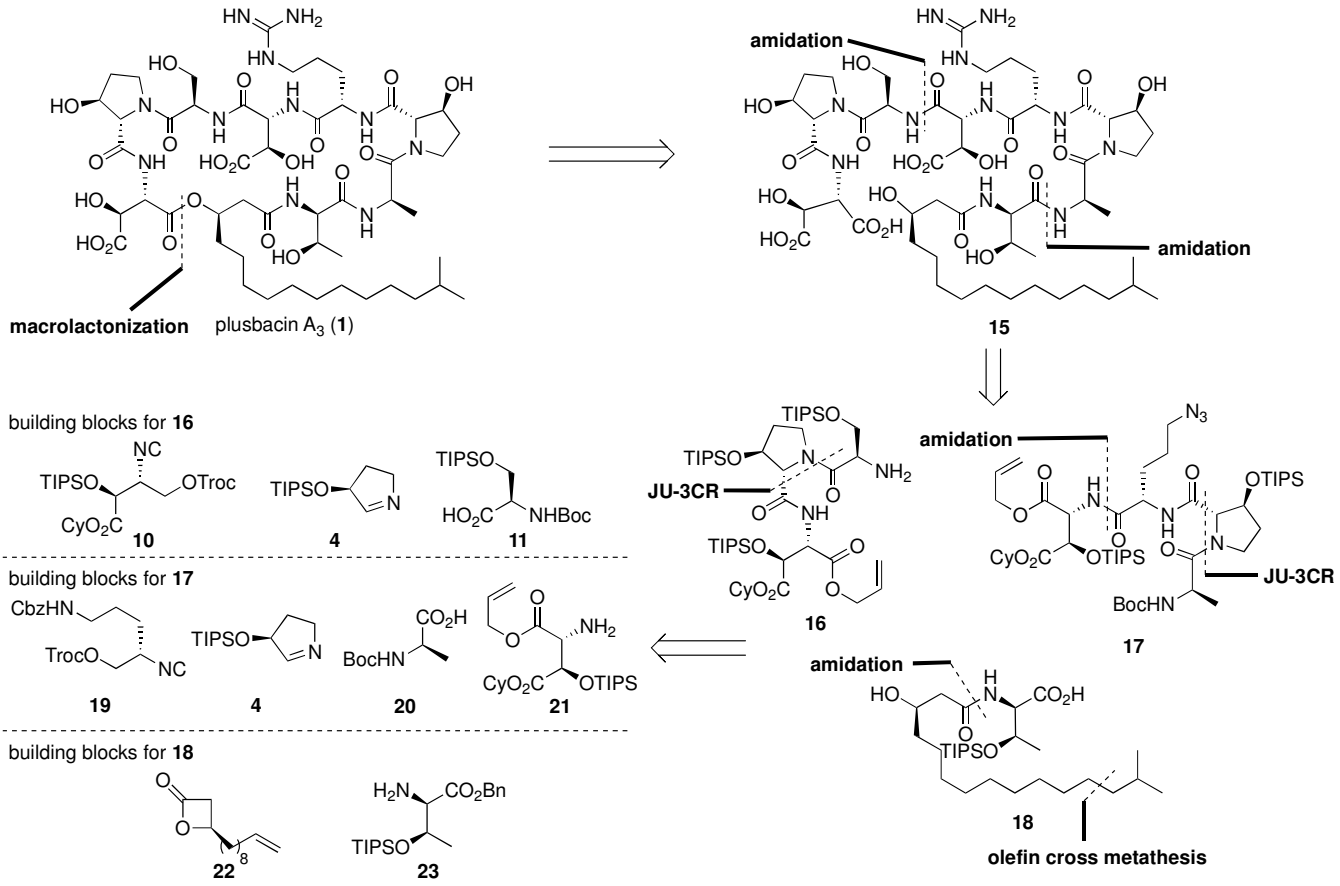


Scheme 5. Generation of trimer **14** from isocyanide **12**.



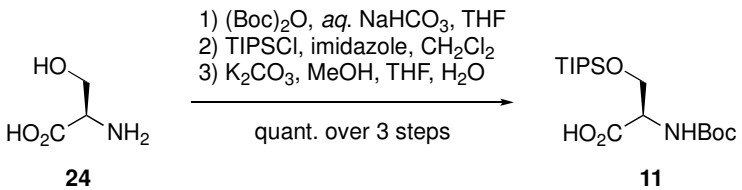
With these initial investigations into the JU-3CR in hand, a retrosynthetic analysis of plusbacin A_3 (**1**) was conducted as shown in Scheme 6. The 28-membered macrocycle was to be synthesized via a macrolactonization of carboxylic acid **15**, which was disconnected to peptide segments **16**, **17** and **18** via amidation. Segment **16** was prepared via the JU-3CR using alkyl isocyanide **10**, cyclic imine **4** and carboxylic acid **11**, and **17** can be constructed by the same strategy via the JU-3CR using alkyl isocyanide **19**, cyclic imine **4** and carboxylic acid **20** followed by amidation with **21**. Amide **18**, containing a lipid side chain, can be generated by the coupling of **22** and **23**.

Scheme 6. Retrosynthetic analysis of plusbacin A_3 (**1**).



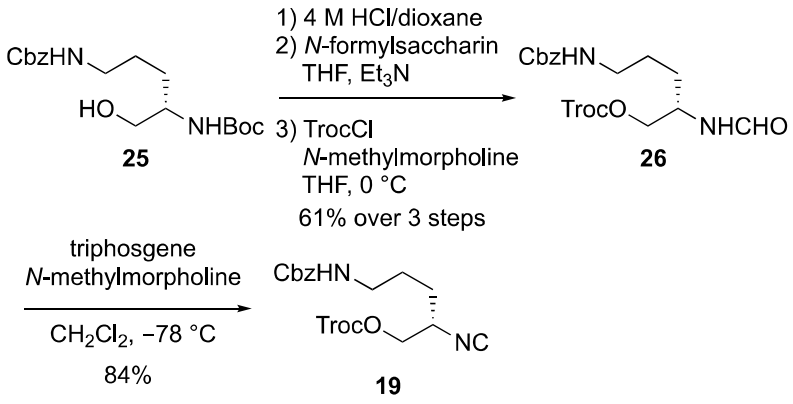
First, the building blocks required for the synthesis of **1** (**11**, **19**, **20**, **21**, **22**, and **23**) were prepared. Suitably protected serine **11** was synthesized in three steps from **24** by a Boc protection of the amino group, triisopropylsilylation and hydrolysis of the silyl ester (Scheme 7).

Scheme 7. Synthesis of carboxylic acid **11**.



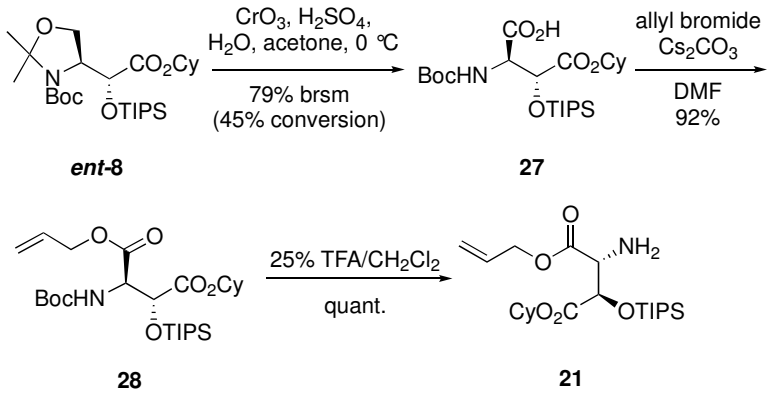
The Boc protecting group on known alcohol **25**[20] was removed under acidic conditions and the liberated amine was formylated. The primary alcohol was Troc-protected to give **26** in 61% yield over three steps. Treatment of **26** with triphosgene provided isocyanide **19** in 84% yield (Scheme 8).

Scheme 8. Synthesis of isocyanide **19**.



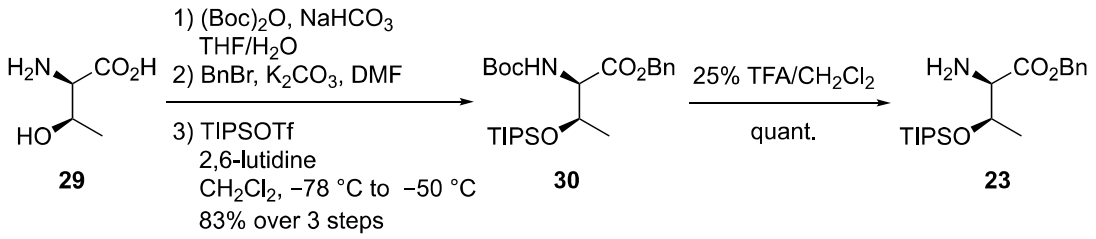
Protected D-Asp(β-OH) **21** was synthesized from ***ent*-8**. The isopropylidene group of ***ent*-8** was removed, and the generated primary alcohol was oxidized to carboxylic acid **27**. The carboxylic acid of **27** was alkylated using allyl bromide, and the Boc group of **28** was removed to afford amine **21** (Scheme 9).

Scheme 9. Synthesis of amine **21**.



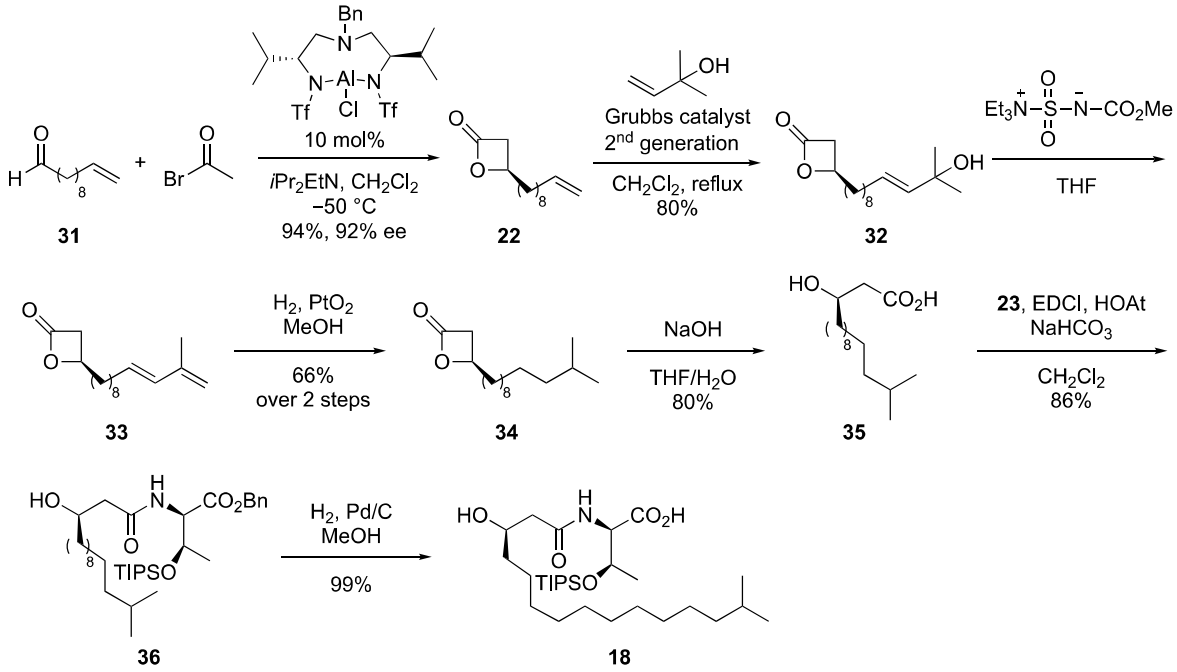
Suitably protected *allo*-D-Thr **23** was prepared by a sequential Boc, benzyl and triisopropylsilyl protections of **29** to give **30**, which was followed by Boc deprotection of **30** under acidic conditions (Scheme 10).

Scheme 10. Synthesis of protected *allo*-D-Thr **23**.



Synthesis of amide **18**, containing the lipid side chain, began from β-lactone **22**, which had been constructed via an enantioselective [2+2]cycloaddition reaction using aldehyde **31** and a ketene generated from acetyl bromide in the presence of the optically active Al(Ⅲ)–triamine complex[21] (94% yield, 92% ee) (Scheme 11). Obtained **22** and 2-methylbut-3-en-2-ol were treated with Grubbs 2nd generation catalyst[22] to give olefin **32** in 81% yield. When 3-methylbut-1-en was used for this cross-metathesis reaction, the double bond was isomerized, and a complex mixture of products containing shorter carbon chains was produced. Metathesis product **32** was dehydrated using Burgess reagent[23] to give **33**. The diene of **33** was then hydrogenated under PtO_2 catalysis to provide desired **34** in 66% yield over two steps. The use of Pd/C as a catalyst led to a complex mixture due to reduction of the C-O bond. Lactone **34** was converted to carboxylic acid **35** in 80% yield, and it was then condensed with **23** using EDCI, 1-hydroxy-7-azabenzotriazole (HOAt) and $NaHCO_3$ to give amide **36** in 86% yield. The benzyl group of **36** was removed by hydrogenolysis catalyzed by Pd/C to afford **18** in 99% yield.

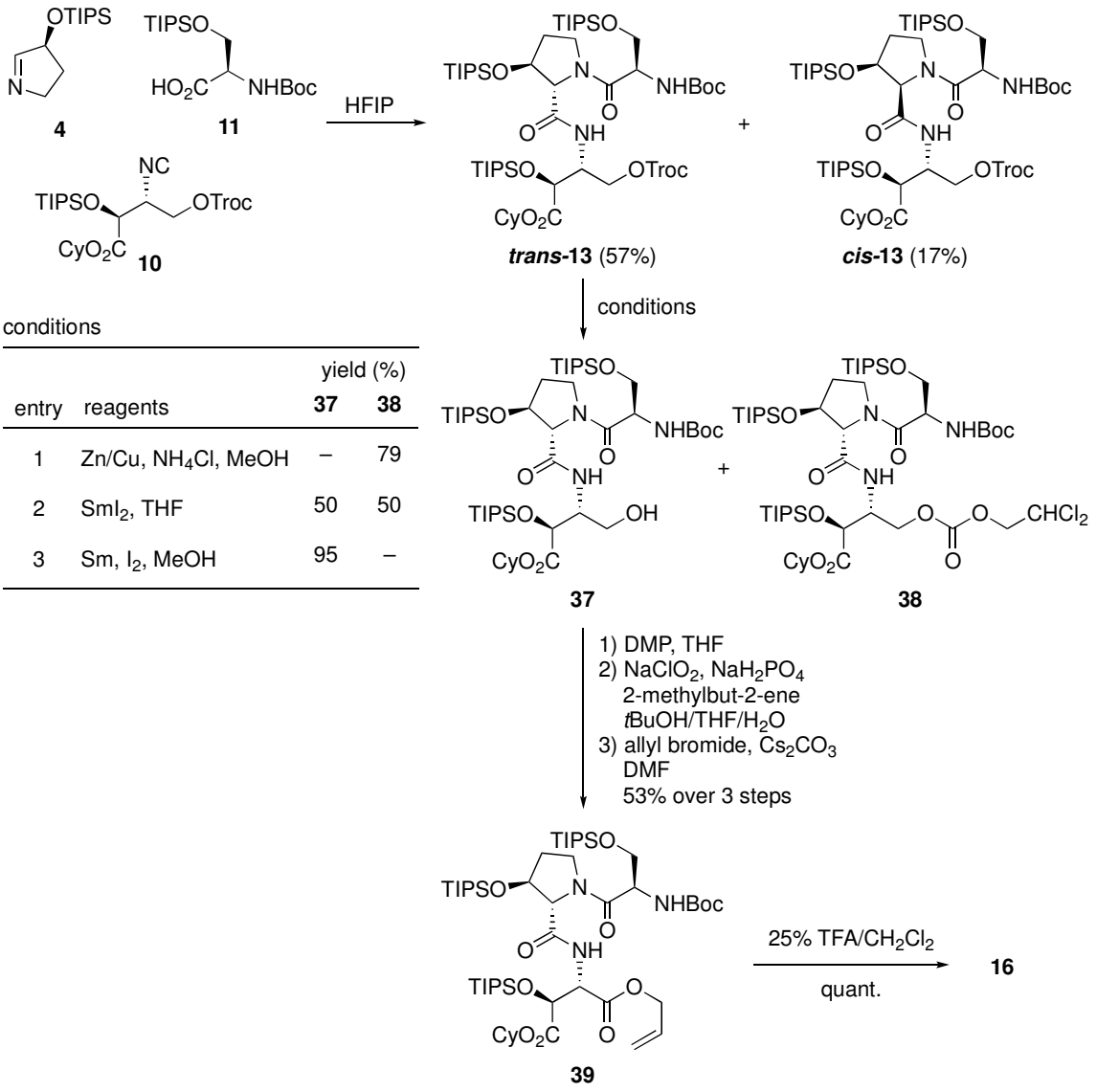
Scheme 11. Synthesis of amide **18**.



The synthesized building blocks **4**, **10** and **11** were used for the key JU-3CR (Scheme 12). In our previous report,[11] the solvent-dependent diastereodivergent JU-3CR was examined in either toluene or HFIP. The non-polar solvent (toluene) predominantly provided *cis* products, while the polar solvent (HFIP) produced *trans* products. Thus, HFIP was selected as a solvent of the preparation of *trans* tripeptide **13**. The reaction of **4**, **10** and **11** in HFIP at room temperature for 19.5 h smoothly provided ***trans*-13** as well as ***cis*-13** in yields of 57% and 17%, respectively, and as expected, the *trans* product was obtained as a major product. These two diastereomers were easily separated by silica gel column chromatography. Removal of the Troc protecting group of ***trans*-13** was investigated. As shown in Scheme 12, entry 1, the conditions using a zinc-copper couple in the presence of ammonium chloride provided only dechlorinated derivative **38**. The reaction presumably proceeded via protonation of the organo zinc intermediate. Therefore, we examined the reaction in the absence of a proton source under single-electron reduction conditions using SmI_2. Although desired alcohol **37** was obtained in 50% yield (entry 2), **38** was still produced under these conditions. Hence, the solvolysis of the Troc group was conducted using Sm and I_2 in MeOH (entry 3).[24] The methanolysis cleanly afforded desired **37** in 95% yield, the primary alcohol of **37** was oxidized to a carboxylic acid, and subsequent alkylation afforded

allyl ester **39**. The Boc protecting group of **39** was removed by TFA to provide tripeptide **16** in quantitative yield.

Scheme 12. Synthesis of tripeptide **16** via a JU-3CR.



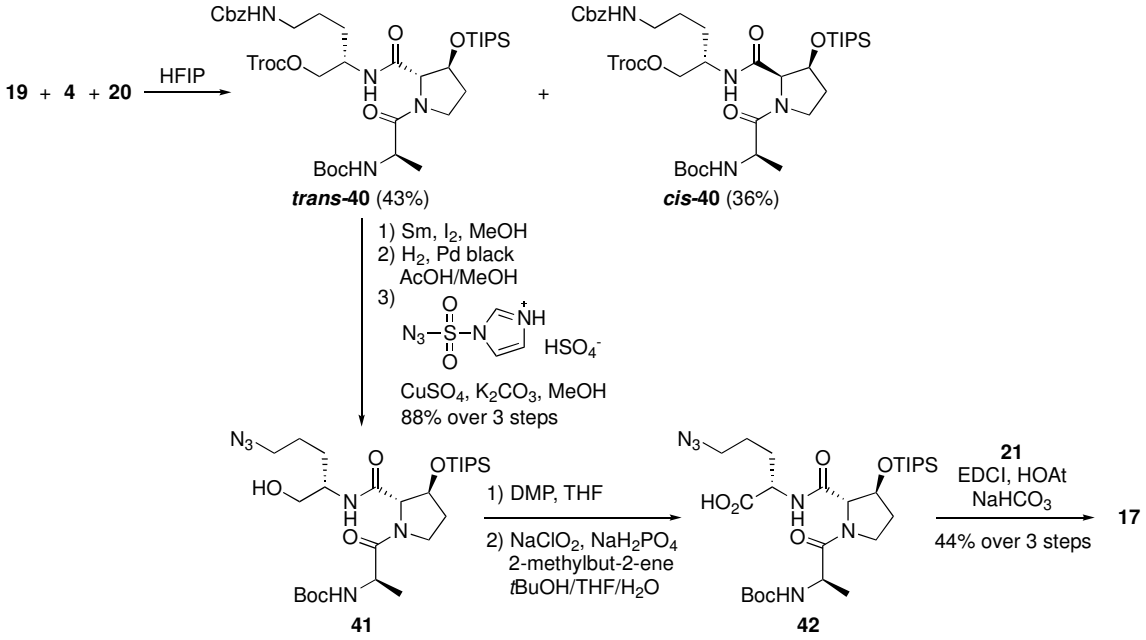
conditions

entry	reagents	yield (%) 37	38
1	Zn/Cu, NH_4Cl, MeOH	–	79
2	SmI_2, THF	50	50
3	Sm, I_2, MeOH	95	–

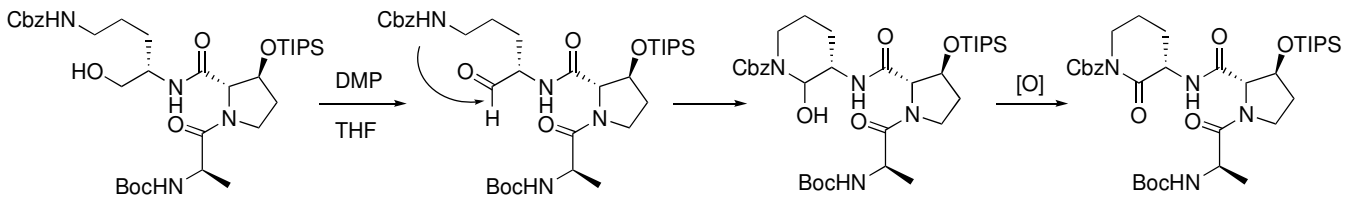
The JU-3CR in HFIP was examined for preparing the *trans* product using building blocks **19**, **4** and **20** (Scheme 13). As a result, desired ***trans*-40** was obtained in moderate yield (43%) along with ***cis*-40** (36%), although the reason for the decreased selectivity was unclear. After the separation of the products of the JU-3CR by silica gel column chromatography, the Troc and Cbz groups of ***trans*-40**

were removed by solvolysis mediated by Sm and I_2 in MeOH and hydrogenolysis, respectively, and the liberated amine was converted to an azide[25] to afford **41** in 88% yield over three steps. The primary alcohol of **41** was oxidized by Dess-Martin periodinane (DMP), which was then treated with sodium chlorite to afford carboxylic acid **42**, which was condensed with amine **21** to provide tetrapeptide **17** in 44% yield over three steps. The temporal transformation to the azide as **41** was nesessary, because the oxidation to an aldehyde from the primary alcohol provided a hemiaminal intermediate, and the second oxidation generated a γ-lactam (Scheme 14).

Scheme 13. Synthesis of tetrapeptide **17** via the JU-3CR.



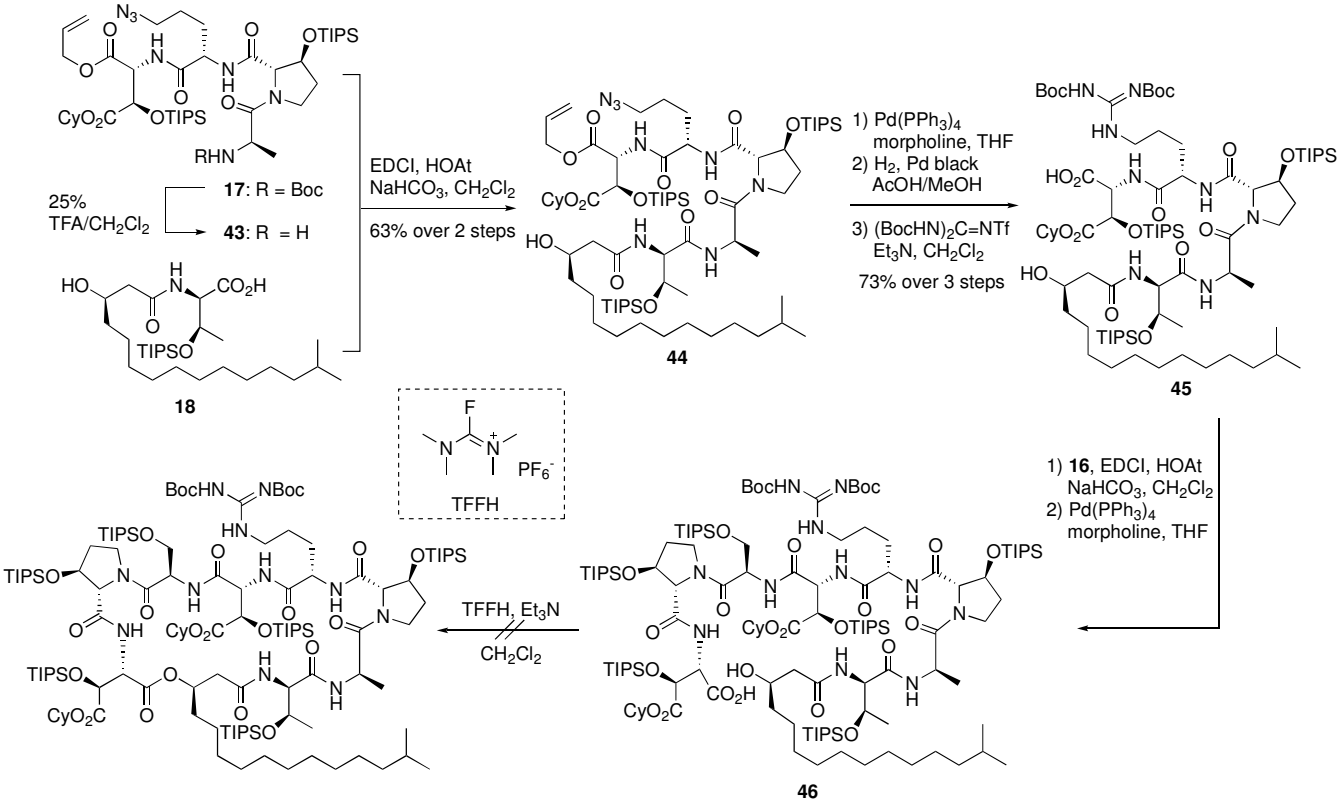
Scheme 14. Generation of a γ-lactam from a Cbz-protected amino alcohol.



With the three segments in hand, their coupling to form linear peptide **46** and its subsequent cyclization were investigated (Scheme 15). The Boc group of tetrapeptide **17** was removed to give

amine **43**, which was condensed with **18** to provide hexapeptide **44** in 63% yield over two steps. The allyl group of **44** was removed with $Pd(PPh_3)_4$ and morpholine, and the liberated amine was converted to a Boc-protected guanidine using Goodman's reagent[26] to afford **45** in 73% yield over three steps from **44**. The amide bond formation between **45** and **16** was promoted by EDCI, HOAt and $NaHCO_3$ and was followed by the removal of the allyl group to provide carboxylic acid **46**. Finally, the hydroxy carboxylic acid moiety was converted to an acyl fluoride with fluoro-*N*,*N*,*N*′,*N*′-bis(tetramethylene)formamidinium hexafluorophosphate (TFFH),[27] and the product was subjected to macrolactonization. However, the desired depsipeptide was not obtained except unanalyzable compounds. Although other macrolactonization conditions were extensively explored, only hydroxy carboxylic acid **46** was recovered.

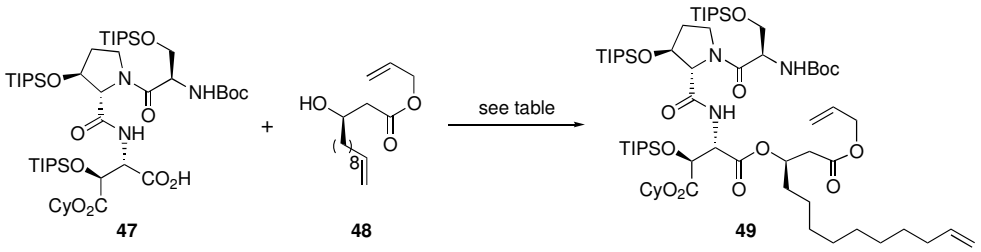
Scheme 15. Attempts toward the total synthesis of plusbacin A_3 (**1**).



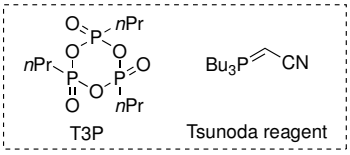
Because the macrolactonization did not proceed, an intermolecular esterification using tripeptide **47** and alcohol **48** was examined to elucidate the reactivity of the esterification under a variety of

conditions (Table 1). However, desired product **49** was not obtained, while elimination product **50** was obtained in moderate yield when EDCI and DMAP were used. These examinations suggested that the bulky environment prevented ester bond formation. Small substrates, such as L-threo-β-hydroxy-Asp, were preferable when this esterification was conducted at an early stage in the synthesis.

Table 1. Examination of intermolecular esterification using tripeptide **47** and alcohol **48**.



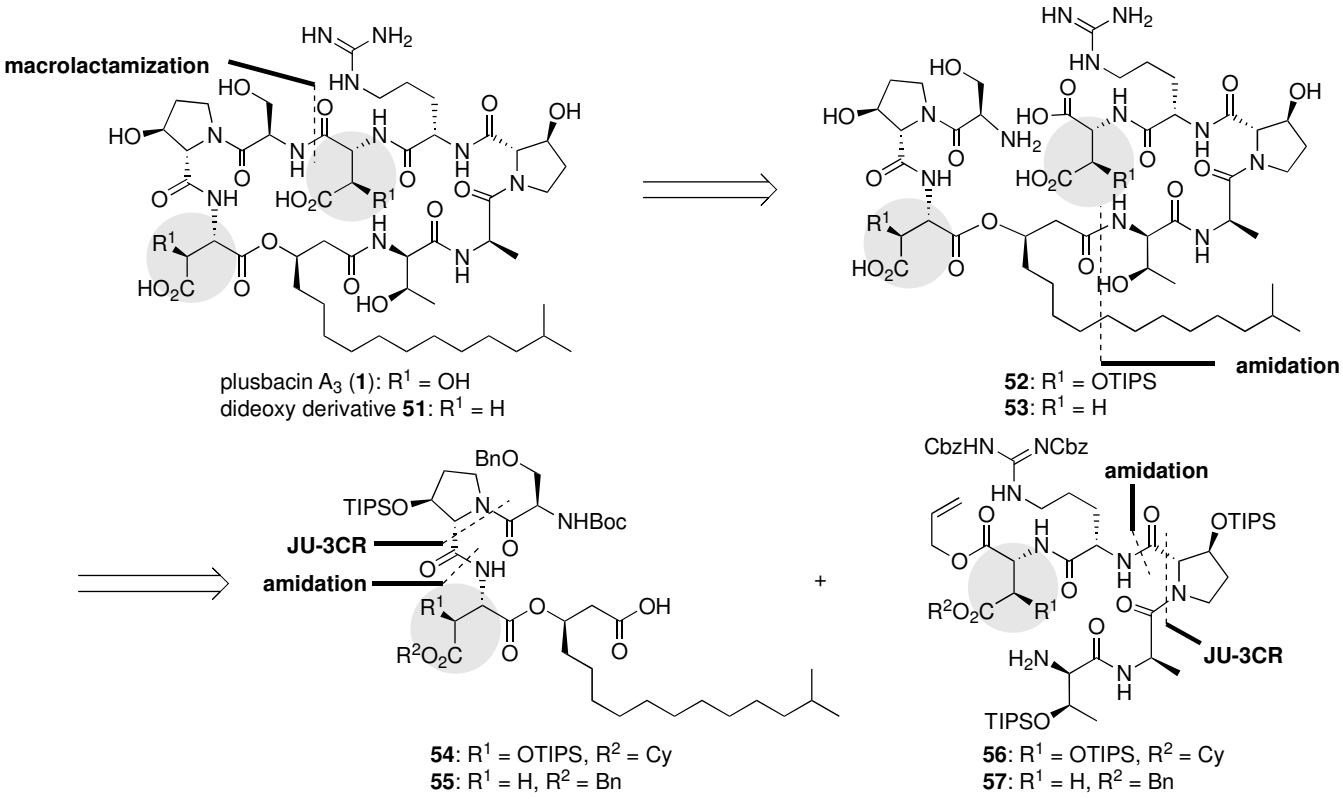
entry	conditions	result
1	EDCI, DMAP, CH_2Cl_2	**50** (39%)
2	T3P, *N*-methylmorpholine, DMF	no reaction
3	TFFH, *N*-methylmorpholine, CH_2Cl_2	decomp.
4	DEAD, PPh_3, benzene	no reaction
5	Tsunoda reagent, benzene	no reaction
6	$Dy(OTf)_3$, toluene, reflux	no reaction



Considering these results, including several failures toward the total synthesis of **1**, the synthetic strategy was revised as shown in Scheme 16. Plusbacin A_3 (**1**) would be generated by macrolactamization via amide bond formation between D-Ser and D-threo-β-hydroxy-Asp in the same way as was reported by VanNieuwenhze et al.[12] Linear peptide **52** can be incorporated into the structure by amidation using depsipeptide **54** and pentapeptide **56**. Depsipeptide **54** was to be synthesized via a JU-3CR followed by amidation using an amine containing the appropriate ester moiety. Although the JU-3CR products from using isocyanide **10** were amides (as shown in Schemes 4 and 12), the

carboxylic acids derived from the JU-3CR products were desirable for the sequential amidation. The convertible isocyanides were selected to address this point because they allow the transformation of the JU-3CR products to the carboxylic acids.[28] Pentapeptide **56** can be constructed via the same strategy, a JU-3CR followed by amidation. As described in later, the synthesis of dideoxy derivative **51** was also planned according to the retrosynthetic analysis of **1**.

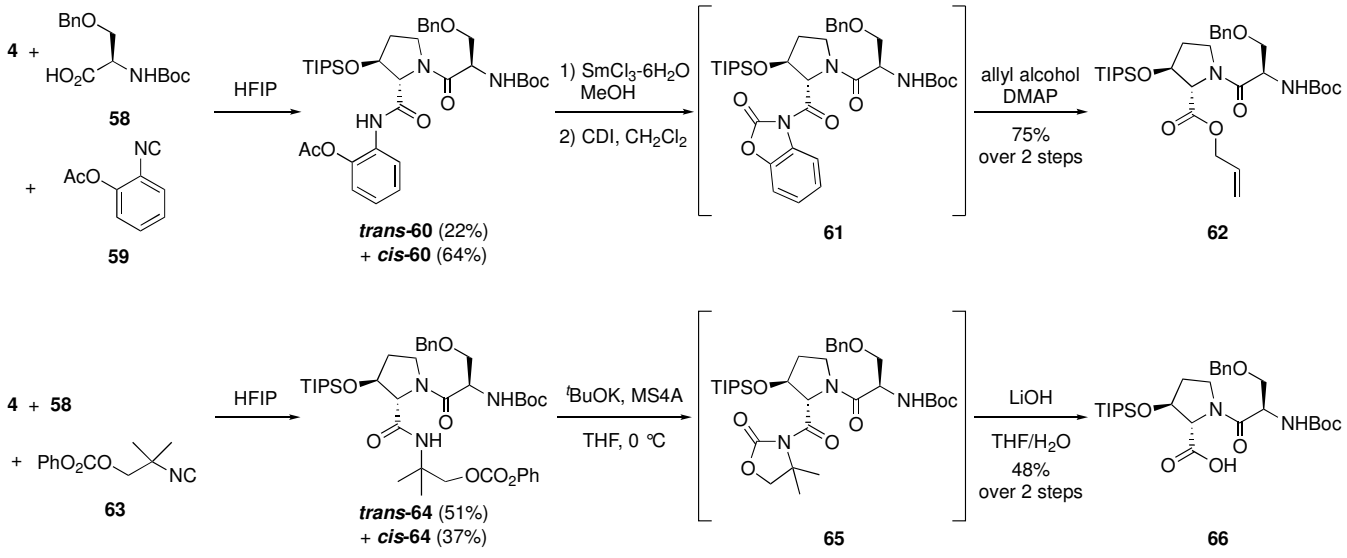
Scheme 16. Retrosynthetic analysis of **1** and dideoxy derivative **51**. The gray circles indicate the deoxygenated fragments.



First, a JU-3CR was examined to construct the carboxylic acid containing the Pro(3-OH) fragment (Scheme 17). In addition to cyclic imine **4** and carboxylic acid **58**, 2-isocyanophenyl acetate (**59**),[28a] as the isocyanide component, was selected for the generation of the protected carboxylic acid via an *N*-acyl oxazolidinone intermediate. The reaction was conducted in HFIP to obtain the *trans*-JU-3CR product, but desired ***trans*-60** was generated in 22% yield as a minor product. The obtained diastereomers were

separated by silica gel column chromatography, and the acetyl group of ***trans*-60** was removed using $SmCl_3$. Treatment of the resulting phenol with *N*,*N*′-carbonyldiimidazole (CDI) produced *N*-acyl oxazolidinone intermediate **61**,[28b] and the condensation with allyl alcohol provided dipeptide **62**. This *cis*-selective conversion can be explained by the lower nucleophilicity of the aryl isocyanide containing the sp^2 carbon atom adjacent to the isocyano group from our previous study.[10] To optimize the *trans*/*cis* selectivity, electron-rich sp^3 alkyl isocyanide **63**[28c] was selected for the diastereoselective JU-3CR. In HFIP, desired *trans*-JU-3CR product **64** was obtained as a major product in 51% yield, while ***cis*-64** was isolated in 37% yield. The obtained diastereomers were separable by silica gel column chromatography. Treatment of ***trans*-64** with t-BuOK and MS (4Å) in THF afforded oxazolidinone intermediate **65**, which was hydrolyzed to carboxylic acid **66**.

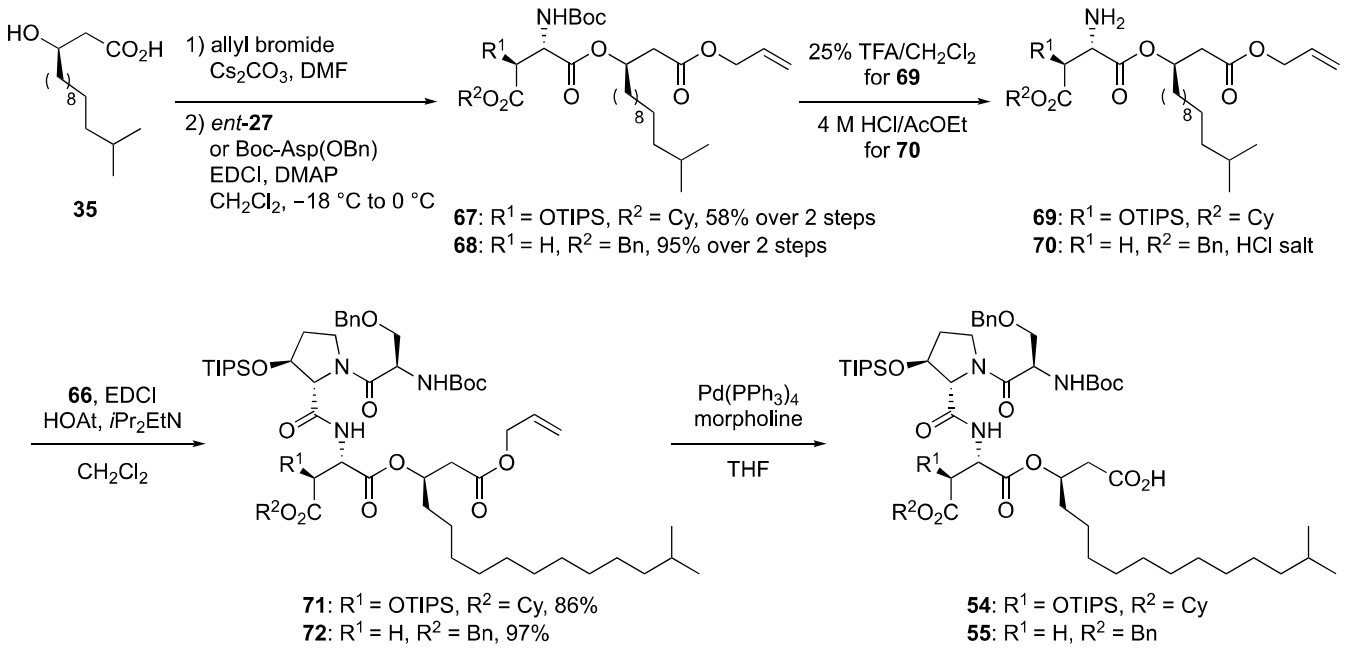
Scheme 17. JU-3CR for the preparation of Pro(3-OH) derivatives **62** and **66**.



Then, the ester bond formation was examined in an earlier stage of this second synthetic pathway (Scheme 18). The carboxylic acid of **35** was alkylated using allyl bromide and Cs_2CO_3, and acylation of the remaining hydroxy group with suitably protected L-Asp(β-OH) (*ent*-**27**)[12] using EDCI and DMAP smoothly provided **67** in 58% yield over two steps. The Boc protecting group was removed under acidic

conditions to afford ester **69**, which was condensed with carboxylic acid **66** to afford **71** in 86% yield over two steps, and the removal of the allyl group afforded carboxylic acid **54**.

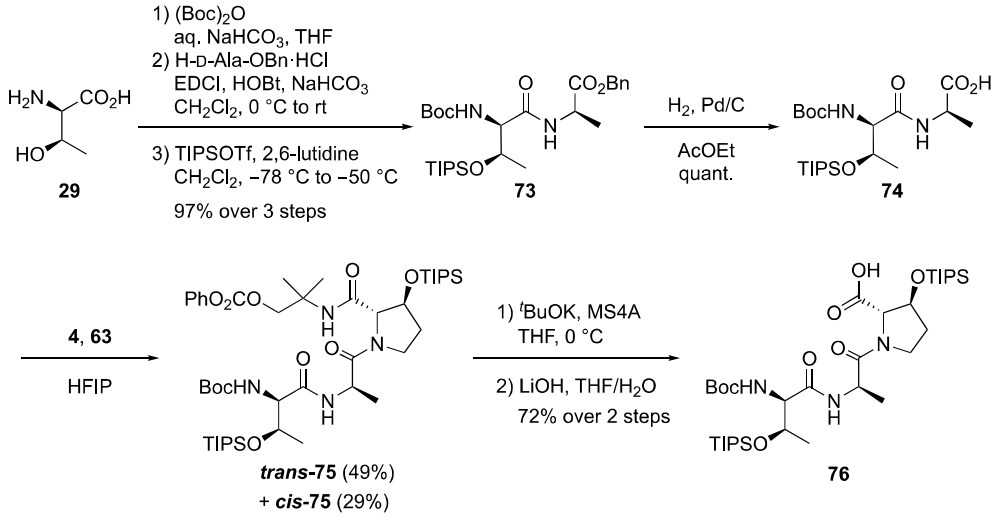
Scheme 18. Synthesis of depsipeptides **54** and **55**.



To examine the JU-3CR to obtain tripeptide **76**, protected dipeptide **74** was first synthesized from *allo*-D-Thr (**29**) via the installation of suitable protecting groups, condensation with H-D-Ala-OBn, and removal of the benzyl group of **73**.

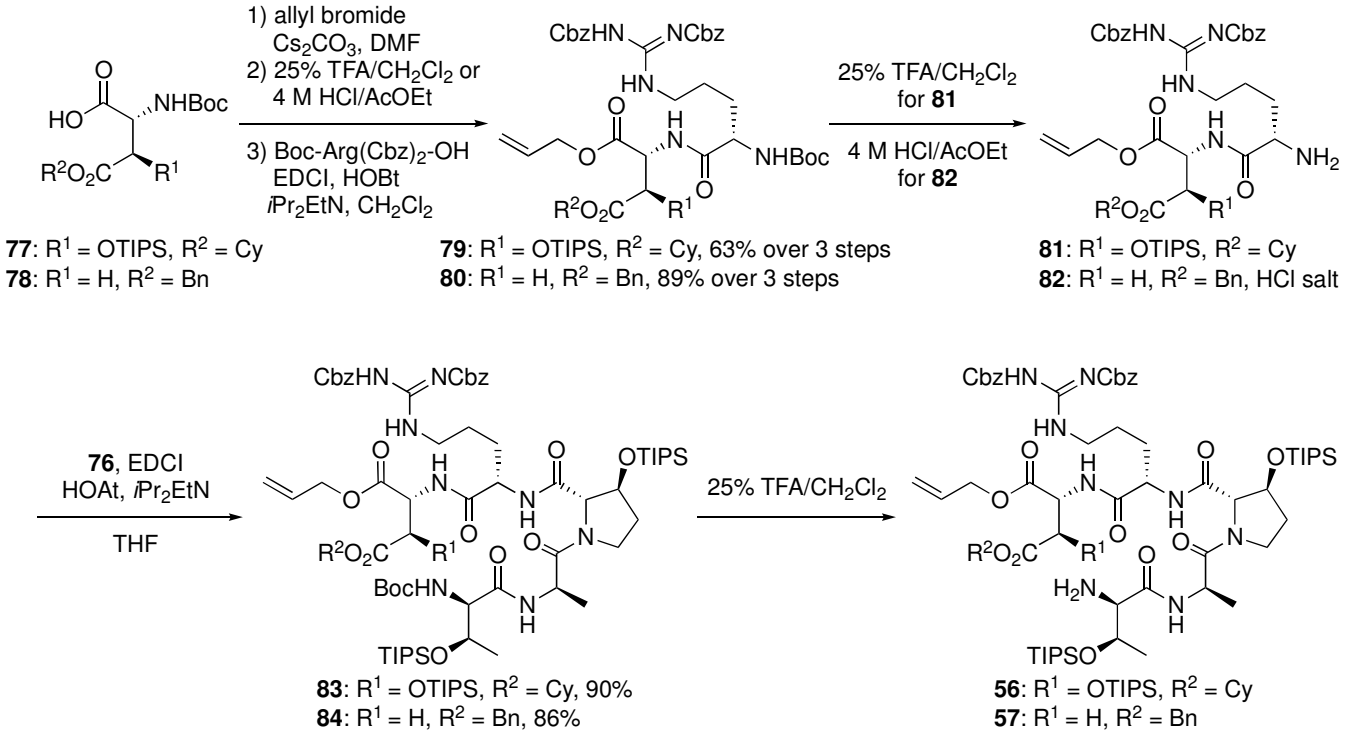
Cyclic imine **4**, alkyl isocyanide **63** and carboxylic acid **74** and HFIP were selected for the *trans*-selective JU-3CR in a similar manner to the synthesis of **64**. As a result, ***trans*-75** was generated in 49% yield as the major product over ***cis*-75**, and ***trans*-75** was separated by silica gel column chromatography. Pure ***trans*-75** was subjected to basic conditions to generate carboxylic acid **76** in 72% yield over two steps (Scheme 19).

Scheme 19. Synthesis of tripeptide **76** via a JU-3CR.



The synthesis of pentapeptide **56** is shown in Scheme 20. The carboxylic acid of **77** was converted to the allyl ester, the Boc group was removed, and the product was condensed with a suitably protected L-Arg to afford dipeptide **79**. The acidic removal of the Boc group produced amine **81**, which was condensed with tripeptide **76** using EDCI, HOAt and i-Pr_2NEt in THF to afford pentapeptide **83** in 90% yield. The Boc group of **83** was removed under acidic conditions to generate amine **56**.

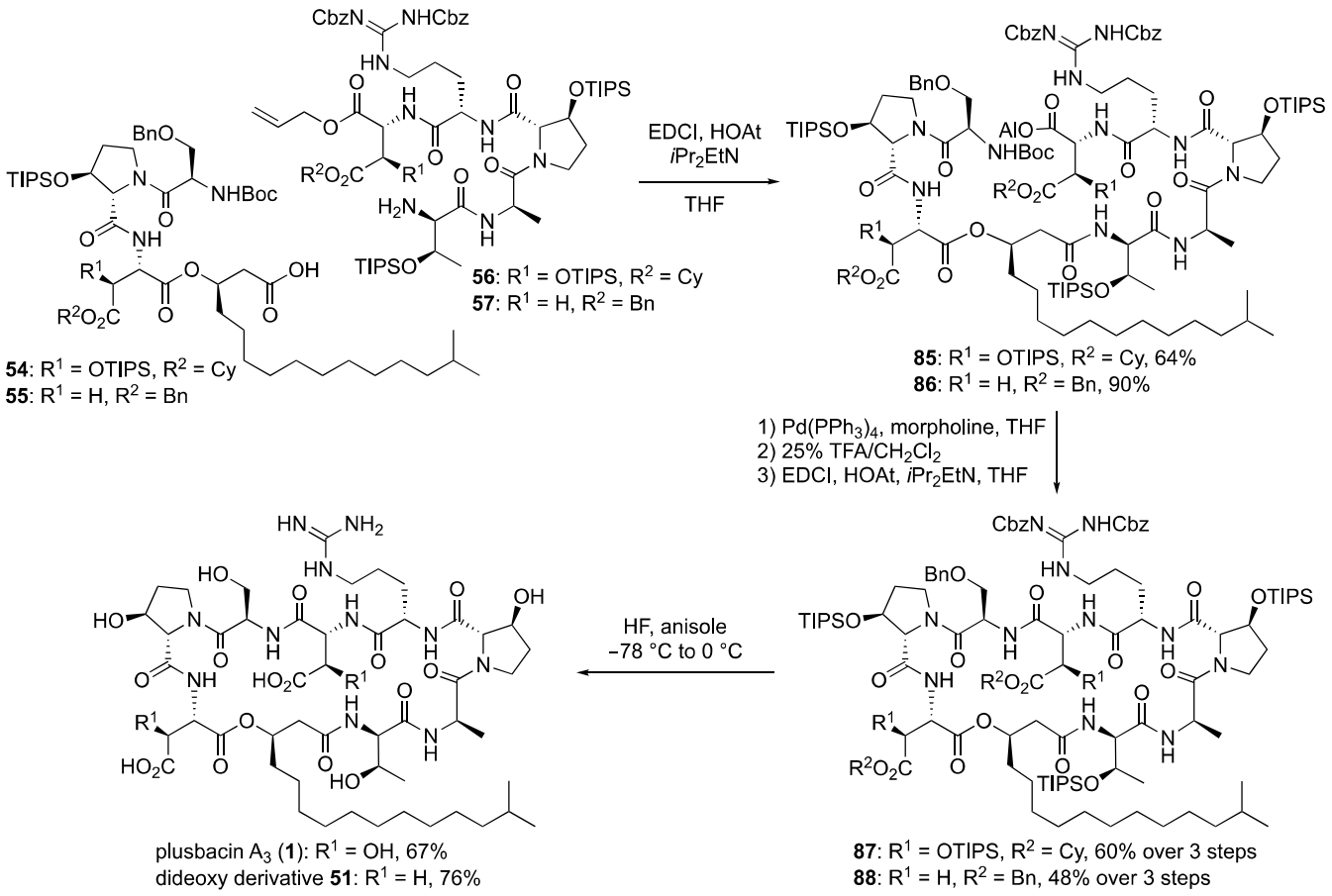
Scheme 20. Synthesis of pentapeptides **56** and **57**.



Synthesized depsipeptide **54** and pentapeptide **56** were condensed using EDCI and HOAt in the presence of i-Pr_2EtN and desired linear peptide **85** was obtained in 64% yield. The allyl ester of **85** was converted to a carboxylic acid, and the Boc protecting group was removed by using 25% TFA/CH_2Cl_2. The macrolactamization using EDCI and HOAt produced cyclic depsipeptide **87** in 60% yield over three steps. Finally, **87** was globally deprotected using HF and anisole, and the crude product was purified by reversed-phase HPLC to complete the synthesis of plusbacin A_3 (**1**).

The synthesis of dideoxy derivative **51** was also conducted to investigate the effects of a hydroxy group on the Asp residues on the biological activities. The same synthetic strategy as was used for **1** was applied by using suitably protected D- or L-Asp, instead of protected D- or L-threo-β-hydroxy-Asp, and desired **51** was obtained as expected (Schemes 16–21).

Scheme 21. Completion the total syntheses of **1** and its dideoxy derivative **51**.



CONCLUSIONS

In conclusion, our synthetic efforts toward the total synthesis of plusbacin A_3 (**1**) and its dideoxy derivative **51** were described. The total syntheses of **1** and **51** have been accomplished via a solvent-dependent diastereodivergent Joullié−Ugi three-component reaction (JU-3CR). This reaction, which used an electron-rich sp^3 alkyl isocyanide in HFIP, allowed the construction of the *trans*-3-hydroxyl proline in one step. Moreover, alkyl convertible isocyanides enabled the subsequent transformation to carboxylic acids for the efficient amidation to afford the desired depsipeptide and pentapeptide. Although macrolactonization in the final stage in the first synthetic strategy failed due to the steric environment, the ester bond formation between a simple Asp derivative and an alkyl alcohol in an earlier stage proceeded smoothly in the second approach. Macrolactamization of the linear peptide followed by global deprotection provided plusbacin A_3 (**1**) and its dideoxy derivative **51**. Studies on a

broad range of structure-activity relationships and the mechanism of action of **1** are now in progress and will be reported in due course.

EXPERIMENTAL SECTION

General Information.

All reactions, except those carried out in an aqueous phase, were performed under an argon atmosphere unless otherwise noted. Isolated yields were calculated by weighing the products. The weights of the starting materials and the products were not calibrated. Materials were purchased from commercial suppliers and used without further purification unless otherwise noted. Solvents were distilled according to the standard protocols. Analytical thin layer chromatography (TLC) analyses were performed on Merck silica gel 60F254 plates. Normal-phase column chromatography separations were performed on Merck silica gel 5715 or Kanto Chemical silica gel 60N (neutral). Flash column chromatography separations were performed on Fuji Sylysia silica gel PSQ 60B. SH-silica gel column chromatography separations were performed on Fuji Sylysia Scavenger SH Silica. ^{1}H NMR spectra were acquired in $CDCl_3$, DMSO-d_6, CD_3CN or D_2O with signals referenced to TMS (0.00 ppm) using JEOL ECA 500 (500 MHz), JEOL ECS 400 (400 MHz) or JEOL ECX 400P (400 MHz) spectrophotometers unless otherwise noted. ^{13}C NMR spectra were acquired in $CDCl_3$, DMSO-d_6, CD_3CN or D_2O with signals referenced to residual solvent peaks using JEOL ECA 500 (125 MHz), JEOL ECS 400 (100 MHz) or JEOL ECX 400P (100 MHz) spectrophotometers. Abbreviations of multiplicity are as follows; s: singlet, d; doublet, t: triplet, q: quartet, sept: septet, m: multiplet, and br: broad. Data are presented as follows; chemical shift (multiplicity, integration, coupling constant). Assignments were based on ^{1}H–^{1}H COSY, HMBC and HMQC NMR spectra. Optical rotations were determined on a JASCO P-1010-GT. IR spectra were acquired on a JASCO FT/IR-460 spectrometer. Mass spectra were recorded on a Thermo Scientific Exactive. The mass analyzer used for the HRMS measurements was TOF. Melting points were measured with a Yanaco MP–S3 melting point apparatus. Synthesis and characterization data of **1**, **4**, **5**, **7**, **8**, ***ent*-27**, **28**, **32**, **34**, **35**, **51**, **67**, **68**, **71**-**74**, ***trans*-75, *cis*-75, 76**, **79**, **80** and **83**-**88** described in reference 11 and 13.

Cyclohexyl (2S, 3R)-3-(formylamino)-4-(2,2,2-trichloroethoxycarbonyloxy)-2-(triisopropylsiloxy)butanoate

A mixture of **8** (103 mg, 0.200 mmol) in CH_2Cl_2 (1 mL) was treated with TFA (1 mL) at 0 °C for 30 min. The reaction was quenched with *sat. aq*. $NaHCO_3$, and the mixture was partitioned between AcOEt

and *sat. aq*. $NaHCO_3$. The organic phase was washed with H_2O (×2) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude aminoalcohol. A mixture of the crude aminoalcohol in THF (2 mL) was treated with *N*-formylsaccharin (66 mg, 0.30 mmol) for 30 min. *N*-Formylsaccharin (44 mg, 0.20 mmol) was added to the mixture, and the whole mixture was stirred for 15 min. The reaction was quenched with *sat. aq*. $NaHCO_3$, and the mixture was partitioned between AcOEt and *sat. aq*. $NaHCO_3$. The organic phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford cyclohexyl (2*S*, 3*R*)-3-(formylamino)-4-hydroxy-2-(triisopropylsiloxy)butanoate. A mixture of cyclohexyl (2*S*, 3*R*)-3-(formylamino)-4-hydroxy-2-(triisopropylsiloxy)butanoate and NMM (66 μL, 0.60 mmol) in THF (2 mL) was treated with TrocCl (41 μL, 0.30 mmol) at 0 °C for 25 min. The mixture was warmed to room temperature, and stirred for 45 min. *N*-Methylmorpholine (NMM, 66 μL, 0.60 mmol) and TrocCl (41 μL, 0.30 mmol) was added to the mixture, which was stirred for 35 min. The reaction was quenched with *sat*. *aq*. $NaHCO_3$, and the mixture was partitioned between AcOEt and *sat. aq*. $NaHCO_3$. The organic phase was washed with H_2O (×2) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography (ϕ 1×4 cm, 40% AcOEt/hexane) to afford cyclohexyl (2*S*, 3*R*)-3-(formylamino)-4-(2,2,2-trichloroethoxycarbonyloxy)-2-(triisopropylsiloxy)butanoate (109 mg, 0.19 mmol, 94% over 3 steps) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (s, 1H, C*H*O), 6.08 (d, 1H, N*H*CHO, $J_{NHCHO,\,3}$ = 8.6 Hz), 4.85-4.67 (m, 5H, CH_2CCl$_3$, H-1', H-3), 4.60 (d, 1H, H-2, $J_{2,\,3}$ = 2.3 Hz), 4.38 (dd, 1H, H-4, $J_{4,\,3}$ = 5.7, $J_{4,\,4}$ = 10.6 Hz), 4.27 (dd, 1H, H-4, $J_{4,\,3}$ = 7.5, $J_{4,\,4}$ = 10.6 Hz), 1.91-1.82 (m, 2H, H-2'), 1.78-1.69 (m, 2H, H-2'), 1.45-1.11 (m, 6H, H-3', H-4'), 1.10-1.02 (m, 21H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 170.0, 163.5, 153.6, 94.3, 77.1, 75.1, 74.7, 72.1, 70.5, 67.5, 65.8, 54.3, 49.7, 31.8, 31.7, 31.5, 25.3, 24.0, 23.9, 18.1, 18.0, 12.6, 12.5; ESIMS-LR *m*/*z*: $[M+Na]^+$ 600.15; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{23}H_{40}O_7NCl_3NaSi$ 598.1539, found 598.1532; $[\alpha]^{20}_D$ +5.18 (*c* 0.54, $CHCl_3$).

Formyl-(3S)-3-(triisopropylsiloxy)-Asp(O-cyclohexyl)-Oallyl

A solution of crude cyclohexyl (2*S*, 3*R*)-3-(formylamino)-4-hydroxy-2-(triisopropylsiloxy)butanoate (45.2 mg, 0.11 mmol) in acetone (2 mL) was treated with 2.5 M Jones reagent (132 μL, 0.33 mmol) at 0 °C for 4 h. The reaction was quenched with ^{i}PrOH (1.0 mL), and the mixture was partitioned between Et_2O and 1 M *aq*. HCl. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude carboxylic acid. A mixture of the crude carboxylic acid and Cs_2CO_3 (53.8 mg, 0.165 mmol) in DMF (1 mL) was treated with allyl bromide (14.3 μL, 0.165 mmol) at room temperature for 14 h. The mixture was partitioned between AcOEt and H_2O. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by

high-flash silica gel column chromatography (3-10-20% AcOEt/hexane) to afford the title compound (12.1 mg, 0.027 mmol, 24% over 4 steps) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25 (s, 1H, C*H*O), 6.29 (d, 1H, β-hydroxy-Asp-N*H*, $J_{\beta\text{-hydroxy-Asp-N}H,\ \beta\text{-hydroxy-Asp-}\alpha\text{-C}H}$ = 9.7 Hz), 5.92 (dddd, 1H, H_c, $J_{Hc,\ Ha}$ = 17.2, $J_{Hc,\ Hb}$ = 10.3, $J_{Hc,\ H\text{-}1}$ = $J_{Hc,\ 1}$ = 6.3 Hz), 5.35 (dd, 1H, H_a, $J_{Ha,\ Hc}$ = 17.2, $J_{Ha,\ H}$ = 1.8 Hz), 5.28 (dd, 1H, H_b, $J_{Hb,\ Hc}$ = 10.3, $J_{Hb,\ H\text{-}1}$ = 1.8 Hz), 5.16 (dd, 1H, β-hydroxy-Asp-α-C*H*, $J_{\beta\text{-hydroxy-Asp-}\alpha\text{-C}H,\ \beta\text{-hydroxy-Asp-}\beta\text{-C}H}$ = 1.7, $J_{\beta\text{-hydroxy-Asp-}\alpha\text{-C}H,\ \text{hydroxy-Asp-N}H}$ = 9.7 Hz), 4.98 (d, 1H, β-hydroxy-Asp-β-C*H*, $J_{\beta\text{-hydroxy-Asp-}\beta\text{-C}H,\ \beta\text{-hydroxy-Asp-}\alpha\text{-C}H}$ = 1.7 Hz), 4.81-4.74 (m, 1H, H-1'), 4.69 (dd, 1H, H-1, $J_{1,\ Hc}$ = 6.3, $J_{1,\ 1}$ =13.2 Hz), 4.59 (dd, 1H, H-1, $J_{1,\ Hc}$ = 6.3, $J_{1,\ 1}$ =13.2 Hz), 1.90-1.81 (m, 2H, H-2'), 1.76-1.69 (m, 2H, H-2'), 1.58-1.51 (m, 1H, H-4'), 1.45-1.18 (m, 5H, H-3', H-4'), 1.16-1.01 (m, 21H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 168.7, 160.8, 131.3, 119.7, 74.9, 72.8, 66.9, 54.4, 31.7, 31.5, 25.3, 24.0, 24.0, 18.0, 18.0, 12.6; ESIMS-LR: *m/z* $[M+Na]^+$ 478.26; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{23}H_{41}O_6NNaSi$ 478.2595, found 478.2601; $[\alpha]^{22}_D$ +7.94 (*c* 0.40, $CHCl_3$).

***Allyl cyclohexyl (2S, 3S)-2-isocyano-3-(triisopropylsiloxy)butandioate* (9)**

A mixture of formyl-(3*S*)-3-(triisopropylsiloxy)-Asp(*O*-cyclohexyl)-*O*allyl (4.3 mg, 0.016 mmol) and NMM (15.8 μL, 0.14 mmol) in CH_2Cl_2 (300 μL) was treated with triphosgene (5.7 mg, 0.019 mol) at −78 °C for 1.5 h. The reaction was quenched with *sat*. *aq*. $NaHCO_3$ (1 mL), and the mixture was partitioned between AcOEt and *sat*. *aq*. $NaHCO_3$. The organic phase was washed with H_2O (×2) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude isocyanide **9** as a pale yellow oil. This compound was directly used to the next reaction without further purification.

***Cyclohexyl (2S, 3R)-4-(2,2,2-trichloroethoxycarbonyloxy)-3-isocyano-2-(triisopropylsiloxy)butanoate* (10)**

A mixture of cyclohexyl (2*S*, 3*R*)-3-(formylamino)-4-(2,2,2-trichloroethoxycarbonyloxy)-2-(triisopropyl-siloxy)butanoate (11.5 mg, 0.020 mmol) and NMM (13.4 μL, 0.12 mmol) in CH_2Cl_2 (400 μL) was treated with triphosgene (4.7 mg, 0.016 mmol) at −78 °C for 45 min. The reaction was quenched with *sat*. *aq*. $NaHCO_3$ (1 mL), and the mixture was partitioned between AcOEt and *sat*. *aq*. $NaHCO_3$. The organic phase was washed with H_2O (×2) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ϕ 0.5 × 2 cm, 10% AcOEt/hexane) to afford compound **10** (9.8 mg, 0.018 mmol, 90%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.96 (dddd, 1H, H-1', $J_{1',\ 2'}$ = $J_{1',\ 2'}$ = 9.2, $J_{1',\ 2'}$ = $J_{1',\ 2'}$ = 4.0 Hz), 4.80 (s, 2H, CH_2CCl_3), 4.57 (d, 1H, H-2, $J_{2,\ 3}$ = 3.4 Hz), 4.51 (dd, 1H, H-4, $J_{4,\ 3}$ = 6.9, $J_{4,\ 4}$ = 10.9 Hz), 4.46 (dd, 1H, H-4, $J_{4,\ 3}$ = 5.7, $J_{4,\ 4}$ = 10.9 Hz), 4.23 (ddd, 1H, H-3, $J_{3,\ 2}$ =3.4 Hz, $J_{3,\ 4}$ = 5.7, $J_{3,\ 4}$ = 6.9 Hz), 1.97-1.87 (m, 2H, H-2'), 1.78-1.72 (m, 2H, H-2'), 1.51-1.12 (m, 6H, H-3', H-4'), 1.11-1.03 (m, 21H, ^{i}Pr$_3$Si);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 161.6, 153.4, 94.1, 75.2, 71.2, 70.0, 56.3, 31.7, 31.6, 25.3, 23.9, 18.0, 12.6; IR (neat) ν 2138.67 cm^{-1}; ESIMS-LR *m/z*: $[M+Na]^+$ 580.14; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{23}H_{38}O_6NCl_3NaSi$ 580.1426, found 580.1426; $[\alpha]^{22}_D$ +1.98 (*c* 1.00, $CHCl_3$).

***Boc-D-Ser(O-triisopropylsilyl)-OH* (11)**

A suspension of **24** (1.05 g, 10.0 mmol) and *sat. aq*. $NaHCO_3$ (40 mL) in THF (80 mL) was treated with $(Boc)_2O$ (3.22 mL, 14.0 mmol) at 0 °C for 10 min. The mixture was warmed to room temperature, and stirred for 13 h. Di-*tert*-butyl dicarbonate (0.92 mL, 4.0 mmol) was added to the mixture, which was stirred for 2 h. The mixture was partitioned between hexane and H_2O, and the aqueous phase was saturated with Na_2SO_4. The aqueous phase was acidified with 1 M *aq*. HCl, and extracted with AcOEt. The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude alcohol. A mixture of the crude alcohol and imidazole (4.77 g, 70 mmol) in CH_2Cl_2 (100 mL) was treated with TIPSCl (7.46 mL, 35 mmol) at 0 °C for 10 min. The mixture was warmed to room temperature, and stirred for 4 h. Imidazole (0.68 g, 10 mmol) and TIPSCl (1.07 mL, 5 mmol) was added to the mixture, which was stirred for 2 h. The mixture was concentrated *in vacuo*, and the residue was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with *sat*. *aq*. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude silyl ester. A mixture of the crude silyl ester in THF/MeOH (60 mL/30 mL) was treated with K_2CO_3 (1.93 g, 14 mmol) at room temperature for 30 min. Water (20 mL) was added to the mixture, which was stirred for 1.5 h. The mixture was partitioned between hexane and H_2O. The aqueous phase was extracted with $CHCl_3$/MeOH = 9/1, and the organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was diluted with AcOEt, which was washed with 0.5 M *aq*. HCl/brine = 1/1 and 1 M *aq*. HCl, dried(Na_2SO_4), filtered, and concentrated *in vacuo* to afford **11** (3.46 g, 9.96 mmol, quant. over 3 steps) as a white solid.

mp: 64-65 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.36 (d, 1H, D-Ser-N*H*, $J_{\text{D-Ser-N}H,\ \text{D-Ser-}\alpha\text{-}CH}$ = 9.6 Hz), 4.39 (dd,1H, **D**-Ser-β-C*H*, $J_{\text{D-Ser-}\beta\text{-}CH,\ \text{D-Ser-}\beta\text{-}CH}$ = 10.3, $J_{\text{D-Ser-}\beta\text{-}CH,\ \text{D-Ser-}\alpha\text{-}CH}$ = 9.6 Hz), 4.19 (dd, 1H, **D**-Ser-β-C*H*, $J_{\text{D-Ser-}\beta\text{-}CH,\ \text{D-Ser-}\beta\text{-}CH}$ = 10.3, $J_{\text{D-Ser-}\beta\text{-}CH,\ \text{D-Ser-}\alpha\text{-}CH}$ = 4.0 Hz), 3.91 (dd,1H, **D**-Ser-α-C*H*, $J_{\text{D-Ser-}\alpha\text{-}CH,\ \text{D-Ser-}\beta\text{-}CH}$ = 9.6, $J_{\text{D-Ser-}\alpha\text{-}CH,\ \text{D-Ser-}\beta\text{-}CH}$ = 4.0 Hz), 1.45 (s, 9H, ^{t}Bu), 1.18-0.89 (m, 21H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.0, 155.7, 80.3, 64.0, 55.5, 28.4, 17.9, 11.9; ESIMS-LR *m/z*: $[M-H]^-$ 360.41; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{17}H_{35}O_5NNaSi$ 384.2182, found 384.2199; $[\alpha]^{20}_D$ −33.51 (*c* 0.88, $CHCl_3$).

***Cyclohexyl (2S,3R)-3-{[Boc-D-Ser(O-triisopropylsilyl)-(3S)-3-(triisopropylsiloxy)-Pro]amino}-4-[(2,2,2-trichloroethoxycarboxyl)oxy]-2-triisopropylsiloxybutanoate* (*trans*-13)**

***Cyclohexyl (2S,3R)-3-{[Boc-D-Ser(O-triisopropylsilyl)-(3S)-3-(triisopropylsiloxy)-D-Pro]amino}-4-[(2,2,2-trichloroethoxycarboxyl)oxy]-2-triisopropylsiloxybutanoate* (*cis*-13)**

A solution of **4** (52 mg, 0.24 mmol) and **11** (289 mg, 0.80 mmol) in HFIP (1 mL) was treated with a solution of **10** (88 mg, 0.24 mmol) in HFIP (2 mL) at room temperature for 24 h. The mixture was concentrated *in vacuo*. The residue was purified by high-flash silica gel column chromatography (0-20% acetone/hexane) to afford ***trans*-13** (105 mg, 0.0904 mmol, 57%) as a colorless amorphous and ***cis*-13** (32 mg, 0.028 mmol, 17%) as a colorless amorphous.

Data for ***trans*-13**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (d, 1H, C-3-N*H*, $J_{\text{C-3-N}H,\text{ H-3}}$ = 9.2 Hz), 5.58 (d, 1H, **D**-Ser-N*H*, $J_{\text{D-Ser-N}H,\text{ D-Ser-α-C}H}$ = 8.1 Hz), 4.78-4.69 (m, 1H, H-1'), 4.77 (s, 2H, CH_2CCl_3), 4.67 (br d, 1H, 3-hydroxy-Pro-β-C*H*, $J_{\text{3-hydroxy-Pro-β-C}H,\text{ 3-hydroxy-Pro-γ-C}H}$ = 3.4 Hz), 4.62-4.53 (m, 4H, **D**-Ser-β-C*H*, H-3, H-2), 4.35 (s, 1H, 3-hydroxy-Pro-α-C*H*), 4.25 (d, 2H, H-4, $J_{\text{H-4, H-3}}$ = 6.9 Hz), 3.95 (dd, 1H, **D**-Ser-α-C*H*, $J_{\text{D-Ser-α-C}H,\text{ D-Ser-β-C}H}$ = 4.6, $J_{\text{D-Ser-α-C}H,\text{ D-Ser-β-C}H}$ = 9.8 Hz), 3.82-3.75 (m, 2H, 3-hydroxy-Pro-δ-C*H*), 2.21-2.13 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.94 (dd, 1H, 3-hydroxy-Pro-γ-C*H*, $J_{\text{3-hydroxy-Pro-γ-C}H,\text{ 3-hydroxy-Pro-δ-C}H}$ = 5.7, $J_{\text{3-hydroxy-Pro-γ-C}H,\text{ 3-hydroxy-Pro-γ-C}H}$ = 13.2 Hz), 1.86-1.48 (m, 4H, H-2'), 1.43 (s, 9H, ^{t}Bu), 1.38-1.20 (m, 6H, H-3', H-4'), 1.19-0.95 (m, 63H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 170.4, 169.5, 155.4, 153.5, 94.5, 79.4, 74.1, 73.6, 70.6, 69.6, 65.9, 63.7, 54.3, 50.7, 45.6, 34.1, 31.6, 31.3, 28.5, 25.3, 23.9, 23.8, 18.1, 12.5, 12.1, 12.0; ESIMS-LR *m*/*z*: $[M+Na]^+$ 1184.55; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{53}H_{100}O_{12}N_3Cl_3NaSi_3$ 1182.5573, found 1182.5568; $[\alpha]^{20}_D$ −6.85 (*c* 0.59, $CHCl_3$).

Data for ***cis*-13**: ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of several rotamers at 20 °C, selected data for the major rotamer) δ 6.60 (d, 1H, C-3-N*H*, $J_{\text{C-3-N}H,\text{ H-3}}$ = 7.6 Hz), 5.09 (d, 1H, **D**-Ser-N*H*, $J_{\text{D-Ser-N}H,\text{ D-Ser-α-C}H}$ = 8.6 Hz), 4.85-4.69 (m, 4H, CH_2CCl_3, H-2, H-1'), 4.62-4.52 (m, 2H, 3-hydroxy-Pro-β-C*H*, H-3), 4.49-4.28 (m, 2H, **D**-Ser-β-C*H*), 4.37 (d, 1H, 3-hydroxy-Pro-α-C*H*, $J_{\text{3-hydroxy-Pro-α-C}H,\text{ 3-hydroxy-Pro-β-C}H}$ = 6.9 Hz), 4.25 (d, 1H, H-4, $J_{\text{H-4, H-3}}$ = 6.9 Hz), 4.26 (dd, 1H, H-4, $J_{\text{H-4, H-3}}$ = 5.8, $J_{\text{D-Ser-β-C}H,\text{ D-Ser-β-C}H}$ = 10.3 Hz), 3.99 (dd, 1H, **D**-Ser-α-C*H*, $J_{\text{D-Ser-α-C}H,\text{ D-Ser-β-C}H}$ = 5.3, $J_{\text{D-Ser-α-C}H,\text{ D-Ser-β-C}H}$ = 10.3 Hz), 3.90-3.81 (m, 1H, 3-hydroxy-Pro-δ-C*H*), 3.81-3.68 (m, 1H, H-4, 3-hydroxy-Pro-δ-C*H*), 2.37-2.27 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 2.19-2.11 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.96-1.87 (m, 2H, H-2'), 1.78-1.67 (m, 2H, H-2'), 1.41 (s, 9H, ^{t}Bu), 1.49-1.20 (m, 6H, H-3', H-4'), 1.18-0.97 (m, 63H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 171.1, 170.9, 168.6, 168.1, 167.9, 155.5, 154.6, 153.6, 153.4, 94.5, 89.3, 79.6, 79.2, 79.0, 77.1, 75.2, 74.8, 74.6, 73.7, 73.2, 71.6, 70.3, 70.2, 65.9, 65.3, 64.2, 63.8, 63.1, 60.1, 53.9, 53.5, 51.7, 51.1, 45.0, 44.7, 43.8, 33.3, 32.7, 31.8, 31.8, 31.6, 30.5, 28.5, 28.4, 25.4, 24.2, 24.2, 24.1, 18.2, 18.1, 18.0, 12.5, 12.4, 12.3, 12.2, 12.0, 12.0; ESIMS-LR *m*/*z*: $[M+Na]^+$ 1184.55; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{53}H_{100}O_{12}N_3Cl_3NaSi_3$ 1182.5573, found 1182.5570; $[\alpha]^{20}_D$ +8.48 (*c* 0.59, $CHCl_3$).

***(S)-5-[(Benzyloxycarbonyl)amino]-2-(formylamino)pentyl 2,2,2-trichloroethyl carbonate* (26)**

Alcohol **25** (2.11 g, 6.00 mmol) was treated with 4 M HCl/dioxane (30 mL) at room temperature for 15 min. The mixture was concentrated *in vacuo* to afford a crude amine hydrochloride salt. A solution

of the crude amine hydrochloride salt and Et_3N (904 μL, 6.00 mmol) in THF (30 mL) was treated with *N*-formylsaccharin (1.39 g, 6.60 mmol) at room temperature for 40 min. The reaction was quenched with *sat. aq*. $NaHCO_3$, and the mixture was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude formamide. A mixture of the crude formamide and NMM (1.45 mL) in THF (30 mL) was treated with TrocCl (909 μL, 6.60 mmol) at 0 °C for 10 min. The mixture was partitioned between AcOEt and H_2O. The organic phase was washed with 1 M *aq*. HCl, H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by high-flash silica gel column chromatography (0-1-2% MeOH/$CHCl_3$) to afford **26** (1.67 g, 3.66 mmol, 61% over 3 steps) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (s, 1H, C*H*O), 7.41-7.29 (m, 5H, Ph), 5.97 (d, 1H, N*H*CHO, $J_{NHCHO,\ H\text{-}2}$ = 7.7 Hz), 5.09 (s, 2H, PhCH_2), 4.98-4.89 (m, 1H, C-5-N*H*), 4.77 (s, 2H, CH_2CCl_3), 4.38-4.19 (m, 3H, H-1, H-2), 3.28-3.13 (m, 2H, H-5), 1.68-1.48 (m, 4H, H-3, H-4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.7, 161.5, 156.7, 153.8, 153.7, 136.5, 128.5, 128.1, 127.9, 94.3, 94.2, 76.8, 70.6, 70.0, 66.5, 51.4, 46.7, 40.4, 40.2, 28.2, 27.9, 26.3, 26.1; ESIMS-LR *m/z*: $[M+H]^+$ 455.95; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{22}O_6N_2Cl_3$ 455.0543, found 455.0542; $[\alpha]^{20}_D$ −11.19 (*c* 0.95, $CHCl_3$).

***(S)-5-[(Benzyloxycarbonyl)amino]-2-isocyanopentyl 2,2,2-trichloroethyl carbonate* (19)**

A solution of compound **26** (547 mg, 1.20 mmol) and NMM (793 μL, 7.20 mmol) in CH_2Cl_2 (8 mL) was treated with triphosgene (285 mg, 0.96 mmol) at −78 °C for 30 min. The mixture was partitioned between AcOEt and *sat. aq*. $NaHCO_3$. The organic phase was washed with *sat. aq*. $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by silica gel column chromatography (ϕ 2 cm × 6 cm, 35% AcOEt/hexane) to afford **19** (442 mg, 1.01 mmol, 84%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49-7.22 (m, 5H, Ph), 5.10 (s, 2H, PhCH_2), 4.86-4.72 (m, 3H, CH_2CCl_3, C-5-N*H*), 4.28 (d, 2H, H-1, $J_{1,\ 2}$ = 5.5 Hz), 3.99-3.88 (m, 1H, H-2), 3.33-3.19 (m, 2H, H-5), 1.82-1.64 (m, 4H, H-3, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.8, 156.6, 153.6, 136.5, 128.7, 128.3, 128.2, 94.1, 68.9, 66.9, 53.1, 40.0, 28.3, 26.3; IR (neat) ν 2140.60 cm^{-1}; ESIMS-LR *m/z*: $[M+Na]^+$ 469.07; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{20}O_5N_2Cl_3$ 437.0432, found 437.0429; $[\alpha]^{22}_D$ −0.88 (*c* 1.00, $CHCl_3$).

***Boc-allo-D-Thr(O-triisopropylsilyl)-OBn* (30)**

A suspension of **29** (595 mg, 5.0 mmol) and *sat. aq*. $NaHCO_3$ (7.5 mL) in THF (15 mL) was treated with $(Boc)_2O$ (2.07 mL, 9.0 mmol) at room temperature for 4 d. The mixture was partitioned between hexane and H_2O, and the aqueous phase was saturated with Na_2SO_4. The aqueous phase was acidified with 1 M *aq*. HCl, and extracted with AcOEt. The organic phase was dried (Na_2SO_4), filtered, and

concentrated *in vacuo* to afford a crude carboxylic acid. A solution of the crude carboxylic acid and K_2CO_3 (828 mg, 6.0 mmol) in DMF (25 mL) was treated with BnBr (713 μL, 6.0 mmol) at room temperature for 24 h. The mixture was partitioned between AcOEt and H_2O. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude alcohol. A solution of the crude alcohol and 2,6-lutidine (1.16 mL, 10.0 mmol) in CH_2Cl_2 (25 mL) was treated with TIPSOTf (1.48 mL, 5.5 mmol) at −78 °C. Then the mixture was warmed to −50 °C, and stirred for 190 min. The reaction was quenched with MeOH (2 mL), and partitioned between AcOEt and *sat. aq*. $NaHCO_3$. The organic phase was washed with 1 M *aq*. HCl, *sat. aq*. $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by high-flash silica gel column chromatography (3-20% AcOEt/hexane) to afford **30** (1.93 g, 4.14 mmol, 83% over 3 steps) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.29 (m, 5H, Ph), 5.37 (d, 1H, *allo*-**D**-Thr-N*H*, $J_{allo\text{-D-Thr-N}H,\ allo\text{-D-Thr-}\alpha\text{-C}H}$ = 8.0 Hz), 5.23 (d, 1H, PhC*H*, $J_{\text{PhC}H,\ \text{PhC}H}$ = 12.1 Hz), 5.15 (d, 1H, PhC*H*, $J_{\text{PhC}H,\ \text{PhC}H}$ = 12.1 Hz), 4.36-4.28 (m, 2H , *allo*-D-Thr-α-C*H*, *allo*-**D**-Thr-β-C*H*), 1.43 (s, 9H, ^{t}Bu), 1.25 (d, 3H, *allo*- D-Thr-γ-C*H*, $J_{allo\text{-D-Thr-}\gamma\text{-C}H,\ allo\text{-D-Thr-}\gamma\text{-C}H}$ = 6.3 Hz), 1.08-1.01 (m, 21H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 155.4, 135.6, 128.6, 128.4, 79.8, 70.3, 67.0, 60.1, 28.4, 20.7, 18.1, 18.1, 12.6; ESIMS-LR *m*/*z*: $[M+H]^+$ 466.40; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{25}H_{44}O_5NSi$ 466.2989, found 466.3006; $[\alpha]^{20}_D$ −20.10 (*c* 0.75, $CHCl_3$).

***(R)-(3-Hydroxy-14-methylpentadecanyl)-allo-D-Thr(O-triisopropylsilyl)-OBn* (36)**

Compound **30** (373 mg, 0.80 mmol) was treated with 25% TFA/CH_2Cl_2 (8 mL) at room temperature for 10 min. The reaction was quenched with *sat. aq*. $NaHCO_3$, and the mixture was partitioned between AcOEt and H_2O. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford crude amine **23**. A solution of the crude amine **23**, **35** (218 mg, 0.80 mmol), $NaHCO_3$ (202 mg, 2.40 mmol) and HOAt (327 mg, 2.40 mmol) in CH_2Cl_2 (8.0 mL) was treated with EDCI (460 mg, 2.40 mmol) at room temperature for 60 min. The mixture was partitioned between AcOEt and *sat. aq*. $NaHCO_3$, and the organic phase was washed with 1 M *aq*. HCl, H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by high-flash silica gel column chromatography (30% AcOEt/hexane) to afford **36** (425 mg, 0.69 mmol, 86%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.31 (m, 5H, Ph), 6.57 (d, 1H, *allo*-**D**-Thr-N*H*, $J_{allo\text{-D-Thr-N}H,\ allo\text{-D-Thr-}\alpha\text{-C}H}$ = 7.7 Hz), 5.24 (d, 1H, PhC*H*, $J_{\text{PhC}H,\ \text{PhC}H}$ = 12.0 Hz), 5.15 (d, 1H, PhC*H*, $J_{\text{PhC}H,\ \text{PhC}H}$ = 12.0 Hz), 4.62 (dd, 1H, *allo*-D-Thr-α-C*H*, $J_{allo\text{-D-Thr-}\alpha\text{-C}H,\ allo\text{-D-Thr-N}H}$ = 7.8, $J_{allo\text{-D-Thr-}\alpha\text{-C}H,\ allo\text{-D-Thr-}\beta\text{-C}H}$ = 2.8 Hz), 4.31 (dq, 1H, *allo*-D-Thr-β-C*H*, $J_{allo\text{-D-Thr-}\beta\text{-C}H,\ allo\text{-D-Thr-}\alpha\text{-C}H}$ = 2.8, $J_{allo\text{-D-Thr-}\beta\text{-C}H,\ allo\text{-D-Thr-}\gamma\text{-C}H}$ = 6.4 Hz), 3.98-3.88 (m, 1H, H-3), 3.50 (d, 1H, O*H*, $J_{OH,\ 3}$ = 3.2 Hz), 2.37 (dd, 1H, H-2, $J_{2,\ 2}$ = 15.1, $J_{2,\ 3}$ = 2.8 Hz),

2.30 (dd, 1H, H-2, $J_{2,2}$ = 15.1, $J_{2,3}$ = 8.7 Hz), 1.58-1.46 (m, 1H, H-14), 1.46-1.37 (m, 2H, H-4), 1.34-1.21 (m, 18H, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 1.28 (d, 3H, *allo*-D-Thr-γ- C*H*, $J_{allo\text{-D-Thr-}\gamma\text{-C}H,\ allo\text{-D-Thr-}\beta\text{-C}H}$ = 6.4 Hz), 1.07-0.98 (m, 21H, ^{i}Pr$_3$Si), 0.86 (d, 6H, H-15, $J_{15,14}$ = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 169.8, 135.3, 128.7, 128.5, 70.0, 68.8, 67.3, 58.7, 42.9, 39.1, 37.0, 30.0, 29.8, 29.8, 29.7, 29.6, 28.1, 27.5, 25.6, 22.8, 20.7, 18.1, 18.1; ESIMS-LR *m*/*z*: $[M+Na]^+$ 642.45; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{36}H_{65}O_5NNaSi$ 642.4524, found 642.4535; $[\alpha]^{20}_D$ −24.20 (*c* 0.49, $CHCl_3$).

***(R)-(3-Hydroxy-14-methylpentadecanyl)-allo-D-Thr(O-triisopropylsilyl)-OH* (18)**

A mixture of **36** (298 mg, 0.48 mmol) and 10% Pd/C (30 mg) in MeOH (8 mL) was vigorously stirred at room temperature for 5 h under H_2 atmosphere. The catalyst was filtered through a Celite pad, and the filtrate was concentrated *in vacuo* to afford **18** (254 mg, 0.48 mmol, 99%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.87 (d, 1H, *allo*-**D**-Thr-N*H*, $J_{allo\text{-D-Thr-N}H,\ allo\text{-D-Thr-}\alpha\text{-C}H}$ = 8.2 Hz), 4.59 (dd, 1H, *allo*-D-Thr-α-C*H*, $J_{allo\text{-D-Thr-}\alpha\text{-C}H,\ allo\text{-D-Thr-N}H}$ = 7.7, $J_{allo\text{-D-Thr-}\alpha\text{-C}H,\ allo\text{-D-Thr-}\beta\text{-C}H}$ = 3.6 Hz), 4.38 (dq, 1H, *allo*-D-Thr-β-C*H*, $J_{allo\text{-D-Thr-}\beta\text{-C}H,\ allo\text{-D-Thr-}\alpha\text{-C}H}$ = 3.6, $J_{allo\text{-D-Thr-}\beta\text{-C}H,\ allo\text{-D-Thr-}\gamma\text{-C}H}$ = 6.3 Hz), 4.05-3.96 (m, 1H, H-3), 2.40 (dd, 1H, H-2, $J_{2,2}$ = 15.1, $J_{2,3}$ = 3.2 Hz), 2.34 (dd, 1H, H-2, $J_{2,2}$ = 15.1, $J_{2,3}$ = 9.7 Hz), 1.59-1.45 (m, 1H, H-14), 1.28 (d, 3H, *allo*-**D**-Thr-γ- C*H*, $J_{allo\text{-D-Thr-}\gamma\text{-C}H,\ allo\text{-D-Thr-}\beta\text{-C}H}$ = 6.3 Hz), 1.35-1.18 (m, 20H, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 1.09-1.00 (m, 21H, ^{i}Pr$_3$Si), 0.85 (d, 6H, H-15, $J_{15,14}$ = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2, 172.7, 69.1, 69.0, 58.7, 43.4, 39.2, 36.9, 30.1, 29.9, 29.8, 29.8, 29.8, 29.7, 28.1, 27.5, 25.7, 22.8, 20.1, 19.1, 18.1, 18.1, 17.8, 12.5, 12.4; ESIMS-LR *m*/*z*: $[M+Na]^+$ 552.41; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{29}H_{59}O_5NNaSi$ 552.4055, found 552.4070; $[\alpha]^{20}_D$ −35.94 (*c* 0.45, $CHCl_3$).

***Cyclohexyl (2S,3R)-3-{[Boc-D-Ser(O-triisopropylsilyl)-(3S)-3-(triisopropylsiloxy)-Pro]amino}-4-hydroxy-2-triisopropylsiloxybutanoate* (37)**

***Cyclohexyl (2S,3R)-3-{[Boc-D-Ser(O-triisopropylsilyl)-(3S)-3-(triisopropylsiloxy)-Pro]amino}-4-[(2,2-dichloroethoxycarboxyl)oxy]-2-triisopropylsiloxybutanoate* (38)**

A mixture of ***trans*-13** (7.1 mg, 0.0061 mmol) in THF (50 μL) was treated with 0.1 M solution of SmI_2 in THF (300 μL, 0.03 mmol) at room temperature and stirred for 1 min. The reaction was quenched with air, and the mixture was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with 1 M *aq*. HCl, *sat*. *aq*. $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ϕ 0.5 cm×2 cm, 5-15% AcOEt/hexane) to afford **37** (3.4 mg, 0.0034 mmol, 50 %) as a colorless oil and **38** (3.8 mg, 0.0034 mmol, 50%) as a colorless oil.

Data for **37**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (d, 1H, C-3-N*H*, $J_{C\text{-}3\text{-}NH,\ 3}$ = 8.7 Hz), 5.49 (d, 1H, **D**-Ser-N*H*, $J_{D\text{-}Ser\text{-}NH,\ D\text{-}Ser\text{-}\alpha\text{-}CH}$ = 6.4 Hz), 4.79-4.68 (m, 1H, H-1'), 4.64 (d, 1H, 3-hydroxy-Pro-β-C*H*, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\beta\text{-}CH,\ 3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH}$ = 2.8 Hz), 4.54-4.46 (m, 2H, H-2, D-Ser-α-C*H*), 4.40 (s, 1H, 3-hydroxy-Pro-α-C*H*), 4.31-4.23 (m, 1H, H-3), 3.93 (dd, 1H, **D**-Ser-β-C*H*, $J_{D\text{-}Ser\text{-}\beta\text{-}CH,\ D\text{-}Ser\text{-}\alpha\text{-}CH}$ = 5.0, $J_{D\text{-}Ser\text{-}\beta\text{-}CH,\ D\text{-}Ser\text{-}\beta\text{-}CH}$ = 10.1 Hz), 3.85-3.73 (m, 4H, H-4, **D**-Ser-β-C*H*, 3-hydroxy-Pro-δ-C*H*), 3.73-3.64 (m, 1H, H-4), 2.50 (t, 1H, O*H*, $J_{OH,\ 4}$ = 6.9 Hz), 2.29-2.15 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.97 (dd, 1H, 3-hydroxy-Pro-γ-C*H*, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH,\ 3\text{-}hydroxy\text{-}Pro\text{-}\delta\text{-}CH}$ = 5.8, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH,\ 3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH}$ = 12.8 Hz), 1.89-1.65 (m, 2H, H-2'), 1.64-1.19 (m, 6H, H-3', H-4'), 1.42 (s, 9H, ^{t}Bu), 1.18-0.94 (m, 63H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 170.1, 169.1, 155.7, 79.7, 74.1, 74.0, 71.3, 70.3, 63.3, 61.7, 54.9, 54.4, 45.6, 34.0, 31.6, 31.5, 28.5, 25.4, 23.9, 18.1, 12.4, 12.1, 12.0; ESIMS-LR *m/z*: $[M+Na]^+$ 1008.65; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{50}H_{99}O_{10}N_3NaSi_3$ 1008.6531, found 1008.6542; $[\alpha]^{20}_D$ −6.32 (*c* 0.30, $CHCl_3$).

Data for **38**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (d, 1H, C-3-N*H*, $J_{C\text{-}3\text{-}NH,\ 3}$ = 9.2 Hz), 5.86 (dd, 1H, H-3'', $J_{3'',\ 2''}$ = $J_{3'',\ 2''}$ = 6.3 Hz), 5.58 (d, 1H, **D**-Ser-N*H*, $J_{D\text{-}Ser\text{-}NH,\ D\text{-}Ser\text{-}\alpha\text{-}CH}$ = 8.0 Hz), 4.76-4.69 (m, 1H, H-1'), 4.67 (d, 1H, 3-hydroxy-Pro-β-C*H*, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\beta\text{-}CH,\ 3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH}$ = 3.5 Hz), 4.60-4.52 (m, 4H, **D**-Ser-β-C*H*, H-2, H-3), 4.50 (dd, 1H, H-2'', $J_{2'',\ 3''}$ = 6.3, $J_{3'',\ 3''}$ = 7.5 Hz), 4.47 (dd, 1H, H-2'', $J_{2'',\ 3''}$ = 6.3, $J_{3'',\ 3''}$ = 7.5 Hz), 4.35 (s, 1H, 3-hydroxy-Pro-α-C*H*), 4.21 (d, 2H, H-4 $J_{4,\ 3}$ = 6.9 Hz), 3.95 (dd, 1H, **D**-Ser-α-C*H*, $J_{D\text{-}Ser\text{-}\alpha\text{-}CH,\ D\text{-}Ser\text{-}\beta\text{-}CH}$ = 4.6, $J_{D\text{-}Ser\text{-}\alpha\text{-}CH,\ D\text{-}Ser\text{-}\beta\text{-}CH}$ = 9.8 Hz), 3.84-3.75 (m, 2H, H-4, 3-hydroxy-Pro-δ-C*H*), 2.21-2.11 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.94 (dd, 1H, 3-hydroxy-Pro-γ-C*H*, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH,\ 3\text{-}hydroxy\text{-}Pro\text{-}\delta\text{-}CH}$ = 5.8, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH,\ 3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH}$ = 12.6 Hz), 1.89-1.64 (m, 2H, H-2'), 1.52-1.20 (m, 15H, H-3', H-4',^{t}Bu), 1.20-0.82 (m, 63H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 170.8, 170.4, 169.4, 155.4, 79.4, 74.0, 73.6, 71.4, 70.7, 69.6, 68.0, 65.8, 65.1, 63.7, 55.1, 54.4, 34.1, 31.6, 31.3, 29.8, 28.5, 28.1, 25.3, 23.8, 18.3, 18.1, 12.5, 12.1, 12.0; ESIMS-LR *m/z*: $[M+Na]^+$ 1148.60; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{53}H_{101}O_{12}N_3Cl_2NaSi_3$ 1148.5962, found 1148.5975; $[\alpha]^{20}_D$ −9.84 (*c* 0.69, $CHCl_3$).

***Boc-D-Ser(O-triisopropylsilyl)-(3S)-3-(triisopropylsiloxy)-Pro-(3S)-3-(triisopropylsiloxy)-Asp(O-cyclohexyl)-Oallyl* (39)**

A solution of **37** (151 mg, 0.153 mmol) in THF (2 mL) was treated with Dess-Martin periodinane (1.27 g, 3.0 mmol) at room temperature for 55 min. The reaction was quenched with *sat. aq*. $Na_2S_2O_3$/*sat. aq*. $NaHCO_3$ = 1/1, and the mixture was partitioned between AcOEt and H_2O. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude aldehyde. A solution of the crude aldehyde, $NaH_2PO_4 \cdot 2H_2O$ (70.2 mg, 0.45 mmol) and 2-methylbut-2-ene (100 μL) in THF/^{t}BuOH/H_2O (900 μL/900 μL/150 μL) was treated with a solution of $NaClO_2$ (40.7 mg, 0.45 mmol) in H_2O (150 μL) at room temperature for 50 min. The mixture was partitioned between

AcOEt and 1 M *aq*. HCl. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude carboxylic acid. A solution of the crude carboxylic acid and Cs_2CO_3 (78.2 mg, 0.24 mmol) in DMF (1.5 mL) was treated with allyl bromide (18.2 μL, 0.21 mmol) at room temperature for 16 h. The mixture was partitioned between AcOEt and H_2O. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by high-flash silica gel column chromatography (50% AcOEt/hexane) to afford **39** (83.5 mg, 0.080 mmol, 53% over 3 steps) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz, a mixture of several rotamers at 20 °C, selected data for the major rotamer) δ 7.33 (d, 1H, β-hydroxy-Asp-N*H*, $J_{\beta\text{-hydroxy-Asp-N}H,\ \beta\text{-hydroxy-Asp-}\alpha\text{-C}H}$ = 9.2 Hz), 5.89 (dddd, 1H, H_c, $J_{Hc,\ Ha}$ = 17.2, $J_{Hc,\ Hb}$ = 10.3, $J_{Hc,\ 1}$ = $J_{Hc,\ 1}$ = 5.7 Hz), 5.53 (d, 1H, **D**-Ser-N*H*, $J_{\text{D-Ser-N}H,\ \text{D-Ser-}\alpha\text{-C}H}$ = 8.6 Hz), 5.32 (d, 1H, H_a, $J_{Ha,\ Hc}$ = 17.2 Hz), 5.24 (d, 1H, H_b, $J_{Hb,\ Hc}$ = 10.3 Hz), 5.00 (br d, 1H, β-hydroxy-Asp-α-C*H*, $J_{\beta\text{-hydroxy-Asp-}\alpha\text{-C}H,\ \beta\text{-hydroxy-Asp-N}H}$ = 9.2 Hz), 4.94 (br s, 1H, β-hydroxy-Asp-β-C*H*), 4.76-4.68 (m, 1H, H-1'), 4.69 (d, 1H, 3-hydroxy-Pro-β-C*H*, $J_{\text{3-hydroxy-Pro-}\beta\text{-C}H,\ \text{3-hydroxy-Pro-}\alpha\text{-C}H}$ = 2.9 Hz), 4.64-4.54 (m, 3H, **D**-Ser-α-C*H*, H-1), 4.41 (s, 1H, 3-hydroxy-Pro-α-C*H*), 3.94 (dd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\ \text{3-hydroxy-Pro-}\delta\text{-C}H}$ = 9.7, $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\ \text{3-hydroxy-Pro-}\gamma\text{-C}H}$ = 6.3 Hz), 3.84-3.75 (m, 2H, **D**-Ser-β-C*H*), 3.69 (dd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\ \text{3-hydroxy-Pro-}\delta\text{-C}H}$ = 9.7, $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\ \text{3-hydroxy-Pro-}\gamma\text{-C}H}$ = 9.2 Hz), 2.21-2.11 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.94 (dd, 1H, 3-hydroxy-Pro-γ-C*H*, $J_{\text{3-hydroxy-Pro-}\gamma\text{-C}H,\ \text{3-hydroxy-Pro-}\gamma\text{-C}H}$ = 12.6, $J_{\text{3-hydroxy-Pro-}\gamma\text{-C}H,\ \text{3-hydroxy-Pro-}\delta\text{-C}H}$ = 5.7 Hz), 1.83-1.60 (m, 4H, H-2'), 1.52-1.17 (m, 15H, ^{t}Bu, H-3', H-4'), 1.13-0.83 (m, 63H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 169.8, 169.5, 168.8, 155.2, 131.5, 119.2, 79.2, 74.2, 73.4, 72.7, 69.6, 66.6, 64.1, 55.8, 54.2, 45.6, 34.2, 31.6, 31.2, 28.5, 25.3, 23.8, 23.7, 18.1, 18.0, 18.0, 12.5, 12.1, 12.0; ESIMS-LR *m/z*: $[M+Na]^+$ 1062.67; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{53}H_{101}O_{11}N_3NaSi_3$1062.6636, found 1062.6665; $[\alpha]^{20}_D$ −10.20 (*c* 0.68, $CHCl_3$).

***(2S)-5-[(Benzyloxycarbonyl)amino]-2-[(Boc-D-Ala-(3S)-3-(triisopropylsiloxy)-Pro)amino]pentyl 2,2,2-trichloroethyl carbonate* (*trans*-40)**

***(2S)-5-[(Benzyloxycarbonyl)amino]-2-[(Boc-D-Ala-(3S)-3-(triisopropylsiloxy)-D-Pro)amino]pentyl 2,2,2-trichloroethyl carbonate* (*cis*-40)**

A solution of **4** (771 mg, 3.19 mmol) and **20** (1.61 mg, 8.52 mmol) in HFIP (25 mL) was treated with a solution of **19** (932 mg, 2.13 mmol) in HFIP (10 mL) at room temperature for 19.5 h. The mixture was concentrated *in vacuo*, and the mixture was partitioned between AcOEt and *sat. aq*. $NaHCO_3$. The organic phase was washed with *sat. aq*. $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by high-flash silica gel column

chromatography (5-25% acetone/hexane) to afford ***trans*-40** (794 mg, 0.91 mmol, 43%) as a colorless oil and ***cis*-40** (666 mg, 0.77 mmol, 36%) as a colorless oil.

Data for ***trans*-40**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.28 (m, 5H, Ph), 6.96 (d, 1H, 3-hydroxy-Pro-N*H*, $J_{\text{3-hydroxy-Pro-N}H,\text{ H-2}}$ = 8.7 Hz), 5.30 (br s, 1H, C-5-N*H*), 5.16 (d, 1H, **D**-Ala-N*H*, $J_{\text{D-Ala-N}H,\text{ D-Ala-}\alpha\text{-C}H}$ = 6.8 Hz), 5.11 (d, 1H, PhC*H*, $J_{\text{PhC}H,\text{ PhC}H}$ = 12.2 Hz), 5.06 (d, 1H, PhC*H*, $J_{\text{PhC}H,\text{ PhC}H}$ = 12.2 Hz), 4.79 (d, 1H, Cl_3CCH, $J_{\text{Cl3CC}H,\text{ Cl3CC}H}$ = 11.9 Hz), 4.75 (d, 1H, Cl_3CCH, $J_{\text{Cl3CC}H,\text{ Cl3CC}H}$ = 11.9 Hz), 4.78-4.70 (m, 1H, 3-hydroxy-Pro-β-C*H*), 4.41 (s, 1H, 3-hydroxy-Pro-α-C*H*), 4.36 (dq, 1H, D-Ala-α-C*H*, $J_{\text{D-Ala-}\alpha\text{-C}H,\text{ D-Ala-N}H}$ = 6.8, $J_{\text{D-Ala-}\alpha\text{-C}H,\text{ D-Ala-}\beta\text{-C}H}$ = 6.9 Hz), 4.22-4.12 (m, 2H, H-1), 4.11-3.99 (m, 1H, H-2), 3.81 (dd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\text{ 3-hydroxy-Pro-}\delta\text{-C}H}$ = $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\text{ 3-hydroxy-Pro-}\gamma\text{-C}H}$ = 8.7 Hz), 3.63 (ddd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\text{ 3-hydroxy-Pro-}\delta\text{-C}H}$ = $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\text{ 3-hydroxy-Pro-}\gamma\text{-C}H}$ = $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\text{ 3-hydroxy-Pro-}\gamma\text{-C}H}$ = 8.7 Hz), 3.27-3.12 (m, 2H, H-5), 2.22-2.07 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.97 (dd, 1H, 3-hydroxy-Pro-γ-C*H*, $J_{\text{3-hydroxy-Pro-}\gamma\text{-C}H,\text{ 3-hydroxy-Pro-}\gamma\text{-C}H}$ = 12.8, $J_{\text{3-hydroxy-Pro-}\gamma\text{-C}H,\text{ 3-hydroxy-Pro-}\delta\text{-C}H}$ = 8.7 Hz), 1.71-1.45 (m, 4H, H-3, H-4), 1.41 (s, 9H, ^{t}Bu), 1.24 (d, 3H, **D**-Ala-β-C*H*, $J_{\text{D-Ala-}\beta\text{-C}H,\text{ D-Ala-}\alpha\text{-C}H}$ = 6.9 Hz), 1.16-0.94 (m, 21H, $^i\underline{\text{Pr}}_3$Si); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 169.5, 156.6, 155.7, 153.9, 136.7, 128.6, 128.3, 128.2, 94.5, 80.2, 77.0, 73.3, 69.9, 69.6, 66.7, 48.3, 48.2, 45.3, 40.6, 33.9, 28.5, 18.0, 16.2, 18.0, 17.1, 12.0; ESIMS-LR *m*/*z*: $[M+Na]^+$ 889.32; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{38}H_{61}O_{10}N_4Cl_3NaSi$ 889.3115, found 889.3136; $[\alpha]^{20}_D$ −2.53 (*c* 4.57, $CHCl_3$).

Data for ***cis*-40**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.24 (m, 5H, Ph), 6.02 (d, 1H, 3-hydroxy-Pro-N*H*, $J_{\text{3-hydroxy-Pro-N}H,\text{ H-2}}$ = 8.7 Hz), 5.66-5.57 (m, 1H, C-5-N*H*), 5.40 (d, 1H, **D**-Ala-N*H*, $J_{\text{D-Ala-N}H,\text{ D-Ala-}\alpha\text{-C}H}$ = 8.2 Hz), 5.15 (d, 1H, PhC*H*, $J_{\text{PhC}H,\text{ PhC}H}$ = 12.4 Hz), 5.05 (d, 1H, PhC*H*, $J_{\text{PhC}H,\text{ PhC}H}$ = 12.4 Hz), 4.77 (d, 1H, Cl_3CCH, $J_{\text{Cl3CC}H,\text{ Cl3CC}H}$ = 11.9 Hz), 4.72 (d, 1H, Cl_3CCH, $J_{\text{Cl3CC}H,\text{ Cl3CC}H}$ = 11.9 Hz), 4.73-4.66 (m, 1H, 3-hydroxy-Pro-β-C*H*), 4.46 (d, 1H, 3-hydroxy-Pro-α-C*H*, $J_{\text{3-hydroxy-Pro-}\alpha\text{-C}H,\text{ 3-hydroxy-Pro-}\beta\text{-C}H}$ = 5.5 Hz), 4.48-4.42 (m, 1H, D-Ala-α-C*H*), 4.30 (dd, 1H, H-1, $J_{1,\,1}$ = 11.0, $J_{1,\,2}$ = 2.8 Hz), 4.25-4.10 (m, 2H, H-1, H-2), 3.84-3.64 (m, 2H, 3-hydroxy-Pro-δ-C*H*), 3.24-3.13 (m, 2H, H-5), 2.16-2.00 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.70-1.47 (m, 4H, H-3, H-4), 1.41 (s, 9H, ^{t}Bu), 1.27 (d, 3H, **D**-Ala-β-C*H*, $J_{\text{D-Ala-}\beta\text{-C}H,\text{ D-Ala-}\alpha\text{-C}H}$ = 6.9 Hz), 1.13-0.97 (m, 21H, $^i\underline{\text{Pr}}_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 167.6, 156.6, 155.5, 153.9, 136.8, 128.5, 128.4, 128.1, 128.0, 127.8, 94.3, 80.0, 76.8, 76.3, 71.7, 70.8, 66.6, 65.6, 48.2, 47.8, 45.2, 40.6, 34.1, 29.7, 28.5, 25.5, 18.2, 18.1, 18.0, 12.3, 12.1; ESIMS-LR *m*/*z*: $[M+Na]^+$ 889.31; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{38}H_{61}O_{10}N_4Cl_3NaSi$ 889.3115, found 889.3127; $[\alpha]^{20}_D$ −19.12 (*c* 0.52, $CHCl_3$).

***N*-[(*S*)-4-Azide-1-(hydroxymethyl)butyl]-[(Boc-D-Ala-(3*S*)-3-(triisopropylsiloxy)-Pro)]amide (41)**

A mixture of compound ***trans*-40** (495 mg, 0.57 mmol) and metallic Sm (85.7 mg, 0.57 mmol) in MeOH (15 mL) was treated with I_2 (145 mg, 0.57 mmol) at room temperature for 110 min. The reaction

was quenched with *sat. aq.* $Na_2S_2O_3$. The mixture was partitioned between Et_2O and *sat. aq*. $NaHCO_3$. The organic phase was washed with 1 M *aq*. HCl and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude alcohol. A mixture of the crude alcohol and Pd black (46 mg) in 5% AcOH/MeOH (10 mL) was vigorously stirred at room temperature for 3.5 h under H_2 atmosphere. The catalyst was filtered through a Celite pad, and the filtrate was concentrated *in vacuo* to afford a crude aminoalcohol. A mixture of the crude aminoalcohol, K_2CO_3 (394 mg, 2.85 mmol) and $CuSO_4 \cdot 5H_2O$ (1.4 mg, 0.006 mmol) in MeOH (10 mL) was treated with imidazole-1-sulfonyl azide hydrogen sulfate (464 mg, 1.71 mmol) at room temperature for 10.5 h. The mixture was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by high-flash silica gel column chromatography (5-25% acetone/hexane) to afford **41** (292 mg, 0.50 mmol, 88% over 3 steps) as a white amorphous.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.70 (d, 1H, 3-hydroxy-Pro-N*H*, $J_{\text{3-hydroxy-Pro-N}H,\ \text{H-2}}$ = 8.6 Hz), 5.04 (d, 1H, D-Ala-N*H*, $J_{\text{D-Ala-N}H,\ \text{D-Ala-α-C}H}$ = 5.7 Hz), 4.76 (br s, 1H, 3-hydroxy-Pro-β-C*H*), 4.51 (s, 1H, 3-hydroxy-Pro-α-C*H*), 4.34 (dq, 1H, **D**-Ala-α-C*H*, $J_{\text{D-Ala-α-C}H,\ \text{D-Ala-N}H}$ = 5.7, $J_{\text{D-Ala-α-C}H,\ \text{D-Ala-β-C}H}$ = 6.9 Hz), 3.96-3.88 (m, 1H, 3-hydroxy-Pro-δ-C*H*), 3.88-3.81 (m, 1H, H-2), 3.72 (ddd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{\text{3-hydroxy-Pro-δ-C}H,\ \text{3-hydroxy-Pro-δ-C}H}$ = $J_{\text{3-hydroxy-Pro-δ-C}H,\ \text{3-hydroxy-Pro-γ-C}H}$ = $J_{\text{3-hydroxy-Pro-δ-C}H,\ \text{3-hydroxy-Pro-γ-C}H}$ = 8.6 Hz), 3.68-3.61 (m, 1H, H-1), 3.55-3.47 (m, 1H, H-1), 3.34-3.23 (m, 2H, H-5), 3.08 (br s, 1H, O*H*), 2.07-1.99 (m, 2H, 3-hydroxy-Pro-γ-C*H*), 1.66-1.54 (m, 4H, H-3, H-4), 1.44 (s, 9H, ^{t}Bu), 1.31 (d, 3H, **D**-Ala-β-C*H*, $J_{\text{D-Ala-β-C}H,\ \text{D-Ala-α-C}H}$ = 6.9 Hz), 1.16-1.02 (m, 21H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 169.3, 156.1, 80.4, 73.8, 70.2, 64.6, 51.8, 51.3, 48.5, 45.3, 33.8, 28.5, 28.0, 25.7, 18.0, 16.5, 12.1; ESIMS-LR *m/z*: $[M+H]^+$ 585.48; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{27}H_{53}O_6N_6Si$ 585.3796, found 585.3823; $[\alpha]^{20}_D$ −13.90 (*c* 2.60, $CHCl_3$).

***H-(3S)-3-(triisopropylsiloxy)-Asp(O-cyclohexyl)-OAllyl* (21)**

A solution of **28** (20.6 mg, 0.039 mmol) in CH_2Cl_2 (300 μL) was treated with TFA (100 μL) at room temperature for 15 min. The reaction was quenched with *sat. aq*. $NaHCO_3$, and the mixture was partitioned between AcOEt and *sat. aq*. $NaHCO_3$. The organic phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **21**. The amine was directly used to the next reaction without further purification.

***(2S)-5-Azide-2-[Boc-D-Ala-(3S)-3-(triisopropylsiloxy)-Pro]amino-N-[(3R)-3-(triisopropylsiloxy)-D-Asp(O-cyclohexyl)-Oallyl]pentanamide* (17)**

A solution of **41** (23.0 mg, 0.039 mmol) in THF (500 μL) was treated with Dess-Martin periodinane (33.1 mg, 0.078 mmol) at room temperature for 130 min. The reaction was quenched with *sat. aq.* $Na_2S_2O_3$/*sat*. *aq*. $NaHCO_3$ = 1/1, and the mixture was partitioned between AcOEt and H_2O. The organic

phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude aldehyde. A solution of the crude aldehyde, $NaH_2PO_4 \cdot 2H_2O$ (18.3 mg, 0.12 mmol) and 2-methylbut-2-ene (50 μL) in THF/^{t}BuOH/H_2O (600 μL/600 μL/100 μL) was treated with a solution of $NaClO_2$ (18.3 mg, 0.12 mmol) in H_2O (100 μL) at room temperature for 130 min. The mixture was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford crude carboxylic acid **42**. A mixture of the crude carboxylic acid **42**, amine **21** (0.039 mmol), $NaHCO_3$ (9.8 mg, 0.12 mmol) and HOAt (15.9 mg, 0.12 mmol) in CH_2Cl_2 (400 μL) was treated with EDCI (22.4 mg, 0.12 mmol) at room temperature for 140 min. The mixture was partitioned between AcOEt and *sat. aq*. $NaHCO_3$. The organic phase was washed with 1 M *aq*. HCl, *sat. aq*. $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by high-flash silica gel column chromatography (40% AcOEt/hexane) to afford **17** (17.2 mg, 0.17 mmol, 44% over 3 steps) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz, a mixture of several rotamers at 20 °C, selected data for the major rotamer) δ 7.32 (d, 1H, Orn-α-N*H*, $J_{\text{Orn-α-N}H,\ \text{Orn-α-C}H}$ = 8.2 Hz), 6.90 (d, 1H, β-hydroxy-Asp-N*H*, $J_{\text{β-hydroxy-Asp-N}H,\ \text{β-hydroxy-Asp-α-C}H}$ = 9.6 Hz), 5.92 (dddd, 1H, H_c, $J_{Hc,\ Ha}$ = 17.9, $J_{Hc,\ Hb}$ = 11.0, $J_{Hc,\ H\text{-}1}$ = $J_{Hc,\ 1}$ = 5.9 Hz), 5.34 (dd, 1H, H_a, $J_{Ha,\ Hc}$ = 17.9, $J_{Ha,\ 1}$ = 1.4 Hz), 5.36-5.31 (m, 1H, D-Ala-N*H*), 5.26 (dd, 1H, H_b, $J_{Hb,\ Hc}$ = 11.0, $J_{Hb,\ H\text{-}1}$ = 1.4 Hz), 5.02 (dd, 1H, β-hydroxy-Asp-α-C*H*, $J_{\text{β-hydroxy-Asp-α-C}H,\ \text{β-hydroxy-Asp-N}H}$ = 9.6, $J_{\text{β-hydroxy-Asp-α-C}H,\ \text{β-hydroxy-Asp-β-C}H}$ = 1.8 Hz), 4.93 (d, 1H, β-hydroxy-Asp-β-C*H*, $J_{\text{β-hydroxy-Asp-β-C}H,\ \text{β-hydroxy-Asp-α-C}H}$ = 1.8 Hz), 4.78-4.70 (m, 2H, H-1', 3-hydroxy-Pro-β-C*H*), 4.67 (dddd, 1H, H-1, $J_{1,\ 1}$ = 13.3, $J_{1,\ Hc}$ = 5.9, $J_{1,\ Hb}$ = $J_{1,\ Ha}$ = 1.4 Hz), 4.56 (dddd, 1H, H-1, $J_{1,\ 1}$ = 13.3, $J_{1,\ Hc}$ = 5.9, $J_{1,\ Hb}$ = $J_{1,\ Ha}$ = 1.4 Hz), 4.47 (dq, 1H, **D**-Ala-α-C*H*, $J_{\text{D-Ala-α-C}H,\ \text{D-Ala-N}H}$ = $J_{\text{D-Ala-α-C}H,\ \text{D-Ala-β-C}H}$ = 6.9 Hz), 4.40 (s, 1H, 3-hydroxy-Pro-α-C*H*), 4.34 (ddd, Orn-α-C*H*, $J_{\text{Orn-α-C}H,\ \text{Orn-α-N}H}$ = 8.2, $J_{\text{Orn-α-C}H,\ \text{Orn-β-C}H}$ = $J_{\text{Orn-α-C}H,\ \text{Orn-β-C}H}$ = 9.6 Hz), 3.80 (dd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{\text{3-hydroxy-Pro-δ-C}H,\ \text{3-hydroxy-Pro-δ-C}H}$ = $J_{\text{3-hydroxy-Pro-δ-C}H,\ \text{3-hydroxy-Pro-γ-C}H}$ = 9.6 Hz), 3.68 (m, 1H, 3-hydroxy-Pro-δ-C*H*), 3.29 (ddd, 1H, Orn-δ-C*H*, $J_{\text{Orn-δ-C}H,\ \text{Orn-δ-C}H}$ = 9.2, $J_{\text{Orn-δ-C}H,\ \text{Orn-γ-C}H}$ = $J_{\text{Orn-δ-C}H,\ \text{Orn-γ-C}H}$ = 5.0 Hz), 3.26 (ddd, 1H, Orn-δ-C*H*, $J_{\text{Orn-δ-C}H,\ \text{Orn-δ-C}H}$ = 9.2, $J_{\text{Orn-δ-C}H,\ \text{Orn-γ-C}H}$ = $J_{\text{Orn-δ-C}H,\ \text{Orn-γ-C}H}$ = 5.0 Hz), 2.31-2.16 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 2.04-1.95 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.95-1.78 (m, 4H, Orn-β-C*H*, H-2'), 1.76-1.62 (m, 4H, Orn-γ-C*H*, H-2'), 1.43 (s, 9H, ^{t}Bu), 1.47-1.18 (m, 6H, H-3', H-4'), 1.30 (d, 3H, **D**-Ala-β-C*H*, $J_{\text{D-Ala-β-C}H,\ \text{D-Ala-α-C}H}$ = 6.9 Hz), 1.17-0.95 (m, 42H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 170.6, 169.8, 169.6, 168.7, 155.4, 131.5, 119.3, 79.8, 74.4, 73.1, 72.7, 69.3, 66.6, 55.9, 52.7, 51.0, 48.1, 45.2, 34.0, 31.7, 31.4, 28.8, 28.4, 25.3, 24.8, 23.9, 23.9, 18.0, 18.0, 17.9, 12.5, 12.1; ESIMS-LR *m/z*: $[M+Na]^+$ 1030.61; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{49}H_{89}O_{11}N_7NaSi_2$ 1030.6051, found 1030.6079; $[\alpha]^{20}_D$ −18.03 (*c* 1.72, $CHCl_3$).

(2S)-5-Azide-2-{[(3R)-3-hydroxy-14-methylpentadecanoyl]-allo-D-Thr(O-triisopropylsiloxy)-Boc-D-Ala-(3S)-3-(triisopropylsiloxy)-Pro}amino-N-[(3R)-3-(triisopropylsiloxy)-D-Asp(O-cyclohexyl)-Oallyl]pentanamide **(44)**

A mixture of **17** (195 mg, 0.193 mmol) in CH_2Cl_2 (1.5 mL) was treated with TFA (500 μL) at room temperature for 35 min. The reaction was quenched with *sat. aq*. $NaHCO_3$, and the mixture was partitioned between AcOEt and *sat. aq*. $NaHCO_3$. The organic phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford crude amine **43**. A mixture of the crude amine **43**, **18** (112.5 mg, 0.212 mmol), $NaHCO_3$ (53.4 mg, 0.636 mmol) and HOAt (86.6 mg, 0.636 mmol) in CH_2Cl_2 (2 mL) was treated with EDCI (121.9 mg, 0.636 mmol) at room temperature for 20 h. The mixture was partitioned between AcOEt and *sat. aq.* $NaHCO_3$. The organic phase was washed with 1 M *aq*. HCl, *sat. aq*. $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The residue was purified by high-flash silica gel column chromatography (40% AcOEt/hexane) to afford **44** (173 mg, 0.122 mmol, 63% over 2 steps) as a white amorphous.

^{1}H NMR ($CDCl_3$, 500 MHz, a mixture of several rotamers at 20 °C, selected data for the major rotamer) δ 7.46 (d, 1H, **D**-Ala-N*H*, $J_{\text{D-Ala-N}H,\text{ D-Ala-α-C}H}$ = 7.4 Hz), 7.22 (Orn-α-N*H*, $J_{\text{Orn-N}H,\text{ Orn-α-C}H}$ = 8.2 Hz), 6.84 (d, 1H, **D**-β-hydroxy-Asp-N*H*, $J_{\text{D-β-hydroxy-Asp-N}H,\text{ D-β-hydroxy-Asp-α-C}H}$ = 9.6 Hz), 6.52 (d, 1H, *allo*-**D**-Thr-N*H*, $J_{\textit{allo}\text{-D-Thr-N}H,\ \textit{allo}\text{-D-Thr-α-C}H}$ = 6.9 Hz), 5.92 (dddd, 1H, H_c, $J_{Hc,\ Ha}$ = 17.4, $J_{Hc,\ Hb}$ = 11.0, $J_{Hc,\ 1'}$ = $J_{Hc,\ 1'}$ = 6.0 Hz), 5.33 (d, 1H, H_a, $J_{Ha,\ Hc}$ = 17.4 Hz), 5.25 (d, 1H, H_b, $J_{Hb,\ Hc}$ = 11.0 Hz), 5.01 (dd, 1H, **D**-β-hydroxy-Asp-α-C*H*, $J_{\text{D-β-hydroxy-Asp-α-C}H,\text{ D-β-hydroxy-Asp-N}H}$ = 9.6, $J_{\text{D-β-hydroxy-Asp-α-C}H,\text{ D-β-hydroxy-Asp-β-C}H}$ = 1.8 Hz), 4.78-4.61 (m, 4H, *allo*- **D**-Thr-α-C*H*, 3-hydroxy-Pro-β-C*H*, H-1', H-1''), 4.56 (dd, 1H, $J_{1',\ 1'}$ = 13.3, $J_{1',\ Hc}$ = 6.0 Hz), 4.49-4.40 (m, 2H, **D**-Ala-α-C*H*, *allo*-**D**-Thr-β-C*H*), 4.35 (ddd, 1H, Orn-α-C*H*, $J_{\text{Orn-α-C}H,\text{ Orn-α-N}H}$ = 8.2, $J_{\text{Orn-α-C}H,\text{ Orn-β-C}H}$ = $J_{\text{Orn-α-C}H,\text{ Orn-β-C}H}$ = 7.3 Hz), 4.30 (s, 1H, 3-hydroxy-Pro-α-C*H*), 4.08-3.98 (m, 1H, H-3), 3.86-3.78 (m, 1H, 3-hydroxy-Pro-δ-C*H*), 3.64 (ddd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{\text{3-hydroxy-Pro-δ-C}H,\text{ 3-hydroxy-Pro-δ-C}H}$ = $J_{\text{3-hydroxy-Pro-δ-C}H,\text{ 3-hydroxy-Pro-γ-C}H}$ = $J_{\text{3-hydroxy-Pro-δ-C}H,\text{ 3-hydroxy-Pro-γ-C}H}$ = 9.6 Hz), 3.34 (ddd, 1H, Orn-δ-C*H*, $J_{\text{Orn-δ-C}H,\text{ Orn-δ-C}H}$ = 12.8, $J_{\text{Orn-δ-C}H,\text{ Orn-γ-C}H}$ = $J_{\text{Orn-δ-C}H,\text{ Orn-γ-C}H}$ = 6.9 Hz), 3.28 (ddd, 1H, Orn-δ-C*H*, $J_{\text{Orn-δ-C}H,\text{ Orn-δ-C}H}$ = 12.8, $J_{\text{Orn-δ-C}H,\text{ Orn-γ-C}H}$ = $J_{\text{Orn-δ-C}H,\text{ Orn-γ-C}H}$ = 6.9 Hz), 2.38 (dd, 1H, H-2, $J_{2,\ 2}$ = 13.7, $J_{2,\ 3}$ = 2.8 Hz), 2.28-2.09 (m, 2H, 3-hydroxy-Pro-γ-C*H*, H-2''), 2.01-1.66 (m, 6H, Orn-β-C*H*, Orn-γ-C*H*, H-2''), 1.63-1.18 (m, 38H, **D**-Ala-β-C*H*, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-3'', H-4'', ^{t}Bu), 1.18-0.93 (m, 63H, ^{i}Pr$_3$Si), 0.85 (d, 6H, H-15, $J_{\text{H-15,\ H-14}}$ = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 172.4, 170.9, 169.8, 169.7, 169.5, 168.8, 131.5, 119.4, 74.6, 73.7, 72.8, 69.6, 69.5, 68.4, 66.8, 59.4, 55.9, 52.8, 47.0, 45.4, 43.9, 39.2, 28.1, 34.1, 31.8, 31.6, 30.1, 30.0, 29.9, 29.8, 29.1, 28.1, 27.6, 25.5, 25.4, 24.9, 24.0, 22.8, 19.6, 18.2, 18.2, 18.1, 18.0, 17.3, 12.6, 12.6, 12.1; ESIMS-LR

m/z: $[M+Na]^+$ 1441.96; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{73}H_{138}O_{13}N_8NaSi_3$ 1441.9583, found 1441.9631; $[\alpha]^{20}_D$ −17.02 (*c* 0.67, $CHCl_3$).

[(3R)-3-Hydroxy-14-methylpentadecanoyl]-allo-D-Thr(O-triisopropylsiloxy)-Boc-D-Ala-(3S)-3-(triisopropylsiloxy)-Pro-Arg(Cbz)$_2$-(3R)-3-(triisopropylsiloxy)-D-Asp(O-cyclohexyl)-Oallyl **(45)**

A solution of **44** (143.6 mg, 0.101 mmol) and morpholine (35.2 μL, 0.404 mmol) in THF (2 mL) was treated with $Pd(PPh_3)_4$ (3.5 mg, 0.003 mmol) at room temperature for 30 min. The mixture was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The catalyst was removed by SH-silica gel column chromatography (ϕ 1 cm × 4 cm, 1% MeOH/$CHCl_3$), and the filtrate was concentrated *in vacuo* to afford a crude carboxylic acid. A mixture of the crude carboxylic acid and Pd black (28 mg) in 50% AcOH/MeOH (2 mL) was vigorously stirred at room temperature for 3.5 h under H_2 atmosphere. The catalyst was filtered through a Celite pad, and the filtrate was concentrated *in vacuo* to afford a crude amine. A suspension of the crude amine and Et_3N (41.8 μL, 0.30 mmol) in CH_2Cl_2 (1 mL) was treated with *N*, *N'*-diBoc-*N''*-triflylguanidine (58.7 mg, 0.15 mmol) at room temperature for 17.5 h. The mixture was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by high-flash silica gel column chromatography (1% MeOH/$CHCl_3$) to afford **45** (118 mg, 0.074 mmol, 73% over 3 steps) as a white amorphous.

^{1}H NMR ($CDCl_3$, 500 MHz, a mixture of several rotamers at 20 °C, selected data for the major rotamer) δ 11.47 (br s, 1H, Arg-ω-N*H*), 10.61 (br s, 1H, Arg-δ-N*H*), 8.29 (m, 1H, *allo*-**D**-Thr-N*H*), 7.91 (br s, 1H, Arg-α-N*H*), 7.69 (d, 1H, **D**-β-hydroxy-Asp-N*H*, $J_{\text{D-β-hydroxy-Asp-N}H,\ \text{D-β-hydroxy-Asp-α-C}H}$ = 10.1 Hz), 7.44 (d, 1H, **D**-Ala-N*H*, $J_{\text{D-Ala-N}H,\ \text{D-Ala-α-C}H}$ = 8.2 Hz), 5.22-5.18 (m, 1H, **D**-β-hydroxy-Asp-α-C*H*), 4.82-4.62 (m, 4H, **D**-β-hydroxy-Asp-β-C*H*, *allo*-**D**-Thr-α-C*H*, 3-hydroxy-Pro-β-C*H*, H-1'), 4.58-4.14 (m, 5H, **D**-Ala-α-C*H*, *allo*-**D**-Thr-β-C*H*, Arg-α-C*H*, 3-hydroxy-Pro-α-C*H*, C-3-O*H*), 4.02-3.91 (m, 1H, H-3), 3.79-3.64 (m, 2H, 3-hydroxy-Pro-δ-C*H*), 3.52-3.24 (m, 2H, Arg-δ-C*H*), 2.45 (dd, 1H, H-2, $J_{2,\,2}$ = 15.6, $J_{2,\,3}$ = 2.7 Hz), 2.30 (dd, 1H, H-2, $J_{2,\,2}$ = 15.6, $J_{2,\,3}$ = 9.2 Hz), 2.13-1.64 (m, 12H, H-4, H-2', 3-hydroxy-Pro-γ-C*H*, Arg-β-C*H*, Arg-γ-C*H*), 1.50 (s, 9H, ^{t}Bu), 1.48 (s, 9H, ^{t}Bu), 1.61-1.20 (m, 39H, *allo*-**D**-Thr-γ-C*H*, **D**-Ala-β-C*H*, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-3', H-4'), 1.20-0.95 (m, 63H, ^{i}Pr$_3$Si), 0.85 (d, 6H, H-15, $J_{15,\,14}$ = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8, 173.1, 171.4, 170.4, 170.3, 169.1, 163.6, 156.3, 153.3, 132.2, 128.7, 122.3, 118.4, 83.2, 79.4, 74.5, 74.2, 72.4, 70.4, 69.5, 68.7, 59.5, 56.3, 53.0, 47.7, 45.5, 44.1, 40.7, 39.2, 37.7, 33.7, 31.6, 31.4, 30.1, 30.0, 29.9, 29.8, 29.8, 28.4, 28.2, 28.1, 28.0, 27.6, 26.0, 25.6, 25.4, 23.9, 22.8, 19.7, 18.4, 18.2, 18.2, 18.1, 16.1, 13.0, 12.6,

12.5, 12.1; ESIMS-LR *m/z*: $[M+H]^+$ 1596.09; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{81}H_{155}O_{17}N_8Si_3$ 1596.0813, found 1596.0860; $[\alpha]^{20}_D$ −15.30 (*c* 1.55, $CHCl_3$).

(R)-3-Hydroxytridec-12-enoic acid

A mixture of **22** (105 mg, 0.50 mmol) in THF (2 mL) was treated with a solution of NaOH (22 mg, 0.55 mmol) in H_2O (2 mL) at room temperature for 40 min. The mixture was partitioned between 1 M *aq.* HCl and AcOEt, and the organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was recrystalized from hexane to afford (*R*)-3-hydroxytridec-12-enoic acid (83 mg, 0.36 mmol, 73%) as a white solid.

mp 55-56 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) 5.81 (dddd, 1H, H-12, $J_{12, Hb}$ = 17.4, $J_{H\text{-}12, Ha}$ = 10.5, $J_{12, 11}$ = $J_{12, 11}$ = 6.9 Hz), 4.99 (d, 1H, H_b, $J_{Hb, 12}$ = 17.4 Hz), 4.93 (d, 1H, H_a, $J_{Ha, 12}$ = 10.5 Hz), 4.08-3.98 (m, 1H, H-3), 2.58 (dd,1H, H-2, $J_{2, 2}$ = 16.5, $J_{2, 3}$ = 3.2 Hz), 2.48 (dd,1H, H-2, $J_{2, 2}$ = 16.5, $J_{2, 3}$ = 8.7 Hz), 2.03 (ddd, 2H, H-11, $J_{11, 10}$ = $J_{11, 10}$ = $J_{11, 12}$ = 6.9 Hz), 1.61-1.24 (m, 14H, H-4, H-5, H-6, H-7, H-8, H-9, H-10); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.2, 139.3, 114.3, 68.1, 41.2, 36.6, 33.9, 29.6, 29.6, 29.5, 29.2, 29.0, 25.6; ESIMS-LR *m/z*: $[M+H]^+$ 229.18; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{25}O_3$ 229.1804, found 229.1822; $[\alpha]^{20}_D$ −14.56 (*c* 0.53, $CHCl_3$).

***Allyl (R)-3-hydroxytridec-12-enoate* (48)**

A suspension of (*R*)-3-hydroxytridec-12-enoic acid (114 mg, 0.50 mmol) and Cs_2CO_3 (195 mg, 0.60 mmol) in DMF (5 mL) was treated with allyl bromide (51.8 μL, 0.60 mmol) at room temperature for 3 h. The mixture was partitioned between AcOEt and H_2O, and the organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by high-flash silica gel column chromatography (20% Et_2O/hexane) to afford allyl (*R*)-3-hydroxytridec-12-enoate (70.5 mg, 0.26 mmol, 53%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (dddd, 1H, H_c, $J_{Hc, Ha}$ = 17.2, $J_{Hc, Hb}$ = 10.9, $J_{Hc, H\text{-}1'}$ = $J_{Hc, H\text{-}1'}$ = 5.7 Hz), 5.79 (dddd, 1H, H-12, $J_{12, Hd}$ = 17.4, $J_{12, He}$ = 10.4, $J_{12, 11}$ = $J_{12, 11}$ = 6.3 Hz), 5.31 (d, 1H, H_a, $J_{Ha, Hc}$ = 17.2 Hz), 5.24 (d, 1H, H_b, $J_{Hb, Hc}$ = 10.3 Hz), 4.97 (ddd, 1H, H_d, $J_{Hd, 12}$ = 17.4, $J_{Hd, 11}$ = 3.5, $J_{Hd, 11}$ = 1.7 Hz), 4.91 (d, 1H, H_e, $J_{He, 12}$ = 10.4 Hz), 4.60 (d, 2H, H-1', $J_{1', Hc}$ = 5.7 Hz), 4.03-3.96 (m, 1H, H-3), 2.91 (s, 1H, O*H*), 2.52 (dd, 1H, H-2, $J_{2, 2}$ = 16.6, $J_{2, 3}$ = 3.5 Hz), 2.42 (dd, 1H, H-2, $J_{2, 2}$ = 16.6, $J_{2, 3}$ = 9.2 Hz), 2.02 (ddd, 2H, H-11, $J_{11, 12}$ = $J_{11, 10}$ = 6.3, $J_{11, 10}$ = 6.9 Hz), 1.55-1.47 (m, 2H, H-4), 1.46-1.23 (m, 12H, H-5, H-6, H-7, H-8, H-9, H-10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 139.3, 132.0, 118.7, 114.2, 68.1, 65.4, 41.4, 36.6, 33.9, 29.6, 29.5, 29.2, 29.0, 25.6; ESIMS-LR *m/z*: $[M+Na]^+$ 291.11; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{29}O_3$ 269.2117, found 269.2131; $[\alpha]^{20}_D$ −15.40 (*c* 0.50, $CHCl_3$).

***Boc-D-Ser(O-triisopropylsilyl)-(3S)-3-(triisopropylsiloxy)-Pro-(3S)-3-(triisopropylsiloxy)-Asp(O-cyclohexyl)-OH* (47)**

A solution of **37** (87.9 mg, 0.089 mmol) in THF (3 mL) was treated with Dess-Martin periodinane (945 mg, 2.23 mmol) at room temperature for 60 min. The reaction was quenched with *sat. aq*. $Na_2S_2O_3$/*sat. aq*. $NaHCO_3$ = 1/1, and the mixture was partitioned between AcOEt and H_2O. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude aldehyde. A solution of the crude aldehyde, $NaH_2PO_4 \cdot 2H_2O$ (41.7 mg, 0.27 mmol) and 2-methylbut-2-ene (50 μL) in THF/^{t}BuOH/H_2O (450 μL/450 μL/100 μL) was treated with a solution of $NaClO_2$ (24.1 mg, 0.27 mmol) in H_2O (50 μL) at room temperature for 50 min. The mixture was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by high-flash silica gel column chromatography (0-1-2% MeOH/$CHCl_3$) to afford Boc-**D**-Ser(*O*-triisopropylsilyl)-(3*S*)-3-(triisopropylsiloxy)-Pro-(3*S*)-3-(triisopropylsiloxy)-Asp(*O*-cyclohexyl)-OH (52.6 mg, 0.053 mmol, 59% over 2 steps) as a colorless amorphous.

^{1}H NMR ($CDCl_3$, 500 MHz, a mixture of several rotamers at 20 °C, selected data for the major rotamer) δ 7.18 (d, 1H, β-hydroxy-Asp-N*H*, $J_{\beta\text{-hydroxy-Asp-N}H,\ \beta\text{-hydroxy-Asp-}\alpha\text{-C}H}$ = 6.9 Hz), 5.55 (d, 1H, D-Ser-N*H*, $J_{\text{D-Ser-N}H,\ \text{D-Ser-}\alpha\text{-C}H}$ = 8.1 Hz), 4.99-4.90 (m, 2H, β-hydroxy-Asp-α-C*H*, β-hydroxy-Asp-β-C*H*), 4.78-4.71 (m, 1H, H-1), 4.67-4.58 (m, 2H, **D**-Ser-α-C*H*, 3-hydroxy-Pro-β-C*H*), 4.37 (s, 1H, 3-hydroxy-Pro-α-C*H*), 3.94 (dd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\ \text{3-hydroxy-Pro-}\delta\text{-C}H}$ = 9.8, $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\ \text{3-hydroxy-Pro-}\gamma\text{-C}H}$ = 6.3 Hz), 3.88-3.80 (m, 2H, **D**-Ser-β-C*H*), 3.77 (dd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\ \text{3-hydroxy-Pro-}\delta\text{-C}H}$ = 9.8, $J_{\text{3-hydroxy-Pro-}\delta\text{-C}H,\ \text{3-hydroxy-Pro-}\gamma\text{-C}H}$ = 8.6 Hz), 2.21-2.11 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.98 (dd, 1H, 3-hydroxy-Pro-γ-C*H*, $J_{\text{3-hydroxy-Pro-}\gamma\text{-C}H,\ \text{3-hydroxy-Pro-}\gamma\text{-C}H}$ = 13.2, $J_{\text{3-hydroxy-Pro-}\gamma\text{-C}H,\ \text{3-hydroxy-Pro-}\delta\text{-C}H}$ = 6.3 Hz), 1.87-1.63 (m, 4H, H-2), 1.57-1.19 (m, 6H, H-3, H-4), 1.19-0.88 (m, 63H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 169.7, 155.3, 79.6, 74.5, 73.8, 72.3, 63.9, 55.6, 54.4, 45.9, 34.4, 31.5, 31.3, 28.5, 25.3, 23.8, 34.4, 31.5, 31.3, 28.5, 25.3, 23.8, 18.1, 18.0, 12.4, 12.1, 12.0; ESIMS-LR *m*/*z*: $[M+Na]^+$ 1022.63; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{50}H_{97}O_{11}N_3NaSi_3$ 1022.6323, found 1022.6338; $[\alpha]^{20}_D$ –4.19 (*c* 0.43, $CHCl_3$).

***Cyclohexyl 1-[(allyloxycarbonyl)methyl]undec-10-enyl 2-[Boc-D-Ser(O-triisopropylsilyl)-(3S)-3-(triisopropylsiloxy)-Pro]aminobutendioate* (50)**

A solution of **47** (5.0 mg, 0.0050 mmol), **48** (2.0 mg, 0.0075 mmol) and DMAP (0.61 mg, 0.0050 mmol) in CH_2Cl_2 (50 μL) was treated with EDCI (1.0 mg, 0.0050 mmol) at room temperature for 130 mim. The mixture was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (25% Et_2O/hexane), PTLC (25% Et_2O/hexane), and flash silica

gel column chromatography (ϕ 0.5 cm×1.5 cm, 25% Et_2O/hexane) to afford **50** (2.1 mg, 0.0020 mmol, 39%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.91 (dddd, H_C, $J_{Hc, Ha}$ = 17.2, $J_{Hc, Hb}$ = 10.9, $J_{Hc, H\text{-}1'}$ = $J_{Hc, H\text{-}1'}$ = 5.8 Hz), 5.80 (dddd, H-12, $J_{12, Hd}$ = 17.2, $J_{12, H3}$ = 10.3, $J_{12, 11}$ = $J_{12, 11}$ = 6.3 Hz), 5.66 (**D**-Ser-N*H*, $J_{D\text{-}Ser\text{-}NH, D\text{-}Ser\text{-}\alpha\text{-}CH}$ = 8.6 Hz), 5.52 (s, 1H, dehydro-Asp-β-C*H*), 5.38-5.30 (m, 1H, H-3), 5.31 (dd, 1H, H_a, $J_{Ha, Hc}$ = 17.2 Hz), 5.24 (d, 1H, H_b, $J_{Hb, Hc}$ = 10.9 Hz), 4.99 (dd, 1H, H_d, $J_{Hd, 12}$ = 17.2 Hz), 4.92 (d, 1H, H_e, $J_{He, 12}$ = 10.3 Hz), 4.88-4.81 (m, 1H, H-1"), 4.72-4.64 (m, 2H, **D**-Ser-α-C*H*, 3-hydroxy-Pro-β-C*H*), 4.58 (d, 2H, H-1', $J_{1', Hc}$ = 5.8 Hz), 4.50 (s, 1H, 3-hydroxy-Pro-α-C*H*), 3.98 (dd, 1H, **D**-Ser-β-C*H*, $J_{D\text{-}Ser\text{-}\beta\text{-}CH, D\text{-}Ser\text{-}\beta\text{-}CH}$ = 9.8, $J_{D\text{-}Ser\text{-}\beta\text{-}CH, D\text{-}Ser\text{-}\alpha\text{-}CH}$ = 8.0 Hz), 3.89-3.76 (m, 3H, **D**-Ser-β-C*H*, 3-hydroxy-Pro-δ-C*H*), 2.72 (dd, 1H, H-2, $J_{2, 2}$ = 15.7, $J_{2, 3}$ = 6.8 Hz), 2.59 (dd, 1H, H-2, $J_{2, 2}$ = 15.7, $J_{2, 3}$ = 5.7 Hz), 2.20-2.11 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 2.07-1.95 (m, 3H, 3-hydroxy-Pro-γ-C*H*, H-11), 1.81 (m, 2H, H-2"), 1.71 (m, 2H, H-2"), 1.50-1.18 (m, 20H, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-3", H-4"), 1.14-0.94 (m, 42H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 155.4, 139.4, 132.1, 118.7, 114.3, 79.6, 73.9, 73.4, 73.4, 73.0, 72.3, 69.9, 65.6, 54.1, 45.5, 39.2, 38.8, 34.4, 34.0, 33.8, 32.1, 31.6, 29.8, 29.6, 29.5, 29.4, 29.2, 29.1, 28.5, 25.4, 25.1, 24.9, 23.7, 22.8, 18.1, 18.1, 14.3, 12.1, 12.0; ESIMS-LR *m/z*: $[M+Na]^+$ 1098.68; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{57}H_{101}O_{12}N_3NaSi_2$ 1098.6816, found 1098.6824; $[\alpha]^{20}_D$ −1.66 (*c* 0.18, $CHCl_3$).

2-[Boc-D-Ser(OBn)-(3S)-3-(triisopropylsiloxy)-Pro]aminophenyl acetate (trans-60)

2-[Boc-D-Ser(OBn)-(3S)-3-(triisopropylsiloxy)-D-Pro]aminophenyl acetate (cis-60)

A solution of **4** (241 mg, 1.00 mmol) and **58** (443 mg, 1.50 mmol) in HFIP (2 mL) was treated with a solution of **59** (242 mg, 1.50 mmol) in HFIP (3 mL) at room temperature for 2 h. The mixture was concentrated *in vacuo*, and the residue was purified by high-flash silica gel column chromatography (0-5-10-40% AcOEt/hexane) to afford ***trans*-60** (167 mg, 0.22 mmol, 22%) as a yellow oil and ***cis*-60** (489 mg, 0.64 mmol, 64%) as a colorless foam.

Data for ***trans*-60**: ^{1}H NMR ($CDCl_3$, 500 MHz, a mixture of several rotamers at 20 °C, selected data for the major rotamer) δ 9.44 (s, 1H, Ar-N*H*), 8.24 (d, 1H, H-6, $J_{6, 5}$ = 8.1 Hz), 7.38-7.24 (m, 5H, Ph), 7.18 (ddd, 1H, H-5, $J_{5, 6}$ = 8.1, $J_{5, 4}$ = 5.7, $J_{5, 3}$ = 2.9 Hz), 7.10-7.04 (m, 2H, H-3, H-4), 5.23 (d, 1H, **D**-Ser-N*H*, $J_{D\text{-}Ser\text{-}NH, D\text{-}Ser\text{-}\alpha\text{-}CH}$ = 8.1 Hz), 4.97 (d, 1H, 3-hydroxy-Pro-β-C*H*, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\beta\text{-}CH, 3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH}$ = 2.9 Hz), 4.75 (ddd, 1H, **D**-Ser-α-C*H*, $J_{D\text{-}Ser\text{-}\alpha\text{-}CH, D\text{-}Ser\text{-}NH}$ = 8.1, $J_{D\text{-}Ser\text{-}\alpha\text{-}CH, D\text{-}Ser\text{-}\beta\text{-}CH}$ = $J_{D\text{-}Ser\text{-}\alpha\text{-}CH, D\text{-}Ser\text{-}\beta\text{-}CH}$ = 6.3 Hz), 4.63 (s, 1H, 3-hydroxy-Pro-α-C*H*), 4.54 (s, 2H, PhC*H*), 3.89 (ddd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\delta\text{-}CH, 3\text{-}hydroxy\text{-}Pro\text{-}\delta\text{-}CH}$ = 10.1, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\delta\text{-}CH, 3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH}$ = 6.9, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\delta\text{-}CH, 3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH}$ = 5.8 Hz), 3.83 (dd, 1H, 3-hydroxy-Pro-δ-C*H*, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\delta\text{-}CH, 3\text{-}hydroxy\text{-}Pro\text{-}\delta\text{-}CH}$ = 10.1, $J_{3\text{-}hydroxy\text{-}Pro\text{-}\delta\text{-}CH, 3\text{-}hydroxy\text{-}Pro\text{-}\gamma\text{-}CH}$ = 9.2 Hz), 3.67-3.59 (m, 2H, **D**-Ser-β-C*H*), 2.46 (s, 3H, CH_3), 2.30-2.21 (m, 1H, 3-hydroxy-Pro-

γ-C*H*), 2.03 (dd, 1H, 3-hydroxy-Pro-γ-C*H*, $J_{\text{3-hydroxy-Pro-γ-C}H,\ \text{3-hydroxy-Pro-γ-C}H}$ = 12.6, $J_{\text{3-hydroxy-Pro-γ-C}H,\ \text{3-hydroxy-Pro-δ-C}H}$ = 5.8 Hz), 1.38 (s, 9H, ^{t}Bu), 1.13-1.00 (m, 21H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0, 169.3, 167.7, 155.3, 140.1, 137.6, 130.6, 128.6, 127.9, 127.7, 126.3, 124.3 ,122.3, 121.9, 80.3, 73.4, 72.5, 69.9, 69.7, 52.3, 45.9, 34.0, 28.3, 21.2, 18.1, 12.1; ESIMS-LR *m/z*: $[M+Na]^+$ 720.37; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{37}H_{55}O_8N_3NaSi$ 720.3651, found 720.3651; $[\alpha]^{20}_D$ –40.50 (*c* 0.53, $CHCl_3$).

Data for ***cis*-60**: ^{1}H NMR ($CDCl_3$, 500 MHz, a mixture of several rotamers at 20 °C, selected data for the major rotamer) δ 7.94 (d, 1H, H-6, $J_{6,\ 5}$ = 7.5 Hz), 7.67 (s, 1H, Ar-N*H*), 7.31-7.21 (m, 5H, Ph), 7.18-7.05 (m, 3H, H-3, H-4, H-5), 5.31 (d, 1H, **D**-Ser-N*H*, $J_{\text{D-Ser-N}H,\ \text{D-Ser-α-C}H}$ = 8.6 Hz), 4.72 (m, 2H, 3-hydroxy-Pro-β-C*H*, **D**-Ser-α-C*H*), 4.62 (d, 1H, 3-hydroxy-Pro-α-C*H*, $J_{\text{3-hydroxy-Pro-α-C}H,\ \text{3-hydroxy-Pro-β-C}H}$ = 6.9 Hz), 4.52 (d, 1H, PhC*H*, $J_{\text{PhC}H,\ \text{PhC}H}$ = 12.0 Hz), 4.52 (d, 1H, PhC*H*, $J_{\text{PhC}H,\ \text{PhC}H}$ = 12.0 Hz), 3.97-3.90 (m, 1H, 3-hydroxy-Pro-δ-C*H*), 3.82-3.72 (m, 1H, 3-hydroxy-Pro-δ-C*H*), 3.69-3.61 (m, 2H, **D**-Ser-β-C*H*), 2.34 (s, 3H, CH_3), 2.37-2.28 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 2.19-2.11 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.43 (s, 9H, ^{t}Bu), 1.13-0.94 (m, 21H, ^{i}Pr$_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 168.8, 166.4, 155.4, 141.6, 137.5, 129.6, 128.5, 127.9, 127.8, 127.7, 126.1, 125.0, 123.6, 122.2, 80.1, 73.4, 71.9, 70.4, 65.0, 54.5, 45.3, 33.5, 28.4, 28.1, 21.2, 18.0, 17.9, 12.2; ESIMS-LR *m/z*: $[M+Na]^+$ 720.37; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{37}H_{55}O_8N_3NaSi$ 720.3651, found 720.3655; $[\alpha]^{20}_D$ +8.98 (*c* 1.07, $CHCl_3$).

***Boc-D-Ser(OBn)-(3S)-3-(triisopropylsiloxy)-Pro-Oallyl* (62)**

A solution of ***trans*-60** (98.6 mg, 0.129 mmol) in MeOH was treated with $SmCl_3 \cdot 6H_2O$ (94.1 mg, 0.258 mmol) at room temperature for 48 h. The mixture was concentrated *in vacuo*, and the residue was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude phenol. A mixture of the crude phenol in CH_2Cl_2 (1.3 mL) was treated with 1,1'-carbonyldiimidazole (105 mg, 0.65 mmol) at room temperature for 40 min. Allyl alcohol (175 μL, 2.6 mmol) and DMAP (15.8 mg, 0.129 mmol) was added to the mixture, which was stirred for 250 min. The mixture was partitioned between AcOEt and 1 M *aq*. HCl. The organic phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by high-flash silica gel column chromatography (3-13-20% AcOEt/hexane) to afford **62** (58.0 mg, 0.096 mmol, 74% over 2 steps) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.22 (m, 5H, Ph), 5.23 (d, 1H, **D**-Ser-N*H*, $J_{\text{D-Ser-N}H,\ \text{D-Ser-α-C}H}$ = 8.1 Hz), 5.89 (dddd, 1H, H_c, $J_{\text{Hc, Ha}}$ = 17.2, $J_{\text{Hc, Hb}}$ = 10.9, $J_{\text{Hc, 1}} = J_{\text{Hc, 1}}$ = 5.2 Hz), 5.40 (d, 1H, **D**-Ser-N*H*, $J_{\text{D-Ser-N}H,\ \text{D-Ser-α-C}H}$ = 8.1 Hz), 5.35 (dd, 1H, H_a, $J_{\text{Ha, Hc}}$ = 17.2, $J_{\text{Ha, H-1}}$ = 1.8 Hz), 5.22 (dd, 1H, H_a, $J_{\text{Ha, Hc}}$ = 10.9, $J_{\text{Ha, H-1}}$ = 1.2 Hz), 4.75 (ddd, 1H, **D**-Ser-α-C*H*, $J_{\text{D-Ser-α-C}H,\ \text{D-Ser-N}H}$ = 8.1, $J_{\text{D-Ser-α-C}H,\ \text{D-Ser-β-C}H}$ = 5.2,

$J_{\text{D-Ser-α-C}H,\ \text{D-Ser-β-C}H}$ = 6.9 Hz), 4.68-4.58 (m, 2H, 3-hydroxy-Pro-β-C*H*, H-1), 4.56-4.46 (m, 3H, H-1, PhC*H*), 4.44 (s, 1H, 3-hydroxy-Pro-α-C*H*), 3.92-3.83 (m, 2H, 3-hydroxy-Pro-δ-C*H*), 3.65 (dd, 1H, **D**-Ser-β-C*H*, $J_{\text{D-Ser-β-C}H,\ \text{D-Ser-β-C}H}$ = 9.2, $J_{\text{D-Ser-β-C}H,\ \text{D-Ser-α-C}H}$ = 5.2 Hz), 3.59 (dd, 1H, **D**-Ser-β-C*H*, $J_{\text{D-Ser-β-C}H,\ \text{D-Ser-β-C}H}$ = 9.2, $J_{\text{D-Ser-β-C}H,\ \text{D-Ser-α-C}H}$ = 6.9 Hz), 2.17-2.08 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.98-1.91 (m, 1H, 3-hydroxy-Pro-γ-C*H*), 1.43 (s, 9H, ^{t}Bu), 1.15-0.97 (m, 21H, $^i\underline{\text{Pr}}_3$Si); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 169.7, 155.3, 138.0, 131.7, 128.5, 127.7, 127.7, 118.6, 79.9, 74.3, 73.4, 70.9, 68.9, 66.0, 51.9, 45.5, 34.3, 28.5, 28.4, 18.0, 18.0, 12.1; ESIMS-LR *m/z*: $[M+Na]^+$ 627.34; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{32}H_{52}O_7N_2NaSi$ 627.3436, found 627.3440; $[\alpha]^{20}_D$ –0.90 (*c* 1.29, $CHCl_3$).

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXXXXX.
^{1}H and ^{13}C NMR and IR spectra for new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: ichikawa@pharm.hokudai.ac.jp

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by grants from JSPS (Japan Society for the Promotion of Science) Grant-in-Aid for Scientific Research (B) (SI, No. 16H05097), MEXT (Ministry of Education, Culture, Sports, Science and Technology), Japan, under the "Support Program for Implementation of New Equipment Sharing System", the Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science research (BINDS)), and Takeda Science Foundation. We thank Ms. S. Oka (Center for Instrumental Analysis, Hokkaido University) for measurement of the mass spectra.

REFERENCES

(1) Goffin, C.; Ghuysenm, J.-M. *Microbiol. Mol. Biol. Rev.* **1998**, *62*, 1079.

(2) Nieto, M.; Perkins, H. R. *Biochem. J.* **1971**, *123*, 773.

(3) (a) Poole, K. *Cell. Mol. Life. Sci.* **2004**, *61*, 2200. (b) Périchon, B.; Courvalin, P. *Antimicrob. Agents Chemother.* **2009**, *53*, 4580.

(4) (a) Ling, L. L.; Schneider, T.; Peoples, A. J.; Spoering, A. L.; Engels, I.; Conlon, B. P.; Mueller, A.; Hughes, D. E.; Epstein, S.; Jones, M.; Lazarides, L.; Steadman, V. A.; Cohen, D. R.; Felix, C. R.; Fetterman, K. A.; Millett, W. P.; Nitti, a. G.; Zullo, A. M.; Chem, C.; Lewis, K. *Nature* **2015**, *517*, 455. (b) Pallanza, R.; Berti, M.; Scotti, E.; Arioli, V. *J. Antibiot.* **1984**, *37*, 318. (c) O'Sullivan, J.; McCullough, J. E.; Tymiak, A. A.; Kirsch, D. R.; Trejo, W. H.; Principe, P. A. *J. Antibiot.* **1988**, *41*, 1740. (d) von Nussbaum, F.; Anlauf, S.; Benet-Buchholz, J.; Häbich, D.; Köbberling, J.; Musza, L.; Telser, J.; Rübsamen-Waigmann, H.; Brunner, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 2039. (e) Rusin, A. Singh, G.; Severin, A.; Yang, Y.; Duchin, R. G.; Sutherland, A. G.; Minnick, A.; Greenstein, M.; May, M. K.; Shlaes, D. M.; Bradfold, P. A. *Antimicrob. Agents Chemother.* **2004**, *48*, 728.

(5) (a) Shoji, J.; Hinoo, H.; Katayama, T.; Matsumoto, K.; Tanimoto, T.; Hattori T.; Higashiyama, I.; Miwa, H.; Motokawa, K.; Yoshida, T. *J. Antibiot.* **1991**, *45*, 817. (b) Shoji, J.; Hinoo, H.; Katayama, T.; Nakagawa, Y.; Ikenishi, Y.; Iwatani, K.; Yoshida, T. *J. Antibiot.* **1992**, *45*, 824.

(6) (a) Maki, H.; Miura, K.; Yamano, Y. *Antimicrob. Agents Chemother.* **2001**, *45*, 1823. (b) Muller, A.; Munch, D.; Schmidt, Y.; Reder-Christ, K.; Schiffer, G.; Bendas, G.; Gross, H.; Sahl. H.-G.; Schneider, T.; Brotz-Oesterhelt, H. *J. Biol. Chem.* **2012**, *287*, 20270. (c) O'Connor, R. D.; Singh, M.; Chang, J.; Kim, S. J.; VanNieuwenhze, M.; Schaefer, J. *J. Phys. Chem. B* **2017**, *121*, 1499.

(7) Kim, J. H.; Yang, M. S.; Lee, W. S.; Park, K. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2877.

(8) Kumar, T.; Chandrasekhar, S. *Synthesis* **2012**, *44*, 2889.

(9) (a) Hashizume, H.; Hirokawa, S.; Sawa, R.; Muraoka, Y.; Ikeda, D.; Naganawa, H.; Igarashi, M. *J. Antibiot.* **2004**, *57*, 52. (b) Sugawara, K.; Numata, K.; Konishi, M.; Kawaguchi, H. *J. Antibiot.* **1984**, *37*, 958. (c) Sheehan, J. C.; Mania, D.; Nakamura, S.; Stock, J. A.; Maeda, K. *J. Am. Chem. Soc.* **1968**, *90*, 462.

(10) (a) Nutt, R. F.; Joullié, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 5852. (b) Flanagman, D. M.; Joullié, M. M. *Synth. Commun.* **1989**, *19*, 1.

(11) Katsuyama, A.; Matsuda, A.; Ichikawa, S. *Org. Lett.* **2016**, *18*, 2552.

(12) Wohlrab, A.; Lamer, R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 4175.

(13) Katsuyama, A.; Paudel, A.; Panthee, S.; Hamamoto, H.; Kawakami, T.; Hojo, H.; Yakushiji, F.; Ichikawa, S. *Org. Lett.* **2017**, *19*, 3771.

(14) Davies, C. D.; Elliott, M. C.; Hill-Cousins, J.; Khan, M. A.; Maqbool, T.; Wood, J. L. *Synlett* **2008**, 2028.

(15) (a) Hart, W. D.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115. (b) Schedler, D. J. A.; Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1993**, *34*, 5035.

(16) Srivastava, A. K.; Panda, G. *Chem. Eur. J.* **2008**, *14*, 4675.

(17) Ikawa, T.; Sajiki, H.; Hirota, K. *Tetrahedron* **2005**, *61*, 2217.

(18) Cochet, T.; Bellosta, V.; Greiner, A.; Roche, D.; Cossy, J. *Synlett* **2011**, 1920.

(19) Pirali, T.; Tron, G. C.; Masson, G.; Zhu, J. *Org. Lett.* **2007**, *9*, 5275.

(20) Martin, O. R.; Zhou, W.; Wu, X.; Front-Deschamps, S.; Moutel, S.; Schidl, K.; Jeandet, P.; Zbaeren, C.; Bauer, J. A. *J. Med. Chem.* **2006**, *49*, 6000.

(21) Nelson, S. G.; Peele, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742.

(22) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P. Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(23) Atkins, G. M. Jr.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744.

(24) Yanada, R.; Negoro, N.; Bessho, K.; Yanada, K. *Synlett* **1995**, 1261.

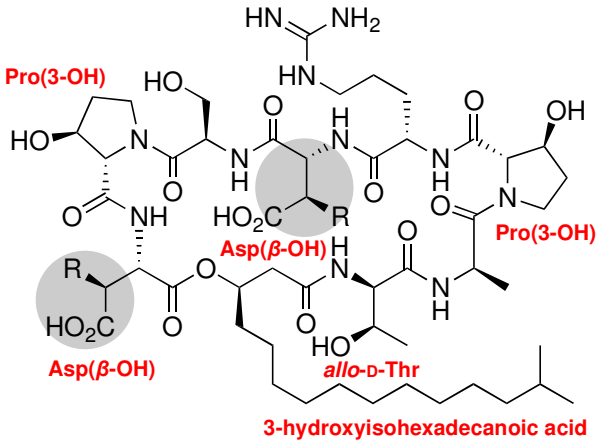
(25) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797.

(26) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804.

(27) (a) Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401. (b) Carpinp, L. A.; Sadat-Aalaee, D.; Chao, H. G.; Deselms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651.

(28) (a) Pirrung, M. C.; Ghorai, S. *J. Am. Chem. Soc.* **2006**, *128*, 11772. (b) Borthwick, A. D.; Davies, D. E.; Exall, A. M.; Hatley, R. J. D.; Hughes, J. A.; Irving, W. R.; Livemore, D. G.; Sollis, S. L.; Nerozzi, F.; Valko, K. L.; Allen, M. J.; Perren, M.; Shabbir, S. S.; Woollard, P. M.; Price, M. A. *J. Med. Chem.* **2006**, *46*, 4159. (c) Rikimaru, K.; Yanagisawa, A.; Kan, T.; Fukuyama, T. *Heterocycles* **2007**, *73*, 403. (d) van der Heijden, G.; Jong, J. A. W. (Sjaak); Ruijter, E.; Orru, R. V. A. *Org. Lett.* **2016**, *18*, 984. (e) Lindhorst, T.; Bock, H.; Ugi, I. *Tetrahedron* **1999**, *55*, 7411.

SYNOPSIS TOC



plusbacin A_3: R = OH
dideoxy derivative: R = H