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Toward the Total Synthesis of Onchidin, a Cytotoxic Cyclic Depsipeptide from a Mollusc

Shū Kobayashi,* Jun Kobayashi, Ryo Yazaki, and Masaharu Ueno[a]

Abstract: The total synthesis of onchidin (**1**), a cytotoxic, C_2-symmetric cyclic decadepsipeptide from a marine mollusc, according to the published structure, is described. A novel β-amino acid, (2*S*,3*S*)-3-amino-2-methyl-7-octynoic acid (AMO), was efficiently prepared in high yield with high diastereo- and enantioselectivity based on a catalytic asymmetric three-component Mannich-type reaction with a chiral zirconium catalyst. The formation of sterically unfavorable *N*-methyl amide and hindered ester bonds were successfully demonstrated, and final macrocyclization was achieved at a secondary-amide site. Completion of the synthesis of **1** suggested that a revision of the structure of the natural product is required. Two diastereomers were also synthesized as candidates for the actual structure of onchidin. Furthermore, efficient solid-phase methods were employed for the combinatorial synthesis of other derivatives to clarify the real structure of onchidin. The solid-phase assembly of a pentadepsipeptide containing all the building blocks was established followed by dimeric cyclization in solution.

Keywords: amino acids · Mannich reaction · natural products · total synthesis · zirconium

Introduction

The oceans of the world contain a bewildering diversity of wildlife. A huge number of uncommon animals, plants, and microorganisms inhabit this environment, and the natural products derived from them are often structurally different from those from terrestrial life forms and show various interesting biological activities. Therefore, marine organisms are seen as rich sources of potential drugs and useful chemicals.[1] Some of the most characteristic compounds are cyclic peptides and depsipeptides. This class of metabolites generally offers an unrivaled chemical diversity and contain non-proteinogenic α- and β-amino acids, in addition to unusual acid moieties such as D-amino and hydroxy acids. Although unusual amino acid units attract considerable interest, they often complicate structural determination and chemical synthesis.

Onchidin is a cytotoxic cyclic depsipeptide isolated from the pulmonate mollusc *Onchidium sp.*[2] The structure of onchidin was determined by extensive spectroscopic analysis, selective hydrolysis, and chiral GC–MS. It is composed of two identical halves linked together in a head-to-tail fashion. Therefore, onchidin has a C_2 axis of symmetry and constitutes the only example reported to date of a cyclic, dimeric, and symmetric depsipeptide from a mollusc. The structure contains two units of (*S*)-valine (Val), two units of (*S*)-*N*-methylvaline (MeVal), and four units of (*S*)-2-hydroxyisovaleric acid (Hiv), which are all lipophilic and bulky residues derived from valine. Besides these known α-amino and α-hydroxy acids, onchidin incorporates two identical units of a novel β-amino acid, (2*S*,3*S*)-3-amino-2-methyl-7-octynoic acid (AMO). It was found that this type of α-methyl-β-amino acid is a crucial component of many biologically active cyclic peptides of marine origin. Representative examples are nodularin[3] and microcystin,[4] which are notorious for their hepatotoxicity, and majusculamide C,[5] dolastatin 11 and 12,[6] and kulokekahilide-1,[7] which are valued for their antifungal and antineoplastic activity.

AMO has been reported as a component of the new cyclic depsipeptide, malevamide C,[8] isolated from the cyanobacterium *Symploca laete-viridis.* Also, the 2-*nor*-analogue of AMO is part of dolastatin 17[9] from *Dolabella auricularia*, and a number of peptides containing 3-hydroxy-7-octynoic acid have been reported from *Philinopsis speciosa*[10] and *Onchidium*.[11] However, efficient and general methods for the preparation of optically pure α-alkyl-β-amino acids are

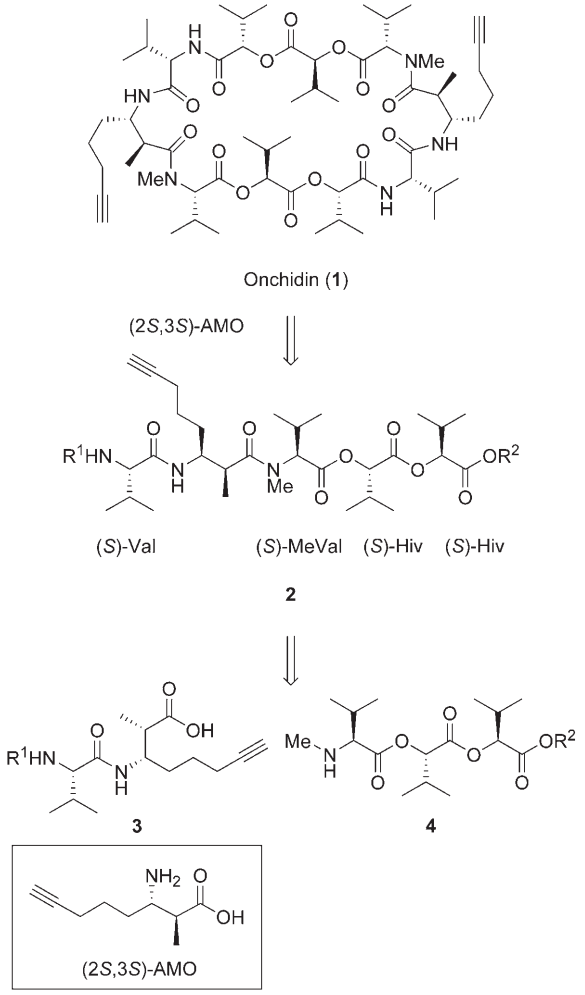
[a] Prof. Dr. S. Kobayashi, Dr. J. Kobayashi, R. Yazaki, Dr. M. Ueno
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5864-0634
E-mail: skobayas@mol.f.u-tokyo.ac.jp

still limited and in general involve lengthy synthetic sequences and the use of chiral auxiliaries.[12]

Our research has focused on the efficient synthesis of β-amino acid derivatives based on catalytic enantioselective Mannich-type reactions, and we have recently carried out the catalytic asymmetric synthesis of the AMO unit by utilizing a chiral zirconium catalyst prepared in situ from Zr(O*t*Bu)$_4$, 6,6′-bis(pentafluoroethyl)-1,1′-binaphthalene-2,2′-diol (6,6′-$(C_2F_5)_2$BINOL), and *N*-methylimidazole (NMI).[13] With an the efficient synthetic method for the preparation of AMO in hand, we undertook the first total synthesis of **1**, the proposed structure of onchidin.

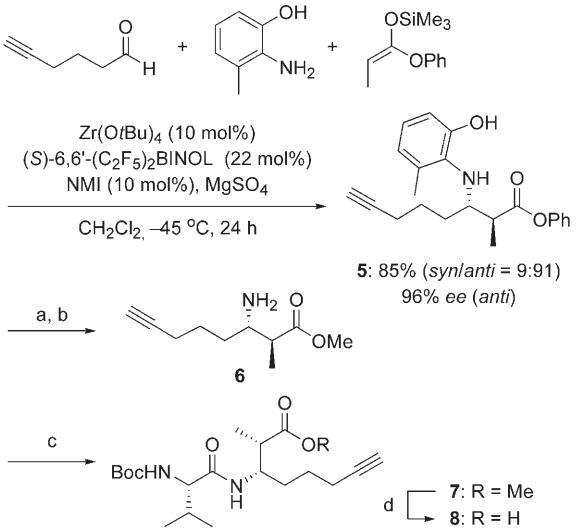
Results and Discussion

The retrosynthetic analysis of **1** is shown in Scheme 1. Symmetrical pentadepsipeptide coupling and macrocyclization of the 32-membered decadepsipeptide are envisaged at the Val–Hiv secondary-amide site. It is important to select suitable sites for disconnection because there are some rather difficult coupling positions: the *N*-methyl amide bond and sterically hindered ester bonds. Fragment esterification of tripeptide (Val–AMO–MeVal) with the ester unit (Hiv–Hiv) is anticipated to be problematic as, in addition to the general difficulties of esterificaton between fragments that bear bulky side chains, the carboxylic acid coupling partner contains *N*-methylvaline, which is especially known to decelerate or preclude sensitive esterifications and increase the chances of low reactivity, competitive side reactions, and epimerization.[14] Therefore, to achieve a convergent synthetic route, we chose the *N*-methyl amide bond as a fragment-coupling site, and half-fragment **2** was disconnected to Val–AMO dipeptide **3** and MeVal–Hiv–Hiv fragment **4**.



Scheme 1. Retrosynthetic analysis of **1**, the proposed structure of onchidin.

Catalytic asymmetric synthesis of the (2*S*,3*S*)-AMO unit was initially performed with a chiral zirconium catalyst by using (*S*)-6,6′-$(C_2F_5)_2$BINOL (Scheme 2). The three-component Mannich-type reaction of 5-hexynal, 2-amino-*m*-cresol, and the ketene silyl acetal derived from phenyl propionate gave the desired Mannich adduct **5** in 85% yield with high stereoselectivity (*syn*/*anti* = 9:91, *anti*: 96% *ee*).[13] On the other hand, we recently found that the chiral zirconium catalyst can be isolated as a white powder or clear single crystals.[15] We used the white powder for the preparation of **5** (Scheme 3). When 10 mol% of the white powder was used, the desired adduct was obtained quantitatively with excellent stereoselectivity (*syn*/*anti* = 5:95, *anti*: 96% *ee*). Notably, the yield and selectivity were improved by using the powdered catalyst, compared to those with the Zr catalyst prepared in situ, and that handling of the catalyst and application to large-scale synthesis are much easier with the isolat-



Scheme 2. Catalytic asymmetric synthesis of AMO and synthesis of Val–AMO fragment. Reagents and conditions: a) K_2CO_3, MeOH, 0°C→RT (94%); b) $(NH_4)_2Ce(NO_3)_6$, MeCN/H_2O, −10°C (62%); c) Boc-(*S*)-Val, EDC, HOBt, Et_3N, CH_2Cl_2, room temperature (82%); d) LiOH, THF/MeOH/H_2O, room temperature (quant). Boc = *tert*-butoxycarbonyl, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxybenzotriazole.

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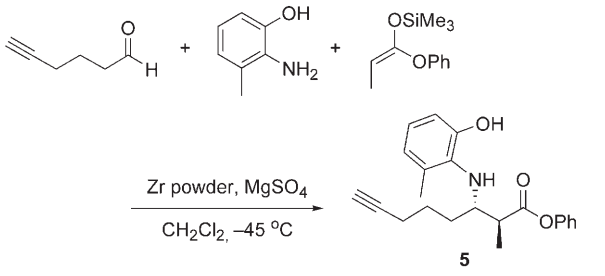


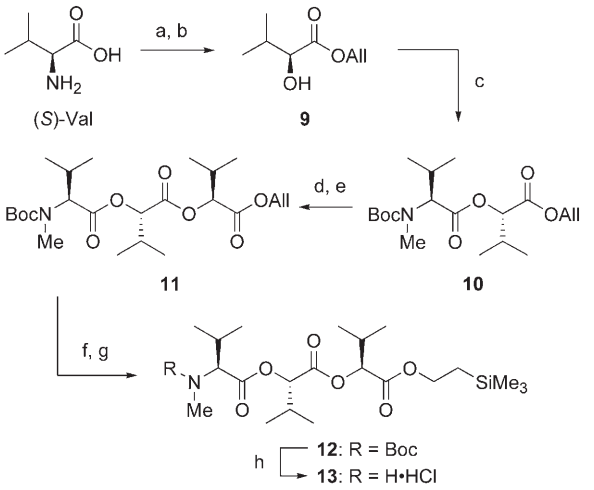
Zr, 10 mol%, 24 h: quant, *syn*/*anti* = 5:95, 96% *ee* (*anti*)
Zr, 5 mol%, 48 h: 77% yield, *syn*/*anti* = 6:94, 94% *ee* (*anti*)
Zr, 5 mol%, 48 h: 78% yield, *syn*/*anti* = 4:96, 92% *ee* (*anti*) at –20 °C

Scheme 3. Catalytic asymmetric Mannich-type reaction with chiral Zr powder.

ed Zr powder. When 5 mol% of the Zr powder was used, the yield and selectivity were slightly decreased.

Conversion of **5** into the methyl ester and isolation of the pure *anti* isomer followed by deprotection of the amino group with cerium ammonium nitrate (CAN)[16] afforded (2*S*,3*S*)-AMO methyl ester **6** (Scheme 2). Coupling of **6** with Boc-(*S*)-Val using EDC, HOBt, and Et_3N followed by recrystallization of the product obtained provided optically pure dipeptide **7** in 82% yield. Subsequent hydrolysis of the methyl ester by treatment of LiOH gave *N*-Boc-protected dipeptide fragment **8** in quantitative yield.

The synthesis of the MeVal–Hiv–Hiv fragment is shown in Scheme 4. (*S*)-Hiv was prepared from (*S*)-Val by diazotization and hydrolysis and was protected as its allyl ester **9**. Formation of the sterically hindered ester bond between **9**

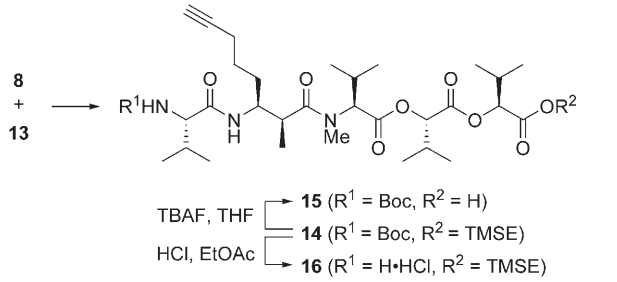


Scheme 4. Preparation of the MeVal–Hiv–Hiv fragment. Reagents and condition: a) 1 M H_2SO_4, 1 M $NaNO_3$, 0 °C→RT (66%); b) allyl bromide, K_2CO_3, TBAI, DMF, room temperature (97%); c) Boc-(*S*)-MeVal, EDC, DMAP, CH_2Cl_2, room temperature (74%); d) [$Pd(PPh_3)_4$], morpholine, THF, room temperature; e) **9**, EDC, DMAP, CH_2Cl_2, room temperature (71%, 2 steps); f) [$Pd(PPh_3)_4$], morpholine, THF, room temperature; g) TMSEOH, EDC, DMAP, CH_2Cl_2, room temperature (81%, 2 steps); h) HCl, EtOAc, room temperature (quant). DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, TBAI = tetra-*n*-butylammonium iodide, TMSE = 2-trimethylsilylethyl.

and (*S*)-MeVal was conducted by using EDC and DMAP to afford **10** in good yield (74%). Removal of the allyl group of **10** with [$Pd(PPh_3)_4$] and morpholine gave the corresponding acid, which was further coupled with **9** using EDC and DMAP to provide the tridepsipeptide fragment **11** (71%, 2 steps). During preliminary investigations, the Boc group of **11** was removed, and the resulting *N*-methylamine was coupled with acid **8**. However, it was not possible to remove the allyl group of the pentadepsipeptide with [$Pd(PPh_3)_4$] without compromising the integrity of the sensitive acetylenic moiety of AMO; therefore, an alternative route was devised. Accordingly, allyl ester **11** was converted into the corresponding TMSE ester **13**. The TMSE protecting group[17] is advantageous as it can be cleaved selectively in the presence of the Boc group and the depsipeptide esters without damaging the terminal acetylene. HCl in EtOAc was used for Boc deprotection of **12** to afford the desired secondary-amine fragment as its hydrochloride salt **13** in quantitative yield.

Next, the coupling reaction of Val–AMO fragment **8** with MeVal–Hiv–Hiv fragment **13** was investigated. *N*-methyl amidation is generally difficult because the reactivity of secondary amines is rather low in peptide-coupling reactions, and this often leads to undesired side reactions and extensive epimerization. This is especially true in this case, as amine fragment **13** contains sterically hindered valine residues. Nevertheless, with the expectation that the epimerization rate may be somewhat suppressed as the carboxylic acid partner to be activated is a β-amino acid instead of the usual α-amino acid, we examined the coupling of **8** with **13** by using various condensation reagents (Table 1). Although low reactivity was observed with the use of PyBOP[18] or BOPCl,[19] which are known to be effective for some cases

Table 1. Coupling of acid **8** with seconday amine **13**.

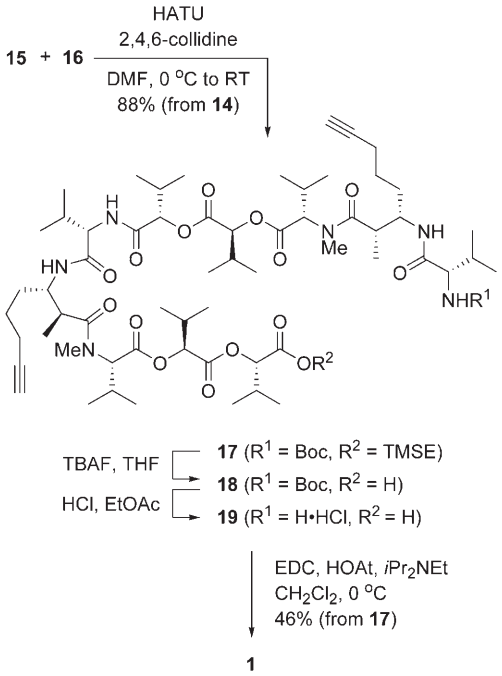


Entry	Conditions[a]	**14** [%]
1	PyBOP, iPr_2NEt, CH_2Cl_2	4
2	BOPCl, Et_3N, CH_2Cl_2	4
3	PyBroP, iPr_2NEt, CH_2Cl_2	39
4	HATU, 2,4,6-collidine, DMF	45
5	HATU, iPr_2NEt, DMF	68

[a] The coupling reaction was performed in the presence of condensation reagent (1.5–2.0 equiv) and base (3.0 equiv) at 0 °C→RT for 20–40 h. BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, PyBOP = benzotriazol-1-yloxy-trispyrrolidinophosphonium hexafluorophosphate, PyBroP = bromotrispyrrolidinophosphonium hexafluorophosphate, TBAF = tetra-*n*-butylammonium fluoride.

of this type of sterically unfavorable coupling, the combination of PyBroP,[20] iPr$_2$NEt or HATU,[21] and 2,4,6-collidine proved particularly effective to afford the desired pentadepsipeptide **14** in moderate yield. The best result was obtained by treatment of HATU (2.0 equiv) with iPr$_2$NEt (3.0 equiv) as a base, which provided the product in 68% yield, with no epimerization according to ^{1}H and ^{13}C NMR analyses. Subsequent deprotection of the carboxylic acid (TBAF in THF) or the amine terminus (HCl in EtOAc) of **14** afforded **15** and **16**, respectively. In the course of these deprotection steps, the terminal acetylene moiety or the depsipeptide esters and *N*-methylamide, which are sensitive to acids, were not affected at all.

Coupling of the half-units, subsequent deprotection of both termini, and final macrocyclization of the pentadepsipeptide were then examined (Scheme 5). Despite anxiety



Scheme 5. Completion of the synthesis of **1**, the proposed structure of onchidin.

about the bulkiness of both coupling partners affecting reactivity, the union of acid **15** with amine **16** proceeded by utilizing HATU and 2,4,6-collidine to give linear decadepsipeptide **17** in relatively high yield (88% from **14**). Cleavage of the TMSE group followed by Boc deprotection under the same conditions mentioned above provided cyclization precursor **19**. Macrocyclization of **19** was achieved with HATU (5.0 equiv) and 2,4,6-collidine (10 equiv) in CH_2Cl_2 (1 mM) to afford the cyclic decadepsipeptide corresponding to the published structure of onchidin (**1**). However, under these conditions the reaction was found to be suboptimal ($\approx$14% yield) because of side reactions such as oligomerization or higher-order macrocyclization. Usual silica-gel chromatography of the crude mixture provided the clean product for ^{1}H and ^{13}C NMR analyses, whereas purification by reverse-phase HPLC was needed for more-detailed analysis. In subsequent investigations, the yield was increased slightly to 31% with the use of diphenoxyphosphinyl azide (DPPA; 5.0 equiv)[22] and $NaHCO_3$ (10 equiv) in DMF (3 mM), and it was finally found that the cyclization in the presence of EDC (5.0 equiv), 1-hydroxy-7-azabenzotriazole (HOAt; 5.5 equiv),[21] and iPr$_2$NEt (5.0 equiv) in CH_2Cl_2 (1 mM) proceeded smoothly and cleanly to provide **1** in a reproducible 46% yield over three steps.

However, comparison of the ^{1}H and ^{13}C NMR spectroscopic data of **1** with those reported[2] for onchidin revealed that they were not identical. There were significant differences primarily in the ^{1}H and ^{13}C NMR chemical shifts of the α-C atoms and the *N*-Me groups in (*S*)-MeVal, and the amide protons of (2*S*,3*S*)-AMO and (*S*)-Val, although they were identical with regard to molecular symmetry: the synthetic sample showed complete C_2 symmetry, and only signals for the monomer were observed in NMR spectra at room temperature in $CDCl_3$. The optical rotation of our sample ($[\alpha]_D^{22} = -68.3°$ ($CHCl_3$)) also differed from that of the natural product ($[\alpha]_D^{25} = -140.9°$ ($CHCl_3$))[2] in magnitude. Furthermore, although biological activity against KB and P-388 cells ($IC_{50} = 8\ \mu g\,mL^{-1}$) was reported for onchidin,[2] our material showed almost no activity.

We were confident that our synthetic strategy had delivered the published structure. Our strategy was reliable because all the α-amino and β-hydroxy acids were pepared in optically pure form from natural (*S*)-valine or its derivatives, and the absolute stereochemistry of the novel β-amino acid, AMO, was unambiguously confirmed as mentioned below. As the NMR spectral data and FAB or ESI MS analyses are fully consistent with the structure proposed for onchidin, it seems likely that we have synthesized the target compound **1** shown in the literature, and that the actual structure of onchidin is a diastereomer or other related isomer of **1**. It is important to note that even in an age when methods for structural analysis are highly developed, total synthesis is often the only reliable method for unambiguous determination of structure when the compound is not readily available from natural sources.

As the interpretation of the sequence and the relative configuration of each component in large macrocyclic depsipeptides by spectral means is not trivial, it is apparent that a revision of the structure of the natural product is required. Therefore, we set out to establish the actual structure of the natural sample and to explain previous discrepancies in the NMR spectroscopic data. Accordingly, we synthesized two diastereomers as candidates (Scheme 6). In the literature, the absolute configuration of the new β-amino acid, AMO, was determined to be 2*S*,3*S* solely based on an NOE experiment, although all the α-hydroxy and amino acids were proven to have absolute *S* stereochemistry by chiral GC–MS analysis. With the expectation that the actual structure of AMO is its enantiomer, diastereomer **20**, which contains (2*R*,3*R*)-AMO, was synthesized according to the previous procedure. Catalytic enantioselective Mannich-type reaction

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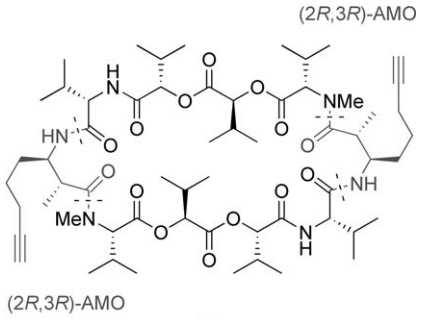

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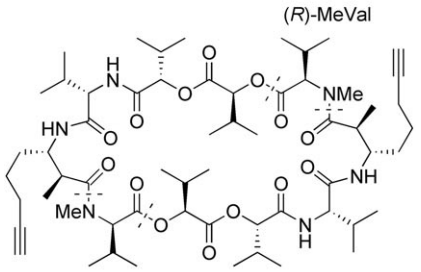

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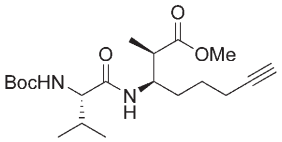
Scheme 6. Selected diastereomers of **1**.



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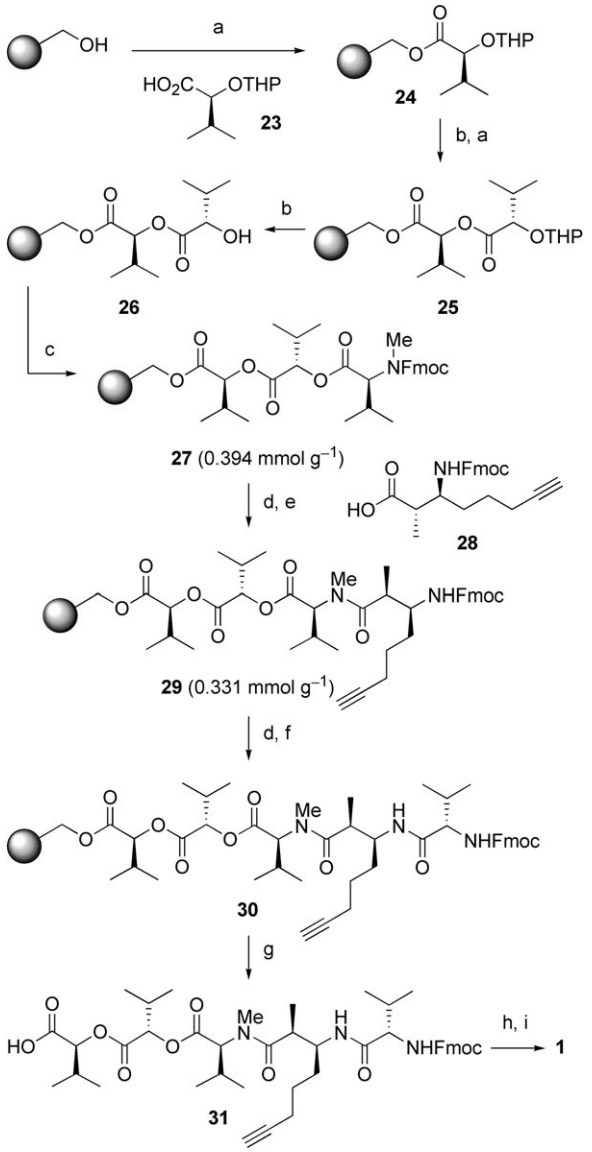
Scheme 7. Structure of **22**.

with (*R*)-6,6′-$(C_2F_5)_2$BINOL, further conversion, and coupling with Boc-(*S*)-Val provided dipeptide **22**, recrystallization of which afforded the optically pure product, whose absolute stereochemistry was confirmed by X-ray crystal-structure analysis (Scheme 7). Similarly, **22** was subjected to the same sequence of reactions described above to give **20**. However, the NMR spectroscopic data of synthetic **20** were also not identical to that of the reported material and were relatively similar to those of synthetic **1**.

Next, we synthesized diastereomer **21**, which contains nonnatural (*R*)-MeVal instead of (*S*)-MeVal. This determination arose from the observation that significant differences between **1** and the natural sample were observed especially in the ^{1}H and ^{13}C NMR chemical shifts of the α-H and α-C atoms and the *N*-Me groups in (*S*)-MeVal, and that MeVal has a nonnatural *R* stereochemistry in onchidin B, which has a similar origin and structure to onchidin. Modified fragment (*R*)-MeVal–(*S*)-Hiv–(*S*)-Hiv was prepared according to Scheme 4, and further couplings, deprotections, and cyclization also proceeded smoothly to afford **21** without any difficulties. To our disappointment, **21** was also found to be a diastereomer of the natural product by ^{1}H and ^{13}C NMR analyses. Furthermore, the ^{1}H NMR spectra of **21** showed four or more rotamers in $CDCl_3$ at room temperature, which almost become a single conformer at 100–150 °C in [D_6]DMSO, whereas the spectra of **1** and **20** showed a completely symmetrical single structure at room temperature in $CDCl_3$.

As for depsipeptides that contain as many as ten residues, such as onchidin, there is an enormous variety of possible isomers and related compounds given the number of asymmetric centers, variation, and potential sequences of amino acids. Therefore, more-efficient synthetic methods are necessary for the determination of the actual structure of onchidin and the study of structure–activity relationships. To achieve a more-efficient synthetic route to onchidin analogues, we decided to perform a solid-phase synthesis of **1** (Scheme 8). Our plan involved 1) the preparation of the



Scheme 8. Efficient synthetic method for onchidin derivatives utilizing solid-phase synthesis. Reagents and conditions: a) **23**, DIC, DMAP, THF; b) *p*-TsOH, CH_2Cl_2/MeOH; c) Fmoc-(*S*)-MeVal, DIC, DMAP, THF; d) piperidine, DMF; e) **28**, HATU, *i*Pr_2NEt, DMF (twice) (89% from **27**); f) Fmoc-(*S*)-Val, HATU, *i*Pr_2NEt, DMF; g) TFA/CH_2Cl_2 (quant from **29**); h) Et_2NH, THF; i) EDC, HOAt, *i*Pr_2NEt, DMF (30% from **31**). DIC = diisopropylcarbodiimide, Fmoc = 9-fluorenylmethoxycarbonyl, *p*-Ts = toluenesulfonyl, TFA = trifluoroacetic acid, THP = 2-tetrahydropyranyl.

linear depsipeptide by the usual solid-phase peptide synthesis from the C to the N terminus, 2) cleavage of the free carboxylic acid to provide the cyclization precursor, and 3) cyclisation of the precursor in the solution phase. We decided to make the cyclization site and the half-peptide unit identical to those of the previous solution-phase route and employ an Fmoc protection strategy on Wang resin. The hydroxy group of the α-hydroxy acid was protected as its THP ether.[23] DIC and DMAP were utilized in the first attachment and subsequent condensations involving ester bonds. Esterification of the Wang resin (1.10 mmol g^{-1}) with Hiv unit **23** and removal of the THP group were repeated twice to give **26**. Despite the sterically bulky nature of the coupling partners, the reaction proceeded smoothly, and the structure of the didepsipeptide was confirmed by analysis of the cleavage product of resin **26**. With the same method, Fmoc-(*S*)-MeVal was added to the diester to afford **27**, the loading level of which was determined to be 0.394 mmol g^{-1} by UV/Vis spectroscopic analysis. Aware of the fact that *N*-methyl amidation reactions in the solid phase can be rather difficult due to low reactivity of the substrate, we relied again on the remarkable efficiency of the HATU/*i*Pr_2NEt system. This coupling of the AMO unit **28** with the secondary amine derived from **27** was run twice with the preactivation method, and **29** was obtained with relatively high efficiency (0.331 mmol g^{-1}, 89% yield from **27**). Further introduction of Fmoc-(*S*)-Val by using HATU afforded pentadepsipeptide resin **30**, and half-unit **31** was cleaved from the resin with TFA/CH_2Cl_2 (1:1) in quantitative yield from **29**. To improve still further the efficiency of the sequence, we attempted simply to couple the pentadepsipeptide and perform the ring closure in a single reaction. Purification of **31** by silica-gel chromatography followed by removal of the Fmoc group with Et_2NH in THF provided free linear pentadepsipeptide. Treatment of the amino acid with EDC (5.0 equiv), HOAt (5.0 equiv), *i*Pr_2NEt (5.0 equiv), and CH_2Cl_2 (1 mM) provided the desired cyclic dimer in 30% yield. Several by-products such as a cyclic monomer, a range of oligomers, and higher-order macrocycles were also obtained, although we did not determine the structures of these compounds. Furthermore, when the reaction was performed in 5 mM CH_2Cl_2, the yield was slightly decreased to 24%.

We believe that this synthetic route, which utilizes a combination of the half-unit synthesis in the solid phase and direct cyclic dimerization in solution, could realize the more-efficient synthesis of various onchidin isomers and make a great contribution to both the determination of the structure of the naturally occuring material and the study of structure–activity relationships.

Conclusions

We have synthesized **1**, which has the proposed structure of onchidin, along with diastereomers **20** and **21** and shown unambiguously that their structures differ from that of the naturally occuring compound. As a result, we conclude that the presumed structure of the natural sample has been misassigned. Catalytic asymmetric Mannich-type reaction provided an efficient and simple way to a new β-amino acid synthesis, and this utility was demonstrated in the synthesis of **1** by a more-efficient synthetic route using a combination of solid and liquid phases. The synthesis is expected to contribute to the structural determination and study of structure–activity relationships of onchidin derivatives.

Experimental Section

General

Melting points were uncorrected. Optical rotations were recorded on a JASCO P-1010 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-610 infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (0.00 ppm) or residual proton resonances in $CDCl_3$ (7.26 ppm) served as internal standards for ^1H NMR spectroscopy, and $CDCl_3$ (77.0 ppm) was used as an internal standard for ^{13}C NMR spectroscopy. HPLC was carried out with a SHIMADZU LC-10AT liquid chromatograph, a SHIMADZU SPD-10 A UV/Vis detector, and a SHIMADZU C-R6 A or C-R8 A chromatograph. EI MS analysis was carried out with a SHIMADZU GCMS-QP5050 A spectrometer. EI HRMS and FAB MS analyses were carried out with a JEOL JMS-SX 102 spectrometer. ESI HRMS analysis was also carried out with a BRUKER DALTONICS BioTOF II spectrometer. X-ray crystal-structure analysis was performed with a Rigaku R-AXIS RAPID Imaging Plate diffractometer. Solid-phase synthesis was performed with a EYELA CCS-1200R Personal Organic Synthesizer. Column chromatography was performed with silica gel 60 (Merck), and preparative TLC was carried out with Wakogel B-5F or silica gel 60 F_{254} (0.5 mm; Merck). Dichloromethane was distilled from P_2O_5, then from CaH_2, and dried over 4-Å molecular sieves. All other solvents and chemical compounds were purified based on standard procedures. All reactions were carried out under argon atmosphere in well-dried glassware. Compound **9**[24] and (*S*)-*N*-Boc-*N*-methylvaline[25] were prepared from (*S*)-valine according to the literature procedures.

Syntheses

5-Hexyn-1-al: 5-Hexyn-1-ol (5.00 g, 50.9 mmol) in CH_2Cl_2 (80 mL) was added to a suspension of celite (38 g), which had been dried under reduced pressure, and pyridinium chlorochromate (PCC; 16.5 g, 76.4 mmol) in CH_2Cl_2 (90 mL) at room temperature. The reaction mixture was stirred for 3 h and then diluted with Et_2O (200 mL). After filtration and concentration under reduced pressure (room temperature, 200 mmHg), the crude product was purified by distillation to afford 5-hexyn-1-al (2.66 g, 54%). B.p.: 72–74 °C (70 mmHg); ^1H NMR ($CDCl_3$): $\delta = 1.86$ (dt, $J = 6.8$, 7.2 Hz, 2H), 1.99 (t, $J = 2.7$ Hz, 1H), 2.27 (dt, $J = 2.7$, 6.8 Hz, 2H), 2.61 (dt, $J = 1.4$, 7.2 Hz, 2H), 9.81 ppm (t, $J = 1.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) $\delta = 17.7$, 20.8, 42.5, 69.3, 83.1, 201.6 ppm.

5:[13] $Zr(OtBu)_4$ (192 mg, 0.50 mmol) in CH_2Cl_2 (1.0 mL) and *N*-methylimidazole (41.1 mg, 0.50 mmol) in CH_2Cl_2 (0.50 mL) were added to a solution of (*S*)-6,6′-bis(pentafluoroethyl)-1,1′-bi-2-naphthol (575 mg, 1.1 mmol) in CH_2Cl_2 (1.0 mL) at room temperature, and the mixture was stirred for 1 h at the same temperature. 5-Hexyn-1-al (577 mg, 6.0 mmol) in CH_2Cl_2 (1.0 mL) was added to a mixture of 2-amino-*m*-cresol (616 mg, 5.0 mmol) and $MgSO_4$ (1.50 g) in CH_2Cl_2 (1.0 mL) at room temperature. The mixture was stirred for 20 min at the same temperature and then cooled to −45 °C. A solution of the catalyst and the ketene silyl acetal derived from phenyl propionate (1.33 g, 6.0 mmol) in CH_2Cl_2 (1.0 mL) were successively added to the aldimine solution prepared in situ. The mixture was stirred for 24 h, and saturated aqueous $NaHCO_3$ was then added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over $NaSO_4$. After

filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography (hexane/EtOAc) to give **5** (1.29 g, 73%). The diastereomeric ratio was determined by ^{1}H NMR analysis (*syn*/*anti* = 7:93), and the optical purity was determined by HPLC analysis (*anti*: 95% *ee*). IR (neat): $\tilde{\nu}$ = 3366, 3299, 2942, 2863, 1739, 1489, 1458, 1190, 1161, 744, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$): *anti* isomer: δ = 1.41 (d, J = 7.2 Hz, 3H), 1.60–1.75 (m, 4H), 1.94 (t, J = 2.6 Hz, 1H), 2.14–2.19 (m, 2H), 2.28 (s, 3H), 2.88 (dq, J = 7.0, 7.2 Hz, 1H), 3.61–3.67 (m, 1H), 6.66–6.93 (m, 3H), 7.06–7.40 (m, 5H); *syn* isomer: δ = 1.38 (d, J = 7.3 Hz, 3H), 1.60–1.75 (m, 4H), 1.95 (t, J = 2.7 Hz, 1H), 2.14–2.19 (m, 2H), 2.26 (s, 3H), 2.97 (dq, J = 3.0, 7.3 Hz, 1H), 3.61–3.67 (m, 1H), 6.66–6.93 (m, 3H), 7.06–7.40 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): *anti* isomer: δ = 14.0, 18.4, 18.5, 24.3, 31.5, 43.8, 57.7, 68.9, 83.7, 113.7, 121.4, 122.4, 123.3, 125.9, 129.4, 130.8, 132.2, 150.0, 150.4, 175.3; *syn* isomer: δ = 10.9, 18.2, 18.4, 25.6, 30.8, 41.9, 58.0, 68.9, 83.6, 113.6, 121.4, 122.3, 124.3, 126.0, 129.4, 131.2, 132.4, 150.4, 151.3, 174.5 ppm; MS (EI): m/z = 351 $[M]^+$; elemental analysis: calcd (%) for $C_{22}H_{25}NO_3$: C 75.19, H 7.17, N 3.99; found: C 74.92, H 7.35, N 3.97; HPLC (Daicel Chiralcel OD-H (double), hexane/*i*PrOH = 19:1, flow rate = 0.50 mL min^{-1}): *anti* isomer: t_R = 54.0 min (minor = 2*R*,3*R*), t_R = 63.6 min (major = 2*S*,3*S*); *syn* ismer: t_R = 49.6 min (minor = 2*S*,3*R*), t_R = 67.6 min (major = 2*R*,3*S*).

Methyl (2*S*,3*S*)-3-(2-hydroxy-6-methylphenyl)amino-2-methyl-7-octynoate:[13] K_2CO_3 (497 mg, 3.6 mmol) was added to a solution of **5** (1.26 g, 3.6 mmol) in MeOH (50 mL) at 0°C. After the mixture was stirred for 10 min at the same temperature, H_2O (50 mL) was added. The layers were separated and the organic layer was retained. The aqueous layer was extracted with CH_2Cl_2 (3×60 mL), and the combined organic extracts were dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography (hexane/Et_2O) to give the desired methyl ester (979 mg, 94%) as a single diastereomer. $[\alpha]_D^{28}$ = −5.3 (c = 0.51, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3362, 3297, 2952, 2858, 1719, 1462, 1203, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.27 (d, J = 7.2 Hz, 3H), 1.47–1.65 (m, 4H), 1.93 (t, J = 2.7 Hz, 1H), 2.11–2.17 (m, 2H), 2.25 (s, 3H), 2.63 (dq, J = 7.2, 7.9 Hz, 1H), 3.47–3.53 (m, 1H), 3.73 (s, 3H), 6.63–6.85 ppm (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 14.7, 18.3, 18.5, 24.1, 31.7, 44.1, 52.0, 57.6, 68.8, 83.6, 113.9, 122.1, 123.4, 130.6, 132.3, 150.4, 177.5 ppm; MS (EI): m/z = 289 $[M]^+$; elemental analysis: calcd (%) for $C_{17}H_{23}NO_3$: C 70.56, H 8.01, N 4.84; found: C 70.32, H 8.09, N 4.55.

6:[13] CAN[16] (6.83 g, 13 mmol) in H_2O (35 mL) was slowly added to a solution of methyl (2*S*,3*S*)-3-(2-hydroxy-6-methylphenyl)amino-2-methyl-7-octynoate (901 mg, 3.1 mmol) in MeCN (26 mL) at −10°C over 15 min. After being stirred for 20 min, the reaction mixture was diluted with H_2O (35 mL), the layers were separated, and the organic layer was retained. The aqueous layer was extracted with Et_2O (3×100 mL). The combined organic layers were washed with HCl (0.3 M, 3×80 mL), all the aqueous layers were combined, and the pH of the solution was raised to >8 by treatment with Na_2CO_3 at 0°C. The insoluble inorganic materials were filtered through a pad of celite, the aqueous layer was extracted with EtOAc (3×160 mL), and the combined organic layer was dried over Na_2SO_4. Filtration and concentration under reduced pressure afforded **6** (354 mg, 62%). $[\alpha]_D^{17}$ = +6.7 (c = 0.32, $CHCl_3$);[12] $[\alpha]_D$ = +8.3 (c = 0.50, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3290, 2950, 2876, 2115, 1733, 1203, 1171 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.19 (d, J = 7.0 Hz, 3H), 1.37–1.80 (m, 6H), 1.96 (t, J = 2.7 Hz, 1H), 2.20–2.25 (m, 2H), 2.49 (dq, J = 6.8, 7.0 Hz, 1H), 2.91 ppm (m, 1H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$); δ = 14.2, 18.3, 25.0, 33.7, 46.0, 51.6, 53.6, 68.6, 84.1, 175.8 ppm; HRMS (EI): m/z calcd for $C_{10}H_{17}NO_2$: 183.1259 $[M]^+$; found: 183.1265.

7: EDC (516 mg, 2.7 mmol), HOBt (364 mg, 2.7 mmol), and Et_3N (545 mg, 5.4 mmol) were added to a solution of **6** (329 mg, 1.8 mmol) and *N*-Boc-(*S*)-valine (468 mg, 2.2 mmol) in CH_2Cl_2 (10 mL) at room temperature. After being stirred overnight, the reaction mixture was diluted with EtOAc (200 mL). The organic layer was separated, washed with HCl (1 M, 2×80 mL), saturated aqueous $NaHCO_3$ (2×80 mL), and brine (80 mL), and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography (hexane/EtOAc) to afford **7** (566 mg, 82%). $[\alpha]_D^{18}$ = −31.0 (c = 1.01, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3312, 2961, 1738, 1683, 1650, 1523, 1249, 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.92 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 7.3 Hz, 3H), 1.45 (s, 9H), 1.53–1.65 (m, 4H), 1.93 (t, J = 2.6 Hz, 1H), 2.14–2.24 (m, 3H), 2.70 (dq, J = 3.9, 7.3 Hz, 1H), 3.69 (s, 3H), 3.91 (dd, J = 5.7, 8.4 Hz, 1H), 4.06–4.13 (m, 1H), 5.02 (d, J = 8.4 Hz, 1H), 6.73 ppm (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 15.2, 17.6, 18.0, 19.4, 24.9, 28.3, 30.4, 33.0, 42.5, 50.6, 51.7, 60.4, 68.7, 79.8, 83.8, 155.7, 171.6, 175.9 ppm; MS (FAB): m/z = 383 $[M+H]^+$; elemental analysis: calcd (%) for $C_{20}H_{34}N_2O_5$: C 62.80, H 8.96, N 7.32; found: C 62.66, H 8.97, N 7.47.

22: This was obtained according to the same procedure as for the synthesis of **7**. Dipeptide **22** was recrystallized (Et_2O/hexane), and the absolute stereochemistry of the AMO moiety was unambiguously determined to be 2*R*,3*R* by X-ray crystal-structure analysis. $[\alpha]_D^{17}$ = +3.2 (c = 1.07, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3306, 2971, 1721, 1685, 1651, 1523, 1172, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.92 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 7.2 Hz, 3H), 1.45 (s, 9H), 1.53–1.64 (m, 4H), 1.93 (t, J = 2.3 Hz, 1H), 2.11–2.21 (m, 3H), 2.72 (dq, J = 3.9, 7.2 Hz, 1H), 3.70 (s, 3H), 3.92 (dd, J = 5.9, 8.3 Hz, 1H), 4.06–4.13 (m, 1H), 5.06 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 14.9, 17.6, 18.0, 19.3, 24.9, 28.2, 30.5, 32.7, 42.3, 50.6, 51.7, 60.3, 68.7, 79.7, 83.7, 155.7, 171.6, 175.8 ppm; MS (FAB): m/z = 383 $[M+H]^+$; elemental analysis: calcd (%) for $C_{20}H_{34}N_2O_5$: C 62.80, H 8.96, N 7.32; found: C 62.68, H 9.03, N 7.32.

10: EDC (3.44 g, 18 mmol) and DMAP (1.83 g, 15 mmol) were added to a solution of (*S*)-*N*-Boc-*N*-methylvaline[25] (4.16 g, 18 mmol) and **9**[24] (2.37 g, 15 mmol) in CH_2Cl_2 (60 mL) at room temperature. After being stirred overnight, the reaction mixture was washed with H_2O (70 mL) and brine (70 mL) and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography (hexane/EtOAc) to afford **10** (4.13 g, 74%). $[\alpha]_D^{28}$ = −92.3 (c = 0.96, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2967, 2877, 1743, 1698, 1466, 1391, 1191, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$): mixture of two rotamers: δ = 0.92 (d, J = 6.6 Hz, 3H), 0.97–1.07 (m, 9H), 1.46 (s, 9H), 2.17–2.33 (m, 2H), 2.83 (s, 1.5H, one rotamer), 2.86 (s, 1.5H, other rotamer), 4.24 (d, J = 10.5 Hz, 0.5H, one rotamer), 4.54 (d, J = 10.5 Hz, 0.5H, other rotamer), 4.64–4.66 (m, 2H), 4.84 (d, J = 4.2 Hz, 1H), 5.25 (dd, J = 1.3, 10.5 Hz, 1H), 5.34 (dd, J = 1.3, 17.2 Hz, 1H), 5.84–5.98 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): mixture of two rotamers: δ = 17.0, 18.7 and 18.7, 18.8, 19.6 and 19.8, 27.5, 28.3, 30.0, 30.4 and 30.6, 63.1 and 64.8, 65.6 and 65.6, 76.9, 79.8 and 80.2, 118.8 and 118.8, 131.5, 155.4 and 155.9, 169.0, 170.6 and 171.1 ppm; MS (EI): m/z = 371 $[M]^+$; elemental analysis: calcd (%) for $C_{19}H_{33}NO_6$: C 61.43, H 8.95, N 3.77; found: C 61.48, H 8.67, N 3.65.

11: Morpholine (7.78 g, 89 mmol) in THF (10 mL) was slowly added to a solution of $[Pd(PPh_3)_4]$ (1.03 g, 0.89 mmol) and **10** (3.32 g, 8.9 mmol) in THF (40 mL) at room temperature. After being stirred overnight, the reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (120 mL), washed with HCl (1 M, 2×50 mL) and H_2O (100 mL), and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the residue was dissolved in Et_2O (120 mL), filtered, and concentrated. The crude acid was dissolved in CH_2Cl_2 (30 mL) followed by the sequential addition of **9**[24] (1.18 g, 7.4 mmol), EDC (1.71 g, 8.9 mmol), and DMAP (1.36 g, 11 mmol) at room temperature. After being stirred overnight, the reaction mixture was diluted with EtOAc (150 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL) and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography (hexane/EtOAc) to afford **11** (2.48 g, 71%, 2 steps). $[\alpha]_D^{16}$ = −86.7 (c = 1.11, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2970, 2876, 1751, 1700, 1469, 1391, 1193, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$): mixture of two rotamers: δ = 0.91 (d, J = 6.1 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.03–1.07 (m, 12H), 1.46 (s, 9H), 2.18–2.35 (m, 3H), 2.84 (s, 1.5H, one rotamer), 2.85 (s, 1.5H, other rotamer), 4.24 (d, J = 10.5 Hz, 0.5H, one rotamer), 4.52 (d, J = 10.5 Hz, 0.5H, other rotamer), 4.64 (d, J = 5.9 Hz, 2H), 4.91–4.93 (m, 2H), 5.25 (dd, J = 1.2, 10.5 Hz, 1H), 5.33 (dd, J = 1.2, 17.2 Hz, 1H), 5.85–5.94 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): mixture of two rotamers: δ = 16.8, 17.1, 18.6, 18.7 and 18.8, 18.8, 19.7 and 19.8, 27.6, 28.3, 30.1, 30.1, 30.4 and 30.8, 63.3 and 64.7, 65.7, 76.5, 77.1 79.8 and 80.2, 119.0, 131.4, 155.4 and 156.0, 168.7, 168.9, 170.5 and 171.0 ppm; MS (FAB): m/z = 472 $[M+H]^+$; elemental

analysis: calcd (%) for $C_{24}H_{41}NO_8$: C 61.13, H 8.76, N 2.97; found: C 60.89, H 8.69, N 3.05.

12: Morpholine (4.02 g, 46 mmol) in THF (10 mL) was slowly added to a solution of $[Pd(PPh_3)_4]$ (533 mg, 0.46 mmol) and **11** (2.18 g, 4.6 mmol) in THF (25 mL) at room temperature. After being stirred overnight, the reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (60 mL), washed with HCl (1 M, 2×30 mL) and H_2O (60 mL), and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the residue was dissolved in Et_2O (60 mL), filtered, and concentrated. The crude acid was dissolved in CH_2Cl_2 (20 mL) followed by the sequential addition of 2-(trimethylsilyl)ethanol (0.79 mL, 5.5 mmol), EDC (1.32 g, 6.9 mmol), and DMAP (564 mg, 4.6 mmol) at room temperature. After being stirred overnight, the reaction mixture was diluted with EtOAc (300 mL), saturated aqueous $NaHCO_3$ (150 mL), and brine (150 mL) and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography (hexane/EtOAc) to afford **12** (1.99 g, 81%, 2 steps). $[\alpha]_D^{16} = -76.3$ ($c = 1.16$, $CHCl_3$); IR (neat): $\tilde{\nu} = 2967, 2876, 1747, 1701, 1469, 1391, 1183, 1126\ cm^{-1}$; ^1H NMR ($CDCl_3$): mixture of two rotamers: $\delta = 0.00$ (s, 9H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.98–1.05 (m, 14H), 1.42 (s, 9H), 2.12–2.36 (m, 3H), 2.80 (s, 1.5H, one rotamer), 2.81 (s, 1.5H, other rotamer), 4.15–4.21 (m, 2H), 4.20 (d, $J = 10.5$ Hz, 0.5H, one rotamer), 4.48 (d, $J = 10.5$ Hz, 0.5H, other rotamer), 4.84 (d, $J = 4.2$ Hz, 1H), 4.87 ppm (d, $J = 4.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): mixture of two rotamers: $\delta = -1.7$, 16.8, 17.1, 17.3, 18.6, 18.7, 18.8, 19.7 and 19.8, 27.6, 28.3, 30.0, 30.0, 30.4 and 30.8, 63.2 and 64.7, 63.5, 76.5, 77.2, 79.8 and 80.2, 155.4 and 156.0, 168.9, 169.1, 170.5 and 171.0 ppm; MS (FAB): $m/z = 532$ $[M+H]^+$; elemental analysis: calcd (%) for $C_{26}H_{49}NO_8Si$: C 58.73, H 9.29, N 2.63; found: C 58.72, H 9.20, N 2.67.

14: $LiOH \cdot H_2O$ (55.9 mg, 1.3 mmol) was added to a solution of **7** (170 mg, 0.44 mmol) in THF/MeOH/H_2O (3:1:1, 10 mL) at 0 °C, and the reaction mixture was gradually warmed to room temperature. After being stirred for 18 h, HCl (1 M, 10 mL) was added, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL) and dried over Na_2SO_4. After filtration and concentration under reduced pressure, **8** (164 mg, quant) was obtained and was used directly in the next step without further purification. A solution of **12** (1.67 g, 3.1 mmol) in HCl (4 M)/EtOAc (15 mL) was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the residual HCl was removed by adding Et_2O (15 mL) to the hydrochloride salt **13** followed by its removal under reduced pressure. After repeating this procedure three times, **13** (1.47 g, quant) was obtained and used in the following reaction without further purification. Saturated aqueous $NaHCO_3$ (10 mL) was added to a solution of **13** (198 mg, 0.42 mmol) in CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5.0 mL), and the combined organic extracts were dried over Na_2SO_4. After filtration and concentration under reduced pressure, the resulting free amine (185 mg, quant) was obtained. Acid **8** (164 mg, 0.45 mmol) in CH_2Cl_2 (3.0 mL) was added to this sample of amine. The solvent was removed under reduced pressure, and the residue was treated with benzene (2.0 mL) followed by its removal under reduced pressure. After repeating this procedure twice, the residue was dried well in vacuo. The resulting residue was dissolved in DMF (4.0 mL) and treated with iPr$_2$NEt (164 mg, 1.3 mmol) and HATU (322 mg, 0.85 mmol) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for an additional 21 h. The solution was diluted with EtOAc (60 mL), washed with citric acid (1 M, 40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (40 mL), and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography (hexane/EtOAc) to afford **14** (225 mg, 68%). $[\alpha]_D^{24} = -65.6$ ($c = 1.24$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3312, 2966, 2883, 1746, 1647, 1508, 1368, 1179\ cm^{-1}$; ^1H NMR ($CDCl_3$): mixture of two rotamers: $\delta = 0.01$ (s, 9H), 0.81 (d, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 6.7$ Hz, 3H), 0.94–1.07 (m, 20H), 1,14 (d, $J = 7.0$ Hz, 3H), 1.41 (s, 9H), 1.46–1.50 (m, 4H), 1.87 (t, $J = 2.6$ Hz, 1H), 2.07–2.26 (m, 4H), 2.28–2.35 (m, 2H), 2.83 (s, 1H, one rotamer), 2.91–2.98 (m, 1H), 3.02 (s, 2H, other rotamer), 3.95–3.97 (m, 1H), 4.03–4.04 (m, 1H), 4.17–4.21 (m, 2H), 4.85 (d, $J = 4.3$ Hz, 1H), 4.91 (d, $J = 4.0$ Hz, 1H), 4.96 (d, $J = 10.4$ Hz, 1H), 5.04 (d, $J = 8.5$ Hz, 1H), 7.74 (d, $J = 9.1$ Hz, 0.75H, one rotamer), 7.78 ppm (d, $J = 9.4$ Hz, 0.25H, other rotamer); ^{13}C NMR ($CDCl_3$): mixture of two rotamers: $\delta = -1.7$, 15.4, 17.0, 17.1, 17.2, 17.4, 17.9 and 18.0, 18.6, 18.7, 18.8, 19.5, 19.8, 25.0 and 25.2, 27.5, 28.2 and 28.3, 29.0 and 32.0, 30.0, 30.0, 30.6, 33.3 and 33.4, 38.3 and 38.8, 51.5 and 51.8, 60.0 and 60.1, 61.1, 63.6 and 63.7, 68.5, 76.9 and 77.4, 77.3 and 77.5, 79.5, 83.9 and 84.1, 155.7, 168.4 and 168.7, 169.0 and 169.1, 169.4 and 170.2, 171.7, 176.6 and 176.7 ppm; MS (FAB): $m/z = 783$ $[M+H]^+$; elemental analysis: calcd (%) for $C_{40}H_{71}N_3O_{10}Si$: C 61.43, H 9.15, N 5.37; found: C 61.14, H 9.14, N 5.47.

17: A solution of **14** (81.0 mg, 0.10 mmol) in THF (2.0 mL) was treated with TBAF in hexane (1 M, 0.26 mL, 0.26 mmol) at 0 °C. After being stirred at 0 °C for 5 min, the reaction mixture was warmed to room temperature and stirred for an additional 20 min. The solution was diluted with EtOAc (30 mL), washed with HCl (0.5 M, 3×15 mL), H_2O (15 mL), and brine (15 mL), and dried over Na_2SO_4. Filtration and concentration under reduced pressure afforded **15**. Another sample of **14** (80.2 mg, 0.10 mmol) was treated with HCl (4 M)/EtOAc (5.0 mL), and the mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the residual HCl was removed by adding Et_2O (5.0 mL) to the hydrochloride salt **16** followed by its removal under reduced pressure. After repeating this procedure three times, **16** was obtained. Acid **15** in CH_2Cl_2 (5.0 mL) was added to this sample of **16**. The solvent was removed under reduced pressure, and the residue was treated with benzene (1.5 mL) followed by its removal under reduced pressure. After repeating this procedure twice, the residue was dried well in vacuo. The resulting residue was dissolved in DMF (2.5 mL) and was treated with 2,4,6-collidine (37.3 mg, 0.31 mmol) and HATU (58.5 mg, 0.15 mmol) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for an additional 25 h. The solution was diluted with EtOAc (30 mL), washed with citric acid (1 M, 20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography (hexane/EtOAc) to afford **17** (121 mg, 88%). $[\alpha]_D^{18} = -70.2$ ($c = 1.11$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3309, 2967, 2876, 1745, 1649, 1510, 1465, 1186\ cm^{-1}$; ^1H NMR ($CDCl_3$): mixture of some rotamers: $\delta = 0.00$ (s, 9H), 0.80–1.21 (m, 56H), 1.40 (s, 9H), 1.44–1.54 (m, 8H), 1.86 (br s, 1H), 1.90 (br s, 1H), 2.08–2.31 (m, 12H), 2.82 (s, 1.2H, rotamer), 2.90–2.97 (m, 2H), 3.00 (s, 2.4H, rotamer), 3.02 (s, 2.4H, rotamer), 3.95–4.11 (m, 3H), 4.13–4.31 (m, 3H), 4.84–5.04 (m, 7H), 6.67 (d, $J = 8.3$ Hz, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 7.69 (d, $J = 9.3$ Hz, 0.75H, rotamer), 7.75 ppm (d, $J = 8.8$ Hz, 0.25H, rotamer); ^{13}C NMR ($CDCl_3$): major rotamer: $\delta = -1.7$, 15.3, 15.3, 17.0, 17.1, 17.2, 17.3, 17.5, 17.7, 17.9, 18.0, 18.5, 18.6, 18.7, 18.7, 18.7, 19.0, 19.3, 19.4, 19.8, 19.9, 25.2, 25.2, 27.5, 27.6, 28.3, 29.0, 30.0, 30.1, 30.6, 30.7, 31.2, 32.0, 32.1, 33.2, 33.4, 38.2, 38.4, 51.6, 51.7, 58.4, 58.5, 61.2, 61.4, 63.5, 68.5, 68.6, 76.9, 77.5, 77.6, 77.8, 79.3, 79.4, 83.9, 84.0, 155.6, 168.3, 168.4, 168.6, 169.0, 170.1, 170.4, 170.5, 171.6, 176.5, 176.6 ppm; HRMS (ESI): m/z calcd for $C_{70}H_{121}N_6O_{17}Si$: 1345.8552 $[M+H]^+$; found: 1345.8601.

1: TBAF in hexane (1 M, 0.072 mL, 0.072 mmol) was added to a solution of **17** (39.1 mg, 0.029 mmol) in THF (0.71 mL) at 0 °C. After being stirred at 0 °C for 5 min, the reaction mixture was warmed to room temperature and stirred for an additional 50 min. The solution was diluted with EtOAc (30 mL), washed with HCl (0.5 M, 3×10 mL), H_2O (10 mL), and brine (10 mL), and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product **18** was obtained. Crude **18** was treated with HCl (4 M)/EtOAc (1.5 mL), and the mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the residual HCl was removed by adding Et_2O (3.0 mL) to the hydrochloride salt **19** followed by its removal under reduced pressure. After repeating this procedure three times, **19** was obtained. Hydrochloride salt **19** in CH_2Cl_2 (5.8 mL) was slowly added to a solution of EDC (27.7 mg, 0.15 mmol), HOAt (19.7 mg, 0.15 mmol), and iPr$_2$NEt (18.8 mg, 0.15 mmol) in CH_2Cl_2 (23 mL) at 0 °C. After being stirred at 0 °C for 24 h, the reaction mixture was diluted with $CHCl_3$ (30 mL), washed with citric acid (1 M, 10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography ($CHCl_3$/EtOAc) to afford **1** (15.1 mg, 46%).

Further purification was performed using reverse-phase HPLC for spectroscopic analysis in detail. $[\alpha]_D^{22} = -68.3$ ($c = 0.18$, $CHCl_3$); IR (neat): $\tilde{\nu} =$ 3307, 2964, 2928, 1746, 1680, 1634, 1512, 1189, 1129 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.81$ (d, $J = 6.8$, 6H), 0.90 (d, $J = 7.1$ Hz, 6H), 0.93 (d, $J =$ 6.8 Hz, 6H), 0.96 (d, $J = 7.1$ Hz, 6H), 1.00 (d, $J = 6.8$ Hz, 6H), 1.04 (d, $J =$ 6. 8 Hz, 6H), 1.04 (d, $J = 6.8$ Hz, 6H), 1.06 (d, $J = 6.6$ Hz, 6H), 1.15 (d, $J = 7.3$ Hz, 6H), 1.25–1.67 (m, 8H), 1.88 (t, $J = 2.6$ Hz, 2H), 2.05–2.20 (m, 6H), 2.37–2.47 (m, 4H), 2.61–2.65 (m, 2H), 2.76 (dq, $J = 2.3$, 7.2 Hz, 2H), 2.86 (s, 6H), 3.89–3.94 (m, 2H), 4.42 (dd, $J = 3.2$, 8.3 Hz, 2H), 5.21 (d, $J =$ 2.7 Hz, 2H), 5.32 (d, $J = 11.2$ Hz, 2H), 5.59 (d, $J = 2.7$ Hz, 2H), 6.37 (d, $J = 8.3$ Hz, 2H), 8.99 ppm (d, $J = 9.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta =$ 15.3, 16.1, 16.4, 16.5, 17.6, 18.1, 18.7, 19.0, 19.5, 20.0, 25.5, 26.6, 28.0, 30.0, 30.1, 31.2, 34.0, 39.0, 52.3, 58.7, 59.7, 68.7, 75.3, 78.3, 83.8, 165.2, 169.7, 170.5, 170.6, 176.3 ppm; MS (FAB): $m/z = 1128$ $[M+H]^+$, 1150 $[M+Na]^+$; HRMS (ESI): m/z calcd for $C_{60}H_{99}N_6O_{14}$: 1127.7214 $[M+H]^+$; found: 1127.7161; m/z calcd for $C_{60}H_{98}N_6NaO_{14}$: 1149.7033 $[M+Na]^+$; found: 1149.6999; HPLC for analysis (GL Sciences Inertsil C8–3, 5 μm, 4.6×250 mm, $MeCN/H_2O = 7:3$, flow rate = 1.0 mL min^{-1}): $t_R = 17.6$ min; HPLC for preparation (GL Science Inertsil C8–3, 5 μm, 10×250 mm, $MeCN/H_2O = 7:3$, flow rate = 4.5 mL min^{-1}): $t_R = 24.8$ min.

20: $[\alpha]_D^{21} = -107.4$ ($c = 0.79$, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 0.90$ (d, $J =$ 5.8, 6H), 0.90 (d, $J = 6.7$ Hz, 6H), 0.94 (d, $J = 6.7$ Hz, 6H), 0.96 (d, $J =$ 7.0 Hz, 6H), 0.97 (d, $J = 6.7$ Hz, 6H), 0.98 (d, $J = 6.$ 7 Hz, 6H), 1.03 (d, $J = 7.0$ Hz, 6H), 1.08 (d, $J = 6.4$ Hz, 6H), 1.10 (d, $J = 7.0$ Hz, 6H), 1.44–1.54 (m, 8H), 1.89 (t, $J = 2.6$ Hz, 2H), 2.12–2.17 (m, 2H), 2.19–2.26 (m, 4H), 2.28–2.42 (m, 6H), 2.88 (dq, $J = 3.0$, 7.0 Hz, 2H), 2.96 (s, 6H), 4.03–4.06 (m, 2H), 4.39 (dd, $J = 5.3$, 8.7 Hz, 2H), 5.09 (d, $J = 4.9$ Hz, 2H), 5.13 (d, $J = 10.7$ Hz, 2H), 5.29 (d, $J = 3.0$ Hz, 2H), 6.73 (d, $J = 8.5$ Hz, 2H), 7.47 ppm (d, $J = 5.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 14.4$, 16.7, 17.2, 17.6, 17.9, 18.6, 19.0, 19.2, 19.5, 19.9, 24.9, 26.6, 29.3, 29.7, 30.3, 31.1, 32.0, 38.6, 51.1, 58.8, 60.9, 68.6, 76.9, 79.7, 84.0, 168.3, 169.5, 170.6, 170.7, 175.7 ppm; HRMS (ESI): m/z calcd for $C_{60}H_{99}N_6O_{14}$: 1127.7214 $[M+H]^+$; found: 1127.7158; m/z calcd for $C_{60}H_{98}N_6NaO_{14}$: 1149.7033 $[M+Na]^+$; found: 1149.7004.

21: $[\alpha]_D^{17} = -17.8$ ($c = 0.17$, $CHCl_3$); ^1H NMR ([D_6]DMSO, 150 °C, DMSO: $\delta = 2.50$ ppm): $\delta = 0.88$ (d, $J = 6.8$, 6H), 0.90 (d, $J = 6.8$ Hz, 6H), 0.92 (d, $J = 6.8$ Hz, 6H), 0.95 (d, $J = 6.8$ Hz, 6H), 0.97 (d, $J = 6.8$ Hz, 6H), 1.00 (d, $J =$ 7. 8 Hz, 6H), 1.02 (d, $J = 7.1$ Hz, 6H), 1.04 (d, $J = 6.8$ Hz, 6H), 1.06 (d, $J = 6.8$ Hz, 6H), 1.40–1.62 (m, 8H), 2.09–2.34 (m, 6H), 2.37 (t, $J = 2.6$ Hz, 2H), 2.49–2.75 (m, 8H, overlapped by the peaks of DMSO and H_2O), 3.05 (brs, 3H), 3.13 (brs, 3H), 3.89–3.95 (m, 2H), 4.19 (dd, $J = 6.1$, 8.1 Hz, 2H), 4.76–4.81 (m, 2H), 4.97 (d, $J = 5.1$ Hz, 2H), 5.01 (d, $J =$ 4.9 Hz, 2H), 7.55 (d, $J = 8.6$ Hz, 2H), 7.87 (d, $J = 7.6$ Hz, 2H); HRMS (ESI): m/z calcd for $C_{60}H_{99}N_6O_{14}$: 1127.7214 $[M+H]^+$; found: 1127.7182; m/z calcd for $C_{60}H_{98}N_6NaO_{14}$: 1149.7033 $[M+Na]^+$; found: 1149.7019.

27: Wang resin (1.10 mmol g^{-1} 400 mg, 0.44 mmol) was washed with THF (3×5 mL, 3 min), suspended with THF (4.0 mL), and treated with **23**,[22] DIC (0.20 mL, 1.3 mmol), and DMAP (53.8 mg, 0.44 mmol). After being shaken for 12 h at room temperature, Ac_2O (0.19 mL, 2.0 mmol) and pyridine (0.16 mL, 2.0 mmol) were added, and the mixture was shaken for 1 h to block any unreacted hydroxy groups on the resin. The resulting resin was filtered, washed successively with THF (3×5 mL, 3 min), MeOH (2×5 mL, 3 min), DMF (2×5 mL, 3 min), MeOH (2×5 mL, 3 min), DMF (2×5 mL, 3 min), CH_2Cl_2 (3×5 mL, 3 min), and Et_2O (2× 5 mL, 3 min), and dried in vacuo to afford resin **24** (489 mg). After swelling of **24** (489 mg) in CH_2Cl_2 (5 mL, 30 min) and subsequent filtration, the resin was suspended in CH_2Cl_2/MeOH (97:3) (10 mL), treated with *p*-TsOH·H_2O (50.0 mg, 0.26 mmol) for 1.5 h at room temperature, and filtered. After repeating this procedure, the resulting resin was washed with CH_2Cl_2 (3×5 mL, 2 min), MeOH (5 mL, 2 min), CH_2Cl_2 (5 mL, 2 min), MeOH (5 mL, 2 min), CH_2Cl_2 (3×5 mL, 2 min), and Et_2O (2×5 mL, 2 min), and dried in vacuo. The resulting resin was coupled with **23**[23] followed by the removal of the THP group according to the same procedure mentioned above to give resin **26** (487 mg). Resin **26** (416 mg) was coupled with Fmoc-(*S*)-MeVal (467 mg, 1.3 mmol) by using DIC (0.20 mL, 1.3 mmol) and DMAP (53.8 mg, 0.44 mmol) according to the same procedure mentioned above to afford resin **27** (548 mg). To determine the loading level of **27**, a weighed sample of the dry **27** (10.0 mg) was treated with 20% piperidine in DMF (5.0 mL) for 5 min at room temperature to release the Fmoc group. After accurate dilution with the same solution, the loading level of **27** was determined to be 0.394 mmol g^{-1} by UV/Vis spectroscopic analysis.

29: After swelling of **27** (310 mg) in DMF (4 mL, 30 min) and subsequent filtration, the resin was treated with 20% piperidine in DMF (4.0 mL) for 5 min at room temperature. After filtration, the resulting resin was washed with DMF (4 mL, 2 min) and again treated with 20% piperidine in DMF (4.0 mL) for 2 min at room temperature. After filtration, the resin was washed successively with DMF (2×4 mL, 2 min), MeOH (2× 4 mL, 2 min), DMF (2×4 mL, 2 min), MeOH (2×4 mL, 2 min), CH_2Cl_2 (3×4 mL, 2 min), and Et_2O (2×4 mL, 2 min), and dried in vacuo. The resulting resin was swelled in DMF (4 mL, 30 min), filtered, and suspended with DMF (0.40 mL). HATU (212 mg, 0.56 mmol) and *i*Pr_2NEt (144 mg, 1.1 mmol) were added to a solution of **28** (222 mg, 0.56 mmol) in DMF (2.0 mL), and the reaction mixture was stirred for 10 min at room temperature. The reaction solution was added to the resin with DMF (0.8 mL), and the resulting mixture was shaken for 12 h. After filtration, the resulting resin was washed with DMF (3×3 mL, 3 min), MeOH (3 mL, 3 min), CH_2Cl_2 (3 mL, 3 min), MeOH (3 mL, 3 min), CH_2Cl_2 (3× 3 mL, 3 min), and Et_2O (2×3 mL, 3 min), and dried in vacuo. After this coupling procedure was repeated, resin **29** (290 mg, 0.311 mmol g^{-1}, 89% yield from **27**) was obtained.

30: The Fmoc group of **29** was removed by the procedure mentioned above. The resulting resin was coupled with Fmoc-(*S*)-Val (181 mg, 0.53 mmol) by treatment with HATU (203 mg, 0.53 mmol) and *i*Pr_2NEt (138 mg, 1.1 mmol) according to the procedure mentioned above to afford resin **30** (299 mg).

Cleavage of the Fmoc-protected amino acid **31** from the resin and synthesis of **1**: After swelling of **30** (299 mg) in CH_2Cl_2 (3 mL, 30 min) and subsequent filtration, the resin was treated with TFA/CH_2Cl_2 (1:1, 5.0 mL) for 1 h at room temperature. After filtration and washing of the resin with CH_2Cl_2 (5×3 mL, 3 min), all the filtrates were combined, diluted with CH_2Cl_2 (15 mL), washed with H_2O (2×10 mL), and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography ($CHCl_3$/MeOH/AcOH) to afford resin **31** (77.6 mg, quant from **29**). Diethylamine (0.50 mL) was added to a solution of **31** (77.6 mg) in THF (1.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, then at room temperature for 2 h, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (96 mL) and treated with EDC (92.2 mg, 0.48 mmol), HOAt (65.7 mg, 0.48 mmol), and *i*Pr_2NEt (62.4 mg, 0.48 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then at room temperature for 39 h, diluted with $CHCl_3$, washed with citric acid (1 M, 10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by silica-gel chromatography ($CHCl_3$/EtOAc) to afford **1** (32.6 mg, 30%, 2 steps).

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