Article

Toward the Creation of Induced Pluripotent Small (iPS) Molecules: Establishment of a Modular Synthetic Strategy to the Heronamide C-type Polyene Macrolactams and Their Conformational and Reactivity Analysis

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Abstract

A highly modular synthetic strategy to the heronamide C-type polyene macrolactams was established by synthesizing 8-deoxyheronamide C (**2**). The developed strategy enabled not only the total synthesis of 8-deoxyheronamide C (**2**) but also the unified synthesis of four heronamide-like molecules named "heronamidoids" (**5**–**8**). Conformational and reactivity analysis of the heronamidoids clarified that (1) the C19 stereochemistry mainly affected the conformation of the amide linkage, resulting in the change of alignment of two polyene units and reactivity towards photochemical [6π+6π] cycloaddition, and (2) the C8,C9-diol moiety is important for the conversion to the heronamide A-type skeleton from the heronamide C skeleton.

Introduction

Polyene macrolactams are a growing family of structurally diverse natural products possessing a broad spectrum of biological activities, which include antibacterial,[1,2] antifungal,[1,3] antitrypanosomal,[4] anti-inflammatory,[5] and anticancer activities.[2,6-8] Some of them have been isolated from cultures of symbiotic microbes[1,9] or co-cultures of two different microorganisms,[10] suggesting that these compounds possess as-yet-unknown roles in mutualism and chemical communication between living species.

Among this class of natural products, heronamides[3,11-14] and the related compounds[15-21] constitute an intriguing and remarkable class not only because of their structural diversity and complexity (Figure 1; see also Supporting Figure 1 for the structure of all reported heronamides) but also because of their biogenesis and potent biological activity.[22-24] Biogenetic relationships among heronamides A–C and D–F have been examined in detail by our group[3,25] and others[26-28] both experimentally[25,26,28] and computationally.[27] For example, we demonstrated that conversion of heronamide C (**1**) to heronamides A and B took place in a thermal/aerobic and a photochemical fashion, respectively.[3,25] From the viewpoint of biological activity, heronamide C (**1**) induces a reversible morphological change against HeLa cells.[11] Moreover, **1** and 8-deoxyheronamide C (**2**), a biogenetic precursor of heronamides A–C, have been shown to bind to lipid membranes made up of phospholipids with saturated hydrocarbon chains and to exhibit growth inhibition against fission yeast with an as-yet-unrevealed mode of action.[3]

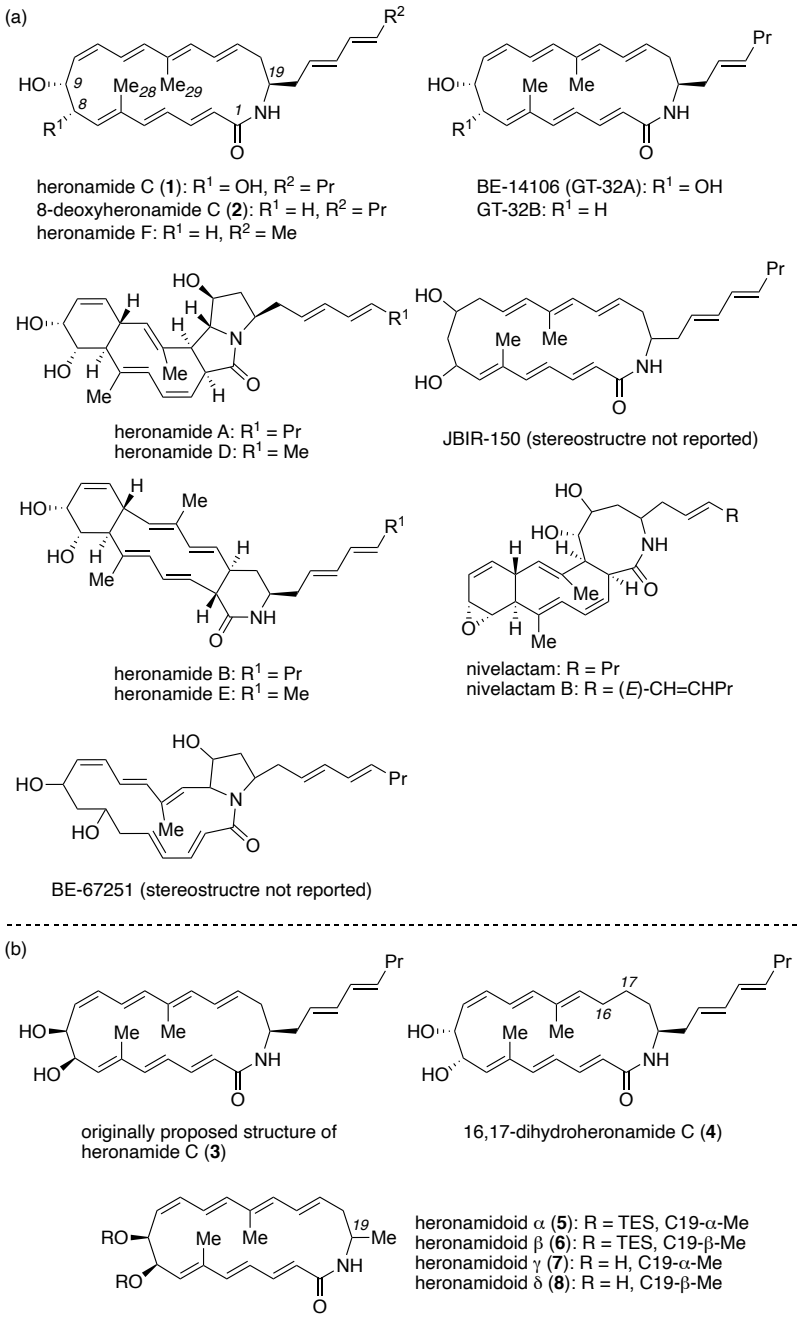


Figure 1. Structures of heronamides (selected) and related polyene macrolactams.

a) Natural products, b) synthetic analogues.

Intrigued by the chemistry and biological activity of heronamides, we have been undertaking

synthetic and chemical biology research programs. Our synthetic efforts culminated in the first total synthesis of the originally proposed structure of heronamide C (**3**)[29] (Figure 1b), structure revision of heronamide C, and the synthesis of the revised structure of heronamide C (**1**).[25] However, to synthesize each of these structures, we had to develop different tactics, as shown in Figure 2 and discussed in detail later. Moreover, our previous synthetic strategies to the polyene fragments relied on classical Wittig-type homologation sequences[29] and Ti-mediated alkyne-alkyne coupling,[25] which has low functional group compatibility, so that we were forced to take longer synthetic steps. Therefore, we decided to develop general synthetic tactics to synthesize not only natural products and molecular probes for the mode-of-action analysis, but also heronamide-like "induced pluripotent small" (iPS) molecules, that were named after iPS cells[30] and would differentiate into diverse molecular entities having different biological activity in response to external stimuli, such as heat and light, as heronamide C (**1**) does.

Toward this end, we re-examined the methods for construction of the framework of polyenes and their cyclization and established a unified modular strategy for the heronamide C-type macrolactams, including 8-deoxyheronamide C (**2**), *ent*-heronamide C (*ent*-**1**), heronamide-like molecules named “heronamidoids α–δ” (**5**–**8**), and 16,17-dihydroheronamide C (**4**), which was originally designed as a stable analog of **1** for the mode-of-action study. Herein and in a subsequent note,[31] we report our efforts to develop (1) the modular synthetic strategy toward the heronamide C-

type macrolactams, (2) the design and synthesis of the heronamide C analogues mentioned above, and (3) the biological activity of *ent*-heronamide C (*ent*-**1**) and 16,17-dihydroheronamide C (**4**). This article mainly focuses on the development of the modular strategy by executing the synthesis of 8-deoxyheronamide C (**2**) and heronamidoids, as well as their conformational and reactivity analysis towards the creation of iPS molecules. Following this article, we have also provided a note focused on the design, synthesis and biological activity of *ent*-heronamide C (*ent*-**1**) and 16,17-dihydroheronamide C (**4**).

Results and Discussion

Establishment of a modular synthetic strategy to heronamide C-type polyene macrolactams: Synthesis of 8-deoxyheronamide C

Our previous strategies towards the heronamide C-skeleton are summarized in Figure 2. To synthesize the originally proposed structure **3** (Figure 1b), intermolecular Stille coupling between C11 iodide and C12 tributylstannane was first chosen as a key reaction (Figure 2a). However, the reaction gave the coupling product only in 8% yield[29] and the resulting unstable nonaene intermediate could not be used further. On the other hand, its intramolecular version, i.e., intramolecular Stille coupling, worked to give the corresponding macrocycle in 48% yield (Figure 2b), which could be used for the total synthesis of **3**.[29] Unfortunately, the same strategy did not work for the substrate designed for the

total synthesis of **1** (Figure 2c).[25] After many attempts, a ring-closing metathesis strategy using diacetate substrate was found to be effective in 11% but reproduceable yield (Figure 2d), culminating in the total synthesis of **1**.[25] However, the RCM strategy did not work for the substrate for the 8-deoxyheronamide C synthesis (Figure 2e: data not shown).

The difficulty of constructing the macrocyclic frameworks was attributed to the assembly of unstable polyene systems and the following construction of the polyene macrocycles. As for the macrocycle structure, DFT calculation suggested that the heronamide-C macrocycle had a strained barrel-like structure with a bended C19-C7 trienamide unit and a C10-C17 tetraene unit that were in perfect alignment (Figure 2f).

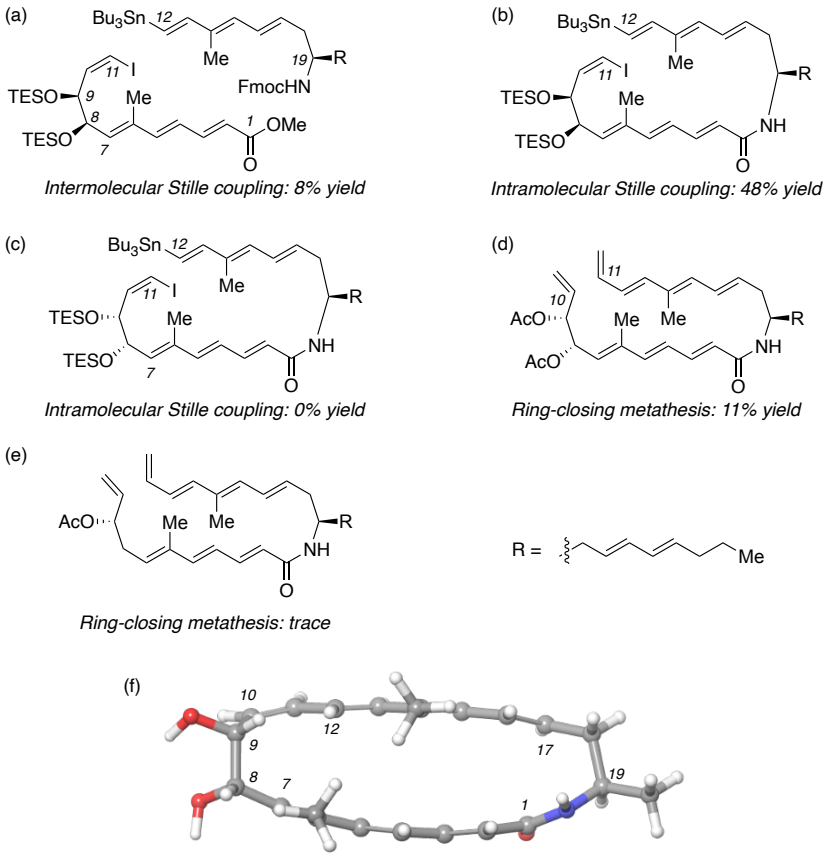
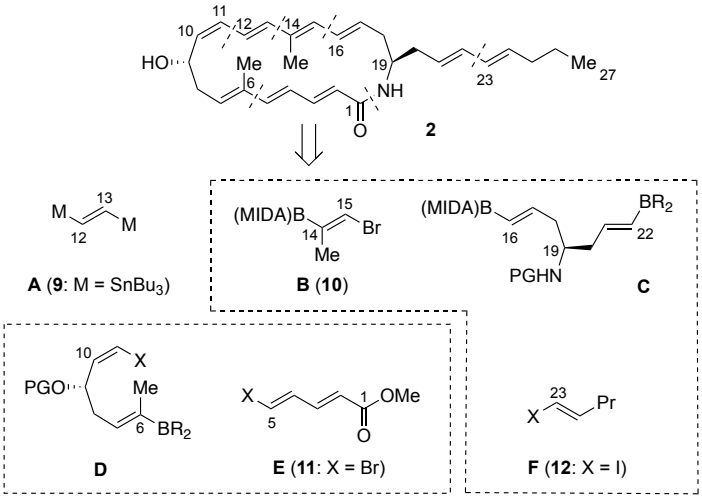


Figure 2. Previous synthetic strategies for the construction of heronamide C-type macrocycles, and calculated conformation of the heronamide C macrocycle. (a–e) Key reactions of the previous strategies, (f) DFT-calculated structure of the heronamide C macrocycle.

Thus, as stated before, we decided to develop a general strategy to synthesize not only natural products but also their derivatives. Again, our great interest is the creation of heronamide C-like induced pluripotent small (iPS) molecules. Like iPS cells,[30] iPS molecules should differentiate in response to various external stimuli and environments into diverse molecular entities, such as various heronamides, each having a different biological activity.

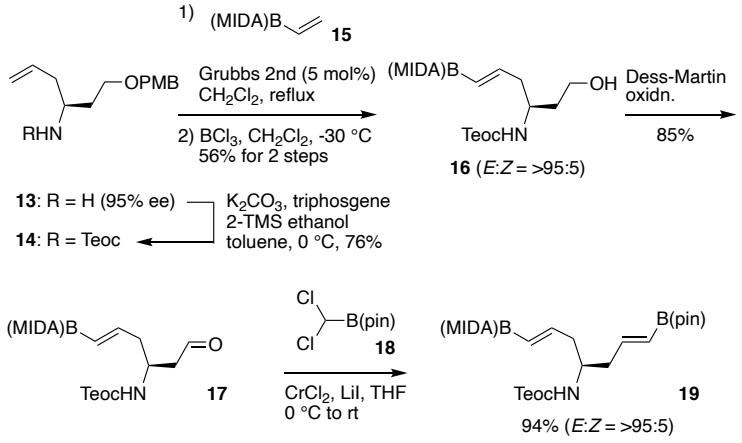
To develop the general strategy, we decided to take a modular approach to search for an efficient way to construct the macrocyclic skeleton. A modular and unified strategy is well suited for the synthesis of analogs and derivatives.[32,33] Toward this end, we selected 8-deoxyheronamide C (**2**) as an initial target, and it was divided into six fragments **A**–**F**, as shown in Scheme 1. In this retrosynthetic disconnection, modular Suzuki coupling[34] utilizing MIDA boronate ester[35] was chosen as a primary strategy for the fragment assembly. However, for the connection of the C11-C14 linkage, vinyldistannane **9** was finally selected as a linchpin (vide infra). Fragments **9**,[36] **10**,[37] **11**[38] and **12**[39] have been described in the literature; thus, we first developed the chiral synthesis of fragments **C** and **D**.



Scheme 1. Retrosynthetic disconnection of 8-deoxyheronamide C (**2**) and fragment assembly

C16-C22 Pseudosymmetric fragment **C** was synthesized as shown in Scheme 2. The starting

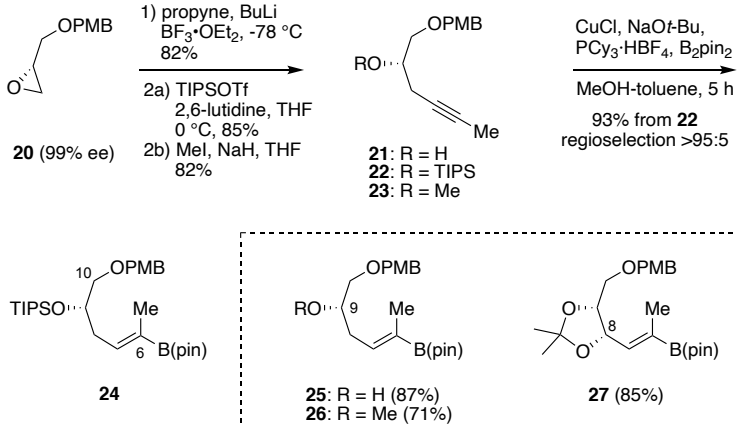
homoallylamine **14** was prepared in 95% ee by using a Kobayashi transfer aminoallylation reaction[40] and the following Teoc protection. As an amine protecting group, we utilized the Teoc group because it was found to be well compatible with the Suzuki coupling conditions utilized later. Olefin metathesis of **14** with vinylboronic acid MIDA ester (**15**)[41] and the following removal of the PMB group using BCl_3 afforded (*E*)-vinylboronic acid ester **16** in 56% yield over 2 steps. Compound **16** was oxidized using Dess-Martin periodinane to give aldehyde **17** in 85% yield. Then, Takai-Utimoto olefination of aldehyde **17** using dichloromethylboronic acid pinacol ester **18**[42] afforded (*E*,*E*)-bisvinylboronic acid diester **19**, i.e., fragment **C**, exclusively in 94% yield.



Scheme 2. Synthesis of C16-C22 pseudosymmetric fragment **19**

A synthetic equivalent of C6-C10 Fragment **D** was synthesized from known chiral epoxide **20**[43] (Scheme 3). Introduction of a propyne unit using Yamaguchi conditions[44] followed by TIPS

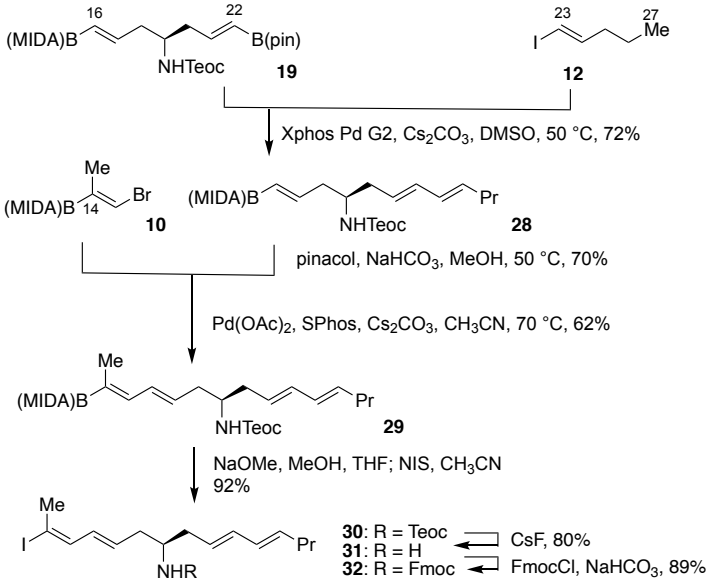
protection of the resulting alcohol afforded internal alkyne **22** in 70% yield in 2 steps. Compound **22** was treated under the borylcupration/protonation conditions developed by Ito[45,46] with a slight modification to give C6-C10 vinylboronic acid ester **24** in 93% yield and in a regioselective manner. It should be noted that the regioselectivity of this Cu(I)-mediated reaction (>95:5) was not affected by the protection form on the C9 hydroxyl group (i.e., compounds **25** and **26**) or the presence of C8 oxygen functionality (compound **27**), suggesting the broad substrate scope of this reaction. Compound **27** and its enantiomer could be used for the synthesis of the natural form of heronamide C (**1**) and its enantiomer (*ent*-**1**), respectively.



Scheme 3. Synthesis of C6-C10 Fragment **24**

Having all fragments in hand, we next focused on the fragment assembly. Installation of C14-C17 and C21-C24 diene units onto C16-C22 pseudosymmetric diboronic acid ester **19** (i.e., **B** + **C** + **F** in Scheme 1) was accomplished by using the MIDA boronate strategy utilizing successive

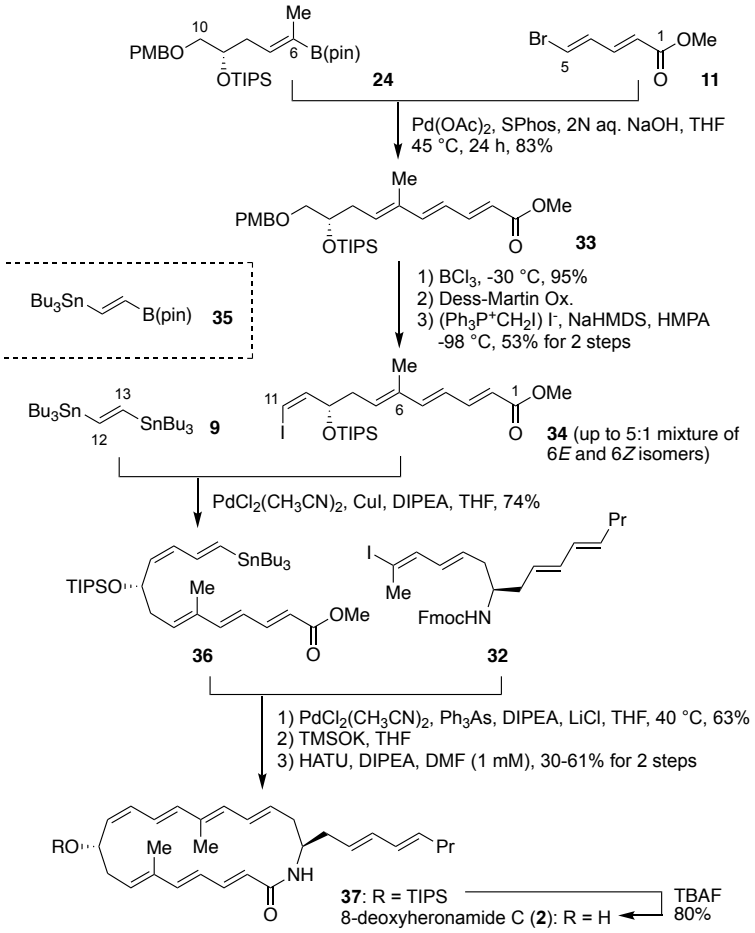
Suzuki coupling reactions[47] (Scheme 4). Installation of the C23-C27 side-chain unit onto **19** was performed first: Coupling of **19** and **12** (i.e., **C** + **F**) was achieved by using Xphos Pd G2 precatalyst to give triene **28** in 72% yield. In contrast, the combination of $Pd(OAc)_2$ and SPhos in CH_3CN was most suitable for the coupling of pinacol ester derived from **28** with C14-C15 MIDA ester **10** to produce tetraene **29** in 62% yield. Successive substitution of the boronic acid ester unit to iodine and the exchange of the amine protecting group from Teoc group to the more labile Fmoc group furnished C14-C27 tetraene fragment **32** in a straightforward manner (66% overall yield).



Scheme 4. Fragment assembly: Installation of C14-C17 fragment **10** and C21-C24 diene fragment **12** on C16-C22 pseudosymmetric amine **19**

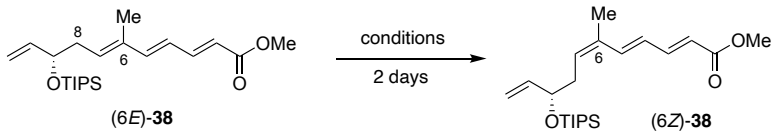
Assembly of all fragments and the endgame are summarized in Scheme 5. Coupling of C6-

C10 fragment **24** and C1-C5 bromodienylester **11** afforded (*E,E,E*)-triene **33** in 83% yield. Introduction of the (*Z*)-vinyl iodide moiety was accomplished in 3 steps including the Stork-Wittig reaction to give C1-C11 tetraene **34** in 53% for three steps. However, to our surprise, tetraene **34** was isolated as an up to 5:1 hardly separable mixture of (6*E*)- and (6*Z*)-isomers, indicating the isomerization of C6-C7 trisubstituted olefin.



Scheme 5. Assembly of all fragments and total synthesis of 8-deoxyheronamide C (**2**)

To understand the origin of the isomerization, separable deiodinated tetraene (6*E*)-**38** was prepared from **34** (Bu_3SnH, $Pd(PPh_3)_4$, benzene, at 40 °C; then separated from (6*Z*)-**38**), and treated under the conditions listed in Table 1. It was observed that (6*E*)-**38** isomerized in a neat form (entry 1) or in $CDCl_3$ solution under light or dark conditions (entries 2, 3). However, (*6E*)-**38** did not isomerize at all under the basic conditions under a fluorescent lamp (entry 4). These results suggested that the isomerization proceeded in the presence of trace acid, possibly through a conjugated pentadienyl cation produced by facile protonation at C7 (Figure 3). Unfortunately, we were unable to completely suppress the isomerization from (6*E*)-**34** to (6*Z*)-**34**.



(6*E*)-**38** (6*Z*)-**38**

entry	conditions	ratio (6*E*:6*Z*)
1	neat, 4 °C [a]	1 : 0.2
2	fluorescent lamp, $CDCl_3$, rt [b]	1 : 0.27
3	dark, $CDCl_3$, rt [b]	1 : 0.08
4	fluorescent lamp, pyridine-d_5, rt [b]	1 : 0

a) stored in a refrigerator; b) stored in an NMR tube.

Table 1. Isomerization of the C6-trisubstituted olefin of (6*E*)-**38**

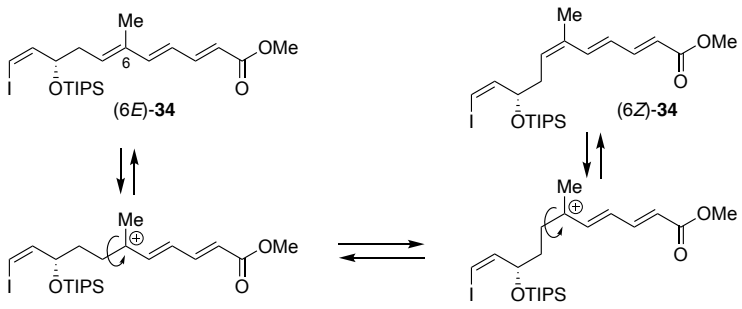


Figure 3. Proposed mechanism for the isomerization of C6-trisubstituted olefin of (6*E*)-**34**

By using an *E*/*Z* mixture of **34**, introduction of the C12-C13 olefin unit was accomplished using an excess amount (15 equiv.) of vinyldistannane **9** under Stille coupling conditions to give pentaene **36** in 74% yield (Scheme 5). Stille coupling of vinylboronic acid ester counterpart **35** with **34** also proceeded well to give pentaenyl boronic acid ester **39** (Figure 4a) in 88% yield, but the resulting **39** was relatively unstable compared with **36**. Thus, we chose Stille coupling for construction of the C11-C14 linkage.

Intermolecular Stille coupling of pentaene **36** and tetraene **32** utilizing triphenylarsine as ligand proceeded to give an unstable coupling product in 63% yield. Concomitant deprotection of the C1-methyl ester and Fmoc group using TMSOK followed by macrolactamization using HATU gave TIPS-protected 8-deoxyheronamide C (**37**) in 30~61% yield in two steps. A macrocyclic product having 6Z-stereochemistry was not observed. Finally, deprotection of the TIPS group using TBAF furnished 8-deoxyheronamide C (**2**) in 80% yield. All the physicochemical data of synthetic compound **2** are in good agreement with those of natural 8-deoxyheronamide C.

It should be noted that, in the endgame strategy, the order of coupling (**34** + **9**, then **32**) was quite important: Coupling of **32** with **9** under standard conditions ($PdCl_2(CH_3CN)_2$, DIPEA, THF, rt) gave pentaene **40** (Figure 4b), but the following coupling with **34** did not give any coupling product. In addition, intramolecular Stille coupling of **41** (Figure 4c), which is a similar strategy to those shown in Figure 2b and 2c, did not give the desired macrocycle.

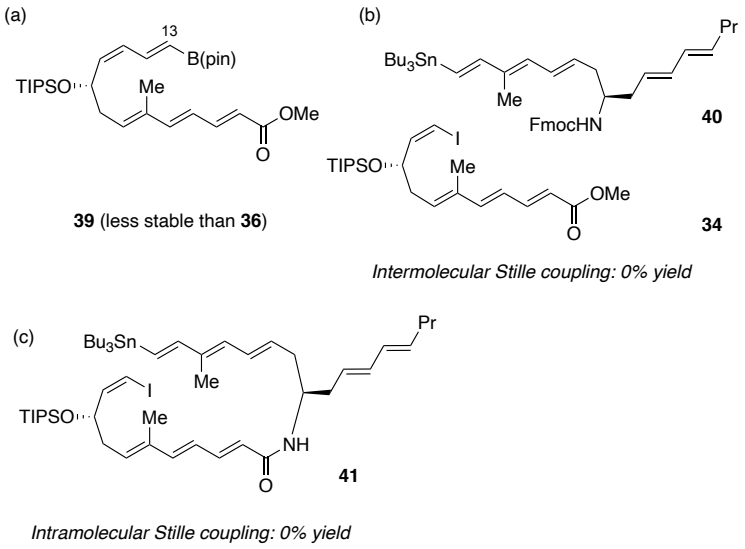


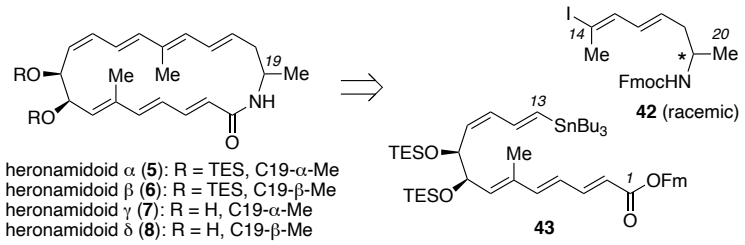
Figure 4. Unsuccessful strategies

Synthesis of heronamide-like molecules (heronamidoids) via a unified strategy

As described earlier, we previously had to adopt different strategies for the synthesis of different macrocyclic structures (Figure 2),[25,29] presumably because the macrocycles take different stable conformations depending on the substitution pattern and/or relative stereochemistry of

substituents. Thus, the next question is whether the developed strategy described herein could be applied to the synthesis of macrolactams having different substitution patterns.

To answer this question, we next planned to synthesize simple heronamide C-like molecules that we named heronamidoids α–δ (**5**–**8**), which have heronamide C type- and originally proposed structure-type substitution patterns (Scheme 6). In addition, we planned to utilize these molecules as scaffolds of iPS molecules.

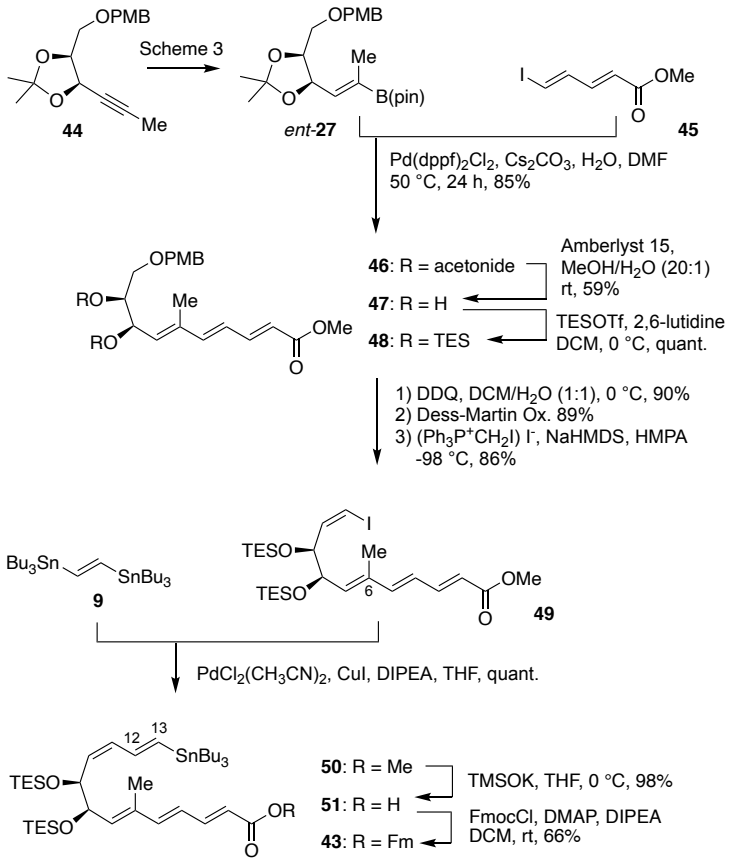


Scheme 6. Retrosynthetic disconnection of heronamidoids α–δ (**5**–**8**). Fm = fluorenylmethyl.

Heronamidoids α–δ (**5**–**8**) possess a common C1-C13 carboxylic acid moiety and only differ in their C19 stereochemistries and C8,C9-oxygen-protecting forms. As such, they could be simultaneously synthesized by using racemic C14-C20 amine fragment **42** and optically active C1-C13 carboxylic acid fragment **43**, which could be synthesized from D-ribose. In addition, we modified the C1-ester of common C1-C13 carboxylic acid fragment **43** as a fluorenylmethyl ester, because the deprotection of C1 methyl ester in **36** (Scheme 5) required an excess amount of TMSOK (usually more

than 8 equiv.) to complete, and an aqueous workup was required to remove this reagent before the next macrolactamization. Linear macrocyclization precursors are unstable and difficult to handle; thus we here wanted to make the deprotection sequence and the macrolactamization sequence in a single pot. Fluorenylmethyl ester was a good choice for this purpose because it can be deprotected under the same conditions that are used to remove a Fmoc group.

The synthesis of common C1-C13 carboxylic acid fragment **43** is summarized in Scheme 7. Vinylboronic acid pinacol ester *ent*-**27**, which was prepared from internal alkyne **44**[25,29] by borylcupration/protonation chemistry as described in Scheme 3, was coupled with iododienylester **45**[48] to give the coupling product **46** in 81% yield. When bromodienylester **11** was used as in Scheme 5, only a small amount of **46** was obtained (>20% yield). Two-step exchange of the diol protecting group (acetonide to diTES) followed by the 3-step protocol including the Stork-Wittig reaction produced tetraene **49** in 41% overall yield (5 steps). Interestingly, no isomerization at C6 was observed in these intermediates. Elongation of the C12-C13 olefin with vinyldistannane **9** proceeded to give the desired pentaene **50** in quantitative yield. Finally, the methyl ester of **50** was exchanged to afford fluorenylmethyl ester **43** in 65% yield for 2 steps.

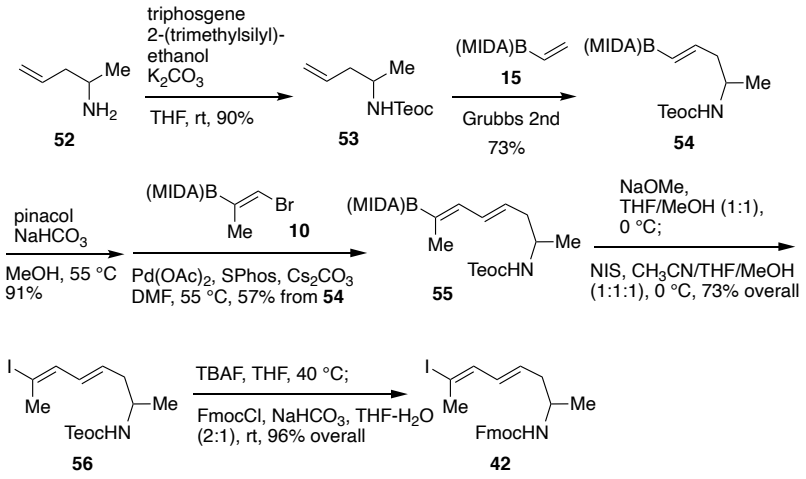


Scheme 7. Synthesis of the C1-C13 carboxylic acid fragment **43** of heronamidoids α–δ (**5**–**8**).

Fm = fluorenylmethyl.

Racemic C14-C20 amine fragment **42** was synthesized as follows (Scheme 8). Known racemic homoallylamine **52**,[49] which was prepared from pent-4-en-2-ol in 3 steps, was protected to give Teoc carbamate **53** in 90% yield. Compound **53** was reacted with MIDA boronate **15** in the presence of Grubbs 2nd catalyst to give MIDA boronate **54** in 73% yield. The second Suzuki coupling was performed using vinyl boronic acid pinacol ester derived from **54** and MIDA boronate **10** to afford MIDA boronate **55** in 57% yield from **54**. The MIDA boronate moiety was exchanged for iodine as

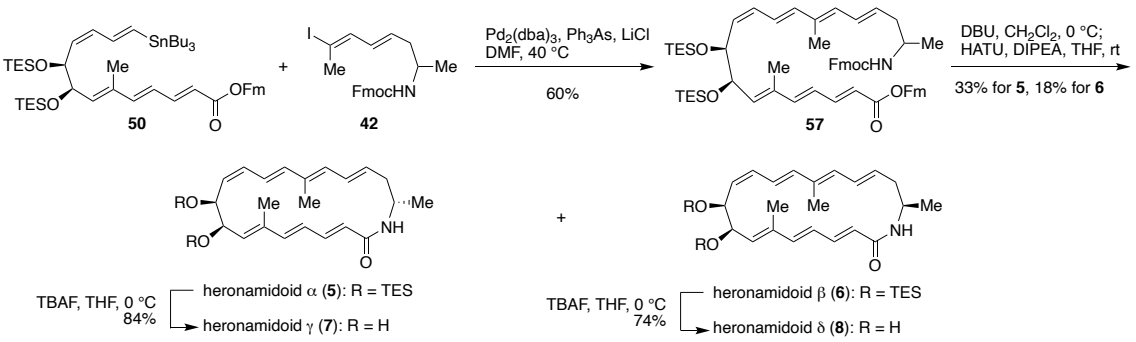
carried out in Scheme 4 (i.e., compound **29** to **30**) to give vinyl iodide **56** in 73% overall yield. Finally, amine protection was exchanged from the Teoc group to the Fmoc group to give the desired fragment **42** in 96% overall yield.



Scheme 8. Synthesis of C14-C29 amine fragment **42** of heronamidoids α–δ (**5**–**8**).

The revised endgame strategy could be successfully applied to the synthesis of heronamidoids (Scheme 9). Stille coupling of the two fragment **50** and **42** proceeded to afford heptaene **57** in 60% yield, and the following deprotection-macrocyclization sequence worked to give heronamidoid α (**5**) and β (**6**) in 33% and 18% yield in 2 steps, respectively. Heronamidoid α (**5**) and β (**6**) could be easily separated by silica gel column chromatography. Deprotection of the TES groups with TBAF led to heronamidoids γ (**7**) and δ (**8**) in 74% and 84% yield, respectively. The stereostructures of heronamidoids γ (**7**) and δ (**8**) were determined by comparing their ^{1}H-NMR data with those of the

revised structure (**1**)[25] and the originally proposed structure of heronamide C (**3**)[29]: ^{1}H-NMR comparison in pyridine-d_5 showed that a spectrum of heronamidoid γ (**7**) was highly similar to that of the revised structure **1**, and a spectrum of heronamidoid δ (**8**) was highly similar to that of the originally proposed structure **3**, indicating that the relative stereochemistries of **7** and **8** are identical with those of **1** and **3**, respectively.



Scheme 9. Assembly of all fragments: Synthesis of heronamidoids α–δ (**5**–**8**)

Conformational and reactivity analysis of heronamidoids

As described earlier, heronamide C "differentiates" into heronamides A and B upon heating under an aerobic condition and irradiation, respectively. Thus, we are interested in the conformation and reactivity of heronamidoids. Stable conformation of heronamide C (**1**) was previously analyzed in detail,[3] and heronamidoid γ (**7**) showed NMR spectra very similar to that of **1**. Thus, we concluded that heronamidoid γ (**7**) and heronamide C (**1**) took a very similar conformation (Figure 5, left). For

heronamidoid δ (**8**), we carefully analyzed the NOESY data and clarified that **8** has a distinct conformation around the amide moiety compared with **7** (Figure 5b). The DFT-calculated structure of the stable conformer of **8** did not conflict with the NMR data, as shown in Figure 5 (right-hand column). These analyses indicated that heronamidoid δ (**8**) favored the contracted *s-trans–s-cis* conformation around C2-C1-N-C19 bonds, whereas heronamidoid γ (**7**) adopted an extended *s-cis–s-cis* conformation. That is, a C1-C2 bond in **8** flipped to avoid 1,3-diaxial-like interaction between a C1-carbonyl oxygen and a C19-methyl group, while both the C2-C7 triene and the C10-C17 tetraene retained the all *s-trans* conformation.

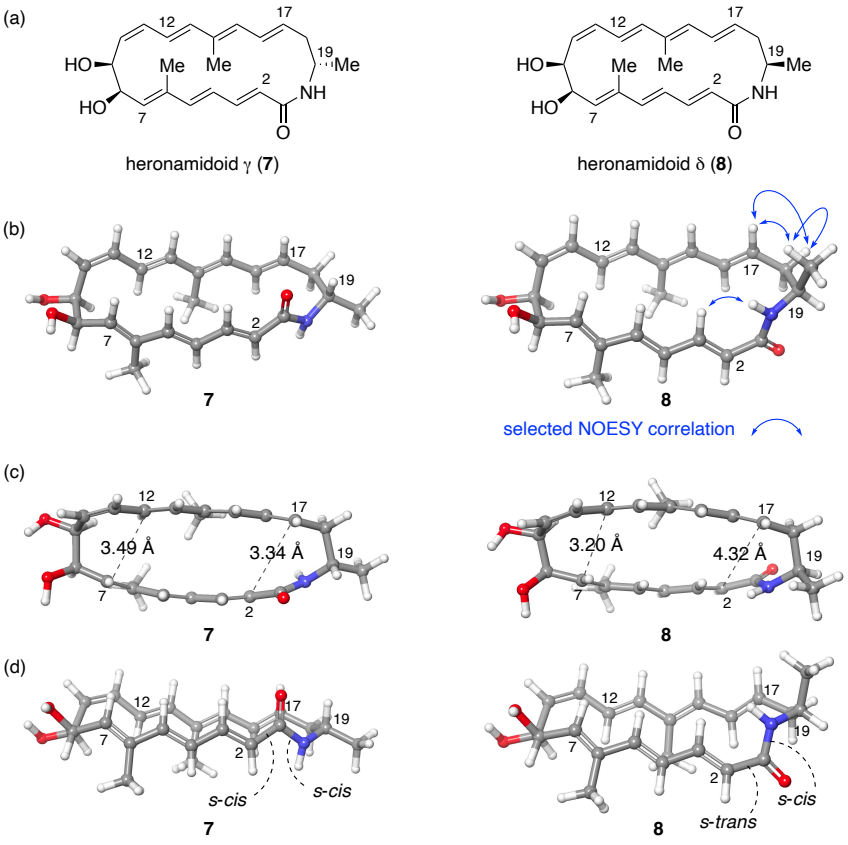
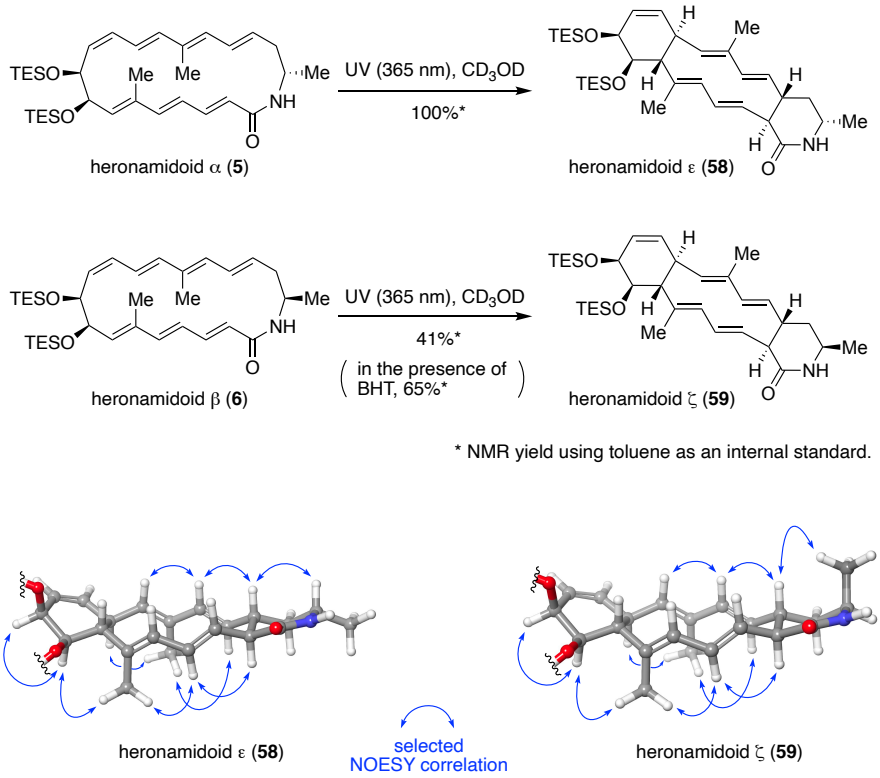


Figure 5. Stable conformation of heronamidoids γ (**7**) and δ (**8**).

(a) Chemical and (b) DFT-calculated structure of heronamidoid γ (**7**) and δ (**8**). (c–d) Top (c) and side view (d) of these molecules.

We then analyzed the reactivity of heronamidoids. Because of the low solubility of heronamidoids γ (**7**) and δ (**8**) in many organic solvents, we were able to utilize only heronamidoids α (**5**) and β (**6**) for this purpose. We first tested the photochemical conditions (Scheme 10). When heronamidoids α (**5**) and β (**6**) were dissolved separately in CD_3OD in NMR tubes and irradiated at 365 nm, the formation of heronamide B-type [6π+6π] photoadducts, i.e., heronamidoids ε (**58**) and ζ (**59**), were observed, respectively. Notably, heronamidoid α (**5**) was converted to ε (**58**) quantitatively, whereas the conversion of heronamidoid β (**6**) to ζ (**59**) was only 41% under the same conditions. Other products were not observed. The conversion of **6** to **59** was improved to 65% in the presence of dibutylhydroxytoluene (BHT), an autoxidation inhibitor.



Scheme 10. Photochemical reaction of heronamidoids α (**5**) and β (**6**).

The difference in reactivity of heronamidoids α (**5**) and β (**6**) under photochemical conditions could be attributed to differences in the stable conformation between the two molecules, especially the distance and alignment of reacting centers. As seen in Figure 5c, the calculated C7-C12 and C2-C17 atom distances in the stable conformer of **7** were 3.49 and 3.34 Å, respectively, whereas they were 3.20 and 4.32 Å for **8**. Moreover, in the stable conformer of **7**, the C2-C7 triene and C10-C17 tetraene aligned perfectly to lead to the [6π+6π] cycloadduct, whereas **8** had to change its conformation to one having an extended *s-cis–s-cis* conformation to lead to the [6π+6π] cycloadduct (Figure 5d). Presumably, π-orbitals of C2 and C17 carbons in the stable conformation of **8**, and thus

6, are too far from each other and not sufficiently aligned to overlap each other; thus, the bond flip has to occur for the [6π+6π] cycloaddition.

From the photochemical study of heronamidoids α (**5**) and β (**6**), it was concluded that the C8,C9-free diol is not necessary for [6π+6π] cycloaddition, leading to heronamide B-type molecules, and heronamide C-type relative stereochemistry is perfectly matched for the [6π+6π] cycloaddition. Interestingly, when synthetic 8-deoxyheronamide C (**2**) was irradiated under the same conditions, only degradation—but not the corresponding [6π+6π] cycloadduct—was observed. This result indicated that consecutive C8, C9 oxygen functionality is necessary for the cycloaddition. It is interesting to note that heronamides A–C were isolated from a marine-derived *Streptomyces* sp. residing in shallow-water sediment (–1 m),[11] implying the possibility that heronamide C (**1**) functions as a photosensor for the producing microorganisms.

We also tried to employ various thermal/aerobic conditions for heronamidoids α (**5**) and β (**6**), including various solvents ($CDCl_3$, DMSO-d_6, DMF/DMSO (1:1)), elevated temperature (50~70 °C), longer reaction time (1 week), and in the presence of oxidant (oxygen atmosphere and mCPBA). However, we could not obtain solid evidence for the formation of any of heronamide A-type products, and only degradation was observed in each case. These results suggested that the consecutive C8, C9 free diol, while not necessary for the [6π+6π] cycloaddition, is important for the formation of heronamide A-type products.

Conclusion

In this study, we established the modular synthetic access to heronamide C-type polyene macrolactams featuring modular Suzuki coupling utilizing MIDA boronate ester and vinylboronic acid pinacol esters that could be obtained by borylcupration/protonation of internal alkynes. By using this synthetic strategy, 8-deoxyheronamide C (**2**) and heronamidoids α–δ (**6**–**8**) were successfully synthesized. Conformational and reactivity analysis of heronamidoids showed that the conformation around the C1 amide moiety was dependent on the chirality at C19, which had a significant impact on the efficiency of photochemical [6π+6π] cycloaddition.

By using the modular synthetic strategy, various heronamide-like iPS molecules can now be synthesized. The synthetic studies are now in progress and will be reported in due course. In addition to the synthesis of heronamide-like iPS molecules, the developed strategy paves the way for the synthesis of heronamide C probes to be used for mode-of-action studies, which will be reported in a subsequent paper.[31]

Experimental Section

General Remarks

All reactions were carried out under an argon atmosphere with dehydrated solvents under anhydrous conditions, unless otherwise noted. Dehydrated THF and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. Other solvents were dehydrated and distilled according to standard protocols. Reagents were obtained from commercial suppliers and used without further purification, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates (Merck Kieselgel 60 F254). Column chromatography was performed on Silica gel 60N (Kanto Chemical; spherical, neutral, 63–210 μm) or Chromatorex® NH-DM1020 (Fuji Silysia Chemical; aminopropyl-modified type, 75–150 μm), and flash column chromatography was performed on Silica gel 60N (Kanto Chemical; spherical, neutral, 40–50 μm). Optical rotations were measured on a JASCO P-2200 Digital Polarimeter at rt, using the sodium D line. IR spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer or Travel-IR™. ^{1}H-NMR (400 and 600 MHz) and ^{13}C-NMR spectra (100 and 150 MHz) were recorded on JEOL JNM-AL-400 and JEOL JNM-ECA-600 spectrometers, respectively. For ^{1}H-NMR spectra, chemical shifts (δ) are given from TMS (0.00 ppm) in $CDCl_3$ or a C2 proton (8.71 ppm) of deuteriopyridine in pyridine-d_5 as internal standards. For ^{13}C-NMR spectra, chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm) or a C2 carbon of pyridine-d_5 (149.2 ppm) as internal standards. The following

abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, sept = septet, m = multiplet, br = broad. Mass spectra were recorded on JEOL JMS-DX303, JEOL JNM-AL500, JEOL JMS-700, and Thermo Scientific Exactive mass spectrometers.

Homoallylamine 13

To a solution of (1*R*,3*R*,4*S*)-3-amino-1,7,7-trimethyl-3-(2-propen-1-yl)bicyclo[2.2.1]heptan-2-one[40] (5.19 g, 25.1 mmol) and 3-[(4-methoxyphenyl)methoxy]propanal[50] (4.88 g, 25.1 mmol) in 1,2-dichloroethane (50 mL) was added 10-camphorsulfonic acid (875 mg, 3.77 mmol) at 0 °C. After 15 min, the mixture was warmed to room temperature. After stirring 22.5 h, a solution of $NH_2OH \cdot AcOH$ (0.5 M in methanol, 100 mL) was added to the mixture. After stirring at 50 °C for 3 h, the mixture was cooled to room temperature and then acidified with 6 N aqueous HCl to pH ~1. The mixture was washed with CH_2Cl_2, basified with 6 N aqueous NaOH to pH ~10, and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1/20) to give chiral amine **13** (3.61g, 15.4 mmol, 61%) as a yellow oil.

13: $[\alpha]_D^{20}$ +7.85 (*c* 0.992, $CHCl_3$); IR (neat): 3374, 2932, 2857, 1612, 1513, 1248, 1095, 821 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.78 (m, 1H), 5.11–5.07 (m, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.57 (m, 2H), 2.98 (quint, *J* = 4.0 Hz, 1H), 2.26–2.20 (m, 1H),

2.06–1.98 (m, 1H), 1.75 (ddt, J = 14.0, 6.4, 6.0 Hz, 1H), 1.55 (ddt, J = 14.0, 7.6, 6.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.2, 135.5, 130.5, 129.2, 117.5, 113.8, 72.6, 67.7, 55.2, 48.6, 42.5, 36.9; HRMS (EI): calcd for $C_{14}H_{21}NO_2$ ($[M]^+$) 235.1572, found 235.1541.

Teoc-protected homoallylamine 14

To a solution of K_2CO_3 (5.30 g, 38.2 mmol) and 2-(trimethylsilyl)ethanol (1.20 mL, 8.68 mmol) in toluene (18 mL) was added triphosgen (821 mg, 2.78 mmol) at 0 °C. After warming to room temperature with stirring for 1 h, the mixture was cooled to 0 °C. A solution of amine **13** (810 mg, 3.47 mmol) in toluene (5 mL) was added *via* cannula, and the resulting mixture was warmed to room temperature. After stirring for 11 h, the reaction was quenched by saturated aq. NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/10) to give Teoc-protected homoallylamine **14** (1.01 g, 2.65 mmol, 76%) as a colorless oil.

14: $[\alpha]_D^{25}$ +31.9 (*c* 0.64, $CHCl_3$); IR (neat): 3330, 2952, 1699, 1514, 1250, 837 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.81–5.71 (m, 1H), 5.08−5.05 (m, 2H), 4.84 (bs, 1H), 4.42 (s, 2H), 4.12 (t, J = 8.0 Hz, 2H), 3.81 (m, 4H), 3.56−3.51 (m, 2H), 2.28–2.25 (m, 2H), 1.90–1.81 (m, 1H), 1.69–1.64 (m, 1H), 0.97 (t, J = 8.0, 2H), 0.04 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.2, 156.3, 134.4, 130.3, 129.2, 117.7, 113.8, 72.8, 67.1, 62.7, 55.2, 48.7, 39.3,

33.8, 17.7, -1.50; HRMS (EI): calcd for $C_{20}H_{33}NO_4Si$ (M^+) 379.2179, found 379.2189.

Alcohol 16

To a solution of Teoc-protected homoallylamine **14** (1.34 g, 3.54 mmol) and vinyl MIDA boronate **15** (972 mg, 5.31 mmol) in degassed CH_2Cl_2 (35 mL) was added Grubbs 2nd generation catalyst (150 mg, 0.177 mmol, 5 mol%) at room temperature. The mixture was heated to reflux with stirring for 12 h. The mixture was cooled to room temperature, and the reaction was quenched by ethylvinyl ether. After stirring 30 min, the residue was concentrated in vacuo, and purified by silica gel column chromatography (EtOAc) to give fractions containing the desired product. This mixture was taken on to the next step without other purification.

To a solution of the mixture in CH_2Cl_2 (24 mL) was slowly added BCl_3 (1.0 M in CH_2Cl_2, 3.3 mL, 3.3 mmol) at -30 °C. After stirring for 20 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/MeOH = 50/1 to 15/1) to give alcohol **16** (806 mg, 1.95 mmol, 55% for 2 steps) as a white amorphous solid.

16: $[\alpha]_D^{20}$ +18.6 (*c* 1.00, $CHCl_3$); IR (neat): 3381, 2953, 1764, 1693, 1644, 1531, 1250, 1027, 861 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.21 (dt, *J* = 18.4, 6.8 Hz, 1H), 5.53 (d, *J* = 18.4 Hz, 1H), 4.66 (d, *J*

= 8.4 Hz, 1H), 4.16–4.06 (m, 2H), 3.91 (bs, 1H), 3.82–3.67 (m, 6H), 2.84 (s, 3H), 2.72 (bs, 1H), 2.40–2.30 (m, 2H), 1.84 (m, 1H), 1.50–1.43 (m, 1H), 0.97 (t, *J* = 8.4, 2H), 0.05 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.4, 157.3, 142.8, 63.3, 61.5, 58.9, 47.8, 46.9, 41.3, 37.7, 17.7, -1.49; HRMS (ESI): calcd for $C_{17}H_{31}BN_2O_7SiNa$ ($[M+Na]^+$) 437.1892, found 437.1886.

Aldehyde 17

To a solution of alcohol **16** (738 mg, 1.78 mmol) in CH_2Cl_2 (14 mL) were added pyridine (0.43 mL, 5.34 mmol) and Dess-Martin Periodinane (1.13 g, 2.67 mmol) at 0 °C. After stirring for 5 min, the reaction mixture was allowed to warm to room temperature. After stirring for 3.5 h, sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ were added to the reaction mixture, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc to EtOAc/MeOH = 50/1) to give aldehyde **17** (625 mg, 1.52 mmol, 85%) as a white amorphous solid.

17: $[\alpha]_D^{21}$ +0.6 (*c* 0.33, $CHCl_3$); IR (neat): 3338, 2954, 1765, 1719, 1249 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.74 (bs, 1H), 6.12 (dt, *J* = 17.6, 7.2 Hz, 1H), 5.54 (d, *J* = 17.6 Hz, 1H), 5.01 (bs, 1H), 4.15–4.08 (m, 3H), 3.89 (d, *J* = 16.8 Hz, 2H), 3.73 (d, *J* = 16.8 Hz, 2H), 2.85 (s, 3H), 2.68–2.67 (m, 2H), 2.41 (m, 2H), 0.95 (t, *J* = 8.4 Hz, 2H), 0.03 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 201.2, 168.4, 156.2, 142.0, 63.1, 61.5, 48.1, 46.9, 46.4, 40.7, 17.7, -1.52; HRMS (ESI): calcd for $C_{17}H_{29}BN_2O_7SiK$

([M+K]$^{+}$) 451.1474, found 451.1469.

Pinacol ester 19

To a solution of flame-dried $CrCl_2$ (428 mg, 3.48 mmol) in THF (5 mL) were added 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **18**[42] (0.15 mL, 0.957 mmol) *via* syringe and a solution of aldehyde **17** (180 mg, 0.435 mmol) and LiI (256 mg, 1.91 mmol) in THF (3.7 mL) *via* cannula at 0 °C. After stirring for 5 min, the reaction mixture was allowed to warm to room temperature. After stirring for 9.5 h, the reaction was quenched with H_2O, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 10/1) to give pinacol ester **19** (218 mg, 0.407 mmol, 94%, *E*/*Z* = >99:1) as a white amorphous solid.

19: $[\alpha]_D^{20}$ –2.64 (*c* 3.05, $CHCl_3$); IR (neat): 3347, 2979, 1766, 1699, 1640, 1365, 1250, 1145, 1027, 997 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.53 (dt, *J* = 18.0 Hz, 6.8 Hz, 1H), 6.15 (dt, *J* = 18.0, 6.8 Hz, 1H), 5.51 (d, *J* = 18.0 Hz, 1H × 2), 4.52 (bs, 1H), 4.09 (t, *J* = 7.2 Hz, 2H), 3.80–3.68 (m, 5H), 2.83 (s, 3H), 2.35−2.22 (m, 4H), 1.27 (s, 12H), 0.95 (t, *J* = 7.2 Hz, 2H), 0.035 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.7, 156.3, 148.8, 143.3, 83.2, 62.9, 61.3, 50.3, 46.6, 41.2, 40.9, 24.7, 17.7, –1.49; HRMS (ESI): calcd for $C_{24}H_{42}B_2N_2O_8SiNa$ ([M+Na]$^{+}$) 559.2795, found 559.2789.

Alcohol 21

THF (86 mL) in a dried flask was cooled to -78 °C. To the flask were added propyne (3% in heptane, 111 mL, 59.3 mmol) and *n*-BuLi (1.6 M in hexane, 24.8 mL, 38.7 mmol). After stirring for 15 min, $BF_3 \cdot OEt_2$ (4.93 mL, 39.2 mmol) was added to the resulting mixture at the same temperature. After 35 min, a solution of (2*S*)-2-[[(4-methoxyphenyl)methoxy]methyl]oxirane (**20**) (4.97 g, 25.6 mmol) in THF (10 mL) was added *via* cannula to the resulting solution at -78 °C. After stirring for 15 min, the reaction was quenched with sat. aq. NH_4Cl, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/6) to give alcohol **21** (4.92 g, 82%) as a yellow oil.

21: $[\alpha]_D^{21}$ +11.4 (*c* 1.18, $CHCl_3$); IR (neat): 3449, 2916, 1612, 1514, 1248 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.50 (s, 2H), 3.92–3.88 (m, 1H), 3.81 (s, 3H), 3.56 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.45 (dd, *J* = 10.4, 6.8 Hz, 1H), 2.39–2.37 (m, 3H), 1.78 (t, *J* = 2.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.3, 130.0, 129.4, 113.8, 78.0, 74.3, 73.1, 72.8, 69.1, 55.3, 23.8, 3.5; HRMS (EI): calcd for $C_{14}H_{18}O_3$ (M^+) 234.1256, found 234.1241.

TIPS ether 22

To a solution of the alcohol **21** (2.86 g, 12.2 mmol) in THF (61 mL) were added 2,6-lutidine (5.11 mL, 43.9 mmol) and TIPSOTf (5.91 mL, 22.0 mmol) at 0 °C. After stirring for 10 min, the reaction was quenched with sat. aq. $NaHCO_3$ and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/80) to give TIPS ether **22** (4.04 g, 85%) as a colorless oil.

22: $[\alpha]_D^{21}$ +4.7 (*c* 1.25, $CHCl_3$); IR (neat): 2942, 2865, 1514, 1464, 1248 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.03−4.01 (m, 1H), 3.80 (s, 3H), 3.54−3.48 (m, 2H), 2.48−2.34 (m, 2H), 1.75 (t, *J* = 1.8 Hz, 3H), 1.09−1.04 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.1, 130.6, 129.2, 113.6, 77.1, 75.9, 73.3, 73.0, 70.8, 55.3, 25.1, 18.0, 12.4, 3.5; HRMS (EI): calcd for $C_{23}H_{38}O_3Si$ (M^+) 390.2590, found 390.2585.

Vinylboronic acid pinacol ester 24

To a solution of TIPS ether **22** (390 mg, 1.00 mmol) in toluene (4.0 mL) were added CuCl (30 mg, 0.30 mmol), NaO*t*-Bu (78 mg, 0.81 mmol), $PCy_3 \cdot HBF_4$ (133 mg, 0.36 mmol), B_2pin_2 (508 mg, 2.0 mmol) and MeOH (0.16 mL, 4.0 mmol) at room temperature, and the reaction mixture was stirred for 5 h. The reaction was quenched with H_2O (5 mL) and the mixture was extracted with EtOAc (5 mL x

3). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/30 to 1/15) to give vinylboronic acid pinacol ester **24** (482 mg, 0.93 mmol, 93%) as a colorless oil.

24: $[\alpha]_D^{31}$ – 1.9 (*c* 0.703, $CHCl_3$); IR (neat): 3464, 2943, 2866, 1717, 1612, 1524, 1464, 1249 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 7.7 Hz, 2H) , 6.86 (d, *J* = 7.7 Hz, 2H), 6.39 (t, *J* = 7.0 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J*, = 11.6 Hz, 1H), 4.08–4.01 (m, 1H), 3.80 (d, *J* = 1.0 Hz, 3H), 3.44–3.36 (m, 2H), 2.50–2.34 (m, 2H), 1.69 (s, 3H), 1.25 (s, 12H), 1.08–1.03 (m, 21H) ; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.1, 142.1, 130.7, 129.2, 113.7, 83.0, 74.3, 73.0, 71.4, 53.4, 34.4, 24.8, 18.1, 14.1, 12.5; HRMS (ESI): calcd for $C_{29}H_{51}BO_5SiNa$ $[M+Na]^+$ 541.3494 , found 541.3491.

Vinylboronic acid pinacol ester 25

Vinylboronic acid pinacol ester **25** was synthesized in 87% yield from alcohol **23** by using the bolylcupration/protonation sequence described above.

25: Colorless oil; IR (neat): 3467, 2978, 2932, 2062, 1632, 1623, 1586, 1513 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.33 (t, *J* = 7.3 Hz, 1H), 4.48 (s, 2H), 3.95–3.89 (m, 1H), 3.81 (s, 3H), 3.51 (dd, *J* = 9.2 Hz, 3.4 Hz, 1H), 3.35 (dd, *J* = 9.2 Hz, 7.3 Hz, 1H), 2.39–2.30 (m, 3H), 1.69 (s, 3H), 1.26 (s, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.3, 140.7, 130.0, 129.4, 113.8, 83.2, 73.8, 73.0, 69.9, 55.2, 32.7, 24.8, 14.1; HRMS (EI): calcd for $C_{20}H_{31}BO_5$

(M^+) 362.2265, found 362.2269.

Methyl ether 23

To a solution of alcohol **21** (120 mg, 0.510 mmol) in THF (5.0 mL) was added NaH (60% in mineral oil, 49 mg, 1.2 mmol) at 0 °C. After stirring for 30 min, MeI (38 μL, 0.61 mmol) was added and the resulting mixture was allowed to warm to room temperature. After stirring for 1.5 h, the reaction was quenched with sat. aq. NH_4Cl (5 mL), and the mixture was extracted with EtOAc (5 mL x 3). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/8) to give methyl ether **23** (105 mg, 0.42 mmol, 82%) as a colorless oil.

23: IR (neat): 2918, 2861, 2360, 1613, 1513, 1464, 1248, 1107 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.50 (s, 2H), 3.80 (s, 3H), 3.61–3.51 (m, 2H), 3.49–3.43 (m, 1H), 3.43 (s, 3H), 2.43–2.39 (m, 2H), 1.76 (t, *J* = 2.5 Hz, 3H) ; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.1, 130.3, 129.4, 113.7, 78.9, 77.1, 75.1, 73.0, 70.6, 57.5, 55.2, 21.0, 3.5; HRMS (EI): calcd for $C_{15}H_{20}O_3$ (M^+) 248.1412, found 248.1409.

Vinylboronic acid pinacol ester 26

Vinylboronic acid pinacol ester **26** was synthesized in 71% yield from internal alkyne **23** by using

the bolylcupration/protonation sequence described above.

26: Colorless oil; IR (neat): 2978, 2930, 1632, 1514, 1370, 1303, 1248, 1137 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.31 (t, *J* = 6.6 Hz, 1H), 4.48 (s, 2H), 3.80 (s, 3H), 3.49–3.40 (m, 3H), 3.38 (s, 3H), 2.39 (dd, *J* = 6.6 Hz, 5.7 Hz, 2H), 1.71 (s, 3H), 1.23 (s, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.1, 141.2, 130.4, 129.2, 113.7, 83.1, 79.7, 73.0, 71.5, 57.4, 55.2, 30.4, 24.8, 14.1; HRMS (EI): calcd for $C_{21}H_{33}BO_5$ (M^+) 376.2421, found 376.2419.

Vinylboronic acid pinacol ester 27 and *ent*-27

Vinylboronic acid pinacol ester **27** and *ent*-**27** were obtained in 85% and 98% yield, respectively, from (4*R*,5*S*)- and (4*S*,5*R*)-4-{[(4-methoxybenzyl)oxy]methyl}-2,2-dimethyl-5-(prop-1-yn-1-yl)-1,3-dioxolane, which were synthesized from L-ribose and D-ribose, respectively, following a reported procedure,[29] by using the bolylcupration/protonation sequence described above.

27: Colorless oil; $[\alpha]^{D}_{24}$ +16.8 (*c* 3.27, $CHCl_3$); IR(neat): 2981, 1613, 862 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.28 (d, *J* = 8.2 Hz, 1H), 5.03 (t, *J* = 8.2 Hz, 1H), 4.49–4.36 (m, 3H), 3.80 (s, 3H), 3.47–3.37 (m, 2H), 1.73 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H) 1.22 (s, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.1, 139.8, 130.2, 129.6, 113.9, 108.5, 83.4, 76.6, 73.6, 73.1, 69.4, 55.1, 27.8, 25.3, 24.8, 14.5; HRMS (ESI): calcd for $C_{23}H_{35}O_6BNa$ (M^++Na) 441.2424, found 441.2419.

Data for *ent*-**27** were identical with those for **27** except for the value of specific rotation. *ent*-**27**: $[\alpha]_D^{24}$ –16.8 (*c* 3.27, $CHCl_3$).

Triene 28

To a solution of vinylboronic acid pinacol ester **19** (100 mg, 0.187 mmol) and vinyl iodide **12** (0.13 mL, 1.4 mmol) in degassed DMSO (2.5 mL) were added Cs_2CO_3 (370 mg, 1.12 mmol) and 2nd generation XphosPd precatalyst (15 mg, 0.019 mmol) at room temperature. After stirring for 10 min, the reaction mixture was warmed to 50 °C with stirring for 4 h. After cooling, the reaction was quenched with NH_4Cl, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 4/1) to give triene **28** (64 mg, 72%) as a white amorphous solid.

28: $[\alpha]_D^{23}$ −6.4 (*c* 0.48, $CHCl_3$); IR (neat): 3336, 2955, 1766, 1698, 1291, 1250, 990 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.16 (dt, *J* = 18.0, 7.2 Hz, 1H), 6.03 (m, 2H), 5.62 (dt, *J* = 14.4, 7.2 Hz, 1H), 5.53–5.44 (m, 2H), 4.50 (bs, 1H), 4.10 (t, *J* = 5.2 Hz, 2H), 3.85–3.67 (m, 5H), 2.83 (s, 3H), 2.38–2.23 (m, 4H), 2.04 (dt, *J* = 7.6, 7.2 Hz, 2H), 1.40 (sext, *J* = 7.2 Hz, 2H), 0.97–0.88 (m, 5H), 0.35 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.6, 156.4, 143.6, 133.9, 129.9, 126.3, 62.9, 61.3, 51.0, 46.5, 41.0,

38.1, 34.6, 22.4, 17.7, 13.7, -1.50; HRMS (ESI): calcd for $C_{23}H_{39}BN_2O_6SiNa$ ([M+Na]$^+$) 501.2568, found 501.2563.

Pinacol ester S1

To a solution of triene **28** (267 mg, 0.559 mmol) in MeOH (2.8 mL) were added $NaHCO_3$ (235 mg, 2.80 mmol) and pinacol (105 mg, 0.894 mmol) at room temperature. After stirring for 5 min, the reaction mixture was warmed to 50 °C with stirring for 4 h. After cooling, the reaction was quenched by sat. aq. NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/10) to give pinacol ester **S1** (176 mg, 70%) as a colorless oil.

S1: $[\alpha]_D^{26}$ –5.0 (*c* 2.0, $CHCl_3$); IR (neat): 3331, 2956, 1697, 1639, 1363, 1250, 1146 837 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.54 (dt, *J* = 17.6, 7.2 Hz, 1H), 6.02 (m, 2H), 5.59 (dt, *J* = 14.0, 7.2 Hz, 1H), 5.52–5.48 (m, 2H), 4.46 (bs, 1H), 4.13 (t, *J* = 8.0 Hz, 2H), 3.77 (bs, 1H), 2.35–2.23 (m, 4H), 2.03 (dt, *J* = 7.6, 7.2 Hz, 2H), 1.40 (sext, *J* = 7.6 Hz, 2H), 1.26 (s, 12H), 0.98–0.88 (m, 5H), 0.29 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.0, 149.2, 133.7, 133.5, 130.0, 126.5, 83.1, 62.7, 50.0, 40.5, 37.3, 34.6, 24.7, 22.4, 17.7, 13.6, -1.54; HRMS (ESI): calcd for $C_{24}H_{44}BNO_4SiNa$ ([M+Na]$^+$) 472.3030, found 472.3025.

Tetraene 29

To a solution of pinacol ester **S1** and MIDA boronate **10**[37] (75.0 mg, 0.271 mmol) in degassed MeCN (1.1 mL) were added Cs_2CO_3 (178 mg, 0.545 mmol), SPhos (18 mg, 0.0436 mmol) and $Pd(OAc)_2$ (4.9 mg, 0.0218 mmol) at room temperature. The reaction mixture was warmed to 70 °C and stirred for 5 h. Then, the mixture was cooled to room temperature and quenched with sat. aq. NH_4Cl. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1/80) to give tetraene **29** (37.4 mg, 62%) as a white amorphous.

29: $[\alpha]_D^{28}$ +1.5 (*c* 0.33, $CHCl_3$); IR (neat): 3330, 2955, 1767, 1698, 1249 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.51–6.39 (m, 2H), 6.03 (m, 2H), 5.77–5.71 (m, 1H), 5.62 (dt, *J* = 14.0, 7.2 Hz, 1H), 5.49 (dt, *J* = 13.6, 7.2 Hz, 1H), 4.48 (bs, 1H), 4.13 (t, *J* = 7.6 Hz, 2H), 3.82−3.69 (m, 5H), 2.81 (s, 3H), 2.32−2.24 (m, 4H), 2.04 (dt, *J* = 7.2, 6.4 Hz, 2H), 1.77 (s, 3H), 1.40 (sext, *J* = 7.2 Hz, 2H), 0.99–0.89 (m, 5H), 0.034 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.4, 156.1, 137.2, 133.7, 133.6, 131.9, 129.9, 129.1, 126.5, 62.8, 61.8, 50.6, 46.6, 37.6, 37.3, 34.6, 22.4, 17.7, 14.8, 13.6, -1.52; HRMS (ESI): calcd for $C_{26}H_{43}BN_2O_6SiNa$ ($[M+Na]^+$) 541.2881, found 541.2876.

Vinyl iodide 30

To a solution of tetraene **29** (81.0 mg, 0.156 mmol) in MeOH (0.7 mL) and THF (0.7 mL) was added

NaOMe (5.0 M solution in MeOH, 0.1 mL, 0.5 mmol) at 0 °C. After stirring for 20 min at the same temperature, *N*-iodosuccinimide (42.0 mg, 0.187 mmol) in MeCN (0.7 mL) was added, and the mixture was warmed to room temperature. After stirring for 30 min, the reaction was quenched with sat. aq. NH_4Cl and sat. aq. $Na_2S_2O_3$. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/20) to give vinyl iodide **30** (70 mg, 92%) as a yellow oil.

30: $[\alpha]_D^{29}$ +5.2 (*c* 0.25, $CHCl_3$); IR (neat): 3324, 2954, 1689, 1528, 1511, 1250, 1059 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.72 (d, *J* = 11.2 Hz, 1H), 6.16 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.02 (m, 2H), 5.64–5.58 (m, 2H), 5.47 (dt, *J* = 14.4, 7.2 Hz, 1H), 4.43 (bs, 1H), 4.13 (t, *J* = 7.6 Hz, 2H), 3.73 (bs, 1H), 2.48 (s, 3H), 2.28–2.22 (m, 4H), 2.04 (dt, *J* = 7.2, 6.8 Hz, 2H), 1.40 (sext, *J* = 7.2 Hz, 2H), 0.98–0.88 (m, 5H), 0.034 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.1, 140.2, 133.8, 133.7, 130.5, 129.9, 128.2, 126.3, 95.9, 62.9, 50.4, 37.5, 34.6, 28.0, 22.4, 17.7, 13.7, –1.50; HRMS (ESI): calcd for $C_{21}H_{36}INO_2SiNa$ ($[M+Na]^+$) 512.1458, found 512.1452.

Amine 31

To a solution of vinyl iodide **30** (24.9 mg, 50.9 μmol) in DMSO (0.5 mL) was added CsF (54 mg, 356 μmol) at room temperature. After stirring for 2 h at 70 °C, the mixture was quenched with sat. aq.

NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1/80) to give amine **31** (14.1 mg, 80%) as a yellow oil.

31: $[\alpha]_D^{22}$ −2.2 (*c* 0.28, $CHCl_3$); IR (neat): 3366, 2957, 2925, 2871, 1598, 1433, 989 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.74 (d, *J* = 11.2 Hz, 1H), 6.20 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.05 (m, 2H), 5.67–5.58 (m, 2H), 5.51 (dt, *J* = 14.0, 7.2 Hz, 1H), 2.87 (bs, 1H), 2.62 (s, 3H), 2.49–2.21 (m, 2H), 2.09–2.02 (m, 4H), 1.40 (sext, *J* = 7.6 Hz, 2H), 0.903 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 140.4, 133.5, 133.4, 132.0, 130.1, 128.1, 127.8, 95.7, 50.8, 40.8, 40.7, 34.7, 28.0, 22.5, 13.7; HRMS (ESI): calcd for $C_{15}H_{24}IN$ ($[M+H]^+$) 346.1032, found 346.1026.

Fmoc carbamate 32

To a solution of amine **31** (10 mg, 29 μmol) in THF (0.2 mL) and H_2O (0.1 mL) were added $NaHCO_3$ (3.4 mg, 40.6 μmol) and FmocCl (9.0 mg, 34.8 μmol) at 0 °C. After stirring for 10 min at the same temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/20) to give Fmoc carbamate **32** (14.7 mg, 89%) as a white solid.

32: $[a]_D^{25}$ +3.6 (*c* 0.28, $CHCl_3$); IR (neat): 3326, 2955, 2925, 1686, 1539, 1259 cm^{-1}; ^{1}H-NMR (400

MHz, $CDCl_3$): major rotamer, δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 6.72 (d, *J* = 10.8 Hz, 1H), 6.20–5.97 (m, 3H), 5.64–5.44 (m, 3H), 4.60 (d, *J* = 7.6 Hz, 1H), 4.38 (bs, 2H), 4.22 (t, *J* = 5.6 Hz, 1H), 3.78 (bs, 1H), 2.46 (s, 3H), 2.25 (m, 4H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.39 (sext, *J* = 7.2 Hz, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): major rotamer, δ 155.8, 144.0, 141.3, 140.2, 134.0, 130.4, 129.9, 128.4, 127.7, 127.0, 126.2, 125.0, 120.0, 96.2, 66.5, 50.6, 47.3, 37.5, 34.6, 28.0, 22.4, 13.7; HRMS (ESI): calcd for $C_{30}H_{35}O_2NI$ ($[M+H]^+$) 568.1712, found 568.1707.

Triene 33

To a solution of pinacol ester **24** (972 mg, 1.87 mmol) and vinyl bromide **11** (425 mg, 2.24 mmol) in degassed THF (19 mL) were added 2 M aq. NaOH (3.1 mL, 6.2 mmol), $Pd(OAc)_2$ (67.5 mg, 0.30 mmol) and SPhos (246.2 mg, 0.60 mmol) at room temperature. After stirring for 10 min, the reaction mixture was warmed to 45 °C with stirring for 4 h. After cooling, the reaction was quenched with sat. NH_4Cl, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 4/1) to give triene **33** (776 mg, 83%) as a colorless oil.

33: $[\alpha]_D^{27}$ −6.9 (*c* 0.33, $CHCl_3$); IR (neat): 2944, 2865, 2360, 1718, 1614 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 15.0, 11.1 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.57 (d,

J = 15.4 Hz, 2H), 6.24 (dd, *J* = 15.0, 11.1 Hz, 1H), 5.88 (d, *J* = 15.4 Hz, 1H), 5.80 (t, *J* = 7.3 Hz, 1H), 4.43 (s, 2H), 4.08–4.02 (m, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.45–3.40 (m, 1H), 3.35–3.30 (m, 1H), 2.50–2.40 (m, 2H), 1.78 (s, 3H), 1.05–1.03 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.7, 159.2, 146.1, 145.7, 135.1, 134.2, 130.4, 129.3, 123.8, 119.2, 113.7, 73.5, 73.0, 71.0, 55.2, 51.4, 34.2, 18.1, 12.5; HRMS (EI): calcd for $C_{29}H_{46}O_5Si$ (M^+) 502.3115, found 502.3111.

Alcohol **S2**

To a solution of the triene **33** (308 mg, 0.612 mmol) in CH_2Cl_2 (6.1 mL) were slowly added BCl_3 (1.0 M in CH_2Cl_2, 0.857 mL, 0.857 mmol) at -30 °C. After stirring for 20 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/8) to give alcohol **S2** (201 mg, 86%) as a colorless oil.

S2: $[\alpha]_D^{21}$ +11.4 (*c* 1.50, $CHCl_3$); IR (neat): 3479, 2944, 2867, 1718, 1613 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 15.2, 11.6 Hz, 1H), 6.57 (d, *J* = 15.2 Hz, 1H), 6.26 (dd, *J* = 15.2, 11.6 Hz, 1H), 5.88 (d, *J* = 15.2 Hz, 1H), 5.70 (t, *J* = 7.2 Hz, 1H), 3.97−3.93 (m, 1H), 3.75 (s, 3H), 3.62−3.46 (m, 2H), 2.61−2.46 (m, 2H), 1.90 (t, *J* = 4.8 Hz, 1H), 1.81 (s, 3H), 1.08 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.7, 145.5, 145.4, 135.7, 133.0, 124.4, 119.6, 72.3, 65.6, 51.4, 33.4, 18.1, 12.4; HRMS

(EI): calcd for $C_{18}H_{31}O_4Si$ ([M-*i*Pr]$^+$) 339.1986, found 339.1996.

Aldehyde S3

To a solution of the alcohol **S2** (876 mg, 2.29 mmol) in CH_2Cl_2 (15 mL) were added pyridine (0.5 mL, 6.41 mmol) and Dess-Martin periodinane (1.36 g, 3.21mmol) at 0 °C. After stirring for 5 min, the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, the reaction was quenched with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/10) to give aldehyde **S3** (630 mg, 72%) as colorless oil.

S3: $[\alpha]_D^{23}$ −14.1 (*c* 1.16, $CHCl_3$); IR (neat): 2946, 2720, 1718, 1615, 1463, 1433 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.65 (brs, 1H), 7.33 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.55 (d, *J* = 15.2 Hz, 1H), 6.26 (dd, *J* = 15.6, 11.2 Hz, 1H), 5.88 (d, *J* = 15.6 Hz, 1H), 5.75 (t, *J* = 7.6 Hz, 1H), 4.18 (brt, *J* = 6.0 Hz, 1H), 3.74 (s, 3H), 2.65−2.55 (m, 2H), 1.79 (s, 3H), 1.11−1.06 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 203.7, 167.3, 145.0, 144.8, 135.9, 130.5, 124.5, 119.6, 76.8, 51.2, 32.7, 17.6, 12.2, 11.9; HRMS (EI): calcd for $C_{21}H_{36}O_4Si$ (M^+) 380.2383, found 380.2393.

Vinyl iodide 34

To a solution of (iodomethyl)triphenylphosphonium iodide (1.40 g, 2.60 mmol) in THF (12 mL) was added sodium bis(trimethylsilyl)amide (1.9 M in tetrahydrofuran, 1.2 mL, 2.19 mmol) at rt. After stirring for 15 min, the reaction mixture was cooled to −98 °C. HMPA (0.9 mL, 5.1 mmol) was added to the cooled mixture, the solution was stirred for 5 min, and a solution of aldehyde **S3** (405 mg, 0.73 mmol) in THF (3.0 mL) was added to the mixture. After stirring for 15 min, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/30) to give vinyl iodide **34** (391 mg, 73%) as a colorless oil. Almost no C6-isomerization was observed in this example, but usually an up to 5:1 hardly separable mixture of (6*E*)-**34** and (6*Z*)-**34** was obtained.

34: $[\alpha]_D^{23}$ −100 (*c* 0.63, $CHCl_3$); IR (neat): 2944, 2866, 1717, 1615, 1262, 1238, 1139 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.58 (d, *J* = 15.2 Hz, 1H), 6.23−6.21 (m, 3H), 5.90−5.82 (m, 2H), 4.57 (q, *J* = 6.4 Hz, 1H), 3.75 (s, 3H), 2.55−2.43 (m, 2H), 1.80 (s, 3H), 1.09−1.05 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.7, 145.8, 145.6, 144.4, 135.6, 133.0, 124.1, 119.4, 80.2, 75.1, 51.4, 36.6, 18.0, 12.5, 12.3; HRMS (ESI): calcd for $C_{22}H_{37}IO_3Si$ ($[M+Na]^+$) 527.1577, found 527.1432.

Tetraenes (6*E*)- and (6*Z*)-38

To a 5:1 mixture of vinyl iodide (6*E*)- and (6*Z*)-**34** (30 mg, 0.059 mmol) and $Pd(PPh_3)_4$ (10.2 mg, 8.9 μmol) in benzene (1.2 mL) was added Bu_3SnH (20.4 μL, 0.077 mmol) at room temperature. After stirring for 21 h, the reaction was quenched with sat. aq. H_2O (1 mL). The mixture was extracted three times with EtOAc (3 mL x 3). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/20) to give a 5:1 mixture of tetraenes (6*E*)- and (6*Z*)-**38** (105 mg, 0.42 mmol, 82%) as a colorless oil. (6*E*)- and (6*Z*)-**38** were separated by preparative TLC (CH_2Cl_2/hexane = 1/4).

(6*E*)-**38**: colorless oil; $[\alpha]_D^{22}$ +23.0 (c 0.620, $CHCl_3$); IR (neat): 2945, 2866, 1719, 1615, 1238, 1139 cm-1; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 15.6, 11.6 Hz, 1H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.24 (dd, *J* = 15.6, 11.6 Hz, 1H), 5.89–5.74 (m, 3H), 5.17 (d, *J* = 17.6 Hz, 1H), 5.15 (d, *J* = 10.4 Hz, 1H), 4.32–4.05 (m, 1H), 3.75 (s, 3H), 2.50–2.40 (m, 2H), 1.78 (s, 3H), 1.06 (m, 21H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.7, 145.9, 145.6, 141.2, 135.0, 133.9, 123.9, 119.3 114.2, 73.5, 51.4, 37.8, 18.0, 12.5, 12.4; HRMS (EI): calcd for $C_{22}H_{38}O_3Si$ (M^+) 378.2590, found 378.2571.

(6*Z*)-**38**: colorless oil; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 15.0, 11.1 Hz, 1H), 6.94 (d, *J* = 15.0 Hz, 1H), 6.34 (dd, *J* = 15.5, 11.1 Hz, 1H), 5.91 (d, *J* = 15.6 Hz, 1H), 5.84–5.78 (m, 1H), 5.64 (t, *J* = 7.5 Hz, 1H), 5.17 (d, *J* = 16.8 Hz, 1H), 5.06 (d, *J* = 12.0 Hz, 1H), 4.33–4.21 (m, 1H), 3.75 (s, 3H), 2.52–2.41 (m, 2H), 1.87 (s, 3H), 1.10–0.96 (m, 21H).

Dienyl stannane 36

To a solution of vinyl iodide **34** (15.0 mg, 0.0297 mmol) and (*E*)-1,2-bis(tributylstannyl)ethylene (**9**) (271 mg, 0.445 mmol) in THF (0.6 mL) were added *i*Pr$_2$NEt (26 μL, 0.149 mmol), CuI (6.8 mg, 0.0356 mmol) and $PdCl_2(MeCN)_2$ (0.7 mg, 3 μmol) at room temperature. After stirring for 80 min, $PdCl_2(MeCN)_2$ (1.0 mg, 3.9 μmol) was added at room temperature. After stirring for 40 min, the reaction was quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/40, containing 1% Et_3N) to give the dienyl stannane **36** (15 mg, 74%) as a pale yellow oil.

36: $[\alpha]_D^{25}$ −48.0 (*c* 0.365, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, major isomer): δ 7.33 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.70 (dd, *J* = 18.8, 11.2 Hz, 1H), 6.54 (d, *J* = 15.6 Hz, 1H), 6.28–6.20 (m, 2H), 5.95−5.85 (m, 2H), 5.75 (t, *J* = 6.0 Hz, 1H), 4.83−4.76 (m, 1H), 3.74 (s, 3H), 2.60−2.37 (m, 2H), 1.79 (s, 3H), 1.49 (sext, *J* = 7.2 Hz, 6H), 1.35–1.26 (m, 12H), 1.05 (m, 21H), 0.89 (t, *J* = 8.0 Hz, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$, major isomer): δ 167.7, 145.9, 145.6, 136.3, 134.0, 133.7, 133.3, 130.9, 128.6, 124.0, 119.3, 68.6, 51.4, 38.3, 29.1, 27.2, 18.1, 18.0, 13.7, 12.3, 9.6; HRMS (ESI, EI, FAB): not detected.

Nonene S4

To a solution of vinyl iodide **32** (3.0 mg, 0.0059 mmol) and vinyl stannane **36** (7.4 mg, 0.0106 mmol) in THF (0.06 mL) were added DIPEA (7.2 μL, 0.0416 mmol) and Ph_3As (1.8 mg, 0.0059 mmol), $PdCl_2(MeCN)_2$ (0.1 mg, 0.4 μmol) at room temperature. After stirring for 20 min, additional $PdCl_2(MeCN)_2$ (1.0 mg, 0.0039 mmol) and LiCl (2.0 mg) were added at room temperature. After stirring for 1 h, the mixture was warmed to 40 °C and stirred for 1 h. The reaction was allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/8 containing 1% Et_3N) to give nonene **S4** (3.0 mg, 60%) as a yellow oil.

S4: $[\alpha]_D^{21}$ –11 (*c* 0.27, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, major isomer): δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 6.54 (d, *J* = 15.6 Hz, 1H), 6.42−6.20 (m, 4H), 6.10–5.92 (m, 5H), 5.87–5.40 (m, 5H), 4.79–4.67 (m, 2H), 4.37 (bs, 2H), 4.22 (d, *J* = 6.8 Hz, 1H), 3.79−3.68 (m, 4H), 2.55–2.17 (m, 6H), 2.03 (q, *J* = 7.2 Hz, 2 H), 1.83 (s, 3H), 1.79 (s, 3H), 1.39 (q, *J* = 7.2 Hz, 2 H), 1.10–1.05 (m, 21H), 0.89 (t, *J* = 7.2 Hz, 3H); HRMS (ESI) calcd for $C_{54}H_{74}O_5NSi$ ($[M+H]^+$) 844.5336, found 844.5331.

Macrolactam 37

To a solution of nonene **S4** (3.0 mg, 3.6 μmol) in THF (0.1 mL) was added TMSOK (3.1 mg, 24.2

μmol) at 0 °C. After stirring for 5 min, the mixture was warmed to room temperature. After 2.5 h, additional TMSOK (1.0 mg, 7.8 μmol) was added and the mixture was stirred for 2.5 h. The reaction was diluted with Et_2O and quenched with sat. aq. NH_4Cl, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. This mixture was used in the next step without purification.

The crude mixture was dissolved in DMF (1.8 mL), and then DIPEA (2.5 μL, 14.4 μmol) and HATU (2.1 mg, 5.4 μmol) were added to the mixture at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched by the addition of pH 6.8 phosphate buffer. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/8) to give macrolactam **37** (1.3 mg, 61% for 2 steps) as a yellow oil.

37: ^{1}H-NMR (600 MHz, pyridine-d_5): δ 7.75 (d, J = 10.2 Hz, 1H), 7.46 (dd, J = 14.4, 10.2 Hz, 1H), 7.62–6.48 (m, 3H), 6.42–6.23 (m, 5 H), 6.16–6.12 (m, 1H), 6.00–5.84 (m, 3H), 5.71 (q, J = 7.2 Hz, 2H), 5.61–5.54 (m, 3H), 4.99 (t, J = 8.4 Hz, 1H), 4.65 (m, 1H), 2.98 (m, 2H), 2.66 (m, 2H), 2.57–2.46 (m, 3H), 2.39–2.38 (m, 1H), 2.11–2.07 (m, 2H), 1.95 (s, 3H), 1.87 (s, 3H), 1.47–1.38 (m, 4H), 1.24 (m, 21H), 0.94 (t, J = 6.6 Hz, 3H); HRMS (ESI) calcd for $C_{38}H_{60}O_2NSi$ ($[M+H]^+$) 590.4393, found 590.4388.

8-Deoxyheronamide C (2)

To a solution of macrolactam **37** (3.4 mg, 5.77 μmol) in THF (0.3 mL) were added AcOH (3.4 μL, 57.7 μmol) and TBAF (1.0 M in THF, 30 μL, 30 μmol) at 0 °C. After stirring for 40 min, the mixture was supplemented with TBAF (1.0 M in THF, 60 μL, 60 μmol) at room temperature. After stirring for 3 h, the mixture was supplemented with TBAF (1.0 M in THF, 60 μL, 60 μmol) at room temperature. After stirring for 3 h at room temperature, sat. aq. NH_4Cl was added and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($MeOH/CHCl_3$ = 1/40) to give 8-deoxyheronamide C (**2**) (1.3 mg, 80%) as a white solid.

2: See the subsequent paper[31] for CD spectrum; ^{1}H-NMR (600 MHz, pyridine-d_5): δ 7.52 (d, J = 10.8 Hz, 1H), 7.27 (dd, J = 15.6, 10.8 Hz), 6.52 (bs, 1H), 6.37 (dd, J = 14.4, 10.8 Hz, 1H), 6.26 (d, J = 15.0 Hz, 1H), 6.12–6.10 (m, 6H), 6.03 (d, J = 10.8 Hz, 1H), 5.96 (dd, J = 15.0, 10.2 Hz, 1H), 5.80–5.75 (m, 1H), 5.69–5.66 (m, 2H), 5.56–5.50 (m, 1H), 5.46 (t, J = 9.0 Hz, 1H), 4.93–4.88 (m, 1H), 4.450–4.42 (m, 1H), 3.03–2.97 (m, 1H), 2.50–2.42 (m, 2H), 2.38–2.29 (m, 2H), 2.01–1.89 (m, 3H), 1.70 (s 3H), 1.65 (s, 3H), 1.28–1.26 (m, 2H), 0.76 (t, J = 7.8 Hz, 3H); ^{13}C-NMR (150 MHz, pyridine-d_5): δ 168.6, 145.1, 142.1, 137.4, 135.7, 134.4, 134.3, 131.7, 131.6, 131.54, 131.51, 129.6, 129.3, 124.9, 124.5, 68.6, 50.8, 42.0, 39.4, 37.5, 35.3, 23.2, 14.2, 13.0, 12.1; HRMS (ESI) calcd for $C_{29}H_{40}O_2N$ ($[M+H]^+$) 434.3059, found 434.3059.

Triene 46

To a solution of boronic acid pinacol ester *ent*-**27** (553 mg, 1.32 mmol) and vinyl iodide **45** (472 mg, 1.98 mmol) in degassed DMF (6.6 mL) and H_2O (0.71 mL) were added Cs_2CO_3 (1.72 g, 5.29 mmol) and Pd(dppf)Cl_2 (77 mg, 0.106 mmol) at room temperature, and the solution was allowed to warm to 50 °C. After stirring for 12 h, the reaction mixture was quenched with pH 6.8 phosphate buffer (5 mL) and H_2O (5 mL) and extracted with EtOAc (15 mL x 3). The combined organic layer was washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to give triene **46** (456 mg, 1.13 mmol, 85%) as a yellow oil. Spectroscopic data for **46** were identical with those reported previously.[29]

Diol 47

Diol **47** was synthesized according to the reported procedure,[29] and the spectroscopic data were identical to those reported therein.

Disilylether 48

Disilylether **48** was synthesized according to the reported procedure,[29] and the spectroscopic data were identical to those reported therein.

Alcohol S5

Alcohol **S5** was synthesized according to the reported procedure,[29] and the spectroscopic data were identical to those reported therein.

Aldehyde S6

Aldehyde **S6** was synthesized according to the reported procedure,[29] and the spectroscopic data were identical to those reported therein.

Vinyl iodide 49

Vinyl iodide **49** was synthesized according to the reported procedure,[29] and the spectroscopic data were identical to those reported therein.

Dienyl stannane 50

To a solution of vinyl iodide **49** (23.9 mg, 0.040 mmol) and (*E*)-1,2–bis(tributylstannyl)ethylene **9** (366 mg, 0.604 mmol) in THF (0.8 mL) were added $PdCl_2(MeCN)_2$ (0.5 mg, 0.002 mmol), CuI (9.2 mg, 0.048 mmol) and DIPEA (35 μL, 0.20 mmol) at room temperature. After stirring for 30 min, the reaction mixture was quenched with pH 6.8 phosphate buffer (3.0 mL) and the mixture was extracted

with EtOAc (15 mL x 3). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/25) to give dienylstannane **50** (32.1 mg, 0.041 mmol, 100%) as a colorless oil.

50: $[\alpha]_D^{24}$ +32 (*c* 0.74, $CHCl_3$); IR (neat): 2955, 1721, 1618, 1142, 960 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 15.1, 11.2 Hz, 1H), 6.57 (d, *J* = 15.1 Hz, 1H), 6.29 (dd, *J* = 15.1, 11.2 Hz, 1H), 6.25 (d, *J* = 18.5 Hz, 1H), 6.00 (dd, *J* = 10.2, 10.2 Hz, 1H), 5.89 (d, *J* = 15.1 Hz, 1H), 5.65 (d, *J* = 8.9 Hz, 1H), 5.27 (dd, *J* = 10.2, 10.2 Hz, 1H), 4.50 (dd, *J* = 10.2, 5.4 Hz, 1H), 4.36 (dd, *J* = 8.9, 5.4 Hz, 1H), 3.75 (s, 3H), 1.81 (s, 3H), 1.35–1.26 (m, 9H), 0.92–0.87 (m, 30H), 0.56–0.51 (m, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.5, 145.5, 145.3, 142.1, 138.6, 136.1, 134.0, 132.9, 130.4, 125.1, 119.9, 73.1, 72.5, 51.4, 29.1, 27.3, 13.7, 13.1, 9.5, 6.8, 4.9; HRMS (EI): calcd for $C_{39}H_{74}O_4Si_2Sn$ (M^+) 782.4148, found 782.4156.

Carboxylic acid 51

To a solution of methyl ester **50** (816 mg, 1.04 mmol) in THF (10 mL) was added TMSOK (1.19 g, 8.35 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was quenched with pH 6.8 phosphate buffer (10 mL) and the mixture was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue

was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1/50) to give carboxylic acid **51** (783 mg, 1.02 mmol, 98%) as a colorless oil.

51: $[\alpha]_D^{24}$ +26 (*c* 1.0, $CHCl_3$); IR (neat): 2955, 1686, 1612, 1260 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 15.0, 11.6 Hz, 1H), 6.77 (dd, *J* = 18.4, 10.1 Hz, 1H), 6.48 (d, *J* = 15.5 Hz, 1H), 6.33 (dd, *J* = 15.5, 11.6 Hz, 1H), 6.27 (d, *J* = 18.4 Hz, 1H), 6.01 (dd, *J* = 10.1, 8.7 Hz, 1H), 5.90 (d, *J* = 15.0 Hz, 1H), 5.69 (d, *J* = 8.7 Hz, 1H), 5.28 (dd, *J* = 10.1, 10.1 Hz, 1H), 4.51 (dd, *J* = 8.7, 5.3 Hz, 1H), 4.38 (dd, *J* = 8.7, 5.3 Hz, 1H), 1.83 (s, 3H), 1.47–1.23 (m, 9H), 0.98–0.81 (m, 30H), 0.57–0.52 (m, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.6, 147.4, 146.4, 142.2, 139.1, 136.2, 134.1, 133.0, 130.5, 125.1, 119.6, 73.2, 72.5, 29.1, 27.4, 13.7, 13.2, 9.5, 6.9, 5.1; HRMS (EI): calcd for $C_{38}H_{72}O_4Si_2Sn$ (M^+) 768.3991, found 768.3967.

Fluorenylmethyl ester 43

To a solution of carboxylic acid **51** (27.3 mg, 0.036 mmol) in DCM (0.7 mL) were added DIPEA (0.06 ml, 0.36 mmol), DMAP (3.0 mg, 0.021 mmol) and FmocCl (28 mg, 0.11 mmol) at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was quenched with pH 6.8 phosphate buffer (5.0 mL) and the mixture was extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/50) to give fluorenylmethyl ester **43** (22.2

mg, 0.024 mmol, 66%) as a yellow oil.

43: $[\alpha]_D^{24}$ +28 (*c* 0.94, $CHCl_3$); IR (neat): 2954, 1715, 1616, 1235, 739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 6.8 Hz, 2H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.41 (dd, *J* = 7.8, 6.8 Hz, 2H), 7.41 (dd, *J* = 15.6, 11.2 Hz, 1H), 7.32 (dd, *J* = 7.8, 7.3 Hz, 2H), 6.78 (dd, *J* = 18.5, 10.7 Hz, 1H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.35 (dd, *J* = 15.6, 11.2 Hz, 1H), 6.27 (d, *J* = 18.5 Hz, 1H), 6.02 (dd, *J* = 10.7, 7.8 Hz, 1H), 6.01 (d, *J* = 15.6 Hz, 1H), 5.69 (d, *J* = 8.3 Hz, 1H), 5.28 (dd, *J* = 10.7, 10.7 Hz, 1H), 4.52 (dd, *J* = 7.8, 5.4 Hz, 1H), 4.44 (d, *J* = 6.8 Hz, 2H), 4.38 (dd, *J* = 8.3, 5.4 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 1H), 1.84 (s, 3H), 1.36–1.25 (m, 9H), 0.98–0.82 (m, 30H), 0.57–0.52 (m, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.0, 145.8, 145.7, 143.9, 142.1, 141.3, 138.8, 136.2, 134.0, 133.0, 131.1, 130.4, 127.7, 127.1, 125.1, 120.0, 119.9, 73.1, 72.5, 66.3, 46.9, 29.1, 27.3, 13.7, 13.2, 9.5, 6.8, 5.0; HRMS (ESI): calcd for $C_{52}H_{82}O_4NaSi_2Sn$ (M^++Na) 969.4666, found 969.4663.

Carbamate **53**

To a solution of 2-(trimethylsilyl)ethanol (0.19 mL, 1.30 mmol) and K_2CO_3 (898 mg, 6.50 mmol) in THF (2.0 mL) was added triphosgene (193 mg, 0.650 mmol) in THF (2.5 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was cooled to -20 °C. To the cooled mixture was added a solution of amine **52** (27.7 mg, 0.325 mmol) in THF (2.5 mL) at -20 °C, and the mixture was allowed to warm to room temperature. After stirring for 2 h, the reaction was quenched with sat. aq.

$NaHCO_3$ (5.0 mL). The mixture was extracted with Et_2O and the combined organic layers were dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Et_2O/pentane = 1/1) to give carbamate **53** (67.4 mg, 0.294 mmol, 90%) as a yellow oil.

53: IR (neat): 1690 $cm^{-}1$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.76 (ddt, *J* = 17.2, 14.0, 7.0 Hz, 1H), 5.07 (d, *J* = 17.2 Hz, 1H), 5.07 (d, *J* = 14.0 Hz, 1H), 4.48 (brs, 1H), 4.12 (t, *J* = 8.4 Hz, 2H), 3.80–3.67 (m, 1H), 2.20 (t, *J* = 7.0 Hz, 2H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.96 (t, *J* = 8.4 Hz, 2H), 0.022 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.1, 134.3, 117.8, 62.7, 46.2, 41.1, 20.6, 17.7, -1.52; HRMS (ESI): calcd for $C_{11}H_{23}O_2NNaSi$ (M^{+}+Na) 252.1396, found 252.1382.

MIDA boronate **54**

To a solution of carbamate **53** (746 mg, 3.25 mmol) and vinyl MIDA boronate **15** (457 mg, 2.50 mmol) in degassed DCM (25 mL) was added Grubbs 2nd catalyst (147 mg, 0.175 mmol). After stirring for 18 h under reflux, the reaction was allowed to cool to room temperature and quenched with ethyl vinyl ether (5.0 mL). The mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1/20) to give a mixture of MIDA boronate **54** and styrenyl MIDA boronate. The mixture was separated by silica gel column chromatography (MeOH/DCM= 1/30) to give MIDA boronate **54** (697 mg, 1.80 mmol, 73%) as a white amorphous solid.

54: IR (ATR): 1760, 1691, 1247, 834 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.14 (dt, *J* = 15.2, 9.0 Hz, lH), 5.50 (d, *J* = 17.6 Hz, 1H), 4.64 (d, *J* = 7.6 Hz, 1H), 4.09 (t, *J* = 9.0 Hz, 2H), 3.94 (d, *J* = 16.6 Hz, 2H), 3.81–3.70 (m, 1H), 3.73 (d, *J* = 16.6 Hz, 2H), 2.84 (s, 3H), 2.34–2.22 (m, 2H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 9.0 Hz, 2H), 0.037 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.0, 156.2, 143.4, 62.8, 61.3, 46.9, 46.6, 43.2, 21.1, 17.7, -1.51; HRMS (ESI): calcd for $C_{16}H_{29}O_6N_2BNaSi$ (M^++Na) 407.1786, found 407.1777.

Pinacol ester S7 and MIDA boronate 55

To a solution of MIDA boronate **54** (500 mg, 1.30 mmol) in MeOH (13 mL) were added $NaHCO_3$ (634 mg, 7.55 mmol) and pinacol (461 mg, 3.90 mmol). After stirring for 4 h at 55 °C, the reaction mixture was allowed to cool to room temperature. The reaction mixture was filtered through a glass filter, and the filtered solid was washed with EtOAc. The combined filtrate and EtOAc wash were concentrated *in vacuo*. The residue was partitioned between EtOAc (60 mL) and brine (25 mL)-pH 6.8.0 buffer (25 mL), and the aqueous layer was extracted with EtOAc (60 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography (EtOAc/hexane = 1/15 to 1/10) to give crude pinacol ester **S7** containing pinacol (455.7 mg, containing 422 mg of the desired product as judged from ^{1}H-NMR, 91% calculated yield), which was used in the next step without further purification.

S7: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.55 (dt, *J* = 18.0, 7.6 Hz, 1H), 5.52 (brs, 1H), 5.48 (brs, 1H), 4.45 (1H, br), 4.13 (2H, m), 3.82 (1H, br), 2.33 (1H, m), 1.27 (12H, s), 1.15 (d, *J* = 6.0 Hz, 3H), 0.97 (brt, *J* = 8.4 Hz, 2H), 0.03 (s, 9H).

To a solution of crude pinacol ester **S7** (55 mg, containing 51 mg of **55**, 0.144 mmol) in degassed THF (2.0 mL) were added MIDA boronate **10** (40.0 mg, 0.144 mmol), Cs_2CO_3 (141 mg, 0.432 mmol), $Pd(OAc)_2$ (2.60 mg, 0.0115 mmol) and SPhos (9.0 mg, 0.023 mmol). After stirring at 35 °C for 24 h, the reaction mixture was filtered through a glass filter, and the filtered solid was washed with acetone. The combined filtrate and acetone wash were concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1/20) to give MIDA boronate **55** (38.6 mg, 0.0909 mmol, 63%) as a yellow oil.

55: IR (neat): 3389, 2954, 1767, 1297, 968 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3CN): δ 6.49 (dd, *J* = 15.0, 10.8 Hz, 1H), 6.30 (d, *J* = 10.8 Hz, 1H), 5.74 (dt, *J* = 15.0, 15.2 Hz, 1H), 5.28 (brs, 1H), 4.08 (t, *J* = 8.4 Hz, 2H), 3.94 (d, *J* = 16.8 Hz, 2H), 3.79 (d, *J* = 16.8 Hz, 2H), 3.66 (quint, *J* = 6.8 Hz, lH), 2.73 (s, 3H), 2.28–2.25 (m, 2H), 1.72 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 8.4 Hz, 2H), 0.035 (s, 9H); ^{13}C-NMR (100 MHz, CD_3CN): δ 169.4, 156.8, 140.8, 137.5, 133.0, 129.7, 62.9, 62.7, 47.7, 47.3, 40.6, 20.9, 18.3, 15.0, -1.48; HRMS (ESI): calcd for $C_{19}H_{33}O_6N_2BNaSi$ (M^++Na) 447.2099, found 447.2093.

Vinyl iodide **56**

To a cooled (0 °C) solution of MIDA boronate **55** (42.4 mg, 0.100 mmol) in MeOH (0.4 mL) and THF (0.4 mL) was added NaOMe (5.0 M in MeOH, 64 μL, 0.32 mmol). The reaction mixture was allowed to warm to room temperature over 20 min. After cooling to 0 °C, *N*-iodosuccinimide (27.0 mg, 0.120 mmol) in MeCN (0.4 mL) was added, and the mixture was allowed to warm to room temperature. After stirring for 20 min, the reaction was quenched with pH 6.8 phosphate buffer (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL). The mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/10) to give vinyl iodide **56** (29.0 mg, 0.0734 mmol, 73%) as a colorless oil.

56: IR (neat): 2952, 1690, 1249, 1061, 963 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.73 (d, *J* = 10.6 Hz, 1H), 6.17 (dd, *J* = 15.0, 10.6 Hz, 1H), 5.61 (ddd, *J* = 15.0, 7.2, 7.2 Hz, 1H), 4.41 (br s, 1H), 4.13 (t, *J* = 8.7 Hz, 2H), 3.78 (br s, 1H), 2.49 (s, 3H), 2.26–2.20 (m, 2H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.97 (t, *J* = 8.7 Hz, 2H), 0.035 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.9, 140.2, 130.6, 128.2, 95.9, 62.8, 46.4, 39.9, 28.0, 20.6, 17.7, –1.5; HRMS (EI): calcd for $C_{14}H_{26}NO_2SiI$ (M^+) 395.0777, found 395.0771.

Fmoc carbamate **42**

To a solution of Teoc carbamate **56** (579 mg, 1.46 mmol) in THF (29 mL) was added TBAF (13.1 mL,

13.1 mmol) at 0 °C. After stirring for 3 h at 40 °C, the reaction was quenched with 1N aq. HCl (13 mL) and the mixture was extracted with AcOEt (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by amine-coated silica gel column chromatography (AcOEt/hexane = 1/1) to give crude amine, which was used in the next step without further purification. To a solution of the crude amine in THF (9.7 mL) and H_2O (4.9 mL) were added FmocCl (454 mg, 1.75 mmol) and $NaHCO_3$ (172 mg, 2.04 mmol) at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was quenched with pH 6.8 phosphate buffer (10 mL) and the mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/DCM = 1/150) to give Fmoc carbamate **42** (665 mg, 1.41 mmol, 96%) as a white solid.

42: mp. 82–83 °C (recrystallized from EtOAc); IR (neat): 3325, 2966, 1797, 1510, 1058 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, -30 °C): δ 7.80 (d, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 2H), 7.44 (dd, *J* = 7.7, 7.2 Hz, 2H), 7.34 (dd, *J* = 7.7, 7.7 Hz, 2H), 6.71 (d, *J* = 11.1 Hz, 1H), 6.18 (dd, *J* = 16.4, 11.1 Hz, 1H), 5.60 (ddd, *J* = 16.4, 7.7, 7.7 Hz, 1H), 4.72 (d, *J* = 9.2 Hz, 1H), 4.46–4.30 (m, 2H), 4.21 (t, *J* = 6.5 Hz, 1H), 3.83–3.76 (m, 1H), 2.46 (s, 3H), 2.31–2.20 (m, 2H), 1.13 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.5, 143.8, 141.2, 140.1, 130.4, 128.1, 127.5, 126.9, 124.8, 119.8, 96.0, 66.3, 47.2, 46.5, 39.7, 27.9, 20.4; HRMS (EI): calcd for $C_{23}H_{24}INO_2$ (M^+) 473.0852, found 473.0881.

Heptaene 57

To a solution of fluorenylmethyl ester **50** (60 mg, 0.063 mmol) and vinyliodide **42** (60 mg, 0.13 mmol) in DMF (1.2 mL) were added $Pd_2(dba)_3 \cdot CHCl_3$ (16 mg, 0.016 mmol), Ph_3As (9.6 mg, 0.032 mmol) and LiCl (5.4 mg, 0.13 mmol) at room temperature. After stirring for 4 h at 40 °C, the reaction was quenched with pH 6.8 phosphate buffer (10 mL) and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/10) to give a diastereomixture of heptaene **54** (38.2 mg, 0.038 mmol, 60%) as a colorless oil.

54: IR (neat): 2953, 1712, 1615, 1330, 1003, 739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 6.8 Hz, 2H), 7.76 (d, *J* = 6.8 Hz, 2H), 7.62 (d, *J* = 6.8 Hz, 2H), 7.58 (d, *J* = 6.8 Hz, 2H), 7.44−7.37 (m, 1H), 7.40 (dd, *J* = 14.0, 6.8 Hz, 4H), 7.21 (dd, *J* = 14.0, 6.8 Hz, 4H), 6.62 (d, *J* = 15.5 Hz, 1H), 6.51−6.41 (m, 2H), 6.35 (dd, *J* = 15.5, 10.6 Hz, 1H), 6.25 (d, *J* = 15.0 Hz, 1H), 6.15−6.10 (m, 1H), 6.11 (dd, *J* = 11.1, 11.1 Hz, 1H), 6.01 (d, *J* = 15.0 Hz, 1H), 5.71−5.64 (m, 1H), 5.70 (d, *J* = 8.7 Hz, 1H), 5.35 (dd, *J* = 10.1, 10.1 Hz, 1H), 4.65–4.59 (m, 1H), 4.49 (dd, *J* = 8.7, 4.8 Hz, 1H), 4.44 (d, *J* = 7.2 Hz, 2H), 4.40−4.36 (m, 3H), 4.28 (t, *J* = 7.2 Hz, 1H), 4.22 (t, *J* = 5.8 Hz, 1H), 3.85–3.78 (m, 1H), 2.33−2.28 (m, 2H), 1.86 (s, 3H), 1.84 (s, 3H), 1.20 (br s, 3H), 0.93−0.89 (m, 18H), 0.58−0.51 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.0, 155.6, 145.7, 144.0, 143.9, 141.2, 138.7, 138.6, 134.2, 134.1,

134.04, 134.02, 131.7, 131.6, 130.8, 130.4, 129.8, 127.7, 127.6, 127.03, 127.00, 125.13, 125.08, 124.98, 123.6, 120.0, 119.9, 73.1, 72.9, 66.3, 47.3, 46.8, 40.3, 20.5, 13.2, 12.6, 6.8, 4.9; HRMS (ESI): calcd for $C_{63}H_{79}O_6NNaSi_2$ (M^++Na) 1024.5338, found 1024.5338.

Heronamidoids α (5) and β (6)

To a solution of heptaene **54** (86.4 mg, 0.086 mmol) in DCM (2.0 mL) was added DBU (0.052 ml, 0.34 mmol) at 0 °C. The mixture was stirred for 1 h. To the cooled mixture were added THF (8.6 mL), HATU (327 mg, 0.86 mmol) and DIPEA (0.2 mL, 1.03 mmol). After stirring for 18 h, the reaction was quenched with pH 6.8 phosphate buffer (10 mL). The mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/4) to give heronamidoid β (**6**) (8.8 mg, 0.015 mmol, 18%) as a colorless oil and heronamidoid α (**5**) (16.6 mg, 0.028 mmol, 33%) as a colorless oil.

Heronamidoid α (**5**): $[\alpha]_D^{24}$ –13 (*c* 0.50, $CHCl_3$); IR (neat): 2954, 2876, 1670, 1457, 1117 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.93 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.20 (d, *J* = 15.8 Hz, 1H), 6.10–6.05 (m, 4H), 5.96–5.88 (m, 2H), 5.68 (d, *J* = 15.1 Hz, 1H), 5.63 (ddd, *J* = 15.1, 10.3, 4.8 Hz, 1H), 5.52 (dd, *J* = 8.9, 8.9 Hz, 1H), 5.30 (d, *J* = 8.2 Hz, 1H), 4.76 (d, *J* = 11.0 Hz, 1H), 4.66 (d, *J* = 8.2 Hz, 1H), 4.37 (d, *J* = 8.9 Hz, 1H), 4.25–4.18 (m, 1H), 2.53−2.47 (m, 1H) 1.81 (s, 3H), 1.77−1.71 (m, 1H), 1.59

(s, 3H), 1.26–1.23 (m, 3H), 0.98−0.89 (m, 18H), 0.66−0.58 (m, 12H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 167.5, 144.8, 142.5, 140.32, 140.26, 136.7, 133.5, 131.20, 131.17, 130.42, 130.40, 130.3, 129.1, 124.1, 124.0, 121.9, 74.6, 71.4, 45.8, 44.0, 29.7, 12.5, 12.3, 6.8, 4.9; HRMS (EI): calcd for $C_{34}H_{57}NO_3Si_2$ (M^+) 583.3877, found 583.3890.

Heronamidoid β (**6**): $[\alpha]_D^{24}$ –71 (*c* 0.70, $CHCl_3$); IR (neat): 2953, 2875, 1647, 1457, 1238 cm^{-1}; ^{1}H-NMR (600 MHz, CD_3OD): δ 6.85 (dd, *J* = 16.0, 10.1 Hz, 1H), 6.32−6.15 (m, 6H), 6.08 (dd, *J* = 15.1, 10.5 Hz, 1H), 5.86−5.82 (m, 1H), 5.79 (d, *J* = 16.0 Hz, 1H), 5.51 (dd, *J* = 11.0, 8.2 Hz, 1H), 5.31 (d, *J* = 9.2 Hz, 1H), 4.73 (d, *J* = 9.2 Hz, 1H), 4.44 (d, *J* = 8.2 Hz, 1H), 4.10–4.05 (m, 1H), 2.71−2.66 (m, 1H), 2.14 (dd, *J* = 12.4, 3.2 Hz, 1H), 1.86 (s, 3H), 1.63 (s, 3H), 1.25 (d, *J* = 7.3 Hz, 3H), 1.00−0.94 (m, 18H), 0.70−0.58 (m, 12H); ^{13}C-NMR (150 MHz, CD_3OD): δ 170.2, 145.6, 142.5, 140.2, 138.1, 135.6, 134.3, 133.5, 133.2, 131.5, 129.7, 129.3, 127.0, 126.3, 125.3, 76.6, 73.8, 46.0, 38.1, 18.6, 12.80, 12.76, 7.2, 5.9; HRMS (EI): calcd for $C_{34}H_{57}NO_3Si_2$ (M^+) 583.3877, found 583.3862.

Heronamidoid γ (7):

To a solution of heronamidoid α (**5**) (7.0 mg, 0.012 mmol) in THF (1.2 mL) was added TBAF (72 μL, 0.054 mmol) at 0 °C. After stirring for 6 h at same temperature, pH 6.8 phosphate buffer (7 mL) was added and the mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was

purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1/15) to give heronamidoid γ (**7**) (2.4 mg, 0.010 mmol, 84%) as a white solid.

Heronamidoid γ (**7**): $[\alpha]_D^{24}$ – 567 (*c* 0.15, MeOH); IR (neat): 3280, 2925, 1646, 1609, 989 cm^{-1}; ^{1}H-NMR (600 MHz, C_5D_5N): δ 7.71 (d, *J* = 10.1 Hz, 1H), 7.40 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.50−6.15 (m, 8H), 6.09 (d, *J* = 11.0 Hz, 1H), 5.87−5.82 (m, 2H), 5.31 (dd, *J* = 8.3, 2.7 Hz, 1H), 5.20−4.70 (m, 1H), 4.54–4.53 (m, 1H), 2.41−2.40 (m, 1H), 1.92 (dd, *J* = 23.4, 11.4 Hz, 1H), 1.79 (s, 3H), 1.72 (s, 3H), 1.17 (d, *J* = 6.7 Hz, 3H); ^{13}C-NMR (150 MHz, CD_3OD): δ 177.4, 145.2, 143.0, 139.1, 138.5, 134.9, 134.2, 132.2, 132.0, 131.5, 131.4, 130.1, 126.4, 125.3, 124.0, 73.6, 71.5, 30.7, 24.8, 20.8, 13.9, 12.7; HRMS (ESI): calcd for $C_{22}H_{30}O_3N$ (M^++H) 356.2220, found 356.2213.

Heronamidoid δ (8)

To a solution of heronamidoid β (**6**) (5.3 mg, 0.0091 mmol) in THF (0.9 mL) was added TBAF (36 μL, 0.036 mmol) at 0 °C. After stirring for 1 h at the same temperature, pH 6.8 phosphate buffer (3.0 mL) was added, and the mixture was extracted with EtOAc (8 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1/15) to give heronamidoid δ (**8**) (2.4 mg, 0.0068 mmol, 74%) as a white solid.

Heronamidoid δ (**8**): $[\alpha]_D^{24}$ –246 (*c* 0.18, MeOH); IR (neat): 3336, 2924, 1647, 1044 cm^{-1}; ^{1}H-NMR

(600 MHz, C_5D_5N, -30 °C): δ 8.13 (d, *J* = 7.6 Hz, 1H), 7.06 (dd, *J* = 15.8, 10.3 Hz, 1H), 6.53 (dd, *J* = 13.1, 13.1 Hz, 1H), 6.48−6.24 (m, 7H), 6.10 (d, *J* = 15.1 Hz, 1H), 5.98−5.94 (m, 1H), 5.85 (d, *J* = 9.6 Hz, 1H), 5.39 (d, *J* = 9.6 Hz, 1H), 5.11 (d, *J* = 6.9 Hz, 1H), 4.53−4.48 (m, 1H), 3.12−3.06 (m, 1H), 2.15−2.09 (m, 1H), 1.73 (s, 3H), 1.66 (s, 3H), 1.16 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (150 MHz, CD_3OD): δ 170.2, 145.8, 142.6, 138.1, 135.8, 134.3, 133.7, 133.1, 131.5, 131.1, 129.3, 128.4, 127.1, 126.8, 125.3, 73.2, 70.4, 30.8, 20.9, 13.9, 12.8, 12.6; HRMS (ESI): calcd for $C_{22}H_{29}O_3NNa$ (M^++Na) 378.2040, found 378.2035.

Heronamidoid ζ (58)

A 5 mm NMR tube containing a solution of heronamidoid β (**6**) (2.4 mg, 0.0041 mmol), toluene (5.0 μL, 0.047 mmol, internal standard) and CD_3OD (ca. 0.4 mL) was irradiated at 365 nm (CL-1000L, UV crosslinker, UVP) for 45 min. Formation of heronamidoid ζ (**56**) was observed, and the yield was calculated as 41% using an internal standard. The solution was concentrated *in vacuo* to give crude heronamidoid ζ (**58**) as a yellow oil. Severe degradation of this material was observed during silica gel column chromatography.

Heronamidoid β (**58**): IR (neat): 1660 cm^{-1}; ^{1}H-NMR (600 MHz, CD_3OD): δ 5.88–5.85 (m, 1H), 5.87 (dd, *J* = 14.8, 11.0 Hz, 1H), 5.75–5.73 (m, 1H), 5.74 (d, *J* = 15.9 Hz, 1H), 5.61 (d, *J* = 14.8 Hz, 1H), 5.06 (dd, *J* = 15.4, 11.0 Hz, 1H), 4.94 (dd, *J* = 15.9, 9.3 Hz, 1H), 4.88–4.79 (m, 1H), 4.27 (dd, *J* = 4.4,

4.4 Hz, 1H), 3.95 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.71–3.68 (m, 1H), 3.18 (dd, *J* = 10.4, 10.4 Hz, 1H), 2.68 (dd, *J* = 11.0, 10.4 Hz, 1H), 2.60 (dd, *J* = 11.5, 10.4 Hz, 1H), 2.49 (dddd, *J* = 10.4, 10.4, 9.3, 4.9 Hz, 1H), 2.09–2.03 (m, 1H), 1.91–1.88 (m, 1H), 1.66 (s, 3H), 1.64 (s, 3H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.05–0.88 (m, 12H), 0.75–0.52 (m, 18H); ^{13}C-NMR (150 MHz, CD_3OD): δ 175.7, 142.2, 138.0, 135.6, 135.4, 134.3, 134.0, 133.8, 130.7, 129.1, 127.7, 74.2, 70.6, 56.2, 55.8, 47.4, 44.1, 43.6, 35.1, 30.8, 23.0, 14.3, 13.7, 6.7, 4.9; HRMS (EI): calcd for $C_{34}H_{57}O_3NSi_2$ (M^+) 583.3877, found 583.3896.

Heronamidoid ε (59)

A 5 mm NMR tube containing heronamidoid α (**5**) (2.9 mg, 0.0050 mmol), toluene (5.0 μL, 0.047 mmol, internal standard) and CD_3OD (ca. 0.4 mL) was irradiated at 365 nm (CL-1000L, UV crosslinker, UVP) for 45 min. Formation of heronamidoid ε (**55**) was observed, and the yield was calculated using an internal standard to be quantitative. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc/hexane = 1/2) to give heronamidoid ε (**59**) (0.67 mg, 0.00115 mmol, 23%) as a yellow oil.

Heronamidoid ε (**59**): $[\alpha]_D^{24}$ –70 (*c* 0.073, $CHCl_3$); IR (neat): 2925, 2874, 1729, 1664, 1122, 741 cm^{-1}; ^{1}H-NMR (600 MHz, CD_3OD): δ 5.87 (dd, *J* = 15.0, 11.1 Hz, 1H), 5.86 (dd, *J* = 4.5, 1.9 Hz, 1H), 5.74 (dd, *J* = 9.9, 1.9 Hz, 1H), 5.71 (d, *J* = 15.9 Hz, 1H), 5.60 (d, *J* = 11.1 Hz, 1H), 5.03 (dd, *J* = 15.0, 10.1 Hz, 1H), 4.95 (dd, *J* = 15.9, 9.8 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.27 (dd, *J* = 4.5, 3.5 Hz, 1H),

3.94 (dd, J = 11.0, 3.5 Hz, 1H), 3.63–3.57 (m, 1H), 3.16 (dd, J = 11.0, 9.9 Hz, 1H), 2.66 (dd, J = 10.3, 10.1 Hz, 1H), 2.60 (dd, J = 11.0, 10.4 Hz, 1H), 2.41 (ddd, J = 12.6, 11.6, 9.8 Hz, 1H), 2.18–2.14 (m, 1H), 1.66 (s, 3H), 1.64 (s, 3H), 1.54 (ddd, J = 12.6, 12.6, 12.0 Hz, 1H) 1.21 (d, J = 6.2 Hz, 3H), 1.02–0.93 (m, 12H), 0.70–0.63 (m, 18H); ^{13}C-NMR (150 MHz, CD_3OD): δ 175.3, 142.2, 137.9, 135.8, 135.7, 134.2, 133.9, 133.8, 130.7, 129.1, 127.4, 74.1, 70.6, 56.2, 56.0, 49.1, 47.7, 44.1, 37.7, 23.0, 14.2, 13.8, 7.5, 6.9, 6.5; HRMS (ESI): calcd for $C_{34}H_{57}O_3NNaSi_2$ (M^++Na) 606.3769, found 606.3748.

Computational Methods

Conformational search and structure optimization for heronamidoids γ (7) and δ (8)

Conformational searches were carried out for heronamidoids γ (**7**) and δ (**8**) using a 20,000 step Monte Carlo search (Macromodel Version 11.0) with the OPLS2015 force field without solvent. No bond restraints were applied. All conformations within 50 kJ mol^{-1} of the lowest energy structure were recorded. Then, energy minimization and redundant conformer elimination (RMS deviation cutoff = 0.5 Å, comparing heavy atoms and OH, SH) were carried out to obtain energy-minimized structures. The structure of the most stable conformer for each molecule was optimized further at the DFT level as follows.

All DFT calculations were performed with the Gaussian09 Rev. E.01 program. Structure optimization and frequency calculation were carried out with the B3LYP functional including Grimme's D3

dispersion correction with Becke–Johnson (BJ) damping corrections (abbreviated as B3LYP-D3BJ) and the 6-31G* basis set for all atoms. Gibbs free energy (kJ/mol) was calculated based on B3LYP-D3BJ/6-31G* single point energy and frequency. All stationary points were characterized by frequency calculations to confirm their identity as either of the local minima (zero imaginary frequencies). Cartesian coordinates (Angstroms) for the DFT-optimized structures of heronamidoids γ (**7**) and δ (**8**) are listed in Supporting Tables 1 and 2.

Supporting Information

Structure of all reported heronamides; Cartesian coordinates (angstroms) for DFT-optimized structure of heronamidoids γ (**7**) and δ (**8**); copies of the NMR spectra of synthesized compounds (PDF).

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