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Diverse Synthesis of Marine Cyclic Depsipeptide Lagunamide A and Its Analogues

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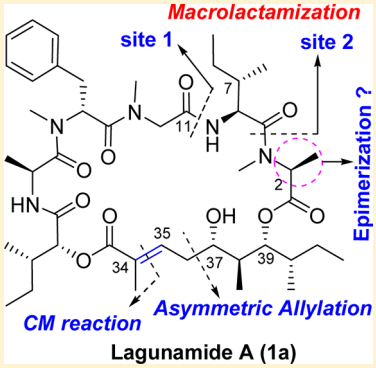
Supporting Information

ABSTRACT: The asymmetric total synthesis of lagunamide A (3.0%, 20 steps longest linear sequence) and its five analogues, including the structure dehydrated at the C37 position, are detailed in this report. The key feature in this diverse synthesis includes the elaboration of four consecutive chiral centers at C37−40 and the final macrocyclization. Starting from chiral aldehyde **10**, we synthesized both 1,3-*anti* and 1,3-*syn* homoallylic alcohols **20a** and **20b** through asymmetric aldol condensation and stereoselective allylation. The following esterification to introduce the L-*N*-Me-Ala unit resulted in significant epimerization. This problem was finally overcome by coupling the alcohols with the corresponding acid chloride of the L-alanine derivative. The key α,β-unsaturated carboxylic acid unit was produced by cross-metathesis (CM) of methacrylaldehyde and related olefins. Interestingly, we found that the C7 configuration dramatically affected the ring closure. Natural lagunamide A (**1a**), its 39-epimer (**1c**), and its 2-epimer (**1d**) were obtained through macrolactamization between alanine and isoleucine moieties.



INTRODUCTION

Cyanobacteria, predominantly with structural skeletons as modified peptides, depsipeptides, polyketides, and peptide−polyketide hybrids,[1] have emerged as a valuable source of marine natural products with remarkable biological activities.[2] As a class of promising compounds in drug discovery, most of these secondary metabolites display a variety of physiological activities, including antimicrobial, antimalarial, cytotoxic, and neurotoxic properties.[2b,3] Although a few of them have been advanced to phase-II clinical trials for treating cancers,[4] most cyanobacterial metabolites have not been well-studied and thus require further investigation of either their structural modifications or their modes of action. In the past decade, dolastatin 10,[5a,b] apratoxins,[5c] palau'amide,[5d] aurilide,[5e,f] kulokekahilide,[5g,h] and largazole[5i,j] have been applied or considered for further clinical development as anticancer drugs because of their potent cytotoxic activities.

Lagunamides A−C (**1**−**3**) (Figure 1) were isolated from the marine cyanobacterium *Lyngbya majuscula* collected in Pulau Hantu Beser, Singapore.[6] These cyclic depsipeptides exhibit potent cytotoxic activity against P388 murine leukemia cell lines (IC_{50} = 6.4, 20.5, and 24.4 nM, respectively) and selective growth inhibitory activities against a panel of other cancer cell lines, including A549, PC3, HCT8, and SK-OV3 (IC_{50} = 1.6−3.8 nM).[1h,6] In addition, they show moderate antiswarming activity against *Pseudomonas aeruginosa* PA10.[6] The structure of lagunamide A was originally assigned on the basis of extensive NMR studies and LC−MS techniques,[6a] but the absolute configurations of the two chiral centers at C7 and C39 were revised by Dai et al.[7] after the asymmetric total synthesis in

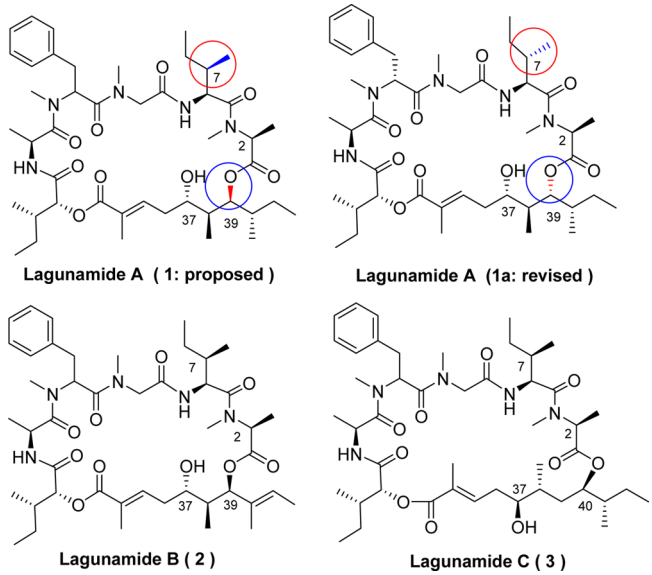


Figure 1. Structures of lagunamides A−C.

2012. Its high efficacy for P388 murine leukemia cell lines and intriguing structure prompted us to develop a general synthetic approach for a series of lagunamides and to study their structure−activity relationship. As one part of our continuous interest in pursuing some diverse syntheses of piperidine

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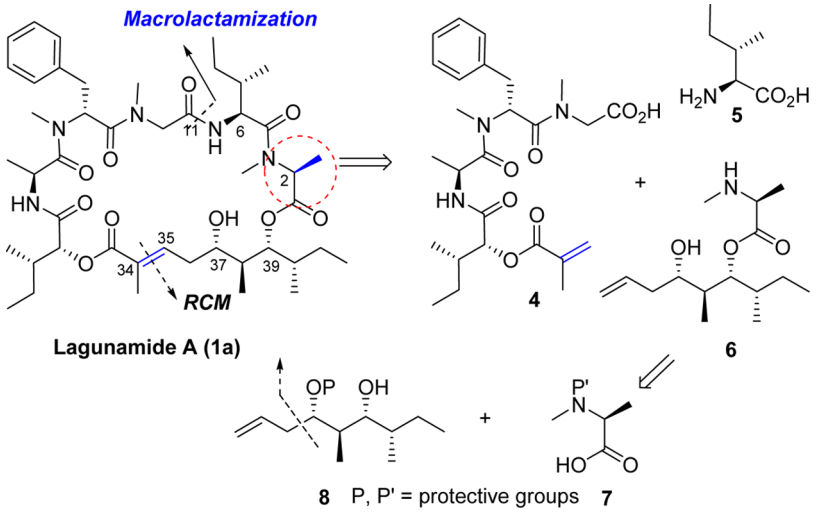
Scheme 1. Retrosynthetic Analysis of Lagunamide A (1a)



alkaloids,[8] ceramides,[9] and depsipeptides,[10] herein we present a general method for the diverse synthesis of lagunamide A (**1a**).

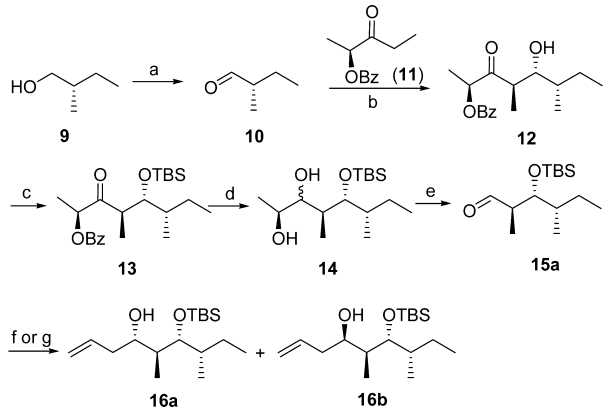
RESULTS AND DISCUSSION

Our synthetic strategy for the diverse synthesis of lagunamide A (**1a**) is illustrated in Scheme 1, with the stereoselective synthesis of non-peptide fragment **6** and the effective macrocyclization as our main focus in constructing our target molecule. As we aimed to achieve a convenient method for the diverse synthesis of **1a** and to study further the structure–activity relationship, we proposed an RCM[11] reaction to form the double bond between C34 and C35 and certainly kept macrolactamization as an alternative approach for ring closure. The key fragment **6** could be prepared from the 1,3-diol moiety **8** and alanine derivative **7**, in which the C2 chirality should be closely monitored in the esterification step.[12]

Our strategy to construct the 1,3-diol moiety **8** was through an asymmetric Paterson *anti*-aldol[13] reaction of **10** and subsequent allylation of **15a**, as outlined in Scheme 2. The *trans*-enolate of ketone **11**, preformed by treatment with $(c\text{-hex})_2BCl$ in the presence of Me_2NEt, reacted with aldehyde **10**, prepared by Swern oxidation[14] of commercially available (*S*)-2-methylbutan-1-ol, to produce the desired *anti* product **12** with high diastereoselectivity (*dr* > 99:1) in 74% yield. After alcohol **12** was protected as its *tert*-butyldimethylsilyl (TBS) ether **13** in 82% yield, ketone **13** was reduced by $NaBH_4$, and subsequent hydrolysis of the benzoate moiety afforded 1,2-diol **14** as a mixture of two diastereomers in 56% overall yield. The key aldehyde **15a** was generated by oxidative cleavage of **14** ($NaIO_4$, MeOH) and then subjected to asymmetric allylation using allylmagnesium chloride. Unfortunately, the diastereoselectivities in forming the homoallylic alcohols **16a** and **16b** were quite low in both cases, slightly favoring the formation of **16b** (**16a**:**16b** = 39:61). Attempts at further improvement using Lewis acids turned out to be unhelpful, probably because of the unfavorable orientation of the C3 substituent in the transition state.

At the time we initiated our synthetic efforts, we had the originally proposed structure **1** as our target molecule. In this case, an alternative aldehyde **15b** was required as a properly assembled substrate for the asymmetric allylation. As shown in Scheme 3, the aldol condensation with the above aldehyde **10**, through Evans' chiral oxazolidinone auxiliary,[15] afforded the

Scheme 2. Preparation of Homoallylic Alcohols 16a and 16b[a]



[a]Reagents and conditions: (a) $(COCl)_2$, DMSO, TEA, −78 °C. (b) $(c\text{-hex})_2BCl$, Me_2NEt, −78 to −26 °C, 74% (two steps), *dr* > 99:1. (c) TBSOTf, 2,6-lutidine, 0 °C, 82%. (d) (1) $NaBH_4$, MeOH/THF, 0 °C; (2) K_2CO_3, MeOH, rt, 56% (two steps). (e) $NaIO_4$, MeOH/H_2O (2/1, v/v), rt, 84%. (f) AllylMgCl, THF, −78 °C, 84% (*dr* 39:61). (g) AllylMgCl, $ZnCl_2$, THF, −78 °C, 59% (*dr* 40:60).

desired *syn* product **17** with high diastereoselectivity (*dr* > 99:1) in 93% yield. Protection of the hydroxy group (TBSOTf, 2,6-lutidine) and subsequent reductive cleavage of the auxiliary[16] ($LiBH_4$, MeOH) produced alcohol **19**, which was subjected to Swern oxidation [DMSO, $(COCl)_2$] to generate the key aldehyde **15b** in 87% overall yield over three steps. The allylation of aldehyde **15b** with allylmagnesium chloride is summarized in Table 1. The reaction in the absence of Lewis acid produced a mixture of two diastereomers with *dr* = 11:89, albeit in favor of the undesired isomer **20b** (Table 1, entry 1). Because of the steric TBS protective group at the C3 position, most Lewis acids did not show any positive effect, although $AlMe_2Cl$ and $InCl_3$ slightly improved the formation of the desired isomer **20a** (Table 1, entries, 2–11). To our delight, zinc chloride could reverse the selectivity, giving the desired product with *dr* = 90:10 (Table 1, entry 12). The two diastereomers **20a** and **20b** could be separated by silica gel chromatography, and their stereochemistries were assigned through chemical transformations to give acetonides **22a** and

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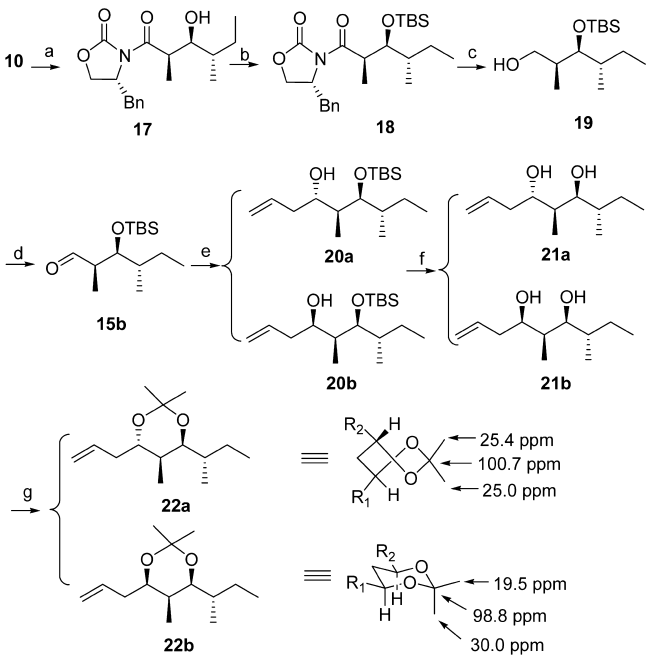
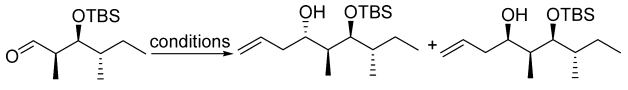
Scheme 3. Preparation of Homoallylic Alcohols 20a and 20b[a]



[a]Reagents and conditions: (a) (*R*)-4-benzyl-3-propionyloxazolidin-2-one, Bu_2BOTf, TEA, CH_2Cl_2, −78 °C, 93%; (b) TBSOTf, 2,6-lutidine, 0 °C, 95%; (c) $LiBH_4$, MeOH/THF, 0 °C; (d) $(COCl)_2$, DMSO, TEA, −78 °C, 92% (two steps); (e) AllylMgCl, THF, −78 °C, 11% (**20a**), 81% (**20b**); (f) 40% aqueous HF, CH_3CN, rt, 95% (**21a**), 92% (**21b**); (g) TsOH, 2,2-dimethoxypropane, acetone, rt, 89% (**22a**), 92% (**22b**).

Table 1. Allylation of Aldehyde 15b



entry	reagent	Lewis acid	yield (%)[c]	20a:20b[d]
1[a]	AllylMgCl	–	92	11:89
2[b]	AllylMgCl	Et_2BOMe	87	16:84
3[b]	AllylMgCl	$CeCl_3$	85	17:83
4[b]	AllylMgCl	$Cu(OTf)_2$	89	14:86
5[b]	AllylMgCl	$AlMe_2Cl$	90	25:75
6[b]	AllylMgCl	$InCl_3$	82	33:67
7[b]	AllylMgCl	$SnCl_2$	85	14:86
8[b]	AllylMgCl	$NiCl_2(PPh_3)_2$	78	20:80
9[b]	AllylMgCl	LiBr	88	17:83
10[b]	AllylMgCl	$Pd(OAc)_2$	89	14:86
11[b]	AllylMgCl	$BF_3{\cdot}Et_2O$	90	15:85
12[b]	AllylMgCl	$ZnCl_2$	90	90:10

[a]AllylMgCl (1.5 equiv), THF, −78 °C. [b]Lewis acid (2.5 equiv), AllylMgCl (1.5 equiv), THF, −78 °C. [c]Combined yields. [d]Determined by isolated products.

22b. Both isomers **20a** and **20b** were treated with a 40% aqueous solution of hydrogen fluoride (40% HF) to remove the TBS group, and the resulting 1,3-diols were protected with 2,2-dimethoxypropane in the presence of a catalytic amount of 4-methylbenzenesulfonic acid (cat. TsOH) to provide acetonides **22a** and **22b**, respectively. The stereochemistries of the *syn*- and *anti*-1,3-diols were determined on the basis of the chemical shifts of the ketal methyl groups in the ^{13}C NMR spectra.[17] For the *syn*-1,3-diol, the full chair conformation of **22b** resulted in significantly different chemical shifts for the two methyl groups (i.e., 19.5 and 30.0 ppm for the equatorial and axial methyls, respectively). On the other hand, the *anti* isomer adopted a twisted chair conformation, having the two methyl groups in similar orientations. The close chemical shifts of 25.0 and 25.4 ppm in compound **22a** clearly demonstrated the *anti*-1,3-diol structure in compounds **20a** and **21a**.

As for the reactions of aldehydes **15a** and **15b** with allylmagnesium chloride, the difference in diastereoselectivities could be explained by the transition states shown in Figure 2. In

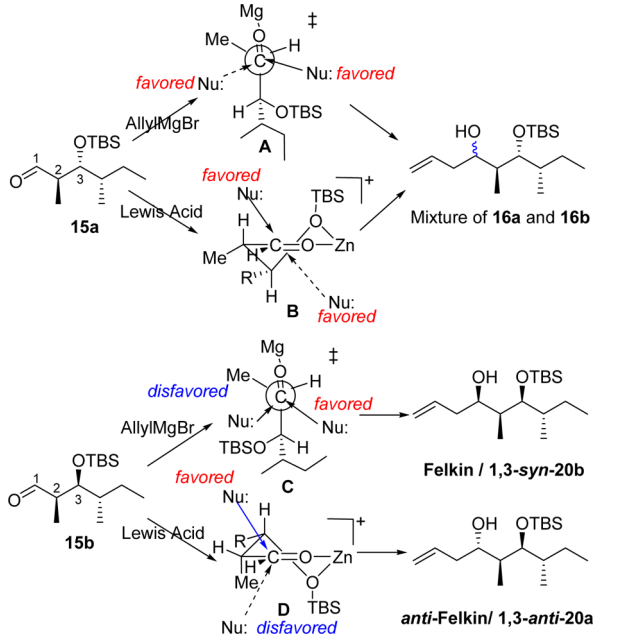


Figure 2. Stereochemistry for the allylation of aldehydes **15a** and **15b**.

the absence of Lewis acid, the stereochemistry was controlled by the Felkin−Anh model.[20] In the reaction with **15b**, both 2-methyl and 3-OTBS groups in the transition state **C** blocked the same side and allowed the allyl group to favorably attack from the other side, affording 1,3-*syn* diol **20b** as the predominant product. In transition state **A** for the reaction with **15a**, the 2-methyl and 3-OTBS groups stayed at either side for nucleophilic attack. As a result, the reaction produced a mixture of two stereoisomers **16a** and **16b**, with slight favor for **16b**, which was formed through the attack from the less hindered 3-OTBS side in model **A**. When the reaction was conducted in the presence of the strong Lewis acid $ZnCl_2$, the zinc cation could coordinate with both the carbonyl and OTBS groups, forming a six-membered-ring transition state.[18] In the reaction with **15b**, one side was blocked by the 2-methyl and TBS groups, and thus, the nucleophilic attack preferred to take place from the less hindered side in transition state **D**, forming the 1,3-*anti*-diol **20a**. On the other hand, in the case of **15a**, either side presented some steric hindrance for allylation, leading to low diastereoselectivity in affording a mixture of **16a** and **16b**. Our observation of the stereochemistry in this allylation process agreed well with the theory of semiempirical calculations (PM3) by Evans.[19]

The enantioselective synthesis of *anti*-1,3-diol **21a** established all four stereocenters for the originally proposed

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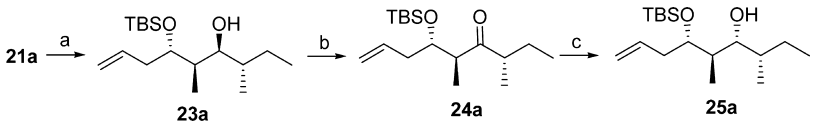
Scheme 4. Preparation of 25a[a]



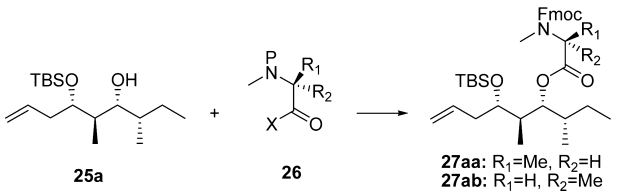
[a]Reagents and conditions: (a) TBSOTf, 2,6-lutidine, −78 °C, 76%; (b) Dess−Martin periodinane, CH_2Cl_2, rt, 92%; (c) Et_3BHLi, THF, −78 °C, 94%.

structure of lagunamide A (**1**). However, we needed to invert one hydroxyl group to achieve the key *syn*-1,3-diol intermediate **8** (P = TBS) for the total synthesis of the revised structure of lagunamide A (**1a**). As shown in Scheme 4, silylation with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine afforded compound **23a** with high regioselectivity (*dr* > 99:1) in 76% yield. Dess−Martin oxidation[21] and subsequent reduction with lithium triethylborohydride (Et_3BHLi) gave the desired steroisomer **25a** with high stereoselectivity (*dr* > 99:1) in 86% overall yield.

The formation of intermediate **27aa** involved the coupling of **25a** and alanine moiety **26**. In spite of many effective methods for such esterification, the classical method with L-*N*-Me-Fmoc-Ala-OH under Yamaguchi conditions[22] resulted in a mixture of diastereomers **27aa** and **27ab** (*dr* = 24:76) in 92% combined yield (Table 2, entry 1). It is worth mentioning that the major product was the wrong isomer with epimerization at the position α to the carbonyl group. Interestingly, when D-*N*-Me-Fmoc-Ala-OH was used for the coupling, almost no epimerization was observed, and the desired diastereomer **27ab** was generated with high diastereoselectivity (*dr* = 98:2) in 89% yield (Table 2, entry 2). The above results suggested that the epimerization likely occurred after the formation of the ester bond. The replacement of *N*-Fmoc with *N*-Boc protection for the L-alanine derivative in the esterification resulted in no improvement under the same coupling conditions (Table 2, entry 3). When other coupling reagents were used, 2-methyl-6-nitrobenzoic anhydride (MNBA)[23] and EDC, showed similar results and 2-chloro-1-methylpyridinium iodide[24] afforded no desired product (Table 2, entries 4−6). As the base DMAP might be the cause for the epimerization, we attempted the coupling using the acid chloride *N*-Me-Fmoc-Ala-Cl.[7,12] It clearly showed that the reaction proceeded with less epimerization when less DMAP was employed in the esterification (Table 2, entries 7 and 8). Finally, the desired optically pure ester **27aa** was obtained through coupling with L-*N*-Me-Fmoc-Ala-Cl in the absence of DMAP (Table 2, entry 9).

Next, we turned our attention to the preparation of the peptide unit of lagunamide A (**1a**) (Scheme 5). Removal of the Boc group in **28** with TFA and subsequent condensation with D-Boc-*N*-Me-Phe-OH in the presence of HATU/DIPEA afforded dipeptide **29** in 89% yield. Tripeptide **30** was obtained in 68% yield in a similar sequence. Treatment of compound **30** with TFA and subsequent coupling with (2*R*,3*S*)-2-hydroxy-3-methylpentanoic acid in the presence of EDC/HOBt produced a 56% yield of **31**, which was subjected to esterification with methacrylic acid under Yamaguchi conditions to generate **32** in 87% yield. Removal of the allylic group gave free carboxylic acid

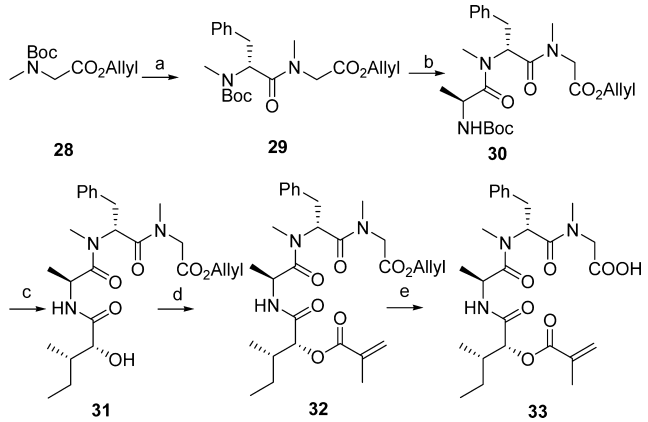
Table 2. Esterification of Alcohol 25a.



	26					
entry	R_1	R_2	X	P	**27aa:27ab**[i]	yield (%)[j]
1[a]	Me	H	OH	Fmoc	24:76	92
2[a]	H	Me	OH	Fmoc	2:98	89
3[b]	Me	H	OH	Boc	24:76	73
4[c]	Me	H	OH	Fmoc	23:77	69
5[d]	Me	H	OH	Fmoc	–	NR
6[e]	Me	H	OH	Fmoc	33:67	48
7[f]	Me	H	Cl	Fmoc	58:42	57
8[g]	Me	H	Cl	Fmoc	70:30	56
9[h]	Me	H	Cl	Fmoc	>99:1	55

[a]$Cl_3C_6H_2COCl$ (1.2 equiv), acid (1.2 equiv), TEA (1.5 equiv), DMAP (2.0 equiv), rt, 30 min. [b](1) Conditions in footnote *a*; (2) TMSOTf, 2,6-lutidine, DCM; (3) FmocOsu, DIPEA, DCM. [c]MNBA (1.2 equiv), acid (2 equiv), TEA (3 equiv), DMAP (0.2 equiv), rt, 30 min. [d]2-Chloro-1-methylpyridinium iodide (2.2 equiv), acid (2 equiv), DIPEA (5 equiv), DCM reflux. [e]EDCI (2 equiv), acid (2 equiv), TEA (2 equiv), DMAP (1 equiv) DCM, rt, 12 h. [f]Acid chloride (5.0 equiv), DIPEA (5.5 equiv), DMAP (0.5 equiv), DCM, −15 °C, 5 h. [g]Acid chloride (5.0 equiv), colidine (10 equiv), DMAP (0.2 equiv), toluene, 60 °C, 8 h. [h]Acid chloride (2.5 equiv), DIPEA (5 equiv), DCM, reflux, 8 h. [i]Determined by HPLC of the crude products. [j]Combined yields of **27aa** and **27ab**.

Scheme 5. Preparation of the Peptide Fragment[a]



[a]Reagents and conditions: (a) (1) TFA/CH_2Cl_2, 0 °C to rt; (2) D-Boc-*N*-Me-Phe-OH, HATU, DIPEA, CH_2Cl_2, 0 °C to rt, 89% (two steps). (b) (1) TFA/CH_2Cl_2, 0 °C to rt; (2) L-Boc-Ala-OH, HATU, DIPEA, CH_2Cl_2, 0 °C to rt, 68% (two steps). (c) (1) TFA/CH_2Cl_2, 0 °C to rt; (2) (2*R*,3*S*)-2-hydroxy-3-methylpentanoic acid, HOBt, EDC, DMF, −15 °C to rt, 56% (two steps). (d) Methacrylic acid, $Cl_3C_6H_2COCl$, TEA, toluene, 87%. (e) $Pd(PPh_3)_4$, PhNHMe, THF, 95%.

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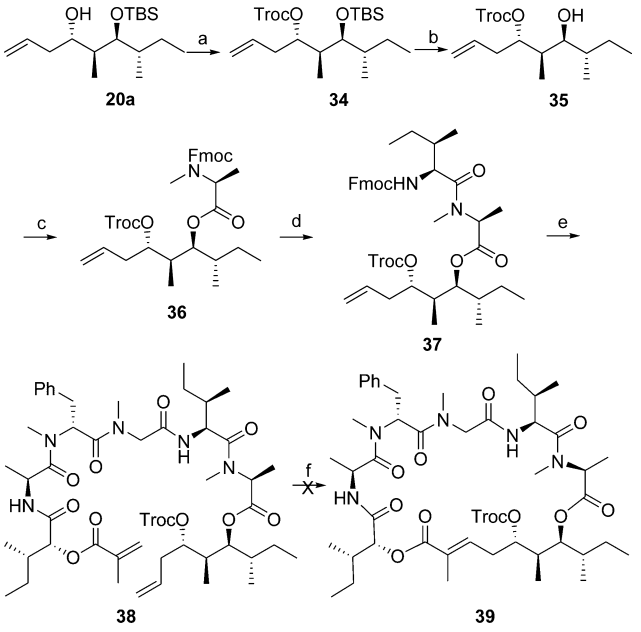
33, which could be used in the following condensation without further purification.

With the peptide unit **33** in hand, we started to evaluate our RCM strategy for macrocyclization using the readily available intermediate **20a**, the correct stereoisomer for the originally proposed structure of lagunamide A (**1**) (Scheme 6). The

Scheme 6. Preparation of RCM Precursor 38[a]

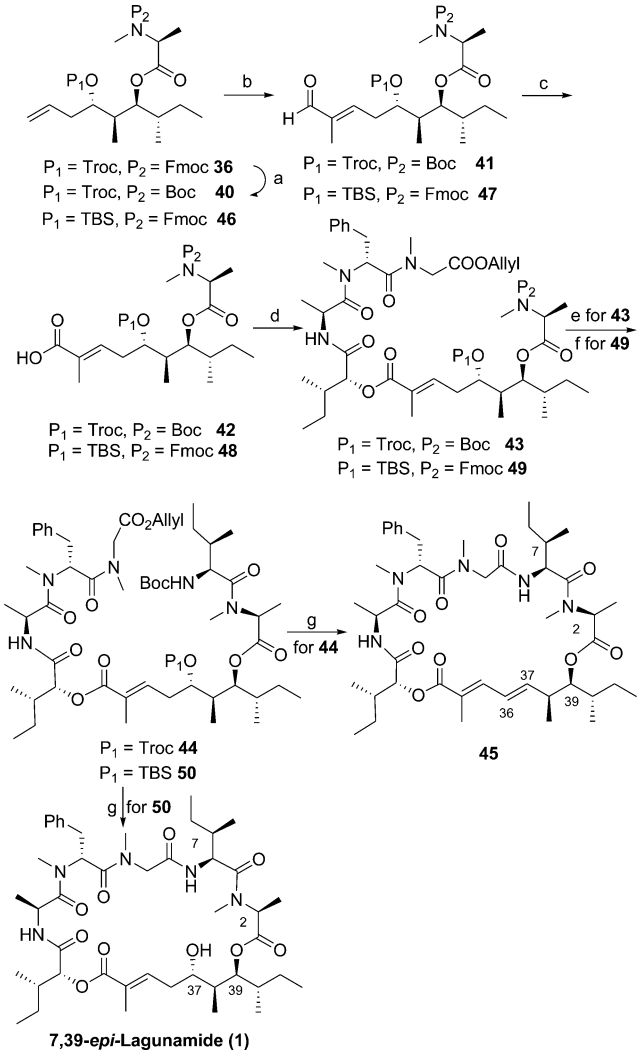


[a]Reagents and conditions: (a) TrocCl, DMAP (cat.), pyridine, CH_2Cl_2, 96%. (b) 40% aqueous HF, CH_3CN, 95%. (c) L-*N*-Me-Fmoc-Cl, DIPEA, CH_2Cl_2, reflux, 61%. (d) (1) Et_2NH/CH_3CN, rt; (2) L-Fmoc-aIle-OH, HATU, DIPEA, CH_2Cl_2, 0 °C to rt, 84% (two steps). (e) (1) Et_2NH/CH_3CN, rt; (2) **33**, HATU, DIPEA, CH_2Cl_2, 0 °C to rt, 73% (two steps). (f) Grubbs 2nd, CH_2Cl_2 (1 mM) at reflux or toluene (1 mM) at 60 °C.

hydroxyl group of **20a** could be protected by 2,2,2-trichloroethyl carbonochloridate (TrocCl) in the presence of pyridine, and subsequent removal of the silyl protecting group with a solution of 40% hydrogen fluoride produced secondary alcohol **35** in 91% overall yield. The *N*-Me-Fmoc-Ala moiety was introduced through our optimized conditions using L-*N*-Me-Fmoc-Ala-Cl to give ester **36** with high diastereoselectivity (*dr* > 99:1) in 61% yield. Removal of the Fmoc protecting group with Et_2NH/CH_3CN and subsequent condensation with *N*-Fmoc-aIle-OH in the presence of HATU/DIPEA produced **37** in 84% overall yield. Finally, the precursor for the RCM reaction, **38**, was obtained after removal of the Fmoc protecting group in **37** and subsequent coupling with carboxylic acid **33** in the presence of HATU/DIPEA. Disappointingly, the RCM reaction of **38** using the Grubbs second-generation catalyst turned out to be unsuccessful. Although various conditions (different solvents and temperature) were screened, no desired cyclization product **39** was obtained.

An alternative strategy using macrolactamization by formation of a peptide bond between C11 and C6 is shown in Scheme 7. Cross-metathesis (CM) of terminal olefin **36** with methacrylaldehyde proceeded smoothly in the presence of the Grubbs second-generation catalyst, giving the desired product (*E*/*Z* > 99:1) in 80% yield. For practical reasons, the *N*-Fmoc protection in **36** was replaced by *N*-Boc. Compound **40** was

Scheme 7. Macrolactamization Strategy[a]



[a]Reagents and conditions: (a) (1) Et_2NH/CH_3CN, rt; (2) Boc_2O, TEA, CH_2Cl_2, rt, 75% (two steps); (b) methacrylaldehyde, Grubbs 2nd, CH_2Cl_2, reflux, *E*:*Z* > 99:1, 81% for **41**, 80% for **47**; (c) $NaClO_2$, NaH_2PO_4, *t*-BuOH, 2-methylbut-2-ene, rt, 93% for **42**, 87% for **48**; (d) **31**, MNBA, DMAP, CH_2Cl_2, rt, 66% for **43**, 60% for **49**; (e) (1) TFA/CH_2Cl_2, rt; (2) L-Boc-aIle-OH, HATU, DIPEA, CH_2Cl_2, 0 °C ~ rt, 82% for **44** (two steps); (f) (1) Et_2NH/CH_3CN, rt; (2) L-Boc-aIle-OH, HATU, DIPEA, CH_2Cl_2, 0 °C ~ rt, 76% for **50** (two steps); (g) (1) $Pd(PPh_3)_4$, PhNHMe, THF, rt; (2) TFA/CH_2Cl_2, 0 °C~ rt; (3) HATU, DIPEA, CH_2Cl_2 (1 mM), rt, 22% for **45**, 30% for **1** (three steps).

easily converted from **36** by deprotection of the Fmoc group (Et_2NH/CH_3CN) and Boc protection (Boc_2O, TEA) in 75% overall yield. Pinnick oxidation[25] of aldehyde **41** generated carboxylic acid **42**, which was coupled with compound **31** using MNBA/DMAP to give **43** in 66% yield. Removal of the Boc protecting group in compound **43** and subsequent reaction with L-Boc-aIle-OH in the presence of HATU/DIPEA produced **44** in 82% overall yield. Sequential cleavage of the allyl ester using $Pd(PPh_3)_4$/*N*-methylaniline and removal of the Boc protecting group with TFA afforded the cyclization precursor, which was subjected to macrolactamization (1 mM in CH_2Cl_2) without further purification. Delightfully, the cyclization proceeded smoothly under HATU/DIEA conditions, but the elimination of OTroc was observed, giving

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diene **45** in 22% yield over three steps. The structure of **45** was unambiguously assigned by NMR spectroscopic data of the pure sample from preparative HPLC.

As the Troc protecting group of the hydroxyl, an ester moiety, was easily eliminated under the basic conditions for the macrolactamization, we considered using silyl protection (TBS) of the hydroxyl group at the C37 position (Scheme 7). Starting from compound **46**, prepared by esterification of **23a** and L-*N*-Me-Fmoc-Ala-Cl under our optimized conditions, the key intermediate **50** was prepared in 32% overall yield through similar operations. Cleavage of the allyl ester using $Pd(PPh_3)_4$/*N*-methylaniline and subsequent removal of the Boc protecting group with TFA generated the cyclization precursor, in which the TBS group was also removed to give a free OH at C37. The final macrolactamization (1 mM in CH_2Cl_2) was performed under HATU/DIEA conditions, successfully yielding the desired product 7,39-*epi*-lagunamide A, that is, the originally proposed structure for natural lagunamide A (**1**), in 30% yield over three steps. The crude 7,39-*epi*-lagunamide A (**1**) was further purified by preparative HPLC, and the NMR spectroscopic data and optical rotation were consistent with the literature values[7] {$[\alpha]_D^{25}$ −32.9 (*c* 0.2, MeOH); lit $[\alpha]_D^{20}$ = −31.0 (*c* 0.5, CH_3OH)}.

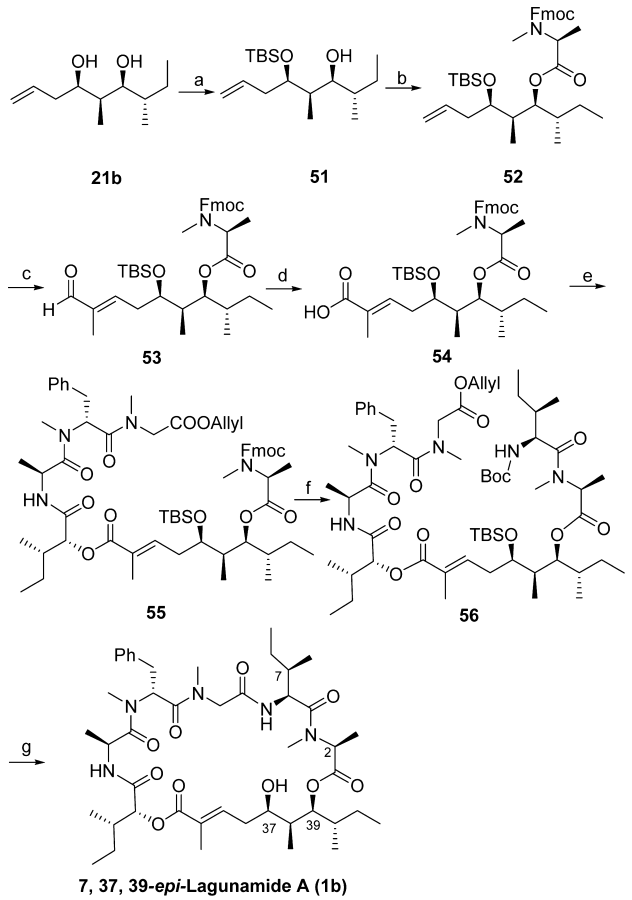
With the readily available diol **21b**, we conducted the synthesis of 7,37,39-*epi*-lagunamide A (**1b**) (Scheme 8). Coupling of secondary alcohol **51**, which was prepared by selective *O*-TBS protection of **21b**, with L-*N*-Me-Boc-Ala-Cl in the presence of DIPEA afforded **52** in 53% yield. Following the previous synthetic sequence (CM reaction, Pinnick oxidation, esterification, and subsequent amidation), the fully protected cyclization precursor **56** was obtained in 30% overall yield. Deprotection of the allyl ester using $Pd(PPh_3)_4$/*N*-methylaniline and removal of both the *N*-Boc and *O*-TBS protecting groups using TFA afforded the cyclization precursor, which was treated with HATU/DIEA (1 mM in CH_2Cl_2) to yield the desired product 7,37,39-*epi*-lagunamide A (**1b**) in 32% yield over three steps. The crude **1b** was further purified by preparative HPLC. Although the optical rotation {$[\alpha]_D^{25}$ −33.2 (*c* 0.18, MeOH); lit $[\alpha]_D^{20}$ = −4.6 (*c* 0.2, CH_3OH)} differed from the literature value, the NMR spectroscopic data were consistent.[7]

Starting with diol **21a**, we prepared the fully protected cyclization precursor **57** through the previous intermediate **49** (Scheme 9). Unfortunately, after sequential deprotection of the allyl ester and the *N*-Boc and *O*-TBS protecting groups, the macrocyclization (1 mM in CH_2Cl_2) to generate the desired 39-*epi*-lagunamide A (**1c**) did not proceed under HATU/DIPEA conditions. This surprising unsuccessful ring closure led us to reconsider another site for macrolactamization.

Scheme 10 shows the synthesis of 39-*epi*-lagunamide A (**1c**), with macrolactamization between the alanine and isoleucine moieties as the key step. In this case, compound **49** was treated with $Pd(PPh_3)_4$ and *N*-methylaniline to cleave the allyl ester, and the resulting free carboxylic acid was coupled with L-Ile-*O*-allyl in the presence of HATU/DIPEA to generate the fully protected cyclization precursor **58** in 85% overall yield. After deprotection of the allyl ester using $Pd(PPh_3)_4$/*N*-methylaniline and the *N*-Fmoc protecting group with Et_2NH/CH_3CN, the macrolactamization (1 mM in CH_2Cl_2) proceeded smoothly under HATU/DIPEA conditions. The desired cyclization product was treated with 40% hydrogen fluoride aqueous solution, successfully giving 39-*epi*-lagunamide A (**1c**) in 38% yield over four steps. The crude **1c** was further purified by preparative HPLC, and the optical rotation was to be $[\alpha]_D^{25}$ −64.7 (*c* 0.04, MeOH).

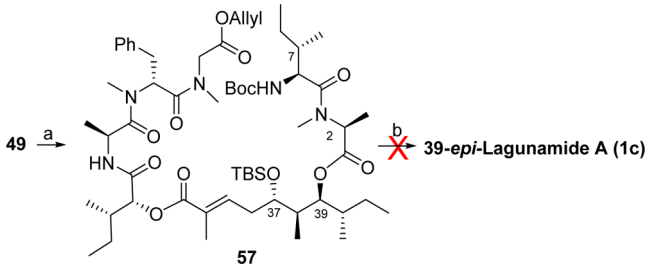
Finally, we accomplished the synthesis of revised structure for natural lagunamide A (**1a**) and its 2-epimer (**1d**) starting from the intermediates **27aa** and **27ab**, respectively. As shown in Scheme 11, the macrolactamization (1 mM in CH_2Cl_2)

Scheme 8. Synthesis of 1b[a]



[a]Reagents and conditions: (a) TBSOTf, 2,6-lutidine, −78 °C, 75%. (b) L-*N*-Me-Fmoc-Cl, DIPEA, CH_2Cl_2, reflux, 58%. (c) Methacrylaldehyde, Grubbs 2nd, CH_2Cl_2, reflux, 83%, *E*:*Z* > 99:1. (d) $NaClO_2$, NaH_2PO_4, *t*-BuOH, 2-methylbut-2-ene, rt, 78%. (e) **31**, MNBA, DMAP, CH_2Cl_2, rt, 63%. (f) (1) Et_2NH/CH_3CN, rt; (2) L-Boc-aIle-OH, HATU, DIPEA, CH_2Cl_2, 0 °C to rt, 75% (two steps). (g) (1) $Pd(PPh_3)_4$, PhNHMe, THF, rt; (2) TFA/CH_2Cl_2, 0 °C to rt; (3) HATU, DIPEA, CH_2Cl_2 (1 mM), rt, 32% (three steps).

Scheme 9. Preparation of 57[a]



[a]Reagents and conditions: (a) (1) Et_2NH/CH_3CN, rt; (2) L-Boc-Ile-OH, HATU, DIPEA, CH_2Cl_2, 0 °C to rt, 79% (two steps). (b) (1) $Pd(PPh_3)_4$, PhNHMe, THF, rt; (2) TFA/CH_2Cl_2, 0 °C to rt; (3) HATU, DIPEA, CH_2Cl_2 (1 mM), rt.

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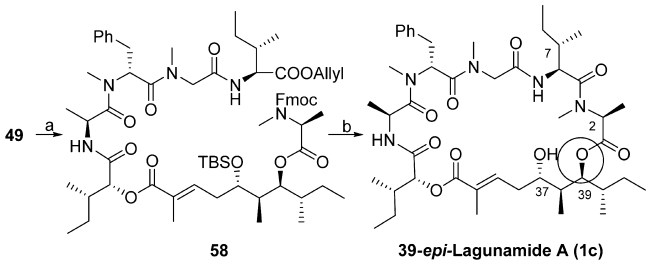
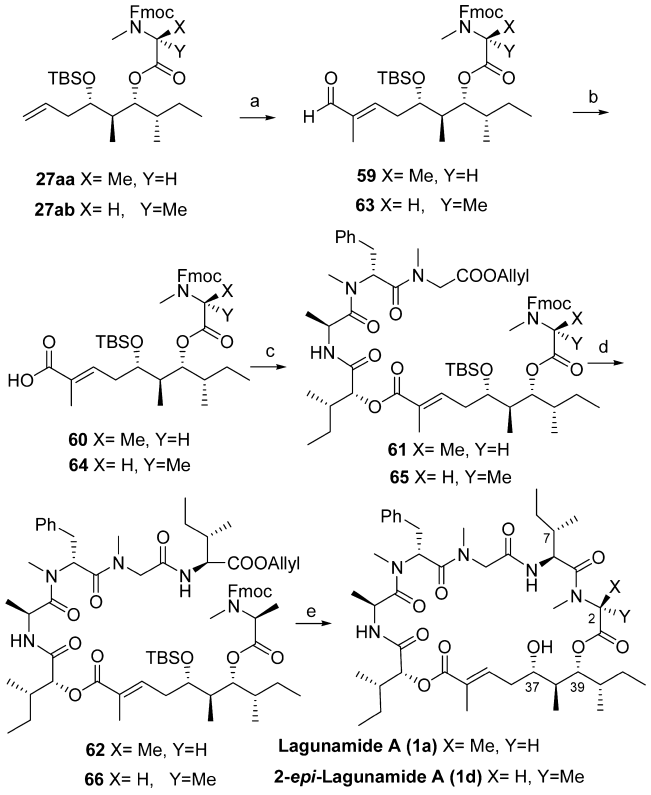
Scheme 10. Synthesis of 1c[a]



[a]Reagents and conditions: (a) (1) $Pd(PPh_3)_4$, PhNHMe, THF, rt; (2) L-Ile-*O*-allyl, HATU, DIPEA, CH_2Cl_2, rt, 85% (two steps). (b) (1) $Pd(PPh_3)_4$, PhNHMe, THF, rt; (2) Et_2NH/CH_3CN, rt; (3) HATU, DIPEA, CH_2Cl_2, rt; (4) 40% aqueous HF, CH_3CN, 38% (four steps).

Scheme 11. Synthesis of 1a and 1d[a]



[a]Reagents and conditions: (a) Methacrylaldehyde, Grubbs 2nd, CH_2Cl_2, reflux, 87% for **59**, 83% for **63**, *E*:*Z* > 99:1. (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH, 2-methylbut-2-ene, rt, 80% for **60**, 81% for **64**. (c) **31**, MNBA, DMAP, CH_2Cl_2, rt, 56% for **61**, 58% for **65**. (d) (1) Et_2NH/CH_3CN, rt; (2) L-Boc-alle-OH, HATU, DIPEA, CH_2Cl_2, 0 °C to rt, 91% for **62**, 80% for **66** (two steps). (e) (1) $Pd(PPh_3)_4$, PhNHMe, THF, rt; (2) Et_2NH/CH_3CN, rt; (3) HATU, DIPEA, CH_2Cl_2, rt; (4) 40% aqueous HF, CH_3CN, 38% for **1a**, 45% for **1d** (four steps).

between the alanine and isoleucine moieties was conducted in both cases using the same strategy that was applied for the synthesis of 39-*epi*-lagunamide A (**1c**). Following a synthetic sequence similar to that described above, both lagunamide A (**1a**) and 2-*epi*-lagunamide A (**1d**) were successfully obtained in parallel. The crude **1a** and **1d** were further purified by preparative HPLC, with optical rotations of $[\alpha]_D^{25}$ −34.9 (*c* 0.04, MeOH) {lit $[\alpha]_D^{25}$ = −36 (*c* 0.5, CH_3OH),[6a] $[\alpha]_D^{20}$ = −33.8 (*c* 0.1, CH_3OH)[7]} and $[\alpha]_D^{25}$ +3.6 (*c* 0.46, MeOH), respectively. The spectroscopic data of ^1H and ^{13}C NMR of lagunamide A (**1a**) agreed with that of the reported data,[6a,7] and the structure of 2-*epi*-Lagunamide A (**1d**) was unambiguously confirmed by two-dimensional NMR.

■ CONCLUSION

We have completed the enantioselective total synthesis of natural lagunamide A (**1a**) and its five analogues (**1**, **1b**−**d**, and **45**) starting from commercially available (*S*)-2-methylbutan-1-ol (**9**). Although the original strategy of using RCM for the macrocyclization did not work, several key homoallylic alcohols could still be applied in cross-metathesis (CM) to produce different C33−C44 units, from which an alternative approach for ring closure was realized through macrolactamization. Further efforts to extend this strategy to synthesize other analogues of lagunamide A are ongoing in our laboratory. The chemistry and related biological data will be published in due course.

■ EXPERIMENTAL SECTION

General. THF was distilled from sodium/benzophenone. Reactions were monitored by thin-layer chromatography (TLC) on glass plates coated with silica gel with fluorescent indicator. Flash chromatography was performed on silica gel (300−400) with petroleum ether/EtOAc (PE/EA) as the eluent. Optical rotations were measured on a polarimeter with a sodium lamp. HRMS was performed on a LCMS-IT-TOF apparatus. IR spectra were recorded using films on a Fourier transform infrared spectrometer. NMR spectra were recorded at 400, 500, or 600 MHz, and chemical shifts (δ) are reported in parts per million referenced to an internal standard [TMS for ^1H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR].

(*R*)-4-Benzyl-3-((2*R*,3*S*,4*S*)-3-hydroxy-2,4-dimethylhexanoyl)-oxazolidin-2-one (17). $(COCl)_2$ (9.8 mL, 0.112 mol) was stirred in CH_2Cl_2 (150 mL) at −78 °C, and then a solution of DMSO (15.9 mL, 0.224 mol) in CH_2Cl_2 (30 mL) was slowly added dropwise. After the mixture was stirred for 1 h, a solution of (*S*)-2-methylbutan-1-ol (**9**) (4.92 g, 0.056 mol) in CH_2Cl_2 (5 mL) was slowly added dropwise, and the resulting mixture was stirred for 2 h. Once TEA (46.5 mL, 0.336 mol) was added dropwise, the mixture was allowed to warm to room temperature, and the reaction was quenched with a saturated NH_4Cl aqueous solution. The organic layer was separated, and the aqueous layer was extracted with DCM (50 mL × 2). The combined organic layers were washed with a 1 M HCl aqueous solution and brine. The resulting organic layer was dried, filtered, and concentrated at 0 °C to give crude aldehyde **10** (ca.10 mL) without further purification. To a cooled (0 °C) solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (6.514 g, 28 mmol) in CH_2Cl_2 (100 mL) were added Bu_2BOTf (1 M in CH_2Cl_2, 33.6 mL, 33.6 mmol) and TEA (4.24 g, 42 mmol). The mixture was stirred for 1 h and then cooled to −78 °C, and crude aldehyde **10** was slowly added dropwise. After the mixture was stirred for 2 h, it was allowed to warm to room temperature and stirred overnight. A mixture of MeOH (10 mL) and 30% H_2O_2 (30 mL) was slowly added dropwise, and the resulting solution was stirred for 8 h at room temperature.The mixture was diluted with water, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2), and the combined organic layers were washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash chromatography on silica gel (PE/EA = 6/1) to give **17** (8.29 g, 93%). $[\alpha]_D^{25}$ = −36.8 (*c* 2.87, $CHCl_3$). IR (film) ν_{max}: 3512, 2965, 2921, 2870, 1781, 1691, 1454, 1386, 1210 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.43−7.17 (m, 5H), 4.73 (ddd, *J* = 10.7, 6.9, 3.2 Hz, 1H), 4.30−4.16 (m, 2H), 4.01−3.96 (m, 1H), 3.67−3.64 (m, 1H), 3.28 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.03−2.97 (m, 1H), 2.82 (dd, *J* = 13.4, 9.4 Hz, 1H), 1.90−1.75 (m, 1H), 1.61−1.48 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.24−1.16 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 152.9, 135.1, 129.5, 129.0, 127.4, 74.8, 66.2, 55.2, 39.5, 37.8, 37.0, 25.2, 14.8, 10.9, 9.7.

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HRMS (ESI): calcd for $[C_{18}H_{25}NO_4 + Na^+]$ 342.1681, found 342.1681.

(*R*)-4-Benzyl-3-((2*R*,3*S*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylhexanoyl)oxazolidin-2-one (18). To a cooled (0 °C) solution of **17** (4.0 g, 12.5 mmol) in CH_2Cl_2 (100 mL) was added dropwise 2,6-lutidine (2.92 mL, 25 mmol) followed by TBSOTf (4.32 mL, 18.8 mmol). After the mixture was stirred for 1 h, it was warmed to room temperature and stirred for 1 h, and then the reaction was quenched with a saturated $NaHCO_3$ aqueous solution. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic layers were washed with brine (30 mL × 2), dried, filtered, and concentrated. The resulting residue was purified by flash chromatography on silica gel (PE/EA = 20/1) to give **18** (5.16 g, 95%). $[\alpha]_D^{25}$ = −47.1 (*c* 1.40, $CHCl_3$). IR (film) ν_{max}: 2959, 2930, 2881, 2857, 1783, 1698, 1462, 1383, 1350, 1252, 1209, 1121, 1103, 1050, 1019, 969, 837, 775, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.22 (m, 5H), 4.66 (ddd, *J* = 9.6, 8.4, 4.8 Hz, 1H), 4.23−4.18 (m, 2H), 4.05−3.95 (m, 2H), 3.31 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.79 (dd, *J* = 13.3, 9.7 Hz, 1H), 1.58−1.45 (m, 2H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.08−1.00 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.11 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 152.9, 135.4, 129.5, 129.0, 127.4, 76.2, 66.0, 55.7, 41.1, 40.9, 37.7, 26.1, 24.9, 18.4, 15.3, 14.0, 12.4, −3.9, −4.2. HRMS (ESI): calcd for $[C_{24}H_{39}NO_4Si + Na^+]$ 456.2546, found 456.2552.

(2*S*,3*S*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhexan-1-ol (19). To a cooled (0 °C) solution of **18** (4.0 g, 9.24 mmol) in THF (30 mL) was added dropwise a solution of $LiBH_4$ (0.3 g, 13.9 mmol) in THF (10 mL). Then MeOH (5 mL) was carefully added dropwise, and the mixture was stirred for 1 h. The reaction was quenched with water, and the mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 20/1) to give **19** (2.2 g, 92%) as a colorless oil. $[\alpha]_D^{25}$ = +6.8 (*c* 0.62, $CHCl_3$). IR (film) ν_{max}: 3346, 2959, 2930, 2858, 1463, 1382, 1361, 1253, 1100, 1047, 1006, 862, 835, 773, 673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (dd, *J* = 5.1, 2.5 Hz, 1H), 3.60 (dd, *J* = 10.3, 7.9 Hz, 1H), 3.49 (dd, *J* = 10.4, 6.1 Hz, 1H), 1.97−1.85 (m, 2H), 1.63−1.51 (m, 2H), 1.16−1.05 (m, 1H), 0.95−0.88 (m, 18H), 0.09 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 76.6, 66.7, 39.4, 38.6, 26.1, 25.8, 18.3, 16.1, 12.1, 11.9, −4.0, −4.3. HRMS (ESI): calcd for $[C_{14}H_{32}O_2Si + Na^+]$ 283.2069, found 283.2075.

(4*S*,5*S*,6*S*,7*S*)-6-(*tert*-Butyldimethylsilyloxy)-5,7-dimethylnon-1-en-4-ol (20a). To a solution of aldehyde **15b** (2.0 g, 7.75 mmol) in THF (40 mL) was added dropwise $ZnCl_2$ (1.0 M in THF, 19.4 mL, 19.4 mmol) at −78 °C, and then allylmagnesium chloride (6.9 mL, 1.0 M in THF, 11.6 mmol) was added dropwise. After the mixture was stirred for 1 h, the reaction was quenched with water, and the solution was warmed to room temperature and acidified with 1 M aqueous citric acid solution. The mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried, and concentrated to give a crude residue, which was purified by flash chromatography on silica gel (PE/EA = 50/1) to give **20a** (2.02 g, 87%) and **20b** (223 mg, 9.6%) as a colorless oil. Data for the major product **20a**: $[\alpha]_D^{25}$ = +6.4 (*c* 0.78, $CHCl_3$). IR (film) ν_{max}: 3490, 2958, 2929, 2858, 1462, 1383, 1254, 1028, 835, 773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.92 (dddd, *J* = 14.4, 12.1, 8.2, 6.1 Hz, 1H), 5.21−5.13 (m, 2H), 3.84 (dd, *J* = 5.4, 2.1 Hz, 1H), 3.66−3.57 (m, 1H), 2.76 (s, 1H), 2.49−2.37 (m, 1H), 2.16−2.05 (m, 1H), 1.77−1.54 (m, 3H), 1.18−1.04 (m, 1H), 0.96−0.90 (m, 15H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.14−0.09 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 117.8, 77.6, 72.4, 41.4, 39.6, 39.0, 26.1, 25.7, 18.3, 16.5, 12.2, 12.1, −4.2. HRMS (ESI): calcd for $[C_{17}H_{36}O_2Si + Na^+]$ 323.2382, found 323.2368.

(4*R*,5*S*,6*S*,7*S*)-6-(*tert*-Butyldimethylsilyloxy)-5,7-dimethylnon-1-en-4-ol (20b). To a cooled (−78 °C) solution of aldehyde **15b** (2.09 g, 8.1 mmol) in anhydrous THF (40 mL) was added allylmagnesium chloride (1.7 M in THF, 7.2 mL, 12.2 mmol). After the mixture was stirred for 30 min, it was quenched with a saturated NH_4Cl aqueous solution and warmed to room temperature. Then the mixture was extracted with EtOAc (50 mL × 3), and the combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 200/1) to give **20b** (2.1 g, 86%) and **20a** (0.29 g, 12%). Data for the major product **20b**: $[\alpha]_D^{25}$ = +20.0 (*c* 1.07, $CHCl_3$). IR (film) ν_{max}: 3469, 3078, 2959, 2930, 2858, 1463, 1382, 1361, 1255, 1096, 1051, 1024, 1005, 913, 835, 773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.90−5.75 (m, 1H), 5.20−5.07 (m, 2H), 3.77−3.71 (m, 1H), 3.71−3.64 (m, 1H), 2.33−2.19 (m, 2H), 2.18−2.11 (m, 1H), 1.76−1.66 (m, 1H), 1.66−1.55 (m, 1H), 1.50−1.37 (m, 1H), 1.19−1.05 (m, 1H), 0.99−0.89 (m, 18H), 0.13−0.08 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4, 117.5, 78.5, 74.41, 40.8, 39.6, 40.0, 29.7, 26.1, 25.8, 18.3, 15.3, 12.3, 8.8, −3.5, −4.3. HRMS (ESI): calcd for $[C_{17}H_{36}O_2Si + H^+]$ 301.2563, found 301.2569.

General Procedure for the Synthesis of 21a and 21b. Compound **20a** or **20b** (300 mg, 1 mmol) was dissolved in CH_3CN (5 mL), and the solution was stirred in a plastic bottle at 0 °C. Then a 40% HF (1 mL) aqueous solution was added dropwise, and the mixture was stirred for 5 h at 0−25 °C. The mixture was diluted with EtOAc (100 mL) and washed with brine (50 mL × 2). The organic layer was dried and concentrated to afford a residue that was purified by flash chromatography on silica gel (PE/EA = 6/1) to give the desired compound.

*(4S,5S,6S,7S)-5,7-Dimethylnon-1-ene-4,6-diol (**21a**).* Colorless oil (177 mg, 95%). $[\alpha]_D^{25}$ = −3.0 (*c* 0.36, $CHCl_3$). IR (film) ν_{max}: 3358, 3077, 2967, 2933, 2878, 1463, 1382, 1339, 1083, 966, 914 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.89−5.75 (m, 1H), 5.17−5.08 (m, 2H), 3.73−3.62 (m, 2H), 3.29−3.05 (m, 2H), 2.39−2.30 (m, 2H), 1.84−1.74 (m, 1H), 1.74−1.65 (m, 1H), 1.53−1.42 (m, 1H), 1.19−1.05 (m, 1H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 117.8, 75.3, 74.5, 40.1, 37.5, 37.5, 25.4, 14.7, 10.9, 10.3. HRMS (ESI): calcd for $[C_{11}H_{22}O_2 + Na^+]$ 209.1517, found 209.1522.

*(4R,5S,6S,7S)-5,7-Dimethylnon-1-ene-4,6-diol (**21b**).* Colorless oil (171 mg, 92%). $[\alpha]_D^{25}$ = −17.2 (*c* 1.14, $CHCl_3$). IR (film) ν_{max}: 3362, 2968, 2932, 2877, 1642, 1463, 1382, 1152, 1086, 966, 914 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.83−5.71 (m, 1H), 5.14−5.04 (m, 2H), 3.87−3.81 (m, 1H), 3.43 (dd, *J* = 9.5, 1.4 Hz, 1H), 3.28−3.16 (m, 2H), 2.33−2.23 (m, 1H), 2.23−2.14 (m, 1H), 1.78−1.65 (m, 2H), 1.52−1.42 (m, 1H), 1.16−1.04 (m, 1H), 0.92−0.83 (m, 6H), 0.76 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0, 117.7, 81.0, 76.4, 39.9, 37.6, 37.1, 25.2, 14.8, 10.7, 4.1. HRMS (ESI): calcd for $[C_{11}H_{22}O_2 + H^+]$ 187.1698, found 187.1700.

General Procedure for the Synthesis of 22a and 22b. A solution of compound **21a** or **21b** (169 mg, 0.91 mmol) and PTSA·H_2O (17 mg, 0.09 mmol) in acetone (10 mL) was stirred at room temperature, and then 2,2-dimethylpropane (1.1 mL, 9.2 mmol) was added dropwise. After the mixture was stirred for 2.5 h, the reaction was quenched with a saturated $NaHCO_3$ aqueous solution, and the mixture was diluted with ether. The organic layer was separated, and the aqueous layer was extracted with ether (30 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography on silica gel (PE/EA = 100/1) to give the desired product.

*(4S,5S,6S)-4-Allyl-6-((S)-sec-butyl)-2,2,5-trimethyl-1,3-dioxane (**22a**).* Colorless oil (183 mg, 89%). $[\alpha]_D^{25}$ = +43.8 (*c* 0.02, $CHCl_3$). IR (film) ν_{max}: 3399, 2963, 2927, 2855, 1740, 1599, 1460, 1252, 1191, 1081 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.96−5.83 (m, 1H), 5.17−5.10 (m, 1H), 5.09−5.04 (m, 1H), 3.46−3.39 (m, 1H), 3.35 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.31 (t, *J* = 6.5 Hz, 2H), 1.85−1.70 (m, 2H), 1.54−1.44 (m, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 1.09−0.98 (m, 1H), 0.93−0.88 (m, 6H), 0.82 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 116.5, 100.7, 74.9, 72.9, 39.2, 37.9, 34.0, 25.4, 25.0, 23.9, 14.3, 11.8, 10.7.

*(4R,5S,6S)-4-Allyl-6-((S)-sec-butyl)-2,2,5-trimethyl-1,3-dioxane (**22b**).* Colorless oil (189 mg, 92%). $[\alpha]_D^{25}$ = +1.6 (*c* 0.13, $CHCl_3$). IR (film) ν_{max}: 3358, 2957, 2911, 2855, 1597, 1458, 1427, 1119 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.86−5.74 (m, 1H), 5.13 (dd, *J* = 17.2,

1.3 Hz, 1H), 5.09−5.03 (m, 1H), 3.92−3.87 (m, 1H), 3.44 (dd, J = 9.8, 1.8 Hz, 1H), 2.37−2.28 (m, 1H), 2.21−2.11 (m, 1H), 1.80−1.67 (m, 1H), 1.59−1.46 (m, 2H), 1.41 (s, 6H), 1.17−1.05 (m, 1H), 0.92−0.84 (m, 6H), 0.79 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.6, 116.7, 98.8, 77.1, 73.4, 37.4, 35.2, 32.3, 30.0, 25.2, 19.5, 13.4, 10.4, 4.4.

(4*S*,5*S*,6*S*,7*S*)-6-(*tert*-Butyldimethylsilyloxy)-5,7-dimethylnon-1-en-4-yl 2,2,2-Trichloroethyl Carbonate (34). A solution of compound **20a** (2.0 g, 6.67 mmol) and DMAP (81 mg, 0.7 mmol) in CH_2Cl_2 (50 mL) was treated with pyrrolidine (1.05 g, 13.4 mmol) and TrocCl (1.7 g, 8 mmol) at 0 °C. After the mixture was stirred for 1 h, it was warmed to room temperature and diluted with CH_2Cl_2 (50 mL). The resulting mixture was washed with 1 M aqueous HCl, sat. $NaHCO_3$, and brine successively and then dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 150/1) to give **34** (3.03 g, 96%). $[\alpha]_D^{25}$ = +31.3 (c 1.23, $CHCl_3$). IR (film) ν_{max}: 2958, 2921, 2855, 1758, 1462, 1380, 1245, 1096, 834 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90−5.77 (m, 1H), 5.20−5.10 (m, 2H), 4.85 (d, J = 11.9 Hz, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.76−4.69 (m, 1H), 3.68 (dd, J = 4.6, 1.8 Hz, 1H), 2.59−2.50 (m, 1H), 2.41−2.31 (m, 1H), 2.04−1.94 (m, 1H), 1.57−1.42 (m, 2H), 1.18−1.07 (m, 1H), 0.97−0.90 (m, 18H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 132.9, 118.4, 94.8, 81.6, 76.6, 74.1, 41.7, 37.7, 35.6, 26.1, 25.8, 18.4, 14.9, 12.2, 11.0, −4.0, −4.4.

(4*S*,5*R*,6*S*,7*S*)-6-Hydroxy-5,7-dimethylnon-1-en-4-yl 2,2,2-Trichloroethyl Carbonate (35). A solution of compound **34** (2.5 g, 5.27 mmol) in CH_3CN (30 mL) was treated with 40% aqueous HF (5 mL) solution at 0 °C. After the mixture was stirred for 5 h, it was warmed to room temperature and diluted with EtOAc (150 mL). Then the mixture was washed with brine (50 mL × 2) and a saturated $NaHCO_3$ aqueous solution (30 mL), dried, filtered, and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 15/1) to give **35** as a colorless oil (1.8 g, 95%). $[\alpha]_D^{25}$ = +14.8 (c 0.76, $CHCl_3$). IR (film) ν_{max}: 2962, 1761, 1653, 1591, 1247, 1119 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90−5.78 (m, 1H), 5.22−5.11 (m, 2H), 4.92 (td, J = 8.3, 3.7 Hz, 1H), 4.87 (d, J = 11.9 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 3.45−3.35 (m, 1H), 2.64−2.54 (m, 1H), 2.48−2.36 (m, 1H), 2.02 (d, J = 4.9 Hz, 1H), 2.01−1.94 (m, 1H), 1.88−1.75 (m, 1H), 1.57−1.45 (m, 1H), 1.20−1.08 (m, 1H), 0.97−0.89 (m, 6H), 0.82 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 132.9, 118.6, 94.7, 81.5, 73.5, 38.2, 37.3, 36.5, 25.7, 14.8, 10.9, 8.6. HRMS (ESI): calcd for $[C_{14}H_{23}Cl_3O_4 + Na^+]$ 383.0560, found 383.0560.

General Procedure for the Synthesis of 23a and 51. A solution of **21a** or **21b** (1.0 g, 5.4 mmol) and 2,6-lutidine (10.8 mmol) in CH_2Cl_2 (50 mL) was treated with TBSOTf (1.18 mL, 5.1 mmol) dropwise over 30 min at −78 °C. After the mixture was stirred for 1 h, the reaction was quenched with water, and the mixture was warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL × 2). The combined organic layers were washed with 1 M HCl (20 mL) aqueous solution and brine (20 mL), dried, filtered, and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 100/1) to give the desired **23a** or **51**, respectively.

*(3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3,5-dimethylnon-8-en-4-ol (**23a**).* Colorless oil (1.22 g, 76%). $[\alpha]_D^{25}$ = −3.4 (c 0.28, $CHCl_3$). IR (film) ν_{max}: 3514, 2960, 2931, 2859, 1641, 1464, 1382, 1255, 1087, 1021, 1004, 915, 837, 776 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73−5.59 (m, 1H), 5.13−5.00 (m, 2H), 3.86−3.75 (m, 1H), 3.73 (s, 1H), 3.68 (d, J = 9.6 Hz, 1H), 2.54−2.44 (m, 1H), 2.42−2.32 (m, 1H), 1.90−1.78 (m, 1H), 1.74 (q, J = 7.0 Hz, 1H), 1.50−1.39 (m, 1H), 1.16−1.03 (m, 1H), 0.96 (d, J = 7.1 Hz, 3H), 0.93−0.84 (m, 12H), 0.71 (t, J = 6.8 Hz, 3H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.3, 117.6, 78.7, 73.7, 40.0, 37.4, 35.1, 25.9, 25.2, 17.9, 14.4, 11.2, 10.9, −4.4, −4.9. HRMS (ESI): calcd for $[C_{17}H_{36}O_2Si + H^+]$ 301.2563, found 301.2569.

*(3S,4S,5R,6R)-6-(tert-Butyldimethylsilyloxy)-3,5-dimethylnon-8-en-4-ol (**51**).* Colorless oil (1.21 g, 75%). $[\alpha]_D^{25}$ = −33.6 (c 0.34, $CHCl_3$). IR (film) ν_{max}: 3516, 3078, 2959, 2930, 2858, 1640, 1463, 1408, 1361, 1256, 1083, 1038, 912, 837, 775, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81−5.67 (m, 1H), 5.15−5.04 (m, 2H), 3.94−3.88 (m, 1H), 3.44−3.37 (m, 1H), 2.78−2.70 (m, 1H), 2.41−2.29 (m, 2H), 1.84−1.72 (m, 2H), 1.57−1.45 (m, 1H), 1.22−1.10 (m, 1H), 0.95−0.89 (m, 15H), 0.80 (d, J = 6.8 Hz, 3H), 0.18−0.12 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.4, 117.2, 78.9, 77.5, 39.7, 37.6, 36.6, 25.9, 25.0, 18.0, 15.0, 10.9, 5.5, −3.7, −4.6. HRMS (ESI): calcd for $[C_{17}H_{36}O_2Si + H^+]$ 301.2563, found 301.2563.

(3*S*,5*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethylnon-8-en-4-one (24a). Compound **23a** (1.2 g, 4 mmol) and DMP (2.04 g, 4.8 mmol) were stirred in CH_2Cl_2 (80 mL) for 1 h, and then the reaction was quenched with saturated $NaHCO_3$ and $Na_2S_2O_3$ aqueous solution. The organic layer was separated, washed with brine, dried, filtered, and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 100/1) to give **24a** (1.1 g, 92%) as a colorless oil. $[\alpha]_D^{25}$ = +123.6 (c 0.47, $CHCl_3$). IR (film) ν_{max}: 3514, 2959, 2855, 1460, 1463, 1255, 1087, 1021, 837, 776 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.95−5.83 (m, 1H), 5.11−5.00 (m, 2H), 4.03−3.95 (m, 1H), 2.90−2.79 (m, 1H), 2.56−2.44 (m, 1H), 2.32−2.24 (m, 1H), 2.24−2.16 (m, 1H), 1.77−1.63 (m, 1H), 1.38−1.25 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.88−0.81 (m, 12H), 0.04 (s, 3H), −0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.0, 133.8, 117.2, 72.8, 49.3, 48.1, 38.1, 25.8, 25.2, 17.9, 14.9, 12.5, 11.7, −4.6, −4.8. HRMS (ESI): calcd for $[C_{17}H_{34}O_2Si + Na^+]$ 321.2226, found 321.2224.

(3*S*,4*R*,5*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethylnon-8-en-4-ol (25a). A solution of **24a** (0.94 g, 3.13 mmol) in anhydrous THF (20 mL) was treated with Et_3BHLi (1 M in THF, 4.7 mL, 4.7 mmol) at −78 °C. After the mixture was stirred for 30 min, the reaction was carefully quenched with MeOH (5 mL), and the mixture was stirred for another 5 min at −78 °C. Once a saturated $NaHCO_3$ aqueous solution was added dropwise, the mixture was warmed to room temperature and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried, filtered, and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 100/1) to give **25a** (0.89 g, 94%) as a colorless oil. $[\alpha]_D^{25}$ = +26.3 (c 1.29, $CHCl_3$). IR (film) ν_{max}: 3517, 3077, 2960, 2931, 2858, 1463, 1380, 1255, 1073, 991, 940, 911, 836, 776 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90−5.77 (m, 1H), 5.07−4.99 (m, 2H), 3.82 (dd, J = 10.7, 5.4 Hz, 1H), 3.42 (d, J = 9.3 Hz, 1H), 2.68 (s, 1H), 2.36−2.27 (m, 1H), 2.27−2.17 (m, 1H), 1.81−1.69 (m, 1H), 1.48−1.36 (m, 2H), 1.35−1.25 (m, 1H), 0.92−0.85 (m, 12H), 0.81 (d, J = 6.5 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H), 0.10−0.04 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 116.9, 76.2, 75.8, 40.6, 39.0, 36.5, 27.2, 25.8, 18.0, 12.8, 12.1, 11.8, −4.3, −4.7. HRMS (ESI): calcd for $[C_{17}H_{36}O_2Si + Na^+]$ 323.2382, found 323.2384.

Allyl 2-((*tert*-Butoxycarbonyl)(methyl)amino)acetate (28). Boc-*N*-Me-Gly-OH (2.0 g, 10.6 mmol), K_2CO_3 (2.92 g, 21.2 mmol), and TBAB (0.34 g, 1.06 mmol) were stirred in DMF (20 mL) at 0 °C, and allyl bromide (1.4 mL, 15.8 mmol) was added dropwise, after which the mixture was stirred for 5 h. Then water (50 mL) was added dropwise, and the resulting mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried, filtered, and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 10/1) to give **28** as a colorless oil (2.2 g, 91%). IR (film) ν_{max}: 2977, 1754, 1702, 1481, 1451, 1391, 1367, 1246, 1192, 1150, 987 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97−5.83 (m, 1H), 5.36−5.28 (m, 1H), 5.27−5.20 (m, 1H), 4.67−4.58 (m, 2H), 4.02−3.97 (m, 1H), 3.93−3.89 (m, 1H), 2.98−2.85 (m, 3H), 1.51−1.37 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 156.1, 155.4, 131.8, 131.7, 118.6, 118.4, 80.1, 65.5, 51.0, 50.3, 35.5, 28.3, 28.2. HRMS (ESI): calcd for $[C_{11}H_{19}NO_4 + Na^+]$ 252.1212, found 252.1210.

(*R*)-Allyl 2-(2-((*tert*-Butoxycarbonyl)(methyl)amino)-*N*-methyl-3-phenylpropanamido)acetate (29). A cooled solution (0 °C) of **28** (1.17 g, 5.1 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (2 mL). After 2 h of stirring, the mixture was concentrated, and the residue was azeotroped with toluene two times. The residue was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. After HATU (2.91 g, 7.66 mmol) and DIPEA (2.53 mL, 15.3 mmol) were added, a solution of D-Boc-*N*-Me-Phe-OH (1.40 g, 5.1 mmol) in CH_2Cl_2 (20

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mL) was added dropwise, and the resulting mixture was stirred for 2 h at 0 °C to room temperature. The reaction was quenched with water, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 three times, and the combined organic layers were washed with brine, dried, and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 6/1, 3/1) to give **29** as a colorless oil (1.77 g, 89%). $[\alpha]_D^{25}$ = +119.7 (*c* 0.98, $CHCl_3$). IR (film) ν_{max}: 2973, 2932, 1751, 1691, 1658, 1453, 1388, 1317, 1191 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.10 (m, 5H), 6.00−5.79 (m, 1H), 5.38−5.23 (m, 2.5H), 5.08−4.99 (m, 0.3H), 4.92−4.84 (m, 0.2H), 4.71−4.61 (m, 1.7H), 4.59−4.51 (m, 0.3H), 4.39 (d, *J* = 17.6 Hz, 0.4H), 4.29 (d, *J* = 17.3 Hz, 0.4H), 4.21−4.03 (m, 0.5H), 3.98 (d, *J* = 17.2 Hz, 0.3H), 3.82 (d, *J* = 17.2 Hz, 0.4H), 3.22−3.07 (m, 0.5H), 3.07−2.98 (m, 3.5H), 2.98−2.90 (m, 1H), 2.88−2.80 (m, 2H), 2.78−2.71 (m, 1H), 1.36−1.11 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 170.6, 170.2, 168.7, 168.6, 168.4, 155.3, 154.3, 153.6, 138.1, 137.6, 131.7, 131.4, 129.5, 129.4, 128.4, 128.2, 126.4, 126.3, 119.4, 118.9, 118.7, 80.5, 80.1, 79.9, 66.3, 65.9, 65.8, 65.7, 58.1, 57.9, 55.8, 55.5, 51.0, 50.7, 50.2, 50.0, 36.06, 35.8, 35.2, 29.6, 29.4, 29.0, 28.2, 28.1, 28.0, 27.8. HRMS (ESI): calcd for $[C_{21}H_{30}N_2O_5 + H^+]$ 391.2233, found 391.2227.

(6*S*,9*R*)-Allyl 9-Benzyl-2,2,6,8,11-pentamethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (30). A solution of compound **29** (2.60 g, 6.67 mmol) in CH_2Cl_2 (6 mL) was treated with TFA (3 mL) at 0 °C. After 2 h of stirring, the mixture was concentrated, and the residue was azeotroped with toluene two times. The residue was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C, and then L-Boc-Ala-OH (1.26 g, 6.67 mmol), HATU (3.80 g, 10.0 mmol), and DIPEA (3.3 mL, 20.0 mmol) were added. After the mixture was stirred for 3 h, the reaction was quenched with water, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 three times, and the combined organic layers were washed with brine, dried, and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 4/1, 2/1) to give **30** as a colorless oil (2.09 g, 68%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.27−7.07 (m, 5H), 5.93−5.67 (m, 1H), 5.36−5.18 (m, 2H), 4.66−4.54 (m, 1.7H), 4.54−4.34 (m, 1H), 4.32−4.16 (m, 1.7H), 4.12−4.03 (m, 1H), 3.96−3.86 (m, 0.6H), 3.20−3.04 (m, 1.3H), 3.05−2.84 (m, 6.7H), 1.46−1.30 (m, 10H), 1.27−1.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 172.9, 170.2, 169.8, 168.8, 168.4, 155.3, 154.9, 136.6, 136.5, 131.6, 131.5, 129.5, 129.3, 128.2, 128.2, 126.6, 119.0, 118.7, 79.4, 66.0, 65.7, 60.3, 53.8, 53.1, 51.1, 50.2, 46.5, 36.3, 35.3, 35.1, 35.1, 30.1, 29.9, 28.3, 28.2, 20.9, 17.6, 17.4, 14.1. HRMS (ESI): calcd for $[C_{24}H_{35}N_3O_6 + Na^+]$ 484.2424, found 484.2425.

Compound 31. A solution of compound **30** (2.07 g, 4.49 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (2.5 mL) at 0 °C. The mixture was stirred for 2 h and then concentrated, and the residue was azeotroped with toluene two times to give the crude amine without further purification. (2*R*,3*S*)-2-Hydroxy-3-methylpentanoic acid (0.71 g, 5.39 mmol) and HOBt (0.86 g, 6.4 mmol) were stirred in DMF (10 mL) at −15 °C, and then EDC·HCl (0.79 g, 4.11 mmol) was added. After 15 min of stirring, a solution of the above crude amine in DMF (2 mL) and TEA (3.1 mL, 22.4 mmol) were added dropwise. After the mixture was stirred for 18 h at 0 °C to room temperature, it was diluted with water (40 mL) and extracted with EtOAc (40 mL × 3). The combined organic layers were washed with brine (25 mL × 3), dried, and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 1/1, 1/2) to give **31** as a colorless oil (1.21 g, 56%). $[\alpha]_D^{25}$ = +123.4 (*c* 1.19, $CHCl_3$). IR (film) ν_{max}: 3397, 2963, 2934, 2876, 1748, 1642, 1497, 1456, 1411, 1268, 1194, 1098, 1052, 985 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.33−6.99 (m, 6H), 6.00−5.65 (m, 2H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.82−4.72 (m, 0.7H), 4.68−4.57 (m, 2H), 4.57−4.49 (m, 0.3H), 4.36−4.32 (m, 0.1H), 4.27 (d, *J* = 16.2 Hz, 0.9H), 4.16−4.07 (m, 0.3H), 4.07−4.00 (m, 1H), 3.92 (d, *J* = 17.2 Hz, 0.7H), 3.62−3.35 (m, 1H), 3.22−3.07 (m, 1.4H), 3.07−2.92 (m, 6.6H), 1.87−1.73 (m, 1H), 1.52−1.40 (m, 1H), 1.36−1.22 (m, 1H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 2.3H), 0.78−0.69 (m, 3.7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 172.6, 170.1, 169.8, 168.8, 168.4, 136.6, 136.4, 131.6, 131.4, 129.4, 129.3, 128.3, 128.2, 126.8, 126.7, 119.0, 118.9, 74.0, 73.8, 66.1, 65.9, 53.9, 53.2, 51.2, 50.2, 45.2, 44.8, 38.6, 38.5, 36.3, 35.3, 35.2, 35.0, 30.4, 30.1, 26.2, 26.1, 17.5, 17.4, 12.7, 12.6, 11.9. HRMS (ESI): calcd for $[C_{25}H_{37}N_3O_6 + H^+]$ 476.2761, found 476.2757.

Compound 32. A solution of methacrylic acid (74 mg, 0.86 mmol) and TEA (0.18 mL, 1.29 mmol) in anhydrous THF (1.5 mL) was treated with $Cl_3C_6H_2COCl$ (0.16 mL, 1.0 mmol) at room temperature for 30 min. Then a solution of **31** (205 mg, 0.43 mmol) in toluene and DMAP (105 mg, 0.86 mmol) were added. After the mixture was stirred for 30 min, the reaction was quenched with water, and the mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 2/1) to give **32** (204 mg, 87%). $[\alpha]_D^{25}$ = +23.1 (*c* 0.71, $CHCl_3$). IR (film) ν_{max}: 3314, 3028, 2965, 2934, 2878, 1748, 1725, 1647, 1497, 1456, 1411, 1294, 1191, 1129, 1049, 986, 942, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26−7.11 (m, 5H), 6.66 (d, *J* = 7.3 Hz, 1H), 6.18 (s, 1H), 5.90−5.81 (m, 1H), 5.70−5.62 (m, 1H), 5.36−5.17 (m, 3H), 4.77−4.67 (m, 1H), 4.65−4.53 (m, 2H), 4.26 (d, *J* = 17.2 Hz, 1H), 3.92 (d, *J* = 17.2 Hz, 1H), 3.68 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.20−3.06 (m, 2H), 3.05−2.90 (m, 6H), 2.05−1.91 (m, 4H), 1.40−1.28 (m, 1H), 1.26−1.11 (m, 3H), 0.92−0.77 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 172.2, 170.0, 169.8, 169.1, 169.0, 168.8, 168.4, 166.1, 166.0, 136.5, 136.4, 135.6, 135.6, 131.6, 131.4, 129.4, 129.2, 128.3, 128.3, 126.8, 126.7, 126.7, 118.9, 118.9, 76.1, 66.1, 65.8, 53.8, 53.1, 51.2, 50.2, 45.3, 44.9, 37.5, 37.4, 36.3, 35.3, 35.2, 35.0, 30.3, 30.1, 29.7, 26.1, 26.1, 18.4, 18.4, 17.4, 17.2, 13.9, 13.8, 11.7. HRMS (ESI): calcd for $[C_{29}H_{41}N_3O_7 + Na^+]$ 566.2842, found 566.2848.

General Procedure for the Synthesis of 27aa, 36, 46, and 52. To a cooled (0 °C) solution of L-Fmoc-Ala-Cl (457 mg, 1.33 mmol) in CH_2Cl_2 (15 mL) was added dropwise DIPEA (0.44 mL, 2.67 mmol) followed by the secondary alcohol (0.67 mmol) in CH_2Cl_2 (5 mL). Then the mixture was warmed to reflux for 8 h and cooled to room temperature again, and water was added. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (30 mL × 2). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 30/1) to give the corresponding title compound.

*(S)-((3S,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3,5-dimethylnon-8-en-4-yl) 2-(((9H-Fluoren-9-yl)methoxy)carbonyl)propanoate (**27aa**).* Colorless oil (224 mg, 55%). $[\alpha]_D^{25}$ = −25.8 (*c* 0.96, $CHCl_3$). IR (film) ν_{max}: 2958, 2921, 2856, 1736, 1703, 1452, 1400, 1316, 1250, 1159, 1077, 775, 757, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.66−7.53 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.35−7.28 (m, 2H), 5.83−5.70 (m, 1H), 5.09−4.83 (m, 4H), 4.58−4.50 (m, 0.5H), 4.44−4.34 (m, 1.5H), 4.31−4.21 (m, 1H), 3.69−3.55 (m, 1H), 3.02−2.89 (m, 3H), 2.25−2.16 (m, 1H), 2.08−1.96 (m, 2H), 1.66−1.56 (m, 1H), 1.46 (d, *J* = 7.4 Hz, 3H), 1.32−1.23 (m, 1H), 1.19−1.04 (m, 1H), 0.95−0.76 (m, 18H), 0.14− −0.07 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 156.5, 143.9, 141.3, 136.9, 127.7, 127.0, 125.0, 119.9, 116.3, 78.1, 72.1, 67.8, 54.1, 47.3, 41.0, 36.2, 35.9, 30.0, 26.9, 25.84, 18.0, 15.2, 12.5, 11.9, 9.8, −4.4, −4.5. HRMS (ESI): calcd for $[C_{36}H_{53}NO_5Si + Na^+]$ 630.3591, found 630.3599.

*(S)-((3S,4S,5S,6S)-3,5-Dimethyl-6-((2,2,2-trichloroethoxy)-carbonyloxy)non-8-en-4-yl) 2-(((9H-Fluoren-9-yl)methoxy)-carbonyl)propanoate (**36**).* Colorless oil (273 mg, 61%). $[\alpha]_D^{25}$ = +0.5 (*c* 0.88, $CHCl_3$). IR (film) ν_{max}: 3065, 2967, 2875, 1757, 1704, 1451, 1382, 1314, 1247, 1155, 1095, 758, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.5 Hz, 2H), 7.69−7.57 (m, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 5.88−5.74 (m, 1H), 5.23−5.12 (m, 2H), 5.12−4.95 (m, 1.7H), 4.94−4.82 (m, 1.3H), 4.74−4.63 (m, 2H), 4.54−4.37 (m, 2H), 4.35−4.26 (m, 1H), 3.01−2.94 (m, 3H), 2.65−2.53 (m, 1H), 2.49−2.36 (m, 1H), 2.20−2.07 (m, 1H), 1.72−1.63 (m, 1H), 1.55−1.49 (m, 3H), 1.48−1.43 (m, 1H), 1.16−1.04 (m, 1H), 1.03−0.96 (m, 3H), 0.94−0.84 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 156.6, 153.8, 144.2, 144.0, 141.4, 132.5, 127.7, 127.1, 125.1, 120.0, 118.8, 94.6, 79.8, 75.8, 67.7, 54.3, 47.3, 36.8, 36.3, 30.3,

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26.9, 25.0, 14.8, 10.9, 9.8. HRMS (ESI): calcd for $[C_{33}H_{40}Cl_3NO_7 + H^+]$ 668.1949, found 668.1951.

*(S)-((3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3,5-dimethylnon-8-en-4-yl) 2-(((9H-Fluoren-9-yl)methoxy)carbonyl)propanoate (**46**).* Colorless oil (240 mg, 59%). $[\alpha]_D^{25} = -1.2$ (*c* 0.98, $CHCl_3$). IR (film) ν_{max}: 2958, 2927, 2857, 1737, 1707, 1451, 1400, 1313, 1250, 1210, 1158, 1078, 836, 757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.5 Hz, 2H), 7.68−7.58 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 5.96−5.82 (m, 1H), 5.14−5.06 (m, 2H), 5.04−4.94 (m, 1.6H), 4.88−4.79 (m, 0.4H), 4.55−4.38 (m, 2H), 4.35−4.26 (m, 1H), 3.69−3.59 (m, 1H), 3.00−2.93 (m, 3H), 2.27−2.18 (m, 2H), 2.02−1.91 (m, 1H), 1.76−1.62 (m, 1H), 1.55−1.44 (m, 4H), 1.20−1.07 (m, 1H), 0.98−0.84 (m, 18H), 0.13−0.05 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 156.5, 144.2, 144.0, 141.4, 135.0, 127.7, 127.1, 125.1, 120.0, 116.9, 79.2, 79.0, 73.3, 67.8, 54.3, 47.3, 39.9, 37.5, 37.1, 37.0, 31.5, 30.3, 29.7, 26.0, 24.1, 23.8, 18.1, 15.9, 15.8, 15.0, 11.5, 9.9, −4.1, −4.2, −4.6. HRMS (ESI): calcd for $[C_{36}H_{53}NO_5Si + H^+]$ 608.3771, found 608.3774.

*(S)-((3S,4S,5R,6R)-6-(tert-Butyldimethylsilyloxy)-3,5-dimethylnon-8-en-4-yl) 2-(((9H-Fluoren-9-yl)methoxy)carbonyl)propanoate (**52**).* Colorless oil (236 mg, 58%). $[\alpha]_D^{25} = -23.5$ (*c* 0.40, $CHCl_3$). IR (film) ν_{max}: 2963, 2932, 2855, 1750, 1704, 1597, 1458, 1309, 1252, 1165, 1129, 1083 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76−7.70 (m, 2H), 7.60−7.49 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.1 Hz, 2H), 5.80−5.64 (m, 1H), 5.07−4.98 (m, 2H), 4.96−4.86 (m, 1.7H), 4.84−4.75 (m, 0.3H), 4.42−4.29 (m, 2H), 4.27−4.17 (m, 1H), 3.52 (dd, *J* = 10.9, 5.5 Hz, 1H), 2.96−2.84 (m, 3H), 2.35−2.18 (m, 2H), 1.92−1.79 (m, 1H), 1.73−1.59 (m, 1H), 1.48−1.33 (m, 4H), 1.07−0.94 (m, 1H), 0.90−0.76 (m, 18H), 0.05−0.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 171.6, 156.5, 155.9, 144.1, 143.9, 141.3, 134.4, 127.7, 127.0, 125.1, 120.0, 117.4, 117.3, 79.2, 79.0, 72.5, 67.9, 67.7, 54.2, 54.0, 47.2, 39.0, 38.0, 36.1, 30.3, 29.7, 25.9, 23.7, 23.5, 18.1, 15.6, 15.5, 15.1, 11.4, 9.8, −4.0, −4.7. HRMS (ESI): calcd for $[C_{36}H_{53}NO_5Si + Na^+]$ 630.3591, found 630.3591.

(*R*)-((3*S*,4*R*,5*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethylnon-8-en-4-yl) 2-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-propanoate (27ab). A solution of D-*N*-Me-Fmoc-Ala-OH (1.37 g, 4.20 mmol) and TEA (0.73 mL, 5.30 mmol) in anhydrous THF (10 mL) was treated with $Cl_3C_6H_2COCl$ (0.66 mL, 4.20 mmol) for 30 min, and then a mixture of compound **25a** (1.05 g, 3.50 mmol) and DMAP (0.85 g, 7.00 mmol) in toluene was added dropwise. After the mixture was stirred for 30 min, the reaction was quenched with water, and the mixture was extracted with EtOAc (30 mL × 3). The mixture was separated, and the organic layer was washed with brine (30 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 30/1) to give **27ab** (1.89 g, 89%) as a colorless oil. $[\alpha]_D^{25} = -17.8$ (*c* 0.67, $CHCl_3$). IR (film) ν_{max}: 2958, 2932, 2857, 1737, 1706, 1452, 1400, 1312, 1251, 1157, 1077, 835, 774, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.65−7.51 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 5.88−5.69 (m, 1H), 5.08−4.88 (m, 3.6H), 4.85−4.74 (m, 0.4H), 4.50−4.33 (m, 2H), 4.31−4.20 (m, 1H), 3.67−3.54 (m, 1H), 2.98−2.87 (m, 3H), 2.26−2.14 (m, 1H), 2.09−1.95 (m, 2H), 1.66−1.55 (m, 1H), 1.45−1.38 (m, 3H), 1.35−1.22 (m, 1H), 1.20−1.07 (m, 1H), 0.96−0.82 (m, 18H), 0.07−0.02 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 156.4, 144.1, 143.9, 141.3, 137.0, 127.7, 127.0, 125.0, 119.9, 116.2, 78.2, 72.3, 67.8, 54.1, 47.2, 40.9, 36.2, 35.8, 30.4, 26.9, 25.8, 18.0, 15.0, 12.4, 12.0, 9.7, −4.4, −4.5. HRMS (ESI): calcd for $[C_{36}H_{53}NO_5Si + Na^+]$ 630.3591, found 630.3582.

(*S*)-(3*S*,4*S*,5*S*,6*S*)-3,5-Dimethyl-6-(((2,2,2-trichloroethoxy)-carbonyl)oxy)non-8-en-4-yl 2-((*tert*-Butoxycarbonyl)(methyl)-amino)propanoate (40). Compound **36** (434 mg, 0.65 mmol) and Et_2NH (2 mL) were stirred in CH_3CN (4 mL) for 10 min at room temperature, and then the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL), Boc_2O (170 mg, 0.78 mmol), and TEA (0.13 mL, 0.98 mmol) were added. The mixture was stirred for 2 h and then diluted with water and extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine (50 mL), dried, filtered, and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 30/1) to give **40** (266 mg, 75%) as a colorless oil. $[\alpha]_D^{25} = -0.42$ (*c* 0.86, $CHCl_3$). IR (film) ν_{max}: 2973, 1758, 1698, 1453, 1389, 1247, 1152 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.85−5.72 (m, 1H), 5.20−5.09 (m, 2H), 5.07−4.98 (m, 1H), 4.94−4.83 (m, 1.5H), 4.76−4.59 (m, 2.5H), 2.90−2.79 (m, 3H), 2.62−2.51 (m, 1H), 2.44−2.34 (m, 1H), 2.18−2.06 (m, 1H), 1.73−1.60 (m, 1H), 1.51−1.42 (m, 12H), 1.35−1.26 (m, 1H), 1.14−1.02 (m, 1H), 1.02−0.95 (m, 3H), 0.92−0.86 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 155.8, 155.4, 153.8, 132.5, 118.7, 94.6, 80.0, 79.7, 79.5, 76.0, 75.6, 54.2, 53.5, 36.8, 36.3, 35.4, 30.5, 30.3, 29.9, 28.4, 26.9, 24.9, 22.7, 15.4, 14.8, 14.1, 10.9, 9.7, 9.7. HRMS (ESI): calcd for $[C_{23}H_{38}Cl_3NO_7 + Na^+]$ 568.1612, found 568.1612.

Compound 37. Compound **36** (450 mg, 0.67 mmol) and Et_2NH (1.5) were stirred in CH_3CN (3 mL) at room temperature for 10 min, and then the mixture was concentrated under reduced pressure. The residue, L-Fmoc-alle (300 mg, 0.85 mmol), HATU (380 mg, 1.0 mmol), and DIPEA (0.22 mL, 1.3 mmol) were stirred in CH_2Cl_2 (10 mL) for 1 h. The reaction was quenched with saturated NH_4Cl aqueous solution, and the mixture was separated. The aqueous layer was extracted with CH_2Cl_2 two times, and the compound organic layers were washed with brine, dried, and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 10/1) to give **37** (438 mg, 84%). $[\alpha]_D^{25} = -4.7$ (*c* 0.84, $CHCl_3$). IR (film) ν_{max}: 3304, 2966, 2932, 1737, 1643, 1450, 1450, 1410, 1381, 1247, 1084, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80−7.72 (m, 2H), 7.60 (d, *J* = 7.1 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.34−7.27 (m, 2H), 5.84−5.70 (m, 1H), 5.65 (d, *J* = 9.2 Hz, 1H), 5.32 (dd, *J* = 14.5, 7.2 Hz, 1H), 5.20−5.08 (m, 2H), 5.08−4.98 (m, 1H), 4.83 (d, *J* = 11.9 Hz, 1H), 4.73 (dd, *J* = 9.2, 3.9 Hz, 1H), 4.68−4.58 (m, 2H), 4.43−4.36 (m, 1H), 4.36−4.28 (m, 1H), 4.26−4.19 (m, 1H), 3.10−2.99 (m, 2.5H), 2.86 (s, 0.5H), 2.60−2.48 (m, 1H), 2.47−2.35 (m, 1H), 2.14−2.03 (m, 1H), 1.85−1.73 (m, 1H), 1.67−1.62 (m, 1H), 1.56−1.49 (m, 1H), 1.45 (d, *J* = 7.3 Hz, 3H), 1.28−1.23 (m, 2H), 1.10−0.94 (m, 6.4H), 0.92−0.78 (m, 8.6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 171.0, 156.5, 153. 8, 143.9, 143.8, 141.3, 132.3, 127.7, 127.6, 127.0, 125.2, 125.1, 124.7, 120.0, 119.9, 118.9, 94.5, 79.8, 76.7, 75.7, 67.0, 53.9, 52.2, 47.2, 37.5, 36.6, 36.3, 36.1, 31.2, 26.7, 24.9, 14.8, 14.2, 13.8, 11.9, 10.8, 9.7. HRMS (ESI): calcd for $[C_{39}H_{51}Cl_3N_2O_8 + Na^+]$ 803.2609, found 803.2612.

Compound 38. To a solution of compound **32** (100 mg, 0.18 mmol) and $Pd(PPh_3)_4$ (42 mg, 0.04 mmol) in anhydrous THF (5 mL) was added PhNHMe (48 mg, 0.45 mmol). The resulting mixture was stirred for 1 h, diluted with EtOAc (30 mL), washed with 1 M aqueous HCl (20 mL × 2), dried, filtered, and concentrated to give crude **33** as a yellow oil without further purification. Then compound **37** (140 mg, 0.18 mmol) and Et_2NH (1 mL) were stirred in CH_3CN (2 mL) for 10 min. After the mixture was concentrated, the residue was dissolved in CH_2Cl_2 (5 mL) and crude **33**, HATU (103 mg, 0.27 mmol), and DIPEA (100 μL, 0.54 mmol) were added successively. The mixture was stirred for another 1 h and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (PE/EA = 1/1) to give **38** as a colorless oil (141 mg, 73%). $[\alpha]_D^{25} = -0.32$ (*c* 0.48, $CHCl_3$). IR (film) ν_{max}: 3311, 2967, 2878, 1757, 1633, 1535, 1463, 1411, 1381, 1248, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.32−7.07 (m, 5H), 6.90−6.74 (m, 2H), 6.28−6.09 (m, 1H), 5.86−5.68 (m, 2H), 5.68−5.58 (m, 1H), 5.35−5.28 (m, 1H), 5.23−5.13 (m, 1.3H), 5.13−5.03 (m, 2H), 5.04−4.93 (m, 1.7H), 4.85−4.77 (m, 1H), 4.77−4.67 (m, 1H), 4.67−4.54 (m, 2H), 4.15−3.92 (m, 2H), 3.23−2.75 (m, 11H), 2.58−2.46 (m, 1H), 2.44−2.31 (m, 1H), 2.12−2.02 (m, 3H), 2.00−1.93 (m, 3H), 1.82−1.71 (m, 1H), 1.68−1.55 (m, 1H), 1.52−1.30 (m, 5.4H), 1.27−1.13 (m, 2.6H), 1.09−0.61 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 172.0, 170.9, 170.3, 169.2, 167.9, 166.1, 153.8, 136.5, 135.6, 132.3, 129.3, 129.2, 128.3, 128.2, 126.7, 118.9, 94.5, 79.7, 76.2, 75.8, 53.9, 52.0, 52.0, 45.0, 38.6, 37.5, 37.4, 36.6, 36.4, 36.3, 36.1, 35.1, 31.1, 30.4, 26.6, 26.0, 24.9, 20.7, 18.3, 17.3, 14.9, 14.7, 14.5, 14.2, 14.0, 13.9, 13.8, 11.9, 11.8, 11.6, 10.8, 9.7. HRMS (ESI): calcd for $[C_{50}H_{76}Cl_3N_5O_{12} + H^+]$ 1044.4634, found 1044.4632.

General Procedure for the Synthesis of 41, 47, 53, 59, and 63. A solution of terminal olefin (4.0 mmol), Grubbs second-

generation catalyst (4 mg, 0.1%), and methacrylaldehyde (80%, 4.2 mL, 40.0 mmol) was refluxed for 2 days in CH_2Cl_2 (100 mL) (catalyst was reloaded about 2 mg/10 h). The mixture was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography on silica gel (PE/EA = 15/1) to give the desired compound.

Compound ***41***. Colorless oil (1.90 g, 81%). $[\alpha]_D^{25}$ = +16.8 (*c* 1.24, $CHCl_3$); IR (film): ν_{max} 3369, 2971, 2916, 2875, 1758, 1693, 1454, 1390, 1367, 1322, 1247, 1154, 1078, 991, 821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.43 (s, 1H), 6.57−6.47 (m, 1H), 5.11−4.98 (m, 1H), 4.95−4.74 (m, 3H), 4.70−4.62 (m, 1H), 2.90−2.75 (m, 3H), 2.23−2.11 (m, 1H), 1.81 (s, 3H), 1.77−1.61 (m, 2H), 1.52−1.42 (m, 14H), 1.15−1.06 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.94−0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 172.3, 172.1, 155.8, 155.4, 154.6, 153.8, 147.1, 146.7, 142.1, 94.4, 80.1, 79.8, 79.1, 79.0, 76.8, 75.8, 75.4, 54.4, 54.2, 53.5, 37.4, 36.3, 31.5, 31.3, 30.5, 30.3, 29.7, 28.4, 24.9, 24.7, 15.5, 14.8, 10.9, 9.8, 9.5. HRMS (ESI): calcd for $[C_{25}H_{40}Cl_3NO_8 + Na^+]$ 610.1717, found 610.1716.

Compound ***47***. Colorless oil (2.08 g, 80%). $[\alpha]_D^{25}$ = −4.7 (*c* 0.94, $CHCl_3$). IR (film) ν_{max}: 2958, 2930, 2857, 1737, 1705, 1452, 1401, 1316, 1251, 1211, 1159, 1077, 1006, 934, 836, 775, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.46−9.42 (m, 1H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.67−7.57 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 6.67−6.56 (m, 1H), 5.00−4.89 (m, 1.6H), 4.88−4.78 (m, 0.4H), 4.58−4.49 (m, 0.3H), 4.49−4.36 (m, 1.7H), 4.35−4.23 (m, 1H), 3.84−3.74 (m, 1H), 3.01−2.90 (m, 3H), 2.61−2.49 (m, 1H), 2.45−2.33 (m, 1H), 2.04−1.91 (m, 1H), 1.83−1.74 (m, 3H), 1.69−1.59 (m, 1H), 1.54−1.43 (m, 4H), 1.20−1.06 (m, 1H), 0.95−0.84 (m, 18H), 0.13−0.01 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0, 171.8, 156.5, 151.0, 144.1, 143.9, 141.4, 140.6, 127.7, 127.1, 125.0, 120.0, 78.7, 72.6, 67.8, 54.4, 47.3, 40.4, 37.2, 32.5, 30.3, 29.7, 26.1, 25.8, 24.1, 18.0, 15.8, 14.9, 11.5, 9.5, −4.4, −4.6. HRMS (ESI): calcd for $[C_{38}H_{55}NO_6Si + Na^+]$ 672.3696, found 672.3702.

Compound ***53***. Colorless oil (2.15 g, 83%). $[\alpha]_D^{25}$ = −7.2 (*c* 0.37, $CHCl_3$). IR (film) ν_{max}: 2958, 2857, 1736, 1692, 1452, 1400, 1313, 1252, 1206, 1164, 1076, 836, 775, 740, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.62−7.48 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.33−7.25 (m, 2H), 6.61−6.47 (m, 1H), 4.91−4.75 (m, 2H), 4.50−4.29 (m, 2H), 4.28−4.17 (m, 1H), 3.74−3.60 (m, 1H), 2.99−2.87 (m, 3H), 2.84−2.67 (m, 1H), 2.50−2.38 (m, 1H), 1.85−1.72 (m, 4H), 1.71−1.55 (m, 2H), 1.47−1.39 (m, 3H), 1.07−0.95 (m, 1H), 0.93−0.73 (m, 18H), 0.07−0.04 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 195.0, 172.2, 156.5, 150.5, 149.9, 144.0, 143.9, 141.3, 140.7, 127.7, 127.0, 125.0, 120.0, 78.5, 78.1, 72.2, 67.8, 54.3, 54.0, 47.2, 39.3, 36.2, 34.0, 30.3, 29.7, 25.8, 24.1, 23.8, 18.0, 15.3, 15.0, 11.2, 11.1, 10.3, 9.6, −4.2, −4.6. HRMS (ESI): calcd for $[C_{38}H_{55}NO_6Si + Na^+]$ 672.3696, found 672.3695.

Compound ***59***. Colorless oil (2.26 g, 87%). $[\alpha]_D^{25}$ = −24.1 (*c* 1.19, $CHCl_3$). IR (film) ν_{max}: 3356, 2959, 2930, 2857, 1737, 1689, 1452, 1399, 1323, 1252, 1206, 1168, 1075, 1007, 948, 837, 776, 758, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.76 (d, *J* = 7.4 Hz, 2H), 7.64−7.51 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 6.55−6.40 (m, 1H), 4.95−4.82 (m, 2H), 4.43−4.33 (m, 2H), 4.31−4.19 (m, 1H), 3.87−3.66 (m, 1H), 3.05−2.87 (m, 3H), 2.54−2.33 (m, 2H), 2.13−2.00 (m, 1H), 1.77−1.68 (m, 3H), 1.68−1.57 (m, 1H), 1.52−1.40 (m, 3H), 1.35−1.22 (m, 1H), 1.20−1.09 (m, 1H), 0.98−0.81 (m, 18H), 0.09− −0.16 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 172.3, 156.6, 153.5, 144.0, 143.8, 141.3, 140.1, 127.7, 127.1, 125.0, 120.0, 77.8, 70.8, 67.8, 54.1, 47.17, 41.3, 36.1, 30.9, 29.9, 26.9, 25.7, 17.9, 15.2, 12.3, 12.0, 9.5, 9.3, −4.4, −4.6. HRMS (ESI): calcd for $[C_{38}H_{55}NO_6Si + Na^+]$ 672.3696, found 672.3695.

Compound ***63***. Colorless oil (2.15 g, 83%). $[\alpha]_D^{25}$ = −16.4 (*c* 0.78, $CHCl_3$). IR (film) ν_{max}: 3400, 2958, 2927, 2857, 1736, 1703, 1452, 1401, 1315, 1251, 1156, 1077, 837, 774, 758, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.42−9.28 (m, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.64−7.48 (m, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 6.57−6.39 (m, 1H), 4.90 (dd, *J* = 10.5, 1.7 Hz, 1H), 4.87−4.69 (m, 1H), 4.59−4.29 (m, 2H), 4.30−4.17 (m, 1H), 3.83−3.59 (m, 1H), 2.96−2.84 (m, 3H), 2.53−2.43 (m, 1H), 2.43−2.29 (m, 1H), 2.14−1.99 (m, 1H), 1.74 (s, 3H), 1.68−1.55 (m, 1H), 1.50−1.35 (m, 3H), 1.33−1.20 (m, 1H), 1.18−1.07 (m, 1H), 0.98−0.77 (m, 18H), 0.06− −0.10 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 171.7, 156.2, 153.2, 143.9, 141.3, 140.1, 127.7, 127.0, 125.0, 120.0, 78.0, 70.9, 67.7, 54.5, 47.2, 41.1, 36.2, 30.8, 26.8, 25.7, 17.9, 15.0, 12.3, 12.0, 9.5, 9.3, −4.5, −4.7. HRMS (ESI): calcd for $[C_{38}H_{55}NO_6Si + Na^+]$ 672.3696, found 672.3694.

General Procedure for the Synthesis of 42, 48, 54, 60, and 64. A solution of aldehyde (1.76 mmol) in *t*-BuOH/2-methyl-2-butene (10/5 mL) was treated with a solution of $NaClO_2$ (80%, 1.58 g, 14.1 mmol) and NaH_2PO_4 (2.75 g, 17.6 mmol) in water (50 mL). After 2 h of stirring, the mixture was extracted with EtOAc (30 mL × 3), and the combined organic layers were washed with brine (30 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 5/1) to give the corresponding title compound.

Compound ***42***. Colorless oil (0.986 g, 93%). $[\alpha]_D^{25}$ = +64.2 (*c* 0.076, $CHCl_3$). IR (film) ν_{max}: 2972, 2937, 1759, 1693, 1454, 1390, 1368, 1324, 1247, 1154, 1093, 996 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.93−6.85 (m, 1H), 5.07−4.97 (m, 1H), 4.96−4.84 (m, 1.5H), 4.82−4.70 (m, 1.5H), 4.70−4.60 (m, 1H), 2.91−2.80 (m, 3H), 2.72−2.61 (m, 2H), 2.20−2.08 (m, 1H), 1.89 (s, 3H), 1.74−1.61 (m, 1H), 1.53−1.41 (m, 12H), 1.33−1.24 (m, 1H), 1.14−1.04 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.93−0.85 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 172.0, 171.2, 155.8, 153.7, 137.7, 137.5, 130.4, 94.5, 80.2, 79.8, 79.5, 79.3, 76.8, 75.8, 75.4, 60.4, 54.2, 53.6, 37.2, 36.3, 31.2, 30.3, 29.7, 28.4, 24.8, 22.7, 21.0, 15.4, 14.8, 14.2, 14.1, 12.3, 10.9, 9.8. HRMS (ESI): calcd for $[C_{25}H_{40}Cl_3NO_9 + Na^+]$ 626.1666, found 626.1662.

Compound ***48***. Colorless oil (1.02 g, 87%). $[\alpha]_D^{25}$ = −6.3 (*c* 0.76, $CHCl_3$). IR (film) ν_{max}: 2959, 2855, 1736, 1706, 1451, 1401, 1316, 1252, 1212, 1158, 1077, 836, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.5 Hz, 2H), 7.68−7.57 (m, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.08−6.97 (m, 1H), 5.02−4.90 (m, 1.7H), 4.86−4.77 (m, 0.3H), 4.58−4.37 (m, 2H), 4.36−4.24 (m, 1H), 3.82−3.70 (m, 1H), 3.01−2.92 (m, 3H), 2.46−2.33 (m, 1H), 2.32−2.21 (m, 1H), 2.04−1.93 (m, 1H), 1.87 (s, 3H), 1.69−1.58 (m, 1H), 1.55−1.43 (m, 4H), 1.20−1.08 (m, 1H), 0.96−0.85 (m, 18H), 0.13−0.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 156.6, 144.0, 141.4, 128.4, 127.7, 127.1, 125.1, 120.0, 79.0, 72.6, 67.8, 54.4, 53.4, 47.3, 40.4, 37.2, 32.4, 30.3, 25.8, 24.0, 18.0, 15.9, 14.9, 12.3, 11.5, 9.7, −4.5, −4.6. HRMS (ESI): calcd for $[C_{38}H_{55}NO_7Si + H^+]$ 666.3826, found 666.3821.

Compound ***54***. Colorless oil (0.913 g, 78%). $[\alpha]_D^{25}$ = −10.0 (*c* 1.39, $CHCl_3$). IR (film) ν_{max}: 2959, 2857, 1736, 1704, 1452, 1401, 1316, 1253, 1213, 1161, 1076, 836, 775, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.4 Hz, 2H), 7.69−7.56 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.1 Hz, 2H), 7.08−6.93 (m, 1H), 5.01−4.90 (m, 1.6H), 4.88−4.78 (m, 0.4H), 4.57−4.38 (m, 2H), 4.35−4.23 (m, 1H), 3.78−3.65 (m, 1H), 3.01−2.92 (m, 3H), 2.65−2.51 (m, 1H), 2.46−2.33 (m, 1H), 1.96−1.84 (m, 4H), 1.77−1.67 (m, 1H), 1.54−1.40 (m, 4H), 1.15−1.02 (m, 1H), 0.98−0.82 (m, 18H), 0.14−0.05 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 171.8, 156.6, 144.0, 141.4, 141.1, 128.6, 127.7, 127.1, 125.1, 120.0, 78.3, 72.6, 67.8, 54.4, 47.3, 39.4, 36.5, 34.0, 30.4, 25.9, 24.1, 18.1, 15.4, 15.0, 12.4, 11.3, 10.3, −4.2, −4.5. HRMS (ESI): calcd for $[C_{38}H_{55}NO_7Si + Na^+]$ 688.3645, found 688.3650.

Compound ***60***. Colorless oil (0.936 g, 80%). $[\alpha]_D^{25}$ = −25.9 (*c* 1.05, $CHCl_3$). IR (film) ν_{max}: 2960, 2927, 2857, 1737, 1692, 1452, 1384, 1319, 1256, 1208, 1165, 1077, 953, 837, 776, 758, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.64−7.51 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 6.95−6.84 (m, 1H), 4.95−4.79 (m, 2H), 4.45−4.34 (m, 2H), 4.28−4.20 (m, 1H), 3.81−3.65 (m, 1H), 2.93 (s, 3H), 2.37−2.21 (m, 2H), 2.11−1.99 (m, 1H), 1.79 (s, 3H), 1.66−1.58 (m, 1H), 1.44 (d, *J* = 7.4 Hz, 3H), 1.28−1.25 (m, 1H), 1.17−1.09 (m, 1H), 0.97−0.80 (m, 18H), 0.09− −0.07 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 172.1, 159.4, 156.5, 144.0, 143.9, 143.3, 142.7, 141.3, 139.6, 127.8, 127.6, 127.0, 125.0, 119.9, 115.7, 78.3, 77.9, 72.8, 70.8, 68.3, 68.0, 67.7, 54.1, 47.2, 41.1, 36.2, 31.9, 30.7, 30.0, 27.7, 26.8, 26.4, 25.7, 24.5, 23.8, 20.5, 20.4, 20.1, 17.9, 15.7, 15.2, 14.5, 12.3, 12.2, 11.9, 11.6, 9.6, 8.1, −4.6, −4.7, −4.8.

HRMS (ESI): calcd for [$C_{38}H_{55}NO_7Si$ + Na^+] 688.3645, found 688.3645.

Compound ***64***. Colorless oil (0.948 g, 81%). $[\alpha]_D^{25}$ = −15.2 (*c* 0.93, $CHCl_3$). IR (film) ν_{max}: 2959, 2932, 2855, 1736, 1702, 1452, 1401, 1311, 1257, 1158, 1077 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.64−7.48 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.05−6.83 (m, 2H), 4.95−4.71 (m, 2H), 4.55−4.32 (m, 2H), 4.29−4.18 (m, 1H), 3.77−3.61 (m, 1H), 3.00−2.84 (m, 3H), 2.39−2.18 (m, 2H), 2.11−1.99 (m, 1H), 1.87−1.78 (m, 3H), 1.66−1.56 (m, 1H), 1.48−1.35 (m, 3H), 1.31−1.21 (m, 1H), 1.20−1.06 (m, 1H), 1.00−0.76 (m, 18H), 0.11−0.05 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 171.6, 156.3, 144.0, 143.9, 143.4, 141.3, 127.9, 127.6, 127.0, 125.0, 119.9, 78.1, 71.0, 67.8, 54.3, 47.2, 41.1, 36.3, 30.7, 30.6, 26.8, 25.7, 17.9, 15.0, 12.3, 12.2, 12.0, 9.6, −4.6, −4.8. HRMS (ESI): calcd for [$C_{38}H_{55}NO_7Si$ + Na^+] 688.3645, found 688.3646.

General Procedure for the Synthesis of 43, 49, 55, 61, and 65. To a solution of the carboxylic acid (0.63 mmol) in CH_2Cl_2 (10 mL) were added successively **31** (600 mg, 1.26 mmol), DMAP (384 mg, 3.15 mmol), and 2-methyl-6-nitrobenzoic anhydride (368 mg, 1.07 mmol). The mixture was stirred for 5 h and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (PE/EA = 2/1) to give the corresponding title compound.

Compound ***43***. Colorless oil (441 mg, 66%). $[\alpha]_D^{25}$ = +38.3 (*c* 1.54, $CHCl_3$). IR (film) ν_{max}: 3409, 3302, 2967, 2934, 2873, 1747, 1650, 1456, 1390, 1246, 1154, 1097, 980, 939, 744, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29−7.15 (m, 5H), 6.88−6.80 (m, 0.6H), 6.69−6.58 (m, 1H), 6.46−6.36 (m, 0.4H), 6.06−5.82 (m, 2H), 5.40−5.16 (m, 3H), 5.04−4.58 (m, 7H), 4.29 (d, *J* = 17.1 Hz, 1H), 3.98 (d, *J* = 17.1 Hz, 1H), 3.25−3.11 (m, 1.5H), 3.09−2.95 (m, 7.5H), 2.88−2.82 (m, 2H), 2.75−2.64 (m, 1H), 2.14−1.92 (m, 5H), 1.88−1.80 (m, 1H), 1.74−1.61 (m, 1H), 1.51−1.42 (m, 12H), 1.34−1.16 (m, 4H), 1.06 (dd, *J* = 18.1, 6.6 Hz, 3H), 0.95−0.82 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 170.6, 170.0, 169.8, 169.6, 169.2, 168.9, 168.4, 167.2, 166.2, 153.8, 136.7, 131.7, 131.5, 129.4, 129.3, 128.3, 128.3, 126.7, 118.9, 94.4, 79.8, 76.8, 76.2, 66.1, 65.8, 53.9, 50.3, 45.0, 37.6, 37.3, 36.4, 36.3, 35.3, 35.1, 30.3, 30.1, 29.7, 28.4, 26.1, 17.4, 15.8, 14.0, 13.9, 12.8, 11.68, 11.4, 10.9, 10.0. HRMS (ESI): calcd for [$C_{50}H_{75}Cl_3N_4O_{14}$ + Na^+] 1083.4243, found 1083.4249.

Compound ***49***. Colorless oil (424 mg, 60%). $[\alpha]_D^{25}$ = +40.3 (*c* 1.28, $CHCl_3$). IR (film) ν_{max}: 3408, 2962, 2932, 2880, 2855, 1741, 1709, 1649, 1453, 1402, 1207, 1079 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.66−7.56 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.29−7.14 (m, 5H), 7.00−6.91 (m, 1H), 6.65−6.56 (m, 1H), 5.99−5.83 (m, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 5.20 (dd, *J* = 13.7, 2.9 Hz, 1H), 4.99−4.89 (m, 1H), 4.83−4.72 (m, 1H), 4.71−4.59 (m, 3H), 4.54−4.38 (m, 2H), 4.34−4.23 (m, 2H), 4.06 (d, *J* = 18.2 Hz, 0.2H), 3.97 (d, *J* = 17.1 Hz, 0.8H), 3.82−3.73 (m, 1H), 3.25−3.12 (m, 1.5H), 3.10−2.90 (m, 10.5H), 2.49−2.36 (m, 1H), 2.33−2.20 (m, 1H), 2.03−1.87 (m, 5H), 1.70−1.60 (m, 1H), 1.42−1.33 (m, 1H), 1.32−1.18 (m, 2H), 1.17−1.08 (m, 1H), 0.98−0.82 (m, 30H), 0.12−0.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 172.2, 171.8, 170.1, 169.9, 169.4, 168.4, 166.6, 156.5, 144.1, 141.3, 140.4, 136.7, 131.7, 131.6, 129.5, 129.3, 128.3, 127.7, 127.1, 126.7, 125.0, 120.0, 118.9, 78.7, 76.2, 72.5, 67.8, 66.1, 65.8, 54.4, 53.8, 53.2, 50.3, 47.3, 45.3, 44.9, 40.3, 37.5, 37.1, 36.3, 35.1, 32.3, 30.3, 30.1, 26.1, 25.9, 18.0, 17.4, 15.9, 14.9, 14.0, 13.9, 12.9, 11.6, 11.5, 9.7, −4.3, −4.6. HRMS (ESI): calcd for [$C_{63}H_{90}N_4O_{12}Si$ + Na^+] 1145.6222, found 1145.6223.

Compound ***55***. Colorless oil (445 mg, 63%). $[\alpha]_D^{25}$ = +39.0 (*c* 1.06, $CHCl_3$). IR (film) ν_{max}: 3411, 2961, 2927, 1740, 1704, 1648, 1453, 1402, 1315, 1251, 1194, 1160, 1079, 836, 775, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.4 Hz, 2H), 7.66−7.54 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.28−7.14 (m, 5H), 7.00−6.89 (m, 1H), 6.74−6.58 (m, 1H), 6.00−5.83 (m, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 3.9 Hz, 1H), 5.27−5.23 (m, 1H), 5.23−5.16 (m, 0.5H), 4.96−4.87 (m, 1.5H), 4.80−4.72 (m, 0.7H), 4.68−4.58 (m, 2.3H), 4.47−4.38 (m, 2H), 4.34−4.24 (m, 2H), 3.95 (d, *J* = 17.2 Hz, 1H), 3.73−3.65 (m, 1H), 3.32−3.24 (m, 0.3H), 3.23−3.12 (m, 1.5H), 3.08−2.92 (m, 10.2H), 2.69−2.55 (m, 0.6H), 2.43−2.31 (m, 0.6H), 2.04−1.98 (m, 1.8H), 1.95 (s, 3H), 1.92−1.81 (m, 1H), 1.77−1.63 (m, 1H), 1.52−1.42 (m, 3H), 1.37−1.32 (m, 1H), 1.29−1.25 (m, 1H), 1.24−1.14 (m, 1H), 1.12−1.00 (m, 1H), 0.97−0.81 (m, 27H), 0.12−0.02 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 172.3, 172.2, 171.8, 170.1, 169.9, 169.4, 168.9, 168.4, 166.5, 156.5, 144.0, 141.3, 140.1, 136.7, 131.7, 131.5, 129.5, 129.3, 128.3, 128.3, 127.7, 127.1, 126.7, 125.0, 120.0, 118.9, 78.1, 76.1, 67.8, 66.1, 65.8, 54.4, 53.8, 53.2, 50.3, 47.3, 45.2, 44.9, 42.8, 41.2, 39.3, 37.5, 36.3, 35.3, 35.1, 33.9, 30.4, 30.3, 26.1, 25.9, 18.2, 18.0, 17.4, 15.6, 15.0, 14.2, 14.0, 13.9, 12.9, 11.7, 11.2, 10.9, 10.3, −3.8, −4.2, −4.6, −4.9. HRMS (ESI): calcd for [$C_{63}H_{90}N_4O_{12}Si$ + Na^+] 1145.6222, found 1145.6193.

Compound ***61***. Colorless oil (396 mg, 56%). $[\alpha]_D^{25}$ = +25.6 (*c* 0.46, $CHCl_3$). IR (film) ν_{max}: 2962, 2932, 1741, 1708, 1649, 1453, 1402, 1317, 1250, 1209, 1094, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.65−7.50 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 8.4 Hz, 2H), 7.24−7.07 (m, 5H), 6.92−6.79 (m, 1H), 5.96−5.78 (m, 1H), 5.36−5.15 (m, 3H), 4.95−4.80 (m, 2H), 4.71−4.53 (m, 3H), 4.47−4.34 (m, 2H), 4.31−4.19 (m, 2H), 4.10 (q, *J* = 7.2 Hz, 1H), 3.99−3.88 (m, 1H), 3.82−3.66 (m, 1H), 3.20−3.07 (m, 2H), 3.05−2.87 (m, 9H), 2.40−2.21 (m, 2H), 2.10−2.03 (m, 1H), 2.00−1.91 (m, 1H), 1.87 (s, 3H), 1.66−1.56 (m, 1H), 1.48−1.38 (m, 3H), 1.33−1.11 (m, 7H), 0.97−0.62 (m, 24H), 0.12− −0.12 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 172.1, 172.0, 171.0, 170.1, 169.9, 169.6, 168.9, 168.4, 166.7, 156.4, 144.1, 143.9, 142.3, 141.3, 136.7, 136.5, 131.6, 131.5, 129.4, 129.3, 128.3, 128.2, 127.9, 127.6, 127.1, 127.0, 126.6, 125.1, 119.9, 118.8, 77.9, 75.9, 70.8, 67.9, 67.7, 66.0, 65.8, 60.3, 54.1, 53.8, 53.1, 51.1, 50.2, 47.2, 45.2, 44.9, 41.2, 37.5, 36.3, 36.2, 35.2, 35.2, 35.1, 31.9, 30.9, 30.2, 30.1, 29.7, 29.3, 27.0, 26.8, 26.2, 26.1, 25.8, 22.7, 21.0, 17.9, 17.2, 16.9, 15.7, 15.2, 14.2, 14.1, 14.0, 13.9, 12.8, 12.4, 11.9, 11.6, 9.8, −4.5, −4.7. HRMS (ESI): calcd for [$C_{63}H_{90}N_4O_{12}Si$ + Na^+] 1145.6222, found 1145.6201.

Compound ***65***. Colorless oil (410 mg, 58%). $[\alpha]_D^{25}$ = +34.8 (*c* 0.56, $CHCl_3$). IR (film) ν_{max}: 2962, 2927, 2850, 1740, 1708, 1648, 1452, 1402, 1309, 1258, 1209, 1079 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.63−7.49 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.25−7.09 (m, 5H), 6.90−6.76 (m, 1H), 6.66−6.52 (m, 1H), 5.94−5.70 (m, 2H), 5.36−5.11 (m, 2H), 4.94−4.84 (m, 1H), 4.83−4.66 (m, 1H), 4.66−4.54 (m, 2H), 4.42−4.32 (m, 2H), 4.29−4.18 (m, 2H), 4.16−4.05 (m, 1H), 3.92 (d, *J* = 17.1 Hz, 1H), 3.78−3.61 (m, 1H), 3.20−3.07 (m, 2H), 3.05−2.83 (m, 9H), 2.36−2.21 (m, 2H), 2.10−1.91 (m, 2H), 1.88 (s, 3H), 1.68−1.54 (m, 1H), 1.48−1.36 (m, 3H), 1.35−1.07 (m, 7H), 0.96−0.80 (m, 21H), 0.79−0.74 (m, 2H), 0.70−0.63 (m, 1H), 0.07− −0.08 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 171.7, 170.0, 169.8, 169.5, 168.9, 168.4, 166.8, 156.3, 144.0, 143.9, 142.3, 141.3, 136.6, 131.6, 131.5, 129.4, 129.2, 128.3, 128.2, 128.0, 127.7, 127.0, 126.6, 125.0, 119.9, 118.9, 78.1, 76.0, 70.9, 67.8, 66.1, 65.8, 54.2, 53.8, 50.2, 47.2, 45.2, 44.9, 41.1, 37.4, 36.3, 35.3, 35.2, 35.1, 30.8, 30.5, 30.3, 30.1, 26.8, 26.2, 26.1, 25.7, 17.9, 17.3, 15.0, 14.1, 13.9, 12.8, 12.4, 11.9, 11.6, 9.7, −4.6, −4.5. HRMS (ESI): calcd for [$C_{63}H_{90}N_4O_{12}Si$ + H^+] 1123.6403, found 1123.6412.

General Procedure for the Synthesis of 50, 56, and 57. Compound **49** (for **50** and **57**) or **55** (for **56**) (0.25 mmol) and Et_2NH (2 mL) were stirred in CH_3CN (4 mL) for 10 min. Then the mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (10 mL). To this solution were added successively L-Boc-aIle-OH (for **50** and **56**) or L-Boc-Ile-OH (for **57**) (65 mg, 0.28 mmol), HATU (192 mg, 0.50 mmol), and DIPEA (0.17 mL, 1.0 mmol). The mixture was stirred for 1 h and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to give the desired compound.

Compound ***50***. Colorless oil (212 mg, 76%). $[\alpha]_D^{25}$ = +45.2 (*c* 0.69, $CHCl_3$). IR (film) ν_{max}: 3325, 2964, 2927, 2875, 1718, 1648, 1498, 1460, 1408, 1250, 1196, 1079 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28−7.12 (m, 5H), 6.99−6.87 (m, 1H), 6.63−6.52 (m, 1H), 5.96−5.83 (m, 1H), 5.38−5.22 (m, 2H), 5.21−4.99 (m, 1.4H), 4.96−4.87 (m, 1H), 4.80−4.69 (m, 1H), 4.68−4.53 (m, 3.6H), 4.41 (d, *J* = 18.2 Hz, 0.2H), 4.27 (d, *J* = 17.1 Hz, 0.8H), 4.05 (d, *J* = 18.1 Hz, 0.2H), 3.95 (d, *J* = 17.1 Hz, 0.8H), 3.80−3.69 (m, 1H), 3.23−3.08 (m, 1.5H), 3.08−2.93 (m, 10.5H), 2.47−2.35 (m, 1H), 2.31−2.17 (m, 1H), 2.03−

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1.94 (m, 2H), 1.88 (s, 3H), 1.78−1.68 (m, 1H), 1.66−1.57 (m, 1H), 1.50−1.37 (m, 15H), 1.27−1.16 (m, 2H), 1.15−1.06 (m, 1H), 0.94−0.79 (m, 33H), 0.11−0.01 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 172.2, 171.5, 170.1, 169.3, 168.8, 168.4, 166.6, 155.9, 140.4, 136.6, 131.6, 131.5, 129.4, 129.3, 128.6, 128.3, 126.6, 118.8, 79.4, 79.0, 76.2, 72.5, 66.1, 65.8, 53.8, 53.4, 53.2, 52.2, 51.2, 50.2, 45.2, 44.9, 40.2, 38.1, 37.4, 36.9, 36.3, 35.2, 35.1, 32.2, 31.3, 30.3, 30.1, 28.3, 26.7, 26.1, 25.8, 23.8, 18.0, 17.4, 17.2, 15.8, 14.3, 14.0, 13.9, 13.7, 12.9, 11.9, 11.6, 11.5, 9.8, −4.3, −4.7. HRMS (ESI): calcd for $[C_{59}H_{99}N_5O_{13}Si + H^+]$ 1114.7087, found 1114.7084.

Compound ***56***. Colorless oil (209 mg, 75%). $[\alpha]_D^{25}$ = +36.1 (*c* 1.99, $CHCl_3$). IR (film) ν_{max}: 3325, 2964, 2933, 1718, 1648, 1498, 1461, 1408, 1250, 1408, 1250, 1194, 1080 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.12 (m, 5H), 6.96−6.87 (m, 1H), 6.68−6.55 (m, 1H), 5.94−5.85 (m, 1H), 5.38−5.30 (m, 2H), 5.26−5.12 (m, 1.5H), 4.95−4.86 (m, 1H), 4.81−4.71 (m, 1H), 4.70−4.57 (m, 3.5H), 4.43 (d, *J* = 18.2 Hz, 0.2H), 4.29 (d, *J* = 17.1 Hz, 0.8H), 4.05 (d, *J* = 18.1 Hz, 0.2H), 3.95 (d, *J* = 17.1 Hz, 0.8H), 3.76−3.65 (m, 1H), 3.30−3.11 (m, 1.6H), 3.10−2.90 (m, 10.4H), 2.64−2.50 (m, 1H), 2.44−2.31 (m, 1H), 2.04−1.97 (m, 1H), 1.93 (s, 3H), 1.90−1.80 (m, 2H), 1.79−1.65 (m, 2H), 1.52−1.34 (m, 15H), 1.24−1.17 (m, 1H), 1.11−1.03 (m, 1H), 0.99−0.78 (m, 33H), 0.10−0.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 172.2, 171.5, 170.1, 169.8, 169.3, 169.2, 168.8, 168.4, 166.5, 156.0, 139.9, 136.7, 131.6, 131.5, 129.4, 129.3, 128.6, 128.3, 128.3, 126.7, 118.9, 79.4, 78.3, 76.1, 72.5, 66.1, 65.8, 60.3, 53.8, 53.4, 52.3, 51.2, 50.3, 45.2, 44.9, 39.3, 37.5, 37.5, 36.3, 36.3, 35.2, 35.1, 33.9, 31.3, 30.3, 30.1, 28.3, 26.7, 26.1, 25.8, 24.0, 21.0, 18.0, 17.4, 15.4, 14.4, 14.2, 14.0, 13.9, 13.7, 12.9, 11.9, 11.6, 11.2, 10.3, −3.9, −4.1, −4.6. HRMS (ESI): calcd for $[C_{59}H_{99}N_5O_{13}Si + H^+]$ 1114.7087, found 1114.7079.

Compound ***57***. Colorless oil (220 mg, 79%). $[\alpha]_D^{25}$ = +30.4 (*c* 0.46, $CHCl_3$). IR (film) ν_{max}: 2964, 2933, 2875, 1735, 1718, 1654, 1649, 1513, 1497, 1460, 1250, 1195, 1079 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.09 (m, 5H), 6.94−6.84 (m, 1H), 6.64−6.53 (m, 1H), 5.94−5.78 (m, 2H), 5.30−5.23 (m, 2H), 5.19−5.10 (m, 1H), 4.94−4.85 (m, 1H), 4.75−4.68 (m, 1H), 4.63−4.54 (m, 3H), 4.52−4.44 (m, 1H), 4.24 (d, *J* = 17.3 Hz, 1H), 3.94 (d, *J* = 17.1 Hz, 1H), 3.76−3.68 (m, 1H), 3.21−3.07 (m, 2H), 3.06−2.79 (m, 10H), 2.45−2.34 (m, 1H), 2.26−2.17 (m, 1H), 2.00−1.90 (m, 2H), 1.86 (s, 3H), 1.77−1.69 (m, 1H), 1.62−1.55 (m, 1H), 1.50−1.30 (m, 15H), 1.21−1.14 (m, 1H), 1.12−1.03 (m, 2H), 0.99−0.67 (m, 33H), 0.09− −0.02 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 172.5, 172.2, 171.4, 170.0, 169.8, 169.4, 169.2, 168.8, 168.4, 166.6, 155.8, 140.4, 136.6, 136.5, 131.6, 131.5, 129.4, 129.2, 128.5, 128.3, 128.2, 126.6, 118.9, 79.5, 78.9, 76.1, 72.3, 66.1, 65.8, 54.7, 53.8, 52.3, 50.2, 44.9, 40.5, 37.9, 37.4, 36.8, 36.3, 35.3, 35.2, 35.0, 32.2, 31.6, 30.3, 30.1, 28.3, 26.1, 25.9, 25.8, 23.9, 23.8, 18.0, 17.3, 17.1, 15.8, 15.6, 14.4, 13.9, 13.9, 12.9, 12.8, 11.6, 11.4, 11.3, 9.8, −4.3, −4.7. HRMS (ESI): calcd for $[C_{59}H_{99}N_5O_{13}Si + H^+]$ 1114.7087, found 1114.7080.

General Procedure for the Synthesis of 58, 62, and 66. Compound **49**, **61**, or **65** (280 mg, 0.25 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in anhydrous THF (5 mL) were treated with PhNHMe (69 mg, 0.63 mmol) at room temperature. After the mixture was stirred for 30 min, the mixture was diluted with EtOAc (100 mL) and then washed with 1 M aqueous HCl (20 mL × 2), dried, filtered, and concentrated to give the crude carboxylic acid as a yellow oil. To a cooled solution (0 °C) of L-Boc-Ile-OAllyl (136 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) was added TFA (1 mL), and the resulting solution was stirred for 2 h. Then the mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (5 mL). The above crude carboxylic acid (in 5 mL of CH_2Cl_2), HATU (190 mg, 0.50 mmol), and DIPEA (0.12 mL, 0.75 mmol) were then added successively. After the mixture was stirred for 1 h, it was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (PE/EA = 1/1) to give the desired compound.

Compound ***58***. Colorless oil (263 mg, 85%). $[\alpha]_D^{25}$ = +36.4 (*c* 1.1, $CHCl_3$). IR (film) ν_{max}: 2965, 2934, 2877, 1735, 1691, 1643, 1577, 1514, 1453, 1397, 1328, 1150 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.4 Hz, 2H), 7.60−7.47 (m, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.31−7.24 (m, 2H), 7.22−7.08 (m, 5H), 6.67−6.58 (m, 1H), 5.87−5.81 (m, 1H), 5.35−5.18 (m, 3H), 4.96−4.84 (m, 2H), 4.75−4.66 (m, 1H), 4.65−4.49 (m, 4H), 4.42−4.31 (m, 2H), 4.27−4.18 (m, 1H), 4.11−4.03 (m, 1H), 4.02−3.94 (m, 1H), 3.74−3.61 (m, 1H), 3.19−3.07 (m, 2H), 3.05−2.94 (m, 6H), 2.92−2.84 (m, 3H), 2.51−2.41 (m, 1H), 2.39−2.27 (m, 1H), 2.00 (s, 3H), 1.96−1.87 (m, 2H), 1.85−1.82 (m, 2H), 1.48−1.36 (m, 4H), 1.24−1.19 (m, 3H), 1.16−1.11 (m, 1H), 1.06−1.00 (m, 1H), 0.98−0.65 (m, 33H), 0.11−0.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 172.4, 171.3, 170.7, 169.9, 169.3, 169.3, 168.6, 168.1, 156.5, 143.9, 141.3, 136.4, 131.5, 129.3, 128.3, 128.2, 127.6, 127.0, 126.7, 125.0, 119.9, 118.9, 67.7, 65.8, 60.3, 56.4, 53.7, 52.6, 47.2, 45.0, 37.7, 37.4, 36.5, 35.1, 30.3, 29.6, 26.1, 26.0, 25.8, 25.1, 22.7, 21.0, 17.9, 17.3, 15.5, 14.2, 13.9, 12.88, 12.7, 12.2, 11.6, 11.5, 11.3, 10.7, 0.42, 0.39, −4.3. HRMS (ESI): calcd for $[C_{69}H_{101}N_5O_{13}Si + Na^+]$ 1258.7063, found 1258.7060.

Compound ***62***. Colorless oil (281 mg, 91%). $[\alpha]_D^{25}$ = +19.5 (*c* 1.02, $CHCl_3$). IR (film) ν_{max}: 3349, 2964, 2927, 1730, 1694, 1648, 1453, 1252, 1209, 1150, 1094 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.63−7.49 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.24−7.09 (m, 5H), 6.89−6.80 (m, 1H), 5.92−5.84 (m, 1H), 5.36−5.16 (m, 3H), 4.91−4.80 (m, 2H), 4.68−4.48 (m, 5H), 4.45−4.32 (m, 2H), 4.28−4.19 (m, 1H), 4.12−4.02 (m, 1H), 3.98−3.89 (m, 1H), 3.79−3.69 (m, 1H), 3.19−3.07 (m, 2H), 3.07−2.88 (m, 9H), 2.37−2.23 (m, 2H), 2.05−1.89 (m, 4H), 1.85 (s, 3H), 1.73−1.54 (m, 2H), 1.49−1.37 (m, 4H), 1.29−1.07 (m, 6H), 0.97−0.70 (m, 30H), 0.07− −0.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 172.0, 171.9, 171.3, 170.7, 169.6, 168.1, 166.8, 156.4, 144.0, 143.9, 142.3, 141.2, 136.4, 131.5, 129.3, 128.3, 127.9, 127.6, 127.0, 126.7, 125.1, 119.9, 118.9, 78.0, 75.9, 70.8, 67.7, 65.8, 56.4, 54.1, 53.7, 52.7, 47.2, 44.9, 41.2, 38.0, 37.7, 37.4, 36.5, 36.2, 35.1, 30.9, 30.3, 30.1, 26.8, 26.1, 25.8, 25.2, 25.1, 23.3, 17.9, 17.1, 15.5, 15.4, 15.2, 13.9, 12.8, 12.4, 11.9, 11.7, 11.6, 11.6, 9.8, −4.5, −4.7. HRMS (ESI): calcd for $[C_{69}H_{101}N_5O_{13}Si + Na^+]$ 1258.7063, found 1258.7063.

Compound ***66***. Colorless oil (247 mg, 80%). $[\alpha]_D^{25}$ = +25.2 (*c* 1.82, $CHCl_3$). IR (film) ν_{max}: 3338, 2964, 2927, 2875, 1737, 1686, 1648, 1453, 1402, 1251, 1211, 1149, 1079 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.69−7.48 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.23−7.05 (m, 5H), 6.89−6.72 (m, 1H), 5.94−5.75 (m, 1H), 5.36−5.13 (m, 2H), 4.95−4.81 (m, 2H), 4.73−4.49 (m, 6H), 4.43−4.31 (m, 2H), 4.29−4.16 (m, 1H), 4.14−3.90 (m, 2H), 3.75−3.59 (m, 1H), 3.19−3.07 (m, 2H), 3.08−2.82 (m, 9H), 2.35−2.20 (m, 2H), 2.10−1.92 (m, 4H), 1.86 (s, 3H), 1.67−1.52 (m, 2H), 1.47−1.27 (m, 6H), 1.27−1.11 (m, 4H), 0.98−0.69 (m, 30H), 0.06− −0.07 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 172.4, 171.8, 171.7, 171.3, 171.2, 170.7, 169.5, 168.1, 166.8, 156.3, 144.0, 143.9, 142.2, 141.3, 136.4, 131.5, 129.3, 129.2, 128.3, 128.2, 127.7, 127.0, 126.7, 125.0, 119.9, 118.9, 78.1, 75.9, 70.9, 67.8, 65.8, 65.7, 56.6, 56.4, 54.2, 53.7, 52.6, 47.2, 45.0, 41.1, 38.0, 37.7, 37.4, 36.5, 36.2, 35.1, 30.8, 30.5, 30.3, 26.8, 26.1, 25.8, 25.7, 25.2, 25.1, 17.9, 17.2, 15.5, 15.5, 15.4, 15.0, 14.0, 12.8, 12.4, 12.0, 11.6, 11.6, 11.5, 9.7, −4.5, −4.6. HRMS (ESI): calcd for $[C_{69}H_{101}N_5O_{13}Si + Na^+]$ 1258.7063, found 1258.7055.

General Procedure for the Synthesis of 45, 1, and 1b. Compound **44**, **50**, or **56** (0.023 mmol), $Pd(PPh_3)_4$ (5 mg, 4.6 μmol), and PhNHMe (6 mg, 0.057 mmol) were stirred in anhydrous THF (3 mL) for 1 h and diluted with EtOAc (50 mL). The mixture was washed with 1 M aqueous HCl (20 × 2), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Then the residue was treated with TFA (1 mL) in CH_2Cl_2 (2 mL) for 1 h and concentrated. The residue was dissolved in CH_2Cl_2 (23 mL), and HATU (87 mg, 0.23 mmol) and DIPEA (57 μL, 0.35 mmol) were added successively. After the mixture was stirred for 3 days, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (PE/acetone = 2/1) to give the corresponding title compound, which was further purified by preparative HPLC (Waters 2535 quaternary gradient module, Waters 2707 autosampler, and Waters 2489 UV/vis detector; SunFire C_{18} column, 10 μm, 19 mm × 250 mm).

Compound ***45***. Amorphous solid (4.2 mg, 22%; MeOH/H_2O = 91/9, 10 mL/min, 270 nm, RT = 19.532 min). $[\alpha]_D^{25}$ = −37.9 (*c* 0.075, CH_3OH). ^{1}H NMR (600 MHz, CD_3OD): δ 7.56 (d, *J* = 11.1 Hz, 1H),

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7.27−7.08 (m, 5H), 6.77 (dd, J = 14.8, 9.9 Hz, 1H), 6.37 (dd, J = 14.9, 11.1 Hz, 1H), 5.52 (dd, J = 10.8, 4.8 Hz, 1H), 4.92 (d, J = 7.8 Hz, 1H), 4.90 (dd, J = 4.8, 1.8 Hz, 1H), 4.73 (dd, J = 10.5, 2.3 Hz, 1H), 4.45 (q, J = 7.0 Hz, 1H), 4.23 (d, J = 18.3 Hz, 1H), 3.90 (q, J = 6.9 Hz, 1H), 3.31 (s, 3H), 3.21 (d, J = 18.2 Hz, 1H), 3.11−3.04 (m, 1H), 3.03 (s, 3H), 2.94 (dd, J = 14.4, 4.8 Hz, 1H), 2.81 (s, 3H), 2.70−2.63 (m, 1H), 1.97 (s, 3H), 1.92−1.81 (m, 2H), 1.76−1.69 (m, 1H), 1.57 (d, J = 6.9 Hz, 3H), 1.51−1.40 (m, 3H), 1.37−1.30 (m, 2H), 1.26−1.20 (m, 1H), 1.06 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H), 0.95−0.90 (m, 9H), 0.86 (t, J = 7.4 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, CD_3OD): δ 173.6, 171.4, 171.3, 171.2, 170.4, 169.4, 169.0, 149.2, 142.1, 137.0, 129.2, 127.6, 126.0, 123.7, 123.4, 80.2, 75.6, 60.4, 53.7, 53.6, 52.7, 51.4, 45.1, 38.2, 37.4, 37.1, 35.2, 34.4, 34.3, 29.2, 26.2, 25.7, 25.0, 14.1, 13.6, 13.4, 12.9, 12.8, 11.7, 11.1, 10.5, 10.5, 9.5. HRMS (ESI): calcd for $[C_{45}H_{69}N_5O_9 + Na^+]$ 846.4993, found 846.4991.

*7,39-epi-Lagunamide A (**1**).* Amorphous solid (5.8 mg, 30%; MeOH/H_2O = 86/14, 10 mL/min, 220 nm, RT = 28.132 min). $[\alpha]_D^{25}$ = −32.9 (c 0.2, CH_3OH) {lit[7] $[\alpha]_D^{20}$ = −31.0 (c 0.5, CH_3OH)}. ^{1}H NMR (500 MHz, MeOD): δ 7.28−7.12 (m, 6H), 5.53 (dd, J = 10.6, 5.1 Hz, 1H), 5.10 (dd, J = 10.3, 1.3 Hz, 1H), 4.98 (d, J = 6.1 Hz, 1H), 4.91−4.90 (m, 1H), 4.50 (q, J = 7.0 Hz, 1H), 4.27 (d, J = 18.3 Hz, 1H), 4.06 (td, J = 9.2, 3.5 Hz, 1H), 3.92 (q, J = 6.8 Hz, 1H), 3.34 (d, J = 18.3 Hz, 1H), 3.33 (s, 3H), 3.09−3.02 (m, 1H), 3.05 (s, 3H), 2.97 (dd, J = 14.4, 5.1 Hz, 1H), 2.84 (s, 3H), 2.52−2.45 (m, 1H), 2.28−2.20 (m, 1H), 1.93 (s, 3H), 1.91−1.87 (m, 1H), 1.85−1.76 (m, 3H), 1.56−1.46 (m, 3H), 1.50 (d, J = 6.9 Hz, 3H), 1.40−1.32 (m, 2H), 1.16−1.09 (m, 1H), 1.03 (t, J = 7.4 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.96−0.87 (m, 15H), 0.81 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, MeOD): δ 175.1, 174.0, 173.4, 172.7, 172.5, 170.4, 169.9, 146.4, 138.4, 130.7, 129.1, 128.5, 127.5, 80.0, 77.2, 72.6, 62.1, 55.2, 53.9, 52.8, 46.4, 42.2, 38.8, 38.7, 38.4, 36.5, 36.0, 35.8, 34.8, 30.6, 27.6, 27.4, 26.8, 15.7, 15.2, 14.8, 14.3, 14.2, 12.8, 12.2, 12.0, 10.9, 9.9. HRMS (ESI): calcd for $[C_{45}H_{71}N_5O_{10} + Na^+]$ 864.5099, found 864.5098.

*7,37,39-epi-Lagunamide A (**1b**).* Amorphous solid (6.2 mg, 32%; MeOH/H_2O = 83/17, 10 mL/min, 220 nm, RT = 18.114 min). $[\alpha]_D^{25}$ = −33.2 (c 0.18, $CHCl_3$) {lit[7] $[\alpha]_D^{20}$ = −4.6 (c 0.2, CH_3OH)}. ^{1}H NMR (500 MHz, MeOD): δ 7.28 (dd, J = 11.2, 3.0 Hz, 1H), 7.25−7.10 (m, 5H), 5.51 (dd, J = 10.6, 5.0 Hz, 1H), 4.96−4.94 (m, 1H), 4.94−4.91 (m, 2H), 4.48 (q, J = 7.0 Hz, 1H), 4.24 (d, J = 18.4 Hz, 1H), 3.91−3.83 (m, 2H), 3.31 (s, 3H), 3.22 (d, J = 18.4 Hz, 1H), 3.09−3.03 (m, 1H), 3.05 (s, 3H), 2.96 (dd, J = 14.4, 5.0 Hz, 1H), 2.86 (s, 3H), 2.67−2.61 (m, 1H), 2.23−2.15 (m, 1H), 1.94 (s, 3H), 1.93−1.87 (m, 1H), 1.83−1.72 (m, 3H), 1.53 (d, J = 6.9 Hz, 3H), 1.50−1.42 (m, 2H), 1.41−1.31 (m, 3H), 1.27−1.20 (m, 1H), 1.11 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, MeOD): δ 175.1, 172.8, 172.7, 171.8, 170.6, 170.4, 146.2, 138.4, 130.7, 129.2, 129.1, 127.5, 79.3, 77.1, 73.1, 61.8, 55.2, 54.0, 52.8, 46.5, 42.2, 38.9, 38.8, 38.7, 36.0, 35.9, 35.8, 30.6, 27.7, 27.0, 26.4, 15.5, 15.1, 14.9, 14.4, 12.7, 12.0, 11.9, 11.1, 9.8. HRMS (ESI): calcd for $[C_{45}H_{71}N_5O_{10} + Na^+]$ 864.5099, found 864.5100.

General Procedure for the Synthesis of 1c, 1a, and 1d. Compound **58**, **62**, or **66** (17 mg, 0.014 mmol), $Pd(PPh_3)_4$ (3.5 mg, 2.8 μmol), and PhNHMe (4 mg, 0.035 mmol) were stirred in anhydrous THF (5 mL) for 30 min and diluted with EtOAc (50 mL). The mixture was washed with 1 M aqueous HCl (20 mL × 2), dried, filtered, and concentrated under reduced pressure. Then the residue was treated with Et_2NH (1 mL) in CH_3CN (2 mL) for 15 min. Volatiles were evaporated, and the residue was dissolved in CH_2Cl_2 (14 mL). To this solution were added HATU (54 mg, 0.14 mmol) and DIPEA (35 μL, 0.21 mmol). After being stirred 3 days, the resulting mixture was concentrated, and the residue was treated with 40% aqueous HF (1 mL) in CH_3CN (4 mL) for 1 h. Then the mixture was diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ aqueous solution (30 mL) and brine (50 mL × 2), dried, filtered, and concentrated, and the residue was purified by flash chromatography on silica gel (PE/acetone = 2/1) give the corresponding title compound.

*7-epi-Lagunamide A (**1c**).* Amorphous solid (4.5 mg, 38%; MeOH/H_2O = 90/10, 10 mL/min, 270 nm, RT = 17.690 min). $[\alpha]_D^{21}$ = −64.7 (c 0.04, MeOH). ^{1}H NMR (500 MHz, MeOD): δ 8.38 (d, J = 6.3 Hz, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.26−7.14 (m, 5H), 7.12 (dd, J = 10.1, 3.2 Hz, 1H), 5.54 (dd, J = 10.7, 5.0 Hz, 1H), 5.04 (d, J = 10.0 Hz, 1H), 4.93 (d, J = 3.1 Hz, 1H), 4.84 (t, J = 8.7 Hz, 1H), 4.49 (p, J = 7.0 Hz, 1H), 4.27 (d, J = 18.2 Hz, 1H), 4.06 (td, J = 9.7, 2.4 Hz, 1H), 3.94 (q, J = 6.8 Hz, 1H), 3.38 (s, 3H), 3.31−3.30 (m, 1H), 3.10−3.06 (m, 1H), 3.05 (s, 3H), 2.97 (dd, J = 14.4, 5.0 Hz, 1H), 2.84 (s, 3H), 2.50−2.42 (m, 1H), 2.28−2.19 (m, 1H), 1.93 (s, 3H), 1.91−1.88 (m, 1H), 1.88−1.74 (m, 3H), 1.71−1.62 (m, 1H), 1.52 (d, J = 6.9 Hz, 3H), 1.51−1.45 (m, 2H), 1.40−1.31 (m, 2H), 1.16−1.09 (m, 1H), 0.98 (t, J = 5.9 Hz, 3H), 0.97−0.87 (m, 18H), 0.80 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, MeOD): δ 173.5, 172.6, 172.1, 171.0, 170.9, 168.9, 168.5, 145.0, 136.8, 129.1, 127.5, 127.0, 125.9, 78.6, 75.6, 70.9, 60.7, 53.6, 52.9, 51.1, 44.9, 40.2, 37.5, 37.1, 36.4, 34.8, 34.2, 34.2, 32.5, 29.0, 26.0, 25.2, 23.8, 14.1, 14.0, 13.5, 12.7, 12.6, 11.2, 10.4, 9.6, 9.3, 8.3. HRMS (ESI): calcd for $[C_{45}H_{71}N_5O_{10} + H^+]$ 842.5279, found 842.5277.

*Lagunamide A (**1a**).* Amorphous solid (4.5 mg, 38%; MeOH/H_2O = 83/17, 10 mL/min, 220 nm, RT = 27.959 min). $[\alpha]_D^{25}$ = −34.9 (c 0.04 CH_3OH) {lit $[\alpha]_D^{25}$ = −36 (c 0.5, CH_3OH),[6a] $[\alpha]_D^{20}$ = −33.8 (c 0.1, CH_3OH)[7]}. ^{1}H NMR (500 MHz, MeOD): δ 7.32 (dd, J = 10.5, 2.2 Hz, 1H), 7.22−7.12 (m, 5H), 5.46 (dd, J = 10.5, 5.1 Hz, 1H), 5.06 (d, J = 6.2 Hz, 1H), 4.93−4.92 (m, 1H), 4.87 (d, J = 3.7 Hz, 1H), 4.50 (q, J = 7.0 Hz, 1H), 4.20 (d, J = 18.4 Hz, 1H), 3.95 (q, J = 6.9 Hz, 1H), 3.75 (dd, J = 10.5, 1.8 Hz, 1H), 3.57 (d, J = 18.3 Hz, 1H), 3.30 (s, 3H), 3.08−3.02 (m, 1H), 3.05 (s, 3H), 2.94 (dd, J = 14.4, 5.1 Hz, 1H), 2.89 (s, 3H), 2.30−2.21 (m, 1H), 2.19−2.12 (m, 1H), 2.07−2.01 (m, 1H), 1.91 (s, 3H), 1.89−1.79 (m, 2H), 1.71−1.61 (m, 2H), 1.55−1.47 (m, 1H), 1.42 (d, J = 6.9 Hz, 3H), 1.38−1.29 (m, 3H), 1.17−1.09 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H), 1.00−0.88 (m, 18H), 0.85 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, MeOD): δ 174.9, 173.0, 172.9, 172.7, 172.6, 171.3, 170.4, 146.9, 138.4, 130.7, 129.1, 128.6, 127.5, 79.0, 77.6, 71.5, 60.3, 55.0, 54.7, 52.7, 46.5, 41.3, 39.4, 38.6, 38.4, 37.7, 36.6, 35.9, 30.6, 28.3, 27.5, 24.7, 16.0, 15.6, 14.6, 13.8, 12.9, 12.5, 12.4, 11.9, 11.7, 10.1. HRMS (ESI): calcd for $[C_{45}H_{71}N_5O_{10} + Na^+]$ 864.5099, found 864.5101.

*2-epi-Lagunamide A (**1d**).* Amorphous solid (5.3 mg, 45%; MeOH/H_2O = 86/14, 10 mL/min, 220 nm, RT = 19.035 min). $[\alpha]_D^{25}$ = +3.6 (c 0.46, CH_3OH). ^{1}H NMR (500 MHz, MeOD): δ 7.27−7.13 (m, 5H), 7.06−7.02 (m, 1H), 5.50 (dd, J = 10.4, 5.3 Hz, 1H), 4.97 (d, J = 7.4 Hz, 1H), 4.90−4.88 (m, 1H), 4.87 (d, J = 3.5 Hz, 1H), 4.57−4.47 (m, 2H), 4.24 (d, J = 18.2 Hz, 1H), 3.87−3.81 (m, 1H), 3.53 (d, J = 18.1 Hz, 1H), 3.24 (s, 3H), 3.08−3.02 (m, 1H), 3.04 (s, 3H), 2.96 (dd, J = 14.4, 5.2 Hz, 1H), 2.89 (s, 3H), 2.33−2.24 (m, 1H), 2.21−2.14 (m, 1H), 2.06−2.00 (m, 1H), 1.91 (s, 3H), 1.90−1.86 (m, 2H), 1.77−1.68 (m, 2H), 1.55−1.50 (m, 1H), 1.48 (d, J = 7.3 Hz, 3H), 1.37−1.26 (m, 3H), 1.19−1.12 (m, 1H), 1.00−0.89 (m, 21H), 0.84 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, MeOD): δ 173.33, 172.28, 171.1, 170.9, 170.7, 169.9, 168.7, 144.4, 136.7, 129.1, 127.5, 125.9, 77.5, 76.0, 70.1, 55.9, 53.8, 53.5, 51.1, 44.7, 40.0, 37.6, 37.0, 36.4, 34.8, 34.2, 32.1, 29.5, 29.0, 26.5, 25.9, 23.4, 14.2, 14.1, 13.4, 12.9, 11.5, 11.0, 10.8, 10.4, 9.9, 8.7. HRMS (ESI): calcd for $[C_{45}H_{71}N_5O_{10} + Na^+]$ 864.5099, found 864.5098.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of related compounds and HPLC graphs for crude **27aa** and **27ab** in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Tan, L. T. *Phytochemistry* **2007**, *68*, 954.
(2) (a) Moor, R. E. *J. Ind. Microbiol.* **1996**, *16*, 134. (b) Jaspars, M.; Lawton, L. A. *Curr. Opin. Drug Discovery Dev.* **1998**, *1*, 77. (c) Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, J. G.; Wright, P. C. *Tetrahedron* **2001**, *57*, 9347. (d) Luesch, H.; Williams, P. G.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2002**, *65*, 996. (e) Ouellette, A. J. A.; Wilhelm, S. W. *Front. Ecol. Environ.* **2003**, *1*, 359. (f) Luesch, H.; Chanda, S. K.; Raya, R. M.; DeJesus, P. D.; Orth, A. P.; Walker, J. R.; Belmonte, J. C. I.; Schultz, P. G. *Nat. Chem. Biol.* **2006**, *2*, 158. (g) Matthew, S.; Salvador, L. A.; Schupp, P. J.; Paul, V. J.; Luesch, H. *J. Nat. Prod.* **2010**, *73*, 1544. (h) Tripathi, A.; Fang, W.; Leong, D. T.; Tan, L. T. *Mar. Drugs* **2012**, *10*, 1126.
(3) Linington, R. G.; Clark, B. R.; Trimble, E. E.; Almanza, A.; Ureña, L. D.; Kyle, D. E.; Gerwick, W. H. *J. Nat. Prod.* **2009**, *72*, 14.
(4) (a) Vaishampayan, U.; Glode, M.; Du, W.; Kraft, A.; Hudes, G.; Wright, J.; Hussain, M. *Clin. Cancer Res.* **2000**, *6*, 4205. (b) Edelman, M. J.; Gandara, D. R.; Hausner, P.; Israel, V.; Thornton, D.; DeSanto, J.; Doyle, L. A. *Lung Cancer* **2003**, *39*, 197. (c) Liang, J.; Moore, R. E.; Moher, E. D.; Munroe, J. E.; Al-awar, R. S.; Hay, D. A.; Varie, D. L.; Zhang, T. Y.; Aikins, J. A.; Martinelli, M. J.; Shih, C.; Ray, J. E.; Gibson, L. L.; Vasudevan, V.; Polin, L.; White, K.; Kushner, J.; Simpson, C.; Pugh, S.; Corbett, T. H. *Invest. New Drugs* **2005**, *23*, 213. (d) Luesch, H.; Moore, R. E.; Paul, V. J.; Mooberry, S. L.; Corbett, T. H. *J. Nat. Prod.* **2001**, *64*, 907.
(5) (a) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6883. (b) Gajula, P. K.; Asthana, J.; Panda, D.; Chakraborty, T. K. *J. Med. Chem.* **2013**, *56*, 2235. (c) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 5418. (d) Williams, P. G.; Yoshida, W. Y.; Quon, M. K.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2003**, *66*, 1545. (e) Suenaga, K.; Mutou, T.; Shibata, T.; Itoh, T.; Kigoshi, H.; Yamada, K. *Tetrahedron Lett.* **1996**, *37*, 6771. (f) Sato, S.-I.; Murata, A.; Orihara, T.; Shirakawa, T.; Suenaga, K.; Kigoshi, H.; Uesugi, M. *Chem. Biol.* **2011**, *18*, 131. (g) Nakao, Y.; Yoshida, W. Y.; Takada, Y.; Kimura, J.; Yang, L.; Mooberry, S. L.; Scheuer, P. J. *J. Nat. Prod.* **2004**, *67*, 1332. (h) Umehara, M.; Negishi, T.; Tashiro, T.; Nakao, Y.; Kimura, J. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7422. (i) Ahmed, S.; Riegsecker, S.; Beamer, M.; Rahman, A.; Bellini, J. V.; Bhansali, P.; Tillekeratne, L. M. V. *Toxicol. Appl. Pharmacol.* **2013**, *270*, 87. (j) Taori, K.; Paul, V. J.; Luesch, H. *J. Am. Chem. Soc.* **2008**, *130*, 1806.
(6) (a) Tripathi, A.; Puddick, J.; Prinsep, M. R.; Rottmann, M.; Tan, L. T. *J. Nat. Prod.* **2010**, *73*, 1810. (b) Tripathi, A.; Puddick, J.; Prinsep, M. R.; Rottmann, M.; Chan, K. P.; Chen, D. Y. K.; Tan, L. T. *Phytochemistry* **2011**, *72*, 2369.
(7) Dai, L.; Chen, B.; Lei, H.; Wang, Z.; Liu, Y.; Xu, Z.; Ye, T. *Chem. Commun.* **2012**, *48*, 8697.
(8) (a) Liu, R.-C.; Wei, J.-H.; Wei, B.-G.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2008**, *19*, 2731. (b) Liu, R.-C.; Huang, W.; Ma, J.-Y.; Wei, B.-G.; Lin, G.-Q. *Tetrahedron Lett.* **2009**, *50*, 4046. (c) Wang, X.-L.; Huang, W.-F.; Lei, X.-S.; Wei, B.-G.; Lin, G.-Q. *Tetrahedron* **2011**, *67*, 4919. (d) Huang, W.; Ma, J.-Y.; Yuan, M.; Xu, L.-F.; Wei, B.-G. *Tetrahedron* **2011**, *67*, 7829.
(9) (a) Huang, W.-F.; Li, Q.-R.; Chao, L.-M.; Lei, X.-S.; Wei, B.-G. *Tetrahedron Lett.* **2010**, *51*, 4317. (b) Xarnod, C.; Huang, W.; Ren, R.-G.; Liu, R.-C.; Wei, B.-G. *Tetrahedron* **2012**, *68*, 6688.
(10) (a) Ma, J.-Y.; Xu, L.-F.; Huang, W.-F.; Wei, B.-G.; Lin, G.-Q. *Synlett* **2009**, 1307. (b) Ma, J.-Y.; Huang, W.; Wei, B.-G. *Tetrahedron Lett.* **2011**, *52*, 4598.
(11) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.
(12) Yu, S.; Pan, X.; Ma, D. *Chem.—Eur. J.* **2006**, *12*, 6572.
(13) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639.
(14) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (c) Tidwell, T. T. *Synthesis* **1990**, 857.
(15) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(16) Smith, A. B., III; Lee, D. *J. Am. Chem. Soc.* **2007**, *129*, 10957.
(17) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
(18) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833.
(19) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. *J. Am. Chem. Soc.* **2001**, *123*, 10840.
(20) (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199−2204.
(21) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(22) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367.
(23) (a) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, 286. (b) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535. (c) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822.
(24) Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045.
(25) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567. (c) Raach, A.; Reiser, O. *J. Prakt. Chem.* **2000**, *342*, 605.