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Aurilide, a cytotoxic depsipeptide from the sea hare *Dolabella auricularia*: isolation, structure determination, synthesis, and biological activity

Kiyotake Suenaga,[b,*] Tsuyoshi Mutou,[a] Takunobu Shibata,[a] Takashi Itoh,[a] Tatsuya Fujita,[a] Noboru Takada,[a] Kozue Hayamizu,[a] Masaki Takagi,[a] Taiji Irifune,[a] Hideo Kigoshi[b,*] and Kiyoyuki Yamada[a]

[a]*Department of Chemistry, Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan*
[b]*Department of Chemistry, University of Tsukuba, 1-1-1 Tennoudi, Tsukuba, Ibaraki 305-8571, Japan*

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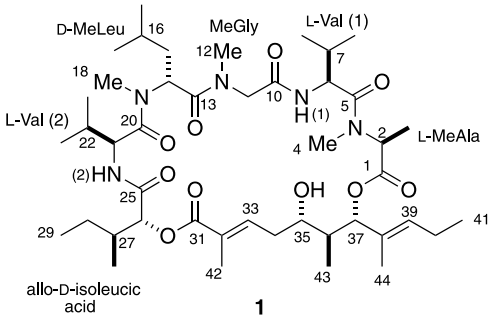
Abstract—The bioassay-guided fractionation of the cytotoxic constituents of the Japanese sea hare *Dollabella auricularia* led to the isolation of aurilide (**1**), a 26-membered cyclodepsipeptide. The gross structure of **1** was established by spectroscopic analysis including 2D NMR techniques. The absolute stereostructure was determined by chiral HPLC analysis of acid hydrolysates of **1** and by the enantioselective synthesis of a degradation product arising from a dihydroxylated fatty acid portion. The enantioselective synthesis of **1** was achieved in 12% overall yield (16 steps) and confirmed the absolute stereostructure of **1**. The cytotoxicity of **1** was evaluated using a synthetic sample, which was found to exhibit potent cytotoxicity against HeLa S_3 cells with an IC_{50} of 0.011 μg/mL. Further biological and pharmacological studies of **1** have been carried out by using synthetic **1**.

1. Introduction

In the 1960s, Pettit and co-workers began intensively investigating the cytostatic and antineoplastic constituents of the Indian Ocean sea hare *Dolabella auricularia*, resulting in the isolation of a number of novel peptide- and depsipeptide-type bioactive compounds termed dolastatins.[1] We have carried out the cytotoxicity-directed examination of the constituents of Japanese specimens of *D. auricularia* and isolated a variety of cytotoxic compounds.[2,3] As part of our study in search for cytotoxic compounds from this animal, the isolation, the structure, and the synthesis of aurilide (**1**), a cytotoxic depsipeptide, have been described in preliminary communications.[4,5] In this article, we report the isolation, the structure determination, and much improved synthesis of aurilide (**1**) together with a discussion of its biological activities, which were evaluated by using synthetic **1**.



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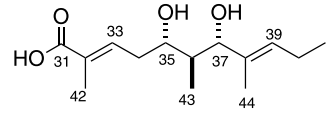

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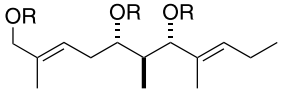

3 R = *p*-BrC_6H_4CO

Keywords: Aurilide; *Dolabella auricularia*; Depsipeptide; Cytotoxicity; Structure determination; Synthesis.
* Corresponding authors. Tel./fax: +81-29-853-4313 (K.S.).; e-mail: suenaga@chem.tsukuba.ac.jp

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2. Results and discussions

2.1. Isolation

The internal organs of the sea hare *D. auricularia*, collected from one site located on the coast of Azuri, Shima peninsula in Mie Prefecture, were extracted with MeOH, and the extracts were partitioned between H_2O and EtOAc. The EtOAc-soluble material was further partitioned between 9:1 MeOH/H_2O and hexane. The material obtained from the aqueous MeOH portion was subjected to cytotoxicity-guided fractionation by repetitive normal- and reversed-phase chromatography and by reversed-phase HPLC to afford aurilide (**1**) as a colorless powder in 1.9×10^{-7}% yield based on wet weight.

2.2. Gross structure

The NMR data (Table 1) coupled with a $[M+Na]^+$ peak at *m/z* 856.5432 ($\Delta+2.0$ mmu) in the HRFABMS of aurilide (**1**) suggested a molecular formula of $C_{44}H_{75}N_5O_{10}$. In the IR spectrum, there were observed bands at 3430, 1735, 1685, 1645, and 1245 cm^{-1} that were assigned to hydroxy, ester, and amide groups. The ^1H NMR data showed the presence of two amide NH groups (δ 7.77 and 6.55) and three *N*-methylamide groups (δ 3.25, 2.91, and 2.57), suggesting the peptidic nature of **1**. Resonances in the ^1H NMR spectrum were assigned by DQF-COSY, HSQC, and HMBC analyses, as shown in Table 1. Although the ^{13}C NMR spectrum could not be obtained due to the scarcity of the sample, carbon chemical shifts were mostly determined by HSQC and HMBC ($J_{CH}=6$ Hz) experiments. These spectroscopic data suggested the presence of five amino acid residues (two valines, *N*-methylglycine, *N*-methylalanine, and *N*-methylleucine), an isoleucic acid residue, and a dihydroxy acid portion (C31–C44). The low-field chemical shift of H-37 (δ 5.18) suggested that the acyloxy group is attached to C37. The stereochemistry of the two trisubstituted olefins of **1** was determined to be *E* on the basis of the ^{13}C chemical shifts of the respective vinyl methyls with *cis* steric interaction (δ_{C42} 12.4 and δ_{C44} 11.1).[6] The degree of unsaturation in **1** suggests the cyclic nature of this molecule. The HMBC correlations shown in Table 1 disclosed two sequences, Val(2)-MeLeu-MeGly and Val(1)-MeAla-**2**. The NOESY correlation of NH(2)/H-26 established the connectivity between isoleucic acid and Val(2). Further evidence for the connectivities of the partial structures could not be obtained from either HMBC experiments or the NOESY data. However, considering the peptidic nature of **1**, the carboxyl carbon (C31) of **2** must be bonded to the hydroxy oxygen atom of isoleucic acid and the carboxyl carbon (C10) of the MeGly should be connected to the amino nitrogen of Val(1). Thus, the gross structure of aurilide is unequivocally shown as **1**.

2.3. Stereochemistry

The absolute stereostructure of **1** was elucidated as follows. Acidic hydrolysis of **1** (9 M HCl, 110 °C, 72 h) followed by reversed-phase HPLC separation afforded four components, MeAla, Val, MeLeu, and isoleucic acid. The absolute configurations of the three components, Val, MeLeu, and isoleucic acid, were determined to be L, D, and allo-D, respectively, by the chiral HPLC analysis. The absolute configuration of MeAla was established to be L by HPLC analysis of the Marfey's derivative.[7] The absolute stereochemistry of three contiguous asymmetric carbons (C35, C36, and C37) in **1** was determined by the enantioselective

Table 1. NMR data for aurilide (**1**) in C_6D_6

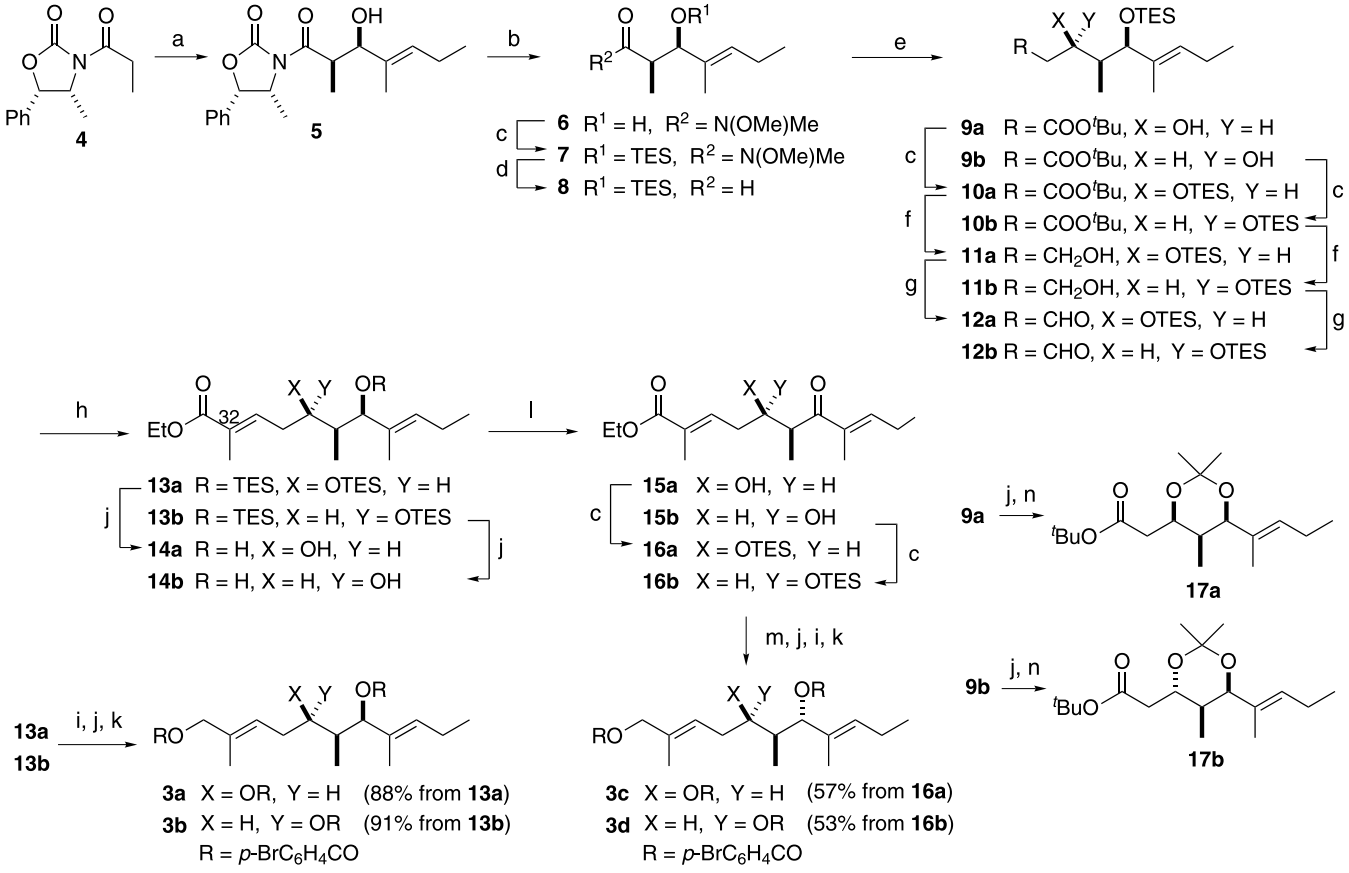
Position	^1H[a]	^{13}C[b]	HMBC[c]	Position	^1H[a]	^{13}C[b]	HMBC[c]
1		169.7	H-2, 3, 37	24	0.85 d (6.6)	18.5	H-23
2	3.10 q (7.0)	59.1	H-3, 4	25		170.0	H-26
3	1.24 d (7.0)	13.6	H-2	26	4.72 d (7.2)	78.5	H-30
4	2.57 s	36.5		27	2.08 m	36.9	H-26, 29, 30
5		172.0	H-2, 4, 6	28a	1.52 m	25.7	H-29, 30
6	5.17 dd (7.0, 7.0)	54.1	H-8, 9	28b	1.14 m		
7	2.08 m	32.7	H-6, 8, 9	29	0.83 t (7.7)	11.5	
8	1.16 d (7.0)	19.9	H-9	30	1.04 d (7.0)	14.8	H-26
9	1.33 d (7.0)	17.8	H-6, 8	31		169.52	H-42
10		169.47	H-11a, 11b	32		128[d]	H-42
11a	4.44 d (17.9)	51.4	H-12	33	7.77 m	145.4	H-34, 42
11b	3.84 d (17.9)			34	2.12 m	30.4	
12	3.25 s	36.4	H-11a, 11b	35	4.00 m	70.9	H-43
13		170.1	H-11b, 12, 14, 15b	36	2.00 m	40.7	H-37, 43
14	5.64 dd (7.0, 7.0)	52.4	H-15a, 15b, 19	37	5.18 d (11.4)	82.2	H-39, 43, 44
15a	2.23 ddd (14.6, 7.0, 7.0)	39.0	H-14, 17, 18	38		131.2	H-37, 40, 44
15b	1.52 ddd (14.6, 7.0, 7.0)			39	5.63 t (7.6)	134.0	H-37. 40, 41, 44
16	1.85 m	25.2	H-17, 18	40	1.95 dt (7.6, 7.6)	21.2	H-41
17	1.07 d (7.0)	23.3	H-15a, 15b, 18	41	0.89 t (7.6)	13.9	H-40
18	1.07 d (7.0)	22.9	H-15a, 15b, 17	42	1.90 s	12.4	
19	2.91 s	30.6	H-14	43	0.62 d (7.0)	9.7	
20		172.1	H-19, 21	44	1.55 s	11.1	H-37, 39
21	4.61 dd (8.8, 8.8)	54.6	H-23, 24	NH (1)	7.77 br d (7.0)		
22	1.98 m	31.1	H-21, 23, 24	NH (2)	6.55 br d (8.8)		
23	0.83 d (6.6)	19.3	H-24				

[a] Recorded at 600 MHz. Coupling constants (Hz) are in parentheses. The signal of one proton (OH) was not observed.
[b] Recorded at 150 MHz by using synthetic **1**.
[c] Recorded at 600 MHz. Parameters were optimized for $J_{CH}=6$ Hz.
[d] Overlapped with the solvent signal.

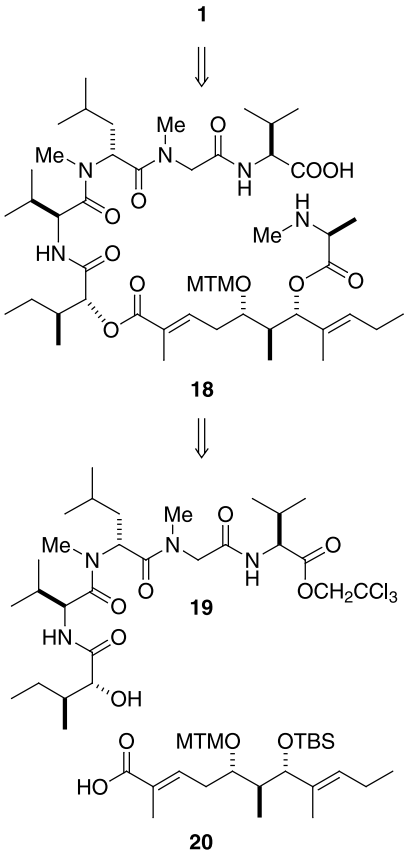
synthesis of tris(*p*-bromobenzoate) **3** that was obtained by the reduction of **1** ($LiAlH_4$, ether) followed by acylation (*p*-BrC_6H_4COCl, pyridine). Thus, the four possible diastereomeric tris(*p*-bromobenzoates) **3a**, **3b**, **3c**, and **3d** were synthesized as follows (Scheme 1). The Evans aldol reaction between imide **4**[8] and *trans*-2-methyl-2-pentenal afforded hydroxy imide **5** in 80% yield as a single diastereomer. Transamidation[9] of **5** (100%) followed by protection of the hydroxy group in **6** provided silyl ether **7** (100%). The amide group in **7** was reduced with DIBAL to give aldehyde **8** (91%). Treatment of **8** with $LiCH_2COO^tBu$ gave a mixture of diastereomeric alcohols **9a** (58%) and **9b** (40%), which could be separated by silica gel column chromatography. The stereochemistry of the hydroxy group in **9a** and **9b** was determined by ^1H and ^{13}C NMR analysis of the derived acetonides **17a** and **17b**, respectively.[10] The hydroxy group in **9a** was silylated to give silyl ether **10a** (99%), which was reduced to alcohol **11a** (94%). Swern oxidation[11] of alcohol **11a** afforded aldehyde **12a** (75%), the Horner–Emmons reaction of which with $(EtO)_2P(O)CH(Me)COOEt$ gave conjugated ester **13a** (88%) along with the 32*Z*-isomer (7%). Reduction of the ester moiety of **13a** followed by desilylation and acylation (*p*-BrC_6H_4COCl, pyridine) yielded tris(*p*-bromobenzoate) **3a** (88% in 3 steps). Tris(*p*-bromobenzoate) **3b** was synthesized from **9b** by the same sequence of reactions as described above. Two other diastereomers, **3c** and **3d**, were also prepared from **13a** and **13b**, respectively. Thus, deprotection of the TES group in **13a** and **13b** gave diols **14a** and **14b**, which were oxidized with MnO_2 to enones **15a** and **15b**, respectively. The hydroxy group of **15a** and **15b** was silylated to give silyl ethers **16a** and **16b**, which were transformed into **3c** and **3d** by the following sequence of reactions: (i) 1,2-reduction of the keto group, (ii) desilylation, (iii) DIBAL reduction, and (iv) *p*-bromobenzoylation. Among the four synthetic diastereomers, **3a**, **3b**, **3c**, and **3d**, the ^1H NMR and the CD spectra of **3d** were identical to those for natural **3**, establishing the absolute stereochemistry of **3**. On the basis of these findings, the complete stereostructure of aurilide was determined as shown in formula **1**.

2.4. Synthesis

Although aurilide (**1**) was isolated from a strongly cytotoxic fraction of the sea hare, the scarcity of the natural supply has prevented the evaluation of its cytotoxicity. To confirm the stereostructure of **1** and to obtain **1** in adequate quantities for biological and pharmacological studies, the enantioselective synthesis of aurilide (**1**) was carried out. A retrosynthetic analysis of aurilide (**1**) is shown in Scheme 2. A key step in the synthesis of aurilide (**1**) is the 26-membered ring



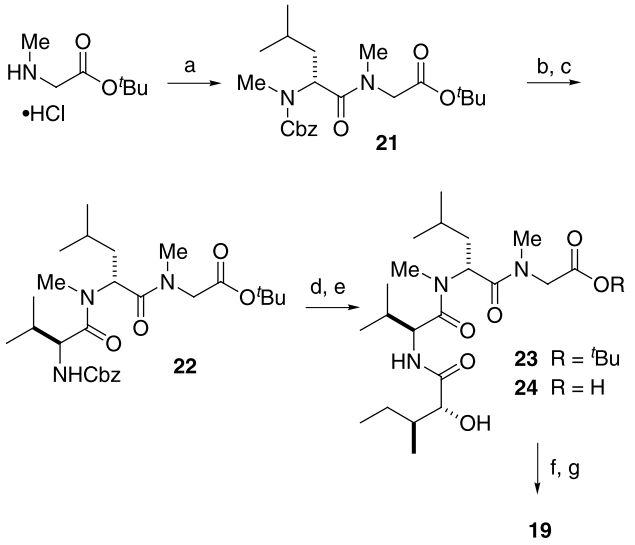
Scheme 1. *Reagents and conditions*: (a) Bu_2BOTf, Et_3N, *trans*-2-methyl-2-pentenal, CH_2Cl_2, −78 °C, 80%; (b) $Me_2AlN(Me)OMe$, THF, toluene, 0 °C, 100%; (c) TESCl, imidazole, DMF, rt, (**7**) 100%, (**10a**) 99%, (**10b**) 95%, (**16a**) 85%, (**16b**) 89%; (d) DIBAL, THF, hexane, −78 °C, 91%; (e) $LiCH_2COO^tBu$, THF, −78 °C, (**9a**) 58%, (**9b**) 40%; (f) DIBAL, CH_2Cl_2, hexane, −23 °C, (**11a**) 94%, (**11b**) 93%; (g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, (**12a**) 75%, (**12b**) 84%; (h) $(EtO)_2P(O)CH(Me)COOEt$, NaH, DME, −23 °C, (**13a**) 88%, (**13b**) 86%; (i) DIBAL, CH_2Cl_2, hexane, −23 °C; (j) HF·pyridine, pyridine, THF, rt, (**14a**) 98%, (**14b**) 98%; (k) *p*-BrC_6H_4COCl, pyridine, rt; (l) MnO_2, CH_2Cl_2, rt, (**15a**) 69%, (**15b**) 60%; (m) $NaBH_4$, $CeCl_3\cdot H_2O$, EtOH, −23 °C; (n) $Me_2C(OMe)_2$, PPTS, acetone, rt.



Scheme 2. Retrosynthetic analysis of aurilide (**1**).

closure. We planned to construct the cyclic structure of **1** by the macrolactamization of amino acid **18**, which was synthesized from pentapeptide **19** and the protected dihydroxy acid **20**.

Pentapeptide **19** was prepared as follows (Scheme 3).

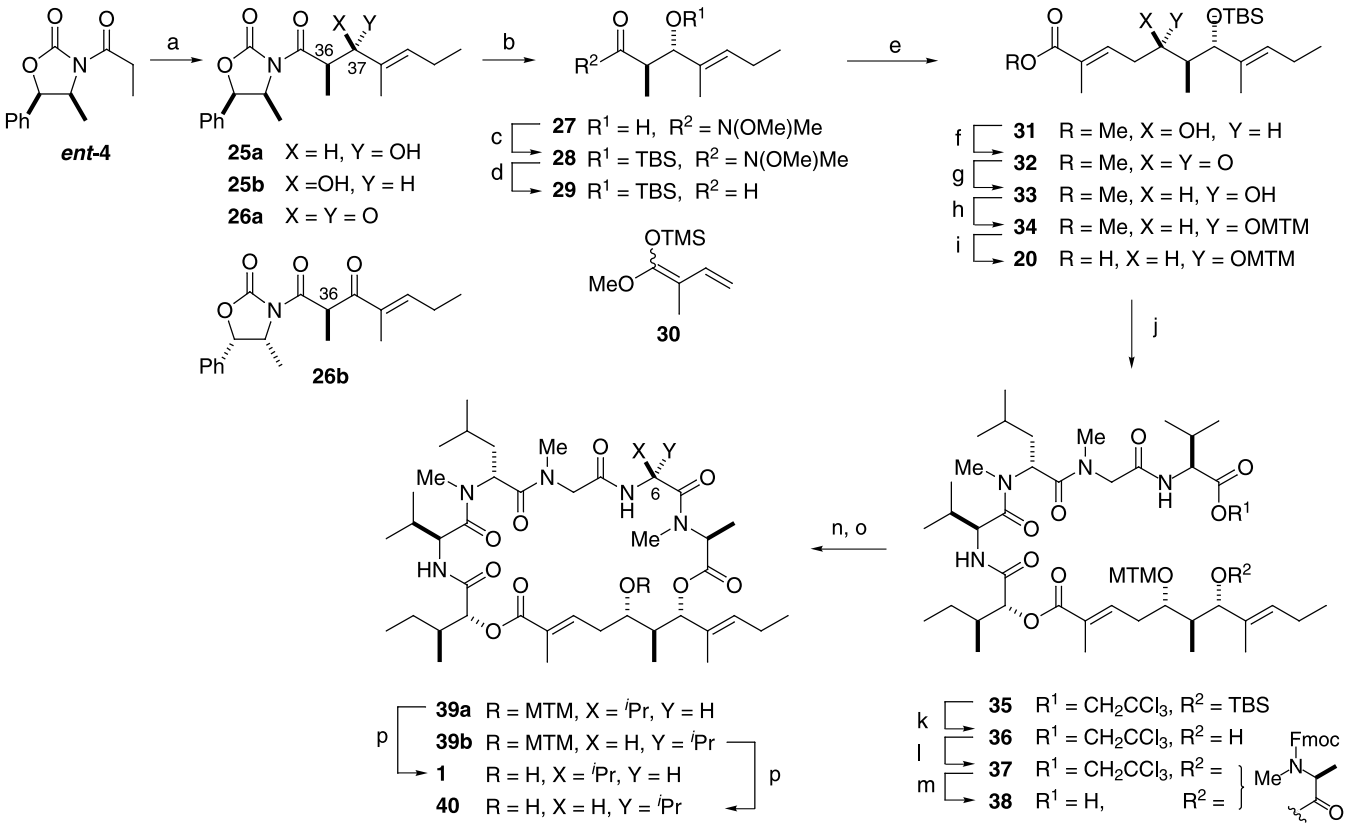


Scheme 3. *Reagents and conditions*: (a) Cbz-D-MeLeu, DEPC, Et_3N, DMF, 0 °C, 98%; (b) H_2, 10% Pd–C, EtOH, rt; (c) Cbz-L-Val, PyBOP, *i*-Pr_2EtN, CH_2Cl_2, rt, 92% (2 steps); (d) H_2, 10% Pd-C, EtOH, CH_2Cl_2, rt; (e) sodium salt of allo-D-isoleucic acid, EDCI·HCl, HOBt, DMF, rt, 95% (2 steps); (f) TMSOTf, 2,6-lutidine, 0 °C, 100%, (g) L-Val-OCH_2CCl_3, EDCI·HCl, HOBt, DMF, CH_2Cl_2, rt, 98%.

Condensation of *N*-methylglycine *tert*-butyl ester hydrochloride and *N*-Cbz-*N*-methyl-D-leucine using DEPC[12] gave dipeptide **21**. Deprotection of the Cbz group of **21** followed by coupling with *N*-Cbz-L-valine using (benzotriazole-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP)[13] afforded tripeptide **22**, which was converted into tetrapeptide **23** by condensation with sodium salt of allo-D-isoleucic acid[14] using EDCI·HCl[15] and 1-hydroxybenztriazole (HOBt).[16] Deprotection of the *tert*-butyl group (TMSOTf, 2,6-lutidine)[17] gave carboxylic acid **24**, which was condensed with L-valine 2,2,2-trichloroethyl ester to provide pentapeptide **19**.

Synthesis of the protected dihydroxy acid **20** began with an anti-selective aldol reaction (Scheme 4).[18] The aldol reaction between imide *ent*-**4** and *trans*-2-methyl-2-pentenal under Heathcock conditions afforded hydroxy imide **25a** (67%) along with the *syn*-isomer **25b** (14%). The stereochemistry of **25a** was determined as follows. Transamidation of **25a** and its *syn*-diastereomer **5** (Scheme 1), which was prepared by Evans aldol reaction, gave diastereomeric amides **27** (84%) and **6**, respectively, indicating that the relative stereochemistry between C36 and C37 in **25a** was *anti*. On the other hand, the oxidation of **25a** and **5** afforded diastereomeric ketones **26a** and **26b**, respectively, establishing that the absolute configuration of C36 in **25a** was *R*. From these results, the stereochemistry of **25a** was determined to be 36*R* and 37*S* (*anti*), as expected from the results of Heathcook and co-workers.[18] The hydroxy group in **27** was silylated to give silyl ether **28** (100%), the amide group of which was reduced with DIBAL to provide aldehyde **29** (93%). The vinylogous Mukaiyama aldol reaction[19] between **29** and silyl ketene acetal **30**[20] afforded methyl ester **31** in 87% yield as a single diastereomer.[21,22] This stereoselectivity can be explained by a transition state model proposed by Evans and co-workers.[23] Configuration inversion of the C35 hydroxy group in **31** was effected as follows: Dess–Martin oxidation[24] of **31** afforded ketone **32** (94%), and reduction of the resulting keto group in **32** stereoselectively ($\alpha/\beta=20/1$) proceeded to give alcohol **33** (82%), which had the desired stereochemistry at C35.[21] Protection of the hydroxy group in **33** was effected by treatment with DMSO, Ac_2O, and AcOH[25] to give (methylthio)methyl (MTM) ether **34** (74%) along with ketone **32** (10%). The ester group of **34** was hydrolyzed with LiOH in aqueous MeOH to afford the protected dihydroxy acid **20** in 89% yield.

The coupling reaction between pentapeptide **19** and the protected dihydroxy acid **20** was effected with EDCI·HCl and DMAP to provide ester **35** (91%), which was converted into alcohol **36** (100%). Esterification of **36** with *N*-Fmoc-*N*-methyl-L-alanine gave the *N*-methylalanine ester **37**[26] (94%), the 2,2,2-trichloroethyl group of which was removed to afford carboxylic acid **38** (97%). Deprotection of the Fmoc group in **38** followed by macrolactamization with EDCI·HCl and 1-hydroxy-7-azabenzotriazole (HOAt)[27] in CH_2Cl_2–DMF (10:1) provided lactam **39a** (66%) along with lactam **39b** (24%), which resulted from epimerization at C6. Macrolactamization with other reagents such as Bop-Cl,[28] PyBOP,[13] DPPA,[29] and EDCI·HCl and HOBt gave lactam **39a** in low yield. Finally, the MTM group in **39a** was removed with $AgNO_3$[30] to give aurilide (**1**) (93%), while



Scheme 4. *Reagents and conditions*: (a) Bu_2BOTf (2 equiv), *i*-Pr_2EtN, *trans*-2-methyl-2-pentenal, Et_2O, −100 °C→−78 °C, 67%; (b) $Me_2AlN(Me)OMe$, THF, toluene, 50 °C, 84%; (c) TBSCl, imidazole, DMF, rt, 100%; (d) DIBAL, THF, hexane, −78 °C, 93%; (e) **30**, $BF_3{\cdot}Et_2O$, CH_2Cl_2–Et_2O (10:1), −78 °C, 87%; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 94%; (g) $NaBH_4$, MeOH, −23 °C, 82%; (h) DMSO, Ac_2O, AcOH, 40 °C, 74%; (i) LiOH, H_2O, MeOH, 30 °C, 89%; (j) **19**, EDCI·HCl, DMAP, CH_2Cl_2, rt, 91%; (k) HF·pyridine, pyridine, THF, 40 °C, 100%; (l) Fmoc-L-MeAla, EDCI·HCl, DMAP, CH_2Cl_2, 0 °C, 94%; (m) Zn, NH_4OAc, THF, H_2O, rt, 97% (n) Et_2NH, MeCN, rt, (o) EDCI·HCl, HOAt, CH_2Cl_2–DMF (10:1), rt, (**39a**) 66%, (**39b**) 24% (2 steps); (p) $AgNO_3$, 2,6-lutidine, THF, H_2O, (**1**) 93%, (**40**) 97%.

6-*epi*-aurilide (**40**) was obtained (97%) from **39b** under identical conditions. Synthetic aurilide (**1**) was found to be identical to natural **1** in all respects, including the spectroscopic (UV, IR, ^1H NMR, MS, and $[\alpha]_D$) and chromatographic properties. Thus, the stereostructure of aurilide was unambiguously confirmed to be that shown in **1**. In comparison with the previous synthesis of **1** reported as a communication[5] in 1997 (overall yield 3.9%), the synthetic procedures have been much improved as regards the present synthesis of **1**, especially in terms of the vinylogous Mukaiyama aldol reaction and macrolactamization (overall yield 12%), resulting in a supply of **1** on a gram scale. The availability of an ample amount of **1** by synthesis enabled us to perform various biological and pharmacological studies of aurilide (**1**). Recently, Takahashi, Doi, and co-workers achieved a solid-phase library synthesis of aurilide (**1**) and related analogs.[31]

2.5. Biological activity

Aurilide (**1**) exhibited strong cytotoxicity against HeLa S_3 tumor cells with an IC_{50} value of 0.011 μg/mL, while the cytotoxicity of 6-*epi*-aurilide (**40**) ($IC_{50}>4$ μg/mL) was much weaker than that of **1**. These results indicated that the cytotoxicity of **1** depends markedly on the stereochemistry at C6 of **1**. Aurilide (**1**) was evaluated in vitro in the NCI 60 cell lines: **1** was found to exhibit a high level of cytotoxicity (the mean panel GI_{50} concentration was 0.12 μg/mL) against the tested cell lines and to be particularly active against ovarian, renal, and prostate cancer cell lines. Interestingly, **1** was not cytocidal but cyctostatic against leukemia cell lines. Aurilide (**1**) showed unusually high in vivo antitumor activity in the NCI's hollow fiber assays,[32] but did not have significant antitumor activity owing to toxicity in the in vivo human tumor xenograft tests. Aurilide (**1**) showed strong microtubule stabilization properties, but the mechanism was different from that of taxol, as determined by immunofluorescence analysis: aurilide (**1**) does not seem to interact directly with tubulin.

3. Conclusion

A novel cytotoxic 26-membered depsipeptide, aurilide (**1**), was isolated from the Japanese sea hare *Dolabella auricularia*. Its structure was established by a combination of spectroscopic analysis, chiral HPLC analysis, and organic synthetic methods. The enantioselective total synthesis of **1** was achieved in 12% overall yield (16 steps). Whereas the natural sample of **1** was obtained from the sea hare *D. auricularia* in sub-milligram quantities, the synthetic sample was available on a gram scale. Aurilide (**1**) was found to reveal a high level of cytotoxicity in vitro against the NCI 60 cell lines and show unusually high in vivo

antitumor activity in the NCI's hollow fiber assays, while **1** did not have significant antitumor activity in the in vivo human tumor xenograft tests. Recently, a structurally related cytotoxin, kulokekahalide-2, has been isolated from the cephalaspidean mollusk *Philinopsis speciosa*.[33]

4. Experimental

4.1. General

Melting points are uncorrected. NMR spectra were measured at 270, 400 or 600 MHz for ^{1}H and 100 or 150 MHz for ^{13}C. *J* values are given in Hz. Both TLC analysis and preparative TLC were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Fuji Silysia silica gel BW-820 MH and FL-60D, and E. Merck aluminum oxide 90 (activity II–III) were used for column chromatography unless otherwise noted. Organic solvents for anhydrous reactions were distilled from the following drying agents: THF and ether (Na-benzophenone ketyl), benzene (Na), triethylamine (calcium hydride), DMSO (calcium hydride under reduced pressure), CH_2Cl_2 (P_2O_5), acetone (anhydrous K_2CO_3), and MeOH (Mg). All moisture-sensitive reactions were performed under an atmosphere of nitrogen.

4.1.1. Extraction and isolation. Specimens of *D. auricularia* (31 kg wet wt) were collected by hand at a depth of 0–1 m on the coast of the Shima Peninsula, Mie Prefecture, Japan, in May 1993 and stored at −20 °C for several months until extraction. The specimens were separated into the internal organs and the thick outer skin, and the former (15.7 kg) was extracted with MeOH (32 L) at room temperature for 5 days. The methanolic extract was concentrated to ca. 2 L in vacuo and extracted with EtOAc (3×2 L). The EtOAc portion (77 g) was dissolved in 9:1 MeOH/H_2O (770 mL), and the solution was washed with hexane (2×770 mL). The aqueous MeOH portion (22.8 g) was chromatographed on silica gel (450 g), using 1:1 toluene/EtOAc (1.8 L) followed by EtOAc (1.8 L) as eluent. The fraction (1.35 g) eluted with EtOAc was then chromatographed on silica gel (70 g, 2:1 hexane/acetone) to give active fraction (447 mg, IC_{50} against HeLa S_3 cells = 3.26 μg/mL). Using the same procedure as described above, the sea hare (76 kg wet wt) collected in 1993 and 1994 were extracted and separated to yield an additional active fraction (2.51 g). They were combined and subjected to RP-MPLC (Develosil ODS 30/60, 70%→100% MeOH). The fraction (1.3 g) eluted with 83–93% MeOH was further separated by RP-MPLC (Develosil ODS 30/60, 80%→100% MeOH). The fraction (139 mg, IC_{50} = 0.45 μg/mL) eluted with 80–87% MeOH was chromatographed on silica gel (8 g, 15:1, 10:1, 5:1 $CHCl_3$–acetone, and acetone, successively). The fraction (48 mg, IC_{50} = 0.28 μg/mL) eluted with 5:1 $CHCl_3$–acetone was further separated by RP-HPLC [Develosil ODS-HG-5 (ϕ10×250 mm), MeCN–MeOH–H_2O 75:5:40→75:5:0, flow rate 2 mL/min]. The fraction (13.5 mg, IC_{50} = 0.091 μg/mL) eluted with 75:5:27–75:5:21 MeCN–MeOH–H_2O was separated by RP-HPLC [Develosil ODS-HG-5 (ϕ10×250 mm), 80% MeOH, flow rate 2 mL/min] to afford an active fraction (2.2 mg, IC_{50} = 0.047 μg/mL t_R = 33–40 min). Using the same procedure as described above, the sea hare (156 kg wet wt) collected in 1991–1995 were extracted and separated to yield an additional active fraction (6.6 mg). They were combined and further separated by RP-HPLC [Develosil ODS-HG-5 (ϕ20×250 mm), 70% MeCN, flow rate 5 mL/min]. The active fraction (1.7 mg, IC_{50} = 0.017 μg/mL, t_R = 47–55 min) was further purified by preparative TLC (silica gel 200×200×0.25 mm, benzene–acetone 3:1) followed by RP-HPLC [Develosil ODS-HG-5 (ϕ20×250 mm), 80% MeOH, flow rate 5 mL/min] to give aurilide (**1**) (0.5 mg, 1.9×10^{-7}%, t_R = 39 min) as a colorless powder. $[\alpha]_D^{25}$ = −17 (*c* 0.058, MeOH); UV (MeOH) λ_{max} 220 nm (sh) (ε 17000); IR ($CHCl_3$) 3430 (br), 1735, 1685, 1645, 1245 cm^{-1}; ^{1}H NMR data, see Table 1; HRMS (FAB) calcd for $C_{44}H_{75}N_5NaO_{10}$ $[(M+Na)^+]$ 856.5412, found 856.5432.

4.1.2. Absolute stereochemistry of the peptide moiety. Aurilide (**1**) (0.26 mg) was treated with 9 M HCl (0.1 mL) at 110 °C for 72 h. The product mixture was diluted with H_2O (1 mL), concentrated, and separated by RP-HPLC [Develosil ODS-HG-5 (ϕ4.6×250 mm), MeCN/H_2O/CF_3COOH 1:99:0.05 (20 min), 1:99:0.05 to 10:90:0.05 (20 min, linear gradient), and then 10:90:0.05 (20 min); flow rate, 1.0 mL/min; detection at 205 nm] to give *N*-methyl-alanine (t_R = 3 min), valine (t_R = 5 min), *N*-methyl leucine (t_R = 21 min), and isoluecic acid (t_R = 55 min). The absolute configurations of three components, MeAla, Val, and isoleucic acid were determined by chiral HPLC analysis: column, CHIRALPAK MA(+) (4.6×50 mm); solvent, 2 mM $CuSO_4$ for Val and MeLeu and 2 mM $CuSO_4$/MeCN 9:1 for isoleucic acid; flow rate, 1.0 mL/min; detection at 254 nm. The retention times (min) of the authentic samples: L-Val (8.0), D-Val (4.0), L-MeLeu (9.0), D-MeLeu (6.7), L-isoleucic acid (64), D-isoleucic acid (39), allo-L-isoleucic acid (52), and allo-D-isoleucic acid (32). A solution of *N*-methyl alanine derived from **1** in H_2O (50 μL) was treated with 1% solution of Marfey's reagent in acetone (20 μL) and 1 M $NaHCO_3$ (5 μL) at 40 °C for 1 h followed by addition of 2 M HCl (2.5 μL). The mixture was analyzed by RP-HPLC [Develosil ODS-HG-5 (4.6×250 mm); solvent, MeOH/0.02 M NaOAc (pH 4.0) 1:1; flow rate 1.0 mL/min; detection at 340 nm]. The retention times (min) of the authentic Marfey derivatives of MeAla: L-MeAla (5.3) and D-MeAla (6.3).

4.1.3. Degradation of aurilide. To a stirred solution of aurilide (**1**) (0.3 mg) in ether (0.2 mL) cooled at 0 °C was added 1 M solution of lithium aluminum hydride in ether (0.01 mL, 0.01 mmol), and the mixture was stirred at room temperature for 1.3 h. The reaction was quenched by addition of ice (1 g) and 1 M HCl, and the mixture was extracted with EtOAc (3×4 mL). The combined extracts were washed with 0.2 M HCl (1 mL), saturated aqueous $NaHCO_3$ (1 mL), and brine (2 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was dissolved in pyridine (0.2 mL) and reacted with *p*-bromobenzoyl chloride (50 mg, 0.23 mmol) at room temperature for 17 h. The mixture was diluted with 5% aqueous $NaHCO_3$ (2 mL), stirred at room temperature for 1 h, and extracted with ether (3×4 mL). The combined extracts were washed with 5% aqueous $NaHCO_3$ (2×3 mL), H_2O (3 mL), and brine (3 mL), successively, dried (Na_2SO_4), and concentrated.

The residual oil was purified by preparative TLC (silica gel 200×100×0.25 mm, hexane–acetone 3:1) followed by HPLC [Develosil 60-5 (ϕ10×250 mm), hexane–EtOAc–MeOH 20:1:0.1, flow rate 2 mL/min, detection UV_{254}] to give tris(*p*-bromobenzoate) **3** (0.05 mg) as a colorless powder: CD (MeOH) λ_{ext} 253 nm ($\Delta\varepsilon$ −56), 238 nm ($\Delta\varepsilon$ +94); ^{1}H NMR (600 MHz, C_6D_6) δ 0.83 (t, J=7.3 Hz, 3H), 0.86 (d, J=7.3 Hz, 3H), 1.50 (s, 3H), 1.54 (s, 3H), 1.80–1.89 (m, 2H), 2.44–2.40 (m, 2H), 2.58 (ddq, J=9.9, 4.4, 7.3 Hz, 1H), 4.42 (d, J=12.5 Hz, 1H), 4.48 (d, J=12.5 Hz, 1H), 5.49 (br t, J=7.3 Hz, 1H), 5.57 (d, J=9.9 Hz, 1H), 5.63–5.58 (m, 2H), 7.61 (d, J=8.4 Hz, 2H), 7.78 (d, J=8.4 Hz, 2H), 7.90 (d, J=8.4 Hz, 2H). The signals due to six protons in **3** were not observed due to the overlap with the solvent signals.

4.1.4. Hydroxy imide 5. To a stirred solution of imide **4** (1.36 g, 5.84 mmol) in CH_2Cl_2 (10 mL) cooled at 0 °C were added 1 M solution of dibutylboron triflate in CH_2Cl_2 (6.4 mL, 6.4 mmol) and triethylamine (1.19 mL, 8.56 mmol), successively. The reaction mixture was stirred at 0 °C for 30 min and cooled to −78 °C. A solution of *trans*-2-methyl-2-pentenal (0.45 mL, 3.9 mmol) in CH_2Cl_2 (2.0 mL, 1.5 mL rinse) was added, and the reaction mixture was stirred at −78 °C for 1.5 h and at 0 °C for 0.5 h. After the reaction was quenched by addition of 0.5 M phosphate buffer (pH 7, 10 mL) and MeOH (20 mL), 30% aqueous hydrogen peroxide (10 mL) in MeOH (20 mL) was added slowly, and the resulting solution was stirred at 0 °C for 1 h. The organic solvents were evaporated, and the mixture was cooled to 0 °C. Saturated aqueous $Na_2S_2O_3$ (15 mL) was added slowly, and the mixture was extracted with ether (2×50 mL). The extracts were combined, washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane–EtOAc 7:1→5:1→4:1) to give **5** (1.03 g, 80% from *trans*-2-methyl-2-pentenal) as colorless crystals along with recovered **4** (459 mg). **5**. mp 96–97 °C (pentane–ether). $[\alpha]_D^{31}$ = +30.6 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3600, 3530 (br), 1780, 1695, 1455, 1345, 1190, 955 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (d, J=6.6 Hz, 3H), 0.99 (t, J=7.6 Hz, 3H), 1.17 (d, J=6.9 Hz, 3H), 1.63 (d, J=0.7 Hz, 3H), 2.08 (dq, J=7.6, 7.6 Hz, 2H), 2.75 (d, J=3.3 Hz, 1H), 3.99 (dq, J=4.0, 6.9 Hz, 1H), 4.36 (m, 1H), 4.77 (dq, J=7.3, 6.6 Hz, 1H), 5.55 (m, 1H), 5.67 (d, J=7.3 Hz, 1H), 7.27–7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3 (q), 13.2 (q), 14.1 (q), 14.3 (q), 20.6 (t), 40.6 (d), 54.9 (d), 75.4 (d), 78.9 (d), 125.6 (d, 2C), 128.1 (d), 128.7 (d, 2C), 128.8 (d), 132.8 (s), 133.1 (s), 152.6 (s), 176.9 (s); MS (FAB) *m/z*, 354 $(M+Na)^+$; HRMS (FAB) calcd for $C_{19}H_{25}NNaO_4$ $[(M+Na)^+]$ 354.1681, found 354.1669. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.90; H, 7.60; N, 4.23. Found C, 68.84; H, 7.69; N, 4.19.

4.1.5. Amide 6. To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (306 mg, 3.14 mmol) in THF (2 mL) cooled at −10 °C was added a 2.0 M solution of trimethylaluminum in toluene (1.5 mL, 3.0 mmol) dropwise. The resulting solution was stirred at 0 °C for 5 min and at room temperature for 15 min. The solution was recooled to 0 °C, and a solution of hydroxy imide **5** (516 mg, 1.56 mmol) in THF (3 mL) was added. The reaction mixture was stirred at 0 °C for 1 h, and transferred into a vigrously stirred mixture of CH_2Cl_2 (7.5 mL) and 0.5 M HCl (7.5 mL) at 0 °C. The resulting two-phase mixture was stirred at 0 °C for 50 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×10 mL). The organic layer and extracts were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (20 g, hexane–EtOAc 3: 1→2:1→EtOAc) to give **6** (339 mg, 100%) as a colorless oil and 4-(*R*)-methyl-5-(*S*)-phenyl-2-oxazolidinone (272 mg) as colorless crystals. **6**. $[\alpha]_D^{27}$ = −8.0 (*c* 1.33, $CHCl_3$); IR ($CHCl_3$) 3430 (br), 1630, 1460, 1420, 1390, 995 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (t, J=7.6 Hz, 3H), 1.10 (d, J=6.9 Hz, 3H), 1.59 (d, J=0.7 Hz, 3H), 2.06 (dq, J=7.6, 7.6 Hz, 2H), 3.07 (m, 1H), 3.20 (s, 3H), 3.72 (s, 3H), 3.80 (br d, J=1.0 Hz, 1H), 4.26 (m, 1H), 5.58 (tq, J=7.6, 0.7 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 10.3 (q), 13.4 (q), 14.1 (q), 20.8 (t), 32.0 (q), 33.3 (d), 61.5 (q), 75.3 (d), 128.0 (d), 132.1 (s). A signal due to carbonyl carbon was not observed; MS (FAB) *m/z* 238 $(M+Na)^+$; HRMS (FAB) calcd for $C_{11}H_{21}NNaO_3$ $[(M+Na)^+]$ 238.1420, found 238.1419.

4.1.6. Silyl ether 7. To a stirred solution of amide **6** (320 mg, 1.49 mmol) in DMF (2 mL) were added imidazole (295 mg, 4.33 mmol) and triethylsilyl chloride (0.3 mL, 1.8 mmol). The mixture was stirred at room temperature for 45 min and diluted with H_2O (6 mL), and the resulting mixture was extracted with hexane (4×8 mL). The combined extracts were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (15 g, hexane–EtOAc 8:1→5:1) to give **7** (489 mg, 100%) as a colorless oil. $[\alpha]_D^{26}$ = +0.9 (*c* 1.58, $CHCl_3$); IR ($CHCl_3$) 1650, 1460, 1420, 1385, 1065, 995, 865 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.57 (q, J=7.9 Hz, 6H), 0.88 (t, J=7.6 Hz, 3H), 0.92 (t, J=7.9 Hz, 9H), 1.18 (d, J=6.9 Hz, 3H), 1.59 (br s, 3H), 1.94 (dq, J=7.3, 7.6 Hz, 2H), 3.08 (s, 3H), 3.13 (m, 1H), 3.61 (s, 3H), 4.10 (d, J=9.2 Hz, 1H), 5.30 (br t, J=7.3 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 4.79 (t, 3C), 6.8 (q, 3C), 11.0 (q), 13.7 (q), 14.8 (q), 20.7 (t), 32.0 (q), 40.4 (d), 61.4 (q), 80.2 (d), 129.2 (d), 135.0 (s), 176.0 (s); MS (FAB) *m/z* 352 $(M+Na)^+$; HRMS (FAB) calcd for $C_{17}H_{35}NNaO_3Si$ $[(M+Na)^+]$ 352.2284, found 352.2293.

4.1.7. Aldehyde 8. To a stirred solution of silyl ether **7** (470 mg, 1.43 mmol) in THF (5 mL) cooled at −78 °C was added a 0.98 M solution of diisobutylaluminum hydride in hexane (2.2 mL, 2.2 mmol) dropwise. The solution was stirred at −78 °C for 2 h, and the reaction was quenched by addition of acetone (0.2 mL). The solution was stirred at −78 °C for 5 min and then transferred into a vigorously stirred mixture of CH_2Cl_2 (20 mL) and 0.5 M tartaric acid (20 mL) at room temperature. The resulting two-phase mixture was stirred at room temperature for 30 min. The layers were separated, and the aqueous layer was extracted with EtOAc (2×20 mL). The organic layer and the extracts were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (15 g, hexane–EtOAc 50:1→30:1) to give **8** (350 mg, 91%) as a colorless oil. $[\alpha]_D^{26}$ = −2.3 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 2730, 1720, 1455, 1215, 1070, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (q,

J=7.8 Hz, 6H), 0.93 (t, J=7.8 Hz, 9H), 0.95 (t, J=7.8 Hz, 3H), 1.03 (d, J=6.8 Hz, 3H), 1.57 (br s, 3H), 1.94–2.10 (m, 2H), 2.51 (ddq, J=2.0, 6.8, 6.8 Hz, 1H), 4.25 (d, J=6.8 Hz, 1H), 5.40 (br t, J=6.8 Hz, 1H), 9.66 (d, J=2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.8 (t, 3C), 6.8 (q, 3C), 9.2 (q), 12.0 (q), 13.8 (q), 20.7 (t), 51.0 (d), 77.9 (d), 129.4 (d), 134.2 (s), 204.7 (d); MS (FAB) m/z 293 $[(M+Na)]^+$; HRFABMS calcd for $C_{15}H_{30}NaO_2Si$ $[(M+Na)]^+$ 293.1913, found 293.1910.

4.1.8. Aldols 9a and 9b. To a 0.5 M solution of lithium diisopropylamide prepared from diisopropylamine (0.36 mL, 2.6 mmol), a 1.58 M solution of BuLi in hexane (1.6 mL, 2.5 mmol), and THF (3.0 mL) at −78 °C was added *tert*-butyl acetate (0.38 mL, 2.82 mmol), and the mixture was stirred at −78 °C for 25 min. A solution of aldehyde **8** (344 mg, 1.27 mmol) in THF (3 mL) was added, and the resulting mixture was stirred at −78 °C for 45 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (8 mL), and the mixture was extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 30 g, benzene→benzene–EtOAc 50:1) to give **9a** (286 mg, 58%) and **9b** (196 mg, 40%) as a colorless oil, respectively.

Compound **9a**. $[\alpha]_D^{26}$=+9.1 (c 1.36, $CHCl_3$); IR ($CHCl_3$) 3520 (br), 1715, 1455, 1370, 1240, 1155, 1010, 870 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (q, J=7.8 Hz, 6H), 0.93 (d, J=6.8 Hz, 3H), 0.94 (t, J=7.8 Hz, 9H), 0.97 (t, J=7.8 Hz, 3H), 1.45 (s, 9H), 1.54 (br s, 3H), 1.98–2.11 (m, 3H), 2.26 (dd, J=3.9, 16.1 Hz, 1H), 2.49 (dd, J=9.3, 16.1 Hz, 1H), 2.71 (d, J=3.4 Hz, 1H), 4.00 (m, 1H), 4.01 (d, J=7.3 Hz, 1H), 5.40 (br t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 6.9 (q, 3C), 8.1 (q), 11.7 (q), 13.8 (q), 20.8 (t), 28.1 (q, 3C), 41.0 (t), 41.1 (d), 68.9 (d), 80.8 (s), 81.0 (d), 129.1 (d), 135.0 (s), 172.1 (s); MS (FAB) m/z 409 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{42}NaO_4Si$ $[(M+Na)^+]$ 409.2750, found 409.2729.

Compound **9b**. $[\alpha]_D^{26}$=−5.5 (c 1.36, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1715, 1460, 1370, 1240, 1155, 1010, 870 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (q, J=7.8 Hz, 6H), 0.79 (d, J=6.8 Hz, 3H), 0.94 (t, J=7.8 Hz, 9H), 0.96 (t, J=7.8 Hz, 3H), 1.46 (s, 9H), 1.57 (br s, 3H), 1.73 (m, 1H), 2.03 (dq, J=7.3, 7.3 Hz, 2H), 2.39 (dd, J=9.3, 16.1 Hz, 1H), 2.45 (dd, J=2.9, 16.1 Hz, 1H), 3.48 (d, J=3.9 Hz, 1H), 3.86 (m, 1H), 4.13 (d, J=4.4 Hz, 1H), 5.36 (br t, J=7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.8 (t, 3C), 6.9 (q, 3C), 10.2 (q), 12.8 (q), 13.4 (q), 20.8 (t), 28.1 (q, 3C), 39.7 (t), 41.9 (d), 69.6 (d), 78.2 (d), 81.0 (s), 128.2 (d), 134.9 (s), 172.7 (s); MS (FAB) m/z 409 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{42}NaO_4Si$ $[(M+Na)^+]$ 409.2750, found 409.2774.

4.1.9. Silyl ethers 10a and 10b. To a stirred solution of aldol **9a** (84.3 mg, 0.218 mmol) in DMF (0.2 mL) were added imidazole (68.0 mg, 1.00 mmol) and triethylsilyl chloride (0.07 mL, 0.42 mmol). The mixture was stirred at room temperature for 1.5 h and diluted with H_2O (2 mL), and the resulting mixture was extracted with hexane (3× 5 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–benzene 3:1→2:1) to give **10a** (105 mg, 99%) as a colorless oil. Using the same procedure as described above, **10b** (70.1 mg, 95%) was obtained from **9b** (40.0 mg, 0.15 mmol) as a colorless oil.

Compound **10a**. $[\alpha]_D^{27}$=+2.0 (c 1.20, $CHCl_3$); IR ($CHCl_3$) 1715, 1455, 1370, 1240, 1155, 1035, 1010, 870 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52–0.62 (m, 12H), 0.92 (t, J=8.3 Hz, 9H), 0.93 (d, J=6.8 Hz, 3H), 0.95 (t, J=7.8 Hz, 9H), 0.98 (t, J=7.3 Hz, 3H), 1.45 (s, 9H), 1.53 (br s, 3H), 1.62 (m, 1H), 2.00 (ddq, J=7.3, 14.6, 7.3 Hz, 1H), 2.08 (ddq, J=7.3, 14.6, 7.3 Hz, 1H), 2.38 (dd, J=5.9, 14.6 Hz, 1H), 2.44 (dd, J=7.8, 14.6 Hz, 1H), 3.91 (d, J=8.8 Hz, 1H), 4.00 (ddd, J=2.0, 5.9, 7.8 Hz, 1H), 5.32 (br dd, J=7.3, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (t, 3C), 5.4 (t, 3C), 6.9 (q, 3C), 7.0 (q, 3C), 8.9 (q), 10.9 (q), 13.8 (q), 20.8 (t), 28.1 (q, 3C), 41.3 (d), 42.4 (t), 69.2 (d), 80.21 (s), 80.24 (d), 129.8 (d), 135.9 (s), 170.7 (s); MS (FAB) m/z 523 $(M+Na)^+$.

Compound **10b**. $[\alpha]_D^{26}$=−24.8 (c 0.81, $CHCl_3$); IR ($CHCl_3$) 1725, 1460, 1370, 1240, 1160, 1050, 1010 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.49–0.62 (m, 12H), 0.91 (t, J=7.3 Hz, 3H), 0.92 (t, J=7.9 Hz, 9H), 0.93 (t, J=7.9 Hz, 9H), 0.96 (d, J=6.8 Hz, 3H), 1.43 (s, 9H), 1.60 (br s, 3H), 1.81 (m, 1H), 2.02 (dq, J=7.3, 7.3 Hz, 2H), 2.15–2.29 (m, 2H), 3.58 (d, J=8.9 Hz, 1H), 4.03 (ddd, J=3.6, 3.6, 7.6 Hz, 1H), 5.23 (br t, J=6.8 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.1 (t, 3C), 6.90 (q, 3C), 6.93 (q, 3C), 10.1 (q), 11.2 (q), 13.7 (q), 20.8 (t), 28.1 (q, 3C), 38.5 (t), 43.4 (d), 69.6 (d), 79.8 (s), 81.2 (d), 129.5 (d), 135.2 (s), 171.3 (s); MS (FAB) m/z 523 $(M+Na)^+$.

4.1.10. Alcohols 11a and 11b. To a stirred solution of silyl ether **10a** (70.7 mg, 0.141 mmol) in CH_2Cl_2 (1 mL) cooled at −23 °C was added a 0.98 M solution of diisobutylaluminum hydride in hexane (0.72 mL, 0.71 mmol), and the mixture was stirred at −23 °C for 2 h. The reaction was quenched by addition of acetone (0.1 mL) and saturated aqueous Na/K tartrate (5 mL), and the mixture was stirred at room temperature for 45 min and extracted with hexane (3×8 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–ether 9:1→5:1) to give **11a** (57.3 mg, 94%) as a colorless oil. Using the same procedure as described above, **11b** (51.8 mg, 93%) was obtained from **10b** (65.1 mg, 0.130 mmol) as a colorless oil.

Compound **11a**. $[\alpha]_D^{27}$=−0.4 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3630, 3480 (br), 1460, 1415, 1380, 1235, 1035, 1005, 870 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, J=7.8 Hz, 6H), 0.59 (q, J=7.8 Hz, 6H), 0.91 (d, J=6.8 Hz, 3H), 0.92 (t, J=7.8 Hz, 9H), 0.95 (t, J=7.8 Hz, 9H), 0.97 (t, J=7.3 Hz, 3H), 1.51 (br s, 3H), 1.65 (ddq, J=3.4, 7.3, 6.8 Hz, 1H), 1.72–1.85 (m, 2H), 1.90 (br s, 1H), 1.93–2.12 (m, 2H), 3.61 (ddd, J=6.3, 6.3, 10.7 Hz, 1H), 3.71 (ddd, J=6.3, 6.3, 10.7 Hz, 1H), 3.77 (ddd, J=3.4, 5.9, 5.9 Hz, 1H), 3.93 (d, J=7.3 Hz, 1H), 5.34 (br t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (t, 3C), 5.4 (t, 3C), 6.9 (q, 3C), 7.0 (q, 3C), 9.5 (q), 11.6 (q),13.9 (q), 20.8 (t), 37.4 (t),

40.8 (d), 60.2 (t), 71.0 (d), 79.5 (d), 129.3 (d), 135.6 (s); MS (FAB) *m/z* 453 $(M+Na)^+$; HRMS (FAB) calcd for $C_{23}H_{50}NaO_3Si_2$ $[(M+Na)^+]$ 453.3196, found 453.3196.

Compound **11b**. $[\alpha]_D^{30}=-31.4$ (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 3510 (br), 1455, 1415, 1240, 1045, 1005, 870, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, $J=7.8$ Hz, 6H), 0.60 (q, $J=7.8$ Hz, 6H), 0.92 (t, $J=7.8$ Hz, 9H), 0.94 (t, $J=7.3$ Hz, 3H), 0.95 (t, $J=7.8$ Hz, 9H), 0.97 (d, $J=6.8$ Hz, 3H), 1.48 (m, 1H), 1.60 (br s, 3H), 1.65 (m, 1H), 1.82 (ddq, $J=3.4$, 9.8, 6.8 Hz, 1H), 2.01 (dq, $J=7.3$, 7.3 Hz, 2H), 2.19 (br s, 1H), 3.59 (d, $J=9.8$ Hz, 1H), 3.60–3.74 (m, 3H), 5.22 (br t, $J=7.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.1 (t, 3C), 6.8 (q, 3C), 6.9 (q, 3C), 10.0 (q), 10.9 (q), 13.7 (q), 20.7 (t), 32.7 (t), 43.4 (d), 61.8 (t), 72.4 (d), 81.3 (d), 129.5 (d), 135.4 (s); MS (FAB) *m/z* 453 $(M+Na)^+$; HRMS (FAB) calcd for $C_{23}H_{50}NaO_3Si_2$ $[(M+Na)^+]$ 453.3196, found 453.3180.

4.1.11. Aldehydes 12a and 12b. To a stirred solution of oxalyl chloride (0.020 mL, 0.23 mmol) in CH_2Cl_2 (1.0 mL) cooled at −78 °C was added a 1.4 M solution of DMSO in CH_2Cl_2 (0.50 mL, 0.71 mmol) dropwise. The resulting solution was stirred at −78 °C for 5 min, and a solution of alcohol **11a** (63.0 mg, 0.147 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was stirred at −78 °C for 20 min, and triethylamine (0.20 mL, 1.43 mmol) was added. The resulting mixture was stirred at −78 °C for 40 min, warmed to 0 °C, and stirred for 40 min. The mixture was diluted with H_2O (3 mL) and extracted with hexane (3× 6 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (1 mL) and brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–CH_2Cl_2 2:1) to give **12a** (47.5 mg, 75%) as a colorless oil. Using the same procedure as described above, **12b** (42.5 mg, 84%) was obtained from **11b** (50.8 mg, 0.118 mmol) as a colorless oil.

Compound **12a**. $[\alpha]_D^{27}=+4.2$ (*c* 1.31, $CHCl_3$); IR ($CHCl_3$) 2730, 1720, 1460, 1415, 1240, 1035, 1005, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, $J=7.8$ Hz, 6H), 0.57 (q, $J=7.8$ Hz, 6H), 0.92 (d, $J=6.8$ Hz, 3H), 0.92 (t, $J=7.8$ Hz, 9H), 0.94 (t, $J=7.8$ Hz, 9H), 0.98 (t, $J=7.3$ Hz, 3H), 1.53 (br s, 3H), 1.62 (ddq, $J=3.4$, 7.3, 6.8 Hz, 1H), 1.95–2.13 (m, 2H), 2.59 (ddd, $J=2.4$, 6.4, 16.1 Hz, 1H), 2.64 (ddd, $J=2.4$, 6.4, 16.1 Hz, 1H), 3.97 (d, $J=7.3$ Hz, 1H), 4.13 (ddd, $J=3.4$, 6.4, 6.4 Hz, 1H), 5.35 (br t, $J=6.8$ Hz, 1H), 9.75 (t, $J=2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (t, 3C), 5.3 (t, 3C), 6.89 (q, 3C), 6.92 (q, 3C), 9.4 (q), 11.6 (q), 13.8 (q), 20.2 (t), 42.3 (d), 49.8 (t), 68.2 (d), 79.0 (d), 129.6 (d), 135.6 (s), 201.7 (d); MS (FAB) *m/z* 451 $(M+Na)^+$; HRMS (FAB) calcd for $C_{23}H_{48}NaO_3Si_2$ $[(M+Na)^+]$ 451.3040, found 451.3020.

Compound **12b**. $[\alpha]_D^{30}=-31.2$ (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 2730, 1725, 1460, 1415, 1240, 1055, 1005, 870, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, $J=7.8$ Hz, 6H), 0.56 (q, $J=7.8$ Hz, 6H), 0.92 (t, $J=7.8$ Hz, 9H), 0.94 (t, $J=7.3$ Hz, 3H), 0.94 (t, $J=7.8$ Hz, 9H), 0.96 (d, $J=6.8$ Hz, 3H), 1.61 (br s, 3H), 1.88 (ddq, $J=3.4$, 9.3, 6.8 Hz, 1H), 2.02 (dq, $J=7.3$, 7.3 Hz, 2H), 2.24 (ddd, $J=2.0$, 2.4, 15.6 Hz, 1H), 2.46 (ddd, $J=3.4$, 9.3, 15.6 Hz, 1H), 3.55 (d, $J=9.3$ Hz, 1H), 4.09 (ddd, $J=2.4$, 3.4, 9.3 Hz, 1H), 5.23 (br t, $J=7.3$ Hz, 1H), 9.72 (dd, $J=2.0$, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.0 (t, 3C), 6.8 (q, 3C), 6.9 (q, 3C), 10.0 (q), 11.0 (q), 13.7 (q), 20.7 (t), 43.4 (d), 45.6 (t), 68.2 (d), 81.2 (d), 129.8 (d), 135.2 (s), 202.6 (d); MS (FAB) *m/z* 451 $(M+Na)^+$; HRMS (FAB) calcd for $C_{23}H_{48}NaO_3Si_2$ $[(M+Na)^+]$ 451.3040, found 451.3044.

4.1.12. Conjugated esters 13a and 13b. To a stirred solution of triethyl 2-phosphonopropionate (110 mg, 0.462 mmol) in DME (1.8 mL) cooled at 0 °C was added NaH (10.9 mg of 60% dispersion in mineral oil, 0.273 mmol). The resulting solution was stirred at 0 °C for 5 min and at room temperature for 20 min and re-cooled to −20 °C. A solution of aldehyde **12a** (47.0 mg, 0.110 mmol) in DME (1 mL) was added dropwise, and the mixture was stirred at −10 °C for 1 h. Saturated aqueous NH_4Cl (4 mL) was added, and the mixture was extracted with hexane (3× 6 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 10 g, hexane–ether 100:1) to give **13a** (49.7 mg, 88%) as a colorless oil along with 32*Z* isomer of **13a** (4.1 mg, 7%). Using the same procedure as described above, **13b** (42.5 mg, 86%) was obtained from **12b** (41.5 mg, 0.097 mmol) as a colorless oil along with with 32*Z* isomer of **13b** (6.2 mg, 12%).

Compound **13a**. $[\alpha]_D^{26}=+18.8$ (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 1700, 1650, 1460, 1370, 1280, 1220, 1095, 1005, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, $J=7.8$ Hz, 6H), 0.57 (q, $J=7.8$ Hz, 6H), 0.92 (d, $J=6.4$ Hz, 3H), 0.92 (t, $J=7.8$ Hz, 9H), 0.95 (t, $J=7.8$ Hz, 9H), 0.98 (t, $J=7.8$ Hz, 3H), 1.28 (t, $J=7.3$ Hz, 3H), 1.47 (br s, 3H), 1.56 (m, 1H), 1.83 (br s, 3H), 1.99 (ddq, $J=7.8$, 7.8, 14.6 Hz, 1H), 2.07 (ddq, $J=7.8$, 7.8, 14.6 Hz, 1H), 2.31 (ddd, $J=5.9$, 6.8, 14.6 Hz, 1H), 2.39 (ddd, $J=8.3$, 8.3, 14.6 Hz, 1H), 3.69 (ddd, $J=2.4$, 5.9, 8.3 Hz, 1H), 3.88 (d, $J=8.8$ Hz, 1H), 4.11–4.23 (m, 2H), 5.33 (br t, $J=6.8$ Hz, 1H), 6.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.5 (t, 3C), 6.9 (q, 3C), 7.0 (q, 3C), 9.0 (q), 10.9 (q), 12.6 (q), 13.8 (q), 14.2 (q), 20.8 (t), 35.2 (t), 40.9 (d), 60.4 (t), 71.4 (d), 80.4 (d), 129.0 (s), 130.0 (d), 135.7 (s), 138.8 (d), 167.9 (s); MS (FAB) *m/z* 535 $(M+Na)^+$; HRMS (FAB) calcd for $C_{28}H_{56}NaO_4Si_2$ $[(M+Na)^+]$ 535.3615, found 535.3607.

32Z Isomer of **13a**. $[\alpha]_D^{30}=+1.4$ (*c* 0.49, $CHCl_3$); IR ($CHCl_3$) 1705, 1645, 1455, 1380, 1235, 1005, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.52–0.61 (m, 12H), 0.90 (d, $J=6.8$ Hz, 3H), 0.92 (t, $J=7.8$ Hz, 9H), 0.95 (t, $J=7.8$ Hz, 9H), 0.97 (t, $J=7.3$ Hz, 3H), 1.30 (t, $J=7.3$ Hz, 3H), 1.48 (br s, 3H), 1.56 (m, 1H), 1.88 (d, $J=1.5$ Hz, 3H), 1.99 (ddq, $J=7.3$, 14.6, 7.3 Hz, 1H), 2.06 (ddq, $J=7.3$, 14.6, 7.3 Hz, 1H), 2.6 1–2.77 (m, 2H), 3.65 (ddd, $J=2.4$, 5.4, 8.3 Hz, 1H), 3.88 (d, $J=8.8$ Hz, 1H), 4.19 (q, $J=7.3$ Hz, 2H), 5.33 (br t, $J=7.3$ Hz, 1H), 5.82 (tq, $J=6.4$, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.5 (t, 3C), 6.9 (q, 3C), 7.0 (q, 3C), 8.9 (q), 11.1 (q), 13.9 (q), 14.2 (q), 20.8 (t), 20.9 (q), 35.6 (t), 40.7 (d), 60.1 (t), 72.0 (d), 80.2 (d), 128.5 (s), 129.7 (d), 135.6 (s), 138.3 (d), 167.9 (s); MS (FAB) *m/z* 535 $(M+Na)^+$.

Compound **13b**. $[\alpha]_D^{27}=-38.2$ (*c* 1.10, $CHCl_3$); IR ($CHCl_3$) 1700, 1650, 1460, 1370, 1285, 1240, 1050, 1010 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 0.54 (q, J=7.8 Hz, 6H), 0.56 (q, J=7.8 Hz, 6H), 0.92 (t, J=7.8 Hz, 9H), 0.93 (t, J=7.8 Hz, 9H), 0.95 (t, J=7.3 Hz, 3H), 0.99 (d, J=6.8 Hz, 3H), 1.27 (t, J=7.3 Hz, 3H), 1.59 (br s, 3H), 1.81 (d, J=1.0 Hz, 3H), 1.85 (ddq, J=3.4, 9.3, 6.8 Hz, 1H), 2.01 (dq, J=7.3, 7.3 Hz, 2H), 2.11 (ddd, J=2.9, 7.3, 15.1 Hz, 1H), 2.21 (ddd, J=7.3, 9.3, 15.1 Hz, 1H), 3.57 (ddd, J=2.9, 3.4, 9.3 Hz, 1H), 3.65 (d, J=9.3 Hz, 1H), 4.17 (q, J=7.3 Hz, 2H), 5.25 (br t, J=7.3 Hz, 1H), 6.78 (ddq, J=7.3, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.0 (t, 3C), 6.8 (q, 3C), 6.9 (q, 3C), 10.1 (q), 10.9 (q), 12.6 (q), 13.7 (q), 14.2 (q), 20.8 (t), 30.8 (t), 43.9 (d), 60.3 (t), 71.8 (d), 81.3 (d), 128.2 (s), 129.6 (d), 135.7 (s), 140.6 (d), 168.1 (s); MS (FAB) m/z 535 $(M+Na)^+$; HRMS (FAB) calcd for $C_{28}H_{56}NaO_4Si_2$ $[(M+Na)^+]$ 535.3615, found 535.3605.

32Z isomer of **13b**. $[\alpha]_D^{27}=-46.9$ (c 0.58, $CHCl_3$); IR ($CHCl_3$) 1700, 1650, 1455, 1415, 1375, 1050, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, J=7.8 Hz, 12H), 0.91 (t, J=7.3 Hz, 3H), 0.92 (t, J=7.8 Hz, 9H), 0.93 (t, J=7.8 Hz, 9H), 0.95 (d, J=7.3 Hz, 3H), 1.31 (t, J=7.3 Hz, 3H), 1.56 (br s, 3H), 1.81 (m, 1H), 1.88 (d, J=1.0 Hz, 3H), 1.99 (dq, J=7.3, 7.3 Hz, 2H), 2.48–2.61 (m, 2H), 3.52 (ddd, J=3.9, 3.9, 7.8 Hz, 1H), 3.67 (d, J=9.3 Hz, 1H), 4.19 (q, J=7.3 Hz, 2H), 5.24 (br t, J=7.3 Hz, 1H), 5.97 (tq, J=6.8, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.1 (t, 3C), 6.87 (q, 3C), 6.89 (q, 3C), 10.1 (q), 10.9 (q), 13.7 (q), 14.3 (q), 20.8 (t), 20.9 (q), 31.6 (t), 43.8 (d), 60.0 (t), 72.3 (d), 81.0 (d), 127.3 (s), 129.3 (d), 135.5 (s), 141.5 (d), 168.0 (s); MS (FAB) m/z 535 $(M+Na)^+$.

4.1.13. Tris(*p*-bromobenzoates) 3a and 3b. To a stirred solution of conjugated ester **13a** (15.2 mg, 0.030 mmol) in CH_2Cl_2 (0.5 mL) cooled at −78 °C was added a 1.0 M solution of diisobutylaluminum hydride in hexane (0.12 mL, 0.12 mmol), and the mixture was stirred at −78 °C for 1.5 h. The reaction was quenched by addition of methanol (0.05 mL) and saturated aqueous Na/K tartrate (5 mL), and the mixture was stirred at room temperature for 1 h and extracted with EtOAc (3×6 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated to give a crude alcohol (14.1 mg) as a colorless oil, which was employed in the next experiment without purification. A solution of the crude alcohol (14.1 mg) in a 1:3:5 mixture of HF·pyridine, pyridine, and THF (0.5 mL) was stirred at room temperature for 45 min. The mixture was diluted with EtOAc (2 mL) and poured into saturated aqueous $NaHCO_3$ (5 mL) cooled at 0 °C, and the resulting mixture was extracted with EtOAc (3×5 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated to give a crude triol (8.9 mg) as a colorless oil, which was employed in the next experiment without purification. To a stirred solution of the crude triol (8.9 mg) in pyridine (0.2 mL) was added *p*-bromobenzoyl chloride (80.0 mg, 0.37 mmol). The mixture was stirred at room temperature for 13 h, diluted with hexane (1 mL), and filtered through a cotton plug, and the residue was washed with hexane (5 mL) The filtrate and the washings were combined and treated with 5% aqueous $NaHCO_3$ (3 mL) at room temperature for 30 min. The layers were separated, and the aqueous layer was extracted with hexane (2× 6 mL). The organic layer and the extracts were combined, washed with 5% aqueous $NaHCO_3$ (2×1 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 2 g, hexane–CH_2Cl_2 3:1→2:1→1:1) to give **3a** (20.7 mg, 88% from **13a**) as colorless crystals. Using the same procedure as described above, **3b** (13.5 mg, 90%) was obtained from **13b** (7.0 mg, 0.014 mmol) as a colorless oil.

Compound **3a**. mp 106.0–107.5 °C (hexane–CH_2Cl_2). $[\alpha]_D^{29}=+2.8$ (c 0.28, $CHCl_3$); CD (MeOH); λ_{ext} 253 ($\Delta\varepsilon$ +45.0), 236 nm ($\Delta\varepsilon$ −52.1); UV (MeOH) λ_{max} 244 nm (ε 54500); IR ($CHCl_3$) 1715, 1590, 1485, 1395, 1270, 1115, 1105, 1010, 940 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 0.81 (t, J=7.3 Hz, 3H), 1.17 (d, J=7.0 Hz, 3H), 1.56 (br s, 3H), 1.58 (br s, 3H), 1.82 (ddq, J=7.3, 15.0, 7.3 Hz, 1H), 1.91 (ddq, J=7.3, 15.0, 7.3 Hz, 1H), 2.21–2.28 (m, 2H), 2.61 (ddd, J=7.3, 7.3, 14.3 Hz, 1H), 4.54 (s, 2H), 5.28 (ddd, J=2.9, 6.6, 7.3 Hz, 1H), 5.43 (br ddq, J=7.3, 7.3, 1.1 Hz, 1H), 5.52 (br dd, J=7.3 Hz, 1H), 5.71 (d, J=8.1 Hz, 1H), 7.11–7.18 (m, 6H), 7.70–7.78 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9 (q), 12.0 (q), 13.6 (q), 14.3 (q), 20.8 (t), 30.1 (t), 37.1 (d), 70.2 (t), 74.4 (d), 81.6 (d), 123.4 (d), 128.0 (s), 128.11 (s), 128.12 (s), 129.0 (s), 129.1 (s), 129.3 (s), 129.8 (s), 130.9 (d, 2C), 131.02 (d, 2C), 131.04 (d, 2C), 131.70 (d, 2C), 131.72 (d, 2C), 131.8 (d, 2C), 132.6 (d), 133.6 (s), 164.8 (s), 164.9 (s), 165.5 (s); MS (FAB) m/z 810 $(M+Na)^+$; HRMS (FAB) calcd for $C_{35}H_{35}^{79}Br_3NaO_6$ $[(M+Na)^+]$ 810.9881, found 810.9853. Anal. calcd for $C_{35}H_{35}Br_3O_6$: C, 53.10; H, 4.46. Found C, 53.12; H, 4.42.

Compound **3b**. $[\alpha]_D^{29}=-0.4$ (c 1.04, $CHCl_3$); CD (MeOH) λ_{ext} 253 ($\Delta\varepsilon$ +191), 237 nm ($\Delta\varepsilon$ −88.8); UV (MeOH) λ_{max} 244 nm (ε 59400); IR ($CHCl_3$) 1715, 1590, 1485, 1395, 1270, 1105, 1100, 850 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 0.83 (t, J=7.3 Hz, 3H), 1.02 (d, J=6.6 Hz, 3H), 1.52 (s, 3H), 1.70 (s, 3H), 1.88 (dq, J=7.3, 7.3 Hz, 2H), 2.29 (ddd, J=3.7, 7.0, 15.2 Hz, 1H), 2.32–2.44 (m, 2H), 4.47 (d, J=12.5 Hz, 1H), 4.52 (d, J=12.5 Hz, 1H), 5.28 (ddd, J=3.7, 5.5, 9.2 Hz, 1H), 5.47 (br dd, J=7.0, 7.0 Hz, 1H), 5.58 (br t, J=7.3 Hz, 1H), 5.69 (d, J=6.6 Hz, 1H), 7.08 (d, J=8.4 Hz, 2H), 7.14–7.17 (m, 4H), 7.65 (d, J=8.4 Hz, 2H), 7.70 (d, J=8.4 Hz, 2H), 7.78 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6 (q), 12.5 (q), 13.8 (q), 14.3 (q), 20.9 (t), 28.6 (t), 37.9 (d), 70.1 (t), 74.9 (d), 79.4 (d), 124.1 (d), 128.02 (s), 128.04 (s), 129.01 (s), 129.04 (s), 129.3 (s), 130.6 (s), 130.92 (d, 2C), 130.97 (d, 2C), 131.02 (s), 131.05 (d, 2C), 131.64 (d, 2C), 131.65 (d, 2C), 131.7 (d, 2C), 132.9 (d), 133.6 (s), 164.7 (s), 165.1 (s), 165.4 (s); MS (FAB) m/z 810 $(M+Na)^+$; HRMS (FAB) calcd for $C_{35}H_{35}^{79}Br_3NaO_6$ $[(M+Na)^+]$ 810.9881, found 810.9885.

4.1.14. Diols 14a and 14b. A solution of conjugated ester **13a** (29.3 mg, 0.057 mmol) in a 1:3:5 mixture of HF·pyr-pyridine, pyridine, and THF (0.5 mL) was stirred at room temperature for 40 min. The mixture was diluted with EtOAc (2 mL) and poured into saturated aqueous $NaHCO_3$ (5 mL) cooled at 0 °C, and the resulting mixture was extracted with EtOAc (3×4 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane–ether 3:1→2:1) to give **14a** (15.9 mg, 98%) as a colorless oil. Using the same procedure as described above, **14b** (22.5 mg, 98%)

was obtained from **13b** (41.8 mg, 0.081 mmol) as a colorless oil.

Compound **14a**. $[\alpha]_D^{27}=+3.3$ (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) 3600, 3490 (br), 1700, 1650, 1460, 1280, 1250, 1105, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, $J=$ 6.8 Hz, 3H), 0.98 (t, $J=7.3$ Hz, 3H), 1.28 (t, $J=7.3$ Hz, 3H), 1.54 (br s, 3H), 1.68 (m, 1H), 1.86 (d, $J=1.0$ Hz, 3H), 2.06 (dq, $J=7.3$, 7.3 Hz, 2H), 2.27 (br s, 1H), 2.31 (ddd, $J=$ 7.3, 7.3, 15.1 Hz, 1H), 2.46 (m, 1H), 3.01 (br s, 1H), 3.98 (m, 1H), 4.17 (m, 1H), 4.18 (q, $J=7.3$ Hz, 2H), 5.45 (m, 1H), 6.81 (ddq, $J=7.3$, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (q), 12.6 (q), 13.4 (q), 14.1 (q), 14.2 (q), 20.7 (t), 34.6 (t), 38.8 (d), 60.5 (t), 74.8 (d), 80.4 (d), 126.8 (d), 129.7 (s), 134.7 (s), 138.1 (d), 168.0 (s); MS (FAB) *m/z* 307 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{28}NaO_4$ $[(M+Na)^+]$ 307.1885, found 307.1902.

Compound **14b**. $[\alpha]_D^{27}=-0.3$ (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3600, 3480 (br), 1700, 1650, 1370, 1280, 1085, 1035, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, $J=$ 7.3 Hz, 3H), 0.97 (t, $J=7.3$ Hz, 3H), 1.28 (t, $J=7.3$ Hz, 3H), 1.54 (br s, 3H), 1.73 (m, 1H), 1.86 (br s, 3H), 2.06 (dq, $J=7.3$, 7.3 Hz, 2H), 2.40 (br s, 1H), 2.43 (m, 1H), 2.49 (ddd, $J=7.3$, 7.3, 15.1 Hz, 1H), 2.97 (br d, $J=2.0$ Hz, 1H), 3.79 (m, 1H), 4.18 (q, $J=7.3$ Hz, 2H), 4.34 (br s, 1H), 5.43 (br t, $J=7.3$ Hz, 1H), 6.84 (ddq, $J=7.3$, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (q), 12.7 (q), 13.6 (q), 14.1 (q), 14.2 (q), 20.8 (t), 34.6 (t), 39.4 (d), 60.5 (t), 74.4 (d), 75.5 (d), 126.7 (d), 129.7 (s), 134.6 (s), 138.3 (d), 168.0 (s); MS (FAB) *m/z* 307 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{28}NaO_4$ $[(M+Na)^+]$ 307.1885, found 307.1870.

4.1.15. Enones 15a and 15b. To a stirred solution of diol **14a** (15.9 mg, 0.056 mmol) in CH_2Cl_2 (0.4 mL) was added MnO_2 (23.4 mg, 0.27 mmol), and the mixture was stirred at room temperature for 4 h. Manganese dioxide (107 mg, 1.24 mmol) was added, and the mixture was stirred at room temperature for 4 h. Further, MnO_2 (110 mg, 1.28 mmol) was added, and the mixture was stirred at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 (2 mL) and filtered through a pad of Celite, and the residue was washed with EtOAc (30 mL). The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, benzene–EtOAc 10:1→8:1) to give **15a** (10.9 mg, 69%) as a colorless oil. Using the same procedure as described above, **15b** (7.2 mg, 60%) was obtained from **15b** (12.0 mg, 0.042 mmol) as a colorless oil.

Compound **15a**. $[\alpha]_D^{27}=-11.4$ (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1700, 1650, 1640 (sh), 1460, 1370, 1280, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, $J=$ 7.3 Hz, 3H), 1.17 (d, $J=7.3$ Hz, 3H), 1.29 (t, $J=7.3$ Hz, 3H), 1.77 (br s, 3H), 1.86 (d, $J=1.0$ Hz, 3H), 2.28 (dq, $J=$ 7.3, 7.3 Hz, 2H), 2.31 (m, 1H), 2.43 (ddd, $J=7.3$, 7.3, 15.1 Hz, 1H), 3.23 (dq, $J=3.4$, 7.3 Hz, 1H), 3.33 (d, $J=$ 2.0 Hz, 1H), 4.02 (m, 1H), 4.19 (q, $J=7.3$ Hz, 2H), 6.62 (br t, $J=7.3$ Hz, 1H), 6.80 (ddq, $J=7.3$, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2 (q), 11.8 (q), 12.7 (q), 13.0 (q), 14.3 (q), 22.6 (t), 33.6 (t), 42.2 (d), 60.5 (t), 70.9 (d), 129.9 (s), 135.6 (s), 137.6 (d), 145.8 (d), 167.9 (s), 207.2 (s); MS (FAB) *m/z* 305 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{26}NaO_4$ $[(M+Na)^+]$ 305.1729, found 305.1700.

Compound **15b**. $[\alpha]_D^{27}=-10.9$ (*c* 0.38, $CHCl_3$); IR ($CHCl_3$) 3600, 3480 (br), 1700, 1650, 1640, 1455, 1370, 1275, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, $J=$ 7.3 Hz, 3H), 1.20 (d, $J=6.8$ Hz, 3H), 1.29 (t, $J=7.3$ Hz, 3H), 1.77 (d, $J=1.0$ Hz, 3H), 1.79 (d, $J=1.0$ Hz, 3H), 2.28 (dq, $J=7.3$, 7.3 Hz, 2H), 2.35 (ddd, $J=7.3$, 7.8, 15.3 Hz, 1H), 2.41 (ddd, $J=7.3$, 7.8, 15.3 Hz, 1H), 3.33 (dq, $J=5.4$, 6.8 Hz, 1H), 3.38 (br s, 1H), 3.87 (m, 1H), 4.19 (q, $J=$ 7.3 Hz, 2H), 6.63 (br t, $J=7.3$ Hz, 1H), 6.82 (ddq, $J=7.3$, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1 (q), 12.6 (q), 12.9 (q), 14.3 (q), 16.4 (q), 22.6 (t), 34.8 (t), 42.9 (d), 60.5 (t), 73.7 (d), 129.7 (s), 136.4 (s), 137.8 (d), 146.0 (d), 167.9 (s), 207.3 (s); MS (FAB) *m/z* 305 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{26}NaO_4$ $[(M+Na)^+]$ 305.1729, found 305.1700.

4.1.16. Silyl ethers 16a and 16b. To a stirred solution of enone **15a** (10.4 mg, 0.037 mmol) in DMF (0.2 mL) were added imidazole (20.8 mg, 0.306 mmol) and triethylsilyl chloride (0.015 mL, 0.089 mmol). The mixture was stirred at room temperature for 2 h and diluted with H_2O (3 mL), and the resulting mixture was extracted with hexane (3×2 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (1 g, hexane–ether 8:1) to give **16a** (12.4 mg, 85%) as a colorless oil. Using the same procedure as described above, **16b** (8.7 mg, 89%) was obtained from **15b** (7.0 mg, 0.025 mmol) as a colorless oil.

Compound **16a**. $[\alpha]_D^{28}=-14.9$ (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) 1700, 1650, 1640 (sh), 1480, 1370, 1250, 1095, 1010, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (q, $J=$ 7.8 Hz, 6H), 0.96 (t, $J=7.8$ Hz, 9H), 1.04 (t, $J=7.3$ Hz, 3H), 1.11 (d, $J=6.8$ Hz, 3H), 1.28 (t, $J=7.3$ Hz, 3H), 1.71 (d, $J=1.5$ Hz, 3H), 1.73 (d, $J=1.0$ Hz, 3H), 2.23 (dq, $J=$ 7.3, 7.3 Hz, 2H), 2.25–2.31 (m, 2H), 3.30 (dq, $J=7.3$, 6.8, 1H), 4.08 (dt, $J=7.3$, 4.9 Hz, 1H), 4.12–4.23 (m, 2H), 6.55 (tq, $J=7.3$, 1.0 Hz, 1H), 6.84 (ddq, $J=7.3$, 7.3, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1 (t, 3C), 6.9 (q, 3C), 11.2 (q), 12.6 (q), 13.0 (q), 14.3 (q), 15.5 (q), 22.5 (t), 35.3 (t), 44.9 (d), 60.4 (t), 73.6 (d), 129.4 (s), 136.3 (s), 138.0 (d), 144.5 (d), 167.8 (s), 204.8 (s); MS (FAB) *m/z* 419 $(M+Na)^+$; HRMS (FAB) calcd for $C_{22}H_{40}NNaO_4Si$ $[(M+Na)^+]$ 419.2594, found 419.2574.

Compound **16b**. $[\alpha]_D^{27}=+51.6$ (*c* 0.46, $CHCl_3$); IR ($CHCl_3$) 1700, 1655, 1640 (sh), 1460, 1370, 1250, 1080, 1005, 945 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.52 (q, $J=$ 7.8 Hz, 6H), 0.89 (t, $J=7.8$ Hz, 9H), 0.96 (d, $J=6.8$ Hz, 3H), 1.09 (t, $J=7.3$ Hz, 3H), 1.29 (t, $J=7.3$ Hz, 3H), 1.76 (d, $J=1.0$ Hz, 3H), 1.83 (br s, 3H), 2.26 (dq, $J=7.3$, 7.3 Hz, 2H), 2.30–2.43 (m, 2H), 3.41 (dq, $J=7.3$, 6.8 Hz, 1H), 4.12 (ddd, $J=3.9$, 5.9, 7.3 Hz, 1H), 4.20 (q, $J=7.3$ Hz, 2H), 6.63 (br t, $J=7.3$ Hz, 1H), 6.92 (ddq, $J=7.3$, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 6.8 (q, 3C), 11.5 (q), 12.7 (q), 13.1 (q), 13.6 (q), 14.3 (q), 22.5 (t), 33.4 (t), 45.1 (d), 60.4 (t), 73.3 (d), 129.2 (s), 136.8 (s), 138.4 (d), 144.5 (d), 168.0 (s), 204.5 (s); MS (FAB) *m/z* 419 (M+

Na)$^+$; HRMS (FAB) calcd for $C_{22}H_{40}NNaO_4Si$ [(M+Na)$^+$] 419.2594, found 419.2585.

4.1.17. Tris(*p*-bromobenzoates) 3c and 3d. To a stirred solution of silyl ether **16a** (5.1 mg, 0.013 mmol) in ethanol (0.2 mL) cooled at −78 °C were added $CeCl_3\cdot 7H_2O$ (26.6 mg, 0.071 mmol) and $NaBH_4$ (2.1 mg, 0.056 mmol), and the mixture was stirred at −78 °C for 1 h and −23 °C for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL), and the resulting mixture was extracted with EtOAc (3×5 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 1 g, hexane–ether 15:1→10:1) to give a diastereomeric mixture of alcohols (4.9 mg, α:β=6:1) as a colorless oil, which was employed in the next experiment without separation of the diastereomers. A solution of the diastereomeric mixture of alcohols (4.9 mg, α:β=6:1) in a 1:3:5 mixture of HF·pyr-pyridine, pyridine, and THF (0.5 mL) was stirred at room temperature for 30 min. The mixture was diluted with EtOAc (2 mL) and poured into saturated aqueous $NaHCO_3$ (5 mL) cooled at 0 °C, and the resulting mixture was extracted with EtOAc (3×5 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated to give a crude diol (4.3 mg) as a colorless oil, which was employed in the next experiment without purification. To a stirred solution of crude diol (4.3 mg) in CH_2Cl_2 (0.3 mL) cooled at −78 °C was added a 0.98 M solution of diisobutylaluminum hydride in hexane (0.08 mL, 0.078 mmol), and the mixture was stirred at −23 °C for 1.5 h. The reaction was quenched by addition of MeOH (0.05 mL) and saturated aqueous Na/K tartrate (4 mL), and the mixture was stirred at room temperature for 1 h and extracted with EtOAc (3 × 8 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–ether 9:1→5:1) to give a crude triol (4.0 mg) as a colorless oil, which was employed in the next experiment without purification. To a stirred solution of the crude triol (4.0 mg) in pyridine (0.2 mL) was added *p*-bromobenzoyl chloride (80.0 mg, 0.37 mmol). The mixture was stirred at room temperature for 12 h, diluted with hexane (2 mL), and filtered through a cotton plug, and the residue was washed with hexane (5 mL) The filtrate and the washings were combined and diluted with 5% aqueous $NaHCO_3$ (3 mL), and the mixture was stirred at room temperature for 1 h. The layers were separated, and the aqueous layer was extracted with hexane (3×4 mL). The organic layer and the extracts were combined, washed with 5% aqueous $NaHCO_3$ (2×1 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 2 g, hexane–CH_2Cl_2 2:1→1:1→1:2) to give **3c** (5.5 mg, 57% from **16a**) as colorless crystals along with **3a** (1.0 mg, 10% from **16a**). Using the same procedure as described above, **3d** (6.6 mg, 53% from **16b**) was obtained from **16b** (6.3 mg, 0.016 mmol) as a colorless oil along with **3b** (1.2 mg, 9% from **16b**).

Compound **3c**. $[\alpha]_D^{29}=-10.6$ (*c* 0.36, $CHCl_3$); CD (MeOH); λ_{ext} 252 (Δε −172), 236 nm (Δε +126); UV (MeOH) λ_{max} 244 nm (ε 52100); IR ($CHCl_3$) 1715, 1590, 1485, 1395, 1270, 1115, 1100, 1010 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 0.82 (t, *J*=7.3 Hz, 3H), 0.98 (d, *J*=6.9 Hz, 3H), 1.55 (s, 6H), 1.86 (dq, *J*=7.3, 7.3 Hz, 2H), 2.17 (ddd, *J*=6.6, 7.3, 14.3 Hz, 1H), 2.28 (ddq, *J*=2.2, 9.9, 6.9 Hz, 1H), 2.60 (ddd, *J*=7.3, 7.7, 14.3 Hz, 1H), 4.49 (d, *J*=12.5 Hz, 1H), 4.53 (d, *J*=12.5 Hz, 1H), 5.46 (m, 1H), 5.54 (d, *J*=9.9 Hz, 1H), 5.63 (ddd, *J*=2.2, 6.6, 7.7 Hz, 1H), 5.63 (m, 1H), 7.07–7.12 (m, 4H), 7.14–7.18 (m, 2H), 7.66–7.77 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7 (q), 11.3 (q), 13.7 (q), 14.3 (q), 20.9 (t), 30.4 (t), 37.2 (d), 70.2 (t), 72.7 (d), 81.0 (d), 124.0 (d), 127.8 (s), 127.9 (s), 128.1 (s), 129.0 (s), 129.2 (s), 129.5 (s), 130.2 (s), 130.97 (d, 2C), 130.99 (d, 2C), 131.0 (d, 2C), 131.5 (d, 2C), 131.6 (d, 2C), 131.7 (d, 2C), 133.2 (d), 133.6 (s), 164.7 (s), 165.0 (s), 165.5 (s); MS (FAB) *m/z* 810 (M+Na)$^+$; HRMS (FAB) calcd for $C_{35}H_{35}^{79}Br_3NaO_6$ [(M+Na)$^+$] 810.9881, found 810.9884.

Compound **3d**. $[\alpha]_D^{30}=-5.4$ (*c* 0.37, $CHCl_3$); CD (MeOH); λ_{ext} 254 (Δε −57.0), 236 nm (Δε +91.1); UV (MeOH) λ_{max} 244 nm (ε 61400); IR ($CHCl_3$) 1715, 1590, 1485, 1395, 1270, 1115, 1105, 1010, 850 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 0.83 (t, *J*=7.3 Hz, 3H), 0.86 (d, *J*=7.3 Hz, 3H), 1.50 (s, 3H), 1.54 (s, 3H), 1.80–1.89 (m, 2H), 2.44–2.40 (m, 2H), 2.58 (ddq, *J*=4.4, 9.9, 7.3 Hz, 1H), 4.42 (d, *J*=12.5 Hz, 1H), 4.48 (d, *J*=12.5 Hz, 1H), 5.49 (br t, *J*=7.3 Hz, 1H), 5.57 (d, *J*=9.9 Hz, 1H), 5.58–5.63 (m, 2H), 7.11–7.17 (m, 6H), 7.61 (d, *J*=8.4 Hz, 2H), 7.78 (d, *J*=8.4 Hz, 2H), 7.90 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 (q), 11.6 (q), 13.7 (q), 14.2 (q), 20.9 (t), 28.0 (t), 37.8 (d), 70.1 (t), 74.8 (d), 81.7 (d), 124.4 (d), 128.0 (s), 128.1 (s), 128.2 (s), 129.0 (s), 129.1 (s), 129.2 (s), 130.2 (s), 130.9 (d, 2C), 131.0 (d, 2C), 131.1 (d, 2C), 131.6 (d, 2C), 131.7 (d, 2C), 131.8 (d, 2C), 132.8 (s), 133.4 (d), 164.9 (s), 165.1 (s), 165.4 (s); MS (FAB) *m/z* 810 (M+Na)$^+$; HRMS (FAB) calcd for $C_{35}H_{35}^{79}Br_3NaO_6$ [(M+Na)$^+$] 810.9881, found 810.9894.

4.1.18. Dipeptide 21. To a stirred solution of *N*-methylglycine *tert*-butyl ester hydrochloride (1.09 g, 5.08 mmol) and *N*-benzyloxycarbonyl-*N*-methyl-D-leucine (1.56 g, 5.60 mmol) in DMF (5 mL) cooled at 0 °C were added triethylamine (2.3 mL, 17 mmol) and diethylphosphoryl cyanide (0.84 mL, 2.20 mmol), successively. The reaction mixture was stirred at 0 °C for 3.5 h, diluted with EtOAc–benzene (1:2, 15 mL), washed with 5% aqueous citric acid (5 mL), saturated aqueous $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (62 g, hexane–EtOAc 6:1→3:1) to give **21** (2.03 g, 98%) as a colorless oil. $[\alpha]_D^{33}=+68.8$ (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 1735, 1680, 1655, 1435, 1310, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78–0.98 (m, 6H), 1.42–1.76 (m, 12H), 2.78 (s, 0.3H), 2.84 (s, 0.7H), 2.89 (s, 1.9H), 2.91 (s, 0.5H), 2.94 (s, 1.0H), 3.08 (s, 1.6H), 3.87–4.03 (m, 2H), 4.74–5.23 (m, 3H), 7.28–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3 (q), 23.0 (q), 24.5 (d), 28.0 (q, 3C), 29.2 (q), 36.1 (q), 37.7 (t), 50.6 (t), 52.7 (d), 67.3 (t), 81.7 (s), 127.6 (d, 2C), 127.9 (d), 128.4 (d, 2C), 136.6 (s), 156.4 (s), 168.0 (s), 171.3 (s); MS (FAB) *m/z* 429 (M+Na)$^+$, 407 (M+H)$^+$; HRMS (FAB) calcd for $C_{22}H_{35}N_2O_5$ [(M+H)$^+$] 407.2546, found 407.2553.

4.1.19. Tripeptide 22. A mixture of dipeptide **21** (1.22 g,

3.00 mmol) and 10% Pd on carbon (244 mg) in EtOH (3 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The mixture was filtered through a pad of Celite, and the residue was washed with chloroform. The filtrate and the washings were combined and concentrated to give crude amine (782 mg) as a colorless oil. To a stirred solution of the crude amine (782 mg) and *N*-benzyloxycarbonyl-L-valine (1.41 g, 5.60 mmol) in CH_2Cl_2 (3.0 mL) cooled at 0 °C were added PyBOP (3.21 g, 6.17 mmol) and diisopropylethylamine (2.4 mL, 14 mmol). The reaction mixture was stirred at room temperature for 24 h, diluted with EtOAc (40 mL), washed with 10% aqueous citric acid (2×10 mL), H_2O (5 mL), saturated aqueous $NaHCO_3$ (2× 8 mL), H_2O (5 mL), and brine (8 mL) successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography (i. silica gel 150 g, hexane–EtOAc 4:1→3:1; ii. alumina 20 g, benzene–EtOAc 3:1) to give tripeptide **22** (1.31 g, 92% from **21**) as a colorless oil. $[\alpha]_D^{29}=+82.6$ (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3430, 1735, 1720, 1635, 1505, 1410, 1230, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, $J=6.8$ Hz, 1.05H), 0.82 (d, $J=6.3$ Hz, 1.05H), 0.86 (d, $J=6$,8 Hz, 1.95H), 0.85–0.98 (m, 7.95H), 1.40 (s, 9H), 1.30–1.73 (m, 3H), 1.94 (m, 1H), 2.84 (s, 1.05H), 2.91 (s, 1.95H), 3.00 (s, 3H), 3.70 (d, $J=$ 17.1 Hz, 0.35H), 3.84 (d, $J=16.6$ Hz, 0.65H), 3.95 (d, $J=$ 16.6 Hz, 0.65H), 4.57–4.98 (m, 1.35H), 5.02 (d, $J=12.7$ Hz, 0.35H), 5.04 (s, 1.3H), 5.06 (d, $J=12.7$ Hz, 0.35H), 5.31 (dd, $J=5.9$, 8.8 Hz, 0.35H), 5.49 (dd, $J=6.3$, 8.8 Hz, 0.65H), 5.61 (d, $J=8.8$ Hz, 1H), 7.22–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7 [16.4] (q), 19.5 [19.6] (q), 22.0 [21.8] (q), 22.9 [23.0] (q), 24.5 [24.3] (d), 27.9 [27.8] (q, 3C), 30.4 [30.2] (q), 30.9 [31.0] (d), 36.0 [34.9] (q), 37.7 [37.9] (t), 50.6 [51.9] (t), 50.8 [49.8] (d), 55.78 [55.81] (d), 66.57 [66.60] (t), 81.5 [82.0] (s), 127.78 [127.82] (d, 2C), 127.85 [127.88] (d), 128.28 [128.30] (d, 2C), 136.34 [136.29] (s), 156.2 [156.1] (s), 167.7 [168.2] (s), 170.6 [170.7] (s), 171.7 [171.8] (s). The minor counterparts of doubled signals in the ratio of 1.9:1 are in brackets; MS (FAB) *m*/*z* 528 $(M+Na)^+$; HRMS (FAB) calcd for $C_{27}H_{43}N_3NaO_6$ $[(M+Na)^+]$ 528.3050, found 528.3049.

4.1.20. Tetrapeptide 23. A mixture of tripeptide **23** (3.56 g, 7.05 mmol) and 10% Pd on carbon (437 mg) in EtOH (20 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOH. The filtrate and the washings were combined and concentrated to give a crude amine (2.67 g) as a colorless oil. To a stirred solution of the crude amine (2.67 g), *allo*-D-isoleucic acid sodium salt (1.19 g, 7.78 mmol), and 1-hydroxybenzotriazole (1.88 g, 13.9 mmol) in DMF (14 mL) cooled at 0 °C was added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (2.55 g, 11.7 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc (150 mL), washed with 5% aqueous $NaHCO_3$ (20 mL), 10% aqueous citric acid (20 mL), H_2O (15 mL), and brine (20 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, benzene–acetone 6:1→3:1) to give **23** (3.25 g, 95% from **22**) as colorless crystals. mp 100.5–101.0 °C (hexane–EtOAc). $[\alpha]_D^{28}=+$ 58.8 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3440 (br), 3410, 1735, 1635, 1505, 1465, 1235, 1155 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.79 (d, $J=6.9$ Hz, 1.95H), 0.82 (d, $J=6.8$ Hz, 1.05H), 0.86–1.04 (m, 15H), 1.18–1.90 (m, 6H), 1.45 (s, 3.15H), 1.47 (s, 5.85H), 2.05 (m, 1H), 2.77 (d, $J=5.6$ Hz, 0.65H), 2.79 (d, $J=5.6$ Hz, 0.35H), 2.90 (s, 1.05H), 3.00 (s, 1.95H), 3.06 (s, 3H), 3.72 (d, $J=18.2$ Hz, 0.35H), 3.92 (d, $J=16.8$ Hz, 0.65H), 4.00 (d, $J=16.8$ Hz, 0.65H), 4.05 (dd, $J=2.6$, 5.6 Hz, 1H), 4.54 (d, $J=18.2$ Hz, 0.35H), 4.84 (dd, $J=5.3$, 8.9 Hz, 0.35H), 4.90 (dd, $J=5.3$, 8.9 Hz, 0.65H), 5.37 (dd, $J=5.9$, 8.9 Hz, 0.35H), 5.55 (dd, $J=6.3$, 8.9 Hz, 0.65H), 6.81 (d, $J=8.9$ Hz, 0.35H), 6.88 (d, $J=8.9$ Hz, 0.65H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 [11.9] (q), 12.7 [12.6] (q), 17.25 [17.21] (q), 19.7 (q), 22.2 [22.0] (q), 22.9 [23.0] (q), 24.6 [24.5] (d), 26.2 [26.3] (t), 28.0 [27.9] (q, 3C), 30.7 [30.4] (q), 31.2 [31.0] (d), 36.0 [35.0] (q), 37.8 [37.9] (t), 38.6 [38.8] (d), 50.7 [52.0] (t), 51.1 [50.0] (d), 53.5 [53.8] (d), 73.9 (d), 81.8 [82.3] (s), 167.8 [168.4] (s), 170.5 [170.7] (s), 171.8 [172.0] (s), 173.5 [173.7] (s). The minor counterparts of doubled signals in the ratio of 1.9:1 are in brackets; MS (FAB) *m*/*z* 508 $(M+Na)^+$; HRMS (FAB) calcd for $C_{25}H_{47}N_3NaO_6$ $[(M+Na)^+]$ 508.3362, found 508.3386. Anal. calcd for $C_{25}H_{47}N_3O_6$: C, 61.80; H, 9.75; N, 8.65. Found C, 61.81; H, 10.0; N, 8.56.

4.1.21. Carboxylic acid 24. To a stirred solution of tetrapeptide **23** (181 mg, 0.373 mmol) in THF (4.0 mL) cooled at 0 °C were added 2,6-lutidine (0.26 mL, 2.23 mmol) and trimethylsilyl triflate (0.29 mL, 1.50 mmol), successively. The reaction mixture was stirred at 0 °C for 3 h, diluted with 1 M HCl (5 mL), and extracted with CH_2Cl_2 (5×8 mL). The extracts were combined, washed with brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, $CHCl_3$–MeOH 100:1→60:1→40:1→20:1) to give carboxylic acid **24** (160 mg, 100%) as a colorless powder. $[\alpha]_D^{28}=+116$ (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3400, 3300 (br), 1730, 1640, 1520, 1465, 1410, 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (d, $J=6.8$ Hz, 1.95H), 0.83 (d, $J=6.8$ Hz, 1.05H), 0.88–0.98 (m, 15H), 1.84–1.20 (m, 6H), 2.02 (m, 0.35H), 2.13 (m, 0.65H), 2.92 (s, 1.05H), 2.93 (s, 1.95H), 2.98 (s, 1.05H), 3.08 (s, 1.95H), 3.73 (d, $J=17.6$ Hz, 0.65H), 3.95 (d, $J=18.1$ Hz, 0.35H), 4.06 (d, $J=3.9$ Hz, 0.35H), 4.10 (d, $J=2.4$ Hz, 0.65H), 4.27 (d, $J=$ 18.1 Hz, 0.35H), 4.41 (d, $J=17.6$ Hz, 0.65H), 4.74 (dd, $J=8.3$, 8.8 Hz, 0.65H), 4.79 (dd, $J=6.8$, 9.3 Hz, 0.35H), 5.42 (dd, $J=7.3$, 7.3 Hz, 0.35H), 5.50 (dd, $J=7.3$, 7.3 Hz, 0.65H), 7.41 (d, $J=9.3$ Hz, 0.35H), 7.80 (d, $J=8.8$ Hz, 0.65H). Signals due to two protons (COOH, OH) were not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 [11.6] (q), 12.5 [13.1] (q), 18.0 [17.4] (q), 19.4 [19.5] (q), 22.4 [22.2] (q), 22.8 [23.0] (q), 24.6 [24.4] (d), 26.2 [26.0] (t), 30.6 [30.8] (d), 30.9 [30.5] (q), 36.1 [35.3] (q), 37.9 [38.1] (t), 38.4 [38.2] (d), 49.9 [50.7] (t), 51.7 [51.0] (d), 54.1 [54.0] (d), 74.0 [74.8] (d), 170.5 [169.9] (s), 171.0 [170.6] (s), 172.4 [171.9] (s), 174.8 [174.1] (s). The minor counterparts of doubled signals in the ratio of 1.9:1 are in brackets; MS (FAB) *m*/*z* 452 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{39}N_3NaO_6$ $[(M+Na)^+]$ 452.2737, found 452.2730. Anal. calcd for $C_{21}H_{39}N_3O_6$: C, 58.66; H, 9.32; N, 9.62. Found C, 58.70; H, 9.15; N, 9.78.

4.1.22. Pentapeptide 19. To a stirred solution of carboxylic acid **24** (154 mg, 0.359 mmol) and L-valine 2,2,2-trichloroethyl ester hydrochloride (125 mg, 0.442 mmol) in DMF

(0.5 mL) and CH_2Cl_2 (0.1 mL) cooled at 0 °C were added triethylamine (0.065 mL, 0.47 mmol), 1-hydroxybenzotriazole (73.0 mg, 0.541 mmol), and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (89.0 mg, 0.464 mmol), successively. The reaction mixture was stirred at room temperature for 2 h, diluted with EtOAc (20 mL), washed with 10% citric acid (2×4 mL), H_2O (4 mL) saturated aqueous $NaHCO_3$ (2×2 mL), brine (2 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane–acetone 3:1→2.5: 1) to give **19** (232 mg, 98%) as a colorless powder. $[\alpha]_D^{27}=+46.3$ (*c* 1.41, $CHCl_3$); IR ($CHCl_3$) 3420, 3360 (br), 1755, 1675, 1630, 1515, 1465, 1390, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, $J=6.8$ Hz, 2.55H), 0.81 (d, $J=6.8$ Hz, 0.45H), 0.85–1.07 (m, 21H), 1.23–1.90 (m, 6H), 2.05 (m, 1H), 2.32 (m, 1H), 2.89 (d, $J=4.9$ Hz, 0.15H), 2.93 (d, $J=4.9$ Hz, 0.85H), 2.96 (s, 0.45H), 3.10 (s, 3H), 3.12 (s, 2.55H), 3.93 (d, $J=17.1$ Hz, 0.15H), 3.99 (d, $J=15.6$ Hz, 0.85H), 4.06 (d, $J=15.6$ Hz, 0.85H), 4.13 (dd, $J=2.0$, 4.9 Hz, 1H), 4.27 (d, $J=17.1$ Hz, 0.15H), 4.62 (d, $J=11.7$ Hz, 1H), 4.64 (dd, $J=4.9$, 8.8 Hz, 0.85H), 4.69 (dd, $J=4.9$, 8.3 Hz, 0.15H), 4.82 (m, 0.15H), 4.85 (dd, $J=6.8$, 8.8 Hz, 0.85H), 4.90 (d, $J=11.7$ Hz, 0.85H), 4.92 (d, $J=11.7$ Hz, 0.15H), 5.29 (dd, $J=5.4$, 9.3 Hz, 0.15H), 5.47 (dd, $J=6.3$, 8.3 Hz, 0.85H), 6.74 (d, $J=8.8$ Hz, 0.85H), 6.82–6.89 (m, 0.3H), 6.93 (d, $J=8.8$ Hz, 0.85H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (q), 12.6 (q), 17.39 [17.25] (q), 17.41 [17.7] (q), 19.0 (q), 19.5 (q), 22.0 [21.8] (q), 22.9 [23.1] (q), 24.7 [24.6] (d), 26.2 (t), 30.59 [30.65] (d), 30.74 (q), 31.1 [30.9] (d), 36.5 (q), 37.7 [37.8] (t), 38.6 (d), 51.2 [50.7] (d), 52.6 [52.4] (t), 53.7 [54.0] (d), 57.0 [57.3] (d), 73.95 [74.00] (d), 74.35 [74.40] (t), 94.4 [94.3] (s), 168.6 [168.3] (s), 170.2 [170.7] (s), 171.8 [171.6] (s), 172.3 [172.4] (s), 173.6 [173.7] (s). The minor counterparts of doubled signals in the ratio of 5.7:1 are in brackets; MS (FAB) *m/z* 681 $(M+Na)^+$; HRMS (FAB) calcd for $C_{28}H_{49}^{35}Cl_3N_4NaO_7$ [$(M+Na)^+$] 681.2564, found 681.2579. Anal. calcd for $C_{28}H_{49}Cl_3N_4O_7$: C, 50.90; H, 7.48; N, 8.49. Found C, 50.99; H, 7.52; N, 8.43.

4.1.23. Hydroxy imide 25a. To a stirred solution of imide *ent*-**4** (2.28 g, 9.48 mmol) in ether (28 mL) cooled at 0 °C were added dibutylboron triflate (4.75 mL, 19.0 mmol) and diisoprpylethylamine (1.90 mL, 10.9 mmol), successively. The reaction mixture was stirred at 0 °C for 30 min and cooled to −100 °C. A solution of *trans*-2-methyl-2-pentenal (1.35 mL, 11.8 mmol) in ether (8.0 mL, 2.0 mL rinse) was added, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched by addition of trietylamine (2.0 mL, 14 mmol) and 0.5 M phosphate buffer (pH 7, 40 mL). The reaction mixture was stirred at room temperature for 20 min and extracted with ether (2× 50 mL). The extracts were combined, washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, benzene–ether 80:1→40:1→20:1→10:1) to give **25a** (2.09 g, 67%) and *syn*-hydroxy imide **25b** (453 mg, 14%) as crystals, respectively.

Compound **25a**. Mp 89–90 °C (hexane–ether). $[\alpha]_D^{31}=-30.6$ (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3600, 3520 (br), 1780, 1695, 1455, 1370, 1345, 1190, 955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, $J=6.8$ Hz, 3H), 0.97 (t, $J=7.3$ Hz, 3H), 1.08 (d, $J=6.4$ Hz, 3H), 1.68 (br s, 3H), 2.05 (dq, $J=7.3$, 7.3 Hz, 2H), 2.63 (d, $J=6.4$ Hz, 1H), 4.10 (dd, $J=6.4$, 8.8 Hz, 1H), 4.15 (dq, $J=8.8$, 6.4 Hz, 1H), 4.79 (dq, $J=6.8$, 6.8 Hz, 1H), 5.44 (br t, $J=7.3$ Hz, 1H), 5.67 (d, $J=6.8$ Hz, 1H), 7.28–7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7 (q), 13.9 (q), 14.3 (q), 14.8 (q), 20.8 (t), 40.6 (d), 55.2 (d), 78.9 (d), 81.2 (d), 125.6 (d, 2C), 128.3 (d), 128.7 (d, 2C), 131.3 (d), 133.2 (s), 133.7 (s), 153.4 (s), 176.5 (s); MS (FAB) *m/z* 332 $(M+H)^+$, 354 $(M+Na)^+$. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.90; H, 7.60; N, 4.23. Found C, 68.91; H, 7.78; N, 4.22.

Compound **25b**. mp 148–149 °C (hexane–ether). $[\alpha]_D^{31}=-17.8$ (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 3600, 3530 (br), 1780, 1695, 1455, 1370, 1345, 1190, 955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, $J=6.8$ Hz, 3H), 0.96 (t, $J=7.3$ Hz, 3H), 1.17 (d, $J=6.8$ Hz, 3H), 1.65 (br s, 3H), 1.97–2.13 (m, 2H), 2.56 (br s, 1H), 4.09 (dq, $J=3.4$, 6.8 Hz, 1H), 4.38 (d, $J=3.4$ Hz, 1H), 4.80 (dq, $J=6.8$, 6.8 Hz, 1H), 5.52 (m, 1H), 5.68 (d, $J=6.8$ Hz, 1H), 7.27–7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (q), 13.1 (q), 14.0 (q), 14.6 (q), 20.8 (t), 40.6 (d), 54.8 (d), 75.7 (d), 78.8 (d), 125.6 (d, 2C), 128.4 (d), 128.7 (d, 2C), 128.8 (d), 133.0 (s), 133.2 (s), 152.7 (s), 176.6 (s); MS (FAB) *m/z* 332 $(M+H)^+$, 354 $(M+Na)^+$. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.90; H, 7.60; N, 4.23. Found C, 68.84; H, 7.71; N, 4.25.

4.1.24. Amide 27. To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (1.90 g, 19.5 mmol) in THF (3 mL) cooled at −15 °C was added a 2.0 M solution of trimethylaluminum in toluene (8.9 mL, 17.8 mmol) dropwise. The resulting solution was stirred at 0 °C for 5 min and at room temperature for 20 min. The solution was recooled to 0 °C, and a solution of hydroxy imide **25a** (1.55 g, 4.68 mmol) in THF (12 mL) was added. The reaction mixture was warmed to 50 °C, stirred for 1.5 h, and transferred into a vigorously stirred mixture of CH_2Cl_2 (20 mL) and 0.5 M HCl (20 mL) at 0 °C. The resulting two-phase mixture was stirred at 0 °C for 50 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The organic layer and extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (100 g, hexane–^{i}PrOH 40: 1→35:1→30:1→EtOAc) and FL-60D silica gel (100 g, hexane–ether 3:2→1: 1) to give **27** (846 mg, 84%) as a colorless oil and 4-(*S*)-methyl-5-(*R*)-phenyl-2-oxazolidinone (450 mg) as colorless crystals. **27**. $[\alpha]_D^{30}=-43.8$ (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3600, 3440 (br), 1640, 1460, 1390, 1220, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, $J=7.3$ Hz, 3H), 1.04 (d, $J=6.8$ Hz, 3H), 1.63 (br s, 3H), 2.05 (dq, $J=7.3$, 7.3 Hz, 2H), 2.95 (br s, 1H), 3.13 (m, 1H), 3.21 (s, 3H), 3.73 (s, 3H), 4.12 (d, $J=7.8$ Hz, 1H), 5.45 (br t, $J=7.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0 (q), 13.9 (q), 14.8 (q), 20.7 (t), 31.9 (q), 38.1 (d), 61.4 (q), 79.8 (d), 130.4 (d), 133.9 (s), 176.9 (s); MS (FAB) *m/z* 238 $(M+Na)^+$, 216 $(M+H)^+$; HRMS (FAB) calcd for $C_{11}H_{21}NNaO_3$ [$(M+Na)^+$] 238.1420, found 238.1422.

4.1.25. Silyl ether 28. To a stirred solution of amide **27** (1.34 g, 6.23 mmol) in DMF (6 mL) were added imidazole

(1.65 g, 24.2 mmol) and *tert*-butyldimethylsilyl chloride (1.62 g, 10.4 mmol). The mixture was stirred at room temperature for 3 h, diluted with H_2O (30 mL), and extracted with ether (4×40 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–EtOAc 10:1) to give **28** (2.22 g, 100%) as a colorless oil. $[\alpha]_D^{30}=-21.2$ (*c* 1.60, $CHCl_3$); IR ($CHCl_3$) 1650, 1460, 1390, 1250, 1060, 990, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 3H), −0.03 (s, 3H), 0.79 (s, 9H), 0.83 (d, $J=7.3$ Hz, 3H), 0.94 (t, $J=7.3$ Hz, 3H), 1.55 (br s, 3H), 1.98 (ddq, $J=7.3$, 14.6, 7.3 Hz, 1H), 2.04 (ddq, $J=7.3$, 14.6, 7.3 Hz, 1H), 3.14 (m, 1H), 3.16 (s, 3H), 3.72 (s, 3H), 4.13 (d, $J=9.8$ Hz, 1H), 5.35 (br dd, $J=7.3$, 7.3 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.3 (q), −4.9 (q), 10.1 (q), 13.8 (q), 14.2 (q), 18.0 (s), 20.8 (t), 25.6 (q, 3C), 31.8 (q), 38.7 (d), 61.3 (q), 81.7 (d), 131.1 (d), 134.0 (s), 176.4 (s); MS (FAB) *m/z* 330 $(M+H)^+$; HRMS (FAB) calcd for $C_{17}H_{36}NO_3Si$ $[(M+H)^+]$ 330.2465, found 330.2463.

4.1.26. Aldehyde 29. To a stirred solution of silyl ether **28** (633 mg, 1.92 mmol) in THF (6.5 mL) cooled at −78 °C was added a 0.98 M solution of diisobutylaluminum hydride in hexane (3.9 mL, 3.8 mmol) dropwise. The solution was stirred at −78 °C for 1.5 h, and the reaction was quenched by addition of acetone (0.4 mL). The solution was stirred at −78 °C for 10 min and then transferred into a vigorously stirred mixture of CH_2Cl_2 (30 mL) and 0.5 M tartaric acid (30 mL) at room temperature. The resulting two-phase mixture was stirred at room temperature for 30 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The organic layer and the extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–CH_2Cl_2 20:1→10:1) to give **29** (480 mg, 93%) as a colorless oil. $[\alpha]_D^{32}=-26.2$ (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 2720, 1720, 1470, 1460, 1255, 1060, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 3H), 0.02 (s, 3H), 0.84 (s, 9H), 0.85 (d, $J=6.8$ Hz, 3H), 0.96 (t, $J=7.3$ Hz, 3H), 1.56 (br s, 3H), 1.95–2.12 (m, 2H), 2.55 (ddq, $J=2.9$, 8.8, 6.8 Hz, 1H), 4.05 (d, $J=8.8$ Hz, 1H), 5.36 (br dd, $J=7.3$, 7.3 Hz, 1H), 9.74 (d, $J=2.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (q), −4.5 (q), 10.6 (q), 11.0 (q), 13.7 (q), 18.1 (s), 20.8 (t), 25.7 (q, 3C), 50.1 (d), 80.6 (d), 130.8 (d), 133.8 (s), 205.4 (d); MS (EI) *m/z* 213 $[(M-C_4H_9)^+$, 100), 155 (20), 115 (30); HRMS (EI) calcd for $C_{11}H_{21}O_2Si$ $[(M-C_4H_9)^+]$ 213.1345, found 213.1311.

4.1.27. Methyl ester 31. To a stirred solution of aldehyde **29** (83.9 mg, 0.31 mmol) in CH_2Cl_2 (2.4 mL) and ether (0.24 mL) cooled at −78 °C were added 2-methyl-1-trimethylsiloxy-1-methoxy-1,3-butadiene (**30**) (0.2 mL, 1.01 mmol) and boron trifluoride diethyl etherate (0.06 mL, 0.49 mmol), successively. The reaction mixture was stirred at −78 °C for 2 h and diluted with THF–H_2O–0.3 M HCl (5:1:0.4, 4 mL). The mixture was stirred at room temperature for 15 min and then transferred into saturated aqueous $NaHCO_3$ (5 mL) at 0 °C. The layers were separated, and the aqueous layer was extracted with hexane (3×7 mL). The organic layer and the extracts were combined, washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on FL-60D silica gel (5 g, hexane–ether 10:1) to give **31** (104 mg, 87%) and as a colorless oil. $[\alpha]_D^{30}=+9.0$ (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 3480 (br), 1705, 1650, 1460, 1440, 1285, 1255, 1090, 1020, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 0.91 (d, $J=6.8$ Hz, 3H), 0.97 (t, $J=7.3$ Hz, 3H), 1.52 (br s, 3H), 1.68 (m, 1H), 1.84 (d, $J=1.0$ Hz, 3H), 2.05 (dq, $J=7.3$, 7.3 Hz, 2H), 2.21 (ddd, $J=6.3$, 6.3, 15.1 Hz, 1H), 2.39 (m, 1H), 3.30 (d, $J=2.9$ Hz, 1H), 3.72 (s, 3H), 4.00 (d, $J=4.9$ Hz, 1H), 4.02 (m, 1H), 5.46 (br dd, $J=7.3$, 7.3 Hz, 1H), 6.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (q), −4.5 (q), 11.5 (q), 12.6 (q), 12.7 (q), 13.9 (q), 18.0 (s), 20.8 (t), 25.9 (q, 3C), 33.7 (t), 39.1 (d), 51.7 (q), 70.6 (d), 82.3 (d), 128.86 (s), 128.90 (d), 133.9 (s), 139.3 (d), 168.5 (s); MS (FAB) *m/z* 407 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{40}NaO_4Si$ $[(M+Na)^+]$ 407.2594, found 407.2622.

4.1.28. Ketone 32. To a stirred solution of methyl ester **31** (1.32 g, 3.44 mmol) in CH_2Cl_2 (25 mL) was added Dess–Martin periodinane (2.29 g, 5.41 mmol). The mixture was stirred at room temperature for 1 h and diluted with ether (30 mL), saturated aqueous $Na_2S_2O_3$ (40 mL), and 0.5 M phosphate buffer (pH 7, 40 mL). The resulting mixture was stirred at room temperature for 30 min and extracted with ether (3×50 mL). The combined extracts were washed with H_2O (2×50 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (35 g, hexane–ether 15:1→8:1) to give **32** (1.23 g, 94%) as a colorless oil. $[\alpha]_D^{30}=-44.5$ (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 1710, 1650, 1460, 1435, 1255, 1090, 1050, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 3H), −0.05 (s, 3H), 0.80 (s, 9H), 0.81 (d, $J=6.8$ Hz, 3H), 0.96 (t, $J=7.3$ Hz, 3H), 1.55 (br s, 3H), 1.85 (d, $J=1.0$ Hz, 3H), 1.99–2.11 (m, 2H), 2.82 (dq, $J=9.8$, 6.8 Hz, 1H), 3.41 (d, $J=7.3$ Hz, 2H), 3.74 (s, 3H), 4.06 (d, $J=9.8$ Hz, 1H), 5.35 (br dd, $J=7.3$, 7.3 Hz, 1H), 7.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (q), −4.7 (q), 10.1 (q), 12.9 (q), 13.7 (q), 13.8 (q), 18.0 (s), 20.8 (t), 25.7 (q, 3C), 44.4 (t), 49.5 (d), 51.8 (q), 82.4 (d), 130.1 (s), 131.4 (d), 133.3 (d), 133.7 (s), 168.0 (s), 210.3 (s); MS (FAB) *m/z* 405 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{38}NaO_4Si$ $[(M+Na)^+]$ 405.2437, found 405.2447.

4.1.29. Alcohol 33. To a stirred solution of ketone **32** (234 mg, 0.613 mmol) in methanol (6 mL) cooled at −23 °C was added sodium borohydride (119 mg, 3.15 mmol). The mixture was stirred at −23 °C for 50 min, diluted with saturated aqueous NH_4Cl (20 mL), and extracted with hexane (4×20 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 32 g, hexane-1,2-dichloroethane 3:1→2:1→1:1) to give **33** (193 mg, 82%) along with **31** (9.3 mg, 4%) as a colorless oil, respectively. **33**. $[\alpha]_D^{29}=-28.1$ (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 3450 (br), 1705, 1650, 1460, 1435, 1255, 1095, 1040, 1020, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.09 (s, 3H), 0.65 (d, $J=6.9$ Hz, 3H), 0.89 (s, 9H), 0.96 (t, $J=7.6$ Hz, 3H), 1.56 (br s, 3H), 1.77 (m, 1H), 1.85 (d, $J=1.0$ Hz, 3H), 2.02 (dq, $J=7.6$, 7.6 Hz, 2H), 2.32 (ddd, $J=6.9$, 7.6, 15.8 Hz, 1H), 2.44 (m, 1H), 3.73 (s, 3H), 3.81 (m, 1H), 3.84 (d, $J=8.9$ Hz,

1H), 4.18 (br s, 1H), 5.30 (br t, J=7.6 Hz, 1H), 6.97 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.2 (q), −4.2 (q), 10.8 (q), 12.7 (q), 13.1 (q), 13.6 (q), 18.1 (s), 20.8 (t), 25.8 (q, 3C), 33.6 (t), 41.0 (d), 51.6 (q), 74.1 (d), 86.3 (d), 128.7 (s), 131.0 (d), 134.8 (s), 139.3 (d), 168.5 (s); MS (FAB) *m/z* 407 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{40}NaO_4Si$ $[(M+Na)^+]$ 407.2594, found 407.2601.

4.1.30. (Methylthio)methyl ether 34. To a stirred solution of alcohol **33** (1.47 g, 3.83 mmol) in DMSO (28 mL) was added a 1:5.6 mixture of acetic acid and acetic anhydride (23 mL) at room temperature. The mixture was stirred at 40 °C for 3 h and diluted with hexane (54 mL) and 0.5 M phosphate buffer (pH 7, 90 mL). The layers were separated, and the aqueous layer was extracted with hexane (3× 30 mL). The organic layer and the extracts were combined, washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 130 g, hexane–ether 50:1→10:1) to give **34** (1.29 g, 74%) and **32** (174 mg, 10%) as a colorless oil, respectively. **34**. $[\alpha]_D^{28}$= −85.8 (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 1710, 1650, 1460, 1435, 1280, 1250, 1055, 840 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.05 (s, 3H), 0.01 (s, 3H), 0.71 (d, J=6.9 Hz, 3H), 0.88 (s, 9H), 0.96 (t, J=7.3 Hz, 3H), 1.54 (br s, 3H), 1.85 (d, J=1.3 Hz, 3H), 1.95–2.10 (m, 3H), 2.14 (s, 3H), 2.22–2.32 (m, 2H), 3.66 (d, J=9.2 Hz, 1H), 3.73 (s, 3H), 4.13 (ddd, J=3.0, 5.3, 7.9 Hz, 1H), 4.53 (d, J=11.5 Hz, 1H), 4.63 (d, J=11.5 Hz, 1H), 5.29 (br dd, J=6.9, 6.9 Hz, 1H), 6.91 (ddq, J=6.9, 6.9, 1.3 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.3 (q), −4.4 (q), 10.4 (q), 10.7 (q), 12.7 (q), 13.8 (q), 14.0 (q), 18.1 (s), 20.7 (t), 25.8 (q, 3C), 28.6 (t), 38.3 (d), 51.6 (q), 73.1 (t), 75.7 (d), 80.9 (d), 128.3 (s), 130.0 (d), 134.9 (s), 140.6 (d), 168.5 (s); MS (FAB) *m/z* 467 $(M+Na)^+$; HRMS (FAB) calcd for $C_{23}H_{44}NaO_4SSi$ $[(M+Na)^+]$ 467.2628, found 467.2623.

4.1.31. Carboxylic acid 20. To a stirred solution of (methylthio)methyl ether **34** (806 mg, 1.82 mmol) in MeOH (20 mL) was added 5 M LiOH (5 mL) at room temperature. The mixture was stirred at 30 °C for 11.5 h, acidified with 10% aqueous citric acid (60 mL), and extracted with ether (3×50 mL). The combined extracts were washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 70 g, hexane–ether 8:1→2:1) to give **20** (691 mg, 89%) as a colorless oil. $[\alpha]_D^{28}$= −90.3 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3100 (br), 1685, 1645, 1460, 1290, 1250, 1105, 1055, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H), 0.02 (s, 3H), 0.72 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.96 (t, J=7.3 Hz, 3H), 1.54 (br s, 3H), 1.86 (br s, 3H), 1.95–2.11 (m, 3H), 2.15 (s, 3H), 2.23–2.38 (m, 2H), 3.67 (d, J= 9.3 Hz, 1H), 4.16 (ddd, J=3.4, 3.4, 8.8 Hz, 1H), 4.53 (d, J=11.7 Hz, 1H), 4.63 (d, J=11.7 Hz, 1H), 5.30 (br dd, J= 6.8, 6.8 Hz, 1H), 7.06 (m, 1H). A signal due to one proton (COOH) was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (q), −4.4 (q), 10.4 (q), 10.7 (q), 12.3 (q), 13.8 (q), 14.0 (q), 18.1 (s), 20.8 (t), 25.8 (q, 3C), 28.8 (t), 38.2 (d), 73.1 (t), 75.5 (d), 80.9 (d), 127.8 (s), 130.0 (d), 134.9 (s), 143.3 (d), 173.1 (s); MS (FAB) *m/z* 453 $(M+Na)^+$; HRMS (FAB) calcd for $C_{22}H_{42}NaO_4SSi$ $[(M+Na)^+]$ 453.2471, found 453.2495.

4.1.32. Ester 35. To a stirred solution of carboxylic acid **20** (1.02 g, 2.37 mmol) and pentapeptide **19** (3.57 g, 5.41 mmol) in CH_2Cl_2 (6.4 mL) were added 4-(dimethylamino)pyridine (179 mg, 1.46 mmol) and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (518 mg, 2.70 mmol), and the mixture was stirred at room temperature for 13 h. The mixture was diluted with EtOAc (120 mL), washed with 10% aqueous citric acid (40 mL), H_2O (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (40 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 200 g, benzene–acetone 15:1→9:1→3:1) to give **35** (2.31 g, 91%) as a colorless oil. $[\alpha]_D^{28}$= +14.7 (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 3420, 1755, 1710, 1680, 1640, 1510, 1460, 1250, 1140, 1055, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H), 0.01 (s, 0.45H), 0.02 (s, 2.55H), 0.71 (d, J=7.3 Hz, 3H), 0.79 (d, J=6.8 Hz, 2.55H), 0.83–1.01 (m, 33H), 1.05 (d, J=6.8 Hz, 0.45H), 1.54 (s, 3H), 1.18–1.75 (m, 5H), 1.90 (s, 3H), 1.92–2.12 (m, 5H), 2.08 (s, 0.45H), 2.10 (s, 2.55H), 2.20–2.40 (m, 3H), 2.95 (s, 0.45H), 3.01 (s, 0.45H), 3.03 (s, 2.55H), 3.07 (s, 2.55H), 3.57 (d, J=17.1 Hz, 0.15H), 3.66 (d, J=8.8 Hz, 1H), 3.80 (d, J=15.1 Hz, 0.85H), 4.13 (ddd, J=2.9, 2.9, 9.8 Hz, 1H), 4.21 (d, J=15.1 Hz, 0.85H), 4.35 (d, J= 17.1 Hz, 0.15H), 4.51 (d, J=11.7 Hz, 0.15H), 4.53 (d, J= 11.7 Hz, 0.85H), 4.57–4.64 (m, 2.85H), 4.69 (dd, J=5.4, 8.8 Hz, 0.15H), 4.73 (dd, J=6.8, 8.3 Hz, 0.15H), 4.81 (dd, J=4.9, 8.8 Hz, 0.85H), 4.89 (d, J=11.7 Hz, 0.85H), 4.91 (d, J=11.7 Hz, 0.15H), 5.00 (d, J=3.4 Hz, 0.15H), 5.20 (d, J=2.9 Hz, 0.85H), 5.25 (dd, J=6.8, 8.8 Hz, 0.15H), 5.30 (br t, J=6.8 Hz, 1H), 5.55 (dd, J=6.4, 8.8 Hz, 0.85H), 6.34 (d, J=8.8 Hz, 0.15H), 6.55 (d, J=8.8 Hz, 0.85H), 6.71 (d, J=8.8 Hz, 0.85H), 6.91 (d, J=8.3 Hz, 0.15H), 7.02 (br t, J=7.3 Hz, 0.85H), 7.04 (m, 0.15H); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer) δ −5.3 (q), −4.3 (q), 10.3 (q), 10.7 (q), 11.7 (q), 12.8 (q), 13.8 (q), 13.9 (q), 14.2 (q), 16.7 (q), 17.4 (q), 18.1 (s), 19.1 (q), 19.7 (q), 20.7 (t), 22.2 (q), 23.0 (q), 24.7 (d), 25.8 (q, 3C), 26.2 (t), 28.9 (t), 30.5 (d), 30.6 (q), 31.0 (d), 36.5 (q), 37.3 (d), 37.9 (t), 38.4 (d), 50.8 (d), 53.1 (t), 53.1 (d), 56.8 (d), 73.3 (t), 74.4 (t), 75.9 (d), 76.3 (d), 80.9 (d), 94.4 (s), 127.9 (s), 130.0 (d), 134.8 (s), 142.2 (d), 166.7 (s), 168.7 (s), 170.0 (s), 170.1 (s), 171.4 (s), 171.7 (s); MS (FAB) *m/z* 1093 $(M+Na)^+$; HRMS (FAB) calcd for $C_{50}H_{89}^{35}Cl_3N_4NaO_{10}SSi$ $[(M+Na)^+]$ 1093.5032, found 1093.5020.

4.1.33. Alcohol 36. Ester **35** (83.6 mg, 0.078 mmol) was dissolved in a 5:3:12 mixture of HF·pyridine, pyridine, and THF (2 mL). The solution was stirred at 40 °C for 12 h, diluted with EtOAc (4 mL), and poured into saturated aqueous $NaHCO_3$ (12 mL) cooled at 0 °C. The mixture was extracted with EtOAc (3×8 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, benzene–acetone 8:1→ 5:1) to give **36** (74.5 mg, 100%) as a colorless oil. $[\alpha]_D^{24}$= +38.3 (*c* 1.37, $CHCl_3$); IR ($CHCl_3$) 3420, 3400 (br), 1755, 1710, 1680, 1630, 1510, 1460, 1410, 1240, 1140, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (d, J=6.8 Hz, 3H), 0.78 (d, J=6.8 Hz, 2.55H), 0.84 (d, J=7.3 Hz, 0.45H), 0.85–0.96 (m, 20.55H), 0.98 (d, J=6.8 Hz, 3H), 1.04 (d, J= 6.8 Hz, 0.45H), 1.16–1.48 (m, 3H), 1.53–1.75 (m, 2H), 1.58 (s, 3H), 1.91 (s, 3H), 1.90–2.10 (m, 5H), 2.15 (s, 0.45H),

2.16 (s, 2.55H), 2.28 (m, 1H), 2.40 (m, 1H), 2.53 (m, 1H), 2.87 (br s, 0.15H), 2.92 (br s, 0.85H), 2.94 (s, 0.45H), 3.03 (s, 3H), 3.06 (s, 2.55H), 3.58 (d, J=17.6 Hz, 0.15H), 3.71 (d, J=9.8 Hz, 0.85H), 3.74 (d, J=9.8 Hz, 0.15H), 3.79 (d, J=15.1 Hz, 0.85H), 4.16 (ddd, J=4.9, 5.4, 6.3 Hz, 1H), 4.21 (d, J=15.1 Hz, 0.85H), 4.47 (d, J=17.6 Hz, 0.15H), 4.61 (d, J=11.7 Hz, 1H), 4.59–4.73 (m, 3H), 4.75 (dd, J=7.8, 8.3 Hz, 0.15H), 4.82 (dd, J=8.9, 8.8 Hz, 0.85H), 4.89 (d, J=11.7 Hz, 0.85H), 4.92 (d, J=11.7 Hz, 0.15H), 5.11 (d, J=3.4 Hz, 0.15H), 5.24 (m, 0.15H), 5.27 (d, J=2.8 Hz, 0.85H), 5.30 (br t, J=6.8 Hz, 1H), 5.52 (dd, J=6.4, 8.8 Hz, 0.85H), 6.46 (d, J=8.8 Hz, 0.15H), 6.62 (d, J=9.3 Hz, 0.85H), 6.71 (d, J=8.3 Hz, 0.85H), 6.97 (d, J=8.3 Hz, 0.15H), 7.08 (br t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer) δ 10.3 (q), 11.4 (q), 11.7 (q), 12.7 (q), 13.9 (q), 14.0 (q), 14.3 (q), 16.9 (q), 17.4 (q), 19.1 (q), 19.6 (q), 20.7 (t), 22.2 (q), 23.0 (q), 24.7 (d), 26.1 (t), 30.0 (t), 30.60 (d), 30.63 (q), 31.2 (d), 36.5 (q), 37.2 (d), 37.8 (t), 38.3 (d), 51,1 (d), 52.8 (t), 53.3 (d), 57.0 (d), 73.4 (t), 74.4 (t), 76.1 (d), 77.6 (d), 80.9 (d), 94.4 (s), 127.7 (s), 130.6 (d), 135.0 (s), 141.4 (d), 166.5 (s), 168.7 (s), 169.9 (s), 170.1 (s), 171.6 (s, 2C); MS (FAB) m/z 979 $(M+Na)^+$; HRMS (FAB) calcd for $C_{44}H_{75}^{35}Cl_3N_4NaO_{10}S$ $[(M+Na)^+]$ 979.4166, found 979.4139.

4.1.34. *N*-Methylalanine ester 37. To a stirred solution of alcohol **36** (1.14 g, 1.19 mmol) in CH_2Cl_2 (4 mL) cooled at 0 °C were added *N*-Fmoc-*N*-methyl-L-alanine (578 mg, 1.78 mmol), 4-(dimethylamino) pyridine (78.7 mg, 0.644 mmol), and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (440 mg, 2.30 mmol), and the mixture was stirred at 0 °C for 2 h. The mixture was diluted with EtOAc (120 mL), washed with 10% aqueous citric acid (40 mL), H_2O (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (40 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on alumina (20 g, benzene–EtOAc 1:1) and subsequently on silica gel (50 g, benzene–acetone 10:1→5:1) to give **37** (1.41 g, 94%) as a colorless powder. $[\alpha]_D^{31}=+11.7$ (c 1.07, $CHCl_3$); IR ($CHCl_3$) 3430, 3360 (br), 1750, 1690, 1640, 1510, 1450, 1400, 1310, 1235, 1150, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77–1.02 (m, 30H), 1.15–1.75 (m, 5H), 1.42 (d, J=7.3 Hz, 3H), 1.54 (s, 0.6H), 1.56 (s, 2.4H), 1.90–2.13 (m, 4H), 1.90 (s, 3H), 2.07 (s, 0.6H), 2.10 (s, 2.4H), 2.23–2.41 (m, 4H), 2.92 (s, 3H), 2.95 (s, 0.6H), 3.02 (s, 0.6H), 3.03 (s, 2.4H), 3.06 (s, 2.4H), 3.58 (d, J=17.6 Hz, 0.2H), 3.80 (d, J=15.1 Hz, 0.8H), 3.85 (m, 1H), 4.21 (d, J=15.1 Hz, 0.8H), 4.22–4.94 (m, 7.4H), 4.62 (d, J=11.7 Hz, 1H), 4.80 (dd, J=5.4, 8.8 Hz, 0.8H), 4.89 (d, J=11.7 Hz, 1H), 5.02 (d, J=9.3 Hz, 1H), 5.20 (br d, J=2.4 Hz, 1H), 5.25 (br t, J=7.3 Hz, 0.2H), 5.45–5.50 (m, 1H), 5.55 (dd, J=6.8, 8.9 Hz, 0.8H), 6.45 (d, J=8.3 Hz, 0.2H), 6.59 (d, J=8.8 Hz, 0.8H), 6.61 (d, J=8.3 Hz, 0.2H), 6.71 (d, J=8.8 Hz, 0.8H), 6.88–7.02 (m, 1H), 7.26–7.78 (m, 8H); MS (FAB) m/z 1286 $(M+Na)^+$; HRMS (FAB) calcd for $C_{63}H_{92}^{35}Cl_3N_5NaO_{13}S$ $[(M+Na)^+]$ 1286.5376, found 1286.5390.

4.1.35. Carboxylic acid 38. To a stirred solution of *N*-methylalanine ester **37** (2.39 g, 1.89 mmol) in THF (75 mL) and 1 M NH_4OAc (15 mL) was added activated Zn powder (8.6 g, 132 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate and the washings were combined, washed with 10% aqueous citric acid (2×30 mL), H_2O (30 mL), and brine (30 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (200 g, $CHCl_3$–MeOH 20:1) to give **38** (2.07 g, 97%) as a colorless powder. $[\alpha]_D^{30}=-11.2$ (c 1.12, MeOH); IR (KBr) 3400 (br), 1740 (sh), 1710, 1690, 1530, 1640, 1450, 1400, 1210, 1100, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 0.69–0.91 (m, 30H), 1.09–1.75 (m, 5H), 1.33 (d, J=7.3 Hz, 3H), 1.57 (br s, 3H), 1.81 (br s, 3H), 1.81–2.01 (m, 4H), 2.01 (br s, 3H), 2.04–2.30 (m, 4H), 2.82 (s, 3H), 2.94 (s, 3H), 2.97 (s, 3H), 3.83 (d, J=15.3 Hz, 1H), 4.01 (d, J=15.3 Hz, 1H), 4.20–4.80 (m, 9H), 4.91 (br s, 1H), 5.05 (br s, 1H), 5.37 (br t, J=6.8 Hz, 1H), 5.43 (dd, J=5.9, 9.8 Hz, 1H), 6.78–6.93 (m, 3H), 7.18–7.33 (m, 4H), 7.40–7.53 (m, 2H), 7.63–7.69 (m, 2H). A signal due to one proton (COOH) was not observed; MS (FAB) m/z 1156 $(M+Na)^+$; HRMS (FAB) calcd for $C_{61}H_{91}N_5NaO_{13}S$ $[(M+Na)^+]$ 1156.6232, found 1156.6240.

4.1.36. Lactam 39a. To a stirred solution of carboxylic acid **38** (427 mg, 0.377 mmol) in MeCN (20 mL) was added diethylamine (2 mL), and the mixture was stirred at room temperature for 2.5 h and concentrated. The residual oil was purified by column chromatography on silica gel (12 g, $CHCl_3$–MeOH 30:1→5:1) to give crude amino acid **18** (344 mg) as a colorless powder. To a stirred solution of crude amino acid **18** (344 mg) in CH_2Cl_2 (350 mL) and DMF (35 mL) cooled at 0 °C were added 1-hydroxy-7-azabenzotriazole (546 mg, 3.93 mmol) and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (734 mg, 3.84 mmol), and the mixture was stirred at room temperature for 40.5 h. The mixture was diluted with EtOAc (200 mL), washed with 10% aqueous citric acid (2×30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 40 g, benzene–acetone 10:1→5:1) to give **39a** (222 mg, 66%) and **39b** (80.8 mg, 24%) as a colorless powder, respectively.

Compound **39a**. $[\alpha]_D^{28}=+14.7$ (c 0.48, $CHCl_3$); IR ($CHCl_3$) 3420, 3360, 1735, 1700 (sh), 1685, 1645, 1510, 1460, 1410, 1280, 1250, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 0.80 (d, J=6.8 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H), 0.88 (d, J=6.8 Hz, 3H), 0.88–0.97 (m, 15H), 0.99 (d, J=6.8 Hz, 3H), 1.03 (d, J=6.8 Hz, 3H), 1.24–1.74 (m, 5H), 1.41 (d, J=7.8 Hz, 3H), 1.59 (br s, 3H), 1.88–2.23 (m, 6H), 1.98 (br s, 3H), 2.09 (s, 3H), 2.32–2.45 (m, 2H), 2.96 (s, 3H), 2.98 (s, 3H), 3.09 (s, 3H), 3.47 (d, J=16.6 Hz, 1H), 4.08 (m, 1H), 4.11 (d, J=16.6 Hz, 1H), 4.54 (d, J=11.2 Hz, 1H), 4.58 (d, J=11.2 Hz, 1H), 4.65 (q, J=7.8 Hz, 1H), 4.84 (dd, J=8.9, 8.8 Hz, 1H), 4.93 (d, J=11.2 Hz, 1H), 4.94 (dd, J=3.7, 9.3 Hz, 1H), 4.99 (d, J=3.4 Hz, 1H), 5.27 (t, J=7.3 Hz, 1H), 5.51 (br t, J=6.8 Hz, 1H), 6.63 (d, J=8.8 Hz, 1H), 7.21 (dd, J=5.4, 8.8 Hz, 1H), 7.32 (d, J=9.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer) δ 9.9 (q), 10.8 (q), 11.8 (q), 12.6 (q), 13.7 (q), 14.12 (q), 14.16 (q), 14.21 (q), 16.3 (q), 17.3 (q), 19.6 (q), 20.0 (q), 20.9 (t), 22.4 (q), 23.2 (q), 24.6 (d), 26.2 (t), 28.6 (t), 30.4 (q), 30.5 (d), 31.2 (d), 31.7 (q), 35.7 (q), 36.6 (d), 37.7 (d),

37.8 (t), 51.6 (t), 52.0 (d), 53.3 (d), 53.8 (d), 54.2 (d), 74.3 (t), 76.6 (d), 76.7 (d), 82.0 (d), 128.2 (s), 130.3 (s), 133.8 (d), 143.1 (d), 167.8 (s), 168.4 (s), 169.7 (s), 170.0 (s), 171.6 (s), 171.8 (s), 172.1 (s); MS (FAB) *m/z* 916 $(M+Na)^+$; HRMS (FAB) calcd for $C_{46}H_{79}N_5NaO_{10}S$ $[(M+Na)^+]$ 916.5445, found 916.5430.

Compound **39b**. $[\alpha]_D^{27}=-1.8$ (*c* 0.63, $CHCl_3$); IR ($CHCl_3$) 3410, 1740, 1710, 1695, 1635, 1510, 1465, 1410, 1240, 1095, 1090, 1050 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (major rotamer) δ 0.75 (d, $J=6.6$ Hz, 3H), 0.81 (d, $J=7.6$ Hz, 6H), 0.90 (d, $J=6.6$ Hz, 3H), 0.91–1.00 (m, 18H), 1.30 (m, 1H), 1.36–1.45 (m, 2H), 1.41 (d, $J=7.3$ Hz, 3H), 1.53 (m, 1H), 1.59 (br s, 3H), 1.74 (ddd, $J=7.3$, 7.3, 13.9 Hz, 1H), 1.87 (br s, 3H), 1.88–2.08 (m, 4H), 2.08 (s, 3H), 2.14 (m, 1H), 2.27 (m, 1H), 2.30–2.43 (m, 2H), 2.88 (s, 3H), 2.94 (s, 3H), 3.08 (s, 3H), 3.28 (d, $J=16.8$ Hz, 1H), 3.91 (m, 1H), 4.54 (d, $J=11.7$ Hz, 1H), 4.57 (d, $J=16.8$ Hz, 1H), 4.59 (d, $J=11.7$ Hz, 1H), 4.88 (dd, $J=4.8$, 8.9 Hz, 1H), 4.89 (dd, $J=5.1$, 8.9 Hz, 1H), 5.01 (d, $J=11.0$ Hz, 1H), 5.19 (q, $J=7.3$ Hz, 1H), 5.37 (d, $J=1.8$ Hz, 1H), 5.40 (dd, $J=7.3$, 7.3 Hz, 1H), 5.52 (br t, $J=7.3$ Hz, 1H), 6.67 (d, $J=8.9$ Hz, 1H), 6.97 (d, $J=8.9$ Hz, 1H), 7.01 (br dd, $J=7.3$, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer) δ 9.9 (q), 10.8 (q), 11.8 (q), 12.7 (q), 13.7 (q), 14.1 (q), 14.2 (q), 15.3 (q), 16.4 (q), 17.0 (q), 19.8 (q), 19.9 (q), 20.9 (t), 22.6 (q), 23.0 (q), 24.6 (d), 26.2 (t), 28.4 (t), 30.1 (q), 31.4 (d), 31.6 (q), 32.2 (d), 34.5 (q), 36.2 (d), 37.4 (d), 37.9 (t), 50.9 (d), 51.8 (d), 52.1 (t), 53.0 (d), 53.9 (d), 73.7 (t), 75.7 (d), 76.1 (d), 82.2 (d), 128.7 (s), 130.2 (s), 134.2 (d), 144.8 (d), 166.6 (s), 167.1 (s), 170.1 (s), 170.3 (s), 170.6 (s), 171.2 (s), 171.4 (s); MS (FAB) *m/z* 916 $(M+Na)^+$; HRMS (FAB) calcd for $C_{46}H_{79}N_5NaO_{10}S$ $[(M+Na)^+]$ 916.5445, found 916.5434.

4.1.37. Aurilide (1). To a stirred solution of lactam **39a** (654 mg, 0.732 mmol) in THF (16 mL) and H_2O (4 mL) were added 2,6-lutidine (1.7 mL, 14.6 mmol) and $AgNO_3$ (5.37 g, 31.6 mmol), and the mixture was stirred at 65 °C for 1 h. The mixture was diluted with EtOAc (30 mL) and filtered through a pad of Celite, and the residue was washed with EtOAc (50mL). The filtrate and the washings were combined, washed with 1 M HCl (30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, benzene–acetone 8:1→5:1→3:1) to give 1 (566 mg, 93%) as a colorless powder. Using the same procedure as described above, 40 (3.1 mg, 97%) was obtained from 39b (3.4 mg, 0.15 mmol) as a colorless powder. Synthetic 1. $[\alpha]_D^{27}=-20$ (*c* 0.057, MeOH); UV (MeOH) λ_{max} 220 nm (sh) (ε 21000); IR, ^1H NMR, and FABMS spectra were identical to those of natural 1; ^{13}C NMR, see Table 1; HRMS (FAB) calcd for $C_{44}H_{75}N_5NaO_{10}$ $[(M+Na)^+]$ 856.5411, found 856.5395.

Compound **40**. $[\alpha]_D^{29}=+11$ (*c* 0.062, MeOH); IR ($CHCl_3$) 3500 (br), 3410, 1735 (sh), 1710, 1695 (sh), 1635, 1510, 1460, 1410, 1240, 1195, 1090 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 0.72 (d, $J=7.0$ Hz, 1.65H), 0.73 (d, $J=6.6$ Hz, 1.35H), 0.76 (d, $J=6.3$ Hz, 1.35H), 0.77 (d, $J=6.3$ Hz, 1.65H), 0.79 (d, $J=7.0$ Hz, 1.35H), 0.83 (d, $J=7.3$ Hz, 1.65H), 0.83–1.00 (m, 18H), 1.03 (d, $J=7.0$ Hz, 1.65H), 1.06 (d, $J=7.3$ Hz, 1.35H), 1.12 (d, $J=7.0$ Hz, 1.35H), 1.19 (d, $J=7.0$ Hz, 1.65H), 1.20–1.33 (m, 2H), 1.42–1.62 (m, 3H), 1.52 (br s, 1.65H), 1.55 (br s, 1.35H), 1.76–1.95 (m, 4H), 1.98–2.48 (m, 4H), 2.02 (br s, 1.35H), 2.11 (s, 1.65H), 2.50 (s, 1.65H), 2.53 (d, $J=5.5$ Hz, 0.55H), 2.67 (s, 1.65H), 2.80 (s, 1.35H), 2.89 (s, 1.35H), 2.96 (s, 1.35H), 2.98 (s, 1.65H), 3.36 (d, $J=16.5$ Hz, 0.45H), 3.37 (d, $J=17.2$ Hz, 0.55H), 3.40 (d, $J=5.0$ Hz, 0.45H), 3.79 (m, 0.55H), 3.88 (m, 0.45H), 4.52 (d, $J=17.2$ Hz, 0.55H), 4.53 (q, $J=7.3$ Hz, 0.55H), 4.77 (q, $J=7.3$ Hz, 0.45H), 4.85 (d, $J=16.5$ Hz, 0.45H), 4.96 (dd, $J=5.1$, 8.4 Hz, 0.45H), 4.98 (t, $J=9.2$ Hz, 0.55H), 5.05 (dd, $J=4.8$, 9.2 Hz, 0.55H), 5.10 (dd, $J=4.8$, 8.1 Hz, 0.45H), 5.29 (d, $J=10.3$ Hz, 0.45H), 5.38 (dd, $J=3.7$, 7.4 Hz, 0.45H), 5.39 (d, $J=10.6$ Hz, 0.55H), 5.48 (br t, $J=7.3$ Hz, 0.55H), 5.51 (t, $J=7.3$ Hz, 0.55H), 5.57 (br t, $J=7.3$ Hz, 0.45H), 5.69 (d, $J=3.7$ Hz, 0.45H), 5.90 (d, $J=2.9$ Hz, 0.55H), 6.76–6.81 (m, 1H), 7.35–7.41 (m, 1H), 7.56 (br t, $J=7.3$ Hz, 0.55H), 7.70 (br t, $J=7.3$ Hz, 0.45H); ^{13}C NMR (150 MHz, C_6D_6) δ 11.2 (q), 11.7 (q), 11.9 (q), 12.9 [13.0] (q), 13.9 [13.8] (q), 14.1 [14.3] (q), 14.5 [14.7] (q), 16.5 [16.6] (q), 17.5 [18.4] (q), 19.6 [20.1] (q), 19.8 [20.2] (q), 21.07 [21.11] (t), 22.6 [20.9] (q), 23.1 [23.3] (q), 24.9 [25.3] (d), 26.6 [26.4] (t), 31.2 [29.9] (q), 31.4 [31.0] (d), 32.2 (d), 32.9 [31.4] (t), 35.3 (q), 36.0 [35.8] (q), 37.6 [37.0] (d), 38.6 [37.7] (t), 40.8 [40.5] (d), 51.4 [52.0] (d), 52.1 [52.2] (t), 53.7 (d), 54.1 [54.2] (d), 54.8 (d), 71.7 (d), 76.4 [76.8] (d), 82.5 [82.4] (d), 129.4 [129.3] (s), 131.5 [131.7] (s), 133.1 [133.2] (d), 141.7 [141.8] (d). The minor counterparts of doubled signals in the ratio of 1.2:1 are in brackets. Signals due to carbonyls which could not be assigned major or minor rotamer: δ 166.9, 167.1, 167.8, 168.2, 170.0, 170.3, 171.3, 172.2, 172.4, 173.6; MS (FAB) *m/z* 856 $(M+Na)^+$; HRMS (FAB) calcd for $C_{44}H_{75}N_5NaO_{10}$ $[(M+Na)^+]$ 856.5411, found 856.5393.

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