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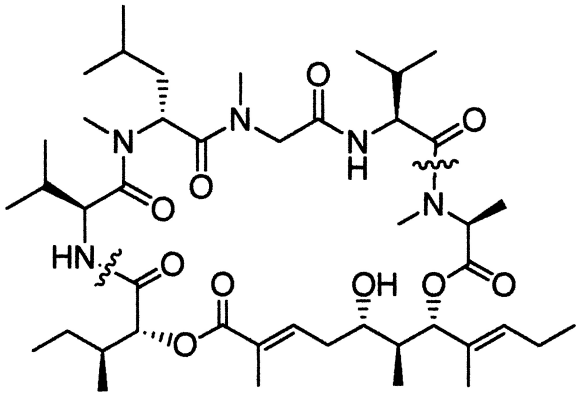

Aurilide (**1**)

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Solid Phase Library Synthesis of Cyclic Depsipeptides: Aurilide and Aurilide Analogues

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A solid-phase combinatorial synthesis approach toward the cyclic depsipeptide aurilide (**1**) and related analogues is described. The peptide moiety **2** was assembled on trityl linker-functionalized SynPhase Crowns using an Fmoc strategy. Optimization of the tetrapeptide assembly **5** was carried out using parallel multiple synthesis and LC/MS analysis. The aliphatic moiety **3a** was coupled with the solid-supported **2** using DIC/HOBt. Following deprotection and cleavage of linear precursor **26**, macrocyclization was achieved under high dilution conditions. Removal of the methylthiomethyl protecting group provided aurilide (**1**) in 11% overall yield. Synthesis of a combinatorial library of aurilide derivatives **4** was accomplished with a similar protocol using the TranSort technique.

Introduction

The solid-phase synthesis[1] of peptide and peptide mimetic libraries has been well developed. However, the preparation of libraries based on naturally occurring cyclic depsipeptides is a developing field.[2]

Aurilide (**1**) is a 26-membered cyclic depsipeptide isolated in 1996 from Japanese sea hare *Dolabella auricularia* and has a potent cytotoxity against HeLa S_3 cells (IC_{50} = 20 nM).[3] To elucidate structure−activity relationships and to find new potent compounds of this class, we planned a library synthesis of aurilide derivatives. The initial approach to the synthesis of cyclic depsipeptide **1** is outlined in Scheme 1. As reported, cyclization can be performed between the *N*-methylalanine and valine residues.[3b] The Val-D-MeLeu-Sar-Val segment **2** can be prepared by extension of the N terminus by Fmoc strategy on the solid-phase. SynPhase Crowns were selected as the solid-support.[4,5] Their modular format facilitates combinatorial synthesis of milligram quantities of discrete compounds (∼8 μmol per support) using the directed split-and-pool method. To avoid the difficulty of esterification on the solid support, the aliphatic moiety **3** was synthesized by solution-phase methods.[6] The key step is the coupling of acid **3** to the polymer-supported tetrapeptides **2**. Following cleavage from the solid-support, cyclization and deprotection yields aurilide (**1**). Diversification of the segment Val-MeLeu-Sar-Val of **2** was explored in order to synthesize a variety of aurilide derivatives **4** where AA_4-AA_3-AA_2-AA_1 was varied as follows. Library A: all possible diastereomers based on the D and L configurations of the chiral amino acid residues. Library B: replacement of the two *N*-methyl residues with corresponding nonmethyl residues (Sar → Gly; MeLeu → Leu). Library C: alternative permutations of the amino acids. The solid-phase synthesis of aurilide derivatives **4** required the assembly and incorporation of the long-chain aliphatic moiety, the efficient incorporation of N-methylated amino acids, and the formation of the Ala lactam with minimal racemization.[7]

Results and Discussion

Preparation of Aliphatic Moiety 3. Carboxylic acid **3** was synthesized by a reported method with slight modification (Scheme 2).[3b] Aldol reaction of **7** with (*E*)-2-methyl-2-pentenal in dry ether at −100 °C provided **8a** and **8b** in 50% yield as a 1:1 diastereomer mixture, and **8a** was carefully separated by silica gel column chromatography. This aldol reaction in CH_2Cl_2 selectively afforded **8b** in 62% yield. Amide transformation of **8a** with *N*,*O*-dimethylhydroxylamine, TBS protection, and DIBAL reduction provided aldehyde **11a**. The Mukaiyama aldol reaction of **11a** with 1-methoxy-2-methyl-1-(trimethylsilyloxy)butadiene afforded **12a**, whose C5 stereochemistry was inversed by oxidation and reduction to provide **13a** in 27% overall yield. Protection of the alcohol **13a** as a methylthiomethyl ether and basic hydrolysis afforded acid **15a**. Coupling of D-*allo*-isoleucic acid ester **16**[8] to conjugated carboxylic acid **15a** with 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride (EDCI)/4-(dimethylamino)pyridine (DMAP), removal of the TBS group (HF·Py), coupling to *N*-methyl-L-alanine (EDCI/DMAP), and deprotection[9] of phenacyl ester (Zn, AcOH) provided **3a** in 30% overall yield. The 7*R* isomer **3b** was also prepared from **8b** by a similar method.

Optimization of Synthesis of Library 25A. D and L Combination: Chemset 5A{*1*−*2, 2, 3*−*4, 1*−*2*}

To determine the most efficient conditions to prepare tetrapeptide library **5A** on SynPhase Crowns (Scheme 3),

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Scheme 1. Strategy for a Solid-Phase Library Synthesis of Auliride (**1**) and Its Derivatives **4**

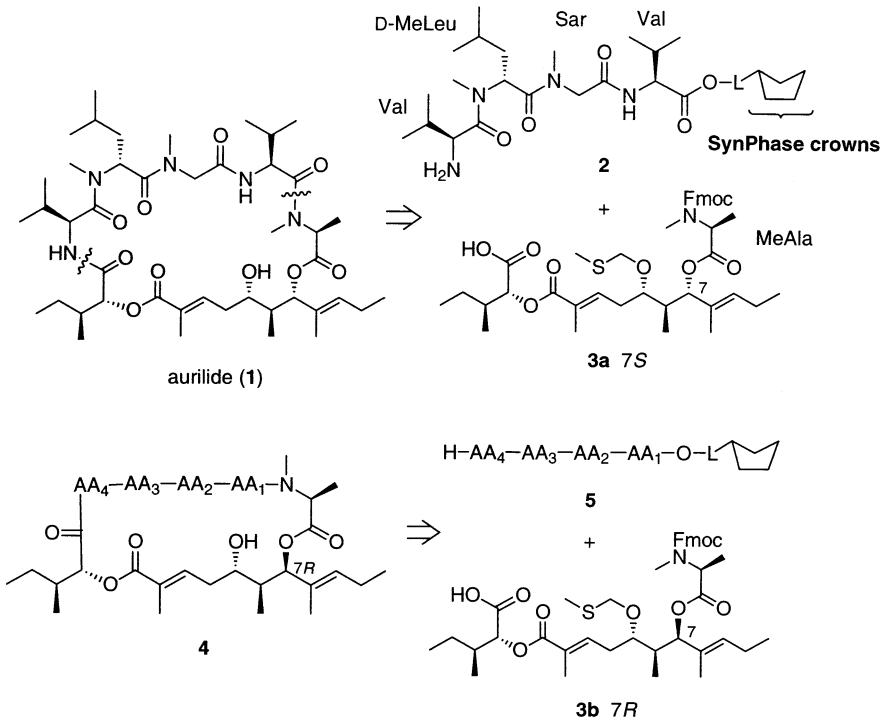


Table 1. Composition of Tetrapeptide Libraries

library	building blocks {*21,22,23,24*}
25A	{*1−2, 2, 3−4, 1−2*}
25B	{*1−2, 1, 1−2, 1−2*}
25C	{*2,4,6,2*}, {*2,3,6,2*}, {*2,2,5,4*}, {*2,4,5,3*}, {*2,3,4,3*}, {*3,4,5,2*}, {*4,2,5,2*}, {*4,3,6,2*}, {*4,3,5,3*}

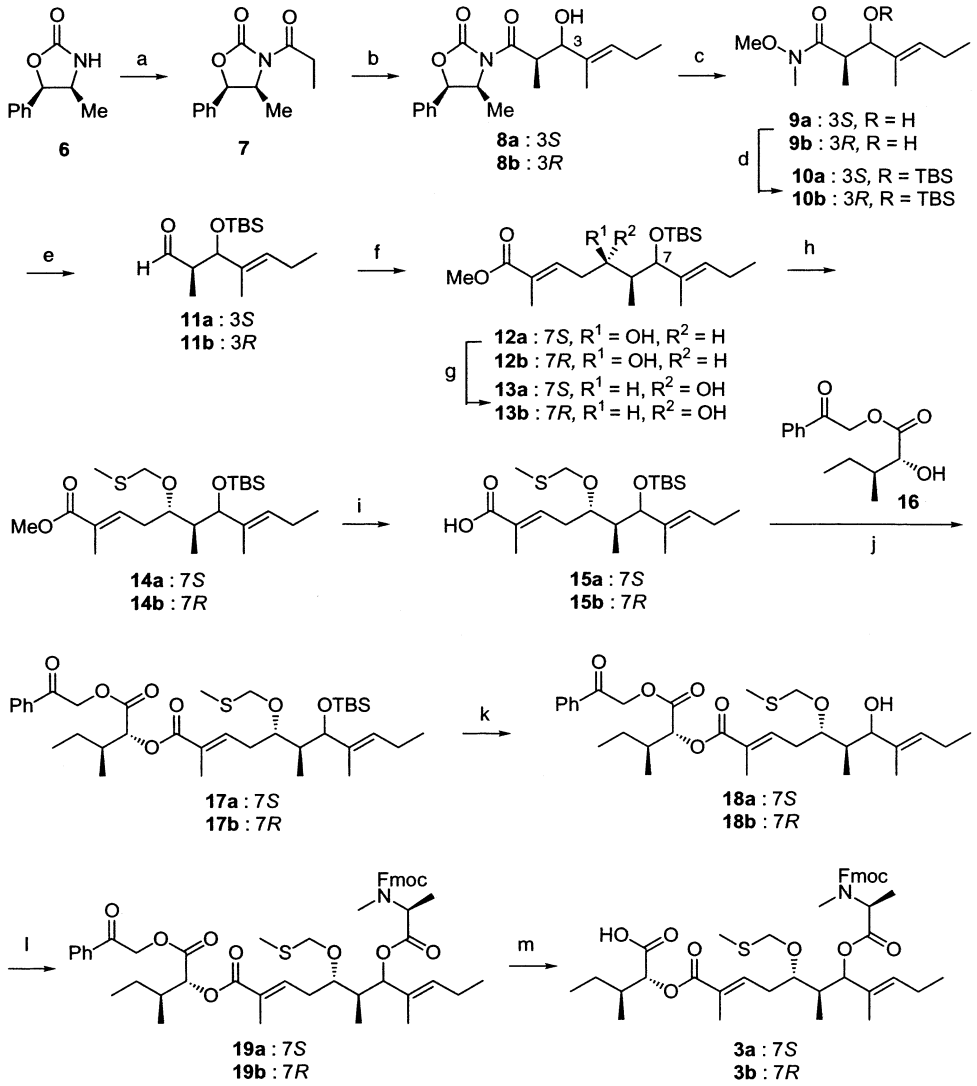
we simultaneously examined three coupling protocols using an Fmoc strategy. The optimization library was assembled using the following amino acids: **21**{*1−2*}, **22**{*2*}, **23**{*3−4*}, and **24**{*1−2*}. Three coupling protocols were explored: method A, Fmoc-Axx-OH/DIC/HOBt (0.1, 0.1, 0.12 M); method B, Fmoc-Axx-OH/HBTU[10]/HOBt/DIEA (0.1, 0.1, 0.1, 0.2 M); and method C, Fmoc-Axx-OH/TFFH[11]/DIEA (0.1, 0.1, 0.2 M), in DMF for 22 h at room temperature. Two linkers, trityl[12] and 4-hydroxymethylphenoxyacetamide (HMP),[13] were also explored in the study. In this rapid optimization, multiple synthesis was performed on SynPhase Crowns using the Multipin format.[4,5] Forty-eight functionalized Crowns (**5A**) were generated in exploring the three variables (eight target sequences **25A** × 2 linkers × 3 coupling methods). TFA cleavage yielded the optimization library **25A**. The 48 samples within library **25A** were analyzed by HPLC and LC/MS. The purities were determined by the ratios of intensities of UV absorption (214 nm). The results are presented in Table 2. The tetrapeptides **25A** were found to be sensitive to acid. Even 5% TFA/CH_2Cl_2 resulted in undesirable amide bond cleavage at the MeLeu-Sar bond. (H-Val-MeLeu-OH was observed as a minor component (25%) with 5% TFA/CH_2Cl_2 and as the major product (75%) with 50% TFA/CH_2Cl_2, data not shown). The acid lability of some N-methylated peptides has been reported.[14] Therefore, it was essential to use the trityl linker for the synthesis of a tetrapeptide moiety of aurilide. The trityl linker can be cleaved under mild conditions (1% TFA/CH_2Cl_2), whereas the HMP linker requires harsher conditions (50% TFA/CH_2Cl_2). The best overall purities (>80%) for the preparation of library **25A** were obtained using assembly method A on the trityl linker. The LC/MS analyses demonstrated that all tetrapeptide isomers gave major products with the desired molecular weight. As

Table 2. LC/MS Analysis of the Major Product Library **25A** with Methods A, B, and C on Trityl Linker[a]

entry	**25A** {21,22,23,24}	H-Val-MeLeu-Sar-Val-OH, chirality at each residue	purity of the major product[b] (%)			retention time[c] (min)
			method A	method B	method C	
1	{*1,2,3,1*}	DL-D	87	79	71	4.9
2	{*2,2,3,1*}	DL-L	89	70	70	4.8
3	{*1,2,4,1*}	DD-D	81	70	70	4.3
4	{*2,2,4,1*}	DD-L	86	86	78	4.2
5	{*1,2,3,2*}	LL-D	81	79	80	4.2
6	{*2,2,3,2*}	LL-L	90	73	65	4.3
7	{*1,2,4,2*}	LD-D	89	66	68	4.8
8	{*2,2,4,2*}[d]	LD-L	88	86	76	4.9

[a] The coupling reaction was carried out at a 0.1 M concentration in DMF for 22 h at room temperature. Method A, Fmoc-Axx-OH/DIC/HOBt; method B, Fmoc-Axx-OH/HBTU/HOBt/DIEA; method C, Fmoc-Axx-OH/TFFH/DIEA. [b] Purity was determined by reversed-phase HPLC (C18) with peak area (UV) at 214 nm. Conditions were shown in the Experimental Section. [c] Positive ion electrospray MS data: $m/z = 415$, $[M + H]^+$ were recorded. [d] Sequence present in natural product **1**.

Scheme 2. Preparation of Aliphatic Moiety **3**.



Reaction conditions: (a) BuLi, propanoyl chloride, THF, −78 °C, 1H, 68%; (b) (*E*)-2-methyl-2-pentenal, Bu_2BOTf, DIEA, −100 °C in ether (**8A** and **8b** (1:1), 50%) and −78 °C in CH_2Cl_2 (8b, 62%); (c) MeNH(OMe)·HCl, $AlMe_3$, THF, rt, 24 h, 45%; (d) TBSCl, imidazole, DMF, rt, 48 h, 90%; (e) DIBAL, THF, −78°C, 1 h, 97%; (f) 1-methoxy-2-methyl-1-(trimethylsiloxy)butadiene, BF_3·OEt_2, CH_2Cl_2/ether = 10:1, −78 °C, 2 h, 78%; (g) Dess−Martin periodinane, CH_2Cl_2, rt, 12 h, 92%; (h) Ac_2O, AcOH, DMSO, rt, 27 h, 87%; (i) LiOH, MeOH, H_2O, rt, 46 h, 94%; (j) EDCI, DMAP, CH_2Cl_2, rt, 96 h, 33%; (k) HF·Py, Py, THF, rt, 3 h, 60%; (l) Fmoc-MeAla-OH, EDCI, DMAP, CH_2Cl_2, rt, 20 h, 90%; (m) Zn, AcOH, ethyl acetate, H_2O, 45 °C, 27 h, quant.

Table 3. LC/MS Analysis of Library **25A** Prepared by Method A, Trityl Linker

entry	**25A** {21,22,23,24}	H-Val-MeLeu-Sar-Val-OH, chirality at each residue	purity in each t_R (%)[a]				MS data[b] (*m*/*z*)
			4.2 min	4.3 min	4.8 min	4.9 min	
1	{*1*,*2*,*3*,*1*}	DL-D	—[c]	—	—	87	415
2	{*2*,*2*,*3*,*1*}	DL-L	—	—	89	—	415
3	{*1*,*2*,*4*,*1*}	DD-D	—	81	—	—	415
4	{*2*,*2*,*4*,*1*}	DD-L	86	-—	-—	—	415
5	{*1*,*2*,*3*,*2*}	LL-D	81	—	—	—	415
6	{*2*,*2*,*3*,*2*}	LL-L	—	90	—	—	415
7	{*1*,*2*,*4*,*2*}	LD-D	—	—	89	—	415
8	{*2*,*2*,*4*,*2*}	LD-L	—	—	—	88	415

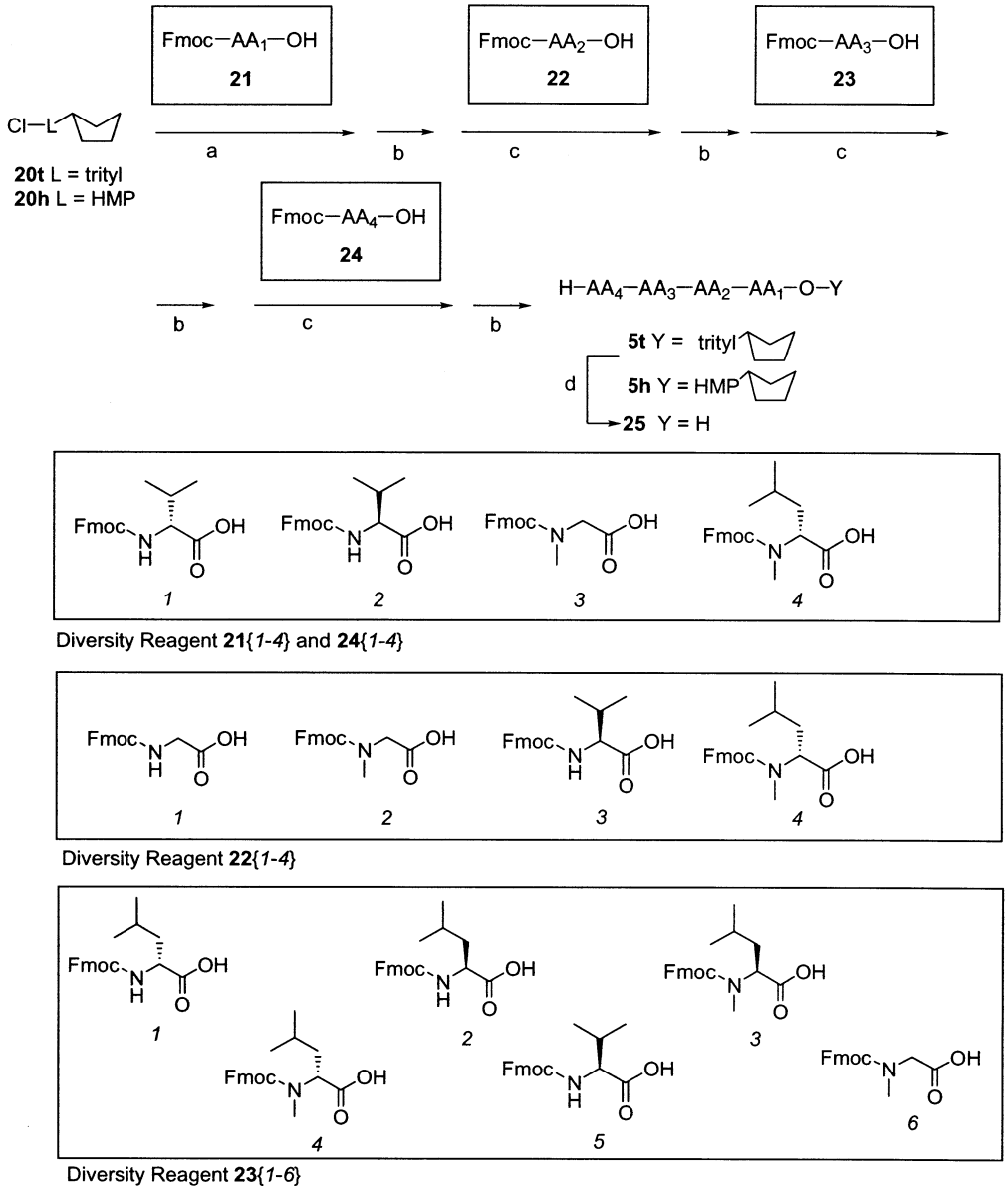
[a] Purity was determined by reversed-phase HPLC (C18) with peak area (UV) at 214 nm. Conditions were shown in the Experimental Section. [b] Positive ion electrospray MS data, expected $[M + H]^+$ observed. [c] Indicates that peaks were not detected at the respective retention time.

expected, a different retention time was observed for each peptide. A diastereomer formed by epimerization of any residue could be identified by comparison with the LC/MS traces of the other diastereomeric tetrapeptides. As shown in the experimental results (Table 3), epimerization was not detected during the coupling protocols by method A (<1%).

Replacement of the Two *N*-Methyl Residues: Library 25B. A second library was synthesized by the same protocols using Val, Gly, Leu, Val (Scheme 3). The target tetrapeptides **25B** were obtained with purities ranging from 77 to 87% (Table 4).

Alternative Permutations of the Amino Acids: Library 25C. The synthesis of the library **25C** was attempted using

Scheme 3



Reaction conditions: (a) For trityl Crowns 20t, (i) 50% AcCl, CH_2Cl_2, rt, 12 h, (ii) Fmoc-Axx-OH (0.1 M), *N*,*N*-diisopropylethylamine (DIEA) (0.25 M), CH_2Cl_2, rt, 12 h; for HMP Crowns 20h, (i) Fmoc-Axx-OH (0.18 M), 1,3-diisopropylcarbodiimide (DIC) (0.18 M), DMAP (3.6 mM), DMF/CH_2Cl_2 (1:4), 40 °C, 24 h. This protocol was repeated twice. (b) 20% Piperidine, DMF, rt, 30 min. (c) Fmoc-Axx-OH (0.1 M), coupling reagent [method A, Fmoc-Axx-OH/DIC/HOBt (1:1:1.2); method B, Fmoc-Axx-OH/HBTU/HOBt/DIEA (1:1:1:2); method C, Fmoc-Axx-OH/TFFH/DIEA (1:1:2); method D, Fmoc-Axx-OH/PyBrOP/DIEA (1:1:2)], DMF, rt, 22 h. (d) For trityl Crowns, 1% TFA, CH_2Cl_2, rt, 1 h; for HMP Crowns, 50% TFA, CH_2Cl_2, rt, 1 h.

Table 4. LC/MS Analysis of **25B** Prepared by Method A on Trityl Linker

entry	**25B** {21,22,23,24}	H-Val-Leu-Gly-Val-OH, chirality at each residue	purity in each t_R(%)[a] 3.1 min	3.9 min	4.3 min	4.4 min	MS data[b] (*m*/*z*)
9	{*1,1,2,1*}	DL-D	–[c]	–	–	84	387
10	{*2,1,2,1*}	DL-L	–	–	77	–	387
11	{*1,1,1,1*}	DD-D	–	77	–	–	387
12	{*2,1,1,1*}	DD-L	77	–	–	–	387
13	{*1,1,2,2*}	LL-D	87	–	–	–	387
14	{*2,1,2,2*}	LL-L	–	87	–	–	387
15	{*1,1,1,2*}	LD-D	–	–	85	–	387
16	{*2,1,1,2*}	LD-L	–	–	–	82	387

[a] Purity was determined by reversed-phase HPLC (C18) with peak area (UV) at 214 nm. Conditions were shown in the Experimental Section. [b] Positive ion electrospray MS data, expected $[M + H]^+$ observed. [c] Indicates that peaks were not detected at the respective retention time.

the DIC/HOBt coupling protocol (method A) on a trityl linker. However, poor coupling efficiencies were observed for *N*-methyl amino acids (data not shown). Therefore, further optimization of the reaction conditions was carried out utilizing DIC, HBTU, TFFH, and PyBrOP[15]. The latter two are known as effective coupling reagents for secondary

Scheme 4

Table 5. Results of Coupling with Various Reagents[a]

		purity[b] (%)			
entry	AA_6-AA_5	method A	method B	method C	method D
1	Val- Val	96	68	78	*c*
2	Val- D-MeLeu	96	85	88	*c*
3	D-MeLeu- Val	60	71	73	74
4	D-MeLeu- D-MeLeu	72	78	58	74

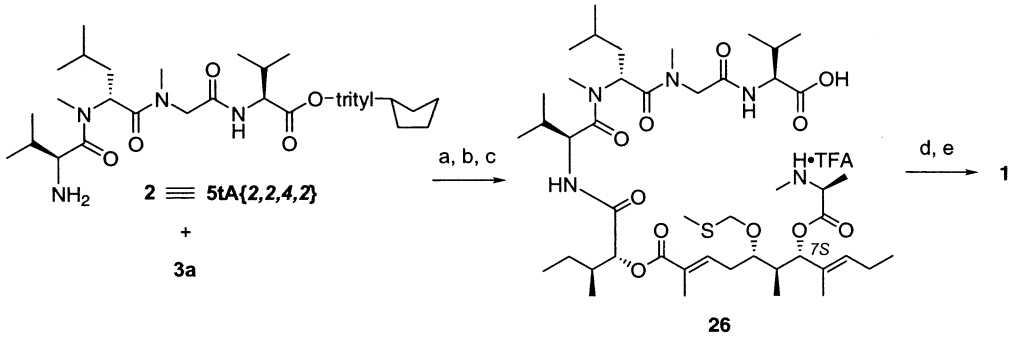
[a] The coupling reaction was carried out in DMF for 24 h at room temperature. Method A, Fmoc-Axx-OH/DIC/HOBt (0.1:0.1:0.12 M); method B, Fmoc-Axx-OH/HBTU/HOBt/DIEA (0.1:0.1:0.1:0.2 M); method C, Fmoc-Axx-OH/TFFH/DIEA (0.1:0.1:0.2 M); method D, Fmoc-Axx-OH/PyBrOP/DIEA (0.1:0.1:0.2 M). [b] Purity was determined by reversed-phase HPLC (C18) with peak area (UV) at 214 nm. Conditions were shown in the Experimental Section. [c] The reaction was not examined.

Table 6. LC/MS Analysis of **25C**

entry	**25C** {21,22,23,24}	sequence	purity[a] (%)	t_R (min)[a]	MS data[b] (*m*/*z*)
17	{*2*,*4*,*6*,*2*}	H-L-Val-Sar-D-MeLeu-L-Val-OH	87	4.7	415
18	{*2*,*3*,*6*,*4*}	H-D-MeLeu-Sar-L-Val-L-Val-OH	91	3.8	415
19	{*2*,*2*,*5*,*4*}	H-D-MeLeu-L-Val-Sar-L-Val-OH	64	4.5	415
20	{*2*,*4*,*5*,*3*}	H-Sar-L-Val-D-MeLeu-L-Val-OH	74	5.1	415
21	{*2*,*3*,*4*,*3*}	H-Sar-D-MeLeu-L-Val-L-Val-OH	72	4.5	415
22	{*3*,*4*,*5*,*2*}	H-L-Val-L-Val-D-MeLeu-Sar-OH	74	4.5	415
23	{*4*,*2*,*5*,*2*}	H-L-Val-L-Val-Sar-D-MeLeu-OH	75	4.3	415
24	{*4*,*3*,*6*,*2*}	H-L-Val-Sar-L-Val-D-MeLeu-OH	77	4.7	415
25	{*4*,*3*,*5*,*3*}	H-Sar-L-Val-L-Val-D-MeLeu-OH	72	4.7	415

[a] Purity was determined by reversed-phase HPLC (C18) with peak area (UV) at 214 nm. Conditions were shown in Experimental Section. [b] Positive ion electrospray MS data, expected $[M + H]^+$ observed.

Scheme 5. Synthesis of Aurilide (**1**)



Reaction conditions: (a) DIC, HOBt, DMF, rt, 96 h; (b) 20% piperidine, DMF, rt, 30 min; (c) 1% TFA, CH_2Cl_2, rt, 1 h; (d) EDCI, HOAt, 10% DMF−CH_2Cl_2, rt, 24 h; (e) $AgNO_3$, 2,6-lutidine, THF−H_2O (4:1), 70 °C, 20 h.

amines (Scheme 4). The results are summarized in Table 5. Library **25C** was synthesized using PyBrOP conditions (method D) for the coupling to support-bound *N*-methyl amino acid residues on the trityl linker; the results are shown in Table 6.

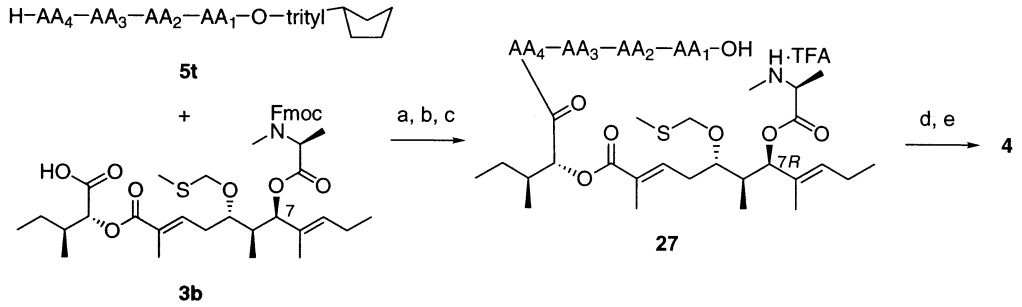
Synthesis of Aurilide (1). The coupling of the aliphatic moiety **3a** to the solid-supported tetrapeptide **2** (L = trityl) is challenging. This coupling was performed using the DIC/HOBt method (Scheme 5). The reaction proceeded slowly; however, after 96 h, the coupling was complete in excellent conversion. After deprotection of the Fmoc group under standard conditions, cleavage from the solid support (1% TFA/CH_2Cl_2) afforded the linear precursor **26** in 33% purity.

The cyclization was performed in the presence of EDCI (10 equiv) and HOAt[16] (10 equiv) in 10% DMF/CH_2Cl_2 (1 mM) for 20 h under high dilution conditions.[17] Removal of the methylthiomethyl group[18] with silver nitrate and 2,6-lutidine furnished aurilide (**1**) with 49% purity. After HPLC separation, **1** was obtained in 11% overall yield. The ^1H NMR (400 MHz, C_6D_6) spectral data of purified **1** were identical to those of the natural product.[3a] The synthetic **1** was shown to have strong cytotoxicity against HeLa S_3 cells-(IC_{50} = 0.087 nM).

Synthesis of Cyclic Depsipeptide Library 4. Synthesis of a cyclic depsipeptide library using various sequences consisting of two Val residues, Sar, and MeLeu and the 7*R* isomer **3b** was carried out (see Scheme 1). We selected **3b** as an aliphatic moiety instead of **3a** because the former was easily prepared stereospecifically via the Evans aldol reaction, as described above.

The libraries **5tA**−**5tC** were coupled to the aliphatic moiety **3b** using DIC and HOBt conditions, and deprotection

Scheme 6. Library Synthesis of Aurilide Derivatives **4**[a]



[a] Reaction conditions are the same as described in Scheme 5.

Table 7. LC/MS Analysis of Linear Precursors **27**

entry	**27**{21,22,23,24}	purity[a] (%)	t_R (min)[a]	entry	**27**{21,22,23,24}	purity[a] (%)	t_R (min)[a]
1	{*1,2,3,1*}	59	6.7	14	{*2,1,2,2*}	70	6.5
2	{*2,2,3,1*}	65	6.7	15	{*1,1,1,2*}	67	6.4
3	{*1,2,4,1*}	50	6.6	16	{*2,1,1,2*}	68	6.4
4	{*2,2,4,1*}	67	6.6	17	{*2,4,6,2*}	56	6.7
5	{*1,2,3,2*}	64	6.6	18	{*2,3,6,4*}	34	6.4
6	{*2,2,3,2*}	54	6.7	19	{*2,2,5,4*}	29	6.6
7	{*1,2,4,2*}	52	6.7	20	{*2,4,5,3*}	41	6.7
8	{*2,2,4,2*}	53	6.7	21	{*2,3,4,3*}	58	6.5
9	{*1,1,2,1*}	67	6.4	22	{*3,4,5,2*}	46	6.6
10	{*2,1,2,1*}	68	6.4	23	{*4,2,5,2*}	38	6.5
11	{*1,1,1,1*}	59	6.3	24	{*4,3,6,2*}	49	6.6
12	{*2,1,1,1*}	60	6.3	25	{*4,3,5,3*}	38	6.5
13	{*1,1,2,2*}	70	6.5				

[a] Purity was determined by reversed-phase HPLC (C8) with peak area (UV) at 214 nm. Conditions were shown in the Experimental Section.

Table 8. LC/MS Analysis of Aurilide Derivatives **4**

entry	product **4** {21,22,23,24}	sequence AA_4-AA_3-AA_2-AA_1	purity[a] (%)	t_R (min)[a]	MS data[b] (*m/z*)
1	{*1,2,3,1*}	D-Val-L-MeLeu-Sar-D-Val	41	10.7	834
2	{*2,2,3,1*}	D-Val-L-MeLeu-Sar-L-Val	26	10.8	834
3	{*1,2,4,1*}	D-Val-D-MeLeu-Sar-D-Val	42	10.3	834
4	{*2,2,4,1*}	D-Val-D-MeLeu-Sar-L-Val	31	10.4	834
5	{*1,2,3,2*}	L-Val-L-MeLeu-Sar-D-Val	45	10.2	834
6	{*2,2,3,2*}	L-Val-L-MeLeu-Sar-L-Val	42	10.2	834
7	{*1,2,4,2*}	L-Val-D-MeLeu-Sar-D-Val	51	10.3	834
8	{*2,2,4,2*}	L-Val-D-MeLeu-Sar-L-Val	57	11.2	834
9	{*1,1,2,1*}	D-Val-L-Leu-Gly-D-Val	25	10.5	806
10	{*2,1,2,1*}	D-Val-L-Leu-Gly-L-Val	47	10.8	806
11	{*1,1,1,1*}	D-Val-D-Leu-Gly-D-Val	36	10.4	806
12	{*2,1,1,1*}	D-Val-D-Leu-Gly-L-Val	42	10.3	806
13	{*1,1,2,2*}	L-Val-L-Leu-Gly-D-Val	36	10.3	806
14	{*2,1,2,2*}	L-Val-L-Leu-Gly-L-Val	58	10.3	806
15	{*1,1,1,2*}	L-Val-D-Leu-Gly-D-Val	48	10.0	806
16	{*2,1,1,2*}	L-Val-D-Leu-Gly-L-Val	45	10.4	806
17	{*2,4,6,2*}	L-Val-Sar-D-MeLeu-L-Val	29	10.3	834
18	{*2,3,6,4*}	D-MeLeu-Sar-L-Val-L-Val	27	10.1	834
19	{*2,2,5,4*}	D-MeLeu-L-Val-Sar-L-Val	20	10.6	834
20	{*2,4,5,3*}	Sar-L-Val-D-MeLeu-L-Val	22	10.3	834
21	{*2,3,4,3*}	Sar-D-MeLeu-L-Val-L-Val	27	10.0	834
22	{*3,4,5,2*}	L-Val-L-Val-D-MeLeu-Sar	25	10.1	834
23	{*4,2,5,2*}	L-Val-L-Val-Sar-D-MeLeu	18	10.2	834
24	{*4,3,6,2*}	L-Val-Sar-L-Val-D-MeLeu	28	10.0	834
25	{*4,3,5,3*}	Sar-L-Val-L-Val-D-MeLeu	21	10.5	834

[a] Purity was determined by reversed-phase HPLC (C8) with peak area (UV) at 214 nm. Conditions were shown in the Experimental Section. [b] Positive ion electrospray MS data, expected $[M + H]^+$ observed.

of the Fmoc group, followed by acid cleavage from the solid-support provided linear precursors **27**, whose cyclization was achieved in parallel under the same conditions as in the synthesis of **1** (Scheme 6). Finally, deprotection of the methylthiomethyl group with silver nitrate provided a library of aurilide derivatives **4** in 11−25% overall yields after purification by reversed-phase HPLC. The purities of the linear precursors **27** and the crude products **4** are shown in Tables 7 and 8. Although it is conceivable that the success of the cyclization is dependent on which amino acids were

used, we did not find such dependence; rather, we obtained all products **4** in moderate yields in this library synthesis. Library C (entries 17−25) provided lower purities than libraries A and B as a result of lower purities of the corresponding linear precursors **27**.

Conclusion

In summary, we have demonstrated the synthesis of aurilide (**1**) and a library of its derivatives **4** by solid support using the Multipin methodology and solution-phase cyclization. The synthetic target **1** was demonstrated to be cytotoxic against HeLa S_3 cells. The optimization of reaction conditions was efficiently performed by the simultaneous syntheses of all diastereomers consisting of D and L residues and their LC/MS analyses. In this synthesis, we demonstrated that a highly functionalized aliphatic moiety can be immobilized on a variety of solid-supported tetrapeptides. The biological activities of library **4** will be assessed, and outcomes will be described elsewhere.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on a JEOL model EX-270 (270 MHz) spectrometer and a JEOL model ECP-400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane, with the solvent resonance as the internal standard (benzene-d_6: δ 7.15). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and assignment. Column chromatography was performed on a Merck silica gel 60 (0.063−0.200 mm). LC/MS were obtained on AppliedBioSystems Mariner TK3500 Biospectrometry Workstation (ESI-TOF) mass spectrometers and a Hewlett-Packerd series 1100 (Waters Symmetry C18 5 μm, 4.6 × 50 mm for analysis of **25** and GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm for analysis of **1**, **4**, **26**, and **27**) with a linear gradient of 10% acetonitrile containing 0.1% formic acid/water containing 0.1% formic acid to 100% acetonitrile containing 0.1% formic acid over 9 min at 1.0 mL/min flow rate. Peak areas (UV) were integrated at 214 nm. HRMS (ESI-TOF) were calibrated with angiotensin I (Sigma), bradykinin (Sigma), and neurotensin (Sigma) as internal standards. Dry CH_2Cl_2 (Kanto Chemical Co., Inc.), DMF (peptide synthesis grade, Wako Pure Chemical Industries, Inc.), and TFA (Peptide Institute, Inc.) were used without further purification.

(4*S*,5*R*)-4-Methyl-5-phenyl-3-propanoyloxazolidin-2-one (7). A −78 °C solution of (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one (**6**) (2.00 g, 11.3 mmol) in THF (50 mL) was treated dropwise with butyllithium in hexanes (1.50 M, 8.3 mL, 12.4 mmol) and stirred at −78 °C. To the mixture was added a solution of propanoyl chloride (1.0 mL, 11.3 mmol) in THF (20 mL) dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and poured into saturated aqueous ammonium chloride at 0 °C. The layers were separated. The aqueous phase was extracted with ether. The combined organic layer was washed with water, washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1) to afford 1.78 g (7.64 mmol, 68% yield) of (4*S*,5*R*)-4-methyl-5-phenyl-3-propanoyloxazolidin-2-one (**7**) as a yellow oil. ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.26−7.46 (m, 5H), 5.67 (d, J = 6.6 Hz, 1H), 4.77 (dq, J = 6.6, 6.6 Hz, 1H), 2.97 (dq, J = 7.3, 7.3 Hz, 2H), 1.19 (t, J = 7.3 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 173.9, 153.2, 133.4, 128.8 × 2, 125.7, 79.1, 54.8, 29.4, 14.6, 8.4; IR (neat) 2920, 2878, 1761, 1685, 1358, 1335, 1237, 1191, 756 cm^{-1}; MS (ESI-TOF) 234.1 [M^+ + H].

(4*S*,5*R*)-3-[(*E*)-(2*R*,3*S*)-3-Hydroxy-2,4-dimethylhept-4-enoyl]-4-methyl-5-phenyloxazolidin-2-one (8a). A −78 °C solution of (4*S*,5*R*)-4-methyl-5-phenyl-3-propanoyloxazolidin-2-one (**7**) (6.95 g, 29.8 mmol) in ether (50 mL) was treated dropwise with dibutylboron triflate in CH_2Cl_2 (Aldrich, 1.0 M, 59.6 mL, 59.6 mmol) and stirred at 0 °C for 1 h. To the resulting mixture was added a solution of DIEA (5.51 mL, 34.3 mmol) in ether (20 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. To the reaction mixture was added a solution of (*E*)-2-methylpent-2-enal (4.25 mL, 37.2 mmol) in ether (30 mL) dropwise at −100 °C. The reaction solution was stirred at −100 °C for 1 h and poured into Na_2HPO_4 (saturated aqueous solution) at 0 °C. The layers were separated. The aqueous phase was extracted with ether. The combined organic layer was washed with saturated aqueous sodium bicarbonate, washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was passed through a short pat of silica gel to afford a 1:1 mixture of **8a** and **8b** (4.98 g, 15.0 mmol, 50% yield). **8a** was partially separated by silica gel column chromatography (hexane/ethyl acetate = 9:1). ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.27−7.46 (m, 5H), 5.67 (d, J = 6.6 Hz, 1H), 5.45 (br t, J = 7.6 Hz, 1H), 4.79 (dq, J = 6.6, 6.6 Hz, 1H), 4.07−4.21 (m, 2H), 2.05 (dq, J = 7.6, 7.6 Hz, 2H), 1.68 (s, 3H), 1.08 (d, J = 6.3 Hz, 3H), 0.97 (t, J = 7.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 176.6, 153.5, 133.7, 133.3, 131.4, 128.8 × 2, 125.7, 81.3, 79.0, 55.3, 40.7, 20.9, 14.9, 14.0, 10.8; IR (neat) 3509, 2966, 2935, 1780, 1695, 1456, 1386, 1197, 1122, 1068, 1020, 958, 767, 700 cm^{-1}; MS (ESI-TOF) 332.2 [M^+ + H].

(4*S*,5*R*)-3-[(*E*)-(2*R*,3*R*)-3-Hydroxy-2,4-dimethylhept-4-enoyl]-4-methyl-5-phenyloxazolidin-2-one (8b). A −78 °C solution of (4*S*,5*R*)-4-methyl-5-phenyl-3-propanoyloxazolidin-2-one (**7**) (1.78 g, 7.63 mmol) in CH_2Cl_2 (40 mL) was treated dropwise with dibutylboron triflate in CH_2Cl_2 (1.0 M, 15.3 mL, 15.3 mmol) and stirred at −78 °C for 1 h. To the resulting mixture was added triethylamine (1.22 mL, 8.78 mmol) dropwise at −78 °C. The mixture was stirred at −78 °C for 1 h. To the reaction mixture was added a solution of (*E*)-2-methylpent-2-enal (1.10 mL, 9.54 mmol) in CH_2Cl_2 (10 mL) dropwise at −78 °C. The reaction solution was stirred at −78 °C for 1 h and poured into Na_2HPO_4 (saturated aqueous solution) at 0 °C. The layers were separated. The aqueous phase was extracted with ether. The combined organic layer was washed with NH_4Cl (saturated aqueous solution), washed with brine, dried over $MgSO_4$, and

concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1) to afford 1.57 g (44.5 mmol, 62% yield) of (4*S*,5*R*)-3-[(*E*)-(2*R*,3*R*)-3-hydroxy-2,4-dimethylhept-4-enoyl]-4-methyl-5-phenyloxazolidin-2-one (**8b**) as a yellow oil. ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.29−7.46 (m, 5H), 5.68 (d, J = 7.3 Hz, 1H), 5.53 (m, 1H), 4.80 (dq, J = 7.3, 6.6 Hz, 1H), 4.38 (br s, 1H), 4.09 (dq, J = 2.6, 6.9 Hz, 1H), 2.07 (m, 2 H), 1.65 (s, 3H), 1.17 (d, J = 6.9 Hz, 3H), 0.96 (t, J = 7.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 176.7, 152.8, 133.3, 133.1, 128.9 × 2, 128.5, 125.7, 79.0, 75.8, 54.9, 40.7, 20.9, 14.7, 14.1, 11.0; MS (ESI-TOF) 354.2 [M^+ + Na].

(*E*)-(2*R*,3*S*)-3-Hydroxy-*N*-methoxy-*N*-methyl-2,4-dimethylhept-4-enoylamide (9a). A suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.08 g, 21.3 mmol) in THF (50 mL) was treated with a solution of trimethylaluminum in hexanes (1.01 M, 14.1 mL, 14.2 mmol) at 0 °C and stirred at room temperature for 1 h. To the resulting mixture was added a solution of (4*S*,5*R*)-3-[(*E*)-(2*R*,3*S*)-3-hydroxy-2,4-dimethylhept-4-enoyl]-4-methyl-5-phenyloxazolidin-2-one (**8a**) (1.57 g, 4.74 mmol) in THF (10 mL) dropwise at 0 °C. The reaction solution was stirred at room temperature for 24 h and quenched with addition of 1 M hydrochloric acid at 0 °C. The layers were separated. The aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with 1 M hydrochloric acid, washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1) to afford 0.46 g (2.14 mmol, 45% yield) of (*E*)-(2*R*,3*S*)-3-hydroxy-*N*-methoxy-*N*-methyl-2,4-dimethylhept-4-enoylamide (**9a**) as a colorless oil. ^{1}H NMR (270 MHz, chloroform-*d*) δ 5.41 (br t, J = 7.3 Hz, 1H), 4.08 (d, J = 8.3 Hz, 1H), 3.70 (s, 3H), 3.17 (s, 3H), 3.00−3.20 (m, 1H), 2.01 (dt, J = 7.3, 7.3 Hz, 2H), 1.59 (br s, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 176.9, 133.9, 130.6, 79.9, 61.5, 38.3, 32.0, 20.9, 14.9, 14.0, 11.1; IR (neat) 3437, 2966, 2936, 2876, 1659, 1645, 1464, 1305, 1181, 991, 856, 753 cm^{-1}; MS (ESI-TOF) 216.2 [M^+ + H].

(*E*)-(2*R*,3*R*)-3-Hydroxy-*N*-methoxy-*N*-methyl-2,4-dimethylhept-4-enoylamide (9b). ^{1}H NMR (270 MHz, chloroform-*d*) δ 5.58 (m, 1 H), 4.26 (d, J = 2.0 Hz, 1H), 3.72 (s, 3H), 3.20 (s, 3H), 3.06 (br s, 1H), 2.06 (dt, J = 7.3, 7.6 Hz, 2H), 1.59 (d, J = 0.7 Hz, 3H), 1.10 (d, J = 7.3 Hz, 2 H), 0.98 (t, J = 6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 178.3, 132.2, 128.2, 75.4, 61.6, 37.0, 32.0, 20.9, 14.2, 13.5, 10.4; MS (ESI-TOF) 216.2 [M^+ + H].

(*E*)-(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-2,4-dimethylhept-4-enoylamide (10a). To a solution of (*E*)-(2*R*,3*S*)-3-hydroxy-*N*-methoxy-*N*-methyl-2,4-dimethylhept-4-enoylamide (**9a**) (0.46 g, 2.14 mmol) and imidazole (0.33 g, 4.82 mmol) in DMF (2 mL) was added *tert*-butylchlorodimethylsilane (0.48 g, 3.21 mmol) at 0 °C. The mixture was stirred at room temperature for 48 h, poured into water at 0 °C, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 92:8) to afford 0.63 g (1.91 mmol, 90% yield) of (*E*)-(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-2,4-dimethylhept-4-enoylamide (**10a**) as a colorless oil. ^{1}H NMR (270 MHz, chloroform-*d*) δ 5.36 (br t, J = 7.6 Hz, 1H), 4.13 (d, J = 9.9 Hz, 1H), 3.72 (s, 3H), 3.16 (s, 3H), 3.05−3.20 (m, 1H), 2.01 (dtt, J = 3.6, 7.6, 7.6 Hz, 2H), 1.55 (br s, 3H), 0.94 (t, J = 7.6 Hz, 3H), 0.81 (d, J = 4.3 Hz, 3H), 0.79 (br s, 9H), −0.02 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 176.5, 134.1, 131.2, 81.8, 61.4, 38.8, 31.9, 25.7, 20.9, 18.1, 14.3, 13.9, 10.2, −4.8, −5.2; IR (neat) 2961, 2933, 2897, 1664, 1472, 1463, 1388, 1255, 1061, 1004, 996, 837, 779 cm^{-1}; MS (ESI-TOF) 330.3 [M^+ + H].

(*E*)-(2*R*,3*R*)-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-2,4-dimethylhept-4-enoylamide (10b). ^{1}H NMR (270 MHz, chloroform-*d*) δ 5.29 (t. J = 6.9 Hz, 1H), 4.09 (d, J = 9.2 Hz, 1H), 3.62 (s, 3H), 3.05−3.20 (m, 1H), 3.08 (s, 3H), 1.93 (m, 2H), 1.56 (s, 3H), 1.16 (d, J = 6.9 Hz, 3H), 0.87 (br s, 12H), −0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 176.1, 135.0, 129.3, 80.4, 61.6, 40.5, 32.1, 25.9, 25.7, 20.8, 18.3, 14.9, 13.8, 11.1, −4.6, −5.0; IR (neat) 3360, 2896, 2872, 2800, 1647, 1448, 1244, 1055, 992, 834, 765 cm^{-1}; MS (ESI-TOF) 330 [M^+ + H].

(*E*)-(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhept-4-enal (11a). A −78 °C solution of (*E*)-(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-2,4-dimethylhept-4-enoylamide (**10a**) (3.52 g, 10.68 mmol) in dry THF (50 mL) was treated dropwise with diisobutylaluminum hydride in toluene (1 M, 22.4 mL, 22.4 mmol) and stirred at −78 °C for 1 h. The reaction mixture was quenched with Na_2SO_4 (saturated aqueous solution) at −78 °C. The suspension was treated with excess $Na_2SO_4 \cdot 10H_2O$ at room temperature, dried over Na_2SO_4, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 19:1) to afford 2.79 g (10.31 mmol, 97% yield) of (*E*)-(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylhept-4-enal (**11a**) as a colorless oil. ^{1}H NMR (270 MHz, chloroform-*d*) δ 9.73 (d, J = 3.0 Hz, 1H), 5.36 (t, J = 7.3 Hz, 1H), 4.04 (d, J = 8.6 Hz, 1H), 2.55 (ddq, J = 3.0, 6.9, 8.6 Hz, 1H), 2.03 (dq, J = 7.3, 7.3 Hz, 1H), 2.02 (dq, J = 7.3, 7.3 Hz, 1H), 1.55 (br s, 3H), 0.95 (t, J = 7.3 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.84 (br s, 9H), 0.01 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 205.5, 133.8, 130.9, 80.7, 50.2, 26.0, 25.8, 20.8, 18.1, 13.8, 11.0, 10.7, −4.4, −5.3; IR (neat) 2961, 2932, 2859, 1732, 1463, 1253, 1061, 837, 776, 609, 537 cm^{-1}.

(*E*)-(2*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhept-4-enal (11b). ^{1}H NMR (270 MHz, chloroform-*d*) δ 9.63 (d, J = 2.0 Hz, 1H), 5.37 (t, J = 7.3 Hz, 1H), 4.22 (d, J = 6.3 Hz, 1H), 2.42−2.50 (m, 1H), 2.00 (dq, J = 7.3, 7.3 Hz, 2H), 1.55 (br s, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H), 0.87 (br s, 9H), 0.07 (s, 3H), −0.00 (s, 3H); ^{13}C NMR (100 MHz, chloroform-*d*) δ 204.5, 135.4, 134.0, 77.9, 51.0, 25.8, 20.7, 18.1, 14.0, 13.8, 9.2, −4.5, −5.3; IR (neat) 2959, 2932, 2859, 1728, 1463, 1253, 1052, 837, 775 cm^{-1}.

Methyl (2*E*,8*E*)-(5*R*,6*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundeca-2,8-dienoate (12a). A −78 °C solution of (*E*)-(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-hept-4-enal (**11a**) (2.79 g, 10.3 mmol) and 1-methoxy-2-methyl-1-(trimethylsilyloxy)butadiene (5.77 g, 30.9 mmol) in CH_2Cl_2/ether (10:1 v/v, 55 mL) was treated with borontrifluoride diethyl ether complex (1.96 mL, 15.5 mmol) and stirred at −78 °C for 2 h. To the reaction mixture was added a mixture of THF/water/1 M hydrochrolic acid (5:1:0.4 v/v, 50 mL) at −78 °C. The layers were separated. The aqueous phase was extracted with ether. The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 92:8) to afford 3.08 g (8.01 mmol, 78% yield) of methyl (2*E*,8*E*)-(5*R*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundeca-2,8-dienoate (**12a**) as a colorless oil. ^{1}H NMR (270 MHz, chloroform-*d*) δ 6.78 (br t, J = 7.3 Hz, 1H), 5.45 (br t, J = 7.6 Hz, 1H), 4.02 (dt, J = 1.3, 5.6 Hz, 1H), 3.99 (d, J = 5.3 Hz, 1H), 3.71 (br s, 3H), 2.33−2.44 (m, 1H), 2.15−2.25 (m, 1H), 2.04 (dq, J = 7.6, 7.6 Hz, 2H), 1.84 (br s, 3H), 1.67 (ddq, J = 1.3, 5.3, 6.6 Hz, 1H), 1.51 (br s, 3H), 0.96 (t, J = 7.6 Hz, 3H), 0.89 (br s, 9H), 0.88−0.91 (m, 3H), 0.07 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, chloroform-*d*) δ 168.6, 139.4, 133.9, 128.9 × 2, 82.4, 70.7, 51.8, 39.1, 33.8, 26.0, 20.9, 18.1, 14.0, 12.8 × 2, 11.6, −4.4, −5.2; IR (neat) 3517, 2959, 2858, 1716, 1652, 1463, 1436, 1285, 1257, 1097, 1055, 837, 777, 670 cm^{-1}; MS (ESI-TOF) 385.3 [M^+ + H], 402.3 [M^+ + Na].

Methyl (2*E*,8*E*)-(5*R*,6*S*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundeca-2,8-dienoate (12b). ^{1}H NMR (270 MHz, chloroform-*d*) δ 6.76 (br t, J = 7.3 Hz, 1), 5.38 (br t, J = 7.3 Hz, 1H), 3.97 (d, J = 6.6 Hz, 1H), 3.78 (ddd, J = 1.7, 5.9, 7.6 Hz, 1H), 3.73 (s, 3H), 2.43 (dt, J = 14.5, 7.6 Hz, 1H), 2.26 (dt, J = 14.5, 7.6 Hz, 1H), 2.04 (ddd, J = 7.3, 7.6, 14.5 Hz, 1H), 2.03 (ddd, J = 7.3, 7.6, 14.5 Hz, 1H), 1.85 (d, J = 1.0 Hz, 3H), 1.61 (m, 1H), 1.53 (s, 3H), 0.96 (t, J = 7.6 Hz, 3H), 0.91 (d, J = 5.0 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 168.5, 138.9, 135.2, 129.3, 129.1, 81.8, 72.4, 51.8, 40.9, 34.7, 26.0, 20.8, 18.2, 13.9, 12.7, 12.2, 7.5, −4.3, −5.0; IR (neat) 3522, 2959, 2858, 1717, 1652, 1472, 1463, 1284, 1060, 870, 837, 775 cm^{-1}; MS (ESI-TOF) 385.3 [M^+ + H].

Methyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundeca-2,8-dienoate (13a). To a solution of methyl (2*E*,8*E*)-(5*R*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundec-2,8-dienoate (**12a**) (3.00 g, 7.80 mmol) in CH_2Cl_2 (50 mL) was added Dess−Martin periodinane (6.62 g, 15.6 mmol) at 0 °C and stirred at room temperature for 12 h. The mixture was concentrated in vacuo, diluted with hexanes, and filtered through Celite. The filtrated was concentrated in vacuo to afford 2.74 g (7.16 mmol, 92% yield) of methyl (2*E*,8*E*)-(6*R*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-oxo-undeca-2,8-dienoate. This compound was used for the next reaction without further purification.

A −23 °C solution of methyl (2*E*,8*E*)-(6*R*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-oxoundeca-2,8-dienoate (1.66 g, 4.34 mmol) in methanol (40 mL) was treated portionwise with sodium borohydride (0.17 g, 4.34 mmol) and stirred at −23 °C for 2 h. The reaction mixture was quenched with citric acid (10% aqueous solution) at 0 °C and concentrated in vacuo. The residue was extracted with ethyl acetate; washed with citric acid (10% aqueous solution), saturated aqueous sodium bicarbonate and brine; dried over sodium sulfate; and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/1,2-dichloroethane = 1:1) to afford 0.58 g (0.58 mmol, 35% yield) of methyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundeca-2,8-dienoate (**13a**) as a colorless oil. ^{1}H NMR (270 MHz, chloroform-*d*) δ 6.93−6.98 (m, 1H), 5.29 (t, J = 7.3 Hz, 1H), 3.82 (d, J = 9.2 Hz, 1H), 3.80 (dt, J = 3.6, 7.6 Hz, 1H), 3.71 (s, 3H), 2.25−2.47 (m, 2H), 2.01 (dq, J = 7.6, 7.6 Hz, 2H), 1.84 (br s, 3H), 1.76 (ddq, J = 9.2, 7.6, 7.6 Hz, 1H), 1.55 (br s, 3H), 0.95 (t, J = 7.6 Hz, 3H), 0.88 (br s, 9H), 0.64 (d, J = 7.3 Hz, 3H), 0.08 (s, 3H), −0.00 (s, 3H); ^{13}C NMR (100 MHz, chloroform-*d*) δ 168.6, 139.4, 134.9, 131.1, 128.7, 86.4, 74.2, 51.7, 41.1, 33.6, 25.9, 20.8, 18.1, 13.7, 13.2, 12.8, 10.9, −4.1, −5.1; IR (neat) 3495, 2931, 2859, 1716, 1652, 1463, 1436, 1251, 1043, 837, 776, 744, 671 cm^{-1}; MS (ESI-TOF) 385.3 [M^+ + H], 402.3 [M^+ + NH_4].

Methyl (2*E*,8*E*)-(5*S*,6*S*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundeca-2,8-dienoate (13b). ^{1}H NMR (270 MHz, chloroform-*d*) δ 6.90 (br t, J = 6.6 Hz, 1H), 5.35 (br t, J = 7.3 Hz, 1H), 4.10 (d, J = 4.6 Hz, 1H), 3.72 (s, 3H), 3.70 (dt, J = 4.0, 7.6 Hz, 1H), 2.26−2.37 (m, 2H), 2.04 (dq, J = 7.3, 7.3 Hz, 2H), 1.86 (br s, 3H), 1.80 (ddq, J = 4.6, 7.3, 7.3 Hz, 1H), 1.62 (s, 3H), 0.96 (t, J = 7.3 Hz, 3H), 0.90 (s, 9H), 0.81 (d, J = 7.3 Hz, 3H), 0.06 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 168.6, 139.2, 134.4, 129.8, 129.2, 80.8, 72.9, 51.8, 43.0, 34.1, 25.9, 20.9, 18.2, 14.0, 13.1, 12.8, 12.2, −4.4, −5.1; IR (neat) 3481, 2959, 2931, 2896, 2858, 1717, 1652, 1472, 1463, 1437, 1283, 1256 cm^{-1}; MS (ESI-TOF) 385.3 [M^+ + NH_4].

Methyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (14a). A solution of methyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6,8-trimethylundeca-2,8-dienoate (**13a**) (1.72 g, 4.47 mmol) in dimethyl sulfoxide (20 mL) was treated with acetic anhydride (20 mL) and acetic acid (20 mL) at room temperature and stirred at room temperature for 27 h. The reaction mixture was concentrated in vacuo and azeotroped with toluene several times. The residue was diluted with ether, washed three times with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 49:1) to afford 1.74 g (3.91 mmol, 87% yield) of methyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methythiomethoxy)undeca-2,8-dienoate (**14a**) as a yellow oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.89−6.93 (m, 1H), 5.28 (br t, J = 6.8 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 11.6 Hz, 1H), 4.11−4.15 (m, 1H), 3.72 (s, 3H), 3.66 (d, 1H, J = 9.2 Hz), 2.16−2.35 (m, 2H), 2.14 (s, 3H), 1.95−2.12 (m, 2H), 1.85 (br s, 3H), 1.53 (br s, 3H), 0.95 (t, J = 7.2 Hz, 3H), 0.87 (br s, 9H), 0.70 (d, J = 6.8 Hz, 3H), 0.00 (s, 3H), −0.05 (s,

3H); ^{13}C NMR (100 MHz, chloroform-*d*) δ 168.6, 140.7, 135.0, 130.0, 128.4, 81.0, 75.7, 73.2, 51.7, 38.3, 28.6, 25.9, 20.8, 18.2, 14.1, 13.9, 12.8, 10.8, 10.5, −4.3, −5.2; IR (neat) 2960, 2930, 2858, 1717, 1653, 1463, 1436, 1248, 1219, 1056, 837, 773 cm^{-1}; MS (ESI-TOF) 462.4 [$M^+ + NH_4$].

Methyl (2*E*,8*E*)-(5*S*,6*S*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (14b). ^{1}H NMR (270 MHz, chloroform-*d*) δ 6.80 (br t, J = 7.3 Hz, 1H), 5.26 (br t, J = 6.9 Hz, 1H), 4.60 (d, J = 11.6 Hz, 1H), 4.49 (d, J = 11.6 Hz, 1H), 3.71 (s, 3H), 3.67 (d, J = 9.2 Hz, 1H), 3.58 (dt, J = 9.6, 3.3 Hz, 1H), 2.07−2.42 (m, 2H), 2.11 (s, 3H), 1.97−2.06 (m, 2H), 1.83 (d, J = 1.0 Hz, 3H), 1.59 (br s, 3H), 0.98 (br s, 3H), 0.95 (t, J = 7.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 168.4, 140.2, 135.3, 130.0, 128.4, 81.4, 75.8, 72.9, 51.6, 38.8, 28.7, 25.9, 20.8, 18.2, 13.8, 12.7, 10.8, 10.6, −4.4, −5.0; IR (neat) 2960, 2858, 1717, 1463, 1436, 1251, 1047, 837, 775, 513 cm^{-1}; MS (ESI-TOF) 462.3 [$M^+ + H$].

(2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoic Acid (15a). A solution of methyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylsulfanylmethyloxy)undeca-2,8-dienoate (**14a**) (1.74 g, 3.91 mmol) in methanol (25 mL) was treated with 1 M aqueous lithum hydroxide (25 mL, 25 mmol) at 0 °C and stirred at room temperature for 46 h. The reaction mixture was acidified with 10% aqueous citric acid at 0 °C and concentrated in vacuo. The residue was extracted with ethyl acetate, washed with 10% aqueous citric acid, washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7:3) to afford 1.59 g (3.69 mmol, 94% yield) of (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoic acid (**15a**). ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.04−7.10 (m, 1H), 5.30 (br t, J = 6.3 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 11.6 Hz, 1H), 4.13−4.19 (m, 1H), 3.67 (d, J = 9.2 Hz, 1H), 2.28−2.42 (m, 2H), 2.15 (s, 3H), 1.89−2.10 (m, 3H), 1.86 (br s, 3H), 1.54 (br s, 3H), 0.96 (t, J = 7.3 Hz, 3H), 0.88 (br s, 9H), 0.72 (d, J = 6.9 Hz, 3H), 0.01 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (100 MHz, chloroform-*d*) δ 173.5, 143.4, 135.0, 127.9, 81.0, 75.5, 73.2, 38.2, 28.9, 25.9, 20.8, 18.2, 14.1, 13.9, 12.4, 10.8, 10.4, −4.3, −5.2; IR (neat) 2960, 2665, 1683, 1645, 1463, 1428, 1290, 1254, 1105, 1049, 837, 775 cm^{-1}; MS (ESI-TOF) 431.3 [$M^+ + H$], 448.4 [$M^+ + NH_4$], 453.5 [$M^+ + Na$].

(2*E*,8*E*)-(5*S*,6*S*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoic Acid (15b). ^{1}H NMR (270 MHz, chloroform-*d*) δ 6.95 (br t, J = 7.3 Hz, 1H), 5.26 (br t, J = 7.3 Hz, 1H), 4.61 (d, J = 11.6 Hz, 1H), 4.49 (d, J = 11.6 Hz, 1H), 3.67 (d, J = 8.9 Hz, 1H), 3.60 (dt, J = 3.3, 6.6 Hz, 1H), 2.13−2.43 (m, 2H), 2.11 (s, 3H), 2.03 (m, 1H), 1.84 (br s, 3H), 1.59 (br s, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 173.2, 143.0, 135.4, 130.1, 128.0, 81.5, 75.7, 72.9, 38.7, 29.1, 25.9, 20.9, 18.3, 13.9 × 2, 12.4, 10.9, 10.7, −4.3, −4.9; IR (neat) 2961, 1646, 1472, 1463, 1424, 1292, 1257, 1046, 837, 755, 681, 567 cm^{-1}.

(1*R*,2*S*)-2-Methyl-1-[(2-oxo-2-phenylethoxy)carbonyl]-butyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (17a). A mixture of (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoic acid (**15a**) (1.59 g, 3.69 mmol), 2-oxo-2-phenylethyl (2*R*,3*S*)-2-hydroxy-3-methylpentanoate (**16**) (1.39 g, 5.54 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (50 mL) was treated with EDCI (2.12 g, 11.1 mmol) at 0 °C. The mixture was stirred at room temperature for 96 h. The reaction mixture was poured into 10% aqueous citric acid. The mixture was extracted with ethyl acetate. The combined organic phase was washed with 10% aqueous citric acid, washed with saturated aqueous sodium bicarbonate, washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 19:1) to afford 0.80 g (1.21 mmol, 33% yield) of (1*R*,2*S*)-2-methyl-1-[(2-oxo-2-phenylethoxy)carbonyl]butyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)-undeca-2,8-dienoate (**17a**) as a yellow oil. ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.44−7.91 (m, 5H), 6.99−7.05 (m, 1H), 5.53 (d, J = 16.2 Hz, 1H), 5.27−5.32 (m, 1H), 5.24 (d, J = 16.2 Hz, 1H), 5.18 (d, J = 3.3 Hz, 1H), 4.61 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 4.16 (dt, J = 9.6, 2.9 Hz, 1H), 3.66 (d, J = 9.2 Hz, 1H), 2.11−2.40 (m, 3H), 2.09 (s, 3H, f), 1.89−2.09 (m, 3H), 1.89 (br s, 3H), 1.54 (br s, 3H), 1.34−1.63 (m, 2H), 1.13 (d, J = 6.6 Hz, 3H), 0.97 (t, J = 7.6 Hz, 3H), 0.95 (t, J = 7.6 Hz, 3H), 0.88 (br s, 9H), 0.71 (d, J = 6.9 Hz, 3H), 0.01 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 191.7, 169.7, 167.6, 141.9, 135.0, 134.3, 134.0, 130.0, 128.9, 128.2, 127.8, 81.0, 75.9, 74.7, 73.2, 66.3, 38.4, 37.0, 28.9, 26.4, 25.9, 20.8, 18.2, 14.3, 14.2, 13.9, 12.7, 11.9, 10.8, 10.4, −4.3, −5.2; IR (neat) 2963, 2930, 2859, 1768, 1713, 1652, 1600, 1451, 1377, 1194, 1133, 1059, 836 cm^{-1}; MS (ESI-TOF) 680.5 [$M^+ + NH_4$].

(1*R*,2*S*)-2-Methyl-1-[(2-oxo-2-phenylethoxy)carbonyl]-butyl (2*E*,8*E*)-(5*S*,6*S*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (17b). ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.45−7.91 (m, 5H), 6.91 (br t, J = 6.6 Hz, 1H), 5.53 (d, J = 16.5 Hz, 1H), 5.24 (d, J = 16.5 Hz, 1H), 5.05−5.20 (m, 1H), 5.19 (d, J = 3.0 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 3.67 (d, J = 8.9 Hz, 1H), 3.59 (dt, J = 9.9, 3.0 Hz, 1H), 2.11−2.40 (m, 3H), 2.08 (s, 3H), 1.97−2.05 (m, 3H), 1.87 (br s, 3H), 1.59 (br s, 3H), 1.15−1.62 (m, 2H), 1.12 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.94 (t, J = 7.6 Hz, 6H), 0.87 (s, 9H), 0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 191.7, 169.7, 167.5, 141.4, 135.4, 134.2, 134.0, 130.1, 129.0, 128.2, 127.8, 81.6, 75.8, 74.7, 72.9, 66.3, 38.8, 37.0, 29.0, 26.4, 25.9, 20.8, 18.3, 14.3, 14.0, 13.9, 12.7, 11.8, 10.8, 10.6, −4.3, −4.9; IR (neat) 2963, 2932, 2859, 1767, 1714, 1463, 1451, 1374, 1250, 1195, 1133, 1047, 837, 775, 753, 689 cm^{-1}; MS (ESI-TOF) 680.4 [$M^+ + NH_4$].

(1*R*,2*S*)-2-Methyl-1-[(2-oxo-2-phenylethoxy)carbonyl]-butyl (2*E*,8*E*)-(5*S*,6*R*,7*S*)-7-Hydroxy-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (18a). To a solution of 2-oxo-2-phenylethyl (2*R*,3*S*)-2-[(2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoyloxy]-3-methylpentanoate (**17a**) (0.80 g, 1.21 mmol) and pyridine (2 mL) in THF (8 mL) was added hydrogen fluoride pyridine complex (5 mL) dropwise at 0 °C. The mixture was stirred at room temperature for 3 h. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic layer was washed with 10% aqueous citric acid, saturated aqueous sodium bicarbonate, and brine; dried over sodium sulfate; and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1) to afford 0.40 g (0.73 mmol, 60% yield) of (1*R*,2*S*)-2-methyl-1-[(2-oxo-2-phenylethoxy)-carbonyl]butyl (2*E*,8*E*)-(5*S*,6*R*,7*S*)-7-hydroxy-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (**18a**) as a yellow oil. ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.45−7.91 (m, 5H), 7.05 (br t, J = 7.3 Hz, 1H), 5.52 (d, J = 16.5 Hz, 1H), 5.35 (br t, J = 7.3 Hz, 1H), 5.26 (d, J = 16.5 Hz, 1H), 5.22 (d, J = 3.0 Hz, 1H), 4.64 (s, 2H), 4.10 (dt, J = 7.3, 2.3 Hz, 1H), 3.78 (d, J = 9.6 Hz, 1H), 2.34−2.52 (m, 3H), 2.16 (s, 3H), 2.15−2.26 (m, 1H), 1.96−2.08 (m, 3H), 1.91 (br s, 3H), 1.59 (br s, 3H), 1.33−1.59 (m, 2H), 1.14 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 7.6 Hz, 3H), 0.95 (t, J = 7.6 Hz, 3H), 0.72 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, chloroform-*d*) δ 191.7, 169.8, 167.5, 140.7, 135.1, 134.2, 134.0, 131.0, 130.9, 129.0, 128.5, 127.8, 81.4, 78.1, 74.8, 73.6, 66.3, 38.2, 37.0, 29.6, 26.4, 20.9, 14.4, 14.0, 12.7, 11.9, 11.8, 10.5; IR (neat) 3519, 2964, 2935, 2878, 1764, 1714, 1650, 1600, 1451, 1376, 1289, 1229, 1192, 1134, 1048, 969, 786, 752, 689 cm^{-1}; MS (ESI-TOF) 566.4 (M + NH_4^+), 571.3 [M^+ + Na].

(1*R*,2*S*)-2-Methyl-1-[(2-oxo-2-phenylethoxy)carbonyl]-butyl (2*E*,8*E*)-(5*S*,6*R*,7*R*)-7-Hydroxy-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (18b). ^{1}H NMR (270 MHz) δ 7.46−7.91 (m, 5 H), 6.94 (br t, J = 7.3 Hz, 1H), 5.53 (d, J = 16.5 Hz, 1H), 5.47 (m, 1H), 5.25 (d, J = 16.5 Hz, 1H), 5.21 (d, J = 3.0 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.18 (d, J = 4.0 Hz, 1H), 3.74 (q, J = 5.6 Hz, 1H), 2.48 (dd, J = 6.6, 6.6 Hz, 2H), 2.18−2.30 (m, 2H), 2.06 (br tt, J = 7.3, 7.3 Hz, 2H), 2.04 (s, 3H), 1.91 (d, J = 0.7 Hz, 3H), 1.55 (br s, 3H), 1.43 (dq, J = 7.3, 7.3 Hz, 2H), 1.14 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 7.6 Hz, 6H), 0.88 (d, J = 6.9 Hz, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 191.7, 169.7, 167.4, 139.6, 134.3, 134.2, 134.0, 129.0, 128.9, 127.8 × 2, 78.3, 74.8, 74.3, 66.3, 38.4, 37.0, 30.5, 26.4, 20.9, 14.5, 14.3, 14.2, 13.0, 12.7, 11.8, 9.7; IR (neat) 3522, 2966, 2934, 2878, 1767, 1714, 1652, 1599, 1451, 1379, 1234, 1196, 1133, 1052, 751, 689 cm^{-1}; MS (ESI-TOF) 566.3 [M^+ + NH_4].

(1*R*,2*S*)-2-Methyl-1-[(2-oxo-2-phenylethoxy)carbonyl]-butyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-{(*S*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)methylamino]propanoyloxy}-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (19a). A solution of (1*R*,2*S*)-2-methyl-1-[(2-oxo-2-phenylethoxy)carbonyl]butyl (2*E*,8*E*)-(5*S*,6*R*,7*S*)-7-hydroxy-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (**18a**) (0.40 g, 0.73 mmol) and (*S*)-2-[(9*H*-fluroren-9-ylmethoxycarbonyl)-methyl-amino]propanoic acid (Fmoc-MeAla-OH) (0.36 g, 1.10 mmol) in CH_2Cl_2 (30 mL) was treated with EDCI (0.28 g, 1.46 mmol) and a catalytic amount of DMAP at 0 °C and stirred at room temperature for 20 h. The mixture was poured into 1 M hydrochloric acid. The layers were separated. The aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with 1 M hydrochloric acid, saturated aqueous sodium bicarbonate, and brine; dried over sodium sulfate; and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1) to afford 0.56 g (0.65 mmol, 90% yield) of (1*R*,2*S*)-2-methyl-1-[(2-oxo-2-phenylethoxy)carbonyl]butyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-{(*S*)-2-[(9*H*-fluoren-9-ylmethoxycarbonyl)methylamino]propanoyloxy}-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (**19a**) as a yellow oil. ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.27−7.91 (m, 13H), 6.85−6.95 (m, 1H), 5.52 (d, J = 16.2 Hz, 1H), 5.40 (t, J = 7.3 Hz, 1H), 5.24 (d, J = 16.2 Hz, 1H), 5.19 (d, J = 3.0 Hz, 1H), 5.12 (d, J = 7.6 Hz, 1H), 4.90−5.05 (m, 1H), 4.58 (d, J = 11.6 Hz, 1H), 4.50 (d, J = 11.6 Hz, 1H), 4.35−4.48 (m, 2H), 4.20−4.30 (m, 1H), 3.60−3.63 (m, 1H), 2.87 (s, 3H), 2.30−2.40 (m, 2H), 2.09−2.25 (m, 2H), 2.09 (s, 3H), 1.88−2.09 (m, 2H), 1.88 (s, 3H), 1.59 (s, 6H), 1.42−1.59 (m, 1H), 1.43 (d, J = 7.3 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H); IR (neat) 2967, 2937, 1739, 1714, 1452, 1379, 1307, 1196, 1134, 1050, 789, 760, 689 cm^{-1}; MS (ESI-TOF) 873.4 [M^+ + NH_4].

(1*R*,2*S*)-2-Methyl-1-[(2-oxo-2-phenylethoxy)carbonyl]-butyl (2*E*,8*E*)-(5*S*,6*S*,7*R*)-7-{(*S*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)methylamino]propanoyloxy}-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (19b). ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.27−7.91 (m, 13H), 6.85−6.95 (m, 1H), 5.52 (d, J = 16.2 Hz, 1H), 5.40 (br t, J = 7.3 Hz, 1H), 5.24 (d, J = 16.2 Hz, 1H), 5.19 (d, J = 3.0 Hz, 1H), 5.12 (d, J = 7.6 Hz, 1H), 4.90−5.05 (m, 1H), 4.58 (d, J = 11.6 Hz, 1H), 4.50 (d, J = 11.6 Hz, 1H), 4.35−4.48 (m, 2H), 4.20−4.30 (m, 1H), 3.60−3.63 (m, 1H), 2.87 (s, 3H), 2.30−2.40 (m, 2H), 2.09−2.25 (m, 2H), 2.09 (s, 3H), 1.88−2.09 (m, 2H), 1.88 (s, 3H), 1.59 (s, 6H), 1.42−1.59 (m, 1H), 1.43 (d, J = 7.3 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H); IR (neat) 2967, 2937, 1739, 1714, 1452, 1379, 1307, 1196, 1134, 1050, 789, 760, 689 cm^{-1}; MS (ESI-TOF) 873.4 [M^+ + NH_4].

(2*R*,3*S*)-2-{(2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-{(*S*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)methyl-amino]propanoyloxy}-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoyloxy}-3-methylpropanoic Acid (3a). A solution of (1*R*,2*S*)-2-methyl-1-[(2-oxo-2-phenylethoxy)carbonyl]butyl (2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-{(*S*)-2-[(9*H*-fluoren-9-ylmethoxycarbonyl)methylamino]-propanoyloxy}-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoate (**19a**) (0.56 g, 0.65 mmol) in acetic acid/ethyl acetate/water (60:35:5 v/v, 30 mL) was treated with activated zinc (0.67 g, 10.2 mmol) at room temperature and stirred at 45 °C for 27 h. The mixture was diluted with ethyl acetate, filtered, and poured into 1 M hydrochloric acid. The layers were separated. The aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with 1 M

hydrochloric acid, washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford 0.48 g (0.65 mmol, quant.) of (2*R*,3*S*)-2-{(2*E*,8*E*)-(5*S*,6*S*,7*S*)-7-{(*S*)-2-[(9*H*-fluoren-9-ylmethoxycarbonyl)methylamino]-propanoyloxy}-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoyloxy}-3-methylpropanoic acid (**3a**). ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.28−7.78 (m, 8H), 6.80−6.90 (m, 1H), 5.40−5.50 (m, 1H), 5.05−5.15 (m, 1H), 4.90−5.00 (m, 1H), 4.70−4.80 (m, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.50 (d, J = 11.6 Hz, 1H), 4.35−4.45 (m, 1H), 4.20−4.30 (m, 1H), 3.55−3.70 (m, 1H), 2.87 (s, 3H), 2.43 (s, 3H), 2.30−2.40 (m, 1H), 2.09 (s, 3H), 2.00−2.20 (m, 4H), 1.87 (s, 3H), 1.59 (br s, 3H), 1.44 (d, J = 7.3 Hz, 3H), 1.30−1.90 (m, 2H, t), 1.01 (d, J = 6.9 Hz, 3H, u), 0.93 (t, J = 7.3 Hz, 3H, v), 0.90 (t, J = 7.3 Hz, 3H, w); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 175.8, 171.0, 167.5, 156.5, 144.0, 141.3, 127.7, 127.0, 125.0, 120.0, 81.0, 80.5, 75.4, 73.3, 67.8, 54.2, 47.2, 36.9, 36.6, 30.2, 30.0, 29.7, 28.9, 26.3, 20.8, 15.1, 14.7, 14.4, 14.1, 13.8, 12.6, 12.2, 11.7, 9.9; MS (ESI-TOF) 755.4 [$M^+ + NH_4$].

(2*R*,3*S*)-2-{(2*E*,8*E*)-(5*S*,6*S*,7*R*)-7-{(*S*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)methyl-amino]propanoyloxy}-2,6,8-trimethyl-5-(methylthiomethoxy)undeca-2,8-dienoyloxy}-3-methylpropanoic Acid (3b). ^{1}H NMR (270 MHz, chloroform-*d*) δ 7.28−7.78 (m, 8H), 6.80−6.90 (m, 1H), 5.40−5.50 (m, 1H), 5.05−5.15 (m, 1H), 4.90−5.00 (m, 1H), 4.70−4.80 (m, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.50 (d, J = 11.6 Hz, 1H), 4.35−4.45 (m, 1H), 4.20−4.30 (m, 1H), 3.55−3.70 (m, 1H), 2.87 (s, 3H), 2.43 (s, 3H), 2.30−2.40 (m, 1H), 2.09 (s, 3H), 2.00−2.20 (m, 4H), 1.87 (s, 3H), 1.59 (br s, 3H), 1.44 (d, J = 7.3 Hz, 3H), 1.30−1.90 (m, 2H), 1.01 (d, J = 6.9 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, chloroform-*d*) δ 175.8, 171.0, 167.5, 156.5, 144.0, 141.3, 127.7, 127.0, 125.0, 120.0, 81.0, 80.5, 75.4, 73.3, 67.8, 54.2, 47.2, 36.9, 36.6, 30.2, 30.0, 29.7, 28.9, 26.3, 20.8, 15.1, 14.7, 14.4, 14.1, 13.8, 12.6, 12.2, 11.7, 9.9; MS (ESI-TOF) 755.4 [$M^+ + NH_4$].

General Procedure for the Attachment of Fmoc Amino Acids on Trityl Alcohol Crown. The trityl alcohol Crowns (SPPSOTRH, 8.5 μmol/crown; batch, 1075-19A) were treated with 50% acetyl chloride in CH_2Cl_2 (v/v) at room temperature for 12 h. After decantation of the reaction solution, the Crowns were washed three times with DMF (5 min per wash) and twice with CH_2Cl_2. These chlorinated Crowns **20t** were used immediately without removing any residual CH_2Cl_2.

The above Crowns **20t** were treated with a solution of Fmoc amino acid (0.10 M) and DIEA (0.25 M) in CH_2Cl_2 and were gently agitated at room temperature for 12 h. After decantation of the reaction solution, the Crowns were washed three times with DMF (5 min per wash), washed with methanol, washed twice with CH_2Cl_2, and dried in vacuo to give Fmoc amino acid-linked Crowns.

General Procedure for the Attachment of Fmoc Amino Acids on HMP Crown. The HMP Crowns **20h** (SPPSO-HMP, 1.9 μmol/crown; batch, 800-10) were treated with a solution of Fmoc amino acid (0.18 M), DIC (0.18 M), DMAP (3.6 mM) in 20% DMF in CH_2Cl_2 at 40 °C and were gently agitated at the same temperature for 24 h. After decantation of the reaction solution, the Crowns were washed three times with 20% DMF in CH_2Cl_2 (5 min per wash), washed twice with CH_2Cl_2, and dried in vacuo. This protocol was repeated to give Fmoc amino acid-linked Crowns.

General Procedure for Removal of Fmoc Group. The Fmoc-protected peptide-linked Crowns were treated with a solution of 20% piperidine in DMF at room temperature for 30 min. After decantation of the reaction solution, the Crowns were washed three times with DMF (5 min per wash), washed twice with CH_2Cl_2, and dried in vacuo to give deprotected peptide-linked Crowns.

General Procedure for the Peptide Bond Formation on Crowns. The deprotected Crowns were treated with a solution of Fmoc amino acid (0.10 M) and coupling reagent (acid/DIC/HOBt = 1:1:1.2; acid/HBTU/HOBt/DIEA = 1:1:1:2; acid/TFFH/DIEA = 1:1:2; acid/PyBrOP/DIEA = 1:1:2) in DMF and were gently shaken at room temperature for 22 h. After decantation of the reaction solution, the Crowns were washed 3 times with DMF (5 min per wash), washed twice with CH_2Cl_2, and dried in vacuo to give acylated Crown.

General Procedure for Cleavage of the Peptides from Trityl Crowns. The trityl-Crowns were treated with a solution of 1% TFA in CH_2Cl_2 at room temperature for 1 h in parallel. The Crowns were filtered and washed with CH_2Cl_2. The filtrate was concentrated to give cleavage products.

General Procedure for Coupling of Chemset 5t with 3. Chemset **5t** was treated with a solution of **3** (0.050 M), DIC (0.050 M), and HOBt (0.060 M) in DMF at room temperature for 96 h. After decantation of the reaction solution, the Crowns were washed three times with DMF (5 min per wash), washed twice with CH_2Cl_2, and dried in vacuo to give the long-chain supported peptides. Fmoc cleavage was carried out as described previously.

General Procedure for the Cyclization Reaction. Acid cleavage of linear precursors from the above Crowns was carried out as described above. The crude products were treated with a solution of EDCI (10 equiv) and HOAt (10 equiv) in CH_2Cl_2/DMF (9:1 v/v, 1 mM) at room temperature for 24 h in parallel. The reaction mixtures were concentrated in vacuo and were azeotroped with toluene several times. The residues were diluted with ethyl acetate; washed with 10% aqueous citric acid, saturated aqueous sodium bicarbonate, and brine; and dried over sodium sulfate. The solutions were filtered, and the filtrates were concentrated in vacuo. This library was used for the next reaction without further purification.

General Procedure for Deprotection of Methylthiomethyl Group. The above library was treated with a solution of silver nitrate (10 equiv) and 2,6-lutidine (10 equiv) in THF/water (4:1 v/v) at 70 °C for 20 h in parallel. The reaction mixtures were cooled to room temperature and diluted with ethyl acetate. To the reaction mixtures was poured aqueous saturated ammonium chloride. The solution was filtered, washed with brine, and dried over sodium sulfate. The solutions were filtered and concentrated in vacuo to give the crude aurilide (**1**) or aurilide derivatives **4.** Purities were analyzed by HPLC (UV, 214 nm). The residues were purified by reversed-phase HPLC.

Aurilide (1). Purity 48%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.7 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.78 (br d, J = 9.2 Hz, 1H), 7.74 (m, 1H), 6.51 (br d, J = 8.7 Hz, 1H), 5.64−5.70 (m, 2H), 5.17 (d, J = 11.6 Hz, 1H), 5.13−5.17 (m, 1H), 4.72 (d, J = 6.3 Hz, 1H), 4.60 (t, J = 8.7 Hz, 1H), 4.42 (d, J = 17.9 Hz, 1H), 3.95−4.02 (m, 1H), 3.83 (d, J = 17.9 Hz, 1H), 3.24 (s, 3H), 3.08 (q, J = 7.2 Hz, 1H), 2.90 (s, 3H), 2.54 (s, 3H), 1.80−2.22 (m, 10H), 1.89 (s, 3H), 1.54 (s, 3H), 1.45−1.56 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 6H), 1.02 (d, J = 6.8 Hz, 3H), 0.89−0.91 (m, 6H), 0.81 (d, J = 7.7 Hz, 3H), 0.81 (t, J = 6.8 Hz, 3H), 0.61 (d, J = 7.2 Hz, 3H); MS (ESI-TOF) 834 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{44}H_{75}N_5O_{10}Na$, 856.54062 $[M + Na]^+$. Found, 856.5407.

Selected Spectral Data of 4. ***4*** {*1,2,3,1*}**.** Purity 41%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.7 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.60−7.67 (m, 1H), 7.10−7.16 (m, 1H), 6.89 (d, J = 9.7 Hz, 1H), 5.88−5.94 (m, 1H), 5.66−5.70 (m, 1H), 5.00−5.10 (m, 1H), 4.86−4.94 (m, 1H), 4.74−4.80 (m, 1H), 4.40−4.46 (m, 1H), 3.96−4.06 (m, 1H), 3.86 (d, J = 16.4 Hz, 1H), 3.48 (d, J = 16.4 Hz, 1H), 3.23 (s, 3H), 3.00−3.10 (m, 1H), 2.99 (s, 3H), 2.54−2.62 (m, 2H), 2.52 (s, 3H), 2.35−2.45 (m, 2H), 2.15−2.28 (m, 2H), 2.11 (dq, J = 6.8, 6.8 Hz, 2H), 1.88−1.98 (m, 2H), 1.76−1.88 (m, 1H), 1.58 (s, 3H), 1.35−1.50 (m, 2H), 1.32 (d, J = 6.8 Hz, 6H), 1.25 (d, J = 6.8 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.05 (t, J = 6.8 Hz, 3H), 0.98 (t, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H);MS (ESI-TOF) 834 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{44}H_{75}N_5O_{10}Na$, 856.54062 $[M + Na]^+$. Found, 856.5409.

4 {*2,2,3,1*}**.** Purity 26%; HPLC (GL Sciences Inc. Inertsil C8−3 3 μm, 4.6 × 75 mm) t_R, 10.8 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.50−7.58 (m, 1H), 6.58 (d, J = 8.7 Hz, 1H), 6.31 (s, 1H), 5.97−6.03 (m, 1H), 5.52−5.73 (m, 2H), 4.80−5.22 (m, 2H), 4.66−4.76 (m, 1H), 4.08−4.26 (m, 1H), 3.58 (d, J = 16.9 Hz, 1H), 3.48 (d, J = 16.9 Hz, 1H), 3.05 (s, 3H), 2.98−3.10 (m, 1H), 2.95 (s, 3H), 2.51 (s, 3H), 2.64−2.70 (m, 2H), 2.54−2.58 (m, 2H), 2.51 (s, 3H), 2.30−2.48 (m, 3H), 2.18−2.28 (m, 1H), 2.13 (dt, J = 6.8, 6.8 Hz, 2H), 1.98−2.06 (m, 1H), 1.88−1.99 (m, 1H), 1.76−1.88 (m, 1H), 1.62 (s, 3H), 1.51 (s, 3H), 1.39 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 1.04−1.09 (m, 6H), 1.02 (d, J = 6.8 Hz, 3H), 0.99 (t, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); MS (ESI-TOF) 834 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{44}H_{75}N_5O_{10}Na$, 856.54062 $[M + Na]^+$. Found, 856.5402.

4 {*1,2,4,1*}**.** Purity 42%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.3 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 6.75−6.80 (m, 1H), 6.06 (br s, 1H), 5.60−5.75 (m, 2H), 5.27−5.35 (m, 2H), 5.12 (d, J = 16.9 Hz, 1H), 5.04 (br t, J = 8.7 Hz, 1H), 4.75−4.85 (m, 1H), 4.59 (t, J = 8.2 Hz, 1H), 4.06 (d, J = 16.9 Hz, 1H), 3.65−3.80 (m, 1H), 3.28−3.35 (m, 1H), 3.01 (s, 3H), 2.84 (s, 3H), 2.75 (s, 3H), 2.20−2.35 (m, 2H), 1.86−2.08 (m, 8H), 2.00 (br s, 3H), 1.54−1.70 (m, 1H), 1.44−1.50 (m, 1H), 1.39 (br s, 3H), 1.25−1.35 (m, 1H), 1.26 (d, J = 6.8 Hz, 6H), 1.09 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 6H), 0.90−0.95 (m, 6H), 0.86 (d, J = 6.3 Hz, 6H), 0.68 (d, J = 6.3 Hz, 3H); MS (ESI-TOF) 834 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{44}H_{75}N_5O_{10}Na$, 856.54062 $[M + Na]^+$. Found, 856.5401.

4 {*2,2,4,1*}**.** Purity 31%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.4 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.50−7.62 (m, 1H), 7.06−7.15 (m, 1H), 6.16 (br s, 1H), 5.82−5.86 (m, 1H), 5.76 (br t, J = 6.8 Hz, 1H), 5.00−5.10 (m, 1H), 4.95−5.00 (m, 1H), 4.86−4.95 (m, 1H), 4.80−4.86 (m, 1H), 4.35 (d, J = 17.4 Hz, 2H), 3.92−3.98 (m, 1H), 3.37 (q, J = 6.8 Hz, 1H), 2.94 (s, 3H), 2.61 (s, 3H), 2.50−2.60 (m, 2H), 2.32−2.40 (m, 2H), 2.20−2.30 (m, 2H), 2.12 (dq, J = 6.8, 6.8 Hz, 2H), 2.08 (s, 3H), 1.82−2.00 (m, 2H), 1.69 (s, 3H), 1.56−1.66 (m, 1H), 1.51 (s, 3H), 1.30−1.48 (m, 2H), 1.34 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.95−1.12 (m, 18H); MS (ESI-TOF) 834 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{44}H_{75}N_5O_{10}Na$, 856.54062 $[M + Na]^+$. Found, 856.5401.

4 {*1,2,3,2*}**.** Purity 45%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.3 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.63 (m, 1H), 7.50 (br d 1H, J = 8.7 Hz), 6.61 (m, 1H), 6.00 (br s, 1H), 5.79 (brs, 1H), 5.32−5.40 (m, 1H), 5.00 (d, J = 16.9 Hz, 1H), 4.85−4.95 (m, 1H), 4.70−4.85 (m, 1H), 3.84 (d, J = 16.9 Hz, 1H), 3.72−3.82 (m, 1H), 3.54 (d, J = 16.9 Hz, 1H), 3.14 (q, J = 6.8 Hz, 1H), 2.93 (s, 3H), 2.68 (s, 3H), 2.61 (s, 3H), 2.38−2.50 (m, 2H), 2.16−2.38 (m, 2H), 1.85−2.10 (m, 6H), 2.02 (s, 3H), 1.54 (s, 3H), 1.32−1.50 (m, 2H), 1.28 (d, J = 6.8 Hz, 6H), 1.08 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.3 Hz, 3H); MS (ESI-TOF) 834 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{44}H_{75}N_5O_{10}Na$, 856.54062 $[M + Na]^+$. Found, 856.5442.

4 {*2,2,3,2*}**.** Purity 42%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.3 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.78−7.86 (m, 1H), 6.74 (d, J = 9.2 Hz, 1H), 6.24 (br s, 1H), 6.02−6.07 (m, 1H), 5.40−5.46 (m, 2H), 5.25 (dd, J = 6.8 Hz, 9.2 Hz, 1H), 5.12 (d, J = 16.9 Hz, 1H), 5.04 (t, J = 8.8 Hz, 1H), 3.36 (q, J = 6.8 Hz, 1H), 3.12 (d, J = 16.9 Hz, 1H), 3.03 (s, 3H), 2.85 (s, 3H), 2.79 (s, 3H), 2.72−2.77 (m, 2H), 2.65−2.71 (m, 2H), 2.50−2.58 (m, 3H), 2.14 (dq, J = 6.8, 6.8 Hz, 2H), 2.04 (s, 3H), 1.70−1.80 (m, 1H), 1.66 (s, 3H), 1.52−1.62 (m, 1H), 1.49 (d, J = 6.8 Hz, 3H), 1.26−1.46 (m, 2H), 1.16 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.00 (f, J = 6.8 Hz, 3H), 0.96 (t, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.83 (t, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); MS (ESI-TOF) 834 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{44}H_{75}N_5O_{10}$-Na, 856.54062 $[M + Na]^+$. Found. 856.5422.

4 {*1,2,4,2*}**.** Purity 51%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.4 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.70 (br t, J = 6.8 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 5.91 (br s, 1H), 5.36 (t, J = 7.2 Hz, 1H) 5.29 (t, J = 6.8 Hz, 1H), 5.04−5.10 (m, 1H), 4.82−4.87 (m, 1H), 4.53 (d, J = 16.9 Hz, 1H), 4.48 (d, J = 6.3 Hz, 1H), 3.74−3.82

(m, 1H), 3.20 (d, J = 16.9 Hz, 1H), 3.10 (q, J = 6.8 Hz, 1H), 2.99 (s, 3H), 2.70 (s, 3H), 2.51 (s, 3H), 2.30−2.48 (m, 2H), 1.80−2.05 (m, 6H), 2.00 (s, 3H), 1.65−1.75 (m, 3H), 1.40−1.55 (m, 3H), 1.44 (s, 3H), 1.26 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 6H), 0.84−0.90 (m, 15H), 0.75 (d, J = 6.8 Hz, 3H); MS (ESI-TOF) 834 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{44}H_{75}N_5O_{10}Na$, 856.54062 $[M + Na]^+$. Found, 856.5411.

4 {*2,2,4,2*}**.** Purity 57%; HPLC (GL Sciences Inc. Inertsil C8−3 3 μm, 4.6 × 75 mm) t_R, 10.5 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.62−7.68 (m, 2H), 6.75 (d, J = 9.2 Hz, 1H), 6.11 (br s, 1H), 5.45−5.52 (m, 1H), 5.13 (m, 1H), 4.88−4.96 (m, 1H), 4.77−4.86 (m, 1H), 4.45 (br s, 1H), 4.24 (d, J = 17.4 Hz, 1H), 4.08−4.16 (m, 1H), 3.77 (d, J = 17.4 Hz, 1H), 3.04 (s, 3H), 2.99 (q, J = 6.8 Hz, 1H), 2.89 (s, 3H), 2.74 (s, 3H), 1.95−2.10 (m, 4H), 1.91 (s, 3H), 1.60−1.76 (m, 3H), 1.50−1.60 (m, 3H), 1.49 (s, 3H), 1.37 (d, J = 6.8 Hz, 3H), 1.20−1.38 (m, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 6H), 0.93 (d, J = 6.8 Hz, 3H), 0.90 (t, J = 6.8 Hz, 3H), 0.80−0.88 (m, 9H); MS (ESI-TOF) 834 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{44}H_{75}N_5O_{10}Na$, 856.54062 $[M + Na]^+$. Found, 856.5408.

4 {*1,1,2,1*}**.** Purity 25%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.4 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.98−8.50 (m, 1H), 7.45−7.55 (m, 2H), 6.86−7.02 (m, 1H), 5.75 (br s, 1H), 5.40−5.50 (m, 2H), 4.36−4.55 (m, 5H), 3.95−4.05 (m, 1H), 3.91 (q, J = 7.2 Hz, 1H), 3.75−3.84 (m, 1H), 2.75 (s, 3H), 2.46−2.56 (m, 1H), 2.15−2.34 (m, 5H), 2.04 (dq, J = 7.2, 7.2 Hz, 2H), 1.97 (s, 3H), 1.74−1.86 (m, 2H), 1.57 (s, 3H), 1.20−1.50 (m, 2H), 1.19 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 7.8 Hz, 3H), 0.92−1.06 (m, 12H), 0.78−0.90 (m, 12H); MS (ESI-TOF) 806 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{42}H_{71}N_5O_{10}Na$, 828.50932 $[M + Na]^+$. Found, 828.5088.

4 {*2,1,2,1*}**.** Purity 47%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.4 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.50−7.58 (m, 1H), 7.25−7.50 (m, 2 H), 5.66−5.74 (m, 1H), 5.49 (br s, 1H), 5.34 (t, J = 6.8 Hz, 1H), 5.00−5.15 (m, 1H), 4.82−4.96 (m, 1H), 4.70−4.78 (m, 1H), 4.13 (dd, J = 6.3, 16.9 Hz, 1H), 3.90−4.06 (m, 2H), 3.76 (dd, J = 6.3, 16.9 Hz, 1H), 3.65−3.72 (m, 1H), 3.04−3.12 (m, 1H), 2.87 (s, 3H), 2.30−2.45 (m, 4H) 2.22−2.32 (m, 1H), 2.10−2.22 (m, 3H), 2.00−2.10 (m, 1H), 1.98 (s, 3H), 1.70−1.85 (m, 2H), 1.50−1.68 (m, 2H), 1.50 (s, 3H), 1.31 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 6H), 1.03 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.92 (t, J = 6.8 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H); MS (ESI-TOF) 806 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{42}H_{71}N_5O_{10}Na$, 828.50932 $[M + Na]^+$. Found, 828.5094.

4 {*1,1,1,1*}**.** Purity 36%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.5 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.66−7.76 (m, 1H), 7.32−7.40 (m, 1H), 7.10−7.20 (m, 2H), 5.83 (br s, 1H), 5.55−5.64 (m, 1H), 5.34 (t, J = 6.8 Hz, 1H), 4.71 (t, J = 8.7 Hz, 1H), 4.45−4.60 (m, 2H), 3.74 (t, 1H, 8.2 Hz), 3.60−3.70 (m, 1H), 3.40−3.50 (m, 1H), 3.30−3.40 (m, 1H), 2.96 (s, 3H), 2.24−2.38 (m, 4H), 2.14−2.22 (m, 1H), 2.01 (s, 3H), 1.99 (dq, J = 7.7, 7.7 Hz, 2H), 1.65−1.75 (m, 1H), 1.40−1.55 (m, 4H), 1.48 (s, 3H), 1.37 (d, J = 6.8 Hz, 3H), 1.16−1.34 (m, 1H), 0.98−1.10 (m, 15H), 0.94 (t, J = 7.2 Hz, 3H), 0.78−0.92 (m, 9H), 0.74 (d, J = 4.3 Hz, 3H); MS (ESI-TOF) 806 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{42}H_{71}N_5O_{10}Na$, 828.50932 $[M + Na]^+$. Found, 828.5092.

4 {*2,1,1,1*}**.** Purity 42%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 9.7 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.65−7.75 (m, 1H), 7.56−7.64 (m, 1H), 7.15−7.25 (m, 1H), 6.08 (m, 1H), 5.85 (br s, 1H), 5.70 (m, 1H), 5.41 (t, J = 6.8 Hz, 1H), 5.00 (t, J = 6.8 Hz, 1H), 4.66−4.74 (m, 1H), 4.45−4.52 (m, 1H), 4.15−4.25 (m, 2H), 3.90−4.00 (m, 1H), 3.64−3.80 (m, 1H), 2.82 (s, 3H), 2.50−2.65 (m, 1H), 2.10−2.40 (m, 6H), 1.90−2.08 (m, 3H), 1.92 (s, 3H), 1.50−1.72 (m, 3H), 1.52 (s, 3H), 1.34 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.82−0.95 (m, 12H), 0.77 (d, J = 6.8 Hz, 3H); MS (ESI-TOF) 806 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{42}H_{71}N_5O_{10}Na$, 828.50932 $[M + Na]^+$. Found, 828.5079.

4 {*1,1,2,2*}**.** Purity 36%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.3 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.35−7.45 (m, 1H), 7.11−7.25 (m, 3H), 5.92 (s, 1H), 5.38 (t, J = 6.8 Hz, 1H), 5.06−5.12 (m, 1H), 4.65 (t, J = 7.7 Hz, 1H), 4.36−4.44 (m, 1H), 4.00−4.20 (m, 3H), 3.76−3.86 (m, 1H), 3.67 (t, J = 8.7 Hz, 1H), 2.74 (s, 3H), 2.56−2.66 (m, 1H), 2.05−2.38 (m, 7H), 2.01 (dq, J = 6.7, 6.7 Hz, 2H), 1.94 (s, 3H), 1.70−1.90 (m, 2H), 1.54−1.66 (m, 2H), 1.50 (s, 3H), 1.38−1.46 (m, 1H), 1.20 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H), 0.94−1.16 (m, 12H), 0.78−0.92 (m, 15H); MS (ESI-TOF) 806 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{42}H_{71}N_5O_{10}Na$, 828.50932 $[M + Na]^+$. Found, 828.5092.

4 {*2,1,2,2*}**.** Purity 58%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.3 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.70−7.80 (m, 1H), 7.05−7.42 (m, 3H), 5.84 (br s, 1H), 5.35−5.44 (m, 1H), 4.76−4.84 (m, 1H), 4.52−4.60 (m, 1H), 4.30−4.46 (m, 1H), 3.96−4.04 (m, 1H), 3.74−3.80 (m, 1H), 3.62−3.68 (m, 1H), 3.42−3.56 (m, 1H), 3.15−3.24 (m, 1H), 2.79 (s, 3H), 2.56−2.70 (m, 3H), 2.05−2.55 (m, 5H), 1.99 (dt, J = 6.8, 6.8 Hz, 2H), 1.90 (s, 3H), 1.74−1.86 (m, 2H), 1.50 (s, 3H), 1.26−1.46 (m, 2H), 1.20 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.70−1.06 (m, 27H); MS (ESI-TOF) 806 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{42}H_{71}N_5O_{10}Na$, 828.50932 $[M + Na]^+$. Found, 828.5092.

4 {*1,1,1,2*}**.** Purity 48%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.3 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.50−7.58 (m, 1H), 7.35−7.45 (m, 1H), 7.15−7.30 (m, 2H), 5.98 (br s, 1H), 5.35 (t, J = 6.8 Hz, 1H), 5.15−5.25 (m, 1H), 4.85 (t, J = 7.7 Hz, 1H), 4.45−4.60 (m, 2H), 4.05−4.25 (m, 2H), 3.90−4.05 (m, 1H), 3.78 (t, J = 8.7 Hz, 1H), 2.78 (s, 3H), 2.05−2.50 (m, 7H), 2.02 (dq, J = 7.2 Hz, 2H), 1.96 (s, 3H), 1.73−1.93 (m, 2H), 1.45−1.65 (m, 3H), 1.51 (s, 3H), 1.30 (d, J = 6.8 Hz, 6H), 1.14 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.90−1.00 (m, 15H), 0.88 (d, J = 6.8 Hz, 3H); MS

(ESI-TOF) 806 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{42}H_{71}N_5O_{10}Na$, 828.50932 $[M + Na]^+$. Found, 828.5092.

4 **{*2,1,1,2*}.** Purity 45%; HPLC (GL Sciences Inc. Inertsil C8-3 3 μm, 4.6 × 75 mm) t_R, 10.3 min; ^{1}H NMR (400 MHz, benzene-d_6) δ 8.20−8.35 (m, 1H), 7.50−7.64 (m, 1H), 6.02 (br s, 1H), 5.27 (t, J = 6.8 Hz, 1H), 5.05−5.14 (m, 1H), 4.80−4.90 (m, 1H), 4.68−4.76 (m, 1H), 4.20−4.35 (m, 2H), 3.92−4.08 (m, 1H), 3.40−3.68 (m, 2H), 2.93 (s, 3H), 2.50−2.62 (m, 1H), 2.20−2.48 (m, 7H), 1.90−2.10 (m, 4H), 1.97 (s, 3H), 1.78−1.88 (m, 1H), 1.60−1.76 (m, 2H), 1.55 (s, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.04−1.08 (m, 6H), 0.97 (d, J = 6.8 Hz, 3H), 0.95 (t, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.80−0.94 (m, 6H); MS (ESI-TOF) 806 $[M + H]^+$; HRMS (ESI-TOF) Calcd for $C_{42}H_{71}N_5O_{10}Na$, 828.50932 $[M + Na]^+$. Found, 828.5089.

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Supporting Information Available. LC/MS and ^{1}H NMR spectra of both **1** and selected derivatives of the library **4**. This material is available free of charge via the Internet at http://pubs.acs.org

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