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Determination of the Absolute Configurations of Microtermolides A and B

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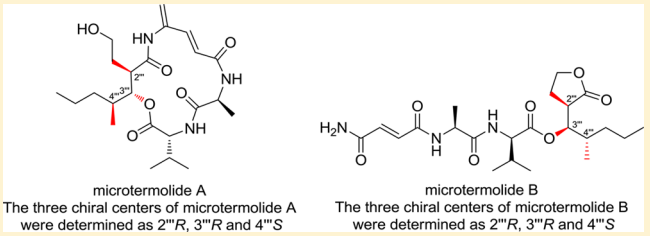
Supporting Information

ABSTRACT: Absolute configurations of the three consecutive chiral centers in the cyclic depsipeptide microtermolide A have been tentatively assigned as 2‴*R*, 3‴*R*, and 4‴*R*. However, on the basis of a structural comparison with vinylamycin, another depsipeptide with a unique 4-amino-2,4-pentadienolate structure, the chiral centers could also be assigned as 2‴*R*, 3‴*R*, and 4‴*S*. Here, the first total synthesis of microtermolide A is reported and the configurations of the three consecutive chiral centers were confirmed to be 2‴*R*, 3‴*R*, and 4‴*S*. A similar approach was used to determine the analogous centers in microtermolide B as 2‴*R*, 3‴*R*, and 4‴*S*.



Depsipeptides with unique 4-amino-2,4-pentadienolate structures include rakicidins,[1−3] BE-43547A1,[4] and vinylamycin,[5] and these compounds have exhibited cytotoxic or antibiotic activities (Figure 1). However, the absolute configurations of most of the chiral centers in these depsipeptides have remained unknown. Recently, total syntheses and degradation of these depsipeptides were used to determine their absolute configurations.[6−11] Microtermolides A and B are also depsipeptides with 4-amino-2,4-pentadienolate moieties, isolated from *Streptomyces* sp.[12] When assayed, neither compound exhibited cytotoxicity or antimicrobial activity. In addition, NMR spectroscopy was used to predict the absolute configurations of the three consecutive chiral centers in each compound. As a result, the three chiral centers in both microtermolides A and B were tentatively assigned as 2‴*R*, 3‴*R*, and 4‴*R* (compounds **1a** and **2a**, respectively),[12] thereby representing an *anti*−*anti* relationship among the chiral centers. However, vinylamycin, an antimicrobial natural product that appears to differ from microtermolide A only by the length of its side chain, had the configurations of its three consecutive chiral centers determined as 2‴*R*, 3‴*R*, and 4‴*S*, thereby representing an *anti*−*syn* relative relationship.[8] Therefore, it was also possible that microtermolides A and B could have an *anti*−*syn* relative stereochemistry for their three consecutive chiral centers (compounds **1b** and **2b**, respectively). In order to unambiguously assign the absolute configurations of microtermolides A and B, compounds **1a**, **1b**, **2a**, and **2b** were synthesized.

Briefly, target compounds **1a** and **1b** were prepared according to a synthetic sequence that was previously reported for the total synthesis of vinylamycin (Scheme 1).[8] To achieve adducts **4a**/**4b** with the desired configurations, these compounds were synthesized with high diastereoselectivity (*dr* > 10:1) via the Mukaiyama aldol reaction.[8] Hydrolysis of **4a**/**4b** was followed by treatment with cesium carbonate (Cs_2CO_3) and allyl bromide to achieve allyl esters **5a**/**5b**. Esterification of

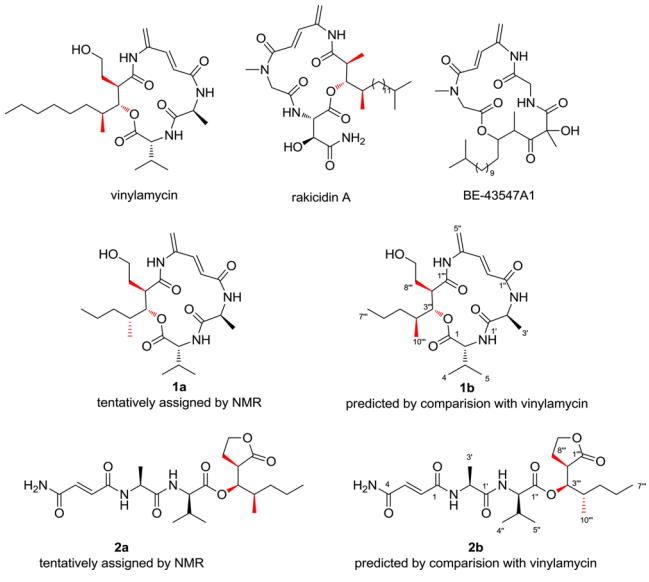


Figure 1. Various proposed structures for microtermolides A (**1a**, **1b**) and B (**2a**, **2b**).

5a/**5b** with Fmoc-D-valine **12** produced compounds **6a** and **6b**. Deprotection of the Fmoc group in **6a**/**6b** then allowed the resulting amines to be coupled with Fmoc-L-alanine **13** to provide compounds **7a**/**7b**. After deprotection of the allyl groups was completed, the resulting acids were coupled with the D-serine derivative **11**, followed by cleavage of the allyl ester and Fmoc protecting groups, and then the resulting intermediates were allowed to undergo a lactamization step based on previously optimized conditions[6] to produce lactams **9a**/**9b**

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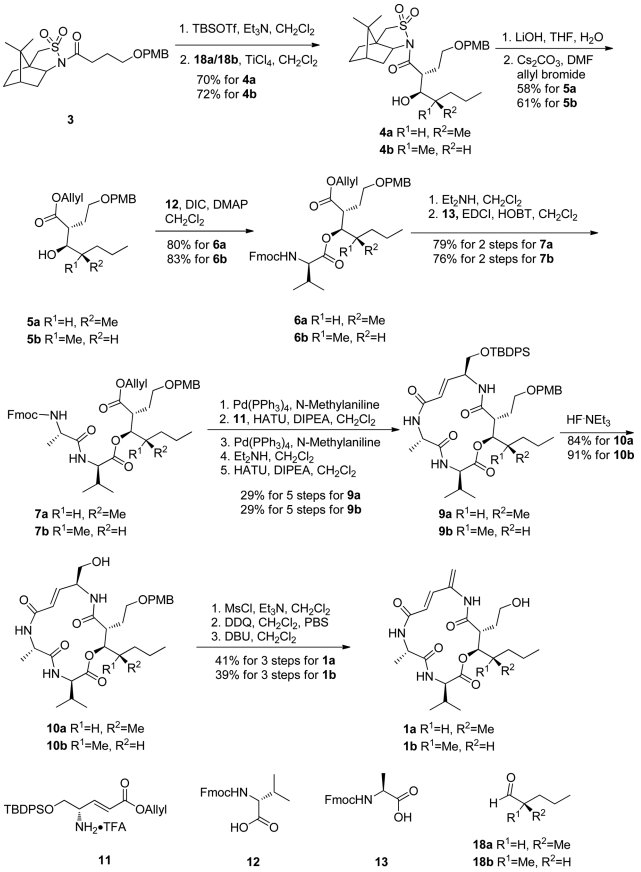
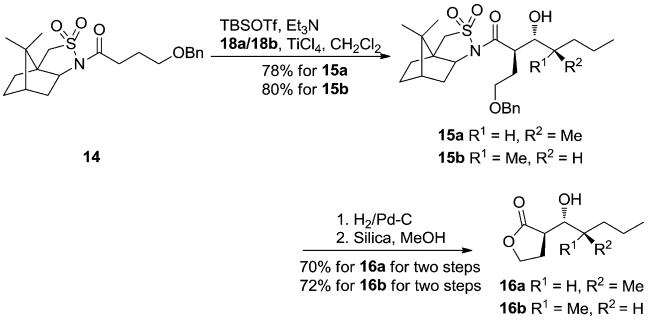
Scheme 1. Total Syntheses of Microtermolide A and C4‴ -*epi*-Microtermolide A



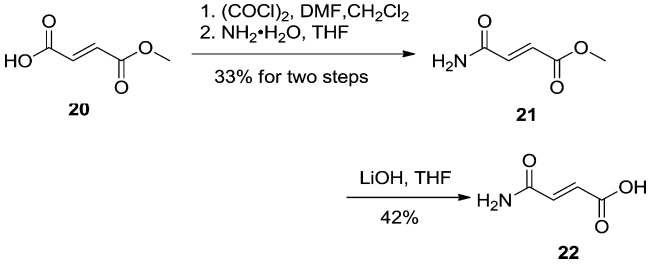
with 29% yield in five steps. Exposure of cyclic compounds **9a** and **9b** to hydrofluoric acid (HF) provided free alcohols **10a**/**10b**. Finally, a mesylation step was followed by deprotection of 4-methoxybenzyl ether (PMB) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and elimination of the methanesulfonyl (Ms) group with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to produce compounds **1a** and **1b**, respectively.

To determine the absolute configuration of microtermolide B, the total synthesis of microtermolide B commenced with the known compound **14**.[8] A Mukaiyama aldol condensation of **14** and **18a**/**18b** produced **15a**/**15b** with high diastereoselectivity (*dr* > 10:1).[8] The benzyl group of **15a**/**15b** was then removed with a palladium on carbon catalyst and hydrogen at atmospheric pressure (Pd−C/H_2). The resulting alcohol was rapidly converted to cyclic products **16a**/**16b** with silica/MeOH (Scheme 2).

Scheme 2. Synthesis of Dihydrofuran-2(3*H*)-ones 16a/16b



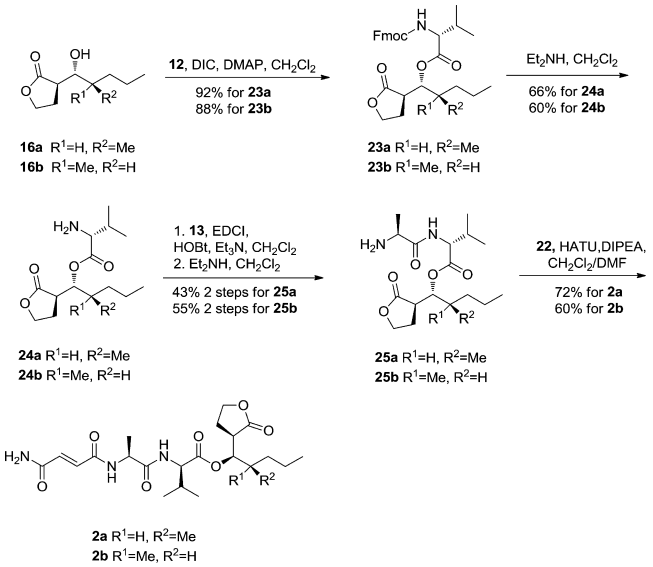
Scheme 3. Synthesis of Unsaturated Acid 22



Known compound **22**[13] was prepared using our concise sequence (Scheme 3). Briefly, compound **20** was treated with oxalyl chloride, followed by an aqueous ammonia solution, to provide amide **21** in 33% yield. The methyl ester was then hydrolyzed to generate the corresponding unsaturated acid **22** in 42% yield.

Esterification of alcohols **16a**/**16b** with Fmoc-D-valine **12** produced compounds **23a**/**23b** (Scheme 4). The Fmoc protecting group was subsequently removed to generate free amines **24a**/**24b**. After **24a**/**24b** were coupled with Fmoc-Ala-OH **13**, followed by removal of the Fmoc group, amines **25a**/**25b** were achieved. In the final step, the secondary amines of **25a**/**25b** were coupled with unsaturated acid **22** to provide compounds **2a**/**2b**.

Scheme 4. Total Syntheses of Microtermolide B and C4‴-*epi*-Microtermolide B



Following the preparation of target molecules **1a**/**2a** and **1b**/**2b**, the four compounds were subjected to ^{1}H and ^{13}C NMR analyses. These data were compared with previously reported data for natural microtermolides A and B.[12] The data for compound **1b** and microtermolide A matched perfectly, while the ^{13}C NMR data for compound **1a** and microtermolide A clearly differed at C-3‴, C-4‴, C-5‴, C-7‴, and C-10‴ (refer to Supporting Information). Thus, the absolute configurations of the three consecutive chiral centers in microtermolide A were unambiguously assigned as 2‴*R*, 3‴*R*, and 4‴*S*, thereby representing an *anti*−*syn* relationship. Similarly, NMR data for compound **2b** and microtermolide B matched. In contrast, the ^{13}C NMR data for compound **2a** and microtermolide B clearly differed at C-3‴, C-4‴, C-5‴, and C-10‴. Thus, the

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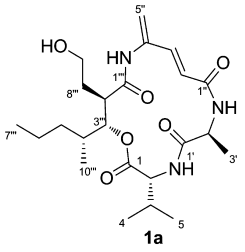
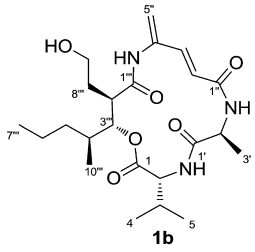
Table 1. ^{1}H and ^{13}C NMR Data Comparison (MeOD-d_4)





	lit. microtermolide A		synthetic microtermolide **1a**				synthetic microtermolide **1b**			
assignment	^{13}C ppm	^{1}H ppm [mult, J (Hz)]	^{13}C ppm	Δppm	^{1}H ppm [mult, J (Hz)]	Δ	^{13}C ppm	Δ	^{1}H ppm [mult, J (Hz)]	Δ
C1, CO	170.4		170.6	0.2			170.3	−0.1		
C2, CH	59.2	4.42 (m)	59.0	−0.2	4.48 (d, 6.6)	0.06	59.2	0	4.43 (d, 7.3)	0.01
C3, CH	33.4	2.07 (dq, 13.7, 6.8)	33.4	0	2.17−2.09 (m)	0.06	33.4	0	2.07 (dq, 14.1, 7.1)	0
C4, CH_3	19.7	0.96 (d, 6.5)	19.9	0.2	0.96 (d, 5.7)	0	19.9	0.2	0.96 (d, 6.6)	0
C5, CH_3	18.5	0.96 (d, 7.0)	18.4	−0.1	0.99 (d, 5.6)	0.03	18.5	0	0.95 (d, 6.6)	−0.01
C1′, CO	175.2		175.0	−0.2			174.9	−0.3		
C2′, CH	52.6	4.40 (m)	52.7	0.1	4.41−4.35 (m)	−0.02	52.8	0.2	4.36 (dd, 10, 6.9)	−0.04
C3′,CH_3	18.5	1.44 (d, 7.0)	18.6	0.1	1.45 (d, 7.0)	0.01	18.6	0.1	1.45 (d, 6.9)	0.01
C1″, CO	169.2		169.2	0			169.2	0		
C2″, CH	118.2	6.24 (d, 15.3)	118.3	0.1	6.20 (d 15.1)	−0.04	118.3	0.1	6.20 (d, 15.1)	−0.04
C3″, CH	141.6	7.11 (d, 14.7)	141.7	0.1	7.14 (d 15.1)	0.03	141.6	0	7.13 (d, 15.2)	0.02
C4″, C	138.6		138.7	0.1			138.6	0		
C5″, CH_2	119.3	5.59 (s)	119.6	0.3	5.60 (s)	0.01	119.6	0.3	5.59 (s)	0
		5.52 (s)			5.54 (s)	0.02			5.54 (s)	0
C1‴, CO	174.3		174.1	−0.2			174.1	−0.2		
C2‴, CH	46.9	3.00 (td, 10.3, 4.1)	46.7	−0.2	3.02 (td, 10.3, 4.7)	0.02	47.0	0.1	2.97 (td, 10.6, 4.9)	−0.03
C3‴, CH	78.0	5.48 (dd, 10.3, 2.1)	80.1	2.1	5.42 (d, 9.9)	−0.06	78.1	0.1	5.49 (d, 10.3)	0.01
C4‴, CH	34.9	1.88 (m)	33.4	−1.5	1.96−1.89 (m)	0.05	34.9	0	1.92−1.85 (m)	0
C5‴, CH_2	37.3	1.34 (m)	35.3	−2.0	1.37−1.29 (m)	−0.01	37.3	0	1.36−1.32(m)	0
		1.16 (m)							1.20−1.11(m)	−0.01
C6‴, CH_2	21.2	1.42 (m)	21.3	0.1	1.37−1.29 (m)		21.3	0.1	1.44−1.36 (m)	−0.02
C7‴, CH_3	14.2	0.90 (t, 7.0)	16.7	2.5	0.95, t (5.6)	0.05	14.2	0	0.90 (t, 7.0)	0
C8‴, CH_2	33.4	1.80 (m)	33.4	0	1.86−1.77 (m)	0.01	33.4	0	1.84−1.76 (m)	0
C9‴, CH_2	59.9	3.66 (m)	59.9	0	3.70−3.64(m)	0.01	59.9	0	3.66 (td, 10.2, 4.5)	0
		3.56 (m)			3.61−3.54 (m)	0.01			3.58−3.55 (m)	0
C10‴, CH_3	13.4	1.06 (d, 7.0)	14.3	0.9	1.80−1.77 (m)		13.4	0	1.06 (d, 6.7)	0

absolute configurations of the three consecutive chiral centers in microtermolide B were unambiguously assigned as 2‴*R*, 3‴*R*, and 4‴*S*, which also represents an *anti*−*syn* relationship. Taken together, these results indicate that the structures of compounds **1b** and **2b** represent the structures of the natural microtermolides A and B, respectively, and assignments of the three chiral centers of each compound have been determined.

Depsipeptides with 4-amino-2,4-pentadienolate structures exhibited important biological activities[1−5,11,12,14,15] and are suitable for further investigation of structure activity relationships (SAR).[16] The determination of the absolute configuration of microtermolides supplied not only two more examples of an *anti*−*syn* relative stereochemistry in depsipeptides with 4-amino-2,4-pentadienolate moieties but also valuable information for further SAR study of this type of depsipeptides.

EXPERIMENTAL SECTION

General Methods and Materials. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates (60-F254). Proton and carbon magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on a 400 MHz spectrometer, as specified. Spectra were acquired in $CDCl_3$ and referenced to the solvent peak at 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C) for $CDCl_3$. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, m = multiplet), coupling constant (Hz), and integration. High-resolution mass spectrometry (HRMS) was performed on a QTOF ESI or MALDI spectrometer. Commercially available dry solvents were used for DMF, CH_2Cl_2, THF, and MeOH. The starting materials **12** and **13** were purchased from Energy Chemical Co.Ltd.

(3*R*,6*S*,14*R*,15*R*,*E*)-14-(2-Hydroxyethyl)-3-isopropyl-6-methyl-11-methylene-15-((*R*)-pentan-2-yl)-1-oxa-4,7,12-triazacyclopentadec-9-ene-2,5,8,13-tetraone (1a). To a solution of **10a** (10 mg, 0.017 mmol) in CH_2Cl_2 (1 mL) were added triethylamine (2.6 mg, 0.025 mmol) and MsCl (2.3 mg, 0.02 mmol) at 0 °C. After being stirred for 0.5 h, the reaction solution was quenched by addition of water (1 mL). The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude mixture was further purified through column chromatography (ethyl acetate/CH_3OH, 10:1) to afford the compound as a solid.

To a solution of the compound above (9 mg, 0.013 mmol) in CH_2Cl_2 (1.4 mL) and PBS (0.1 mL, pH 7.0) was added DDQ (4.4 mg, 0.02 mmol) at 20 °C. After 2 h, the mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic phase was washed by brine and then dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/methanol, 1:0 to 10:1) to give the primary alcohol.

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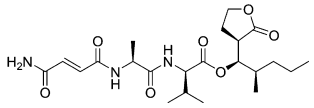
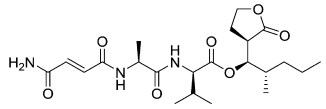
Table 2. ^{1}H and ^{13}C NMR Data Comparison (MeOD-d_4)





	lit. microtermolide B		synthetic microtermolide **2a**				synthetic microtermolide **2b**			
assignment	^{13}C ppm	^{1}H ppm [mult, J (Hz)]	^{13}C ppm	Δppm	^{1}H ppm [mult, J (Hz)]	Δ	^{13}C ppm	Δ	^{1}H ppm [mult, J (Hz)]	Δ
C1, CO	168.7		168.2	−0.5			168.7	0		
C2, CH	134	6.90 (d 15.3)	133.8	−0.2	6.90 (d, 15.3)	0	134.0	0	6.90 (d, 15.3)	0
C3, CH	134.3	6.94 (d 15.3)	134.1	−0.2	6.96 (d, 15.3)	0.02	134.3	0	6.96 (d, 15.3)	0.02
C4, CO	166.2		166.0	−0.2			166.2	0		
C1′, CO	174.5		174.4	−0.1			174.5	0		
C2′, CH	50.5	4.56 (q, 7.0)	50.3	−0.2	4.55 (q, 7.0)	−0.01	50.5	0	4.56 (q, 7.1)	0
C3′, CH_3	18.2	1.39 (d, 7.0)	18.1	−0.1	1.39 (d, 7.1)	0	18.2	0	1.39 (d, 7.0)	0
C1″, CO	172.2		172.2	0			172.3	0.1		
C2″, CH	59.5	4.35 (d, 6.5)	59.5	0	4.34−4.28 (d, 6.1)	−0.04	59.4	−0.1	4.35 (d, 6.1)	0
C3″, CH	31.0	2.21 (m)	31.1	0.1	2.24−2.16 (m)	−0.01	31.3	0.3	2.25−2.17 (m)	0
C4″, CH_3	20.0	0.99 (d, 7.0)	19.7	−0.3	0.99 (d, 6.8)	0	20.0	0	0.98 (d, 6.8)	−0.01
C5″, CH_3	18.3	0.95 (d, 7.0)	18.3	0	0.96 (d, 6.8)	0.01	18.3	0	0.95 (d, 6.8)	0
C1‴,CO	178.6		178.2	−0.4			178.6	0		
C2‴, CH	41.7	3.03 (ddd, 10.7, 9.0, 6.7)	41.5	−0.2	3.08 (ddd, 10.3, 9.1, 6.7)	0.05	41.6	−0.1	3.03 (ddd, 10.7, 9.1, 6.9)	0
C3‴, CH	77.1	5.08 (dd, 7.0, 5.3)	78.2	1.1	5.01 (dd, 7.3, 5.1)	−0.07	77.1	0	5.08 (dd, 6.8, 5.2)	0
C4‴, CH	35.8	1.94 (m)	34.6	−1.2	2.12−2.01 (m)	0.12	35.8	0	1.98−1.89 (m)	0
C5‴, CH_2	36.6	1.32 (m)	35.2	−1.4	1.31−1.27 (m)		36.6	0	1.33−1.29 (m)	0
		1.13 (m)			1.15−1.06 (m)	−0.02			1.17−1.09 (m)	0
C6‴, CH_2	21.0	1.34 (m)	20.5	−0.5	1.31−1.27 (m)		21.0	0	1.37−1.32 (m)	0
C7‴, CH_3	14.5	0.88 (t, 7.3)	14.4	−0.1	0.88 (t, 6.7)	0	14.5	0	0.87 (t, 7.1)	−0.01
C8‴, CH_2	27.0	2.33 (m)	26.4	−0.6	2.36−2.28 (m)	−0.01	27.0	0	2.37−2.29 (m)	0
		2.04 (m)			2.12−2.01 (m)	0.02			2.09−1.99 (m)	0
C9‴, CH_2	67.6	4.31 (td, 8.7, 2.6)	67.6	0	4.34−4.28 (m)	0	67.6	0	4.31 (td, 8.8, 2.7)	0
		4.18 (td, 9.1, 7.0)			4.18 (td, 9.2, 7.0)	0			4.17 (td, 9.3, 6.8)	−0.01
C10‴, CH_3	14.5	0.92 (d 7.0)	16.0	1.5	0.92 (d, 6.9)	0	14.5	0	0.91 (d, 6.8)	−0.01

To a solution of the primary alcohol above in CH_2Cl_2 (0.5 mL) was added DBU (14 mg, 0.09 mmol) at 25 °C. After being stirred for 2 h at this temperature, 1% HCl was added to quench the reaction. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:50) to obtain the title **1a** (3 mg, 41% for three steps) as a solid: ^{1}H NMR (400 MHz, MeOD) δ 7.14 (d, J = 15.1 Hz, 1H), 6.20 (d, J = 15.1 Hz, 1H), 5.60 (s, 1H), 5.54 (s, 1H), 5.42 (d, J = 9.9 Hz, 1H), 4.58 (brs, 1H), 4.48 (d, J = 6.6 Hz, 1H), 4.41−4.35 (m, 1H), 3.70−3.64 (m, 1H), 3.61−3.54 (m, 1H), 3.02 (td, J = 10.3, 4.7 Hz, 1H), 2.17−2.09 (m, 1H), 1.96−1.89 (m, 1H), 1.86−1.77 (m, 2H), 1.61−1.52 (m, 1H), 1.45 (d, J = 7.0 Hz, 3H), 1.37−1.29 (m, 3H), 1.01 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 5.6 Hz, 3H), 0.96 (d, J = 5.7 Hz, 3H), 0.95 (t, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, MeOD) δ 175.0, 174.1, 170.6, 169.2, 141.7, 138.7, 119.6, 118.3, 80.1, 59.9, 59.0, 52.7, 46.7, 35.3, 33.4, 33.4, 33.2, 21.3, 19.9, 18.6, 18.4, 16.7, 14.3; $[M + Na]^+$ calcd for $C_{23}H_{37}N_3O_6Na^+$, 474.2580; found, 474.2578.

1b: $[\alpha]_D^{19}$ = +83.6 (c 0.28, MeOH); IR (KBr, cm^{-1}) ν_{max} 3245, 2960, 2873, 1733, 1671, 1520, 1244, 1038, 982; ^{1}H NMR (400 MHz, MeOD) δ 7.13 (d, J = 15.2 Hz, 1H), 6.20 (d, J = 15.1 Hz, 1H), 5.59 (s, 1H), 5.54 (s, 1H), 5.49 (d, J = 10.3 Hz, 1H), 4.43 (d, J = 7.3 Hz, 1H), 4.36 (q, J = 6.8 Hz, 1H), 3.66 (td, J = 10.2, 4.5 Hz, 1H), 3.57 (dd, J = 16.4, 8.7 Hz, 1H), 2.97 (td, J = 10.6, 4.9 Hz, 1H), 2.07 (dq, J = 14.1, 7.1 Hz, 1H), 1.92−1.85 (m, 1H), 1.84−1.76 (m, 2H), 1.45 (d, J = 6.9 Hz, 3H), 1.44−1.36 (m, 3H), 1.20−1.11 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, MeOD) δ 174.9, 174.1, 170.3, 169.2, 141.6, 138.6, 119.6, 118.3, 78.1, 59.9, 59.2, 52.8, 47.0, 37.3, 34.9, 33.4, 21.3, 19.9, 18.6, 18.5, 14.2, 13.3; $[M + Na]^+$ calcd for $C_{23}H_{37}N_3O_6Na^+$, 474.2580; found, 474.2576.

(1*R*,2*R*)-2-Methyl-1-((*R*)-2-oxotetrahydrofuran-3-yl)pentyl ((*E*)-4-amino-4-oxobut-2-enoyl)-L-alanyl-D-valinate (2a). To a solution of the amine (20 mg, 0.056 mmol) and the unsaturated acid (10 mg, 0.087 mmol) in DMF/CH_2Cl_2 (0.3 mL/1.2 mL) was added DIPEA (56 mg, 0.435 mmol), followed by HATU (66 mg, 0.174 mmol). After 1 h at room temperature, 1% HCl was added to quench the reaction, which was washed with saturated $NaHCO_3$ and brine and evaporated in vacuo. The residue was further purified through chromatography (CH_2Cl_2/CH_3OH, 5%) to give the title product **2a** (15 mg, 60%) as a solid: $[\alpha]_D^{29}$ = −10.3 (c 0.6, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3350, 2959, 2872, 1772, 1726, 1517, 1260, 1100, 872; ^{1}H NMR (400 MHz, MeOD) δ 6.96 (d, J = 15.3 Hz, 1H), 6.90 (d, J = 15.3 Hz, 1H), 5.01 (dd, J = 7.3, 5.1 Hz, 1H), 4.55 (q, J = 7.0 Hz, 1H), 4.34−4.28 (m, 2H), 4.18 (td, J = 9.2, 7.0 Hz, 1H), 3.12−3.05 (m, 1H), 2.36−2.28 (m, 1H), 2.19 (dt, J = 12.8, 6.6 Hz, 1H), 2.12−2.01 (m, 2H), 1.39 (d, J = 7.1 Hz, 3H), 1.31−1.27 (m, J = 3.4 Hz, 2H), 1.25−1.18 (m, 1H), 1.15−1.06 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, MeOD) δ 178.2, 174.4, 172.2, 168.6, 166.0, 134.1, 133.8, 78.2, 67.6, 59.5, 50.3, 41.5, 35.2, 34.6, 31.1, 26.4, 20.5, 19.7, 18.3, 18.1, 16.0, 14.4; HRMS−MALDI (m/z) $[M + Na]^+$ calcd for $C_{22}H_{35}N_3O_7Na^+$, 476.2373; found, 476.2369.

2b: $[\alpha]_D^{29}$ = −4.2(c 0.7, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3294, 2963, 2875, 1771, 1623, 1538, 1166, 1028, 844; ^{1}H NMR (400 MHz, MeOD) δ 6.96 (d, J = 15.3 Hz, 1H), 6.90 (d, J = 15.3 Hz, 1H), 5.08 (dd, J = 6.8, 5.2 Hz, 1H), 4.56 (q, J = 7.1 Hz, 1H), 4.35 (d, J = 6.1 Hz, 1H), 4.31 (td, J = 8.8, 2.7 Hz, 1H), 4.17 (td, J = 9.3, 6.8 Hz, 1H), 3.03 (ddd, J = 10.7, 9.1, 6.9 Hz, 1H), 2.37−2.29 (m, 1H), 2.25−2.17 (m, 1H), 2.09−1.99 (m, 1H), 1.98−1.89 (m, 1H), 1.39 (d, J = 7.1 Hz, 3H), 1.37−1.32 (m, 2H), 1.33−1.29 (m, 1H), 1.17−1.09 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (400 MHz, MeOD) δ 178.6, 174.5, 172.3, 168.7, 166.2, 134.3, 134.0, 77.1, 67.6, 59.4, 50.5,

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41.6, 36.6, 35.8, 31.3, 27.0, 21.0 20.0, 18.3, 18.2, 14.5, 14.5; HRMS−MALDI (m/z) $[M + Na]^+$ calcd for $C_{22}H_{35}N_3O_7Na^+$, 476.2373; found, 476.2369.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b01143.

^1H and ^{13}C NMR, HRMS−MALDI, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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