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Natural Products

Total Synthesis and Structure Elucidation of JBIR-39: A Linear Hexapeptide Possessing Piperazic Acid and γ-Hydroxypiperazic Acid Residues

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Abstract: The total synthesis and stereochemical structural elucidation of JBIR-39, containing four nonproteinogenic piperazic acid (Piz) residues, is reported. The synthesis includes $Sc(OTf)_3$-catalyzed acylation of a Piz(γ-OTBS) derivative with piperazic acid chloride, providing the desired Piz-Piz(γ-OTBS) dipeptide in high yield without epimerization. After assembling two additional Piz moieties and (*S*)-isoleucic acid at the N-terminus, amidation with the (*R*)-α-methylserine ester at the C-terminus, and deprotection afforded the desired (2*R*,8*S*)-hexapeptide, which is the assumed structure of JBIR-39. Although the spectral data of the (2*R*,8*S*)-hexapeptide was not identical to JBIR-39, further synthesis of three stereoisomers confirmed the stereochemical structure of JBIR-39 to be (2*S*,6*S*,8*S*,11*R*,16*S*,21*R*,26*S*,27*S*).

Introduction

Piperazic acid (Piz)-containing natural products are known to exhibit antitumor and antimycobacterial activities.[1] Piz-containing linear peptides and cyclic peptides are intriguing targets for total synthesis because of their unique structural features and biological activities.[2] JBIR-39 (**1**), a linear hexapeptide isolated from *Streptomyces sp*. Sp080513SC-24 in 2011, is composed of (*S*)-isoleucic acid and five rare nonproteinogenic amino acid residues (two D-Piz, L-Piz, *cis*-Piz(γ-OH), and (*R*)-α-methylserine).[3] The planar structure of **1** has been elucidated by 1D and 2D NMR spectroscopic analysis and by mass spectroscopy analysis, and the absolute configuration of each amino acid residue was determined by the Marfey's method; except for *cis*-Piz(γ-OH), the relative stereochemistry of which was determined by NOE observation. This structure was also found in a cyclohexadepsipeptide, piperidamycins isolated from mutant strains of a soil-isolated *Streptomyces sp*. by Hosaka et al. in 2009 (Figure 1).[4] Although piperidamycins are known to exhibit potent antibacterial activity, only their planar structures were reported. Whereas JBIR-39 (**1**) did not display

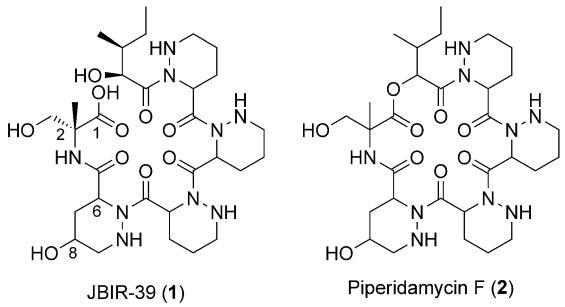

Figure 1. Reported structure of JBIR-39 (**1**) and pipepidamycin F (**2**).

antibacterial activity against *Micrococcus luteus* and *Escherichia coli*, we initially planned the total synthesis of JBIR-39 (**1**), which is speculated to be precursor of piperidamycin F (**2**), to determine the unknown configurations toward elucidation of their structure-activity relationships. The key issue in the synthetic studies of **1** and **2** would be an efficient construction of the unique sequence of the Piz-Piz-Piz-Piz(γ-OH) moiety. In 2009, Ma et al. reported the total synthesis of a cyclohexadepsipeptide, piperazimycin A (**4**), possessing a (*R*,*S*)-Piz(γ-Cl)-(*S*,*S*)-Piz(γ-OH) dipeptide unit (Figure 2). They were unable to install the dipeptide by acylation of H-(*S*,*S*)-Piz(γ-OH) ester with acid chloride (*R*,*S*)-Piz(γ-Cl)-Cl, so the piperazine ring of (*R*,*S*)-Piz(γ-Cl) residue was constructed after coupling its linear precursor.[5] In 2010, Kennedy and Lindsley demonstrated direct acylation

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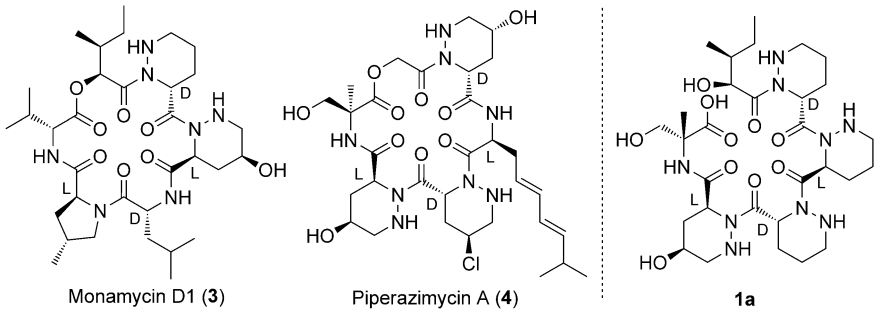


Figure 2. Structures of piperazic acid-containing natural products, monamycin D1 (**3**) and piperazimycin A (**4**) isolated from *Streptomyces sp*. and the assumed structure **1a** as JBIR-39.

of H-(*S*,*S*)-Piz (γ-OTBS)-OMe with Boc-(*R*,*S*)-Piz(Boc) (γ-Cl)-OH by using TCFH/CH_2Cl_2/collidine in 62% yield; however, amidation of H-(*S*,*S*)-Piz(Teoc)(γ-OTBS)-OH with α-methylserine ester (HATU/HOAt/CH_2Cl_2/collidine) resulted in low yield (26%).[6] Thus, efficient methods for the formation of Piz-Piz-Piz-Piz(γ-OH) from Piz(γ-OH) as well as the amidation at the C-terminus of the Piz(γ-OH) unit with α-methylserine ester should be required in the synthesis of both **1** and **2**. Herein, we report a total synthesis and structure elucidation of JBIR-39 (**1b**) utilizing $Sc(OTf)_3$-catalyzed direct acylation of a H-Piz(γ-OH) derivative with hindered acid chlorides.

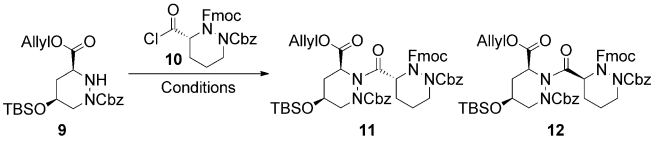
Results and Discussion

Monamycin D1 (**3**)[7] and piperazimycin A (**4**),[8] isolated from *Streptomyces sp.*, are cyclodepsipeptides possessing a Piz-Piz unit. Both are composed of the (*R*)- and (*S*)-configured amino acid moieties in alternating order (Figure 2). Similar to the structural features of **3** and **4**, we assumed the structure of **1a** for JBIR-39.

Our synthetic plan for **1a** included i) acylation at the N-terminus of tetrapiperazic acid derivative **7** with (*S*)-isoleucic acid chloride **8**; ii) amidation at the C-terminus of the Piz(γ-OTBS)-OH moiety in pentapeptide **5** with (*R*)-α-methylserine ester **6**, and iii) removal of all protecting groups (Figure 3). Synthesis of Piz-Piz derivatives has been reported;[5,6,9] however, there have been no reports on the synthesis of tri- or tetra-piperazic acid derivatives. Given that the N1 atom of Piz derivatives is relatively unreactive,[10] reactive acid chlorides such as **10** are usually used as reagents for the acylation of Piz derivatives. The bond formation of a Piz-Piz(γ-OH) sequence is known to be particularly difficult because of the rather lower nucleophilicity of the Piz(γ-OH) derivative. Therefore, development of a concise method for direct acylation of the Piz(γ-OH) derivative should be worthwhile for the synthesis of piperazic acid-containing natural products.

The reaction conditions for acylation of H-Piz(Cbz)(γ-OTBS)-OAllyl (**9**)[11] with Fmoc-Piz(Cbz)-Cl (**10**)[10a,12] were investigated (Table 1). The reaction was performed under conventional con-

Table 1. Acylation of piz(γ-OTBS) derivative **9** with Piz–Cl **10**.



Entry	Reagent	T [°C]	t [h]	Yield of **11** [%][a]	Ratio of **11**/**12**[b]
1[c]	10% $NaHCO_3$ (aq.)	RT	24	23	>95:5
2[c]	2,6-lutidine	RT	13	30	>95:5
3[d]	AgCN (15 mol%)	60	2.5	69	80:20
4[d]	$Sc(OTf)_3$ (10 mol%)	RT	1	86	>95:5
5[d]	$Y(OTf)_3$ (10 mol%)	RT	1	53	73:27
6[d]	$La(OTf)_3$ (10 mol%)	RT	1	60	49:51

[a] Isolated yield. [b] The ratio was determined by HPLC analysis of the peak area at UV 214 nm. [c] Performed in CH_2Cl_2. [d] Performed in toluene.

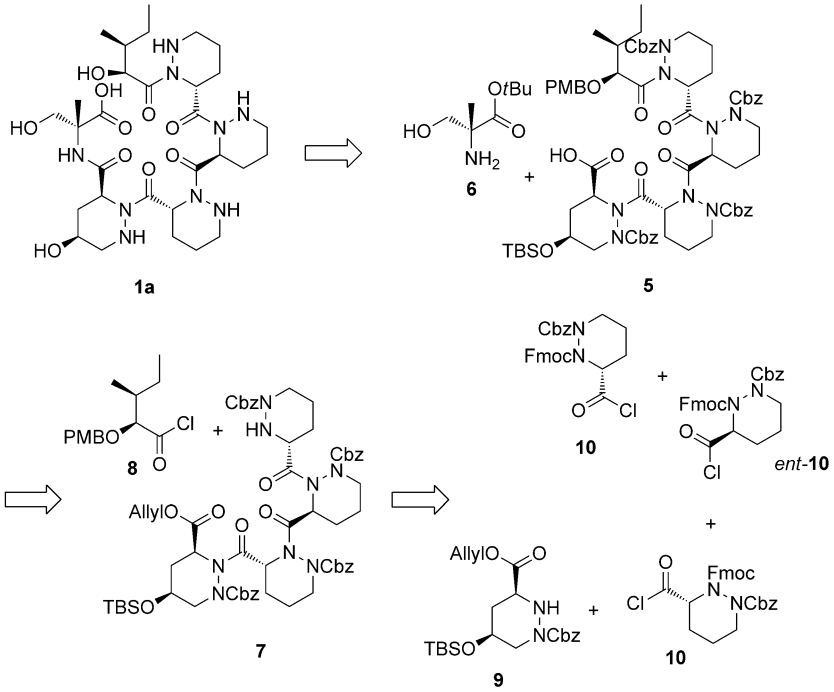
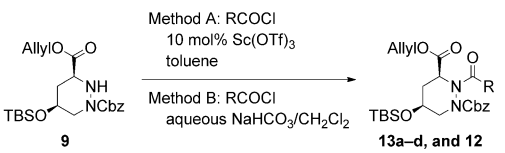


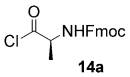
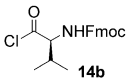
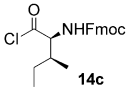
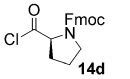
Figure 3. Retrosynthesis of **1a**.

ditions (i.e., 10% aqueous $NaHCO_3$[13] or 2,6-lutidine[14] at room temperature) to provide the desired dipeptide **11** in low yield (entries 1 and 2). The yield increased to 69% when the reaction was performed in the presence of a catalytic amount of AgCN at 60 °C in toluene, which is known to promote the acylation of piperazic acid with acid chlorides.[10b,15] However, considerable epimerization at the α-position of the Piz moiety was observed (**11**/**12** = 80:20, entry 3). To our delight, addition of 10 mol% scandium trifluoromethanesulfonate ($Sc(OTf)_3$)[16] promoted the acylation of **9** at room temperature, leading to the formation of **11** in 86% yield without serious epimerization (**11**/**12** = > 95:5, entry 4). Other Lewis acids ($Y(OTf)_3$ and $La(OTf)_3$)[17] gave poor results because the corresponding ketene would be formed, leading to a mixture of **11** and its epimer **12** (entries 5 and 6).

The scope of the substrates in this $Sc(OTf)_3$-catalyzed acylation of **9** was investigated (Table 2). The reaction with Fmoc-alanyl chloride (**14a**) in the presence of 10 mol% $Sc(OTf)_3$ (Method A) proceeded at 0 °C, leading to the desired dipeptide **13a** in 77% yield (entry 1). The conventional method (method B) using aqueous $NaHCO_3$ gave a better result (98%, entry 2). Interestingly, Method A was more effective than Method B for the acylation of **9** using bulky acid chlorides **14b–c** to afford **13b–c**, respectively, as the sole product (entries 3 vs. 4 and 5 vs. 6). Reactions using acid chlorides **14d** and *ent*-**10** were completed within 4 h (Method A) to provide dipeptides **13d** and **12** in 70 and 82% yield, respectively, without epimerization (entries 7 vs. 8 and 9 vs. 10). Notably, the $Sc(OTf)_3$-catalyzed acylation of H-Piz(γ-OTBS) derivative **9** was remarkably effective for coupling with sterically hindered acid chlorides.

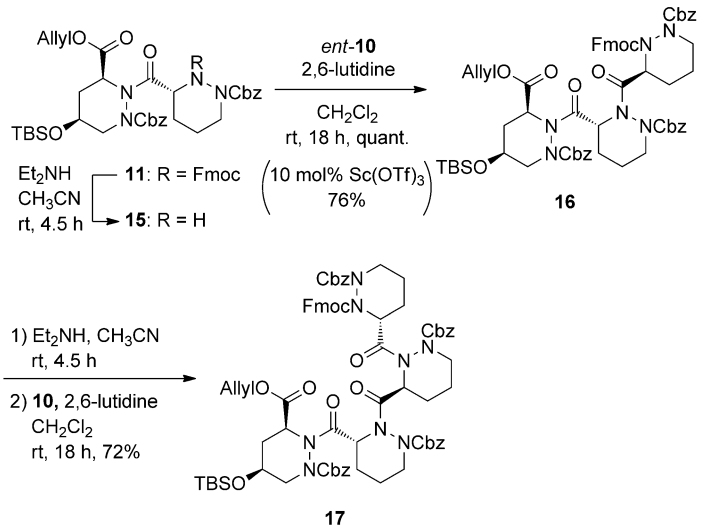
Table 2. Scope and limitation in $Sc(OTf)_3$-catalyzed acylation of **9** with various acid chlorides.



Entry	RCOCl	Method	*t* [h]	*T* [°C]	Product	Yield [%][a]
1	 **14a**	A	4	0	**13a**	77
2		B	18	RT	**13a**	98
3	 **14b**	A	6	RT	**13b**	77
4		B	24	RT	**13b**	24
5	 **14c**	A	9	RT	**13c**	63
6		B	24	RT	**13c**	21
7	 **14d**	A	4	RT	**13d**	70
8		B	21	RT	**13d**	66
9	*ent*-**10**	A	4	RT	**12**	82
10		B	21	RT	**12**	66

[a] Isolated yield.

With the Piz-Piz(γ-OTBS) derivative **11** in hand, the synthesis of tetra-piperazic acid derivative **17** was investigated (Scheme 1). Removal of the Fmoc group in **11**, followed by acylation with *ent*-**10** utilizing 2,6-lutidine, quantitatively provided tri-piperazic acid derivative **16**, whereas the reaction using 10 mol% $Sc(OTf)_3$ afforded **16** in 76% yield. The coupling of tri-piperazic acid derivative **16** with **10** was performed in the same manner to afford the desired tetra-piperazic acid derivative **17** in 72% yield.

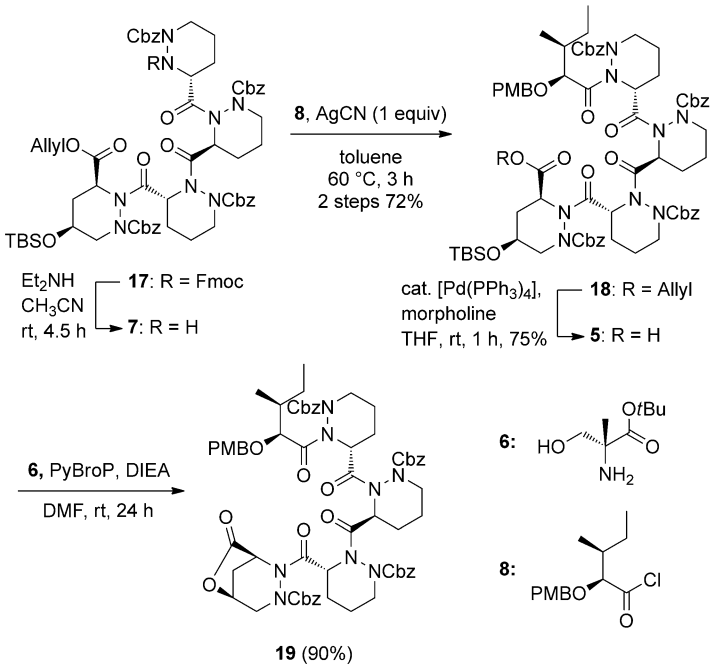


Scheme 1. Synthesis of tetrapiperazic acid derivative **17** from **11**.

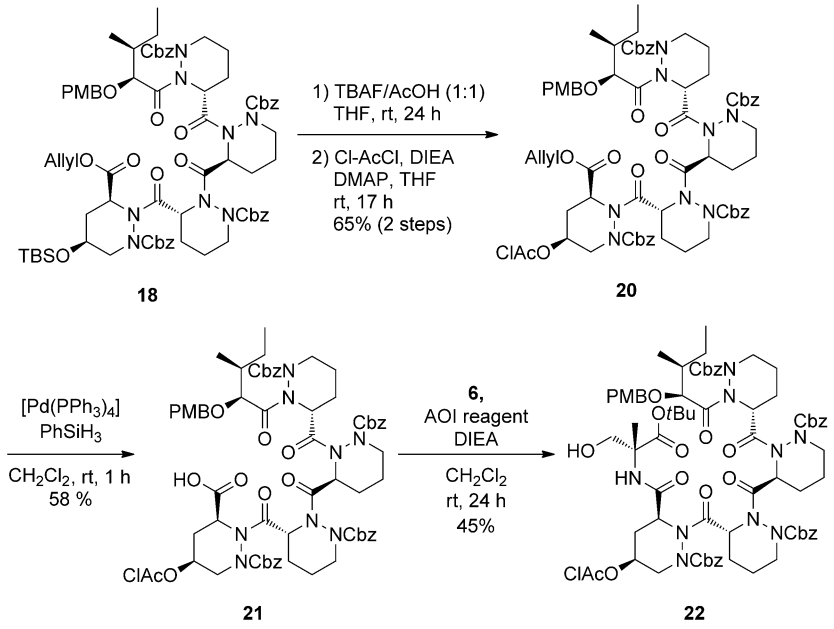
Removal of the Fmoc group in **17**, leading to **7**, followed by amidation with L-isoleucic chloride **8** utilizing AgCN afforded pentapeptide **18** in 72% yield without attaching the PMB group (Scheme 2).[18] Removal of the allyl group in the presence of a catalytic amount of $Pd(PPh_3)_4$ with morpholine provided the corresponding acid **5** in 75% yield. However, amidation of **5** with (*R*)-α-methylserine derivative **6**[19] using PyBroP/DIEA[20] provided lactone **19** in 90% yield, rather than the desired hexapeptide. Removal of the TBS group in acid **5** could occur; consequently, intramolecular esterification led to lactone **19** prior to the intermolecular amidation with α-methylserine derivative **6**.

To avoid lactone formation, the Piz(γ-OTBS) moiety in **18** was transformed into a Piz(γ-OClAc) moiety to yield **20** (Scheme 3). The allyl ester was then converted into the corresponding acid **21** (cat. $Pd(PPh_3)_4/PhSiH_3$), without attaching the chloroacetyl group, in 63% yield. Amidation at the C-terminus of the Piz(γ-OClAc)-OH moiety in pentapeptide **21** with (*R*)-α-methylserine derivative **6** utilizing PyBroP/DIEA or HATU/DIEA[21] failed to yield the desired hexapeptide **22**. However, the use of AOI[22] as a coupling reagent provided **22** in 45% yield.

Removal of all protecting groups in hexapeptide **22** furnished **1a** in 26% overall yield as follows: i) removal of the chloroacetyl group by treatment with thiourea at 50 °C, ii) re-



Scheme 2. Formation of pentapeptide **5** and attempted amidation with α-methylserine ester **6**.



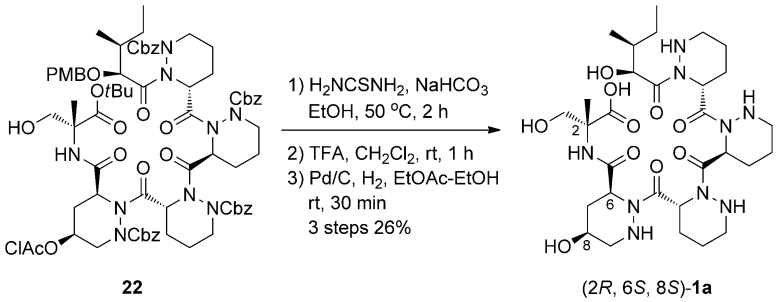
Scheme 3. Synthesis of hexapeptide **22**.

moval of the *tert*-butyl ester under acidic conditions, and iii) removal of the Cbz and PMB groups by hydrogenolysis (Scheme 4). However, the spectral data of **1a** was not identical to those of natural JBIR-39. The main difference in the chemical shifts of the ^{1}H and ^{13}C NMR spectra between the synthetic **1a** and natural JBIR-39 was in the methyl group in the (*R*)-α-methylserine moiety (S114);[23] thus, we supposed that the absolute configuration of the α-methylserine and/or adjacent *cis*-γ-hydroxypiperazic acid was incorrect.

To elucidate the absolute configuration of JBIR-39, we synthesized diastereomers **1b**, **1c**, and **1d**, in a manner similar to the synthesis of **1a**. Amidation of **21** with (*S*)-α-methylserine derivative *ent*-**6** by using the AOI reagent, followed by removal of all protecting groups of **23** afforded (2*S*,6*S*,8*S*)-**1b** (Scheme 5). The diastereomers (2*R*,6*R*,8*R*)-**1c** and (2*S*,6*R*,8*R*)-**1d** were also prepared as follows. Amidation of **24**[23] with **6** and *ent*-**6** was performed by using the AOI reagent to provide (2*R*,6*R*,8*R*)-**25** and (2*S*,6*R*,8*R*)-**26**, respectively, without formation of a lactone. Removal of the TBS, *t*Bu and PMB, and Cbz groups furnished (2*R*,6*R*,8*R*)-**1c** and (2*S*,6*R*,8*R*)-**1d** in moderate yields. Comparing the spectral data of **1b**–**d** with those of natural JBIR-39, we found that the spectral data of **1b** was in good agreement with those of JBIR-39 (S115–S117).[23] Thus, the structure of JBIR-39 was unequivocally determined to be (2*S*,6*S*,8*S*,11*R*,16*S*,21*R*,26*S*,27*S*)-**1b**.[24]

Conclusion

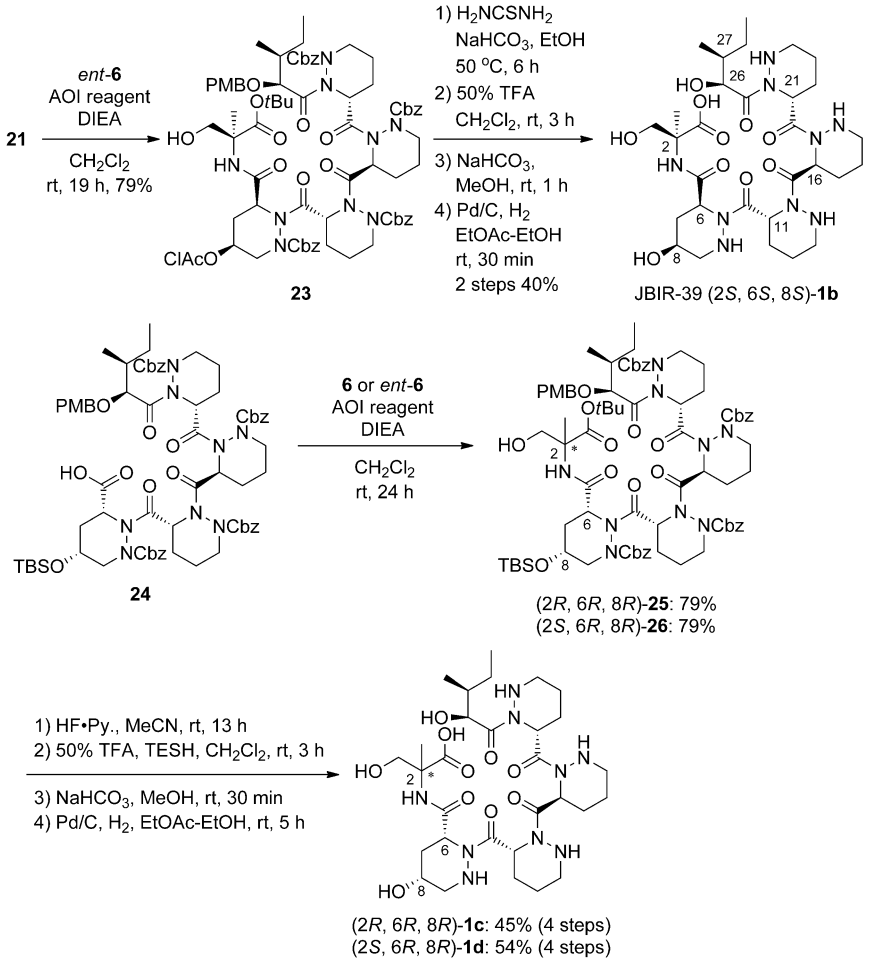
We have demonstrated the total synthesis and structure elucidation of JBIR-39 (**1b**). A catalytic amount of $Sc(OTf)_3$ efficiently promoted direct acylation of γ-hydroxypiperazic acid derivative **9** with piperazic acid chloride **10** to afford Piz-Piz(γ-OTBS) derivative **11** in high yield without epimerization. These reaction conditions were applicable to the acylation with other acid chlorides **14a**–**d** and *ent*-**10**. Unprecedented tri- and tetra-piperazic acid derivatives **16** and **17** were efficiently synthesized from **11** by using acid chlorides *ent*-**10** and **10** with 2,6-lutidine. The AOI reagent was found to be effective for amidation at the C-terminus of the Piz(γ-OTBS)-OH and Piz(γ-OClAc)-OH moieties in pentapeptides **21** and **24** with both (*R*)- and (*S*)-α-methylserine derivatives **6** and *ent*-**6**, leading to four diastereomeric hexapeptides **1a**–**d** in moderate yields. Although (2*R*,6*S*,8*S*)-**1a** initially synthesized was not identical to the natural JBIR-39, the spectral data of (2*S*,6*S*,8*S*)-**1b** was in good agreement with those reported for the natural product. Consequently, the structure of JBIR-39 was unequivocally determined to be **1b**, and its absolute configurations were established to be 2*S*,6*S*,8*S*,11*R*,16*S*,21*R*,26*S*,27*S*. These results are expected to be



22

(2*R*, 6*S*, 8*S*)-**1a**

Scheme 4. Synthesis of (2*R*,6*S*,8*S*)-**1 a**: the incorrect isomer of JBIR-39.



21

23

JBIR-39 (2*S*, 6*S*, 8*S*)-**1b**

24

(2*R*, 6*R*, 8*R*)-**25**: 79%
(2*S*, 6*R*, 8*R*)-**26**: 79%

(2*R*, 6*R*, 8*R*)-**1c**: 45% (4 steps)
(2*S*, 6*R*, 8*R*)-**1d**: 54% (4 steps)

Scheme 5. Synthesis of the JBIR-39 (2*S*,6*S*,8*S*)-(**1 b**) and its diastereomers (2*R*,6*R*,8*R*)-**1 c** and (2*S*,6*R*,8*R*)-**1 d**.

significant for further studies for the total synthesis of piperidamycin antibiotics and their structure-activity relationships.

Experimental Section

General techniques

All commercially available reagents including the substrates were used as received. Anhydrous THF and dichloromethane (Kanto Chemical Co.) were obtained by passing commercially available predried, oxygen-free formulations through activated alumina column. MeOH was distilled from iodine and magnesium turnings. DMF was purchased from Wako (for peptide synthesis, grade: 99.5%). All reactions in solution-phase were monitored by thin-layer chromatography carried out on Merck silica gel plates (0.2 mm, 60F-254) with UV light, and visualized with anisaldehyde, 10% ethanolic phosphomolybdic acid. Silica gel 60N (Kanto Chemical Co. 100–210 μm) was used for column chromatography, and Merck silica gel plates (2.0 mm, 60F-254) were used for preparative thin-layer chromatography. ^{1}H NMR spectra (400 or 600 MHz) and ^{13}C NMR spectra (100 or 150 MHz) were recorded with JEOL JNM-AL400 or JEOL JNM-ECA600 or Varian NMR system 600NBCL spectrometers in the indicated solvent. Chemical shifts (δ) are reported in units of parts per million (ppm) relative to the signal for internal tetramethylsilane (0 ppm for ^{1}H) for solutions in $CDCl_3$. NMR spectral data are reported as follows: chloroform ($CHCl_3$; 7.26 ppm for ^{1}H) or $CDCl_3$ (77.0 ppm for ^{13}C), dimethylsulfoxide (DMSO; 2.50 ppm for ^{1}H) or [D_6]DMSO (39.5 ppm for ^{13}C) when internal standard is not indicated. Multiplicities are reported by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), dt (double triplet), ddd (double double doublet), ddt (double double triplet), dddd (double double double doublet), br s (broad singlet), br d (broad doublet), *J* (coupling constants in Hertz). Gel permeation chromatography was performed on LC-9201 (recycling preparative HPLC), with RI-50 refractive index detector and s-3740 ultra violet detector with polystyrene gel columns (JAIGEL-1H and -2H, 20 mm × 600 mm), using $CHCl_3$ as a solvent (3.5 mL min^{-1}). Mass spectra and high-resolution mass spectra were measured with JEOL JMS-DX303 (EI), MS-AX500 (FAB), or Thermo Scientific Exactive Plus Orbitrap Mass Spectrometer (ESI) instruments. LC spectra were measured with a reversed-phase HPLC (Waters LC/MS system ZQ2000) with Waters 2996 ultraviolet detector with X Bridge^T C18 3.5 μm column using A: methanol and B: H_2O as solvent (flow rate: 1.1 mL min^{-1}, gradient: 0–1 min, A 5%; 1–4 min, A 5–95%; 4–11 min, A 95%; 11–11.1 min, A 5%; 11.1–15 min, A 5%). IR spectra were recorded with a Shimadzu FTIR-

8400. Only the strongest and/or structurally important absorption are reported as the IR data. Specific rotations were measured with a JASCO P-1010 polarimeter. Melting points were measured with a Yazawa Micro Melting Point BY-2 or a Round Science Inc. RFS-10 and are not corrected.

Synthesis

Amine 9: Aqueous LiOH (1 M, 2.0 mL, 0.200 mmol, 5.0 equiv) was added to a solution of L-H-(N^{δ}-Cbz)-Piz(γ-OTBS)-OMe (**S8**)[23] (169 mg, 0.414 mmol, 1 equiv) in anhydrous THF (2.0 mL, 5.0 mL mmol^{-1}) at 0 °C. The mixture was stirred at RT for 2.5 h, then the reaction was quenched with 1 M aqueous HCl at 0 °C and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used for the next reaction without further purification. Allyl bromide (0.043 mL, 0.497 mmol, 1.2 equiv) was added to a solution of the above residue and DIEA (0.216 mL, 1.24 mmol, 3.0 equiv) in anhydrous DMF (2.0 mL, 5.0 mL mmol^{-1}) at 0 °C under argon. The mixture was stirred at RT for 19 h, then the reaction was quenched with 1 M aqueous HCl at 0 °C and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1) to afford amine **9** (132 mg, 0.304 mmol, 2 steps 73%) as a pale-yellow oil. $[\alpha]_D^{25} = +13.5$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$–7.36 (m, 5H), 5.91 (ddt, $J = 6.0$, 10.4, 18.0 Hz, 1H), 5.33 (dd, $J = 1.2$, 18.0 Hz, 1H), 5.26 (dd, $J = 1.2$, 10.4 Hz, 1H), 5.22 (d, $J_{gem} = 12.0$ Hz, 1H), 5.14 (d, $J_{gem} = 12.0$ Hz, 1H), 4.63 (m, 2H), 4.15 (m, 1H), 3.69 (m, 1H), 3.58 (m, 1H), 2.77 (m, 1H), 2.25 (m, 1H), 1.62 (m, 1H), 0.86 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.8$, 155.5, 136.2, 131.4, 128.5, 128.1, 127.9, 119.0, 67.7, 65.8, 65.6, 57.4, 51.5, 37.5, 25.6, 17.9, −4.82, −4.85 ppm; IR (neat): $\tilde{\nu} = 3298$, 2954, 2929, 2886, 2858, 1742, 1703, 1254, 1170, 1122, 1095, 838, 778 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{34}N_2O_5SiNa$: 457.2129 $[M+Na]^+$; found: 457.2117.

Synthesis of acid chlorides 10 and *ent*-10; general procedure

Oxalyl chloride (10 equiv) was added to a solution of Fmoc-L-(N^{δ}-Cbz)-Piz-OH (**S11**)[23] (1.0 equiv) and DMF (1 drop) in benzene (5.0 mL mmol^{-1}) at 0 °C under argon. The mixture was stirred at 80 °C for 3 h, then concentrated in vacuo. The resulting acid chloride **10** was used for the next reaction without further purification.

Dipeptide 11: Scandium triflate (35.0 mg, 0.144 mmol, 0.10 equiv) was added to a solution of **9** (627 mg, 1.41 mmol, 1.0 equiv) and acid chloride **10** (1.87 mmol, 1.3 equiv) in anhydrous toluene (7.0 mL, 5.0 mL mmol^{-1}) at 0 °C under argon. The mixture was stirred at RT for 1.5 h, then the reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the mixture was stirred at RT. The mixture was stirred at the same temperature for 10 min, then extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1) to afford dipeptide **11** (1.13 g, 1.25 mmol, 89%) as a pale-yellow amorphous solid. $[\alpha]_D^{24} = -9.68$ ($c = 0.990$, $CHCl_3$); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ (mixture of rotamers) = 7.83 (m, 2H), 7.58 (m, 2H), 7.13–7.43 (m, 14H), 5.83 (m, 1H), 4.79–5.34 (m, 8H), 4.35–4.64 (m, 3H), 3.79–4.35 (m, 5H), 2.62–3.12 (m, 2H), 1.20–2.08 (m, 6H), 0.76 (s, 9H), 0.01 (s, 3H), −0.01 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 169.0, 166.7, 155.0, 142.9, 141.4, 136.8, 136.2, 132.0, 129.3, 128.9, 128.6, 128.55, 128.51, 128.48, 128.43, 128.39, 128.31, 128.27, 128.22, 128.16, 127.98, 127.86, 127.76, 127.69, 127.57, 127.44, 127.35, 127.1, 125.3, 120.2, 119.92, 119.86, 118.5, 118.2, 68.9, 68.6, 68.1, 68.0, 67.9, 67.8, 67.5, 67.,4, 67.2, 66.2, 66.1, 66.0, 65.9, 63.5, 54.3, 50.6, 49.4, 49.3, 47.0, 32.7, 29.6, 25.71, 25.68, 25.63, 24.3, 24.1, 23.8, 18.1, 18.0, 17.9, −4.9, −5.15, −5.19, −5.3, −5.4 ppm; IR (neat): $\tilde{\nu} = 2954$, 2928, 2856, 1713, 1451, 1410, 1358, 1296, 1253, 1195, 1124, 1089, 837, 741 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{50}H_{59}N_4O_{10}Si$: 903.4000 $[M+H]^+$; found: 903.4001 (See S21 in page S12 of the Supporting Information).

Synthesis of acid chloride 14a, b, c, and d; general procedure

DMF (1 drop) was added to a solution of the corresponding Fmoc-amino acid (1.0 equiv) and oxalyl chloride (10 equiv) in anhydrous CH_2Cl_2 (8.0 mL mmol^{-1}) at 0 °C under argon. The mixture was stirred at RT for 1 h, then concentrated in vacuo. The residue was used for the next reaction immediately without further purification.

Synthesis of dipeptide (method A); general procedure

Scandium triflate (0.10 equiv) was added to a solution of amine **9** (1.0 equiv) and acid chloride **14** or *ent*-**10** (2.0 equiv) in anhydrous toluene (5.0 mL mmol^{-1}) at 0 °C under argon. The mixture was stirred at RT or 0 °C for 4–9 h, then the reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and stirred at RT. The mixture was stirred at the same temperature for 10 min, then extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford dipeptide **13** or **12**.

Synthesis of dipeptide (method B); general procedure

A solution of acid chloride **14** or *ent*-**10** (2.0 equiv) in anhydrous CH_2Cl_2 (5.0 mL mmol^{-1}) was added to a suspension of amine **9** (1.0 equiv) in 10% aqueous $NaHCO_3$ (5.0 mL mmol^{-1}) at 0 °C. The mixture was stirred at RT for 18–24 h, then diluted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford dipeptide **13** or **12**.

Dipeptide 13a: Method A: 0 °C, 4 h; Yield: 12.8 mg (77%, 17.6 μmol); Method B: 24 h; Yeld: 16.0 mg (98%, 22.0 μmol); $[\alpha]_D^{31} = -9.81$ ($c = 0.540$, MeOH); Retention time: 11.3 min; ^{1}H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.76 (m, 2H), 7.57 (m, 2H), 7.08–7.43 (m, 10H), 5.65–5.99 (m, 1H), 5.02–5.40 (m, 5H), 3.46–4.76 (m, 8H), 1.95–2.83 (m, 2H), 1.05–1.78 (m, 4H), 0.83 (m, 9H), −0.10–0.08 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (mixture of rotamers) = 169.2, 155.7, 155.6, 155.0, 143.9, 143.75, 143.72, 141.3, 132.0, 128.6, 128.5, 128.4, 128.2, 128.1, 127.75, 127.71, 127.6, 127.0, 125.25, 125.20, 125.1, 125.0, 120.0, 119.9, 67.0, 66.9, 66.2, 50.2, 47.1, 47.0, 34.1, 31.9, 29.7, 25.8, 25.7, 25.68, 25.63, 19.5, 18.3, 18.0, 17.9, 17.5, 14.1, −4.8, −5.1, −5.2, −5.3 ppm; IR (neat): $\tilde{\nu} =$ 2951, 2928, 2856, 1724, 1683, 1451, 1409, 1253 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{49}N_3O_8SiNa$: 750.3181 $[M+Na]^+$; found: 750.3160.

Dipeptide 13b: Method A: RT, 6 h; Yield: 16.9 mg(77%, 22.4 μmol); Method B: 24 h; Yield: 1.0 mg (24%, 1.32 μmol); $[\alpha]_D^{31} = +0.37$ ($c = 0.40$, MeOH); Retention time: 11.4 min; ^{1}H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.76 (m, 2H), 7.57 (m, 2H), 7.09–7.42 (m, 10H), 5.65–5.97 (m, 1H), 4.94–5.40 (m, 5H), 3.66–4.77 (m, 8H), 1.95–3.07 (m, 3H), 1.05–1.78 (m, 1H), 0.68–1.02 (m, 15H), 0.00–0.08 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ

(mixture of rotamers) = 169.1, 156.4, 143.8, 141.4, 131.8, 131.0, 128.5, 128.3, 127.7, 127.6, 127.0, 125.1, 125.0, 120.0, 119.9, 118.8, 118.5, 67.4, 66.9, 66.2, 65.9, 64.9, 55.0, 54.7, 47.1, 32.5, 31.9, 29.7, 29.5, 29.3, 25.8, 25.7, 25.6, 22.7, 19.9, 18.3, 18.1, 17.9, 17.0, 14.1, −4.9, −5.2 ppm; IR (neat): $\tilde{\nu}$ = 3344, 2928, 2855, 1734, 1685, 1451, 1407, 1254, 1126 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{42}H_{53}N_3O_8SiNa$: 778.3494 $[M+Na]^+$; found: 778.3474.

Dipeptide 13c: Method A: RT, 9 h; Yield: 21.9 mg (63%, 28.4 μmol); Method B: 24 h; Yield: 4.3 mg (21%, 5.58 μmol); $[\alpha]_D^{33}$ = −6.77 (*c* = 0.235, MeOH); Retention time: 11.6 min; ^1H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.76 (m, 2H), 7.56 (m, 2H), 7.09–7.43 (m, 10H), 5.61–5.97 (m, 1H), 5.00–5.46 (m, 5H), 3.47–4.77 (m, 8H), 1.94–2.49 (m, 3H), 1.26–1.84 (m, 3H), 0.55–1.11 (m, 15H), 0.00–0.08 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (mixture of rotamers) = 169.1, 156.3, 143.8, 141.3, 141.2, 132.0, 131.7, 128.6, 128.48, 128.44, 128.2, 127.7, 127.6, 127.0, 125.2, 125.1, 124.9, 120.0, 119.9, 118.7, 66.9, 66.2, 55.2, 47.1, 29.7, 28.1, 26.4, 25.7, 25.7, 25.7, 25.6, 22.7, 17.9, 16.3, 14.1, 1.0, −4.8, −5.2 ppm; IR (neat): $\tilde{\nu}$ = 2958, 2928, 1729, 1680, 1252, 1126, 740 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{43}H_{55}N_3O_8SiNa$: 792.3651 $[M+Na]^+$; found: 792.3628.

Dipeptide 13d: Method A: RT, 4 h; Yield: 9.9 mg (70%, 13.1 μmol); Method B: 21 h; Yield: 9.2 mg (66%, 12.2 μmol); $[\alpha]_D^{33}$ = −16.2 (*c* = 0.470, MeOH); Retention time: 11.9 min; ^1H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.75 (m, 2H), 7.58 (m, 2H), 7.26–7.43 (m, 9H), 5.88 (m, 1H), 5.05–5.44 (m, 5H), 3.95–4.69 (m, 8H), 3.47–3.82 (m, 3H), 1.43–2.33 (m, 6H), 0.80–0.88 (m, 9H), −0.05–0.08 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (mixture of rotamers) = 176.6, 176.0, 169.5, 169.7, 156.0, 154.9, 154.7, 144.0, 143.8, 141.2, 135.9, 132.0, 128.6, 128.4, 128.3, 128.1, 127.6, 127.0, 126.9, 125.2, 125.1, 119.95, 119.93, 118.4, 118.2, 68.2, 68.0, 67.4, 65.8, 65.6, 63.5, 63.3, 55.5, 54.9, 51.6, 50.0, 49.9, 47.1, 46.9, 32.9, 32.8, 31.4, 30.4, 30.2, 29.7, 29.3, 25.8, 25.7, 25.6, 24.6, 23.3, 22.7, 18.3, 14.1, 1.15, 1.02, −5.0, −5.3 ppm; IR (neat): $\tilde{\nu}$ = 2951, 2927, 2854, 1685, 1415, 1252, 1123 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{42}H_{51}N_3O_8SiNa$: 776.3338 $[M+Na]^+$; found: 776.3323.

Dipeptide 12: Method A: RT, 4 h; Yield: 12.4 mg(82%, 13.7 μmol); Method B: 24 h; Yield: 9.4 mg (68%, 10.4 μmol); $[\alpha]_D^{33}$ = +12.0 (*c* = 0.994, $CHCl_3$); Retention time: 12.1 min; ^1H NMR (400 MHz, $[D_6]$DMSO): δ (mixture of rotamers) = 7.73 (m, 2H), 7.56 (m, 2H), 7.07–7.42 (m, 14H), 5.86 (m, 1H), 4.82–5.52 (m, 8H), 4.35–4.75 (m, 3H), 3.50–4.28 (m, 5H), 1.16–2.93 (m, 8H), 0.70–0.94 (m, 9H), −0.21–0.06 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 172.1, 171.6, 170.5, 170.0, 156.2, 156.1, 155.9, 155.7, 155.3, 144.5, 144.1, 144.0, 143.9, 142.1, 142.0, 141.9, 136.8, 136.6, 136.3, 136.2, 132.8, 132.7, 132.6, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 127.7, 127.6, 127.5, 125.7, 125.4, 120.7, 120.4, 118.9, 118.8, 118.7, 118.5, 69.0, 68.7, 68.2, 68.1, 67.9, 66.0, 65.8, 63.8, 63.7, 63.0, 62.9, 52.0, 51.4, 50.6, 50.4, 50.0, 49.5, 49.3, 49.2, 49.1, 47.3, 46.9, 46.2, 45.9, 44.2, 32.7, 32.1, 25.85, 25.78, 25.2, 23.3, 23.2, 22.9, 19.7, 19.4, 18.31, 18.25, −5.2, −5.3, −5.4, −5.5, −5.6 ppm; IR (neat): $\tilde{\nu}$ = 3584, 3063, 3033, 2929, 2855, 1725, 1682, 1451, 1409, 1359, 1250, 1195, 1124, 1079, 1013, 872, 837, 741, 697 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{50}H_{58}N_4O_{10}SiNa$: 925.3814 $[M+Na]^+$; found: 925.3803.

Tripeptide 16: Diethylamine (83.0 μL, 0.803 mmol, 5.0 equiv) was added to a solution of dipeptide **11** (145 mg, 0.161 mmol, 1.0 equiv) in anhydrous acetonitrile (1.6 mL, 10 mL $mmol^{-1}$) at RT under argon. The mixture was stirred at the same temperature for 2 h, then concentrated in vacuo. The residue was used for the next reaction without further purification. A solution of acid chloride *ent*-**10** (0.322 mmol, 2.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL, 6.0 mL $mmol^{-1}$) was added to a solution of the above residue and 2,6-lutidine (56.0 μL, 0.483 mmol, 3.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL, 6.0 mL $mmol^{-1}$) at 0 °C under argon. The mixture was stirred at RT for 18 h, then the reaction was quenched with 1.0 M aqueous HCl at 0 °C, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1) to afford tripeptide **16** (188 mg, 0.164 mmol, 2 steps quant) as a pale-yellow amorphous solid. $[\alpha]_D^{24}$ = −0.251 (*c* = 1.58, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.73 (m, 2H), 7.50 (m, 2H), 6.91–7.63 (m, 19H), 5.70–5.98 (m, 1H), 4.68–5.72 (m, 11H), 4.59 (m, 2H), 3.45–4.62 (m, 7H), 2.51–3.45 (m, 3H), 1.11–2.50 (m, 10H), 0.64–0.97 (m, 9H), −0.23–0.16 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 169.5, 167.6, 155.0, 143.7, 143.0, 141.2, 136.8, 135.8, 135.1, 132.1, 131.9, 131.8, 128.4, 128.2, 128.1, 127.9, 127.8, 127.0, 125.2, 124.9, 119.8, 118.7, 118.0, 117.6, 70.0, 69.7, 68.9, 68.4, 67.9, 67.5, 67.4, 67.2, 67.1, 66.7, 66.1, 65.7, 65.6, 63.2, 62.1, 54.6, 53.9, 53.1, 50.1, 49.6, 49.2, 48.8, 46.8, 46.4, 45.9, 45.5, 45.2, 35.4, 34.7, 34.2, 33.9, 33.4, 33.0, 32.8, 32.3, 31.8, 29.5, 29.3, 25.6, 23.7, 23.5, 22.7, 22.4, 20.3, 19.1, 18.6, 18.4, 18.0, 17.9, 17.4, 16.6, 16.1, −4.5, −5.1, −5.3 ppm; IR (neat): $\tilde{\nu}$ = 2951, 2931, 2857, 1714, 1683, 1405, 1359, 1255, 1128, 979, 837, 740, 697 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{63}H_{72}N_6O_{13}SiNa$: 1171.4824 $[M+Na]^+$; found: 1171.4860 (See S22 in page S12 of the Supporting Information).

Tetrapeptide 17: Diethylamine (75.0 μL, 0.725 mmol, 5.0 equiv) was added to a solution of tripeptide **16** (166 mg, 0.145 mmol, 1.0 equiv) in anhydrous acetonitrile (1.5 mL, 10 mL $mmol^{-1}$) at RT under argon. The mixture was stirred at the same temperature for 15 h, then concentrated in vacuo. The residue was used for the next reaction without further purification. A solution of acid chloride **10** (0.322 mmol, 2.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL, 7.0 mL $mmol^{-1}$) was added to a solution of the above residue and 2,6-lutidine (50.0 μL, 0.435 mmol, 3.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL, 7.0 mL $mmol^{-1}$) at 0 °C under argon. The mixture was stirred at RT for 16 h, then the reaction was quenched with 1.0 M aqueous HCl at 0 °C, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to afford tetrapeptide **17** (147 mg, 0.105 mmol, 2 steps 72%) as a pale-yellow amorphous solid. $[\alpha]_D^{26}$ = −4.97 (*c* = 1.27, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.74 (m, 2H), 7.53 (m, 2H), 7.04–7.51 (m, 24H), 5.71–5.98 (m, 1H), 4.78–5.70 (m, 14H), 3.45–4.70 (m, 10H), 2.25–3.42 (m, 4H), 1.12–2.25 (m, 14H), 0.65–0.93 (m, 9H), −0.22–0.13 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 170.2, 169.1, 167.1, 157.2, 156.7, 155.8, 155.4, 154.2, 153.1, 142.7, 140.9, 135.4, 131.5, 128.2, 128.1, 127.9, 127.7, 127.5, 127.3, 127.2, 126.7, 124.8, 119.5, 117.7, 68.7, 67.8, 65.4, 62.9, 53.8, 53.0, 49.0, 48.6, 46.5, 45.6, 44.1, 25.3, 19.3, 18.8, 18.4, 17.7, −5.5, −5.6 ppm; IR (neat): $\tilde{\nu}$ = 3065, 3017, 2953, 2895, 2857, 1715, 1451, 1410, 1358, 1257, 1127, 1085, 837, 755, 698 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{76}H_{86}N_8O_{16}SiNa$: 1417.5823 $[M+Na]^+$; found: 1417.5825 (See S23 in page S12 of the Supporting Information).

Pentapeptide 18: Diethylamine (16 μL, 0.158 mmol, 5.0 equiv) was added to a solution of tetrapeptide **17** (44 mg, 31.5 μmol, 1.0 equiv) in anhydrous acetonitrile (1.0 mL, 32 mL $mmol^{-1}$) at RT under argon. The mixture was stirred at the same temperature for 5 h, then concentrated in vacuo. The residue was used for the next reaction without further purification. Silver cyanide (4.0 mg, 31.5 μmol, 1.0 equiv) was added to a solution of the above residue and acid chloride **8** (63.1 μmol, 2.0 equiv) in anhydrous toluene (2.0 mL, 64 mL $mmol^{-1}$) at 0 °C under argon. The mixture was

stirred at 60 °C for 15 h, then the reaction was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by gel permeation chromatography (eluted with $CHCl_3$) to afford pentapeptide **18** (35 mg, 24.7 μmol, 2 steps 78%) as a colorless oil. $[\alpha]_D^{20} = -4.70$ ($c = 1.01$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 6.93–7.62 (m, 22H), 6.78 (m, 2H), 5.68–6.15 (m, 1H), 4.85–5.64 (m, 15H), 3.77 (m, 3H), 3.35–4.72 (m, 9H), 2.70–3.28 (m, 4H), 1.12–2.52 (m, 17H), 0.63–0.98 (m, 15H), −0.22–0.08 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 173.3, 170.7, 169.1, 168.1, 159.0, 156.5, 156.38, 156.31, 155.1, 149.8, 148.1, 136.4, 136.3, 135.9, 135.6, 135.5, 132.1, 132.0, 131.95, 131.89, 130.6, 130.4, 129.7, 129.5, 129.4, 129.2, 129.0, 128.6, 128.54, 129.52, 128.42, 128.37, 128.33, 128.31, 128.27, 128.16, 128.0, 127.89, 127.85, 127.79, 127.7, 127.6, 127.43, 127.36, 127.29, 127.22, 127.1, 126.54, 126.49, 123.4, 118.9, 118.8, 118.0, 113.8, 113.7, 113.5, 113.39, 113.36, 113.2, 80.9, 80.2, 71.8, 69.2, 69.1, 68.9, 68.8, 68.7, 68.1, 67.9, 67.8, 67.6, 67.3, 66.5, 66.1, 65.94, 65.87, 65.6, 65.5, 63.3, 62.0, 55.2, 53.9, 51.9, 47.7, 47.5, 46.5, 46.3, 46.0, 45.9, 45.7, 43.1, 37.3, 31.9, 31.2, 29.65, 29.60, 29.5, 29.4, 29.3, 29.2, 29.1, 28.5, 28.4, 25.73, 25.67, 25.64, 25.58, 24.81, 24.76, 24.6, 24.5, 23.5, 23.4, 23.0, 22.6, 18.6, 18.5, 18.39, 18.33, 18.2, 18.10, 18.06, 18.03, 16.53, 16.47, 14.1, 12.02, 11.95, 11.8, 11.7, 0.99, −5.1, −5.16, −5.22, −5.3, −5.4 ppm; IR (neat): $\tilde{\nu} = 2954$, 2932, 1720, 1680, 1455, 1407, 1353, 1253, 1197, 1127, 838, 775 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{75}H_{94}N_8O_{17}SiNa$: 1429.6404 $[M+Na]^+$; found: 1429.6398 (See S27 in page S14 of the Supporting Information).

Acid 5: Morpholine (0.9 μL, 10.5 μmol, 1.5 equiv) was added to a solution of pentapeptide **18** (9.9 mg, 7.03 μmol, 1.0 equiv) and $Pd(PPh_3)_4$ (0.81 mg, 0.703 μmol, 0.10 equiv) in anhydrous THF (1.0 mL, 140 mL mmol^{-1}) at RT under argon. The mixture was stirred at the same temperature for 1 h, then concentrated in vacuo. The residue was purified by gel permeation chromatography (eluted with $CHCl_3$) to afford acid **5** (7.2 mg, 5.24 μmol, 75%) as a yellow oil. $[\alpha]_D^{27} = -4.44$ ($c = 0.195$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 6.99–7.52 (m, 22H), 6.78 (m, 2H), 4.65–6.04 (m, 13H), 3.77 (m, 3H), 3.44–4.68 (m, 7H), 2.47–3.37 (m, 4H), 1.16–2.71 (m, 17H), 0.71–0.92 (m, 15H), −0.19–0.10 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (mixture of rotamers) = 176.1, 132.2, 130.1, 128.6, 128.5, 128.4, 127.9, 113.5, 68.8, 55.2, 31.9, 29.6, 29.3, 28.4, 25.6, 25.5, 22.6, 18.6, 18.0, 17.9, 16.4, 14.0, 11.8, 0.99, −3.6, −5.4 ppm; IR (neat): $\tilde{\nu} = 3363$, 2926, 2359, 1720, 1676, 1406, 1252, 1123 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{72}H_{90}N_8O_{17}SiNa$: 1389.6091 $[M+Na]^+$; found: 1389.6074.

Lactone 19: PyBroP (3.0 mg, 6.36 μmol, 1.5 equiv) was added to a solution of acid **5** (5.8 mg, 4.24 μmol, 1.0 equiv), amine **6** (8.48 μmol, 2.0 equiv), and DIEA (2.2 μL, 12.7 μmol, 3.0 equiv) in anhydrous DMF (1.0 mL, 235 mL mmol−1) at 0 °C under argon. The mixture was stirred at RT for 7 h, then the reaction was quenched with 1 M aqueous HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform/methanol = 100:1) to afford lactone **19** (4.7 mg, 3.80 μmol, 90%) as a colorless oil. $[\alpha]_D^{27} = +7.4$ ($c = 0.410$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 6.99–7.57 (m, 22H), 6.82 (m, 2H), 4.69–5.70 (m, 9H), 3.48–4.65 (m, 14H), 2.57–3.20 (m, 4H), 1.16–2.31 (m, 17H), 0.64–0.98 ppm (m, 6H); IR (neat): $\tilde{\nu} = 2958$, 2931, 1801, 1723, 1677, 1402, 1259, 1123, 1029 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{66}H_{74}N_8O_{16}Na$: 1257.5120 $[M+Na]^+$; found: 1257.5084.

Chloroacetate 20: A 1 M solution of TBAF-AcOH (1:1) in THF (0.450 mL, 0.450 mmol, 5.0 mL mmol^{-1}) was added to a solution of pentapeptide **18** (127 mg, 90.0 μmol, 1.0 equiv) in anhydrous THF (1.8 mL, 20 mL mmol^{-1}) at RT under argon. The mixture was stirred at the same temperature for 24 h, then the reaction was quenched with 1 M aqueous HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used for the next reaction without further purification. DMAP (11 mg, 90.0 μmol, 1.0 equiv) was added to a solution of the above residue, DIEA (78.0 μL, 0.450 mmol, 5.0 equiv) and chloroacetyl chloride (14.3 μL, 0.180 mmol, 2.0 equiv) in anhydrous CH_2Cl_2 (1.8 mL, 20 mL mmol^{-1}) at −40 °C under argon. The mixture was stirred at RT for 17 h, then the reaction was quenched with 1 M aqueous HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform/methanol = 80:1) to afford chloroacetate **20** (93.4 mg, 68.2 μmol, 76%) as a yellow oil. $[\alpha]_D^{20} = +2.34$ ($c = 1.19$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 6.99–7.52 (m, 22H), 6.78 (m, 2H), 5.74–6.16 (m, 1H), 4.74–5.70 (m, 16H), 3.77 (m, 3H), 3.59–4.72 (m, 10H), 2.53–3.43 (m, 4H), 1.11–2.45 (m, 17H), 0.71–0.96 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 173.8, 173.1, 173.0, 172.9, 169.6, 168.9, 168.7, 168.5, 168.2, 166.4, 166.3, 166.1, 165.0, 158.85, 158.77, 157.2, 156.8, 156.2, 155.8, 154.9, 152.9, 136.2, 136.05, 135.25, 135.21, 135.1, 134.9, 131.75, 131.72, 131.69, 131.5, 130.2, 129.2, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.4, 118.8, 118.5, 117.8, 113.4, 113.3, 113.2, 80.6, 71.7, 71.7, 71.6, 69.0, 68.9, 68.8, 68.7, 68.5, 68.4, 68.3, 68.0, 67.4, 67.34, 67.27, 66.7, 65.9, 65.62, 65.55, 66.3, 54.9, 54.0, 53.6, 53.4, 53.2, 47.7, 47.5, 47.1, 46.9, 46.6, 46.4, 46.1, 46.0, 45.9, 45.6, 45.5, 45.3, 45.3, 40.6, 40.3, 40.2, 37.2, 37.1, 37.0, 36.9, 36.8, 36.7, 36.3, 29.4, 29.0, 25.4, 25.1, 24.9, 24.5, 23.9, 23.25, 23.20, 23.13, 23.06, 19.0, 18.8, 18.6, 18.4, 18.3, 18.00, 17.96, 17.92, 17.7, 17.1, 16.2, 11.7, 11.5, 11.1 ppm; IR (neat): $\tilde{\nu} =$ 2961, 2929, 1719, 1680, 1406, 1353, 1250, 1196 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{71}H_{82}N_8O_{18}ClNa$: 1369.5436 $[M+Na]^+$; found: 1369.5460.

Acid 21: Phenylsilane (13 μL, 0.102 mmol, 1.5 equiv) was added to a solution of allyl ester **20** (93.4 mg, 68.2 μmol, 1.0 equiv) and $Pd(PPh_3)_4$ (7.9 mg, 6.82 μmol, 0.10 equiv) in anhydrous CH_2Cl_2 (2.0 mL, 30 mL mmol^{-1}) at RT under argon. The mixture was stirred at the same temperature for 1.5 h, then concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform/methanol = 80:1) to afford acid **21** (57.5 mg, 43.2 μmol, 63%) as a yellow oil. $[\alpha]_D^{20} = +5.28$ ($c = 0.800$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 6.95–7.52 (m, 22H), 6.78 (m, 2H), 4.73–6.12 (m, 14H), 3.77 (m, 3H), 3.34–4.65 (m, 8H), 2.61–3.27 (m, 4H), 1.16–2.44 (m, 17H), 0.71–0.96 ppm (m, 6H); IR (neat): $\tilde{\nu} = 2958$, 2935, 1719, 1676, 1405, 1353, 1253, 1196, 1122, 1035 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{68}H_{77}N_8O_{18}ClNa$: 1351.4937 $[M+Na]^+$; found: 1351.4967.

Hexapeptide 22: AOI reagent (21.8 mg, 57.5 μmol, 3.0 equiv) added to a solution of acid **21** (25.5 mg, 19.2 μmol, 1.0 equiv), amine **6** (38.4 μmol, 2.0 equiv), and DIEA (16.7 μL, 96.0 μmol, 5.0 equiv) in anhydrous CH_2Cl_2 (2.0 mL, 100 mL mmol^{-1}) at 0 °C under argon. The mixture was stirred at RT for 24 h, then the reaction was quenched with 1 M aqueous HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform/methanol = 100:1)

to afford hexapeptide **22** (13.0 mg, 8.72 μmol, 45%) as a colorless oil. $[\alpha]_D^{20} = +7.95$ ($c = 1.12$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 6.95–7.72 (m, 23H), 6.81 (m, 2H), 4.71–6.10 (m, 14H), 3.77 (m, 3H), 3.45–4.72 (m, 10H), 2.49–3.38 (m, 4H), 1.05–2.46 (m, 29H), 0.72–1.04 ppm (m, 6H); IR (neat): $\tilde{\nu} = 3345$, 2965, 2935, 1724, 1676, 1412, 1250 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{76}H_{92}N_9O_{20}ClNa$: 1508.6039 $[M+Na]^+$; found: 1508.6044.

Compound (2*R*,6*S*,8*S*)-1a: Thiourea (5.4 mg, 71.0 μmol, 3.0 equiv) was added to a solution of hexapeptide **22** (35.2 mg, 23.6 μmol, 1.0 equiv) and $NaHCO_3$ (9.9 mg, 0.118 mmol, 5.0 equiv) in ethanol (1.0 mL, 40 mL $mmol^{-1}$) at RT under argon. The mixture was stirred at 50 °C for 2 h, then filtered through a pad of Celite and concentrated in vacuo. The residue was used in the next reaction without further purification. Trifluoroacetic acid (1.0 mL, 40 mL $mmol^{-1}$) was added to a solution of the above residue in anhydrous CH_2Cl_2 (1.0 mL, 40 mL $mmol^{-1}$) at RT under argon. The mixture was stirred at the same temperature for 1 h, then concentrated in vacuo. The residue was used for the next reaction without further purification. Pd/C (10%, 7.0 mg, 20 wt%) was added to a solution of the above residue in ethyl acetate–ethanol (3:1, 2.0 mL, 80 mL $mmol^{-1}$) under argon and the reaction mixture was purged with hydrogen three times. The mixture was stirred at RT for 30 min, then filtered through a pad of Celite and concentrated in vacuo. The residue was purified by reverse-phase HPLC (MeOH–H_2O) to afford (2*R*,6*S*,8*S*)-**1a** (4.3 mg, 6.23 μmol, 3 steps 26%) as a colorless oil. $[\alpha]_D^{33} = -14.2$ ($c = 0.10$, MeOH); ^1H NMR (600 MHz, $[D_6]$DMSO): $\delta =$ 7.68 (s, 1H), 5.56–5.61 (m, 3H), 5.22 (dd, $J = 5.4$, 9.6 Hz, 1H), 5.17 (d, $J = 13.2$ Hz, 1H), 5.12 (d, $J = 12.6$ Hz, 1H), 5.03 (d, $J = 12.6$ Hz, 1H), 4.82 (m, 1H), 4.42 (d, $J = 4.2$ Hz, 1H), 3.79 (d, $J_{gem} = 9.6$ Hz, 1H), 3.67 (m, 1H), 3.56 (d, $J_{gem} = 9.6$ Hz, 1H), 3.00 (m, 3H), 2.79 (m, 2H), 2.59 (m, 3H), 2.16 (m, 1H), 1.98–2.00 (m, 4H), 1.70–1.77 (m, 4H), 1.51 (m, 3H), 1.45 (m, 3H), 1.30 (s, 3H), 1.22–1.31 (m, 1H), 1.02 (m, 1H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.80 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $[D_6]$DMSO): $\delta =$ 174.9, 172.9, 172.8, 172.6, 172.3, 169.8, 71.7, 64.8, 61.1, 52.8, 48.7, 48.6, 48.3, 48.2, 46.9, 46.8, 37.4, 33.6, 29.2, 29.0, 25.9, 22.9, 22.3, 21.3, 20.2, 16.6, 12.1 ppm; IR (neat): $\tilde{\nu} =$ 3585, 2958, 2920, 2853, 1620 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{51}N_9O_{10}ClNa$: 720.3651 $[M+Na]^+$; found: 720.3644.

Hexapeptide 23: AOI reagent (21 mg, 55.7 μmol, 3.0 equiv) was added to a solution of acid **21** (24.7 mg, 18.6 μmol, 1.0 equiv), amine *ent*-**6** (crude, 37.1 μmol, 2.0 equiv), and DIEA (16 μL, 92.9 μmol, 5.0 equiv) in anhydrous CH_2Cl_2 (2.0 mL, 100 mL $mmol^{-1}$) at 0 °C under argon. The mixture was stirred at RT for 19 h, then the reaction was quenched with 1 M aqueous HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform/methanol = 100:1) to afford hexapeptide **23** (21.8 mg, 14.7 μmol, 79%) as a colorless oil. $[\alpha]_D^{20} = +4.09$ ($c = 0.445$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.07–7.53 (m, 23H), 6.81 (m, 2H), 4.71–5.87 (m, 14H), 3.76 (m, 3H), 3.24–4.68 (m, 10H), 2.69–3.32 (m, 4H), 1.12–2.33 (m, 29H), 0.74–0.99 ppm (m, 6H); IR (neat): $\tilde{\nu} =$ 3346, 2961, 2928, 2857, 1724, 1676, 1457, 1405, 1353, 1251 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{76}H_{92}N_9O_{20}ClNa$: 1508.6039 $[M+Na]^+$; found: 1508.6043.

Compound (2*S*,6*S*,8*S*)-1b: Thiourea (4.2 mg, 54.7 μmol, 1.5 equiv) was added to a solution of hexapeptide **23** (54.2 mg, 36.4 μmol, 1.0 equiv) and $NaHCO_3$ (6.1 mg, 72.9 μmol, 2.0 equiv) in ethanol (1.0 mL, 27 mL $mmol^{-1}$) at RT under argon. The mixture was stirred at 50 °C for 6 h, then filtered through a pad of Celite and concentrated in vacuo. The residue was used next reaction without further purification. Trifluoroacetic acid (1.0 mL, 27 mL $mmol^{-1}$) was added to a solution of the above residue in anhydrous CH_2Cl_2 (1.0 mL, 27 mL $mmol^{-1}$) at RT under argon. The mixture was stirred at the same temperature for 1 h, then concentrated in vacuo. The residue was used for the next reaction without further purification. $NaHCO_3$ (15.3 mg, 0.182 mmol, 5.0 equiv) was added to a solution of the above residue in anhydrous methanol (1.0 mL, 27 mL $mmol^{-1}$) at RT under argon. The mixture was stirred at the same temperature for 1 h, then filtered through a pad of Celite and concentrated in vacuo. The residue was used for the next reaction without further purification. Pd/C (10%, 10.8 mg, 20 wt%) was added to a solution of the above residue in ethyl acetate–ethanol (3:1, 2.0 mL, 54 mL $mmol^{-1}$) under argon and the reaction mixture was purged with hydrogen three times. The mixture was stirred at RT for 30 min, then filtered through a pad of Celite and concentrated in vacuo. The residue was purified by reverse-phase HPLC (MeOH–H_2O) to afford (2*S*,6*S*,8*S*)-**1b** (10.1 mg, 14.4 μmol, 4 steps 40%) as a colorless oil. $[\alpha]_D^{33} = -24.7$ ($c = 0.210$, MeOH) [lit. $[\alpha]_D^{25} = -11.0$ ($c = 0.1$, MeOH)]; ^1H NMR (600 MHz, $[D_6]$DMSO): $\delta = 7.89$ (s, c, 1H), 5.53–5.61 (m, 3H), 5.17 (dd, $J = 9.6$, 16.2 Hz, 1H), 5.14 (d, $J =$ 13.2 Hz, 2H), 5.03 (d, $J = 12.0$ Hz, 1H), 4.78 (d, $J = 5.4$ Hz, 1H), 4.43 (d, $J = 4.2$ Hz, 1H), 3.87 (d, $J_{gem} = 10.8$ Hz, 1H), 3.68 (m, 1H), 3.42 (d, $J_{gem} = 10.8$ Hz, 1H), 3.00 (m, 3H), 2.81 (d, $J = 7.8$ Hz, 2H), 2.60 (m, 3H), 2.27 (m, $J = 12.0$ Hz, 1H), 1.90–2.04 (m, 4H), 1.71–1.79 (m, 4H), 1.51 (m, 3H), 1.47 (m, 3H), 1.30 (s, 3H), 1.25–1.34 (m, 1H), 1.03 (m, 1H), 0.87 (d, $J = 7.2$ Hz, 3H), 0.81 ppm (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (150 MHz, $[D_6]$DMSO): $\delta =$ 174.9, 172.9, 172.6, 172.2, 170.1, 71.8, 63.1, 61.2, 59.6, 52.7, 48.8, 48.5, 48.4, 48.2, 46.82, 46.8, 37.4, 33.4, 26.1, 26.0, 25.8, 22.7, 21.3, 21.26, 21.2, 20.5, 16.6, 12.1 ppm; IR (neat): $\tilde{\nu} =$ 3364, 3260, 2954, 2935, 2864, 1621, 1443, 1403, 1249, 915 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{30}H_{51}N_9O_{10}Na$: 720.3657 $[M+Na]^+$; found: 720.3671.

Acid 24: Phenylsilane (6.7 μL, 54.3 μmol, 1.5 equiv) was added to a solution of pentapeptide **S20**[23] (51.0 mg, 36.2 μmol, 1.0 equiv) and $Pd(PPh_3)_4$ (4.2 mg, 3.62 μmol, 0.10 equiv) in anhydrous CH_2Cl_2 (2.0 mL, 55 mL $mmol^{-1}$) at RT under argon. The mixture was stirred at the same temperature for 2.5 h, then concentrated in vacuo. The residue was purified by gel permeation chromatography (eluted with $CHCl_3$) to afford acid **24** (44.9 mg, 32.8 μmol, 91%) as a yellow oil. $[\alpha]_D^{27} = -5.65$ ($c = 0.83$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.03–7.52 (m, 22H), 6.75 (m, 2H), 4.75–6.09 (m, 13H), 3.72 (m, 3H), 3.40–4.63 (m, 7H), 2.51–3.18 (m, 4H), 1.06–2.51 (m, 17H), 0.69–0.92 (m, 15H), −0.21–0.06 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$ 173.3, 172.8, 171.4, 171.0, 160.2, 158.9, 156.4, 154.6, 136.3, 35.5, 135.4, 130.3, 129.5, 129.1, 128.8, 128.5, 128.48, 128.43, 128.35, 128.32, 128.0, 127.9, 127.7, 127.4, 127.2, 126.5, 113.5, 113.4, 113.2, 80.2, 79.9, 71.8, 70.1, 69.9, 69.2, 68.7, 68.8, 68.6, 67.7, 62.6, 60.3, 55.14, 55.11, 53.6, 52.8, 49.8, 47.9, 47.7, 46.1, 44.5, 44.2, 43.0, 37.3, 37.2, 30.7, 29.6, 25.7, 25.5, 23.5, 23.4, 20.9, 19.8, 18.7, 18.4, 17.9, 16.5, 16.4, 16.3, 14.1, 12.0, 11.9, 11.7, −5.45, −5.48, −5.5 ppm; IR (neat): $\tilde{\nu} =$ 2959, 2933, 1725, 1676, 1456, 1410, 1351, 1252, 1122 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{72}H_{90}N_8O_{17}SiNa$: 1389.6091 $[M+Na]^+$; found: 1389.6074.

Hexapeptide 25: AOI reagent (14 mg, 37.2 μmol, 3.0 equiv) was added to a solution of acid **24** (17 mg, 12.4 μmol, 1.0 equiv), amine **6** (24.9 μmol, 2.0 equiv), and DIEA (11 μL, 62.0 μmol, 5.0 equiv) in anhydrous CH_2Cl_2 (2.0 mL, 160 mL $mmol^{-1}$) at 0 °C under argon. The mixture was stirred at RT for 24 h, then the reaction was quenched with 1 M aqueous HCl at 0 °C. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform/methanol = 80:1) to afford hexapeptide **25** (15.0 mg, 9.81 μmol, 79%) as a colorless oil. $[\alpha]_D^{28} =$

−2.29 (c = 0.765, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.67–7.96 (m, 1H), 7.07–7.50 (m, 22H), 6.77 (m, 2H), 4.64–6.12 (m, 13H), 3.73 (s, 3H), 3.43–4.63 (m, 9H), 2.58–3.23 (m, 4H), 1.16–2.48 (m, 29H), 0.69–0.93 (m, 15H), −0.19–0.05 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (mixture of rotamers) = 172.8, 171.6, 1693, 159.0, 156.5, 154.6, 136.4, 135.6, 129.5, 129.2, 128.6, 128.5, 128.4, 128.35, 128.31, 128.0, 127.9, 127.85, 127.81, 113.5, 81.5, 80.2, 71.8, 68.8, 68.7, 67.7, 63.8, 62.7, 55.2, 53.6, 52.1, 47.9, 47.7, 45.7, 44.2, 43.0, 37.2, 31.8, 29.6, 29.5, 29.4, 29.3, 28.6, 27.8, 27.0, 25.8, 25.5, 23.4, 22.6, 20.0, 19.9, 18.7, 18.5, 18.1, 16.4, 14.0, 11.7, 1.0, −5.0, −5.1 ppm; IR (neat): $\tilde{\nu}$ = 3331, 2958, 2931, 1725, 1676, 1406, 1251, 1123 cm^{-1}; HRMS (ESI): m/z calcd for $C_{80}H_{105}N_9O_{19}SiNa$: 1546.7194 $[M+Na]^+$; found: 1546.7177.

Compound (2*R*,6*R*,8*R*)-1 c: Hydrogen fluoride-pyridine (2.8 μL, 30.9 μmol, 3.0 equiv) was added to a solution of hexapeptide **25** (15.3 mg, 10.3 μmol, 1.0 equiv) in anhydrous acetonitrile (2.0 mL, 200 mL mmol^{-1}) at RT under argon. The mixture was stirred at the same temperature for 13 h, then the reaction was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used in the next reaction without further purification. Trifluoroacetic acid (1.0 mL, 100 mL mmol^{-1}) was added to a solution of the above residue and triethylsilane (5.0 μL, 31.3 μmol, 3.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL, 100 mL mmol^{-1}) at RT under argon. The mixture was stirred at the same temperature for 3 h, then concentrated in vacuo. The residue was used for the next reaction without further purification. $NaHCO_3$ (4.5 mg, 51.5 μmol, 5.0 equiv) was added to a solution of the above residue in anhydrous methanol (1.0 mL, 100 mL mmol^{-1}) at RT under argon. The mixture was stirred at the same temperature for 30 min, then filtered through a pad of Celite and concentrated in vacuo. The residue was used for the next reaction without further purification. Pd/C (10%, 2.1 mg, 20 wt%) was added to a solution of the above residue in ethyl acetate–ethanol (3:1, 2.0 mL, 200 mL mmol^{-1}) under argon and the reaction mixture was purged with hydrogen three times. The mixture was stirred at RT for 5 h, then filtered through a pad of Celite and concentrated in vacuo. The residue was purified by reverse-phase HPLC (MeOH-H_2O) to afford (2*R*,6*R*,8*R*)-**1 c** (3.3 mg, 4.73 μmol, 4 steps 45%) as a colorless oil. $[\alpha]_D^{28} = +12.2$ (c = 0.160, MeOH); ^{1}H NMR (600 MHz, [D_6]DMSO): δ = 7.91 (s, 1H), 5.52–5.58 (m, 3H), 5.15 (m, 2H), 5.04 (m, 2H), 4.81 (m, 1H), 4.42 (m, 1H), 4.15 (m, 1H), 3.82 (m, 1H), 3.65 (m, 1H), 3.00 (m, 3H), 2.82 (m, 2H), 2.40–2.85 (m, 3H), 2.20 (m, 2H), 1.90–2.04 (m, 3H), 1.73 (m, 4H), 1.11–1.52 (m, 10H), 1.02 (m, 1H), 0.85 (d, J = 6.6 Hz, 3H), 0.80 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, [D_6]DMSO): δ = 174.6, 173.0, 172.9, 172.54, 172.51, 169.8, 71.6, 63.9, 60.55, 60.53, 55.0, 52.8, 48.4, 48.3, 48.2, 47.5, 46.7, 46.6, 37.2, 29.0, 25.7, 22.7, 21.2, 21.1, 20.9, 20.1, 16.3, 11.8 ppm; IR (neat): $\tilde{\nu}$ = 3274, 2927, 1633, 1241 cm^{-1}; HRMS (ESI): m/z calcd for $C_{30}H_{51}N_9O_{10}Na$: 720.3651 $[M+Na]^+$; found: 720.3644.

Hexapeptide 26: AOI reagent (18 mg, 46.8 μmol, 3.0 equiv) was added to a solution of acid **24** (21.3 mg, 15.6 μmol, 1.0 equiv), amine *ent*-**6** (31.1 μmol, 2.0 equiv), and DIEA (8.0 μL, 46.8 μmol, 3.0 equiv) in anhydrous CH_2Cl_2 (2.0 mL, 130 mL mmol^{-1}) at 0 °C under argon. The mixture was stirred at RT for 24 h, then the reaction was quenched with 1 M aqueous HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform/methanol = 80:1) to afford hexapeptide **26** (20.2 mg, 13.2 μmol, 85%) as a pale-yellow oil. $[\alpha]_D^{24} = -7.46$ (c = 0.700, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.71–7.98 (m, 1H), 7.04–7.54 (m, 22H), 6.78 (m, 2H), 4.72–5.82 (m, 13H), 3.77 (s, 3H), 3.47–4.66 (m, 9H), 2.53–3.28 (m, 4H), 1.15–2.47 (m, 29H), 0.72–0.95 (m, 15H), −0.15–0.08 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (mixture of rotamers) = 171.7, 170.3, 170.0, 159.0, 156.5, 136.4, 135.6, 135.5, 129.5, 129.2, 128.6, 128.5, 128.46, 128.43, 128.41, 128.3, 128.25, 128.23, 128.0, 127.9, 127.8, 126.7, 113.5, 113.4, 81.6, 81.5, 80.3, 71.8, 68.8, 67.8, 66.2, 63.7, 61.7, 55.2, 47.9, 47.7, 44.3, 37.4, 37.3, 29.7, 29.3, 27.95, 27.91, 25.8, 25.7, 25.6, 23.5, 23.4, 22.7, 21.3, 20.5, 19.8, 18.4, 16.6, 16.5, 14.1, 11.8, 1.0, −5.0, −5.1, −5.3 ppm; IR (neat): $\tilde{\nu}$ = 2954, 2933, 1725, 1684, 1457, 1409, 1252, 1125, 755, 699 cm^{-1}; HRMS (ESI): m/z calcd for $C_{80}H_{105}N_9O_{19}SiNa$: 1546.7188 $[M+Na]^+$; found: 1546.7187.

Compound (2*S*,6*R*,8*R*)-1 d: Hydrogen fluoride-pyridine (3.3 μL, 36.7 μmol, 3.0 equiv) was added to a solution of hexapeptide **26** (18.2 mg, 12.2 μmol, 1.0 equiv) in anhydrous acetonitrile (2.0 mL, 160 mL mmol^{-1}) at RT under argon. The mixture was stirred at the same temperature for 10 h, then the reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used in the next reaction without further purification. Trifluoroacetic acid (1.0 mL, 80 mL mmol^{-1}) was added to a solution of the above residue and triethylsilane (5.8 μL, 31.3 μmol, 3.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL, 80 mL mmol^{-1}) at RT under argon. The mixture was stirred at the same temperature for 1 h, then concentrated in vacuo. The residue was used for the next reaction without further purification. $NaHCO_3$ (5.1 mg, 61.0 μmol, 5.0 equiv) was added to a solution of the above residue in anhydrous methanol (1.0 mL, 80 mL mmol^{-1}) at RT under argon. The mixture was stirred at the same temperature for 30 min, then filtered through a pad of Celite and concentrated in vacuo. The residue was used for the next reaction without further purification. Pd/C (10%, 2.4 mg, 20 wt%) was added to a solution of the above residue in ethyl acetate–ethanol (3:1, 2.0 mL, 180 mL mmol^{-1}) under argon, and the reaction mixture was purged with hydrogen three times. The mixture was stirred at RT for 5 h, then filtered through a pad of Celite and concentrated in vacuo. The residue was purified by reverse-phase HPLC (MeOH–H_2O) to afford (2*S*,6*R*,8*R*)-**1 d** (5.0 mg, 7.17 μmol, 4 steps 59%) as a colorless oil. $[\alpha]_D^{23} = +7.27$ (c = 0.205, MeOH); ^{1}H NMR (600 MHz, [D_6]DMSO): δ = 7.68 (s, 1H), 5.52–5.59 (m, 3H), 5.15 (m, 2H), 5.08 (d, J = 12.6 Hz, 1H), 5.05 (d, J = 13.2 Hz, 1H), 4.85 (d, J = 5.4 Hz, 1H), 4.41 (m, 1H), 4.12 (d, J = 7.2 Hz, 1H), 3.73 (d, J = 10.8 Hz, 1H), 3.65 (m, 1H), 3.54 (d, J = 10.8 Hz, 1H), 2.99 (m, 3H), 2.72–2.88 (m, 2H), 2.37–2.62 (m, 3H), 2.16 (m, 2H), 2.01 (m, 3H), 1.72 (m, 4H), 1.22–1.54 (m, 10H), 1.03 (m, 1H), 0.85 (d, J = 6.0 Hz, 3H), 0.81 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, [D_6]DMSO): δ = 174.6, 174.2, 172.8, 172.52, 172.47, 172.3, 71.6, 65.0, 60.6, 60.5, 52.8, 48.3, 48.2, 48.1, 47.4, 46.64, 46.58, 37.2, 32.6, 25.7, 25.1, 22.7, 21.2, 21.1, 20.8, 19.1, 16.3, 11.8 ppm; IR (neat): $\tilde{\nu}$ = 2924, 2853, 1653, 1202, 1136 cm^{-1}; HRMS (ESI): m/z calcd for $C_{30}H_{51}N_9O_{10}Na$: 720.3657 $[M+Na]^+$; found: 720.3640.

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[23] See the Supporting Information.
[24] The incorrect configuration of the α-methylserine moiety in JBIR-39 reported in Ref. [3] was due to alternating R/S configuration of a standard sample on the Marfey's method.

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FULL PAPER

Natural Products

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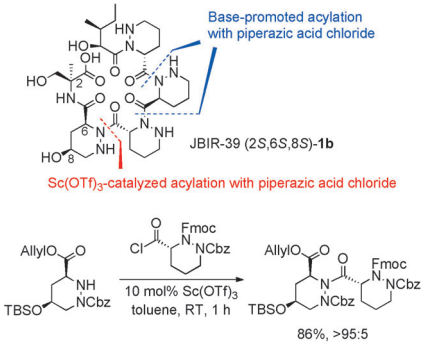
Total Synthesis and Structure Elucidation of JBIR-39: A Linear Hexapeptide Possessing Piperazic Acid and γ-Hydroxypiperazic Acid Residues



Structure solved! The total synthesis and structure elucidation of linear peptide JBIR-39 (**1b**) containing an unprecedented four nonproteinogenic piperazic acid (Piz) residues, was achieved (see scheme). The approach involved efficient $Sc(OTf)_3$-catalyzed direct acylation of Piz(γ-OTBS) derivative with piperazic acid chloride, leading to the Piz-Piz(γ-OTBS) dipeptide in high yield without epimerization.