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Kanato Umeki, Yusuke Ueda, Juri Sakata, Hidetoshi Tokuyama

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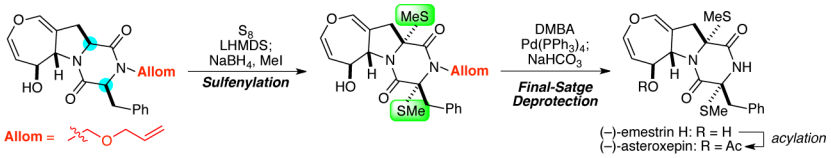

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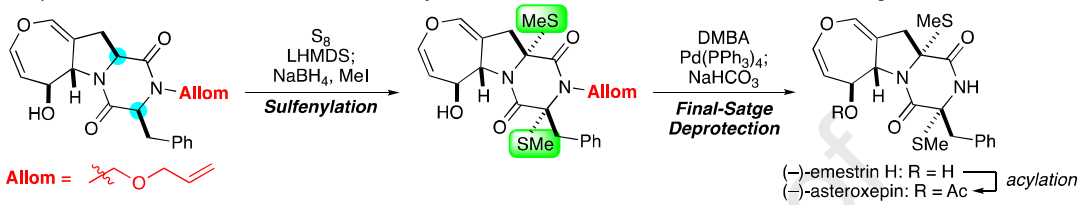
Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan



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Total syntheses of (–)-emestrin H and (–)-asteroxepin

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Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

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ABSTRACT

First total syntheses of (–)-emestrin H and (–)-asteroxepin are described. To find the appropriate protecting group on the amide nitrogen of the diketopiperazine core, we conducted model studies using a simple diketopiperazine derivative. As a result, allyloxymethyl (Allom) group was the most suitable protecting group, which tolerated Nicolaou's sulfenylation conditions, and was easily cleavable under the mild conditions using $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid leaving methylthioethers intact. The general utility of Allom group for protection of amides was studied using simple substrates. Finally, the effectiveness of Allom group was proved by the accomplishment of the first total synthesis of (–)-emestrin H. Allom group was robust enough during installation of two methylthioethers to the diketopiperazine core and easily removed at the final step. The first total synthesis of (–)-asteroxepin was also completed by acylation of (–)-emestrin H.

1. Introduction

Dithiodiketopiperazine alkaloids bearing the sulfur-containing diketopiperazine as a core structure have attracted attention due to their structural diversity and fascinating biological activities [1,2]. Among them, compounds bearing the 4,5-dihydrooxepine ring, such as (–)-acetylaranotin (**1**) [3], (+)-MPC1001B (**7**) [4], and (–)-acetylapoaranotin (**6**) [5], have been challenging synthetic targets and a lot of effort has been made to synthesize these compounds [6,7]. Reisman *et al.* reported the first innovative total synthesis of (–)-acetylaranotin (**1**) in 2012 [8], followed by the first total synthesis of (–)-acetylapoaranotin (**6**) [10]. We also focused on this class of compounds, reporting the second total synthesis of **1** just after Reisman *et al.* in 2012 [9]. Using the synthetic protocol established during the synthetic studies on **1**, which was based on the characteristic proline-fused 4,5-dihydrooxepine ring, we successfully performed the first total synthesis of (+)-MPC1001B (**7**) [11] and determined the structure of (–)-SCH64874 (**3**) and hirsutellomycin (**8**) via semi-synthesis [12]. Despite these synthetic developments over the last decade, the total syntheses of (–)-asteroxepin (**4**) [13] and (–)-emestrin H (**5**) [14] bearing the NH-free diketopiperazine core have not been reported so far.

Our preliminary model studies toward **4** and **5** revealed that the enolate-mediated introduction of two methylthioethers reported by Nicolaou *et al.* [15] was unsuccessful for the unprotected diketopiperazine **13** due to the competitive deprotonation of the unprotected N–H proton (Scheme 1b). Therefore, the major challenge toward the synthesis of **4** and **5** ~~was the~~ selection of the appropriate protecting group for the diketopiperazine ring's NH group. The ideal protecting group (PG in Scheme 1a) should be robust enough to tolerate the strong basic conditions during the introduction of the two-methylthioethers. Moreover, it should be easily and chemoselectively cleaved under the particularly mild conditions in the final stage of the total synthesis without affecting the base-, nucleophile-, and oxidant-sensitive methylthioethers and the acid-sensitive dihydrooxepin structure. However, compared to the many available protecting groups for amines, there are limited choices for amides, especially for diketopiperazines. In

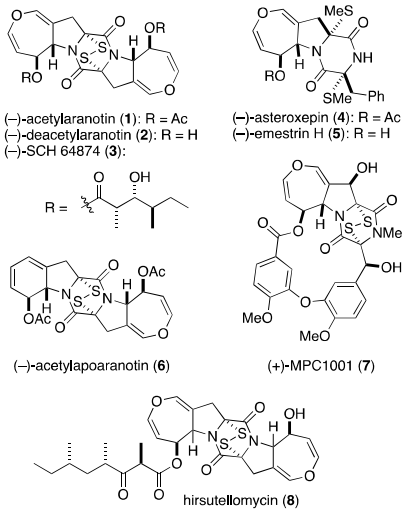
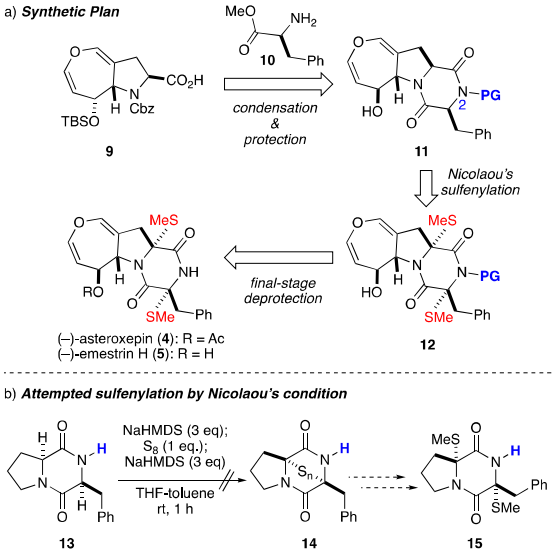


Fig. 1. Dithiodiketopiperazine alkaloids

* Corresponding author. E-mail: tokuyama@mail.pharm.tohoku.ac.jp

functionalized NH-free diketopiperazines and found that the less common allyloxymethyl (Allom) group, which only have been used for a protection of the *N*-3 position in xanthine and the imidazole nitrogen in histidine was the most suitable protecting group [19]. Its efficiency was further demonstrated by the first total synthesis of (–)-asteroxepin (**4**) and (–)-emestrin H (**5**).

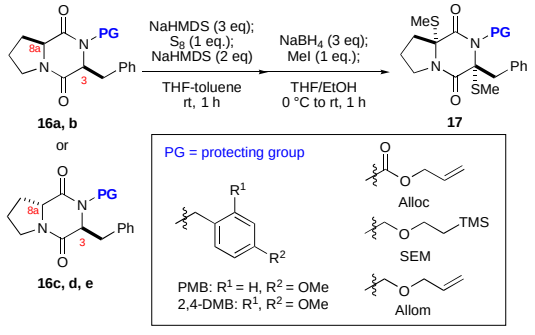


Scheme 1. Synthetic plan and preliminary results.

2. Results and discussion

To identify the most suitable protecting group that would fulfill the abovementioned requirements, we prepared a series of *N*-protected diketopiperazines (**16a–e**) following a conventional method [16,17], which were then subjected to the sulfenylation conditions established by Nicolaou *et al*. (Table 1) [15]. Among the protecting groups in substrates **16a–e**, stable benzylic protecting groups, such as *p*-methoxybenzyl (PMB) in **16a** or 2,4-dimethoxybenzyl (2,4-DMB) in **16b**, were not affected by the sulfenylation conditions, providing dithiodiketopiperazines **17a** and **17b**, respectively, in moderate yields (Table 1, entries 1

Table 1
Protecting groups and introduction of the methylthioether.



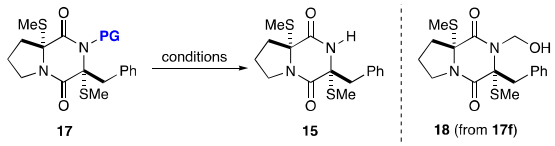
entry	substrate	PG	**17** (%)[c,d]
1	**16a**[a]	PMB	44
2	**16b**[a]	2,4-DMB	57
3	**16c**[b]	Alloc	decomposition
4	**16d**[b]	SEM	68
5	**16e**[b]	Allom	50

[a]C3 (*S*), C8a (*S*) isomer. [b]C3 (*S*), C8a (*R*) isomer. [c]Isolated yield. [d]Obtained as single diastereomer.

16d with the trimethylsilylethoxymethyl (SEM) group and **16e** with the Allom group, afforded the corresponding dimethylthio compounds (**17d** and **17e**) in good yields (Table 1, entries 4 and 5). However, analogue **16c**, protected as urethane with an allyloxycarbonyl group (Alloc), afforded a complex mixture under the same sulfenylation conditions (Table 1, entry 3).

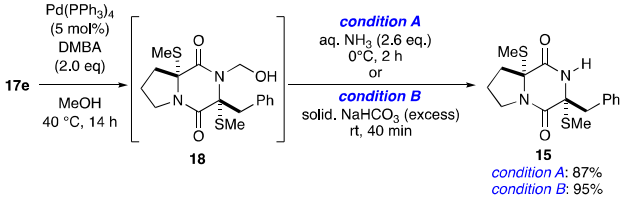
The deprotection of the bis(methylthio) products **17a**, **17b**, **17d**, and **17e** was examined under the most frequently used deprotection conditions for each protecting group (Table 2). Analogues **17a** and **17b** bearing PMB and 2,4-DMB groups were decomposed upon treatment with ceric ammonium nitrate (CAN) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), respectively (Table 2, entries 1 and 2). Moreover, the SEM group in **17d** was stable upon treatment with HF/pyridine and **17d** was recovered (Table 2, entry 3), whereas the use of TBAF in THF/DMF decomposed **17d** (Table 2, entry 4). In contrast to these unsuccessful entries, the Allom group in **17e** could be smoothly removed by a combination of $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid (DMBA) in MeOH yielding **15** in 56% yield, while a substantial amount of the hemiaminal intermediate **18** was also obtained (Table 2, entry 5) [18,19]. The subsequent *in situ* treatment of the reaction mixture with aq. NH_3 was effective in reducing the amount of **18**, affording **15** in 87% yield (Scheme 2). Furthermore, the addition of solid $NaHCO_3$ after the consumption of **17e** improved the yield of **15** to up to 95%.

Table 2
Deprotection conditions.



entry	**17**	reagents	temp.	Time (h)	Yield (%)[a]
1[b]	**17a**	CAN, CH_3CN/H_2O	rt	2	0
2[b]	**17b**	DDQ, CH_3CN/H_2O	60 °C	20	0
3[b]	**17d**	TBAF, THF/DMF	60 °C	1.8	0
4[c]	**17d**	HF/pyridine	60 °C	22	0
5[d]	**17e**	$Pd(PPh_3)_4$, DMBA, MeOH	30 °C	6	56

[a]isolated yield. [b]Decomposition. [c]**17d** was completely recovered. [d]Reaction conditions: **17** (1.0 eq), $Pd(PPh_3)_4$ (45 mol%), DMBA (5.5 eq), MeOH (0.1 M), 30 °C, 6 h. [e]The hemiaminal intermediate **18** was obtained in 38% yield.

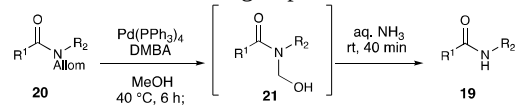


Scheme 2. Removal of the Allom group.

The feasibility of the removal of the Allom protecting group from secondary amides was investigated using a series of *N*-Allom secondary amides (**20**) (see Experimental Section for the preparation and additional data) (Table 3 and Scheme 3). The treatment of the *N*-Allom benzamides **20a–e** and γ-lactam **20f** with $Pd(PPh_3)_4$ and DMBA in MeOH smoothly provided the hemiaminal intermediate **21**, which was converted into amides **19a–e** and **19f**, respectively, in good yields using aq. NH_3 (Table 3, entries 1–6). In contrast, the reaction of *N*-Allom aliphatic amides **20g** under the Pd/*N*,*N*-

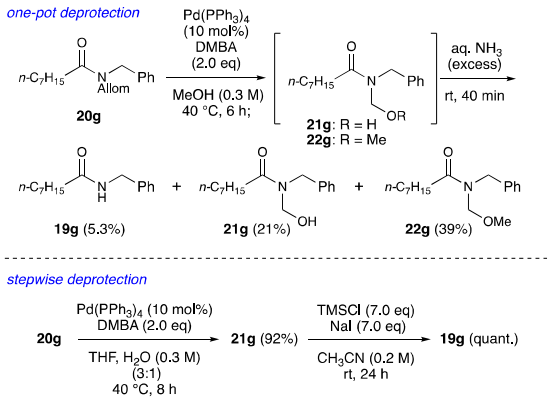
dim … was **21g** (21%), and *N*-MOM amides **22g** (39%) due to the exchange of the OH group in intermediate **21g** with the methoxy group of methanol (Scheme 3). This side reaction was overcome by performing the deprotection of **20g** in THF and H_2O, providing the hemiaminal intermediates **21g**, which were then converted to amides **19g** in good yields using trimethylsilyl iodide (TMSI).

Table 3.
One-pot Removal of the Allom group.



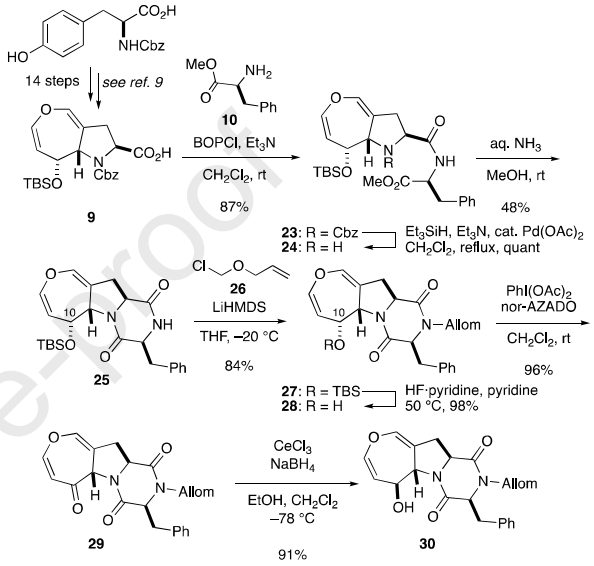
entry	substrate	products	yield (%)
1	**20a**	**19a**	98
2	**20b**	**19b**	86
3	**20c**	**19c**	47
4	**20d**	**19d**	81
5	**20e**	**19e**	78
6	**20f**	**19f**	70

Reaction conditions: **20** (1.0 eq), $Pd(PPh_3)_4$ (10 mol%), DMBA (2.0 eq), MeOH (0.3 M), 40 °C, 6 h, then aq. NH_3 (excess). The yields refer to the isolated products.



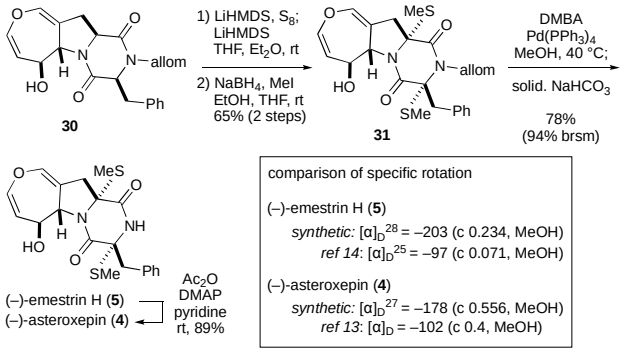
Scheme 3. Stepwise Removal of the Allom group.

The applicability of the Allom protecting group was fully demonstrated by the first total syntheses of (–)-emestrin H (**5**) and (–)-asteroxepin (**4**). The proline-fused dihydrooxepine derivative **9**, which was prepared according to our previously established protocol in the total synthesis of (–)-acetylaranotin (**1**) [9], was first condensed with the (*S*)-phenylalanine methyl … then removed under transfer hydrogenation conditions and the formation of the tricyclic diketopiperazine derivative **25** was promoted upon treatment of the resulting aminoester with ammonium hydroxide. Subsequently, the Allom group was introduced using a combination of the allyloxymethyl chloride (AllomCl) **26** [20] and lithium hexamethyldisilazide (LiHMDS), which afforded the desired product **27** in 84% yield. After desilylation, the stereochemistry of the C-10 hydroxyl group was inverted through a stepwise process [9], which included an oxidation of **28** to ketone using $PhI(OAc)_2$ and 9-azanoradamantane *N*-oxyl (nor-AZADO) [21] and a subsequent Luche reduction, which gave the desired alcohol **30** as the sole isomer.



Scheme 4. Preparation of diketopiperazine 30.

The final steps toward the synthesis of (–)-emestrin H (**5**) and (–)-asteroxepin (**4**) including the crucial introduction of the two methylthioethers and the removal of the Allom protecting group are depicted in Scheme 5. According to the model study (*vide supra*), diketopiperazine **30** was treated with a mixture of excess LiHMDS and S_8 to form an epipolysulfide. Its reduction to the corresponding dithiol with $NaBH_4$ and the subsequent methylation afforded the bis(methylthio) derivative **31** in 65% yield over two steps from **30**. Finally, the Allom group was removed under the optimized conditions affording (–)-emestrin H (**5**) in 78% yield, which was further acetylated to give (–)-asteroxepin (**4**). All properties of synthetic (–)-emestrin H (**5**) and (–)-asteroxepin (**4**) were identical with those reported except magnitude of specific rotations proving the reported absolute stereochemistry of **4** and **5** by this total synthesis [22].



Scheme 5. Final steps of the total syntheses of (–)-emestrin H (5) and (–)-asteroxepin (4).

In conclusion, the total syntheses of (–)-emestrin H (**5**) and (–)-asteroxepin (**4**) have been accomplished for the first time. Their preparation was successful owing to the suitability of the Allom group as protecting group for the amide nitrogen of the highly functionalized dithio-diketopiperazine intermediate. This protecting group could be easily cleaved even in the presence of the acid-sensitive dihydrooxepin structure and the dimethylthioethers, which are sensitive to bases, nucleophiles, and oxidants. Thus, this study demonstrated the application potential of the Allom group not only for the synthesis of other *N*-unprotected diketopiperazine alkaloids, but also for the preparation of various functionalized amides.

4. Experimental section

4.1 General method

Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. Anhydrous THF, Et_2O, CH_2Cl_2, toluene, DMF, and MeCN were purchased from commercial suppliers. Anhydrous MeOH was dried and distilled according to the standard protocols. All reactions were carried out under Ar atmosphere unless otherwise mentioned. Flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40–50 μm). Preparative TLC and analytical TLC was performed on Merck 60 F254 glass plates precoated with a 0.25 mm thickness of silica gel. NMR spectra were recorded on a JNM-AL400 spectrometer and a JEOL ECA600 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm, relative to the central line of a triplet at 77.0 ppm for $CDCl_3$ or a septet at 39.5 ppm for DMSO-d_6. IR spectra were measured on a SHIMADZU FTIR-8300 spectrometer. Mass spectra were recorded on a Bruker micrOTOF (ESI). Optical rotations were measured on a Horiba SEPA-300 highly sensitive polarimeter. Melting point determinations were performed by using a Yanaco MP-500 instrument. Compounds **9** [9], **19a**–**e** [25], **19f** [26], and **19g** [25] were prepared according to the procedures reported in references.

*4.2 Diketopiperazine **16a***

To a solution of *N*-Cbz-L-proline (3.68 g, 14.8mmol) and *N*-PMB-L-phenylalanine methyl ester (4.24 g, 14.2 mmol) in Et_3N and CH_2Cl_2 (5 mL and 30 mL) was added BOP-Cl (3.74 g, 14.7 mmol) at room temperature. After stirring for 24.5 h at room temperature, additional BOP-Cl (1.96 g, 7.70 mmol) was added, and the reaction mixture was stirred for 2.5 h. The reaction was quenched with sat. aq. $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with 1 M aq. HCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:1) to afford amide **32a** (5.80 g, 10.9 mmol, 77%). To a suspension of amide **32a** (5.80 g, 10.9 mmol) and $Pd(OAc)_2$ (983 mg, 4.38 mmol) in CH_2Cl_2 (55.0 mL) was added Et_3N (3.08 mL, 21.9 mmol) at room temperature. After stirring at reflux for 5 min, Et_3SiH (8.74 mL, 54.7 mmol) was added and the mixture was stirred at reflux for 3.5 h. The reaction mixture was diluted with CH_2Cl_2 and the reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (EtOAc) to afford diketopiperazine **16a** (3.00 g, 8.23 mmol, 75%). A white foam; The spectral data of **16a** were identical with those reported in the literature [23].

*4.3 Diketopiperazine **16b***

To a solution of *N*-Cbz-L-proline (1.06 g, 4.25 mmol), *N*-2,4-DMB-L-phenylalanine methyl ester (1.15 g, 3.49 mmol) in Et_3N and CH_2Cl_2 (2.0 mL and 20.0 mL) was added BOP-Cl (1.87 g, 7.35 mmol) at room temperature. After stirring for 20 h at room temperature, the reaction was quenched with 1 M aq. HCl and the resulting mixture was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 3:2 to 6:5) to afford amide **32b** (846 mg, 1.51 mmol, 47%). To a suspension of amide **32b** (846 mg, 1.51 mmol) and $Pd(OAc)_2$ (135 mg, 601 μmol) in CH_2Cl_2 (10.0 mL) was added Et_3N (425 μL, 3.02 mmol) at room temperature. After stirring at reflux for 7 min, Et_3SiH (1.20 mL, 7.51 mmol) was added and the mixture was stirred at reflux for 3.5 h. The reaction mixture was diluted with CH_2Cl_2 and the reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (EtOAc) to afford diketopiperazine **16b** (540 mg, 1.37 mmol, 91%). A white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.20 (4H, m), 7.12–7.06 (2H, m), 6.48–6.43 (2H, m), 5.40 (1H, d, *J* = 14.8 Hz), 4.32 (1H, m), 4.25 (1H, d, *J* = 14.8 Hz), 3.84 (3H, s), 3.81 (3H, s), 3.72 (1H, dd, *J* = 12.0, 6.0 Hz), 3.68–3.61 (1H, m), 3.36–3.27 (2H, m), 3.14–3.07 (1H, m), 1.91–1.81 (1H, m), 1.60–1.42 (2H, m), 0.14–0.01 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 163.9, 160.7, 158.7, 135.1, 131.7, 130.0, 128.3, 127.1, 115.9, 104.4, 98.3, 60.3, 59.0, 55.3, 55.3, 44.0, 40.6, 36.4, 28.4, 20.9; IR (film): 2992, 2952, 2944, 2891, 1656, 1612, 1587, 1508, 1456, 1298, 1289, 1261, 1208, 1184, 1157, 1033, 751, 703 cm^{-1}; $[\alpha]_D^{31}$ = −116 (*c* = 0.66, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{23}H_{26}N_2NaO_4$ [M^++Na] 417.1785, Found 417.1769.

*4.4 Amide **33***

To a solution of *N*-Boc-L-proline (10.8 g, 50.0 mmol) and L-phenylalanine methyl ester (8.95 g, 50.0 mmol) in CH_2Cl_2 (200 mL) were added Et_3N (27.9 mL, 200 mmol), HOBt (6.99 g, 51.7 mmol), and EDCI/HCl (9.91 g, 51.7 mmol) at room temperature. After stirred for 29.5 h at room temperature, the organic phase was washed with 1 M aq. HCl (x3) and sat. aq. $NaHCO_3$ (x2). The resulting organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was used for the next reaction without further purification. To a solution of the crude material in CH_2Cl_2 (120 mL) was added TFA (15 mL) at room temperature. After stirred for 20 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (150 mL) and neutralized by sat. aq. $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (x3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude material, which was purified by flash column chromatography (CH_2Cl_2:MeOH = 10:1) to afford amine amide **33** (6.76 g, 24.5 mmol, 49%, 2 steps from *N*-Boc-L-

prol ... Ac with those reported in the literature [24].

*4.5 Diketopiperazine trans-**13***

To a solution of amide **33** (6.76 g, 24.5 mmol) in MeOH (400 mL) was added $NaHCO_3$ (20.0 g, 85.3 mmol) at room temperature. After stirring for 22.5 h at 65 °C, MeOH was removed under reduced pressure. The residue was diluted with CH_2Cl_2 and filtered through a pad of Celite®. The filtrate was washed with H_2O, and the aqueous phase was extracted with CH_2Cl_2 (x2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by crystallization from EtOAc to afford diketopiperazine *trans*-**13** (3.43 g, 14.1 mmol, 57%). The mother liquor was concentrated *in vacuo* and the second crop was crystallized from EtOAc to afford diketopiperazine *trans*-**13** (643 mg, 2.64 mmol, 11%). A white solid.; fmp: 153.5–154.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.20 (5H, m), 6.31 (1H, s), 4.22 (1H, ddd, *J* = 6.6, 4.0, 3.8 Hz), 3.63 (1H, ddd, *J* = 12.4, 8.5, 8.5 Hz), 3.40 (1H, ddd, *J* = 12.4, 9.4, 3.0 Hz), 3.15 (1H, dd, *J* = 13.9, 6.6 Hz), 3.08 (1H, dd, *J* = 13.9, 4.0 Hz), 2.97 (1H, dd, *J* = 10.4, 6.4 Hz), 2.23–2.15 (1H, m), 1.98–1.90 (1H, m), 1.86–1.64 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 164.8, 135.3, 129.9, 128.5, 127.3, 58.7, 57.6, 44.9, 40.3, 28.8, 21.5; IR (film): 3483, 3238, 3063, 3029, 2981, 2953, 2931, 2886, 1664, 1496, 1454, 1336, 1307, 1296, 1206, 1186, 1115, 1106, 921, 732, 702, 593 cm^{-1}; $[\alpha]_D^{26}$ = +93.0 (*c* = 0.200, H_2O); HRMS (ESI) *m/z*: calcd. for $C_{14}H_{17}N_2O_2$ [M+H$^+$] 245.1285, found 245.1277. The spectral data of *trans*-**13** were identical with those reported in the literature [27].

*4.6 Diketopiperazine**16c***

To a solution of diketopiperazine *trans*-**13** (203 mg, 0.832 mmol) in THF (4.0 mL) was added LiHMDS (1.3 M solution in THF, 650 µL, 845 µmol) at 0 °C. After stirring for 4 min, Alloc-OSu (172 mg, 863 µmol) in THF (1.50 mL) was added at 0 °C. The resulting mixture was stirred for 35 min at room temperature. The reaction was quenched with sat. aq. NH_4Cl, and the resulting mixture was diluted by water. The separated aqueous phase was extracted with CH_2Cl_2 (x3), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (CH_2Cl_2:EtOAc = 5:1 to 3:1) to afford diketopiperazine **16c** (248 mg, 789 µmol, 95%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.26 (3H, m), 7.19–7.14 (2H, m), 5.99–5.87 (1H, m), 5.43 (1H, d, *J* = 17.2 Hz), 5.31 (1H, d, *J* = 10.8 Hz), 5.01 (1H, ddd, *J* = 5.0, 5.0, 1.4 Hz), 4.75 (1H, ddd, *J* = 13.3, 5.8, 1.0 Hz), 4.69 (1H, ddd, *J* = 13.3, 5.6, 1.2 Hz), 3.60–3.50 (1H, m), 3.45–3.37 (1H, m), 3.33–3.22 (2H, m), 2.64 (1H, dd, *J* = 9.6, 6.8 Hz), 2.17–2.07 (1H, m), 1.96–1.79 (2H, m), 1.72–1.57 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 164.0, 151.8, 134.9, 130.7, 129.9, 128.6, 127.5, 119.4, 67.9, 62.3, 58.6, 44.8, 38.2, 29.1, 21.8; IR (film): 3086, 3062, 3028, 2983, 2953, 2885, 1782, 1731, 1672, 1455, 1384, 1270, 1231, 980, 763, 747, 703 cm^{-1}; $[\alpha]_D^{26}$ = +143 (*c* = 0.425, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{18}H_{20}N_2NaO_4$ [M+Na$^+$] 351.1315, Found 351.1319.

*4.7 Diketopiperazine**16d***

To a solution of diketopiperazine *trans*-**13** (1.10 g, 4.51 mmol) in dry DMF (10.0 mL) was added NaH (60% dispersion in mineral oil, 248 mg, 6.20 mmol) at room temperature. After stirring for 15 min, SEMCl (1.60 mL, 9.03 mmol) was added at room temperature, and the resulting mixture was stirred at 60 °C for 18 h. The reaction was quenched with sat. aq. NH_4Cl at room and washed with water (x5) and brine (x1). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:3) to afford diketopiperazine **16d** (1.33 g, 3.55 mmol, 79%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.26 (3H, m), 7.18–7.15 (2H, m), 5.13 (1H, d, *J* = 10.4 Hz), 4.53 (1H, d, *J* = 10.4 Hz), 4.42 (1H, dd, *J* = 5.2, 4.9 Hz), 3.61–3.52 (3H, m), 3.35 (1H, ddd, *J* = 12.1, 9.3, 2.9 Hz), 3.24 (1H, dd, *J* = 14.3, 5.2 Hz), 3.19 (1H, dd, *J* = 14.3, 4.9 Hz), 2.52 (1H, dd, *J* = 10.6, 6.6 Hz), 2.14–2.06 (1H, m), 1.92–1.84 (1H, m), 1.79–1.68 (1H, m), 1.69–1.53 (1H, m), 1.01–0.87 (2H, m), 0.01 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 164.7, 135.2, 129.9, 128.5, 127.5, 73.3, 66.3, 62.1, 57.6, 44.8, 37.6, 29.1, 21.8, 17.9, –1.5; IR (film): 2952, 2890, 1671, 1454, 1440, 1296, 1260, 1249, 1207, 1075, 1044, 860, 837, 749, 703 cm^{-1}; $[\alpha]_D^{25}$ = +55.0 (*c* = 2.71, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{20}H_{30}NaN_2O_3Si$ [M$^+$+Na] 397.1918, Found 397.1909.

*4.8 Diketopiperazine**16e***

To a solution of diketopiperazine *trans*-**13** (880 mg, 3.61 mmol) in dry THF (8.0 mL) was added NaH (60% dispersion in mineral oil, 181 mg, 4.53 mmol) at room temperature. After stirring for 50 min, AllomCl (**26**) [20] (750 µL, 7.23 mmol) was added at room temperature, and the mixture was stirred for 9.5 h at 50 °C. The reaction was quenched with sat. aq. NH4Cl solution at room temperature, and the aqueous phase was diluted by water, extracted with Et_2O (x1) and CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1, then EtOAc only) to afford diketopiperazine **16e** (946 mg, 3.01 mmol, 83%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.24 (3H, m), 7.19–7.14 (2H, m), 5.89 (1H, m), 5.29 (1H, ddd, *J* = 17.6, 1.2, 1.2, Hz), 5.19 (1H, d, *J* = 10.8 Hz), 5.14 (1H, d, *J* = 10.6 Hz), 4.58 (1H, d, *J* = 10.6 Hz), 4.43 (1H, dd, *J* = 4.7, 4.8 Hz), 4.10–3.98 (2H, m), 3.57 (1H, ddd, *J* = 12.3, 8.5, 8.5 Hz), 3.36 (1H, ddd, *J* = 12.3, 9.3, 2.9 Hz), 3.25 (1H, dd, *J* = 14.3, 4.8 Hz), 3.20 (1H, dd, *J* = 14.3, 4.7 Hz), 2.53 (1H, dd, *J* = 10.6, 6.6 Hz), 2.09 (1H, ddd, *J* = 12.0, 6.2, 6.2 Hz), 1.94-1.84 (1H, m), 1.81–1.69 (1H, m), 1.66–1.53 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 164.7, 135.3, 133.8, 129.9, 128.6, 127.5, 117.4, 73.6, 70.1, 62.4, 57.7, 44.9, 37.7, 29.0, 21.8; IR (film): 3028, 2979, 2951, 2883, 1668, 1453, 1440, 1344, 1296, 1261, 1207, 1072, 1057, 923, 748, 703 cm^{-1}; $[\alpha]_D^{26}$ = +60.0 (*c* = 4.41, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{18}H_{22}N_2NaO_3$ [M$^+$+Na] 337.1523, Found 337.1506.

*4.9 Dithiodiketopiperazine **17a** (General Procedure A)*

To a suspension of sulfur S_8 (264 mg, 1.03 mmol) in THF (5.0 mL) was added NaHMDS (0.6 M in toluene, 5.00 mL, 3.00 mmol) at room temperature. After stirring for 1 min, diketopiperazine **16a** (372 mg, 1.02 mmol) in THF (5.0 mL) was added, and the mixture was stirred for 1 min. Then, NaHMDS (0.6 M in toluene, 3.40 mL, 2.04 mmol) was added, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with sat. aq. NH_4Cl, and the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was used for the next reaction without further purification. To a solution of the crude material in THF (10.0 mL) and EtOH (10.0 mL) was added $NaBH_4$ (964 mg, 25.5 mmol) at 0 °C. After

sti m), added at 0 °C, and the resulting mixture was stirred for 19 h at room temperature. The reaction was quenched by sat. aq. NH_4Cl, and the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by flash column chromatography (hexanes:EtOAc = 12:5) to afford bis(metylthio) diketopiperazine **17a** (204 mg, 0.449 mmol, 44%, 2 steps from **16a**). A white solid; mp: 136.7–137.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (2H, d, *J* = 8.8 Hz), 7.31–7.22 (3H, m), 7.09 (2H, d, *J* = 6.0 Hz), 6.83 (2H, d, *J* = 8.8 Hz), 5.18 (1H, d, *J* = 14.4 Hz), 4.54 (1H, d, *J* = 14.4 Hz), 3.79 (3H, s), 3.66–3.48 (2H, m), 3.54 (1H, d, *J* = 13.6 Hz), 3.25 (1H, d, *J* = 13.6 Hz), 2.05-1.91 (2H, m), 2.01 (3H, s), 1.99 (3H, s), 1.58–1.49 (1H, m), 0.81–0.71 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 163.0, 158.6, 134.1, 130.2, 129.6, 128.4, 127.7, 113.3, 78.8, 69.9, 55.1, 46.7, 45.8, 44.1, 32.7, 18.5, 15.0, 14.0 (One signal is missing due to overlap.), IR (film): 2994, 2956, 2933, 2922, 1662, 1512, 1421, 1395, 1352, 1247, 1177, 1033, 756, 703 cm^{-1}; $[\alpha]_D^{25}$ = +0.89 (*c* 0.58, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{24}H_{28}N_2NaO_3S_2$ [M+Na$^+$] 479.1419, Found 479.1434.

*4.10 Dithiodiketopiperazine **17b***

According to the General Procedure A, diketopiperazine **16b** (301 mg, 0.763 mmol) were converted to bis-(methylthio) diketopiperazine **17b** (210 mg, 0.431 mmol, 57 %, 2 steps from **16b**). A white solid; mp: 186.3–186.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (1H, d, *J* = 8.5 Hz), 7.30–7.20 (3H, m), 7.11 (2H, d, *J* = 6.4 Hz), 6.48 (1H, d, *J* = 2.1 Hz), 6.41 (1H, d, *J* = 8.5, 2.1 Hz), 5.07 (1H, d, *J* = 15.8 Hz), 4.68 (1H, d, *J* = 15.8 Hz), 3.90 (3H, s), 3.79 (3H, s), 3.67–3.53 (2H, m), 3.55 (1H, d, *J* = 13.6 Hz), 3.33 (1H, d, *J* = 13.6 Hz), 2.14 (3H, s), 2.14 (3H, s), 2.10–1.94 (2H, m), 1.61–1.50 (1H, m), 0.86–0.73 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 162.9, 159.5, 157.2, 134.2, 130.1, 128.3, 127.5, 127.0, 118.5, 103.5, 98.2, 78.5, 69.7, 55.3, 55.2, 45.8, 44.1, 41.1, 32.5, 18.4, 15.2, 14.2; IR (film): 2998, 2959, 2936, 2921, 2835, 1662, 1616, 1590, 1508, 1455, 1439, 1420, 1396, 1361, 1300, 1261, 1208, 1156, 1120, 1036, 755, 703 cm^{-1}; $[\alpha]_D^{32}$ = +21.3 (*c* = 0.26, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{25}H_{30}N_2NaO_4S_2$ [M+Na$^+$] 509.1539, Found 509.1526.

*4.11 Dithiodiketopiperazine **17d***

According to the General Procedure A, diketopiperazine **16e** (456 mg, 1.22 mmol) were converted to bis-(methylthio) diketopiperazine **17d** (386 mg, 0.828 mmol, 68%, 2 steps from **16d**). A white solid; mp: 82.9–83.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.19 (3H, m), 7.12 (2H, dd, *J* = 7.8, 2.2 Hz), 5.48 (1H, d, *J* = 9.6 Hz), 5.06 (1H, d, *J* = 9.6 Hz), 3.79 (2H, t, *J* = 8.6 Hz), 3.50 (2H, dd, *J* = 9.2, 6.4 Hz), 3.46 (1H, d, *J* = 13.6 Hz), 3.18 (1H, d, *J* = 13.2 Hz), 2.26 (3H, s), 2.14 (3H, s), 2.12–2.04 (1H, m), 2.02–1.89 (1H, m), 1.55–1.46 (1H, m), 1.07–0.96 (2H, m), 0.93–0.84 (1H, m), 0.03 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 163.0, 134.3, 130.6, 128.2, 127.4, 77.3, 73.1, 69.5, 67.4, 45.7, 44.8, 32.7, 18.5, 18.4, 15.3, 14.0, –1.4; IR (film): 2952, 2920, 1669, 1454, 1438, 1416, 1385, 1362, 1248, 1083, 1057, 860, 836, 756, 703 cm^{-1}; $[\alpha]_D^{30}$ = −6.99 (*c* = 2.76, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{34}N_2NaO_3S_2Si$ [M+Na$^+$] 489.1672, Found 489.1649.

*4.12 Dithiodiketopiperazine **17e***

According to the General Procedure A, diketopiperazine **16e** (843 mg, 2.68 mmol) were converted to bis-(methylthio) diketopiperazine **17e** (539 mg, 1.33 mmol, 50% 2 steps from **16e**). A white solid; mp: 84.8–85.2 °C; ^{1}H NMR (400 MHz, 5.51 (1H, d, *J* = 9.8 Hz), 5.36 (1H, dd, *J* = 17.2, 1.6 Hz), 5.21 (1H, dd, *J* = 15.9, 1.8 Hz), 5.11 (1H, d, 9.8 Hz), 4.29 (2H, ddd, *J* = 5.5, 1.5, 1.5 Hz), 3.54–3.47 (2H, m), 3.47 (1H, d, *J* = 13.6 Hz), 3.18 (1H, d, *J* = 13.6 Hz), 2.26 (3H, s), 2.15 (3H, s), 2.14–2.04 (1H, m), 2.03–1.89 (1H, m), 1.58–1.46 (1H, m), 0.98–0.86 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 162.9, 134.4, 134.2, 130.6, 128.2, 127.4, 117.0, 77.3, 73.3, 71.2, 69.6, 45.7, 44.9, 32.8, 18.5, 15.2, 13.9; IR (film): 2952, 2920, 2896, 1669, 1438, 1416, 1385, 1362, 1248, 1083, 1057, 860, 836, 756, 703 cm^{-1}; $[\alpha]_D^{30}$ = −9.65 (*c* = 0.660, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{20}H_{26}N_2NaO_3S_2$ [M+Na$^+$] 429.1277, Found 429.1271.

*4.13 Dithiodiketopiperazine **15***

To a mixture of bis-(methylthio) diketopiperazine **17e** (52.9 mg, 130 μmol) and $Pd(PPh_3)_4$ (7.53 mg, 6.51 μmol) and 1,3-dimethylbarbituric acid (40.7 mg, 260 μmol) was added MeOH (1.3 mL) at room temperature. The resulting suspension was stirred for 14 h at 40 °C. The reaction mixture was cooled to room temperature before addition of excess $NaHCO_3$ (130 mg) and further stirred for 40 min at room temperature. The reaction mixture was diluted by water (1.0 mL), and the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried with anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1 to 1:1) to afford bis-(methylthio) diketopiperazine **15** (41.6 mg, 124 μmol, 95%). A white solid; mp: 159.9–160.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.85 (1H, s), 7.26–7.14 (5H, m), 3.48 (1H, d, *J* = 12.8 Hz), 3.46–3.26 (2H, m), 3.00 (1H, d, *J* = 12.8 Hz), 2.29 (3H, s), 2.11 (3H, s), 2.02 (1H, dd, *J* = 13.2, 7.2 Hz), 1.95–1.81 (1H, m), 1.63–1.52 (1H, m), 0.97 (1H, ddd, *J* = 9.3, 12.1, 12.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.6, 163.2, 134.9, 130.3, 127.8, 126.9, 69.6, 67.4, 44.9, 44.6, 33.7, 18.6, 14.0, 13.2; IR (film): 3211, 3096, 3087, 3062, 2987, 2961, 2922, 2896, 1676, 1659, 1406, 1208, 755, 705 cm^{-1}; $[\alpha]_D^{28}$ = −17.5 (*c* = 0.65, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{16}H_{20}N_2NaO_2S_2$ [M+Na$^+$] 359.0858, Found 359.0835.

*4.14 amide **20a** (General Procedure B)*

To a solution of amide **19a** (1.11 g, 5.26 mmol) and TBAI (195 mg, 0.527 mmol) in THF (21.0 mL) was added LiHMDS (1.3 M solution in THF, 4.46 mL, 5.80 mmol) at −40 °C. After stirring for 30 min, AllomCl (**26**) [20] (0.764 mL, 5.80 mmol) was added at –40 °C, and the mixture was stirred at −40 °C for 14 h. The reaction was quenched with sat. aq. NH_4Cl solution and the mixture was diluted by water. The aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 4:1) to afford amide **20a** (1.43 g, 5.08 mmol, 97%). A colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 7.48–7.42 (5H, m), 7.36–7.26 (5H, m), 5.82–5.75 (1H, m), 5.14 (1H, d, *J* = 17.6 Hz), 5.07 (1H, d, *J* = 10.4 Hz), 4.86–4.67 (4H, m), 3.84 (br, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 171.0, 137.2, 135.4, 134.0, 129.4, 128.0, 127.9, 127.1, 126.6, 126.5, 116.3, 77.0, 68.0, 48.1; IR (film): 3062, 3030, 2942, 2862, 1651, 1496, 1445, 1417, 1267, 1071, 1050, 699 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{19}NNaO_2$ [M+Na$^+$] 304.1308, found 304.1296.

*4.15 amide **20b***

According to the General Procedure B, amide **19b** (55.5 mg, 191 μmol) was converted to amide **20b** (51.6 mg, 143 μmol,

75% ... mg, δ 7.64–7.16 (2H, m), 7.47 (2H, d, *J* = 8.4 Hz), 7.34–7.26 (5H, m), 5.82–5.77 (1H, m), 5.16 (1H, d, *J* = 17.6 Hz), 5.09 (1H, d, *J* = 10.0 Hz), 3.86 (2H, br s); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 170.1, 137.0, 134.5, 133.9, 130.9, 128.7, 128.0, 127.2, 126.7, 122.9, 116.3, 77.0, 68.0, 48,3; IR (film): 3085, 3063, 3030, 2979, 2942, 2898, 2863, 1652, 1590, 1443, 1417, 1360, 1292, 1266, 1072, 1011, 932, 837, 754, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{18}BrNNaO_2$ [M+Na$^+$] 382.0413, Found 382.0403.

*4.16 amide **20c***

According to the General Procedure B, amide **19c** (62.4 mg, 2.43 μmol) was converted to amide **20c** (70.4 mg, 215mmol, 89%). A yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 8.26 (2H, d, *J* = 8.0 Hz), 7.73 (2H, d, *J* = 8.0 Hz), 7.35–7.25 (5H, m), 5.84–5.71 (1H, m), 5.16 (1H, d, *J* = 17.6 Hz), 5.08 (1H, d, *J* = 10.8 Hz), 4.70 (2H, br), 4.64 (2H, br), 3.86 (2H, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 147.9, 141.5, 136.8, 133.9, 128.1, 127.9, 127.3, 126.8, 123.2, 116.5, 68.1, 54.3, 48.5; IR (film): 3080, 3066, 3031, 2945, 2862, 1651, 1602, 1521, 1425, 1349, 1072, 732, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{18}N_2NaO_4$ [M+Na$^+$] 349.1159, Found 349.1140.

*4.17 amide **20d***

According to the General Procedure B, amide **19d** (60.3 mg, 250 μmol) was converted to amide **20d** (68.0 mg, 218 μmol, 87%). A colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 7.49–7.46 (2H, m), 7.35–7.25 (5H, m), 6.99–6.97 (2H, m), 5.86–5.76 (m, 1H), 5.19–5.14 (m, 1H), 5.11–5.08 (m, 1H), 4.69–4.68 (m, 4H), 3.89–3.86 (m, 2H), 3.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 170.8, 160.4, 137.4, 134.0, 128.6, 127.9, 127.4, 127.2, 126.6, 116.3, 113.4, 77.5, 67.9, 59.5, 48.2; IR (film) 1442, 1417, 1358, 1302, 1253, 1175, 1112, 1049, 933, 842, 766, 700, 598 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{19}H_{21}NNaO_3$ [M+Na$^+$] 334.1414, Found 334.1408.

*4.18 amide **20e***

According to the General Procedure B, amide **19e** (74.0 mg, 331 μmol) was converted to amide **20e** (92.1 mg, 314 μmol, 95%). A yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 7.45–7.42 (5H, m), 5.84–5.78 (1H, m), 5.18 (1H, d, *J* = 17.6 Hz), 5.09 (1H, d, *J* = 10.4 Hz), 4.69 (2H, br), 4.54 (2H, br), 3.86 (2H, br), 3.51 (4H, br), 3.26 (3H, br), 1.88–1.85 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 170.9, 135.8, 134.1, 129.1, 127.8, 126.4, 116.1, 95.6, 67.4, 64.8, 54.2, 42.8, 27.9 (One signal is missing due to overlap.); IR (film): 2933, 2883, 1651, 1446, 1419, 1404, 1271, 1147, 1112, 1043, 919, 724, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{23}NNaO_4$ [M+Na$^+$] 316.1519, Found 316.1516.

*4.19 amide **20f***

According to the General Procedure B, amide **19f** (40.5 mg, 251 mmol) was converted to amide **20f** (49.5 mg, 214 μmol, 85%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.21 (5H, m), 5.88–5.81 (1H, m), 5.25 (1H, d, *J* = 16.8 Hz), 5.17–5.12 (2H, m), 4.82 (m, 1H), 4.06 (1H, d, *J* = 10.8 Hz), 3.97–3.94 (m, 2H), 2.64–2.50 (3H, m), 1.99–1.95 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 140.5, 134.0, 128.8, 128.0, 126.5, 116.9, 70.0, 69.4, 60.4, 30.2, 28.1; IR (film): 3081, 3065, 3031, 2979, 2941, 2885, 1704, 1456, 1415, 1392, 1319, 1256, 1227, 1065, 932, 769, 703 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{17}NNaO_2$ [M+Na$^+$] 254.1151, Found 254.1147.

*4.20 amide **20g***

250 μmol) was converted to amide **20g** (71.7 mg, 236 μmol, 95%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.37–7.18 (5H, m), 5.94–5.82 (2H, m), 4.92 (0.7H, s), 4.67 (2H, s), 4.63 (1.3H, s), 4.31 (0.7, d, *J* = 5.2 Hz), 3.94 (1.3H, d, *J* = 6.0 Hz), 2.46 (1.3 H, t, *J* = 7.6 Hz), 2.33 (0.7H, 8.0 Hz), 1.71–1.63 (m, 2H), 1.32–1.35 (m, 8H), 0.88–0.84 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 174.8, 174.1, 137.8, 136.9, 134.3, 133.8, 128.8, 128.4, 128.1, 127.4, 127.2, 126.3, 117.6, 116.9, 76.8, 74.3, 69.5, 68.5, 49.2, 48.3, 33.32, 32.99, 31.63, 31.58, 29.3, 29.2, 29.00, 28.95, 25.3, 25.0, 22.53, 22.50, 14.0; IR (film): 3086, 3064, 3030, 2954, 2926, 2855, 1664, 1496, 1453, 1421, 1359, 1236, 1036, 991, 932, 732, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{19}H_{29}NNaO_2$ [M+Na$^+$] 326.2091, Found 326.2082.

*4.21 amide **19a** (General Procedure C)*

To a mixture of amide **20a** (56.0 mg, 199 μmol) and Pd(PPh_3)$_4$ (23.3 mg, 20.0 μmol) and 1,3-dimethylbarbituric acid (62.2 mg, 398 μmol) was added MeOH (0.67 mL) at room temperature. The resulting suspension was stirred for 6 h at 40 °C. The reaction mixture was cooled to room temperature before addition of excess aq. NH_3 (0.3 ml) and further stirred for 40 min at room temperature. Then, the reaction mixture was diluted by water (1.0 mL) and then the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 3:1) to afford amide **19a** (41.4 mg, 196 μmol, 98%).

*4.22 amide **19b***

According to the General Procedure C, amide **20b** (78.4 mg, 218 μmol) was converted to amide **19b** (54.1 mg, 186 μmol, 86%).

*4.23 amide **19c***

According to the General Procedure C, amide **20c** (37.8 mg, 116 μmol) was converted to amide **19c** (13.9 mg, 54.2 μmol, 47%).

*4.24 amide **19d***

According to the General Procedure C, amide **20c** (65.5 mg, 210 μmol) was converted to amide **19c** (40.9 mg, 170 μmol, 81%).

*4.25 amide **19e***

According to the General Procedure C, amide **20e** (66.7 mg, 227 μmol) was converted to amide **19e** (39.0 mg, 175 μmol, 78%).

*4.26 amide **19f***

According to the General Procedure C, amide **20f** (39.7 mg, 172 μmol) were converted to amide **19f** (19.3 mg, 120 μmol, 70%).

*4.27 hemiaminal **21g***

To a mixture of amide **20g** (20.9 mg, 68.8 μmol) and Pd(PPh_3)$_4$ (8.0 mg, 6.87 μmol) and 1,3-dimethylbarbituric acid (21.5 mg, 134 μmol) were added THF (0.17 mL) and MeOH (0.06 mL) at room temperature. After stirred for 8 h at 40 °C, the reaction was quenched with sat. aq. Na_2CO_3, and the aqueous phase was extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and

co ; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.49–7.28 (8.8H, m), 7.12–7.09 (1.2H, m), 6.48–6.37 (2.4H, m), 6.11 (0.6H, d, *J* = 8.4 Hz), 5.37–5.13 (3H, m), 5.05–4.76 (3H, m), 4.50 (1H, ddd, *J* = 8.4, 8.4, 2.8 Hz), 3.81 (1.2H, s), 3.72 (1.8H, s), 3.26–3.04 (3H, m), 2.76 (0.4H, d, *J* = 15.2 Hz), 2.64 (0.6H, d, *J* = 15.2 Hz), 0.940 (9H, s), 0.120 (3H, s), 0.054 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 171.6, 171.5, 171.4, 171.2, 154.7, 153.9, 145.5, 145.2, 136.1, 135.7, 135.4, 135.0, 129.4, 129.1, 128.5, 128.5, 128.4, 128.3, 128.1, 128.1, 127.9, 127.1, 127.0, 120.3, 118.7, 105.9, 105.5, 67.6, 67.3, 67.1, 65.9, 65.0, 64.4, 61.8, 61.4, 53.0, 52.5, 52.2, 52.1, 37.8, 37.7, 33.3, 32.0, 25.6, 17.8, −4.5, −4.6, −5.0, −5.1 (Five signals are missing due to overlap.); IR (film): 3325, 3031, 2953, 2928, 2895, 2855, 1746, 1713, 1639, 1526, 1437, 1408, 1350, 1318, 1252, 1210, 1142, 1113, 1085, 959, 836, 777, 748, 698 cm^{-1}; $[\alpha]_D^{27}$ = −175 (*c* = 1.20, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{33}H_{42}N_2NaO_7Si$ [M+Na$^+$] 629.2653, found 629.2624.

which was purified by silica gel column chromatography (hexanes:EtOAc = 5:1) to afford amide hemiaminal **21g** (16.6 mg, 63.2 μmol, 92%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.36–7.22 (5H, m), 4.86 (2H, br), 4.86–4.65 (2H, br), 3.69 (0.7H, br), 2.64–2.49 (0.9H, m), 2.31 (1.4H, t, *J* = 8.0 Hz), 1.71–1.61 (m, 2H), 1.25 (br, 8H), 0.88–0.84 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 175.9, 174.2, 138.0, 136.9, 128.9, 128.7, 128.1, 127.6, 127.5, 1 26.4, 72.2, 71.7, 51.5, 48.2, 33.4, 33.1, 31.7, 31.6, 29.4, 29.2, 29. 1, 29.0, 25.4, 24.9, 22.6, 14.0 (Two signals are missing due to overlap.); IR (film): 3371, 3087, 3063, 3030, 2954, 2926, 2870, 2855, 1636, 1629, 1453, 1423, 1041, 1029, 699 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{26}N_2O_2$ [M+H$^+$] 264.1958, Found 264.1946.

*4.28 amide **19g***

To a mixture of hemiaminal **21g** (19.1 mg, 72.7 μmol) and NaI (76.3 mg, 509 μmol) in MeCN (0.36 mL) was added TMSCl (46.0 μL, 495 μmol) at 0 °C. After stirred for 24 h at room temperature, the reaction was quenched with sat. aq. Na_2CO_3, and the aqueous phase was extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 1:1) to afford amide **19g** (17.0 mg, 72.3 μmol, quant).

*4.29 amide **22g***

To a mixture of amide **20g** (17.3 mg, 57.0 μmol) and $Pd(PPh_3)_4$ (6.6 mg, 5.67 μmol) and 1,3-dimethylbarbituric acid (17.8 mg, 114 μmol) was added MeOH (0.2 mL) at room temperature. The resulting suspension was stirred for 16.5 h at 40 °C. Then, the reaction was quenched with sat. aq. Na_2CO_3, and the mixture was extracted with EtOAc (x3). The combined organic extracts were washed with 1 M aq. HCl and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 3:1) to afford amide **19g** (0.7 mg, 3.00 μmol, 5.3%), **21g** (3.2 mg, 12.1 μmol, 21%), and **22g** (6.1 mg, 22.0 μmol, 39%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.37–7.18 (5H, m), 4.85 (0.8H, s), 4.67 (1.2H, s), 4.61 (2H, s), 3.33 (1.2H, s), 3.28 (1.8H, s), 2.46 (1.2H, t, *J* = 7.6 Hz), 2.35 (0.8H, t, *J* = 7.6 Hz), 2.48–1.64 (2H, m), 1.32–1.25 (8H, m), 0.88–0.84 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 175.0, 174.2, 137.8, 136.9, 128.8, 128.5, 128.1, 127.5, 127.3, 126.3, 78.9, 76.0, 56.1, 55.3, 49.1, 48.3, 33.4, 33.0, 31.7, 31.6, 29.3, 29.2, 29.1, 29.0, 25.2, 25.1, 22.57, 22.55, 14.0 (One signal is missing due to overlap.); IR (film): 3087, 3063, 3031, 2953, 2927, 2871, 2855, 1663, 1453, 1420, 1389, 1095, 1077, 699 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{27}NNaO_2$ [M+Na$^+$] 300.1934, Found 300.1921.

*4.30 amide **23***

To a solution of carboxylic acid **9** [9] (491 mg, 1.10 mmol) and L-phenylalanine methyl ester **10** (497 mg, 2.78 mmol) in dry CH_2Cl_2 (15.0 mL) was added Et_3N (612 μL, 4.40 mmol) at room temperature. After stirring for 10 min, BOP-Cl (576 mg, 2.26 mmol) was added, and the mixture was stirred for 2.7 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$, and the mixture was extracted with EtOAc (x3). The combined organic extracts were washed with 1 M aq. HCl and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to

*4.31 Amide **24***

To a suspension of amide **23** (398 mg, 657 μmol) and $Pd(OAc)_2$ (57.8 mg, 257 μmol) in CH_2Cl_2 (12.0 mL) was added Et_3N (300 μL, 2.16 mmol) at room temperature. After stirring for 30 min at reflux, Et_3SiH (1.10 mL, 6.90 mmol) was added, and the mixture. was stirred for 40 min at reflux. The reaction mixture was diluted by CH_2Cl_2 and the reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 6:1 to 2:1) to afford amine **24** (347 mg, quant). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (1H, d, *J* = 8.4 Hz), 7.22–7.16 (3H, m), 7.03 (2H, d, *J* = 6.8 Hz), 6.25 (1H, d, *J* = 2.0 Hz), 6.22 (1H, d, *J* = 8.0 Hz), 4.80 (1H, ddd, *J* = 10.8, 3.2, 3.2 Hz), 4.71 (1H, dd, *J* = 8.0, 7.8 Hz), 4.27 (1H, dd, *J* = 7.8, 2.2 Hz), 3.79 (1H, dd, *J* = 7.2, 5.6 Hz), 3.70 (3H, s), 3.55 (1H, s), 3.19 (1H, dd, *J* = 14.0, 5.8 Hz), 3.01 (1H, dd, *J* = 14.0, 6.6 Hz), 2.73–2.71 (2H, m), 2.28 (1H, s), 0.82 (9H, s), 0.033 (3H, s), 0.022 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 171.9, 145.5, 135.8, 133.1, 129.1, 128.3, 126.9, 120.5, 105.6, 67.9, 63.9, 60.9, 52.5, 52.1, 37.6, 35.0, 25.6, 17.9, -3.8, -4.7; IR (film): 3349, 3029, 2952, 2928, 2893, 2855, 2360, 2341, 1745, 1677, 1644, 1508, 1437, 1360, 1344, 1254, 1200, 1079, 961, 837, 779, 702 cm^{-1}; $[\alpha]_D^{26}$ = –195 (*c* = 1.65, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{25}H_{37}N_2O_5Si^+$ [M+H$^+$] 473.2466, found 473.2451.

*4.32 Dithiodiketopiperazine **25***

To a solution of amine **24** (447 mg, 945 μmol) in MeOH (250 mL) was added 25% aq. NH_3 (15.0 mL) at room temperature. After stirring for 2.7 days at room temperature, the reaction was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to afford diketopiperazine **25** (202 mg, 459 μmol, 48%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.18 (5H, m), 6.41 (1H, s), 6.29 (1H, d, *J* = 8.0 Hz), 5.90 (1H, s), 5.00 (1H, d, *J* = 7.6 Hz), 4.88 (1H, dd, *J* = 8.0, 7.6 Hz), 4.77 (1H, s), 4.23–4.16 (2H, m), 3.51 (1H, dd, *J* = 14.0, 3.6 Hz), 2.89–2.79 (2H, m), 2.52 (1H, dd, *J* = 13.0, 13.0 Hz), 0.79 (9H, s), 0.011 (3H, s), 0.006 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 163.9, 145.0, 135.6, 135.1, 129.3, 128.9, 127.3, 112.4, 106.4, 66.9, 63.1, 57.9, 56.2, 37.3, 33.4, 25.7, 17.8, −4.3, −4.5; IR (film): 3381, 3228, 3220, 2952, 2928, 2895, 2855, 2359, 2341, 1684, 1663, 1444, 1422, 1294, 1256, 1202, 1139, 1083,

$CHCl_3$); HRMS (EI) *m/z*: calcd. for $C_{24}H_{32}N_2O_4Si$ [M$^+$] 440.2131, found 440.2134.

*4.33 Dithiodiketopiperazine **27***

To a solution of diketopiperazine **25** (63.4 mg, 144 μmol) in THF (630 μL) was added LiHMDS (1.3 M solution in THF, 120 μL, 156 μmol) at −40 °C. After stirring for 8 min, AllomCl (**26**) [20] (120 μL, 1.16 mmol) was added at −40 °C, and the mixture was stirred at −20 °C for 17 h. The reaction was quenched with sat. aq. NH_4Cl solution and the mixture was diluted by water. The separated aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 4:1 to 2:1) to afford diketopiperazine **27** (66.3 mg, 120 μmol, 84%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (3H, m), 7.04 (2H, d, *J* = 8.0 Hz), 6.28 (1H, d, *J* = 7.6 Hz), 6.27 (1H, s), 5.96–5.87 (1H, m), 5.51 (1H, d, *J* = 10.8 Hz), 5.31 (1H, dt, *J* = 17.2, 1.6 Hz), 5.24 (1H, dt, *J* = 10.8, 1.2 Hz), 4.87(1H, dd, *J* = 7.8, 7.6 Hz), 4.82 (1H, d, *J* = 7.8 Hz), 4.79 (1H, d, *J* = 10.8 Hz), 4.62 (1H, s), 4.57 (1H, m), 4.12 (1H, dd, *J* = 12.8, 6.0 Hz), 4.07–4.40 (2H, m), 3.42 (1H, dd, *J* = 14.0, 2.8 Hz), 3.21 (1H, dd, *J* = 14.0, 2.8 Hz), 2.44 (1H, dd, *J* = 13.2, 6.0 Hz), 0.94 (1H, dd, *J* = 13.2, 12.8 Hz), 0.79 (9H, s), 0.007 (3H, s), −0.009 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 163.7, 144.9, 134.9, 134.7, 133.4, 130.1, 128.6, 127.4, 118.1, 112.8, 106.4, 72.5, 69.9, 68.6, 62.9, 59.1, 58.2, 36.5, 33.6, 25.8, 18.0, −4.3, −4.5; IR (film): 2952, 2928, 2856, 1662, 1452, 1441, 1295, 1200, 1138, 1092, 1051, 955, 906, 837, 777, 703 cm^{-1}; $[\alpha]_D^{25}$ = −333 (*c* = 0.535, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{28}H_{38}N_2NaO_5Si^+$ [M+Na$^+$] 533.2442, found 533.2417.

*4.34 Dithiodiketopiperazine **28***

To a solid of diketopiperazine **27** (66.3 mg, 120 μmol) was added HF·Py in pyridine (2.00 mL, 1:4, HF·Py containing ~70% hydrogen fluoride and ~30% pyridine) at room temperature. After stirring for 17 h at 45 °C, the reaction mixture was diluted by water at 0 ℃. The separated aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (CH_2Cl_2:EtOAc = 1:5) to afford allyl alcohol **28** (46.6 mg, 118 μmol, 98%). A white solid; mp: 155.5–156.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (3H, m), 7.07–7.04 (2H, m), 6.34 (1H, d, *J* = 8.0 Hz), 6.34 (1H, d, *J* = 2.0 Hz), 5.98–5.91 (1H, m), 5.41 (1H, d, *J* = 10.8 Hz), 5.35 (1H, ddd, *J* = 17.5, 2.9, 1.7 Hz), 5.24 (1H, ddd, *J* = 10.3, 2.9, 1.5 Hz), 5.05 (1H, dd, *J* = 8.2, 8.0 Hz), 4.82 (1H, d, *J* = 10.8 Hz), 4.79–4.76 (2H, m), 4.69 (1H, s), 4.58–4.56 (1H, m), 4.22 (1H, dd, *J* = 12.2, 6.0 Hz), 4.16–4.10 (2H, m), 3.42 (1H, dd, *J* = 14.2, 3.0 Hz), 3.23 (1H, dd, *J* = 14.2, 4.4 Hz), 2.48 (1H, dd, *J* = 14.4, 6.0 Hz), 0.94 (1H, dd, *J* = 14.4, 12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 163.8, 145.1, 135.2, 134.7, 133.6, 130.1, 128.4, 127.3, 117.8, 113.7, 105.7, 73.2, 70.3, 68.1, 62.6, 59.8, 58.3, 36.8, 33.3; $[\alpha]_D^{25}$ = −367 (*c* = 0.260, $CHCl_3$); IR (film): 3425, 3419, 2921, 2359, 2340, 1694, 1659, 1454, 1339, 1296, 1200, 1137, 1074, 1047, 929, 857, 758, 736, 704 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{22}H_{24}N_2NaO_5$ [M+Na$^+$] 419.1577, found 419.1558.

*4.35 Dithiodiketopiperazine **29***

To a solution of allyl alcohol **28** (74.3 mg, 188 μmol) and nor-AZADO (8.50 mg, 61.5 μmol) in dry CH_2Cl_2 (1.40 mL) was added LiHMDS (1.3 M in THF, 725 μL, 943 μmol) at room temperature. After stirring for 5 min, diketopiperazine **30** (18.6 mg, 47.0 μmol) in a mixture of THF (2.0 mL) and Et_2O (1.0 mL) was added at room temperature, and the resulting solution was stirred for 1 min. Then, LiHMDS (1.3 M in THF, 725 μL, 943 μmol) was added, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with aq. NH_4Cl and diluted with water. The separated aqueous phase was extracted with Et_2O (x1) and CH_2Cl_2 (x2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:3) to afford lactone **29** (71.0 mg, 180 μmol, 96%). A white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (3H, m), 7.09 (2H, d, *J* = 8.0 Hz), 7.00 (1H, d, *J* = 7.6 Hz), 6.59 (1H, d, *J* = 2.4 Hz), 6.01–5.91 (1H, m), 5.61 (1H, d, *J* = 7.6 Hz), 5.36 (1H, d, *J* = 18.4 Hz), 5.35 (1H, d, *J* = 10.4 Hz), 5.31 (1H, s), 5.27 (1H, d, *J* = 10.4 Hz), 4.90 (1H, d, *J* = 10.4 Hz), 4.68 (1H, dd, *J* = 4.0, 3.4 Hz), 4.20–4.10 (2H, m), 3.91 (1H, dd, *J* = 13.4, 6.0 Hz), 3.43 (1H, dd, *J* = 14.0, 3.4 Hz), 3.29 (1H, dd, *J* = 14.0, 4.0 Hz), 2.53 (1H, dd, *J* = 15.2, 6.0 Hz), 1.01 (1H, dd, *J* = 13.4, 13.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.9, 164.9, 163.6, 153.3, 136.9, 134.5, 133.4, 130.0, 128.3, 127.1, 117.6, 115.4, 107.8, 73.5, 70.4, 66.3, 60.0, 57.0, 36.9, 31.8; IR (film): 3028, 2925, 2867, 1687, 1667, 1604, 1454, 1350, 1327, 1292, 1204, 1078, 1051, 940, 930, 864, 820, 758, 736 cm^{-1}; $[\alpha]_D^{26}$ = −279 (*c* = 0.445, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{23}N_2O_5$ [M+H$^+$] 395.1601, found 395.1605.

*4.36 Dithiodiketopiperazine **30***

To a solution of lactone **29** (138 mg, 350 μmol) in CH_2Cl_2 (750 μL) and EtOH (500 μL) was added $CeCl_3 \cdot 7H_2O$ (381 mg) in EtOH (2.0 mL) at −78 °C. After stirring for 10 min, $NaBH_4$ in EtOH (22.0 mg, 582 μmol in 550 μL) was added at −78 °C, and the mixture was stirred at −78 °C for 1.6 h. The reaction was quenched with aq. NH_4Cl solution at room temperature. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:3) to afford allyl alcohol **30** (126 mg, 318 μmol, 91%). A white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.23 (3H, m), 7.08 (2H, d, *J* = 6.4 Hz), 6.27 (1H, dd, *J* = 2.2, 2.2 Hz), 6.13 (1H, dd, *J* = 8.0, 2.4 Hz), 6.00–5.90 (1H, m), 5.42 (1H, d, *J* = 10.8 Hz), 5.36 (1H, d, *J* = 17.2 Hz), 5.26 (1H, d, *J* = 10.0 Hz), 5.07 (1H, d, *J* = 3.6 Hz), 4.88 (1H, s), 4.87 (1H, d, *J* = 10.8 Hz), 4.64 (1H, dd, *J* = 3.0, 4.2 Hz), 4.52 (1H, d, *J* = 7.6 Hz), 4.20–4.17 (1H, m), 4.14 (1H, d, *J* = 5.8 Hz), 4.13 (1H, d, *J* = 5.8 Hz), 3.91 (1H, dd, *J* = 13.0, 5.8 Hz), 3.40 (1H, dd, *J* = 13.8, 3.0 Hz), 3.27 (1H, dd, *J* = 13.8, 4.2 Hz), 2.36 (1H, dd, *J* = 13.6, 5.8 Hz), 0.80 (1H, dd, *J* = 13.6, 13.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 165.1, 138.0, 137.0, 134.2, 133.4, 130.2, 128.7, 127.7, 118.1, 109.8, 109.7, 73.2, 70.5, 69.1, 64.1, 59.8, 56.3, 37.0, 33.7; IR (film): 3369, 3011, 2942, 2863, 1661, 1453, 1344, 1296, 1193, 1133, 1078, 1058, 930, 759, 756, 730, 704, 578 cm^{-1}; $[\alpha]_D^{25}$ = −229 (*c* = 1.04, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{24}N_2NaO_5$ [M+Na$^+$] 419.1577, found 419.1564.

*4.37 Dithiodiketopiperazine **31***

To a suspension of sulfur S_8 (63.6 mg, 247 μmol) in Et_2O (1.0 mL) was added LiHMDS (1.3 M in THF, 725 μL, 943 μmol) at room temperature. After stirring for 5 min, diketopiperazine **30** (18.6 mg, 47.0 μmol) in a mixture of THF (2.0 mL) and Et_2O (1.0 mL) was added at room temperature, and the resulting solution was stirred for 1 min. Then, LiHMDS (1.3 M in THF, 725 μL, 943 μmol) was added, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with aq. NH_4Cl and diluted with water. The separated aqueous phase was extracted with Et_2O (x1) and CH_2Cl_2 (x2). The combined organic

and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 16:1 x2, then hexanes:CH_2Cl_2 = 3:5) to afford the mixture of bridged polysulfides. To a solution of the polysulfides in a mixture of THF (3.2 mL) and EtOH (3.2 mL) was added $NaBH_4$ (36.5 mg, 965 μmol) at 0 °C. After stirred for 8 min at room temperature, MeI (1.60 mL, 25.6 mmol) was added at 0 ℃, and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched by aq. NH_4Cl, and the separated aqueous phase was extracted with Et_2O (x1) and CH_2Cl_2 (x2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 16:1, then hexanes:EtOAc = 2:1) to afford bis-(methylthio) diketopiperazine **31** (18.3 mg, 30.3 μmol, 65% 2 steps from **30**). A white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.24 (3H, m), 7.15–7.12 (2H, m), 6.31 (1H, m), 6.17 (1H, dd, *J* = 8.4, 2.4 Hz), 6.03–5.93 (1H, m), 5.40–5.34 (1H, m), 5.53 (1H, d, *J* = 9.6 Hz), 5.24–5.22 (2H, m), 5.12 (1H, d, *J* = 9.6 Hz), 4.91 (1H, dd, *J* = 8.2, 1.8 Hz), 4.58–4.55 (1H, m), 4.42 (1H, d, *J* = 8.0 Hz), 4.30–4.28 (2H, m), 3.48 (1H, d, *J* = 13.2 Hz), 3.23 (1H, d, *J* = 13.2 Hz), 2.55 (1H, d, *J* = 15.2 Hz), 2.29 (3H, s), 2.53 (3H, s), 1.59 (1H, d, *J* = 15.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 166.1, 137.6, 137.2, 134.3, 133.6, 130.7, 128.6, 127.9, 117.2, 110.8, 107.1, 77.5, 73.4, 72.2, 71.3, 67.7, 65.4, 45.0, 38.1, 15.2, 14.0; IR (film): 3370, 3008, 2920, 2852, 1662, 1435, 1416, 1380, 1191, 1136, 1083, 1056, 1050, 772, 756, 704 cm^{-1}; $[\alpha]_D^{25}$ = −123 (*c* = 0.619, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{24}H_{28}N_2NaO_5S_2$ [M+Na$^+$] 511.1332, found 511.1303.

*4.38 (–)-Emestrin H (**5**)*

To a solid of bis-(methylthio) diketopiperazine **31** (6.65 mg, 13.6 μmol) was added $Pd(PPh_3)_4$ (27.2 mM solution in CH_2Cl_2, 25.0 μL 0.682 μmol). The mixture was concentrated under reduced pressure give a pale brown solid. To the solid was added 1,3-dimethylbarbituric acid (4.26 mg, 27.3 μmol) in MeOH (136 μL), and the mixture was stirred for 16.5 h at 40 °C. The reaction mixture was diluted with MeOH (68 μL) and stirred for 2 h. Then, the mixture was cooled to room temperature and diluted with MeOH (200 μL). To the mixture was added $NaHCO_3$ (40.0 mg), and the resulting suspension was stirred for 25 min at room temperature and diluted with CH_2Cl_2 and H_2O. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 3:1 x3) to afford (–)-emestrin H (**5**) (4.46 mg, 10.6 μmol, 78%) and diketopiperazine **30** (1.15 mg, 17%). A white solid; mp: 86.0–87.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34–7.30 (3H, m), 7.19 (2H, d, *J* = 6.6 Hz), 6.36 (1H, s), 6.19 (1H, dd, *J* = 1.8, 8.4 Hz), 6.05 (1H, s), 5.12 (1H, d, *J* = 4.8 Hz), 4.93 (1H, d, *J* = 8.4 Hz), 4.63–4.61 (1H, m), 4.55 (1H, d, *J* = 7.2 Hz), 3.64 (1H, d, *J* = 13.2 Hz), 3.02 (1H, d, *J* = 13.2 Hz), 2.63 (1H, d, *J* = 15.0 Hz), 2.41 (3H, s), 2.23 (3H, s), 1.88 (1H, d, *J* = 15.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.2, 165.4, 137.7, 137.4, 133.2, 130.7, 128.8, 128.1, 110.9, 107.4, 72.3, 68.5, 68.4, 64.9, 46.3, 38.9, 14.7, 14.3; IR (film): 3361, 3224, 3062, 3008, 2918, 2848, 2360, 2341, 1675, 1638, 1409, 1340, 1193, 1139, 1123, 1047, 756, 730, 704, 581, 564 cm^{-1}; $[\alpha]_D^{28}$ = −203 (*c* = 0.234, MeOH) (Lit. $[\alpha]_D^{25}$ = –97 (*c* = 0.071, MeOH)); HRMS (ESI) *m/z*: calcd. for $C_{20}H_{22}N_2NaO_4S_2$ [M+Na$^+$] 441.0913, found 441.0907. The spectral data were identical with those reported in the literature [14].

*4.39 (–)-Asteroxepin (**4**)*

and DMAP (1.23 mg, 10.1 μmol) in pyridine (120 μL) was added Ac_2O in pyridine (0.127 M, 100 μL, 12.7 μmol) at room temperature. After stirring for 50 min at room temperature, additional Ac_2O (13.0 μL, 138 μmol) was added, and the mixture was stirred for 35 min. Then, additional DMAP (5.69 mg, 46.6 μmol) was added, and the mixture was stirred for 45 min at room temperature. The reaction was diluted with CH_2Cl_2, and quenched with aq. 1 M HCl. The separated aqueous phase was extracted with CH_2Cl_2 (x5), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 7:11) to afford (–)-asteroxepin (**4**) (2.60 mg, 5.65 μmol, 89%). A white solid; mp: 189.6–190.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32–7.27 (3H, m), 7.20–7.18 (2H, m), 6.41 (1H, dd, *J* = 2.4, 2.4 Hz), 6.29 (1H, dd, *J* = 8.4, 3.0 Hz), 6.00 (1H, br s), 5.88 (1H, ddd, *J* = 7.5, 2.1, 2.1), 4.89 (1H, br. d, *J* = 7.8 Hz), 4.68 (1H, dd, *J* = 8.4, 1.2 Hz), 3.66 (1H, d, *J* = 13.8 Hz), 2.97 (1H, d, *J* = 13.8 Hz), 2.64 (1H, d, *J* = 15.0 Hz), 2.36 (3H, s), 2.20 (3H, s), 2.13 (3H, s), 1.82 (1H, ddd, *J* = 15.3, 2.1, 2.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1, 165.6, 164.4, 139.7, 137.3, 133.5, 130.9, 128.7, 127.9, 109.1, 105.5, 71.4, 69.9, 68.0, 61.7, 46.4, 39.6, 21.2, 14.5, 14.0; $[\alpha]_D^{27}$ = −178 (c = 0.556, $CHCl_3$) (Lit. $[\alpha]_D$ = −102 (*c* = 0.4, $CHCl_3$)); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{24}N_2NaO_5S_2$ [M+Na$^+$] 483.1019, found 483.0996. The spectral data were identical with those reported in the literature [13].

*4.40 AllomCl (**26**)* [20]

To a mixture of allyl alcohol (40.0 mL, 0.588 mmol) and paraformaldehyde (19.0 g, 0.633 mol) was added anhydrous hydrogen chloride generated from H_2SO_4 and NaCl at room temperature. After stirred for 30 min at room temperature, the mixture was heated by oil bath at 150 °C for 2 h. The resulting mixture was diluted with hexanes, dried over magnesium sulfate, and the hexanes were removed under reduced pressure. The crude material was distilled from anhydrous calcium chloride (37.0 °C/67.5 mmHg) to afford AllomCl (**26**) (25.0 g, 0.234 mol, 40%) as colorless oil.

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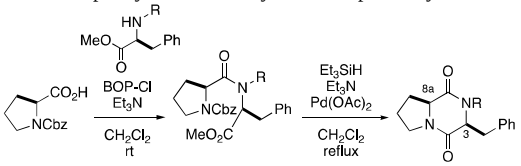
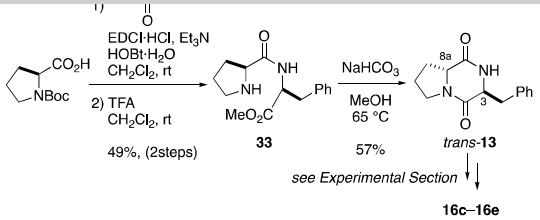
16. Compounds **16a** and **16b** with C3 (*S*) and C8a (*S*) stereochemistries were synthesized by the stepwise condensation of *N*-Cbz-L-proline and *N*-PMB-L-phenylalanine methyl ester or *N*-2,4-DMB-phenylalanine methyl ester, respectively.



32a: R = PMB, 77%
32b: R = 2,4-DMB, 47%
16a, 75%
16b, 91%

17. Compounds **16c–e** were synthesized from *trans*-**13** with C3 (*S*) and C8a (*R*) stereochemistries, which was prepared by the stepwise condensation of *N*-Boc-L-proline and L-phenylalanine methyl ester. During the intramolecular condensation step, the C8a (*S*) stereochemistry was completely isomerized to give *trans*-**13** with C8a (*R*) stereochemistry.



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Total Syntheses of (–)-emestrin H and (–)-asteroxepin

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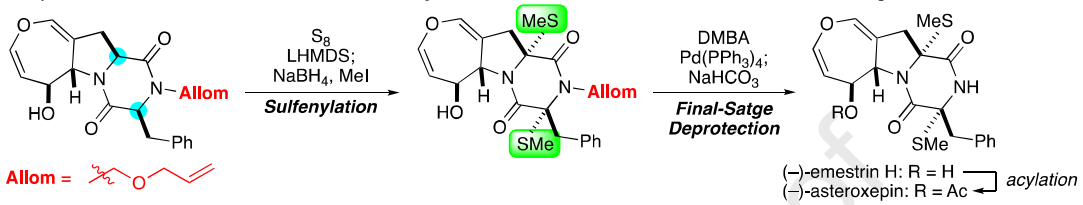
Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan



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Total syntheses of (–)-emestrin H and (–)-asteroxepin

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Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

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ABSTRACT

First total syntheses of (–)-emestrin H and (–)-asteroxepin are described. To find the appropriate protecting group on the amide nitrogen of the diketopiperazine core, we conducted model studies using a simple diketopiperazine derivative. As a result, allyloxymethyl (Allom) group was the most suitable protecting group, which tolerated Nicolaou's sulfenylation conditions, and was easily cleavable under the mild conditions using $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid leaving methylthioethers intact. The general utility of Allom group for protection of amides was studied using simple substrates. Finally, the effectiveness of Allom group was proved by the accomplishment of the first total synthesis of (–)-emestrin H. Allom group was robust enough during installation of two methylthioethers to the diketopiperazine core and easily removed at the final step. The first total synthesis of (–)-asteroxepin was also completed by acylation of (–)-emestrin H.

1. Introduction

Dithiodiketopiperazine alkaloids bearing the sulfur-containing diketopiperazine as a core structure have attracted attention due to their structural diversity and fascinating biological activities [1,2]. Among them, compounds bearing the 4,5-dihydrooxepine ring, such as (–)-acetylaranotin (**1**) [3], (+)-MPC1001B (**7**) [4], and (–)-acetylapoaranotin (**6**) [5], have been challenging synthetic targets and a lot of effort has been made to synthesize these compounds [6,7]. Reisman *et al.* reported the first innovative total synthesis of (–)-acetylaranotin (**1**) in 2012 [8], followed by the first total synthesis of (–)-acetylapoaranotin (**6**) [10]. We also focused on this class of compounds, reporting the second total synthesis of **1** just after Reisman *et al.* in 2012 [9]. Using the synthetic protocol established during the synthetic studies on **1**, which was based on the characteristic proline-fused 4,5-dihydrooxepine ring, we successfully performed the first total synthesis of (+)-MPC1001B (**7**) [11] and determined the structure of (–)-SCH64874 (**3**) and hirsutellomycin (**8**) via semi-synthesis [12]. Despite these synthetic developments over the last decade, the total syntheses of (–)-asteroxepin (**4**) [13] and (–)-emestrin H (**5**) [14] bearing the NH-free diketopiperazine core have not been reported so far.

Our preliminary model studies toward **4** and **5** revealed that the enolate-mediated introduction of two methylthioethers reported by Nicolaou *et al.* [15] was unsuccessful for the unprotected diketopiperazine **13** due to the competitive deprotonation of the unprotected N–H proton (Scheme 1b). Therefore, the major challenge toward the synthesis of **4** and **5** ~~was the~~ selection of the appropriate protecting group for the diketopiperazine ring's NH group. The ideal protecting group (PG in Scheme 1a) should be robust enough to tolerate the strong basic conditions during the introduction of the two-methylthioethers. Moreover, it should be easily and chemoselectively cleaved under the particularly mild conditions in the final stage of the total synthesis without affecting the base-, nucleophile-, and oxidant-sensitive methylthioethers and the acid-sensitive dihydrooxepin structure. However, compared to the many available protecting groups for amines, there are limited choices for amides, especially for diketopiperazines. In

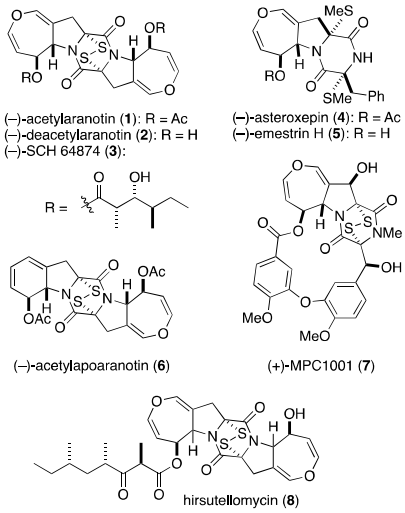
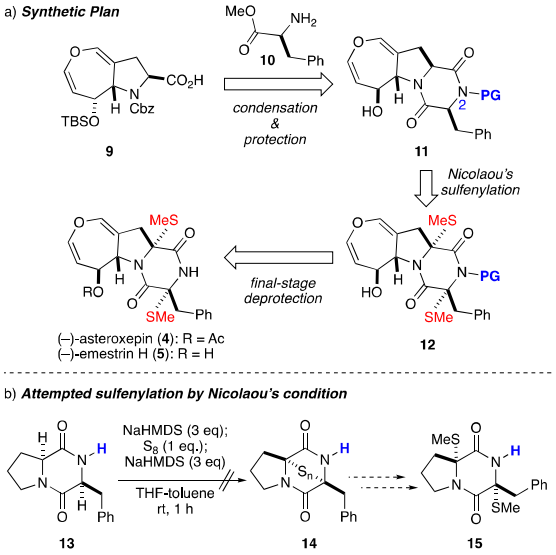


Fig. 1. Dithiodiketopiperazine alkaloids

* Corresponding author. E-mail: tokuyama@mail.pharm.tohoku.ac.jp

functionalized NH-free diketopiperazines and found that the less common allyloxymethyl (Allom) group, which only have been used for a protection of the *N*-3 position in xanthine and the imidazole nitrogen in histidine was the most suitable protecting group [19]. Its efficiency was further demonstrated by the first total synthesis of (–)-asteroxepin (**4**) and (–)-emestrin H (**5**).

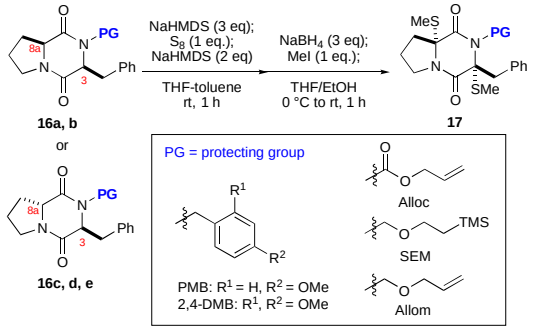


Scheme 1. Synthetic plan and preliminary results.

2. Results and discussion

To identify the most suitable protecting group that would fulfill the abovementioned requirements, we prepared a series of *N*-protected diketopiperazines (**16a–e**) following a conventional method [16,17], which were then subjected to the sulfenylation conditions established by Nicolaou *et al*. (Table 1) [15]. Among the protecting groups in substrates **16a–e**, stable benzylic protecting groups, such as *p*-methoxybenzyl (PMB) in **16a** or 2,4-dimethoxybenzyl (2,4-DMB) in **16b**, were not affected by the sulfenylation conditions, providing dithiodiketopiperazines **17a** and **17b**, respectively, in moderate yields (Table 1, entries 1

Table 1
Protecting groups and introduction of the methylthioether.



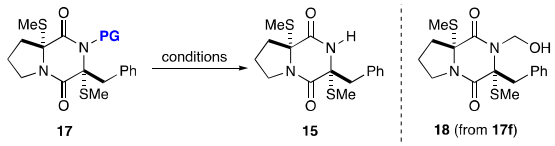
entry	substrate	PG	**17** (%)[c,d]
1	**16a**[a]	PMB	44
2	**16b**[a]	2,4-DMB	57
3	**16c**[b]	Alloc	decomposition
4	**16d**[b]	SEM	68
5	**16e**[b]	Allom	50

[a]C3 (*S*), C8a (*S*) isomer. [b]C3 (*S*), C8a (*R*) isomer. [c]Isolated yield. [d]Obtained as single diastereomer.

16d with the trimethylsilylethoxymethyl (SEM) group and **16e** with the Allom group, afforded the corresponding dimethylthio compounds (**17d** and **17e**) in good yields (Table 1, entries 4 and 5). However, analogue **16c**, protected as urethane with an allyloxycarbonyl group (Alloc), afforded a complex mixture under the same sulfenylation conditions (Table 1, entry 3).

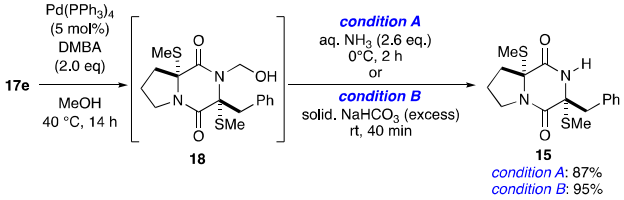
The deprotection of the bis(methylthio) products **17a**, **17b**, **17d**, and **17e** was examined under the most frequently used deprotection conditions for each protecting group (Table 2). Analogues **17a** and **17b** bearing PMB and 2,4-DMB groups were decomposed upon treatment with ceric ammonium nitrate (CAN) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), respectively (Table 2, entries 1 and 2). Moreover, the SEM group in **17d** was stable upon treatment with HF/pyridine and **17d** was recovered (Table 2, entry 3), whereas the use of TBAF in THF/DMF decomposed **17d** (Table 2, entry 4). In contrast to these unsuccessful entries, the Allom group in **17e** could be smoothly removed by a combination of $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid (DMBA) in MeOH yielding **15** in 56% yield, while a substantial amount of the hemiaminal intermediate **18** was also obtained (Table 2, entry 5) [18,19]. The subsequent *in situ* treatment of the reaction mixture with aq. NH_3 was effective in reducing the amount of **18**, affording **15** in 87% yield (Scheme 2). Furthermore, the addition of solid $NaHCO_3$ after the consumption of **17e** improved the yield of **15** to up to 95%.

Table 2
Deprotection conditions.



entry	**17**	reagents	temp.	Time (h)	Yield (%)[a]
1[b]	**17a**	CAN, CH_3CN/H_2O	rt	2	0
2[b]	**17b**	DDQ, CH_3CN/H_2O	60 °C	20	0
3[b]	**17d**	TBAF, THF/DMF	60 °C	1.8	0
4[c]	**17d**	HF/pyridine	60 °C	22	0
5[d]	**17e**	$Pd(PPh_3)_4$, DMBA, MeOH	30 °C	6	56

[a]isolated yield. [b]Decomposition. [c]**17d** was completely recovered. [d]Reaction conditions: **17** (1.0 eq), $Pd(PPh_3)_4$ (45 mol%), DMBA (5.5 eq), MeOH (0.1 M), 30 °C, 6 h. [e]The hemiaminal intermediate **18** was obtained in 38% yield.

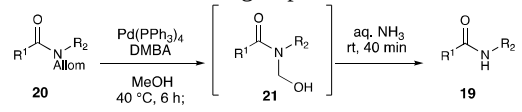


Scheme 2. Removal of the Allom group.

The feasibility of the removal of the Allom protecting group from secondary amides was investigated using a series of *N*-Allom secondary amides (**20**) (see Experimental Section for the preparation and additional data) (Table 3 and Scheme 3). The treatment of the *N*-Allom benzamides **20a–e** and γ-lactam **20f** with $Pd(PPh_3)_4$ and DMBA in MeOH smoothly provided the hemiaminal intermediate **21**, which was converted into amides **19a–e** and **19f**, respectively, in good yields using aq. NH_3 (Table 3, entries 1–6). In contrast, the reaction of *N*-Allom aliphatic amides **20g** under the Pd/*N*,*N*-

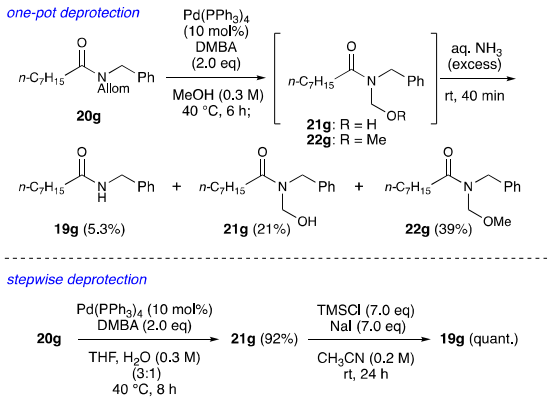
dim … was **21g** (21%), and *N*-MOM amides **22g** (39%) due to the exchange of the OH group in intermediate **21g** with the methoxy group of methanol (Scheme 3). This side reaction was overcome by performing the deprotection of **20g** in THF and H_2O, providing the hemiaminal intermediates **21g**, which were then converted to amides **19g** in good yields using trimethylsilyl iodide (TMSI).

Table 3.
One-pot Removal of the Allom group.



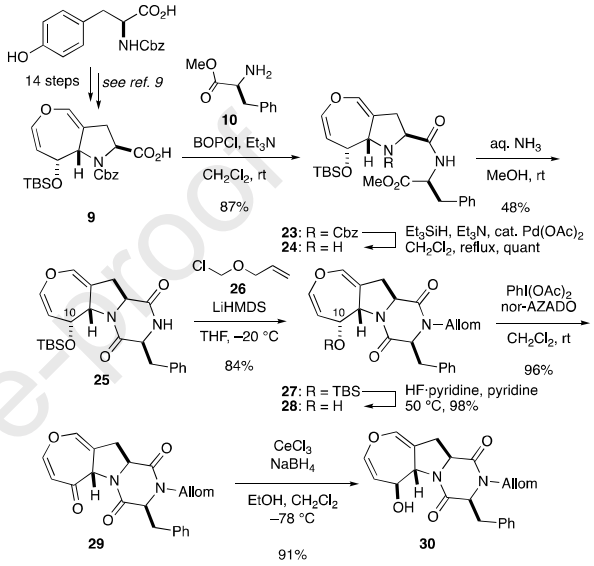
entry	substrate	products	yield (%)
1	**20a**	**19a**	98
2	**20b**	**19b**	86
3	**20c**	**19c**	47
4	**20d**	**19d**	81
5	**20e**	**19e**	78
6	**20f**	**19f**	70

Reaction conditions: **20** (1.0 eq), $Pd(PPh_3)_4$ (10 mol%), DMBA (2.0 eq), MeOH (0.3 M), 40 °C, 6 h, then aq. NH_3 (excess). The yields refer to the isolated products.



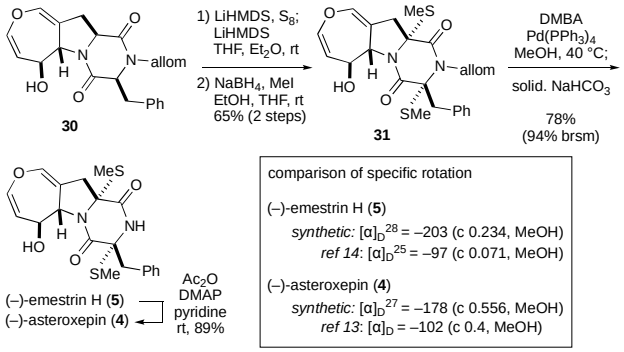
Scheme 3. Stepwise Removal of the Allom group.

The applicability of the Allom protecting group was fully demonstrated by the first total syntheses of (–)-emestrin H (**5**) and (–)-asteroxepin (**4**). The proline-fused dihydrooxepine derivative **9**, which was prepared according to our previously established protocol in the total synthesis of (–)-acetylaranotin (**1**) [9], was first condensed with the (*S*)-phenylalanine methyl … then removed under transfer hydrogenation conditions and the formation of the tricyclic diketopiperazine derivative **25** was promoted upon treatment of the resulting aminoester with ammonium hydroxide. Subsequently, the Allom group was introduced using a combination of the allyloxymethyl chloride (AllomCl) **26** [20] and lithium hexamethyldisilazide (LiHMDS), which afforded the desired product **27** in 84% yield. After desilylation, the stereochemistry of the C-10 hydroxyl group was inverted through a stepwise process [9], which included an oxidation of **28** to ketone using $PhI(OAc)_2$ and 9-azanoradamantane *N*-oxyl (nor-AZADO) [21] and a subsequent Luche reduction, which gave the desired alcohol **30** as the sole isomer.



Scheme 4. Preparation of diketopiperazine 30.

The final steps toward the synthesis of (–)-emestrin H (**5**) and (–)-asteroxepin (**4**) including the crucial introduction of the two methylthioethers and the removal of the Allom protecting group are depicted in Scheme 5. According to the model study (*vide supra*), diketopiperazine **30** was treated with a mixture of excess LiHMDS and S_8 to form an epipolysulfide. Its reduction to the corresponding dithiol with $NaBH_4$ and the subsequent methylation afforded the bis(methylthio) derivative **31** in 65% yield over two steps from **30**. Finally, the Allom group was removed under the optimized conditions affording (–)-emestrin H (**5**) in 78% yield, which was further acetylated to give (–)-asteroxepin (**4**). All properties of synthetic (–)-emestrin H (**5**) and (–)-asteroxepin (**4**) were identical with those reported except magnitude of specific rotations proving the reported absolute stereochemistry of **4** and **5** by this total synthesis [22].



Scheme 5. Final steps of the total syntheses of (–)-emestrin H (5) and (–)-asteroxepin (4).

In conclusion, the total syntheses of (–)-emestrin H (**5**) and (–)-asteroxepin (**4**) have been accomplished for the first time. Their preparation was successful owing to the suitability of the Allom group as protecting group for the amide nitrogen of the highly functionalized dithio-diketopiperazine intermediate. This protecting group could be easily cleaved even in the presence of the acid-sensitive dihydrooxepin structure and the dimethylthioethers, which are sensitive to bases, nucleophiles, and oxidants. Thus, this study demonstrated the application potential of the Allom group not only for the synthesis of other *N*-unprotected diketopiperazine alkaloids, but also for the preparation of various functionalized amides.

4. Experimental section

4.1 General method

Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. Anhydrous THF, Et_2O, CH_2Cl_2, toluene, DMF, and MeCN were purchased from commercial suppliers. Anhydrous MeOH was dried and distilled according to the standard protocols. All reactions were carried out under Ar atmosphere unless otherwise mentioned. Flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40–50 μm). Preparative TLC and analytical TLC was performed on Merck 60 F254 glass plates precoated with a 0.25 mm thickness of silica gel. NMR spectra were recorded on a JNM-AL400 spectrometer and a JEOL ECA600 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm, relative to the central line of a triplet at 77.0 ppm for $CDCl_3$ or a septet at 39.5 ppm for DMSO-d_6. IR spectra were measured on a SHIMADZU FTIR-8300 spectrometer. Mass spectra were recorded on a Bruker micrOTOF (ESI). Optical rotations were measured on a Horiba SEPA-300 highly sensitive polarimeter. Melting point determinations were performed by using a Yanaco MP-500 instrument. Compounds **9** [9], **19a**–**e** [25], **19f** [26], and **19g** [25] were prepared according to the procedures reported in references.

*4.2 Diketopiperazine **16a***

To a solution of *N*-Cbz-L-proline (3.68 g, 14.8mmol) and *N*-PMB-L-phenylalanine methyl ester (4.24 g, 14.2 mmol) in Et_3N and CH_2Cl_2 (5 mL and 30 mL) was added BOP-Cl (3.74 g, 14.7 mmol) at room temperature. After stirring for 24.5 h at room temperature, additional BOP-Cl (1.96 g, 7.70 mmol) was added, and the reaction mixture was stirred for 2.5 h. The reaction was quenched with sat. aq. $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with 1 M aq. HCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:1) to afford amide **32a** (5.80 g, 10.9 mmol, 77%). To a suspension of amide **32a** (5.80 g, 10.9 mmol) and $Pd(OAc)_2$ (983 mg, 4.38 mmol) in CH_2Cl_2 (55.0 mL) was added Et_3N (3.08 mL, 21.9 mmol) at room temperature. After stirring at reflux for 5 min, Et_3SiH (8.74 mL, 54.7 mmol) was added and the mixture was stirred at reflux for 3.5 h. The reaction mixture was diluted with CH_2Cl_2 and the reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (EtOAc) to afford diketopiperazine **16a** (3.00 g, 8.23 mmol, 75%). A white foam; The spectral data of **16a** were identical with those reported in the literature [23].

*4.3 Diketopiperazine **16b***

To a solution of *N*-Cbz-L-proline (1.06 g, 4.25 mmol), *N*-2,4-DMB-L-phenylalanine methyl ester (1.15 g, 3.49 mmol) in Et_3N and CH_2Cl_2 (2.0 mL and 20.0 mL) was added BOP-Cl (1.87 g, 7.35 mmol) at room temperature. After stirring for 20 h at room temperature, the reaction was quenched with 1 M aq. HCl and the resulting mixture was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 3:2 to 6:5) to afford amide **32b** (846 mg, 1.51 mmol, 47%). To a suspension of amide **32b** (846 mg, 1.51 mmol) and $Pd(OAc)_2$ (135 mg, 601 μmol) in CH_2Cl_2 (10.0 mL) was added Et_3N (425 μL, 3.02 mmol) at room temperature. After stirring at reflux for 7 min, Et_3SiH (1.20 mL, 7.51 mmol) was added and the mixture was stirred at reflux for 3.5 h. The reaction mixture was diluted with CH_2Cl_2 and the reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (EtOAc) to afford diketopiperazine **16b** (540 mg, 1.37 mmol, 91%). A white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.20 (4H, m), 7.12–7.06 (2H, m), 6.48–6.43 (2H, m), 5.40 (1H, d, *J* = 14.8 Hz), 4.32 (1H, m), 4.25 (1H, d, *J* = 14.8 Hz), 3.84 (3H, s), 3.81 (3H, s), 3.72 (1H, dd, *J* = 12.0, 6.0 Hz), 3.68–3.61 (1H, m), 3.36–3.27 (2H, m), 3.14–3.07 (1H, m), 1.91–1.81 (1H, m), 1.60–1.42 (2H, m), 0.14–0.01 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 163.9, 160.7, 158.7, 135.1, 131.7, 130.0, 128.3, 127.1, 115.9, 104.4, 98.3, 60.3, 59.0, 55.3, 55.3, 44.0, 40.6, 36.4, 28.4, 20.9; IR (film): 2992, 2952, 2944, 2891, 1656, 1612, 1587, 1508, 1456, 1298, 1289, 1261, 1208, 1184, 1157, 1033, 751, 703 cm^{-1}; $[\alpha]_D^{31}$ = −116 (*c* = 0.66, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{23}H_{26}N_2NaO_4$ [M^++Na] 417.1785, Found 417.1769.

*4.4 Amide **33***

To a solution of *N*-Boc-L-proline (10.8 g, 50.0 mmol) and L-phenylalanine methyl ester (8.95 g, 50.0 mmol) in CH_2Cl_2 (200 mL) were added Et_3N (27.9 mL, 200 mmol), HOBt (6.99 g, 51.7 mmol), and EDCI/HCl (9.91 g, 51.7 mmol) at room temperature. After stirred for 29.5 h at room temperature, the organic phase was washed with 1 M aq. HCl (x3) and sat. aq. $NaHCO_3$ (x2). The resulting organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was used for the next reaction without further purification. To a solution of the crude material in CH_2Cl_2 (120 mL) was added TFA (15 mL) at room temperature. After stirred for 20 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (150 mL) and neutralized by sat. aq. $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (x3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude material, which was purified by flash column chromatography (CH_2Cl_2:MeOH = 10:1) to afford amine amide **33** (6.76 g, 24.5 mmol, 49%, 2 steps from *N*-Boc-L-

prol ... Ac with those reported in the literature [24].

*4.5 Diketopiperazine trans-**13***

To a solution of amide **33** (6.76 g, 24.5 mmol) in MeOH (400 mL) was added $NaHCO_3$ (20.0 g, 85.3 mmol) at room temperature. After stirring for 22.5 h at 65 °C, MeOH was removed under reduced pressure. The residue was diluted with CH_2Cl_2 and filtered through a pad of Celite®. The filtrate was washed with H_2O, and the aqueous phase was extracted with CH_2Cl_2 (x2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by crystallization from EtOAc to afford diketopiperazine *trans*-**13** (3.43 g, 14.1 mmol, 57%). The mother liquor was concentrated *in vacuo* and the second crop was crystallized from EtOAc to afford diketopiperazine *trans*-**13** (643 mg, 2.64 mmol, 11%). A white solid.; mp: 153.5–154.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.20 (5H, m), 6.31 (1H, s), 4.22 (1H, ddd, *J* = 6.6, 4.0, 3.8 Hz), 3.63 (1H, ddd, *J* = 12.4, 8.5, 8.5 Hz), 3.40 (1H, ddd, *J* = 12.4, 9.4, 3.0 Hz), 3.15 (1H, dd, *J* = 13.9, 6.6 Hz), 3.08 (1H, dd, *J* = 13.9, 4.0 Hz), 2.97 (1H, dd, *J* = 10.4, 6.4 Hz), 2.23–2.15 (1H, m), 1.98–1.90 (1H, m), 1.86–1.64 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 164.8, 135.3, 129.9, 128.5, 127.3, 58.7, 57.6, 44.9, 40.3, 28.8, 21.5; IR (film): 3483, 3238, 3063, 3029, 2981, 2953, 2931, 2886, 1664, 1496, 1454, 1336, 1307, 1296, 1206, 1186, 1115, 1106, 921, 732, 702, 593 cm^{-1}; $[\alpha]_D^{26}$ = +93.0 (*c* = 0.200, H_2O); HRMS (ESI) *m/z*: calcd. for $C_{14}H_{17}N_2O_2$ [M+H$^+$] 245.1285, found 245.1277. The spectral data of *trans*-**13** were identical with those reported in the literature [27].

*4.6 Diketopiperazine**16c***

To a solution of diketopiperazine *trans*-**13** (203 mg, 0.832 mmol) in THF (4.0 mL) was added LiHMDS (1.3 M solution in THF, 650 μL, 845 μmol) at 0 °C. After stirring for 4 min, Alloc-OSu (172 mg, 863 μmol) in THF (1.50 mL) was added at 0 °C. The resulting mixture was stirred for 35 min at room temperature. The reaction was quenched with sat. aq. NH_4Cl, and the resulting mixture was diluted by water. The separated aqueous phase was extracted with CH_2Cl_2 (x3), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (CH_2Cl_2:EtOAc = 5:1 to 3:1) to afford diketopiperazine **16c** (248 mg, 789 μmol, 95%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.26 (3H, m), 7.19–7.14 (2H, m), 5.99–5.87 (1H, m), 5.43 (1H, d, *J* = 17.2 Hz), 5.31 (1H, d, *J* = 10.8 Hz), 5.01 (1H, ddd, *J* = 5.0, 5.0, 1.4 Hz), 4.75 (1H, ddd, *J* = 13.3, 5.8, 1.0 Hz), 4.69 (1H, ddd, *J* = 13.3, 5.6, 1.2 Hz), 3.60–3.50 (1H, m), 3.45–3.37 (1H, m), 3.33–3.22 (2H, m), 2.64 (1H, dd, *J* = 9.6, 6.8 Hz), 2.17–2.07 (1H, m), 1.96–1.79 (2H, m), 1.72–1.57 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 164.0, 151.8, 134.9, 130.7, 129.9, 128.6, 127.5, 119.4, 67.9, 62.3, 58.6, 44.8, 38.2, 29.1, 21.8; IR (film): 3086, 3062, 3028, 2983, 2953, 2885, 1782, 1731, 1672, 1455, 1384, 1270, 1231, 980, 763, 747, 703 cm^{-1}; $[\alpha]_D^{26}$ = +143 (*c* = 0.425, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{18}H_{20}N_2NaO_4$ [M+Na$^+$] 351.1315, Found 351.1319.

*4.7 Diketopiperazine**16d***

To a solution of diketopiperazine *trans*-**13** (1.10 g, 4.51 mmol) in dry DMF (10.0 mL) was added NaH (60% dispersion in mineral oil, 248 mg, 6.20 mmol) at room temperature. After stirring for 15 min, SEMCl (1.60 mL, 9.03 mmol) was added at room temperature, and the resulting mixture was stirred at 60 °C for 18 h. The reaction was quenched with sat. aq. NH_4Cl at room and washed with water (x5) and brine (x1). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:3) to afford diketopiperazine **16d** (1.33 g, 3.55 mmol, 79%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.26 (3H, m), 7.18–7.15 (2H, m), 5.13 (1H, d, *J* = 10.4 Hz), 4.53 (1H, d, *J* = 10.4 Hz), 4.42 (1H, dd, *J* = 5.2, 4.9 Hz), 3.61–3.52 (3H, m), 3.35 (1H, ddd, *J* = 12.1, 9.3, 2.9 Hz), 3.24 (1H, dd, *J* = 14.3, 5.2 Hz), 3.19 (1H, dd, *J* = 14.3, 4.9 Hz), 2.52 (1H, dd, *J* = 10.6, 6.6 Hz), 2.14–2.06 (1H, m), 1.92–1.84 (1H, m), 1.79–1.68 (1H, m), 1.69–1.53 (1H, m), 1.01–0.87 (2H, m), 0.01 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 164.7, 135.2, 129.9, 128.5, 127.5, 73.3, 66.3, 62.1, 57.6, 44.8, 37.6, 29.1, 21.8, 17.9, –1.5; IR (film): 2952, 2890, 1671, 1454, 1440, 1296, 1260, 1249, 1207, 1075, 1044, 860, 837, 749, 703 cm^{-1}; $[\alpha]_D^{25}$ = +55.0 (*c* = 2.71, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{20}H_{30}NaN_2O_3Si$ [M$^+$+Na] 397.1918, Found 397.1909.

*4.8 Diketopiperazine**16e***

To a solution of diketopiperazine *trans*-**13** (880 mg, 3.61 mmol) in dry THF (8.0 mL) was added NaH (60% dispersion in mineral oil, 181 mg, 4.53 mmol) at room temperature. After stirring for 50 min, AllomCl (**26**) [20] (750 μL, 7.23 mmol) was added at room temperature, and the mixture was stirred for 9.5 h at 50 °C. The reaction was quenched with sat. aq. NH4Cl solution at room temperature, and the aqueous phase was diluted by water, extracted with Et_2O (x1) and CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1, then EtOAc only) to afford diketopiperazine **16e** (946 mg, 3.01 mmol, 83%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.24 (3H, m), 7.19–7.14 (2H, m), 5.89 (1H, m), 5.29 (1H, ddd, *J* = 17.6, 1.2, 1.2, Hz), 5.19 (1H, d, *J* = 10.8 Hz), 5.14 (1H, d, *J* = 10.6 Hz), 4.58 (1H, d, *J* = 10.6 Hz), 4.43 (1H, dd, *J* = 4.7, 4.8 Hz), 4.10–3.98 (2H, m), 3.57 (1H, ddd, *J* = 12.3, 8.5, 8.5 Hz), 3.36 (1H, ddd, *J* = 12.3, 9.3, 2.9 Hz), 3.25 (1H, dd, *J* = 14.3, 4.8 Hz), 3.20 (1H, dd, *J* = 14.3, 4.7 Hz), 2.53 (1H, dd, *J* = 10.6, 6.6 Hz), 2.09 (1H, ddd, *J* = 12.0, 6.2, 6.2 Hz), 1.94-1.84 (1H, m), 1.81–1.69 (1H, m), 1.66–1.53 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 164.7, 135.3, 133.8, 129.9, 128.6, 127.5, 117.4, 73.6, 70.1, 62.4, 57.7, 44.9, 37.7, 29.0, 21.8; IR (film): 3028, 2979, 2951, 2883, 1668, 1453, 1440, 1344, 1296, 1261, 1207, 1072, 1057, 923, 748, 703 cm^{-1}; $[\alpha]_D^{26}$ = +60.0 (*c* = 4.41, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{18}H_{22}N_2NaO_3$ [M$^+$+Na] 337.1523, Found 337.1506.

*4.9 Dithiodiketopiperazine **17a** (General Procedure A)*

To a suspension of sulfur S_8 (264 mg, 1.03 mmol) in THF (5.0 mL) was added NaHMDS (0.6 M in toluene, 5.00 mL, 3.00 mmol) at room temperature. After stirring for 1 min, diketopiperazine **16a** (372 mg, 1.02 mmol) in THF (5.0 mL) was added, and the mixture was stirred for 1 min. Then, NaHMDS (0.6 M in toluene, 3.40 mL, 2.04 mmol) was added, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with sat. aq. NH_4Cl, and the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was used for the next reaction without further purification. To a solution of the crude material in THF (10.0 mL) and EtOH (10.0 mL) was added $NaBH_4$ (964 mg, 25.5 mmol) at 0 °C. After

sti m), added at 0 °C, and the resulting mixture was stirred for 19 h at room temperature. The reaction was quenched by sat. aq. NH_4Cl, and the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by flash column chromatography (hexanes:EtOAc = 12:5) to afford bis(metylthio) diketopiperazine **17a** (204 mg, 0.449 mmol, 44%, 2 steps from **16a**). A white solid; mp: 136.7–137.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (2H, d, *J* = 8.8 Hz), 7.31–7.22 (3H, m), 7.09 (2H, d, *J* = 6.0 Hz), 6.83 (2H, d, *J* = 8.8 Hz), 5.18 (1H, d, *J* = 14.4 Hz), 4.54 (1H, d, *J* = 14.4 Hz), 3.79 (3H, s), 3.66–3.48 (2H, m), 3.54 (1H, d, *J* = 13.6 Hz), 3.25 (1H, d, *J* = 13.6 Hz), 2.05-1.91 (2H, m), 2.01 (3H, s), 1.99 (3H, s), 1.58–1.49 (1H, m), 0.81–0.71 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 163.0, 158.6, 134.1, 130.2, 129.6, 128.4, 127.7, 113.3, 78.8, 69.9, 55.1, 46.7, 45.8, 44.1, 32.7, 18.5, 15.0, 14.0 (One signal is missing due to overlap.), IR (film): 2994, 2956, 2933, 2922, 1662, 1512, 1421, 1395, 1352, 1247, 1177, 1033, 756, 703 cm^{-1}; $[\alpha]_D^{25}$ = +0.89 (*c* 0.58, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{24}H_{28}N_2NaO_3S_2$ [M+Na$^+$] 479.1419, Found 479.1434.

*4.10 Dithiodiketopiperazine **17b***

According to the General Procedure A, diketopiperazine **16b** (301 mg, 0.763 mmol) were converted to bis-(methylthio) diketopiperazine **17b** (210 mg, 0.431 mmol, 57 %, 2 steps from **16b**). A white solid; mp: 186.3–186.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (1H, d, *J* = 8.5 Hz), 7.30–7.20 (3H, m), 7.11 (2H, d, *J* = 6.4 Hz), 6.48 (1H, d, *J* = 2.1 Hz), 6.41 (1H, d, *J* = 8.5, 2.1 Hz), 5.07 (1H, d, *J* = 15.8 Hz), 4.68 (1H, d, *J* = 15.8 Hz), 3.90 (3H, s), 3.79 (3H, s), 3.67–3.53 (2H, m), 3.55 (1H, d, *J* = 13.6 Hz), 3.33 (1H, d, *J* = 13.6 Hz), 2.14 (3H, s), 2.14 (3H, s), 2.10–1.94 (2H, m), 1.61–1.50 (1H, m), 0.86–0.73 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 162.9, 159.5, 157.2, 134.2, 130.1, 128.3, 127.5, 127.0, 118.5, 103.5, 98.2, 78.5, 69.7, 55.3, 55.2, 45.8, 44.1, 41.1, 32.5, 18.4, 15.2, 14.2; IR (film): 2998, 2959, 2936, 2921, 2835, 1662, 1616, 1590, 1508, 1455, 1439, 1420, 1396, 1361, 1300, 1261, 1208, 1156, 1120, 1036, 755, 703 cm^{-1}; $[\alpha]_D^{32}$ = +21.3 (*c* = 0.26, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{25}H_{30}N_2NaO_4S_2$ [M+Na$^+$] 509.1539, Found 509.1526.

*4.11 Dithiodiketopiperazine **17d***

According to the General Procedure A, diketopiperazine **16e** (456 mg, 1.22 mmol) were converted to bis-(methylthio) diketopiperazine **17d** (386 mg, 0.828 mmol, 68%, 2 steps from **16d**). A white solid; mp: 82.9–83.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.19 (3H, m), 7.12 (2H, dd, *J* = 7.8, 2.2 Hz), 5.48 (1H, d, *J* = 9.6 Hz), 5.06 (1H, d, *J* = 9.6 Hz), 3.79 (2H, t, *J* = 8.6 Hz), 3.50 (2H, dd, *J* = 9.2, 6.4 Hz), 3.46 (1H, d, *J* = 13.6 Hz), 3.18 (1H, d, *J* = 13.2 Hz), 2.26 (3H, s), 2.14 (3H, s), 2.12–2.04 (1H, m), 2.02–1.89 (1H, m), 1.55–1.46 (1H, m), 1.07–0.96 (2H, m), 0.93–0.84 (1H, m), 0.03 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 163.0, 134.3, 130.6, 128.2, 127.4, 77.3, 73.1, 69.5, 67.4, 45.7, 44.8, 32.7, 18.5, 18.4, 15.3, 14.0, –1.4; IR (film): 2952, 2920, 1669, 1454, 1438, 1416, 1385, 1362, 1248, 1083, 1057, 860, 836, 756, 703 cm^{-1}; $[\alpha]_D^{30}$ = −6.99 (*c* = 2.76, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{34}N_2NaO_3S_2Si$ [M+Na$^+$] 489.1672, Found 489.1649.

*4.12 Dithiodiketopiperazine **17e***

According to the General Procedure A, diketopiperazine **16e** (843 mg, 2.68 mmol) were converted to bis-(methylthio) diketopiperazine **17e** (539 mg, 1.33 mmol, 50% 2 steps from **16e**). A white solid; mp: 84.8–85.2 °C; ^{1}H NMR (400 MHz, 5.51 (1H, d, *J* = 9.8 Hz), 5.36 (1H, dd, *J* = 17.2, 1.6 Hz), 5.21 (1H, dd, *J* = 15.9, 1.8 Hz), 5.11 (1H, d, 9.8 Hz), 4.29 (2H, ddd, *J* = 5.5, 1.5, 1.5 Hz), 3.54–3.47 (2H, m), 3.47 (1H, d, *J* = 13.6 Hz), 3.18 (1H, d, *J* = 13.6 Hz), 2.26 (3H, s), 2.15 (3H, s), 2.14–2.04 (1H, m), 2.03–1.89 (1H, m), 1.58–1.46 (1H, m), 0.98–0.86 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 162.9, 134.4, 134.2, 130.6, 128.2, 127.4, 117.0, 77.3, 73.3, 71.2, 69.6, 45.7, 44.9, 32.8, 18.5, 15.2, 13.9; IR (film): 2952, 2920, 2896, 1669, 1438, 1416, 1385, 1362, 1248, 1083, 1057, 860, 836, 756, 703 cm^{-1}; $[\alpha]_D^{30}$ = −9.65 (*c* = 0.660, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{20}H_{26}N_2NaO_3S_2$ [M+Na$^+$] 429.1277, Found 429.1271.

*4.13 Dithiodiketopiperazine **15***

To a mixture of bis-(methylthio) diketopiperazine **17e** (52.9 mg, 130 μmol) and $Pd(PPh_3)_4$ (7.53 mg, 6.51 μmol) and 1,3-dimethylbarbituric acid (40.7 mg, 260 μmol) was added MeOH (1.3 mL) at room temperature. The resulting suspension was stirred for 14 h at 40 °C. The reaction mixture was cooled to room temperature before addition of excess $NaHCO_3$ (130 mg) and further stirred for 40 min at room temperature. The reaction mixture was diluted by water (1.0 mL), and the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried with anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1 to 1:1) to afford bis-(methylthio) diketopiperazine **15** (41.6 mg, 124 μmol, 95%). A white solid; mp: 159.9–160.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.85 (1H, s), 7.26–7.14 (5H, m), 3.48 (1H, d, *J* = 12.8 Hz), 3.46–3.26 (2H, m), 3.00 (1H, d, *J* = 12.8 Hz), 2.29 (3H, s), 2.11 (3H, s), 2.02 (1H, dd, *J* = 13.2, 7.2 Hz), 1.95–1.81 (1H, m), 1.63–1.52 (1H, m), 0.97 (1H, ddd, *J* = 9.3, 12.1, 12.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.6, 163.2, 134.9, 130.3, 127.8, 126.9, 69.6, 67.4, 44.9, 44.6, 33.7, 18.6, 14.0, 13.2; IR (film): 3211, 3096, 3087, 3062, 2987, 2961, 2922, 2896, 1676, 1659, 1406, 1208, 755, 705 cm^{-1}; $[\alpha]_D^{28}$ = −17.5 (*c* = 0.65, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{16}H_{20}N_2NaO_2S_2$ [M+Na$^+$] 359.0858, Found 359.0835.

*4.14 amide **20a** (General Procedure B)*

To a solution of amide **19a** (1.11 g, 5.26 mmol) and TBAI (195 mg, 0.527 mmol) in THF (21.0 mL) was added LiHMDS (1.3 M solution in THF, 4.46 mL, 5.80 mmol) at −40 °C. After stirring for 30 min, AllomCl (**26**) [20] (0.764 mL, 5.80 mmol) was added at –40 °C, and the mixture was stirred at −40 °C for 14 h. The reaction was quenched with sat. aq. NH_4Cl solution and the mixture was diluted by water. The aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 4:1) to afford amide **20a** (1.43 g, 5.08 mmol, 97%). A colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 7.48–7.42 (5H, m), 7.36–7.26 (5H, m), 5.82–5.75 (1H, m), 5.14 (1H, d, *J* = 17.6 Hz), 5.07 (1H, d, *J* = 10.4 Hz), 4.86–4.67 (4H, m), 3.84 (br, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 171.0, 137.2, 135.4, 134.0, 129.4, 128.0, 127.9, 127.1, 126.6, 126.5, 116.3, 77.0, 68.0, 48.1; IR (film): 3062, 3030, 2942, 2862, 1651, 1496, 1445, 1417, 1267, 1071, 1050, 699 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{19}NNaO_2$ [M+Na$^+$] 304.1308, found 304.1296.

*4.15 amide **20b***

According to the General Procedure B, amide **19b** (55.5 mg, 191 μmol) was converted to amide **20b** (51.6 mg, 143 μmol,

75% ... mg, δ 7.64–7.16 (2H, m), 7.47 (2H, d, *J* = 8.4 Hz), 7.34–7.26 (5H, m), 5.82–5.77 (1H, m), 5.16 (1H, d, *J* = 17.6 Hz), 5.09 (1H, d, *J* = 10.0 Hz), 3.86 (2H, br s); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 170.1, 137.0, 134.5, 133.9, 130.9, 128.7, 128.0, 127.2, 126.7, 122.9, 116.3, 77.0, 68.0, 48,3; IR (film): 3085, 3063, 3030, 2979, 2942, 2898, 2863, 1652, 1590, 1443, 1417, 1360, 1292, 1266, 1072, 1011, 932, 837, 754, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{18}BrNNaO_2$ [M+Na$^+$] 382.0413, Found 382.0403.

*4.16 amide **20c***

According to the General Procedure B, amide **19c** (62.4 mg, 2.43 μmol) was converted to amide **20c** (70.4 mg, 215mmol, 89%). A yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 8.26 (2H, d, *J* = 8.0 Hz), 7.73 (2H, d, *J* = 8.0 Hz), 7.35–7.25 (5H, m), 5.84–5.71 (1H, m), 5.16 (1H, d, *J* = 17.6 Hz), 5.08 (1H, d, *J* = 10.8 Hz), 4.70 (2H, br), 4.64 (2H, br), 3.86 (2H, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 147.9, 141.5, 136.8, 133.9, 128.1, 127.9, 127.3, 126.8, 123.2, 116.5, 68.1, 54.3, 48.5; IR (film): 3080, 3066, 3031, 2945, 2862, 1651, 1602, 1521, 1425, 1349, 1072, 732, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{18}N_2NaO_4$ [M+Na$^+$] 349.1159, Found 349.1140.

*4.17 amide **20d***

According to the General Procedure B, amide **19d** (60.3 mg, 250 μmol) was converted to amide **20d** (68.0 mg, 218 μmol, 87%). A colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 7.49–7.46 (2H, m), 7.35–7.25 (5H, m), 6.99–6.97 (2H, m), 5.86–5.76 (m, 1H), 5.19–5.14 (m, 1H), 5.11–5.08 (m, 1H), 4.69–4.68 (m, 4H), 3.89–3.86 (m, 2H), 3.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 170.8, 160.4, 137.4, 134.0, 128.6, 127.9, 127.4, 127.2, 126.6, 116.3, 113.4, 77.5, 67.9, 59.5, 48.2; IR (film) 1442, 1417, 1358, 1302, 1253, 1175, 1112, 1049, 933, 842, 766, 700, 598 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{19}H_{21}NNaO_3$ [M+Na$^+$] 334.1414, Found 334.1408.

*4.18 amide **20e***

According to the General Procedure B, amide **19e** (74.0 mg, 331 μmol) was converted to amide **20e** (92.1 mg, 314 μmol, 95%). A yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 7.45–7.42 (5H, m), 5.84–5.78 (1H, m), 5.18 (1H, d, *J* = 17.6 Hz), 5.09 (1H, d, *J* = 10.4 Hz), 4.69 (2H, br), 4.54 (2H, br), 3.86 (2H, br), 3.51 (4H, br), 3.26 (3H, br), 1.88–1.85 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 170.9, 135.8, 134.1, 129.1, 127.8, 126.4, 116.1, 95.6, 67.4, 64.8, 54.2, 42.8, 27.9 (One signal is missing due to overlap.); IR (film): 2933, 2883, 1651, 1446, 1419, 1404, 1271, 1147, 1112, 1043, 919, 724, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{23}NNaO_4$ [M+Na$^+$] 316.1519, Found 316.1516.

*4.19 amide **20f***

According to the General Procedure B, amide **19f** (40.5 mg, 251 mmol) was converted to amide **20f** (49.5 mg, 214 μmol, 85%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.21 (5H, m), 5.88–5.81 (1H, m), 5.25 (1H, d, *J* = 16.8 Hz), 5.17–5.12 (2H, m), 4.82 (m, 1H), 4.06 (1H, d, *J* = 10.8 Hz), 3.97–3.94 (m, 2H), 2.64–2.50 (3H, m), 1.99–1.95 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 140.5, 134.0, 128.8, 128.0, 126.5, 116.9, 70.0, 69.4, 60.4, 30.2, 28.1; IR (film): 3081, 3065, 3031, 2979, 2941, 2885, 1704, 1456, 1415, 1392, 1319, 1256, 1227, 1065, 932, 769, 703 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{17}NNaO_2$ [M+Na$^+$] 254.1151, Found 254.1147.

*4.20 amide **20g***

250 μmol) was converted to amide **20g** (71.7 mg, 236 μmol, 95%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.37–7.18 (5H, m), 5.94–5.82 (2H, m), 4.92 (0.7H, s), 4.67 (2H, s), 4.63 (1.3H, s), 4.31 (0.7, d, *J* = 5.2 Hz), 3.94 (1.3H, d, *J* = 6.0 Hz), 2.46 (1.3 H, t, *J* = 7.6 Hz), 2.33 (0.7H, 8.0 Hz), 1.71–1.63 (m, 2H), 1.32–1.35 (m, 8H), 0.88–0.84 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 174.8, 174.1, 137.8, 136.9, 134.3, 133.8, 128.8, 128.4, 128.1, 127.4, 127.2, 126.3, 117.6, 116.9, 76.8, 74.3, 69.5, 68.5, 49.2, 48.3, 33.32, 32.99, 31.63, 31.58, 29.3, 29.2, 29.00, 28.95, 25.3, 25.0, 22.53, 22.50, 14.0; IR (film): 3086, 3064, 3030, 2954, 2926, 2855, 1664, 1496, 1453, 1421, 1359, 1236, 1036, 991, 932, 732, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{19}H_{29}NNaO_2$ [M+Na$^+$] 326.2091, Found 326.2082.

*4.21 amide **19a** (General Procedure C)*

To a mixture of amide **20a** (56.0 mg, 199 μmol) and Pd(PPh_3)$_4$ (23.3 mg, 20.0 μmol) and 1,3-dimethylbarbituric acid (62.2 mg, 398 μmol) was added MeOH (0.67 mL) at room temperature. The resulting suspension was stirred for 6 h at 40 °C. The reaction mixture was cooled to room temperature before addition of excess aq. NH_3 (0.3 ml) and further stirred for 40 min at room temperature. Then, the reaction mixture was diluted by water (1.0 mL) and then the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 3:1) to afford amide **19a** (41.4 mg, 196 μmol, 98%).

*4.22 amide **19b***

According to the General Procedure C, amide **20b** (78.4 mg, 218 μmol) was converted to amide **19b** (54.1 mg, 186 μmol, 86%).

*4.23 amide **19c***

According to the General Procedure C, amide **20c** (37.8 mg, 116 μmol) was converted to amide **19c** (13.9 mg, 54.2 μmol, 47%).

*4.24 amide **19d***

According to the General Procedure C, amide **20c** (65.5 mg, 210 μmol) was converted to amide **19c** (40.9 mg, 170 μmol, 81%).

*4.25 amide **19e***

According to the General Procedure C, amide **20e** (66.7 mg, 227 μmol) was converted to amide **19e** (39.0 mg, 175 μmol, 78%).

*4.26 amide **19f***

According to the General Procedure C, amide **20f** (39.7 mg, 172 μmol) were converted to amide **19f** (19.3 mg, 120 μmol, 70%).

*4.27 hemiaminal **21g***

To a mixture of amide **20g** (20.9 mg, 68.8 μmol) and Pd(PPh_3)$_4$ (8.0 mg, 6.87 μmol) and 1,3-dimethylbarbituric acid (21.5 mg, 134 μmol) were added THF (0.17 mL) and MeOH (0.06 mL) at room temperature. After stirred for 8 h at 40 °C, the reaction was quenched with sat. aq. Na_2CO_3, and the aqueous phase was extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and

co ; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.49–7.28 (8.8H, m), 7.12–7.09 (1.2H, m), 6.48–6.37 (2.4H, m), 6.11 (0.6H, d, *J* = 8.4 Hz), 5.37–5.13 (3H, m), 5.05–4.76 (3H, m), 4.50 (1H, ddd, *J* = 8.4, 8.4, 2.8 Hz), 3.81 (1.2H, s), 3.72 (1.8H, s), 3.26–3.04 (3H, m), 2.76 (0.4H, d, *J* = 15.2 Hz), 2.64 (0.6H, d, *J* = 15.2 Hz), 0.940 (9H, s), 0.120 (3H, s), 0.054 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 171.6, 171.5, 171.4, 171.2, 154.7, 153.9, 145.5, 145.2, 136.1, 135.7, 135.4, 135.0, 129.4, 129.1, 128.5, 128.5, 128.4, 128.3, 128.1, 128.1, 127.9, 127.1, 127.0, 120.3, 118.7, 105.9, 105.5, 67.6, 67.3, 67.1, 65.9, 65.0, 64.4, 61.8, 61.4, 53.0, 52.5, 52.2, 52.1, 37.8, 37.7, 33.3, 32.0, 25.6, 17.8, −4.5, −4.6, −5.0, −5.1 (Five signals are missing due to overlap.); IR (film): 3325, 3031, 2953, 2928, 2895, 2855, 1746, 1713, 1639, 1526, 1437, 1408, 1350, 1318, 1252, 1210, 1142, 1113, 1085, 959, 836, 777, 748, 698 cm^{-1}; $[\alpha]_D^{27}$ = −175 (*c* = 1.20, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{33}H_{42}N_2NaO_7Si$ [M+Na$^+$] 629.2653, found 629.2624.

which was purified by silica gel column chromatography (hexanes:EtOAc = 5:1) to afford amide hemiaminal **21g** (16.6 mg, 63.2 μmol, 92%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.36–7.22 (5H, m), 4.86 (2H, br), 4.86–4.65 (2H, br), 3.69 (0.7H, br), 2.64–2.49 (0.9H, m), 2.31 (1.4H, t, *J* = 8.0 Hz), 1.71–1.61 (m, 2H), 1.25 (br, 8H), 0.88–0.84 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 175.9, 174.2, 138.0, 136.9, 128.9, 128.7, 128.1, 127.6, 127.5, 1 26.4, 72.2, 71.7, 51.5, 48.2, 33.4, 33.1, 31.7, 31.6, 29.4, 29.2, 29. 1, 29.0, 25.4, 24.9, 22.6, 14.0 (Two signals are missing due to overlap.); IR (film): 3371, 3087, 3063, 3030, 2954, 2926, 2870, 2855, 1636, 1629, 1453, 1423, 1041, 1029, 699 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{26}N_2O_2$ [M+H$^+$] 264.1958, Found 264.1946.

*4.28 amide **19g***

To a mixture of hemiaminal **21g** (19.1 mg, 72.7 μmol) and NaI (76.3 mg, 509 μmol) in MeCN (0.36 mL) was added TMSCl (46.0 μL, 495 μmol) at 0 °C. After stirred for 24 h at room temperature, the reaction was quenched with sat. aq. Na_2CO_3, and the aqueous phase was extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 1:1) to afford amide **19g** (17.0 mg, 72.3 μmol, quant).

*4.29 amide **22g***

To a mixture of amide **20g** (17.3 mg, 57.0 μmol) and $Pd(PPh_3)_4$ (6.6 mg, 5.67 μmol) and 1,3-dimethylbarbituric acid (17.8 mg, 114 μmol) was added MeOH (0.2 mL) at room temperature. The resulting suspension was stirred for 16.5 h at 40 °C. Then, the reaction was quenched with sat. aq. Na_2CO_3, and the mixture was extracted with EtOAc (x3). The combined organic extracts were washed with 1 M aq. HCl and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 3:1) to afford amide **19g** (0.7 mg, 3.00 μmol, 5.3%), **21g** (3.2 mg, 12.1 μmol, 21%), and **22g** (6.1 mg, 22.0 μmol, 39%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.37–7.18 (5H, m), 4.85 (0.8H, s), 4.67 (1.2H, s), 4.61 (2H, s), 3.33 (1.2H, s), 3.28 (1.8H, s), 2.46 (1.2H, t, *J* = 7.6 Hz), 2.35 (0.8H, t, *J* = 7.6 Hz), 2.48–1.64 (2H, m), 1.32–1.25 (8H, m), 0.88–0.84 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 175.0, 174.2, 137.8, 136.9, 128.8, 128.5, 128.1, 127.5, 127.3, 126.3, 78.9, 76.0, 56.1, 55.3, 49.1, 48.3, 33.4, 33.0, 31.7, 31.6, 29.3, 29.2, 29.1, 29.0, 25.2, 25.1, 22.57, 22.55, 14.0 (One signal is missing due to overlap.); IR (film): 3087, 3063, 3031, 2953, 2927, 2871, 2855, 1663, 1453, 1420, 1389, 1095, 1077, 699 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{27}NNaO_2$ [M+Na$^+$] 300.1934, Found 300.1921.

*4.30 amide **23***

To a solution of carboxylic acid **9** [9] (491 mg, 1.10 mmol) and L-phenylalanine methyl ester **10** (497 mg, 2.78 mmol) in dry CH_2Cl_2 (15.0 mL) was added Et_3N (612 μL, 4.40 mmol) at room temperature. After stirring for 10 min, BOP-Cl (576 mg, 2.26 mmol) was added, and the mixture was stirred for 2.7 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$, and the mixture was extracted with EtOAc (x3). The combined organic extracts were washed with 1 M aq. HCl and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to

*4.31 Amide **24***

To a suspension of amide **23** (398 mg, 657 μmol) and $Pd(OAc)_2$ (57.8 mg, 257 μmol) in CH_2Cl_2 (12.0 mL) was added Et_3N (300 μL, 2.16 mmol) at room temperature. After stirring for 30 min at reflux, Et_3SiH (1.10 mL, 6.90 mmol) was added, and the mixture. was stirred for 40 min at reflux. The reaction mixture was diluted by CH_2Cl_2 and the reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 6:1 to 2:1) to afford amine **24** (347 mg, quant). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (1H, d, *J* = 8.4 Hz), 7.22–7.16 (3H, m), 7.03 (2H, d, *J* = 6.8 Hz), 6.25 (1H, d, *J* = 2.0 Hz), 6.22 (1H, d, *J* = 8.0 Hz), 4.80 (1H, ddd, *J* = 10.8, 3.2, 3.2 Hz), 4.71 (1H, dd, *J* = 8.0, 7.8 Hz), 4.27 (1H, dd, *J* = 7.8, 2.2 Hz), 3.79 (1H, dd, *J* = 7.2, 5.6 Hz), 3.70 (3H, s), 3.55 (1H, s), 3.19 (1H, dd, *J* = 14.0, 5.8 Hz), 3.01 (1H, dd, *J* = 14.0, 6.6 Hz), 2.73–2.71 (2H, m), 2.28 (1H, s), 0.82 (9H, s), 0.033 (3H, s), 0.022 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 171.9, 145.5, 135.8, 133.1, 129.1, 128.3, 126.9, 120.5, 105.6, 67.9, 63.9, 60.9, 52.5, 52.1, 37.6, 35.0, 25.6, 17.9, -3.8, -4.7; IR (film): 3349, 3029, 2952, 2928, 2893, 2855, 2360, 2341, 1745, 1677, 1644, 1508, 1437, 1360, 1344, 1254, 1200, 1079, 961, 837, 779, 702 cm^{-1}; $[\alpha]_D^{26}$ = –195 (*c* = 1.65, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{25}H_{37}N_2O_5Si^+$ [M+H$^+$] 473.2466, found 473.2451.

*4.32 Dithiodiketopiperazine **25***

To a solution of amine **24** (447 mg, 945 μmol) in MeOH (250 mL) was added 25% aq. NH_3 (15.0 mL) at room temperature. After stirring for 2.7 days at room temperature, the reaction was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to afford diketopiperazine **25** (202 mg, 459 μmol, 48%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.18 (5H, m), 6.41 (1H, s), 6.29 (1H, d, *J* = 8.0 Hz), 5.90 (1H, s), 5.00 (1H, d, *J* = 7.6 Hz), 4.88 (1H, dd, *J* = 8.0, 7.6 Hz), 4.77 (1H, s), 4.23–4.16 (2H, m), 3.51 (1H, dd, *J* = 14.0, 3.6 Hz), 2.89–2.79 (2H, m), 2.52 (1H, dd, *J* = 13.0, 13.0 Hz), 0.79 (9H, s), 0.011 (3H, s), 0.006 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 163.9, 145.0, 135.6, 135.1, 129.3, 128.9, 127.3, 112.4, 106.4, 66.9, 63.1, 57.9, 56.2, 37.3, 33.4, 25.7, 17.8, −4.3, −4.5; IR (film): 3381, 3228, 3220, 2952, 2928, 2895, 2855, 2359, 2341, 1684, 1663, 1444, 1422, 1294, 1256, 1202, 1139, 1083,

$CHCl_3$); HRMS (EI) *m/z*: calcd. for $C_{24}H_{32}N_2O_4Si$ [M$^+$] 440.2131, found 440.2134.

*4.33 Dithiodiketopiperazine **27***

To a solution of diketopiperazine **25** (63.4 mg, 144 μmol) in THF (630 μL) was added LiHMDS (1.3 M solution in THF, 120 μL, 156 μmol) at −40 °C. After stirring for 8 min, AllomCl (**26**) [20] (120 μL, 1.16 mmol) was added at −40 °C, and the mixture was stirred at −20 °C for 17 h. The reaction was quenched with sat. aq. NH_4Cl solution and the mixture was diluted by water. The separated aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 4:1 to 2:1) to afford diketopiperazine **27** (66.3 mg, 120 μmol, 84%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (3H, m), 7.04 (2H, d, *J* = 8.0 Hz), 6.28 (1H, d, *J* = 7.6 Hz), 6.27 (1H, s), 5.96–5.87 (1H, m), 5.51 (1H, d, *J* = 10.8 Hz), 5.31 (1H, dt, *J* = 17.2, 1.6 Hz), 5.24 (1H, dt, *J* = 10.8, 1.2 Hz), 4.87(1H, dd, *J* = 7.8, 7.6 Hz), 4.82 (1H, d, *J* = 7.8 Hz), 4.79 (1H, d, *J* = 10.8 Hz), 4.62 (1H, s), 4.57 (1H, m), 4.12 (1H, dd, *J* = 12.8, 6.0 Hz), 4.07–4.40 (2H, m), 3.42 (1H, dd, *J* = 14.0, 2.8 Hz), 3.21 (1H, dd, *J* = 14.0, 2.8 Hz), 2.44 (1H, dd, *J* = 13.2, 6.0 Hz), 0.94 (1H, dd, *J* = 13.2, 12.8 Hz), 0.79 (9H, s), 0.007 (3H, s), −0.009 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 163.7, 144.9, 134.9, 134.7, 133.4, 130.1, 128.6, 127.4, 118.1, 112.8, 106.4, 72.5, 69.9, 68.6, 62.9, 59.1, 58.2, 36.5, 33.6, 25.8, 18.0, −4.3, −4.5; IR (film): 2952, 2928, 2856, 1662, 1452, 1441, 1295, 1200, 1138, 1092, 1051, 955, 906, 837, 777, 703 cm^{-1}; $[\alpha]_D^{25}$ = −333 (*c* = 0.535, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{28}H_{38}N_2NaO_5Si^+$ [M+Na$^+$] 533.2442, found 533.2417.

*4.34 Dithiodiketopiperazine **28***

To a solid of diketopiperazine **27** (66.3 mg, 120 μmol) was added HF·Py in pyridine (2.00 mL, 1:4, HF·Py containing ~70% hydrogen fluoride and ~30% pyridine) at room temperature. After stirring for 17 h at 45 °C, the reaction mixture was diluted by water at 0 ℃. The separated aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (CH_2Cl_2:EtOAc = 1:5) to afford allyl alcohol **28** (46.6 mg, 118 μmol, 98%). A white solid; mp: 155.5–156.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (3H, m), 7.07–7.04 (2H, m), 6.34 (1H, d, *J* = 8.0 Hz), 6.34 (1H, d, *J* = 2.0 Hz), 5.98–5.91 (1H, m), 5.41 (1H, d, *J* = 10.8 Hz), 5.35 (1H, ddd, *J* = 17.5, 2.9, 1.7 Hz), 5.24 (1H, ddd, *J* = 10.3, 2.9, 1.5 Hz), 5.05 (1H, dd, *J* = 8.2, 8.0 Hz), 4.82 (1H, d, *J* = 10.8 Hz), 4.79–4.76 (2H, m), 4.69 (1H, s), 4.58–4.56 (1H, m), 4.22 (1H, dd, *J* = 12.2, 6.0 Hz), 4.16–4.10 (2H, m), 3.42 (1H, dd, *J* = 14.2, 3.0 Hz), 3.23 (1H, dd, *J* = 14.2, 4.4 Hz), 2.48 (1H, dd, *J* = 14.4, 6.0 Hz), 0.94 (1H, dd, *J* = 14.4, 12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 163.8, 145.1, 135.2, 134.7, 133.6, 130.1, 128.4, 127.3, 117.8, 113.7, 105.7, 73.2, 70.3, 68.1, 62.6, 59.8, 58.3, 36.8, 33.3; $[\alpha]_D^{25}$ = −367 (*c* = 0.260, $CHCl_3$); IR (film): 3425, 3419, 2921, 2359, 2340, 1694, 1659, 1454, 1339, 1296, 1200, 1137, 1074, 1047, 929, 857, 758, 736, 704 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{22}H_{24}N_2NaO_5$ [M+Na$^+$] 419.1577, found 419.1558.

*4.35 Dithiodiketopiperazine **29***

To a solution of allyl alcohol **28** (74.3 mg, 188 μmol) and nor-AZADO (8.50 mg, 61.5 μmol) in dry CH_2Cl_2 (1.40 mL) was added LiHMDS (1.3 M in THF, 725 μL, 943 μmol) at room temperature. After stirring for 5 min, diketopiperazine **30** (18.6 mg, 47.0 μmol) in a mixture of THF (2.0 mL) and Et_2O (1.0 mL) was added at room temperature, and the resulting solution was stirred for 1 min. Then, LiHMDS (1.3 M in THF, 725 μL, 943 μmol) was added, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with aq. NH_4Cl and diluted with water. The separated aqueous phase was extracted with Et_2O (x1) and CH_2Cl_2 (x2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:3) to afford lactone **29** (71.0 mg, 180 μmol, 96%). A white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (3H, m), 7.09 (2H, d, *J* = 8.0 Hz), 7.00 (1H, d, *J* = 7.6 Hz), 6.59 (1H, d, *J* = 2.4 Hz), 6.01–5.91 (1H, m), 5.61 (1H, d, *J* = 7.6 Hz), 5.36 (1H, d, *J* = 18.4 Hz), 5.35 (1H, d, *J* = 10.4 Hz), 5.31 (1H, s), 5.27 (1H, d, *J* = 10.4 Hz), 4.90 (1H, d, *J* = 10.4 Hz), 4.68 (1H, dd, *J* = 4.0, 3.4 Hz), 4.20–4.10 (2H, m), 3.91 (1H, dd, *J* = 13.4, 6.0 Hz), 3.43 (1H, dd, *J* = 14.0, 3.4 Hz), 3.29 (1H, dd, *J* = 14.0, 4.0 Hz), 2.53 (1H, dd, *J* = 15.2, 6.0 Hz), 1.01 (1H, dd, *J* = 13.4, 13.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.9, 164.9, 163.6, 153.3, 136.9, 134.5, 133.4, 130.0, 128.3, 127.1, 117.6, 115.4, 107.8, 73.5, 70.4, 66.3, 60.0, 57.0, 36.9, 31.8; IR (film): 3028, 2925, 2867, 1687, 1667, 1604, 1454, 1350, 1327, 1292, 1204, 1078, 1051, 940, 930, 864, 820, 758, 736 cm^{-1}; $[\alpha]_D^{26}$ = −279 (*c* = 0.445, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{23}N_2O_5$ [M+H$^+$] 395.1601, found 395.1605.

*4.36 Dithiodiketopiperazine **30***

To a solution of lactone **29** (138 mg, 350 μmol) in CH_2Cl_2 (750 μL) and EtOH (500 μL) was added $CeCl_3 \cdot 7H_2O$ (381 mg) in EtOH (2.0 mL) at −78 °C. After stirring for 10 min, $NaBH_4$ in EtOH (22.0 mg, 582 μmol in 550 μL) was added at −78 °C, and the mixture was stirred at −78 °C for 1.6 h. The reaction was quenched with aq. NH_4Cl solution at room temperature. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:3) to afford allyl alcohol **30** (126 mg, 318 μmol, 91%). A white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.23 (3H, m), 7.08 (2H, d, *J* = 6.4 Hz), 6.27 (1H, dd, *J* = 2.2, 2.2 Hz), 6.13 (1H, dd, *J* = 8.0, 2.4 Hz), 6.00–5.90 (1H, m), 5.42 (1H, d, *J* = 10.8 Hz), 5.36 (1H, d, *J* = 17.2 Hz), 5.26 (1H, d, *J* = 10.0 Hz), 5.07 (1H, d, *J* = 3.6 Hz), 4.88 (1H, s), 4.87 (1H, d, *J* = 10.8 Hz), 4.64 (1H, dd, *J* = 3.0, 4.2 Hz), 4.52 (1H, d, *J* = 7.6 Hz), 4.20–4.17 (1H, m), 4.14 (1H, d, *J* = 5.8 Hz), 4.13 (1H, d, *J* = 5.8 Hz), 3.91 (1H, dd, *J* = 13.0, 5.8 Hz), 3.40 (1H, dd, *J* = 13.8, 3.0 Hz), 3.27 (1H, dd, *J* = 13.8, 4.2 Hz), 2.36 (1H, dd, *J* = 13.6, 5.8 Hz), 0.80 (1H, dd, *J* = 13.6, 13.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 165.1, 138.0, 137.0, 134.2, 133.4, 130.2, 128.7, 127.7, 118.1, 109.8, 109.7, 73.2, 70.5, 69.1, 64.1, 59.8, 56.3, 37.0, 33.7; IR (film): 3369, 3011, 2942, 2863, 1661, 1453, 1344, 1296, 1193, 1133, 1078, 1058, 930, 759, 756, 730, 704, 578 cm^{-1}; $[\alpha]_D^{25}$ = −229 (*c* = 1.04, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{24}N_2NaO_5$ [M+Na$^+$] 419.1577, found 419.1564.

*4.37 Dithiodiketopiperazine **31***

To a suspension of sulfur S_8 (63.6 mg, 247 μmol) in Et_2O (1.0 mL) was added LiHMDS (1.3 M in THF, 725 μL, 943 μmol) at room temperature. After stirring for 5 min, diketopiperazine **30** (18.6 mg, 47.0 μmol) in a mixture of THF (2.0 mL) and Et_2O (1.0 mL) was added at room temperature, and the resulting solution was stirred for 1 min. Then, LiHMDS (1.3 M in THF, 725 μL, 943 μmol) was added, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with aq. NH_4Cl and diluted with water. The separated aqueous phase was extracted with Et_2O (x1) and CH_2Cl_2 (x2). The combined organic

and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 16:1 x2, then hexanes:CH_2Cl_2 = 3:5) to afford the mixture of bridged polysulfides. To a solution of the polysulfides in a mixture of THF (3.2 mL) and EtOH (3.2 mL) was added $NaBH_4$ (36.5 mg, 965 μmol) at 0 °C. After stirred for 8 min at room temperature, MeI (1.60 mL, 25.6 mmol) was added at 0 ℃, and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched by aq. NH_4Cl, and the separated aqueous phase was extracted with Et_2O (x1) and CH_2Cl_2 (x2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 16:1, then hexanes:EtOAc = 2:1) to afford bis-(methylthio) diketopiperazine **31** (18.3 mg, 30.3 μmol, 65% 2 steps from **30**). A white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.24 (3H, m), 7.15–7.12 (2H, m), 6.31 (1H, m), 6.17 (1H, dd, *J* = 8.4, 2.4 Hz), 6.03–5.93 (1H, m), 5.40–5.34 (1H, m), 5.53 (1H, d, *J* = 9.6 Hz), 5.24–5.22 (2H, m), 5.12 (1H, d, *J* = 9.6 Hz), 4.91 (1H, dd, *J* = 8.2, 1.8 Hz), 4.58–4.55 (1H, m), 4.42 (1H, d, *J* = 8.0 Hz), 4.30–4.28 (2H, m), 3.48 (1H, d, *J* = 13.2 Hz), 3.23 (1H, d, *J* = 13.2 Hz), 2.55 (1H, d, *J* = 15.2 Hz), 2.29 (3H, s), 2.53 (3H, s), 1.59 (1H, d, *J* = 15.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 166.1, 137.6, 137.2, 134.3, 133.6, 130.7, 128.6, 127.9, 117.2, 110.8, 107.1, 77.5, 73.4, 72.2, 71.3, 67.7, 65.4, 45.0, 38.1, 15.2, 14.0; IR (film): 3370, 3008, 2920, 2852, 1662, 1435, 1416, 1380, 1191, 1136, 1083, 1056, 1050, 772, 756, 704 cm^{-1}; $[\alpha]_D^{25}$ = −123 (*c* = 0.619, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{24}H_{28}N_2NaO_5S_2$ [M+Na$^+$] 511.1332, found 511.1303.

*4.38 (–)-Emestrin H (**5**)*

To a solid of bis-(methylthio) diketopiperazine **31** (6.65 mg, 13.6 μmol) was added $Pd(PPh_3)_4$ (27.2 mM solution in CH_2Cl_2, 25.0 μL 0.682 μmol). The mixture was concentrated under reduced pressure give a pale brown solid. To the solid was added 1,3-dimethylbarbituric acid (4.26 mg, 27.3 μmol) in MeOH (136 μL), and the mixture was stirred for 16.5 h at 40 °C. The reaction mixture was diluted with MeOH (68 μL) and stirred for 2 h. Then, the mixture was cooled to room temperature and diluted with MeOH (200 μL). To the mixture was added $NaHCO_3$ (40.0 mg), and the resulting suspension was stirred for 25 min at room temperature and diluted with CH_2Cl_2 and H_2O. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 3:1 x3) to afford (–)-emestrin H (**5**) (4.46 mg, 10.6 μmol, 78%) and diketopiperazine **30** (1.15 mg, 17%). A white solid; mp: 86.0–87.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34–7.30 (3H, m), 7.19 (2H, d, *J* = 6.6 Hz), 6.36 (1H, s), 6.19 (1H, dd, *J* = 1.8, 8.4 Hz), 6.05 (1H, s), 5.12 (1H, d, *J* = 4.8 Hz), 4.93 (1H, d, *J* = 8.4 Hz), 4.63–4.61 (1H, m), 4.55 (1H, d, *J* = 7.2 Hz), 3.64 (1H, d, *J* = 13.2 Hz), 3.02 (1H, d, *J* = 13.2 Hz), 2.63 (1H, d, *J* = 15.0 Hz), 2.41 (3H, s), 2.23 (3H, s), 1.88 (1H, d, *J* = 15.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.2, 165.4, 137.7, 137.4, 133.2, 130.7, 128.8, 128.1, 110.9, 107.4, 72.3, 68.5, 68.4, 64.9, 46.3, 38.9, 14.7, 14.3; IR (film): 3361, 3224, 3062, 3008, 2918, 2848, 2360, 2341, 1675, 1638, 1409, 1340, 1193, 1139, 1123, 1047, 756, 730, 704, 581, 564 cm^{-1}; $[\alpha]_D^{28}$ = −203 (*c* = 0.234, MeOH) (Lit. $[\alpha]_D^{25}$ = –97 (*c* = 0.071, MeOH)); HRMS (ESI) *m/z*: calcd. for $C_{20}H_{22}N_2NaO_4S_2$ [M+Na$^+$] 441.0913, found 441.0907. The spectral data were identical with those reported in the literature [14].

*4.39 (–)-Asteroxepin (**4**)*

and DMAP (1.23 mg, 10.1 μmol) in pyridine (120 μL) was added Ac_2O in pyridine (0.127 M, 100 μL, 12.7 μmol) at room temperature. After stirring for 50 min at room temperature, additional Ac_2O (13.0 μL, 138 μmol) was added, and the mixture was stirred for 35 min. Then, additional DMAP (5.69 mg, 46.6 μmol) was added, and the mixture was stirred for 45 min at room temperature. The reaction was diluted with CH_2Cl_2, and quenched with aq. 1 M HCl. The separated aqueous phase was extracted with CH_2Cl_2 (x5), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 7:11) to afford (–)-asteroxepin (**4**) (2.60 mg, 5.65 μmol, 89%). A white solid; mp: 189.6–190.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32–7.27 (3H, m), 7.20–7.18 (2H, m), 6.41 (1H, dd, *J* = 2.4, 2.4 Hz), 6.29 (1H, dd, *J* = 8.4, 3.0 Hz), 6.00 (1H, br s), 5.88 (1H, ddd, *J* = 7.5, 2.1, 2.1), 4.89 (1H, br. d, *J* = 7.8 Hz), 4.68 (1H, dd, *J* = 8.4, 1.2 Hz), 3.66 (1H, d, *J* = 13.8 Hz), 2.97 (1H, d, *J* = 13.8 Hz), 2.64 (1H, d, *J* = 15.0 Hz), 2.36 (3H, s), 2.20 (3H, s), 2.13 (3H, s), 1.82 (1H, ddd, *J* = 15.3, 2.1, 2.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1, 165.6, 164.4, 139.7, 137.3, 133.5, 130.9, 128.7, 127.9, 109.1, 105.5, 71.4, 69.9, 68.0, 61.7, 46.4, 39.6, 21.2, 14.5, 14.0; $[\alpha]_D^{27}$ = −178 (c = 0.556, $CHCl_3$) (Lit. $[\alpha]_D$ = −102 (*c* = 0.4, $CHCl_3$)); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{24}N_2NaO_5S_2$ [M+Na$^+$] 483.1019, found 483.0996. The spectral data were identical with those reported in the literature [13].

*4.40 AllomCl (**26**)* [20]

To a mixture of allyl alcohol (40.0 mL, 0.588 mmol) and paraformaldehyde (19.0 g, 0.633 mol) was added anhydrous hydrogen chloride generated from H_2SO_4 and NaCl at room temperature. After stirred for 30 min at room temperature, the mixture was heated by oil bath at 150 °C for 2 h. The resulting mixture was diluted with hexanes, dried over magnesium sulfate, and the hexanes were removed under reduced pressure. The crude material was distilled from anhydrous calcium chloride (37.0 °C/67.5 mmHg) to afford AllomCl (**26**) (25.0 g, 0.234 mol, 40%) as colorless oil.

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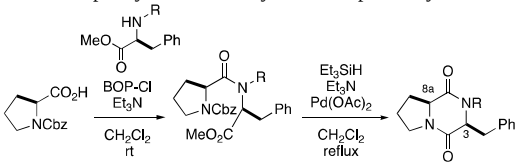
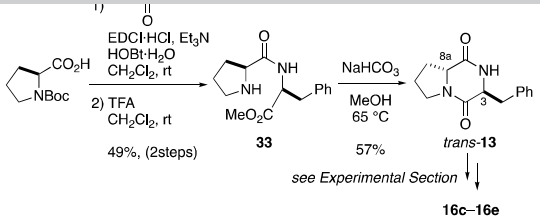
16. Compounds **16a** and **16b** with C3 (*S*) and C8a (*S*) stereochemistries were synthesized by the stepwise condensation of *N*-Cbz-L-proline and *N*-PMB-L-phenylalanine methyl ester or *N*-2,4-DMB-phenylalanine methyl ester, respectively.



32a: R = PMB, 77%
32b: R = 2,4-DMB, 47%
16a, 75%
16b, 91%

17. Compounds **16c–e** were synthesized from *trans*-**13** with C3 (*S*) and C8a (*R*) stereochemistries, which was prepared by the stepwise condensation of *N*-Boc-L-proline and L-phenylalanine methyl ester. During the intramolecular condensation step, the C8a (*S*) stereochemistry was completely isomerized to give *trans*-**13** with C8a (*R*) stereochemistry.



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Total syntheses of (−)-emestrin H and (−)-asteroxepin

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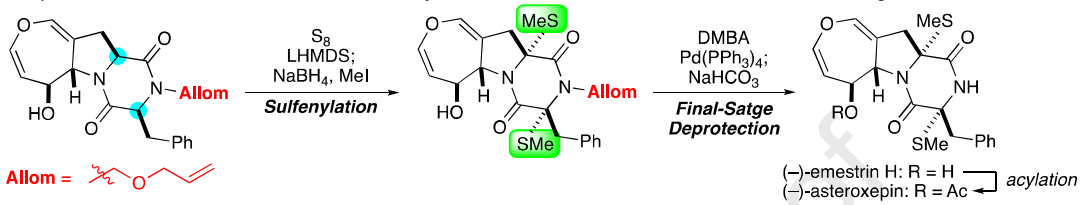
Kanato Umeki, Yusuke Ueda, Juri Sakata, Hidetoshi Tokuyama

Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan



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Total syntheses of (–)-emestrin H and (–)-asteroxepin

Kanato Umeki, Yusuke Ueda, Juri Sakata, and Hidetoshi Tokuyama*

Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

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ABSTRACT

First total syntheses of (–)-emestrin H and (–)-asteroxepin were accomplished. The allyloxymethyl (Allom) group, suitable protecting group for the amide nitrogen of the diketopiperazine which needs to be robust enough to tolerate Nicolaou's sulfenylation condition but also easily cleavable by the exceptionally mild allylic alkylation with Pd/*N*,*N*-dimethylbarbituric acid system, leaving acid, basic, oxidation labile methylthio groups intact was disclosed. The first total synthesis of (–)-emestrin H was accomplished via installation of two methylthio groups to the diketopiperazine core having Allom group, followed by removal of the Allom group at the final step. The total synthesis of (–)-asteroxepin was also completed by acylation of (–)-emestrin H.

1. Introduction

Dithiodiketopiperazine alkaloids bearing the sulfur-containing diketopiperazine as core structure have attracted attention due to their structural diversity and fascinating biological activities [1,2]. Among them, compounds bearing the 4,5-dihydrooxepine ring, such as (−)-acetylaranotin (**1**) [3], (+)-MPC1001B (**7**) [4], and (−)-acetylapoaranotin (**6**) [5], have been challenging synthetic targets and a lot of effort has been made to synthesize these compounds [6,7]. Reisman *et al.* reported the first innovative total synthesis of (−)-acetylaranotin (**1**) in 2012 [8], followed by the first total synthesis of (−)-acetylapoaranotin (**6**) [10]. We also focused on this class of compounds, reporting the second total synthesis of **1** just after Reisman *et al.* in 2012 [9]. Using the synthetic protocol established during the synthetic studies on **1**, which was based on the characteristic proline-fused 4,5-dihydrooxepine ring, we successfully performed the first total synthesis of (+)-MPC1001B (**7**) [11] and determined the structure of (−)-SCH64874 (**3**) and hirsutellomycin (**8**) via semi-synthesis [12]. Despite these synthetic developments over the last decade, the total syntheses of (−)-asteroxepin (**4**) [13] and (−)-emestrin H (**5**) [14] bearing the NH-free diketopiperazine core have not been reported so far.

Our preliminary model studies toward **4** and **5** (Scheme 1a) revealed that the enolate-mediated introduction of two methylthio groups reported by Nicolaou *et al.* [15] was unsuccessful for the unprotected diketopiperazine **13** due to the competitive deprotonation of the unprotected N–H proton (Scheme 1b). Therefore, the major challenge toward the synthesis of **4** and **5** was the selection of the appropriate protecting group for the diketopiperazine ring's NH group. The ideal protecting group (PG in Scheme 1) should be robust enough to tolerate the strong basic conditions during the introduction of the two-methylthio groups. Moreover, it should be easily and chemoselectively cleaved under the particularly mild conditions in the final stage of the total synthesis without affecting the base-, nucleophile-, and oxidant-sensitive methylthio groups and the acid-sensitive dihydrooxepin structure. However, compared to the many available protecting groups for amines, there are limited choices for amides, especially for diketopiperazines. In this study, we

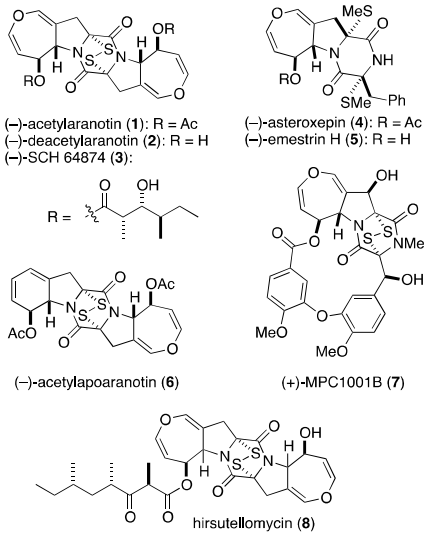
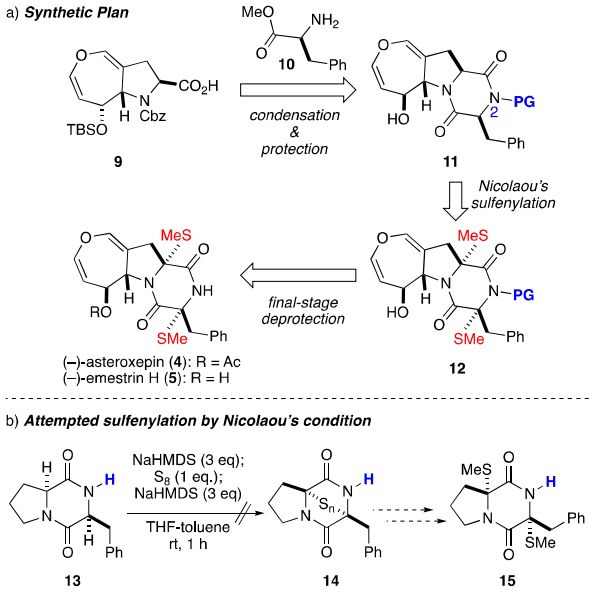


Fig. 1. Dithiodiketopiperazine alkaloids.

* Corresponding author. E-mail: tokuyama@mail.pharm.tohoku.ac.jp

functionalized NH-free diketopiperazines and found that the less common allyloxymethyl (Allom) group was the most suitable protecting group. Its efficiency was further demonstrated by the first total synthesis of (−)-asteroxepin (**4**) and (−)-emestrin H (**5**).

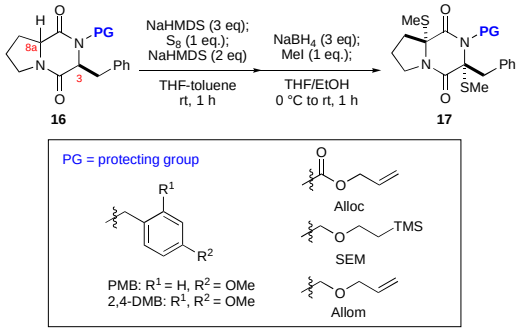


Scheme 1. Synthetic plan and preliminary results.

2. Results and discussion

To identify the most suitable protecting group that would fulfill the abovementioned requirements, we prepared a series of *N*-protected diketopiperazines (**16a–e**) following a conventional method [16,17], which were then subjected to the sulfenylation conditions established by Nicolaou *et al*. (Table 1) [15]. Among the tested analogues **16a–e**, substrates **16a** and **16b** bearing a stable benzylic protecting group, such as *p*-methoxybenzyl (PMB) or 2,4-dimethoxybenzyl (2,4-DMB), were not affected by the sulfenylation conditions, providing dithiodiketopiperazines **17a** and **17b**, respectively, in moderate yields (Table 1, entries 1 and 2). Moreover, substrates protected as *N*,*O*-acetals, such as**16d** with the trimethylsilylethoxymethyl (SEM) group and **16e**

Table 1
Protecting groups and introduction of the methylthio group.



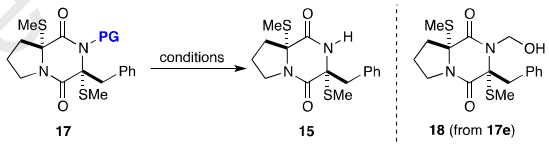
entry	substrate	PG	**17** (%)[c,d]
1	**16a**[a]	PMB	44
2	**16b**[a]	2,4-DMB	57
3	**16c**[b]	Alloc	decomposition
4	**16d**[b]	SEM	68
5	**16e**[b]	Allom	50

[a]C3 (*S*), C8a (*S*) isomer. [b]C3 (*S*), C8a (*R*) isomer. [c]Isolated yield. [d]Obtained as single diastereomer.

thio compounds (**17d** and **17e**) in good yields (Table 1, entries 4 and 5). However, analogue **16c**, protected as urethane with an allyloxycarbonyl group (Alloc), afforded a complex mixture under the same sulfenylation conditions (Table 1, entry 3).

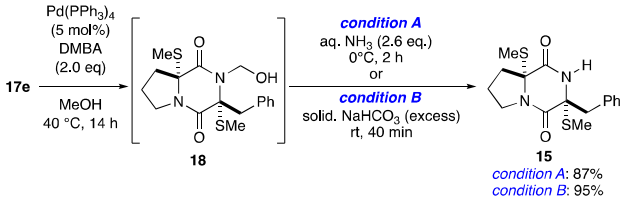
The deprotection of the bis(methylthio) products **17a**, **17b**, **17d**, and **17e** was examined under the most frequently used deprotection conditions for each protecting group (Table 2). Analogues **17a** and **17b** bearing PMB and 2,4-DMB groups were decomposed upon treatment with ceric ammonium nitrate (CAN) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), respectively (Table 2, entries 1 and 2). Moreover, the SEM group in **17d** was stable upon treatment with HF/pyridine and **17d** was recovered (Table 2, entry 4), whereas the use of TBAF in THF/DMF decomposed **17d** (Table 2, entry 3). In contrast to these unsuccessful entries, the Allom group in **17e** could be smoothly removed by a combination of $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid (DMBA) in MeOH yielding **15** in 56% yield, while a substantial amount of the hemiaminal intermediate **18** was also obtained (Table 2, entry 5) [18,19]. The subsequent *in situ* treatment of the reaction mixture with aq. NH_3 was effective in reducing the amount of **18**, affording **15** in 87% yield (Scheme 2). Furthermore, the addition of solid $NaHCO_3$ after the consumption of **17e** improved the yield of **15** to up to 95%.

Table 2
Deprotection conditions.



entry	**17**	reagents	temp.	Time (h)	Yield (%)[a]
1[b]	**17a**	CAN, CH_3CN/H_2O	rt	2	0
2[b]	**17b**	DDQ, CH_3CN/H_2O	60 °C	20	0
3[b]	**17d**	TBAF, THF/DMF	60 °C	1.8	0
4[c]	**17d**	HF/pyridine	60 °C	22	0
5[d]	**17e**	$Pd(PPh_3)_4$, DMBA, MeOH	30 °C	6	56

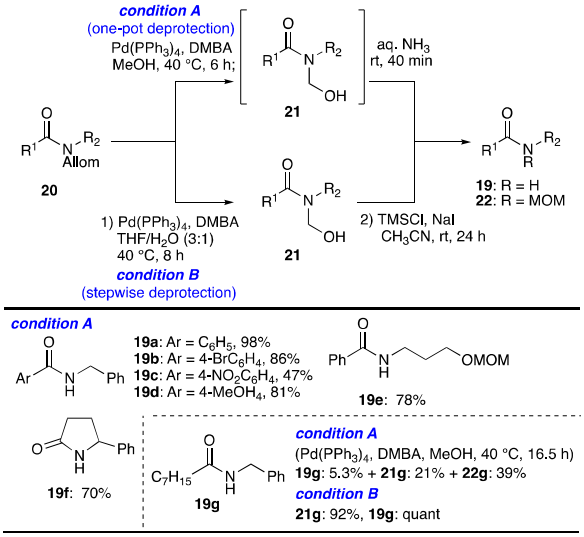
[a]Isolated yield. [b]Decomposition. [c]**17d** was completely recovered. [d]Reaction conditions: **17** (1.0 eq), $Pd(PPh_3)_4$ (45 mol%), DMBA (5.5 eq), MeOH (0.1 M), 30°C, 6 h. The hemiaminal intermediate **18** was obtained in 38% yield.



Scheme 2. Removal of the Allom group.

Feasibility of the deprotection condition of the Allom group from secondary amides was investigated using a series of *N*-Allom secondary amides (**20**) (see Experimental Section for the preparation and additional data) (Scheme 3). Treatment of *N*-Allom benzamides **20a–e** and γ-lactam **20f** with $Pd(PPh_3)_4$ and DMBA in MeOH smoothly provided the hemiaminal intermediate **21**, which was converted into amides **19a–e** and **19f**, respectively, in good yields using aq. NH_3 (condition A). In contrast, the reaction of *N*-Allom aliphatic amides **20g** under the Pd/*N*,*N*-dimethylbarbituric acid/MeOH condition provided a mixture of **19g** (5.3%), **21g** (21%), and *N*-

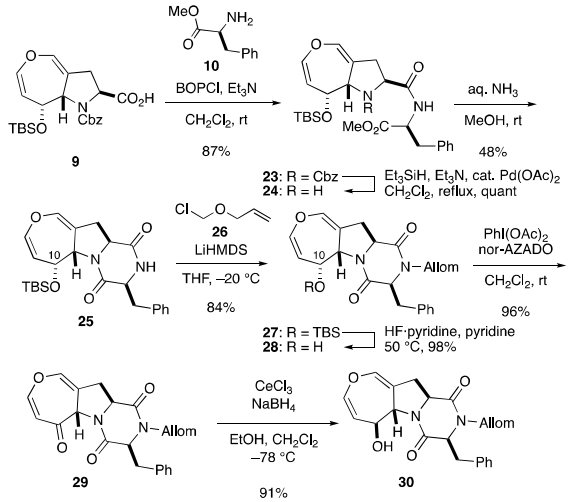
MO de due to an exchange of the OH group in intermediate **21g** with methanol. This side reaction was eliminated by performing the reaction in THF and H_2O, providing the hemiaminal intermediates **21g**, which were then converted to amides **19g** in good yields using trimethylsilyl iodide (TMSI) (condition B).



Reaction conditions: Condition A: **20** (1.0 eq), $Pd(PPh_3)_4$ (10 mol%), DMBA (2.0 eq), MeOH (0.3 M), 40°C, 6 h, then aq. NH_3 (excess). Condition B: **20g** (1.0 eq), $Pd(PPh_3)_4$ (10 mol%) , DMBA (2.0 eq), THF/H_2O (3:1, 0.3 M), then **21g** (1.0 eq), TMSCl (7.0 eq), NaI (7.0 eq), CH_3CN (0.2 M). The yields refer to the isolated products.

Scheme 3. Removal of the Allom group under different conditions.

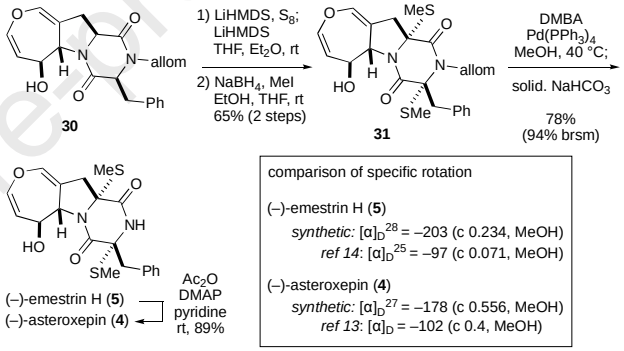
The applicability of the Allom protecting group was fully demonstrated by the first total syntheses of (−)-emestrin H (**5**) and (−)-asteroxepin (**4**). The proline-fused dihydrooxepine derivative **9**, which was prepared according to our previously established protocol in the total synthesis of (−)-acetylaranotin (**1**) [9], was first condensed with the (*S*)-phenylalanine methyl ester (**10**) (Scheme 4). The benzyloxycarbonyl (Cbz) group was then removed under transfer hydrogenation conditions and the formation of the tricyclic diketopiperazine derivative **25** was promoted upon treatment of the resulting aminoester with ammonium hydroxide. Subsequently, the Allom group was introduced using a combination of the allyloxymethyl chloride



Scheme 4. Preparation of diketopiperazine **30**.

(LiHMDS), which afforded the desired product **27** in 84% yield. After desilylation, the stereochemistry of the C-10 hydroxyl group was inverted through a stepwise process [9], which included an oxidation of **28** to ketone using $PhI(OAc)_2$ and 9-azanoradamantane *N*-oxyl (nor-AZADO) [21] and a subsequent Luche reduction, which gave the desired alcohol **30** as the sole isomer.

The final steps toward the synthesis of (−)-emestrin H (**5**) and (−)-asteroxepin (**4**) including the crucial introduction of the two methylthio groups and the removal of the Allom protecting group are depicted in Scheme 5. According to the model study (*vide supra*), diketopiperazine **30** was treated with a mixture of excess LiHMDS and S_8 to form an epipolysulfide. Its reduction to the corresponding dithiol with $NaBH_4$ and the subsequent methylation afforded the bis(methylthio) derivative **31** in 65% yield over two steps from **30**. Finally, the Allom group was removed under the optimized conditions affording (−)-emestrin H (**5**) in 78% yield, which was further acetylated to give (−)-asteroxepin (**4**). All properties of synthetic (–)-emestrin H (**5**) and (–)-asteroxepin (**4**) were identical with those reported except magnitude of specific rotations proving the reported absolute stereochemistry of **4** and **5** by this total synthesis [22].



Scheme 5. Final steps of the total syntheses of (−)-emestrin H (**5**) and (−)-asteroxepin (**4**).

3. Conclusion

In conclusion, the total syntheses of (−)-emestrin H (**5**) and (−)-asteroxepin (**4**) have been accomplished for the first time. Their preparation was successful owing to the suitability of the Allom group as protecting group for the amide nitrogen of the highly functionalized dithio-diketopiperazine intermediate. This protecting group could be easily cleaved even in the presence of the acid-sensitive dihydrooxepin structure and the dimethylthio groups, which are sensitive to bases, nucleophiles, and oxidants. Thus, this study demonstrated the application potential of the Allom group not only for the synthesis of other *N*-unprotected diketopiperazine alkaloids, but also for the preparation of various functionalized amides.

4. Experimental section

4.1 General method

Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. Anhydrous THF, Et_2O, CH_2Cl_2, toluene, DMF, and MeCN were purchased from commercial suppliers. Anhydrous MeOH was dried and distilled according to the standard protocols. All reactions were carried out under Ar atmosphere unless otherwise mentioned. Flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40–50 μm). Preparative

glass plates precoated with a 0.25 mm thickness of silica gel. NMR spectra were recorded on a JNM-AL400 spectrometer and a JEOL ECA600 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm, relative to the central line of a triplet at 77.0 ppm for $CDCl_3$ or a septet at 39.5 ppm for DMSO-d_6. IR spectra were measured on a SHIMADZU FTIR-8300 spectrometer. Mass spectra were recorded on a Bruker micrOTOF (ESI). Optical rotations were measured on a Horiba SEPA-300 highly sensitive polarimeter. Compounds **9** [9], **19a**–**e** [25], **19f** [26], and **19g** [25] were prepared according to the procedures reported in references.

*4.2 Diketopiperazine **16a***

To a solution of *N*-Cbz-L-proline (3.68 g, 14.8mmol) and *N*-PMB-L-phenylalanine methyl ether (4.24 g, 14.2 mmol) in Et_3N and CH_2Cl_2 (5 mL and 30 mL) was added BOP-Cl (3.74 g, 14.7 mmol) at room temperature. After stirring for 24.5 h at room temperature, additional BOP-Cl (1.96 g, 7.70 mmol) was added, and the reaction mixture was stirred for 2.5 h. The reaction was quenched with sat. aq. $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with 1 M aq. HCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:1) to afford amide **32a** (5.80 g, 10.9 mmol, 77%). To a suspension of amide **32a** (5.80 g, 10.9 mmol) and $Pd(OAc)_2$ (983 mg, 4.38 mmol) in CH_2Cl_2 (55.0 mL) was added Et_3N (3.08 mL, 21.9 mmol) at room temperature. After stirring at reflux for 5 min, Et_3SiH (8.74 mL, 54.7 mmol) was added and the mixture was stirred at reflux for 3.5 h. The reaction mixture was diluted with CH_2Cl_2 and the reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (EtOAc) to afford diketopiperazine **16a** (3.00 g, 8.23 mmol, 75%). A white foam; The spectral data of **16a** were identical with those reported in the literature [23].

*4.3 Diketopiperazine **16b***

To a solution of *N*-Cbz-L-proline (1.06 g, 4.25 mmol), *N*-2,4-DMB-L-phenylalanine methyl ether (1.15 g, 3.49 mmol) in Et_3N and CH_2Cl_2 (2.0 mL and 20.0 mL) was added BOP-Cl (1.87 g, 7.35 mmol) at room temperature. After stirring for 20 h at room temperature, the reaction was quenched with 1 M aq. HCl and the resulting mixture was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 3:2 to 6:5) to afford amide **32b** (846 mg, 1.51 mmol, 47%). To a suspension of amide **32b** (846 mg, 1.51 mmol) and $Pd(OAc)_2$ (135 mg, 601 μmol) in CH_2Cl_2 (10.0 mL) was added Et_3N (425 μL, 3.02 mmol) at room temperature. After stirring at reflux for 7 min, Et_3SiH (1.20 mL, 7.51 mmol) was added and the mixture was stirred at reflux for 3.5 h. The reaction mixture was diluted with CH_2Cl_2 and the reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (EtOAc) to afford diketopiperazine **16b** (540 mg, 1.37 mmol, 91%). A white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.20 (4H, m), 7.12–7.06 (2H, m), 6.48–6.43 (2H, m), 5.40 (1H, d, J = 14.8 Hz), 4.32 (1H, m), 4.25 (1H, d, J = 14.8 Hz), 3.84 (3H, s), 3.81 (3H, s), 3.72 (1H, dd, J = 12.0, 6.0 Hz), 3.68–3.61 (1H, m), 3.36–3.27 (2H, m), 3.14–3.07 (1H, m), 1.91–1.81 (1H, m), 1.60–1.42 (2H, m), 0.14–0.01 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 163.9, 160.7, 158.7, 135.1, 131.7, 130.0, 128.3, 127.1, 115.9, 104.4, 98.3, 60.3, 59.0, 55.3, 55.3, 44.0, 40.6, 36.4, 28.4, 20.9; IR (film): 2992, 2952, 2944, 2891, 1656, 1612, 1587, 1508, 1456, 1298, 1289, 1261, 1208, 1184, 1157, 1033, 751, 703 cm^{-1}; $[\alpha]_D^{31}$ = −116 (c = 0.66, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{23}H_{26}N_2NaO_4$ [M^++Na] 417.1785, Found 417.1769.

*4.4 Amide **33***

To a solution of *N*-Boc-L-proline (10.8 g, 50.0 mmol) and L-phenylalanine methyl ether (8.95 g, 50.0 mmol) in CH_2Cl_2 (200 mL) were added Et_3N (27.9 mL, 200 mmol), HOBt (6.99 g, 51.7 mmol), and EDCI/HCl (9.91 g, 51.7 mmol) at room temperature. After stirred for 29.5 h at room temperature, the organic phase was washed with 1 M aq. HCl (x3) and sat. aq. $NaHCO_3$ (x2). The resulting organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude material, which was used for the next reaction without further purification. To a solution of the crude material in CH_2Cl_2 (120 mL) was added TFA (15 mL) at room temperature. After stirred for 20 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (150 mL) and neutralized by sat. aq. $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (x3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude material, which was purified by flash column chromatography (CH_2Cl_2:MeOH = 10:1) to afford amine amide **33** (6.76 g, 24.5 mmol, 49%, 2 steps from *N*-Boc-L-proline). A white solid. The spectral data of **33** were identical with those reported in the literature [24].

*4.5 Diketopiperazine trans-**13***

To a solution of amie **33** (6.76 g, 24.5 mmol) in MeOH (400 mL) was added $NaHCO_3$ (20.0 g, 85.3 mmol) at room temperature. After stirring for 22.5 h at 65 °C, MeOH was removed under reduced pressure. The residue was diluted with CH_2Cl_2 and filtered through a pad of Celite®. The filtrate was washed with H_2O, and the aqueous phase was extracted with CH_2Cl_2 (x2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by crystallization from EtOAc to afford diketopiperazine *trans*-**13** (3.43 g, 14.1 mmol, 57%). The mother liquor was concentrated *in vacuo* and the second crop was crystallized from EtOAc to afford diketopiperazine *trans*-**13** (643 mg, 2.64 mmol, 11%). A white solid.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.20 (5H, m), 6.31 (1H, s), 4.22 (1H, ddd, J = 6.6, 4.0, 3.8 Hz), 3.63 (1H, ddd, J = 12.4, 8.5, 8.5 Hz), 3.40 (1H, ddd, J = 12.4, 9.4, 3.0 Hz), 3.15 (1H, dd, J = 13.9, 6.6 Hz), 3.08 (1H, dd, J = 13.9, 4.0 Hz), 2.97 (1H, dd, J = 10.4, 6.4 Hz), 2.23–2.15 (1H, m), 1.98–1.90 (1H, m), 1.86–1.64 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 164.8, 135.3, 129.9, 128.5, 127.3, 58.7, 57.6, 44.9, 40.3, 28.8, 21.5; IR (film): 3483, 3238, 3063, 3029, 2981, 2953, 2931, 2886, 1664, 1496, 1454, 1336, 1307, 1296, 1206, 1186, 1115, 1106, 921, 732, 702, 593 cm^{-1}; $[\alpha]_D^{26}$ = +93.0 (c = 0.200, H_2O); HRMS (ESI) *m/z*: calcd. for $C_{14}H_{17}N_2O_2$ [M+H^+] 245.1285, found

reported in the literature [27].

*4.6 Diketopiperazine **16c***

To a solution of diketopiperazine *trans*-**13** (203 mg, 0.832 mmol) in THF (4.0 mL) was added LiHMDS (1.3 M solution in THF, 650 μL, 845 μmol) at 0 °C. After stirring for 4 min, Alloc-OSu (172 mg, 863 μmol) in THF (1.50 mL) was added at 0 °C. The resulting mixture was stirred for 35 min at room temperature. The reaction was quenched with sat. aq. NH_4Cl, and the resulting mixture was diluted by water. The separated aqueous phase was extracted with CH_2Cl_2 (x3), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (CH_2Cl_2:EtOAc = 5:1 to 3:1) to afford diketopiperazine **16c** (248 mg, 789 μmol, 95%). A colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.26 (3H, m), 7.19–7.14 (2H, m), 5.99–5.87 (1H, m), 5.43 (1H, d, *J* = 17.2 Hz), 5.31 (1H, d, *J* = 10.8 Hz), 5.01 (1H, ddd, *J* = 5.0, 5.0, 1.4 Hz), 4.75 (1H, ddd, *J* = 13.3, 5.8, 1.0 Hz), 4.69 (1H, ddd, *J* = 13.3, 5.6, 1.2 Hz), 3.60–3.50 (1H, m), 3.45–3.37 (1H, m), 3.33–3.22 (2H, m), 2.64 (1H, dd, *J* = 9.6, 6.8 Hz), 2.17–2.07 (1H, m), 1.96–1.79 (2H, m), 1.72–1.57 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 164.0, 151.8, 134.9, 130.7, 129.9, 128.6, 127.5, 119.4, 67.9, 62.3, 58.6, 44.8, 38.2, 29.1, 21.8; IR (film): 3086, 3062, 3028, 2983, 2953, 2885, 1782, 1731, 1672, 1455, 1384, 1270, 1231, 980, 763, 747, 703 cm^{-1}; $[\alpha]_D^{26}$ = +143 (*c* = 0.425, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{18}H_{21}N_2NaO_4$ [M+Na$^+$] 351.1315, Found 351.1319.

*4.7 Diketopiperazine **16d***

To a solution of diketopiperazine *trans*-**13** (1.10 g, 4.51 mmol) in dry DMF (10.0 mL) was added NaH (60% dispersion in mineral oil, 248 mg, 6.20 mmol) at room temperature. After stirring for 15 min, SEMCl (1.60 mL, 9.03 mmol) was added at room temperature, and the resulting mixture was stirred at 60 °C for 18 h. The reaction was quenched with sat. aq. NH_4Cl at room temperature and the resulting mixture was diluted by EtOAc and washed with water (x5) and brine (x1). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:3) to afford diketopiperazine **16d** (1.33 g, 3.55 mmol, 79%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.26 (3H, m), 7.18–7.15 (2H, m), 5.13 (1H, d, *J* = 10.4 Hz), 4.53 (1H, d, *J* = 10.4 Hz), 4.42 (1H, dd, *J* = 5.2, 4.9 Hz), 3.61–3.52 (3H, m), 3.35 (1H, ddd, *J* = 12.1, 9.3, 2.9 Hz), 3.24 (1H, dd, *J* = 14.3, 5.2 Hz), 3.19 (1H, dd, *J* = 14.3, 4.9 Hz), 2.52 (1H, dd, *J* = 10.6, 6.6 Hz), 2.14–2.06 (1H, m), 1.92–1.84 (1H, m), 1.79–1.68 (1H, m), 1.69–1.53 (1H, m), 1.01–0.87 (2H, m), 0.01 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 164.7, 135.2, 129.9, 128.5, 127.5, 73.3, 66.3, 62.1, 57.6, 44.8, 37.6, 29.1, 21.8, 17.9, –1.5; IR (film): 2952, 2890, 1671, 1454, 1440, 1296, 1260, 1249, 1207, 1075, 1044, 860, 837, 749, 703 cm^{-1}; $[\alpha]_D^{25}$ = +55.0 (*c* = 2.71, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{20}H_{30}NaN_2O_3Si$ [M$^+$+Na] 397.1918, Found 397.1909.

*4.8 Diketopiperazine **16e***

To a solution of diketopiperazine *cis*-**13** (880 mg, 3.61 mmol) in dry THF (8.0 mL) was added NaH (60% dispersion in mineral oil, 181 mg, 4.53 mmol) at room temperature. After stirring for 50 min, AllomCl (**26**) [20] (750 μL, 7.23 mmol) was added at room temperature, and the mixture was stirred for 9.5 h at 50 °C. The reaction was quenched with sat. aq. NH4Cl solution at room temperature, and the resulting mixture was diluted by water. The separated aqueous phase was extracted with Et_2O (x1) and CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1, then EtOAc only) to afford diketopiperazine **16e** (946 mg, 3.01 mmol, 83%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.24 (3H, m), 7.19–7.14 (2H, m), 5.89 (1H, m), 5.29 (1H, ddd, *J* = 17.6, 1.2, 1.2, Hz), 5.19 (1H, d, *J* = 10.8 Hz), 5.14 (1H, d, *J* = 10.6 Hz), 4.58 (1H, d, *J* = 10.6 Hz), 4.43 (1H, dd, *J* = 4.7, 4.8 Hz), 4.10–3.98 (2H, m), 3.57 (1H, ddd, *J* = 12.3, 8.5, 8.5 Hz), 3.36 (1H, ddd, *J* = 12.3, 9.3, 2.9 Hz), 3.25 (1H, dd, *J* = 14.3, 4.8 Hz), 3.20 (1H, dd, *J* = 14.3, 4.7 Hz), 2.53 (1H, dd, *J* = 10.6, 6.6 Hz), 2.09 (1H, ddd, *J* = 12.0, 6.2, 6.2 Hz), 1.94-1.84 (1H, m), 1.81–1.69 (1H, m), 1.66–1.53 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 164.7, 135.3, 133.8, 129.9, 128.6, 127.5, 117.4, 73.6, 70.1, 62.4, 57.7, 44.9, 37.7, 29.0, 21.8; IR (film): 3028, 2979, 2951, 2883, 1668, 1453, 1440, 1344, 1296, 1261, 1207, 1072, 1057, 923, 748, 703 cm^{-1}; $[\alpha]_D^{26}$ = +60.0 (*c* = 4.41, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{18}H_{22}N_2NaO_3$ [M$^+$+Na] 337.1523, Found 337.1506.

*4.9 Dithiodiketopiperazine **17a** (General Procedure A)*

To a suspension of sulfur S_8 (264 mg, 1.03 mmol) in THF (5.0 mL) was added NaHMDS (0.6 M in toluene, 5.00 mL, 3.00 mmol) at room temperature. After stirring for 1 min, diketopiperazine **16a** (372 mg, 1.02 mmol) in THF (5.0 mL) was added, and the mixture was stirred for 1 min. Then, NaHMDS (0.6 M in toluene, 3.40 mL, 2.04 mmol) was added, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with sat. aq. NH_4Cl, and the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was used for the next reaction without further purification. To a solution of the crude material in THF (10.0 mL) and EtOH (10.0 mL) was added $NaBH_4$ (964 mg, 25.5 mmol) at 0 °C. After stirring for 45 min at 0 °C, MeI (3.18 mL, 51.0 mmol) was added at 0 °C, and the resulting mixture was stirred for 19 h at room temperature. The reaction was quenched by sat. aq. NH_4Cl, and the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by flash column chromatography (hexanes:EtOAc = 12:5) to afford bis(metylthio) diketopiperazine **17a** (204 mg, 0.449 mmol, 44%, 2 steps from **16a**). A white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (2H, d, *J* = 8.8 Hz), 7.31–7.22 (3H, m), 7.09 (2H, d, *J* = 6.0 Hz), 6.83 (2H, d, *J* = 8.8 Hz), 5.18 (1H, d, *J* = 14.4 Hz), 4.54 (1H, d, *J* = 14.4 Hz), 3.79 (3H, s), 3.66–3.48 (2H, m), 3.54 (1H, d, *J* = 13.6 Hz), 3.25 (1H, d, *J* = 13.6 Hz), 2.05-1.91 (2H, m), 2.01 (3H, s), 1.99 (3H, s), 1.58–1.49 (1H, m), 0.81–0.71 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 163.0, 158.6, 134.1, 130.2, 129.6, 128.4, 127.7, 113.3, 78.8, 69.9, 55.1, 46.7, 45.8, 44.1, 32.7, 18.5, 15.0, 14.0 (One signal is missing due to overlap.), IR (film): 2994, 2956, 2933, 2922, 1662, 1512, 1421, 1395, 1352, 1247, 1177, 1033, 756, 703 cm^{-1}; $[\alpha]_D^{25}$ = +0.89 (*c* 0.58, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{24}H_{28}N_2NaO_3S_2$ [M+Na$^+$] 479.1419, Found 479.1434.

*4.10 Dithiodiketopiperazine **17b***

According to the General Procedure A, diketopiperazine **16b** (301 mg, 0.763 mmol) were converted to bis-(methylthio) diketopiperazine **17b** (210 mg, 0.431 mmol, 57 %, 2 steps from **16b**). A white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (1H, d,

J = m), (1H, d, *J* = 2.1 Hz), 6.41 (1H, d, *J* = 8.5, 2.1 Hz), 5.07 (1H, d, *J* = 15.8 Hz), 4.68 (1H, d, *J* = 15.8 Hz), 3.90 (3H, s), 3.79 (3H, s), 3.67–3.53 (2H, m), 3.55 (1H, d, *J* = 13.6 Hz), 3.33 (1H, d, *J* = 13.6 Hz), 2.14 (3H, s), 2.14 (3H, s), 2.10–1.94 (2H, m), 1.61–1.50 (1H, m), 0.86–0.73 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 162.9, 159.5, 157.2, 134.2, 130.1, 128.3, 127.5, 127.0, 118.5, 103.5, 98.2, 78.5, 69.7, 55.3, 55.2, 45.8, 44.1, 41.1, 32.5, 18.4, 15.2, 14.2; IR (film): 2998, 2959, 2936, 2921, 2835, 1662, 1616, 1590, 1508, 1455, 1439, 1420, 1396, 1361, 1300, 1261, 1208, 1156, 1120, 1036, 755, 703 cm^{-1}; $[\alpha]_D^{32}$ = +21.3 (*c* = 0.26, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{25}H_{30}N_2NaO_4S_2$ [M+Na$^+$] 509.1539, Found 509.1526.

*4.11 Dithiodiketopiperazine **17d***

According to the General Procedure A, diketopiperazine **16e** (456 mg, 1.22 mmol) were converted to bis-(methylthio) diketopiperazine **17d** (386 mg, 0.828 mmol, 68%, 2 steps from **16d**). A white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.19 (3H, m), 7.12 (2H, dd, *J* = 7.8, 2.2 Hz), 5.48 (1H, d, *J* = 9.6 Hz), 5.06 (1H, d, *J* = 9.6 Hz), 3.79 (2H, t, *J* = 8.6 Hz), 3.50 (2H, dd, *J* = 9.2, 6.4 Hz), 3.46 (1H, d, *J* = 13.6 Hz), 3.18 (1H, d, *J* = 13.2 Hz), 2.26 (3H, s), 2.14 (3H, s), 2.12–2.04 (1H, m), 2.02–1.89 (1H, m), 1.55–1.46 (1H, m), 1.07–0.96 (2H, m), 0.93–0.84 (1H, m), 0.03 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 163.0, 134.3, 130.6, 128.2, 127.4, 77.3, 73.1, 69.5, 67.4, 45.7, 44.8, 32.7, 18.5, 18.4, 15.3, 14.0, –1.4; IR (film): 2952, 2920, 1669, 1454, 1438, 1416, 1385, 1362, 1248, 1083, 1057, 860, 836, 756, 703 cm^{-1}; $[\alpha]_D^{30}$ = −6.99 (*c* = 2.76, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{34}N_2NaO_3S_2Si$ [M+Na$^+$] 489.1672, Found 489.1649.

*4.12 Dithiodiketopiperazine **17e***

According to the General Procedure A, diketopiperazine **16e** (843 mg, 2.68 mmol) were converted to bis-(methylthio) diketopiperazine **17e** (539 mg, 1.33 mmol, 50% 2 steps from **16e**). A white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.18 (3H, m), 7.17–7.10 (2H, m), 5.97 (1H, m), 5.51 (1H, d, *J* = 9.8 Hz), 5.36 (1H, dd, *J* = 17.2, 1.6 Hz), 5.21 (1H, dd, *J* = 15.9, 1.8 Hz), 5.11 (1H, d, 9.8 Hz), 4.29 (2H, ddd, *J* = 5.5, 1.5, 1.5 Hz), 3.54–3.47 (2H, m), 3.47 (1H, d, *J* = 13.6 Hz), 3.18 (1H, d, *J* = 13.6 Hz), 2.26 (3H, s), 2.15 (3H, s), 2.14–2.04 (1H, m), 2.03–1.89 (1H, m), 1.58–1.46 (1H, m), 0.98–0.86 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 162.9, 134.4, 134.2, 130.6, 128.2, 127.4, 117.0, 77.3, 73.3, 71.2, 69.6, 45.7, 44.9, 32.8, 18.5, 15.2, 13.9; IR (film): 2952, 2920, 2896, 1669, 1438, 1416, 1385, 1362, 1248, 1083, 1057, 860, 836, 756, 703 cm^{-1}; $[\alpha]_D^{30}$ = −9.65 (*c* = 0.660, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{20}H_{26}N_2NaO_3S_2$ [M+Na$^+$] 429.1277, Found 429.1271.

*4.13 Dithiodiketopiperazine **15***

To a mixture of bis-(methylthio) diketopiperazine **17e** (52.9 mg, 130 μmol) and $Pd(PPh_3)_4$ (7.53 mg, 6.51 μmol) and 1,3-dimethylbarbituric acid (40.7 mg, 260 μmol) was added MeOH (1.3 mL) at room temperature. The resulting suspension was stirred for 14 h at 40 °C. The reaction mixture was cooled to room temperature before addition of excess $NaHCO_3$ (130 mg) and further stirred for 40 min at room temperature. The reaction mixture was diluted by water (1.0 mL), and the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried with anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1 to 1:1) to afford bis-(methylthio) diketopiperazine **15** (41.6 mg, 124 μmol, 95%). A white solid; ^{1}H 3.48 (1H, d, *J* = 12.8 Hz), 3.46–3.26 (2H, m), 3.00 (1H, d, *J* = 12.8 Hz), 2.29 (3H, s), 2.11 (3H, s), 2.02 (1H, dd, *J* = 13.2, 7.2 Hz), 1.95–1.81 (1H, m), 1.63–1.52 (1H, m), 0.97 (1H, ddd, *J* = 9.3, 12.1, 12.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.6, 163.2, 134.9, 130.3, 127.8, 126.9, 69.6, 67.4, 44.9, 44.6, 33.7, 18.6, 14.0, 13.2 ;IR (film): 3211, 3096, 3087, 3062, 2987, 2961, 2922, 2896, 1676, 1659, 1406, 1208, 755, 705 cm^{-1}; $[\alpha]_D^{28}$ = −17.5 (*c* = 0.65, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{16}H_{12}N_2NaO_2S_2$ [M+Na$^+$] 351.0232, Found 351.0207.

*4.14 amide **20a** (General Procedure B)*

To a solution of amide **19a** (1.11 g, 5.26 mmol) and TBAI (195 mg, 0.527 mmol) in THF (21.0 mL) was added LiHMDS (1.3 M solution in THF, 4.46 mL, 5.80 mmol) at −40 °C. After stirring for 30 min, AllomCl (**26**) [20] (0.764 mL, 5.80 mmol) was added at –40 °C, and the mixture was stirred at −40 °C for 14 h. The reaction was quenched with sat. aq. NH_4Cl solution and the mixture was diluted by water. The aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 4:1) to afford amide **20a** (1.43 g, 5.08 mmol, 97%). A colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 7.48–7.42 (5H, m), 7.36–7.26 (5H, m), 5.82–5.75 (1H, m), 5.14 (1H, d, *J* = 17.6 Hz), 5.07 (1H, d, *J* = 10.4 Hz), 4.86–4.67 (4H, m), 3.84 (br, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 171.0, 137.2, 135.4, 134.0, 129.4, 128.0, 127.9, 127.1, 126.6, 126.5, 116.3, 77.0, 68.0, 48.1; IR (film): 3062, 3030, 2942, 2862, 1651, 1496, 1445, 1417, 1267, 1071, 1050, 699 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{19}NNaO_2$ [M+Na$^+$] 304.1308, found 304.1296.

*4.15 amide **20b***

According to the General Procedure B, amide **19b** (55.5 mg, 191 μmol) was converted to amide **20b** (51.6 mg, 143 μmol, 75%). A yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 7.64–7.16 (2H, m), 7.47 (2H, d, *J* = 8.4 Hz), 7.34–7.26 (5H, m), 5.82–5.77 (1H, m), 5.16 (1H, d, *J* = 17.6 Hz), 5.09 (1H, d, *J* = 10.0 Hz), 3.86 (2H, br s); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 170.1, 137.0, 134.5, 133.9, 130.9, 128.7, 128.0, 127.2, 126.7, 122.9, 116.3, 77.0, 68.0, 48,3; IR (film): 3085, 3063, 3030, 2979, 2942, 2898, 2863, 1652, 1590, 1443, 1417, 1360, 1292, 1266, 1072, 1011, 932, 837, 754, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{18}BrNNaO_2$ [M+Na$^+$] 382.0413, Found 382.0403.

*4.16 amide **20c***

According to the General Procedure B, amide **19c** (62.4 mg, 2.43 μmol) was converted to amide **20c** (70.4 mg, 215mmol, 89%). A yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 8.26 (2H, d, *J* = 8.0 Hz), 7.73 (2H, d, *J* = 8.0 Hz), 7.35–7.25 (5H, m), 5.84–5.71 (1H, m), 5.16 (1H, d, *J* = 17.6 Hz), 5.08 (1H, d, *J* = 10.8 Hz), 4.70 (2H, br), 4.64 (2H, br), 3.86 (2H, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 147.9, 141.5, 136.8, 133.9, 128.1, 127.9, 127.3, 126.8, 123.2, 116.5, 68.1, 54.3, 48.5; IR (film): 3080, 3066, 3031, 2945, 2862, 1651, 1602, 1521, 1425, 1349, 1072, 732, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{18}N_2NaO_4$ [M+Na$^+$] 349.1159, Found 349.1140.

*4.17 amide **20d***

According to the General Procedure B, amide **19d** (60.3 mg, 250 μmol) was converted to amide **20d** (68.0 mg, 218 μmol, 87%). A colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 7.49–7.46 (2H, m), 7.35–7.25 (5H, m), 6.99–6.97 (2H, m),

5.86 ... ord
4.68 (m, 4H), 3.89–3.86 (m, 2H), 3.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 170.8, 160.4, 137.4, 134.0, 128.6, 127.9, 127.4, 127.2, 126.6, 116.3, 113.4, 77.5, 67.9, 59.5, 48.2; IR (film) 1442, 1417, 1358, 1302, 1253, 1175, 1112, 1049, 933, 842, 766, 700, 598 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{19}H_{21}NNaO_3$ [M+Na$^+$] 334.1414, Found 334.1408.

*4.18 amide **20e***

According to the General Procedure B, amide **19e** (74.0 mg, 331 μmol) was converted to amide **20e** (92.1 mg, 314 μmol, 95%). A yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6, VT 80 °C): δ 7.45–7.42 (5H, m), 5.84–5.78 (1H, m), 5.18 (1H, d, *J* = 17.6 Hz), 5.09 (1H, d, *J* = 10.4 Hz), 4.69 (2H, br), 4.54 (2H, br), 3.86 (2H, br), 3.51 (4H, br), 3.26 (3H, br), 1.88–1.85 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, VT 80 °C): δ 170.9, 135.8, 134.1, 129.1, 127.8, 126.4, 116.1, 95.6, 67.4, 64.8, 54.2, 42.8, 27.9 (One signal is missing due to overlap.); IR (film): 2933, 2883, 1651, 1446, 1419, 1404, 1271, 1147, 1112, 1043, 919, 724, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{23}NNaO_4$ [M+Na$^+$] 316.1519, Found 316.1516.

*4.19 amide **20f***

According to the General Procedure B, amide **19f** (40.5 mg, 251 mmol) was converted to amide **20f** (49.5 mg, 214 μmol, 85%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.21 (5H, m), 5.88–5.81 (1H, m), 5.25 (1H, d, *J* = 16.8 Hz), 5.17–5.12 (2H, m), 4.82 (m, 1H), 4.06 (1H, d, *J* = 10.8 Hz), 3.97–3.94 (m, 2H), 2.64–2.50 (3H, m), 1.99–1.95 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 140.5, 134.0, 128.8, 128.0, 126.5, 116.9, 70.0, 69.4, 60.4, 30.2, 28.1; IR (film): 3081, 3065, 3031, 2979, 2941, 2885, 1704, 1456, 1415, 1392, 1319, 1256, 1227, 1065, 932, 769, 703 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{17}NNaO_2$ [M+Na$^+$] 254.1151, Found 254.1147.

*4.20 amide **20g***

According to the General Procedure B, amide **19g** (58.3 mg, 250 μmol) was converted to amide **20g** (71.7 mg, 236 μmol, 95%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.37–7.18 (5H, m), 5.94–5.82 (2H, m), 4.92 (0.7H, s), 4.67 (2H, s), 4.63 (1.3H, s), 4.31 (0.7, d, *J* = 5.2 Hz), 3.94 (1.3H, d, *J* = 6.0 Hz), 2.46 (1.3 H, t, *J* = 7.6 Hz), 2.33 (0.7H, 8.0 Hz), 1.71–1.63 (m, 2H), 1.32–1.35 (m, 8H), 0.88–0.84 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 174.8, 174.1, 137.8, 136.9, 134.3, 133.8, 128.8, 128.4, 128.1, 127.4, 127.2, 126.3, 117.6, 116.9, 76.8, 74.3, 69.5, 68.5, 49.2, 48.3, 33.32, 32.99, 31.63, 31.58, 29.3, 29.2, 29.00, 28.95, 25.3, 25.0, 22.53, 22.50, 14.0; IR (film): 3086, 3064, 3030, 2954, 2926, 2855, 1664, 1496, 1453, 1421, 1359, 1236, 1036, 991, 932, 732, 700 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{19}H_{29}NNaO_2$ [M+Na$^+$] 326.2091, Found 326.2082.

*4.21 amide **19a** (General Procedure C)*

To a mixture of amide **20a** (56.0 mg, 199 μmol) and $Pd(PPh_3)_4$ (23.3 mg, 20.0 μmol) and 1,3-dimethylbarbituric acid (62.2 mg, 398 μmol) was added MeOH (0.67 mL) at room temperature. The resulting suspension was stirred for 6 h at 40 °C. The reaction mixture was cooled to room temperature before addition of excess aq. NH_3 (0.3 ml) and further stirred for 40 min at room temperature. Then, the reaction mixture was diluted by water (1.0 mL) and then the separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated under reduced pressure to give a crude material, which was purified by silica gel amide **19a** (41.4 mg, 196 μmol, 98%).

*4.22 amide **19b***

According to the General Procedure C, amide **20b** (78.4 mg, 218 μmol) was converted to amide **19b** (54.1 mg, 186 μmol, 86%).

*4.23 amide **19c***

According to the General Procedure C, amide **20c** (37.8 mg, 116 μmol) was converted to amide **19c** (13.9 mg, 54.2 μmol, 47%).

*4.24 amide **19d***

According to the General Procedure C, amide **20c** (65.5 mg, 210 μmol) was converted to amide **19c** (40.9 mg, 170 μmol, 81%).

*4.25 amide **19e***

According to the General Procedure C, amide **20e** (66.7 mg, 227 μmol) was converted to amide **19e** (39.0 mg, 175 μmol, 78%).

*4.26 amide **19f***

According to the General Procedure C, amide **20f** (39.7 mg, 172 μmol) were converted to amide **19f** (19.3 mg, 120 μmol, 70%).

*4.27 hemiaminal **21g***

To a mixture of amide **20g** (20.9 mg, 68.8 μmol) and $Pd(PPh_3)_4$ (8.0 mg, 6.87 μmol) and 1,3-dimethylbarbituric acid (21.5 mg, 134 μmol) were added THF (0.17 mL) and MeOH (0.06 mL) at room temperature. After stirred for 8 h at 40 °C, the reaction was quenched with sat. aq. Na_2CO_3, and the aqueous phase was extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 5:1) to afford amide hemiaminal **21g** (16.6 mg, 63.2 μmol, 92%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.36–7.22 (5H, m), 4.86 (2H, br), 4.86–4.65 (2H, br), 3.69 (0.7H, br), 2.64–2.49 (0.9H, m), 2.31 (1.4H, t, *J* = 8.0 Hz), 1.71–1.61 (m, 2H), 1.25 (br, 8H), 0.88–0.84 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 175.9, 174.2, 138.0, 136.9, 128.9, 128.7, 128.1, 127.6, 127.5, 1 26.4, 72.2, 71.7, 51.5, 48.2, 33.4, 33.1, 31.7, 31.6, 29.4, 29.2, 29. 1, 29.0, 25.4, 24.9, 22.6, 14.0 (Two signals are missing due to overlap.); IR (film): 3371, 3087, 3063, 3030, 2954, 2926, 2870, 2855, 1636, 1629, 1453, 1423, 1041, 1029, 699 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{26}N_2O_2$ [M+H$^+$] 264.1958, Found 264.1946.

*4.28 amide **19g***

To a mixture of hemiaminal **21g** (19.1 mg, 72.7 μmol) and NaI (76.3 mg, 509 μmol) in MeCN (0.36 mL) was added TMSCl (46.0 μL, 495 μmol) at 0 °C. After stirred for 24 h at room temperature, the reaction was quenched with sat. aq. Na_2CO_3, and the aqueous phase was extracted with EtOAc (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 1:1) to afford amide **19g** (17.0 mg, 72.3 μmol, quant).

*4.29 amide **22g***

$Pd(PPh_3)_4$ (6.6 mg, 5.67 μmol) and 1,3-dimethylbarbituric acid (17.8 mg, 114 μmol) was added MeOH (0.2 mL) at room temperature. The resulting suspension was stirred for 16.5 h at 40 °C. Then, the reaction was quenched with sat. aq. Na_2CO_3, and the mixture was extracted with EtOAc (x3). The combined organic extracts were washed with 1 M aq. HCl and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 3:1) to afford amide **19g** (0.7 mg, 3.00 μmol, 5.3%), **21g** (3.2 mg, 12.1 μmol, 21%), and **22g** (6.1 mg, 22.0 μmol, 39%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.37–7.18 (5H, m), 4.85 (0.8H, s), 4.67 (1.2H, s), 4.61 (2H, s), 3.33 (1.2H, s), 3.28 (1.8H, s), 2.46 (1.2H, t, *J* = 7.6 Hz), 2.35 (0.8H, t, *J* = 7.6 Hz), 2.48–1.64 (2H, m), 1.32–1.25 (8H, m), 0.88–0.84 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 175.0, 174.2, 137.8, 136.9, 128.8, 128.5, 128.1, 127.5, 127.3, 126.3, 78.9, 76.0, 56.1, 55.3, 49.1, 48.3, 33.4, 33.0, 31.7, 31.6, 29.3, 29.2, 29.1, 29.0, 25.2, 25.1, 22.57, 22.55, 14.0 (One signal is missing due to overlap.); IR (film): 3087, 3063, 3031, 2953, 2927, 2871, 2855, 1663, 1453, 1420, 1389, 1095, 1077, 699 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{27}NNaO_2$ [M+Na$^+$] 300.1934, Found 300.1921.

*4.30 amide **23***

To a solution of carboxylic acid **9** [9] (491 mg, 1.10 mmol) and L-phenylalanine methyl ether **10** (497 mg, 2.78 mmol) in dry CH_2Cl_2 (15.0 mL) was added Et_3N (612 μL, 4.40 mmol) at room temperature. After stirring for 10 min, BOP-Cl (576 mg, 2.26 mmol) was added, and the mixture was stirred for 2.7 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$, and the mixture was extracted with EtOAc (x3). The combined organic extracts were washed with 1 M aq. HCl and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to afford amide **23** (582 mg, 906 μmol, 87%). A white solid; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.56–7.32 (8H, m), 7.32–7.25 (0.70H, m), 7.15–7.05 (1.30H, m), 6.48–6.34 (1.05H+1.30H, m), 6.06 (1.30H, d, *J* = 7.6 Hz), 5.36 (0.35H, d, *J* = 12.4 Hz), 5.29–5.11 (0.35H+1.95H, m), 5.04 (0.35H, ddd, *J* = 7.8, 5.6, 5.6 Hz), 4.96–4.84 (0.70H+1.95H, m), 4.78 (0.35H, dd, *J* = 7.8, 7.8 Hz), 4.53–4.46 (1H, m), 3.83 (0.35H, s), 3.77 (1.95H, s), 3.29–3.03 (3H, m), 2.76 (0.35H, d, *J* = 15.0 Hz), 2.64 (0.65H, d, *J* = 15.0 Hz), 0.940 (9H, s), 0.131 (1.05H, s), 0.122 (1.95H, s), 0.054 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 171.6, 171.5, 171.4, 171.2, 154.7, 153.9, 145.5, 145.2, 136.1, 135.7, 135.4, 135.0, 129.4, 129.1, 128.5, 128.5, 128.4, 128.3, 128.1, 128.1, 127.9, 127.1, 127.0, 120.3, 118.7, 105.9, 105.5, 67.6, 67.3, 67.1, 65.9, 65.0, 64.4, 61.8, 61.4, 53.0, 52.5, 52.2, 52.1, 37.8, 37.7, 33.3, 32.0, 25.6, 17.8, −4.5, −4.6, −5.0, −5.1 (Five signals are missing due to overlap.); IR (film): 3325, 3031, 2953, 2928, 2895, 2855, 1746, 1713, 1639, 1526, 1437, 1408, 1350, 1318, 1252, 1210, 1142, 1113, 1085, 959, 836, 777, 748, 698 cm^{-1}; $[\alpha]_D^{27}$ = −175 (*c* = 1.20, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{33}H_{42}N_2NaO_7Si$ [M+Na$^+$] 629.2653, found 629.2624.

*4.31 Amide **24***

To a suspension of amide **23** (398 mg, 657 μmol) and $Pd(OAc)_2$ (57.8 mg, 257 μmol) in CH_2Cl_2 (12.0 mL) was added Et_3N (300 μL, 2.16 mmol) at room temperature. After stirring for 30 min at reflux, Et_3SiH (1.10 mL, 6.90 mmol) was added, and the mixture. was stirred for 40 min at reflux. The reaction mixture was diluted by CH_2Cl_2 and the reaction was quenched with sat. aq. $NaHCO_3$. The separated aqueous phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 6:1 to 2:1) to afford amine **24** (347 mg, quant). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (1H, d, *J* = 8.4 Hz), 7.22–7.16 (3H, m), 7.03 (2H, d, *J* = 6.8 Hz), 6.25 (1H, d, *J* = 2.0 Hz), 6.22 (1H, d, *J* = 8.0 Hz), 4.80 (1H, ddd, *J* = 10.8, 3.2, 3.2 Hz), 4.71 (1H, dd, *J* = 8.0, 7.8 Hz), 4.27 (1H, dd, *J* = 7.8, 2.2 Hz), 3.79 (1H, dd, *J* = 7.2, 5.6 Hz), 3.70 (3H, s), 3.55 (1H, s), 3.19 (1H, dd, *J* = 14.0, 5.8 Hz), 3.01 (1H, dd, *J* = 14.0, 6.6 Hz), 2.73–2.71 (2H, m), 2.28 (1H, s), 0.82 (9H, s), 0.033 (3H, s), 0.022 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 171.9, 145.5, 135.8, 133.1, 129.1, 128.3, 126.9, 120.5, 105.6, 67.9, 63.9, 60.9, 52.5, 52.1, 37.6, 35.0, 25.6, 17.9, -3.8, -4.7; IR (film): 3349, 3029, 2952, 2928, 2893, 2855, 2360, 2341, 1745, 1677, 1644, 1508, 1437, 1360, 1344, 1254, 1200, 1079, 961, 837, 779, 702 cm^{-1}; $[\alpha]_D^{26}$ = –195 (*c* = 1.65, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{25}H_{37}N_2O_5Si^+$ [M+H$^+$] 473.2466, found 473.2451.

*4.32 Dithiodiketopiperazine **25***

To a solution of amine **24** (447 mg, 945 μmol) in MeOH (250 mL) was added 25% aq. NH_3 (15.0 mL) at room temperature. After stirring for 2.7 days at room temperature, the reaction was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to afford diketopiperazine **25** (202 mg, 459 μmol, 48%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.18 (5H, m), 6.41 (1H, s), 6.29 (1H, d, *J* = 8.0 Hz), 5.90 (1H, s), 5.00 (1H, d, *J* = 7.6 Hz), 4.88 (1H, dd, *J* = 8.0, 7.6 Hz), 4.77 (1H, s), 4.23–4.16 (2H, m), 3.51 (1H, dd, *J* = 14.0, 3.6 Hz), 2.89–2.79 (2H, m), 2.52 (1H, dd, *J* = 13.0, 13.0 Hz), 0.79 (9H, s), 0.011 (3H, s), 0.006 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 163.9, 145.0, 135.6, 135.1, 129.3, 128.9, 127.3, 112.4, 106.4, 66.9, 63.1, 57.9, 56.2, 37.3, 33.4, 25.7, 17.8, −4.3, −4.5; IR (film): 3381, 3228, 3220, 2952, 2928, 2895, 2855, 2359, 2341, 1684, 1663, 1444, 1422, 1294, 1256, 1202, 1139, 1083, 957, 905, 837, 777, 746, 702 cm^{-1}; $[\alpha]_D^{25}$ = −356 (*c* = 0.270, $CHCl_3$); HRMS (EI) *m/z*: calcd. for $C_{24}H_{32}N_2O_4Si$ [M$^+$] 440.2131, found 440.2134.

*4.33 Dithiodiketopiperazine **27***

To a solution of diketopiperazine **25** (63.4 mg, 144 μmol) in THF (630 μL) was added LiHMDS (1.3 M solution in THF, 120 μL, 156 μmol) at −40 °C. After stirring for 8 min, AllomCl (**26**) [20] (120 μL, 1.16 mmol) was added at −40 °C, and the mixture was stirred at −20 °C for 17 h. The reaction was quenched with sat. aq. NH_4Cl solution and the mixture was diluted by water. The separated aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 4:1 to 2:1) to afford diketopiperazine **27** (66.3 mg, 120 μmol, 84%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (3H, m), 7.04 (2H, d, *J* = 8.0 Hz), 6.28 (1H, d, *J* = 7.6 Hz), 6.27 (1H, s), 5.96–5.87 (1H, m), 5.51 (1H, d, *J* = 10.8 Hz), 5.31 (1H, dt, *J* = 17.2, 1.6 Hz), 5.24 (1H, dt, *J* = 10.8, 1.2 Hz), 4.87(1H, dd, *J* = 7.8, 7.6 Hz), 4.82 (1H, d, *J* = 7.8 Hz), 4.79 (1H, d, *J* = 10.8 Hz), 4.62 (1H, s), 4.57 (1H, m), 4.12 (1H, dd, *J* = 12.8, 6.0 Hz), 4.07–4.40 (2H, m), 3.42 (1H, dd, *J* = 14.0, 2.8 Hz), 3.21 (1H, dd, *J* = 14.0, 2.8 Hz), 2.44 (1H, dd, *J* = 13.2, 6.0 Hz), 0.94 (1H, dd, *J* = 13.2, 12.8 Hz), 0.79 (9H, s), 0.007 (3H, s), −0.009 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 163.7, 144.9, 134.9, 134.7, 133.4, 130.1, 128.6, 127.4, 118.1, 112.8, 106.4, 72.5, 69.9, 68.6, 62.9, 59.1, 58.2,

36.5 ... was
1662, 1452, 1441, 1295, 1200, 1138, 1092, 1051, 955, 906, 837, 777, 703 cm^{-1}; $[\alpha]_D^{25}$ = −333 (*c* = 0.535, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{28}H_{38}N_2NaO_5Si^+$ [M+Na^+] 533.2442, found 533.2417.

*4.34 Dithiodiketopiperazine **28***

To a solid of diketopiperazine **27** (66.3 mg, 120 μmol) was added HF·Py in pyridine (2.00 mL, 1:4, HF·Py containing ~70% hydrogen fluoride and ~30% pyridine) at room temperature. After stirring for 17 h at 45 °C, the reaction mixture was diluted by water at 0 ℃. The separated aqueous phase was extracted with CH_2Cl_2 (x4). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (CH_2Cl_2:EtOAc = 1:5) to afford allyl alcohol **28** (46.6 mg, 118 μmol, 98%). A white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (3H, m), 7.07–7.04 (2H, m), 6.34 (1H, d, *J* = 8.0 Hz), 6.34 (1H, d, *J* = 2.0 Hz), 5.98–5.91 (1H, m), 5.41 (1H, d, *J* = 10.8 Hz), 5.35 (1H, dt, *J* = 17.5, 2.9, 1.7 Hz), 5.24 (1H, dt, *J* = 10.3, 2.9, 1.5 Hz), 5.05 (1H, dd, *J* = 8.2, 8.0 Hz), 4.82 (1H, d, *J* = 10.8 Hz), 4.79–4.76 (2H, m), 4.69 (1H, s), 4.58–4.56 (1H, m), 4.22 (1H, dd, *J* = 12.2, 6.0 Hz), 4.16–4.10 (2H, m), 3.42 (1H, dd, *J* = 14.2, 3.0 Hz), 3.23 (1H, dd, *J* = 14.2, 4.4 Hz), 2.48 (1H, dd, *J* = 14.4, 6.0 Hz), 0.94 (1H, dd, *J* = 14.4, 12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 163.8, 145.1, 135.2, 134.7, 133.6, 130.1, 128.4, 127.3, 117.8, 113.7, 105.7, 73.2, 70.3, 68.1, 62.6, 59.8, 58.3, 36.8, 33.3; $[\alpha]_D^{25}$ = −367 (*c* = 0.260, $CHCl_3$); IR (film): 3425, 3419, 2921, 2359, 2340, 1694, 1659, 1454, 1339, 1296, 1200, 1137, 1074, 1047, 929, 857, 758, 736, 704 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{22}H_{24}N_2NaO_5$ [M+Na^+] 419.1577, found 419.1558.

*4.35 Dithiodiketopiperazine **29***

To a solution of allyl alcohol **28** (74.3 mg, 188 μmol) and nor-AZADO (8.50 mg, 61.5 μmol) in dry CH_2Cl_2 (1.40 mL) was added $PhI(OAc)_2$ (64.2 mg, 200 μmol) at room temperature. After stirring for 1.5 h at room temperature, the reaction was quenched with sat. aq. Na_2SO_3 solution and water (1:2). The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:3) to afford lactone **29** (71.0 mg, 180 μmol, 96%). A white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (3H, m), 7.09 (2H, d, *J* = 8.0 Hz), 7.00 (1H, d, *J* = 7.6 Hz), 6.59 (1H, d, *J* = 2.4 Hz), 6.01–5.91 (1H, m), 5.61 (1H, d, *J* = 7.6 Hz), 5.36 (1H, d, *J* = 18.4 Hz), 5.35 (1H, d, *J* = 10.4 Hz), 5.31 (1H, s), 5.27 (1H, d, *J* = 10.4 Hz), 4.90 (1H, d, *J* = 10.4 Hz), 4.68 (1H, dd, *J* = 4.0, 3.4 Hz), 4.20–4.10 (2H, m), 3.91 (1H, dd, *J* = 13.4, 6.0 Hz), 3.43 (1H, dd, *J* = 14.0, 3.4 Hz), 3.29 (1H, dd, *J* = 14.0, 4.0 Hz), 2.53 (1H, dd, *J* = 15.2, 6.0 Hz), 1.01 (1H, dd, *J* = 13.4, 13.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.9, 164.9, 163.6, 153.3, 136.9, 134.5, 133.4, 130.0, 128.3, 127.1, 117.6, 115.4, 107.8, 73.5, 70.4, 66.3, 60.0, 57.0, 36.9, 31.8; IR (film): 3028, 2925, 2867, 1687, 1667, 1604, 1454, 1350, 1327, 1292, 1204, 1078, 1051, 940, 930, 864, 820, 758, 736 cm^{-1}; $[\alpha]_D^{26}$ = −279 (*c* = 0.445, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{23}N_2O_5$ [M+H^+] 395.1601, found 395.1605.

*4.36 Dithiodiketopiperazine **30***

To a solution of lactone **29** (138 mg, 350 μmol) in CH_2Cl_2 (750 μL) and EtOH (500 μL) was added $CeCl_3 \cdot 7H_2O$ (381 mg) in EtOH (2.0 mL) at −78 °C. After stirring for 10 min, $NaBH_4$ in EtOH (22.0 mg, 582 μmol in 550 μL) was added at −78 °C, and quenched with aq. NH_4Cl solution at room temperature. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes:EtOAc = 1:3) to afford allyl alcohol **30** (126 mg, 318 μmol, 91%). A white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.23 (3H, m), 7.08 (2H, d, *J* = 6.4 Hz), 6.27 (1H, dd, *J* = 2.2, 2.2 Hz), 6.13 (1H, dd, *J* = 8.0, 2.4 Hz), 6.00–5.90 (1H, m), 5.42 (1H, d, *J* = 10.8 Hz), 5.36 (1H, d, *J* = 17.2 Hz), 5.26 (1H, d, *J* = 10.0 Hz), 5.07 (1H, d, *J* = 3.6 Hz), 4.88 (1H, s), 4.87 (1H, d, *J* = 10.8 Hz), 4.64 (1H, dd, *J* = 3.0, 4.2 Hz), 4.52 (1H, d, *J* = 7.6 Hz), 4.20–4.17 (1H, m), 4.14 (1H, d, *J* = 5.8 Hz), 4.13 (1H, d, *J* = 5.8 Hz), 3.91 (1H, dd, *J* = 13.0, 5.8 Hz), 3.40 (1H, dd, *J* = 13.8, 3.0 Hz), 3.27 (1H, dd, *J* = 13.8, 4.2 Hz), 2.36 (1H, dd, *J* = 13.6, 5.8 Hz), 0.80 (1H, dd, *J* = 13.6, 13.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 165.1, 138.0, 137.0, 134.2, 133.4, 130.2, 128.7, 127.7, 118.1, 109.8, 109.7, 73.2, 70.5, 69.1, 64.1, 59.8, 56.3, 37.0, 33.7; IR (film): 3369, 3011, 2942, 2863, 1661, 1453, 1344, 1296, 1193, 1133, 1078, 1058, 930, 759, 756, 730, 704, 578 cm^{-1}; $[\alpha]_D^{25}$ = −229 (*c* = 1.04, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{24}N_2NaO_5$ [M+Na^+] 419.1577, found 419.1564.

*4.37 Dithiodiketopiperazine **31***

To a suspension of sulfur S_8 (63.6 mg, 247 μmol) in Et_2O (1.0 mL) was added LiHMDS (1.3 M in THF, 725 μL, 943 μmol) at room temperature. After stirring for 5 min, diketopiperazine **30** (18.6 mg, 47.0 μmol) in a mixture of THF (2.0 mL) and Et_2O (1.0 mL) was added at room temperature, and the resulting solution was stirred for 1 min. Then, LiHMDS (1.3 M in THF, 725 μL, 943 μmol) was added, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with aq. NH_4Cl and diluted with water. The separated aqueous phase was extracted with Et_2O (x1) and CH_2Cl_2 (x2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 16:1 x2, then hexanes:CH_2Cl_2 = 3:5) to afford the mixture of bridged polysulfides. To a solution of the polysulfides in a mixture of THF (3.2 mL) and EtOH (3.2 mL) was added $NaBH_4$ (36.5 mg, 965 μmol) at 0 °C. After stirred for 8 min at room temperature, MeI (1.60 mL, 25.6 mmol) was added at 0 ℃, and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched by aq. NH_4Cl, and the separated aqueous phase was extracted with Et_2O (x1) and CH_2Cl_2 (x2). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 16:1, then hexanes:EtOAc = 2:1) to afford bis-(methylthio) diketopiperazine **31** (18.3 mg, 30.3 μmol, 65% 2 steps from **30**). A white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.24 (3H, m), 7.15–7.12 (2H, m), 6.31 (1H, m), 6.17 (1H, dd, *J* = 8.4, 2.4 Hz), 6.03–5.93 (1H, m), 5.40–5.34 (1H, m), 5.53 (1H, d, *J* = 9.6 Hz), 5.24–5.22 (2H, m), 5.12 (1H, d, *J* = 9.6 Hz), 4.91 (1H, dd, *J* = 8.2, 1.8 Hz), 4.58–4.55 (1H, m), 4.42 (1H, d, *J* = 8.0 Hz), 4.30–4.28 (2H, m), 3.48 (1H, d, *J* = 13.2 Hz), 3.23 (1H, d, *J* = 13.2 Hz), 2.55 (1H, d, *J* = 15.2 Hz), 2.29 (3H, s), 2.53 (3H, s), 1.59 (1H, d, *J* = 15.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 166.1, 137.6, 137.2, 134.3, 133.6, 130.7, 128.6, 127.9, 117.2, 110.8, 107.1, 77.5, 73.4, 72.2, 71.3, 67.7, 65.4, 45.0, 38.1, 15.2, 14.0; IR (film): 3370, 3008, 2920, 2852, 1662, 1435, 1416, 1380, 1191, 1136, 1083, 1056, 1050, 772, 756, 704 cm^{-1}; $[\alpha]_D^{25}$ = −123 (*c* = 0.619, $CHCl_3$); HRMS (ESI) *m/z*: calcd. for $C_{24}H_{28}N_2NaO_5S_2$ [M+Na^+] 511.1332, found 511.1303.

To a solid of bis-(methylthio) diketopiperazine **31** (6.65 mg, 13.6 μmol) was added $Pd(PPh_3)_4$ (0.788 mg, 0.682 μmol) in CH_2Cl_2 (25.0 μL). The mixture was concentrated under reduced pressure give a pale brown solid. To the solid was added 1,3-dimethylbarbituric acid (4.26 mg, 27.3 μmol) in MeOH (136 μL), and the mixture was stirred for 16.5 h at 40 °C. The reaction mixture was diluted with MeOH (68 μL) and stirred for 2 h. Then, the mixture was cooled to room temperature and diluted with MeOH (200 μL). To the mixture was added $NaHCO_3$ (40.0 mg), and the resulting suspension was stirred for 25 min at room temperature and diluted with CH_2Cl_2 and H_2O. The separated aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 3:1 x3) to afford emestrin H (**5**) (4.46 mg, 10.6 μmol, 78%) and diketopiperazine **30** (1.15 mg, 17%). A white solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34–7.30 (3H, m), 7.19 (2H, d, *J* = 6.6 Hz), 6.36 (1H, s), 6.19 (1H, dd, *J* = 1.8, 8.4 Hz), 6.05 (1H, s), 5.12 (1H, d, *J* = 4.8 Hz), 4.93 (1H, d, *J* = 8.4 Hz), 4.63–4.61 (1H, m), 4.55 (1H, d, *J* = 7.2 Hz), 3.64 (1H, d, *J* = 13.2 Hz), 3.02 (1H, d, *J* = 13.2 Hz), 2.63 (1H, d, *J* = 15.0 Hz), 2.41 (3H, s), 2.23 (3H, s), 1.88 (1H, d, *J* = 15.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.2, 165.4, 137.7, 137.4, 133.2, 130.7, 128.8, 128.1, 110.9, 107.4, 72.3, 68.5, 68.4, 64.9, 46.3, 38.9, 14.7, 14.3; IR (film): 3361, 3224, 3062, 3008, 2918, 2848, 2360, 2341, 1675, 1638, 1409, 1340, 1193, 1139, 1123, 1047, 756, 730, 704, 581, 564 cm^{-1}; $[\alpha]_D^{28}$ = −203 (*c* = 0.234, MeOH) (Lit. $[\alpha]_D^{25}$ = –97 (*c* = 0.071, MeOH)); HRMS (ESI) *m/z*: calcd. for $C_{20}H_{22}N_2NaO_4S_2$ [M+Na$^+$] 441.0913, found 441.0907. The spectral data were identical with those reported in the literature [14].

*4.39 (−)-Asteroxepin (**4**)*

To a solution of (–)-emestrin H (**5**) (2.64 mg, 6.32 μmol) and DMAP (1.23 mg, 10.1 μmol) in pyridine (120 μL) was added Ac_2O in pyridine (0.127 M, 100 μL, 12.7 μmol) at room temperature. After stirring for 50 min at room temperature, additional Ac_2O (13.0 μL, 138 μmol) was added, and the mixture was stirred for 35 min. Then, additional DMAP (5.69 mg, 46.6 μmol) was added, and the mixture was stirred for 45 min at room temperature. The reaction was diluted with CH_2Cl_2, and quenched with aq. 1 M HCl. The separated aqueous phase was extracted with CH_2Cl_2 (x5), and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes:EtOAc = 7:11) to afford asteroxepin (**4**) (2.60 mg, 5.65 μmol, 89%). A white solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32–7.27 (3H, m), 7.20–7.18 (2H, m), 6.41 (1H, dd, *J* = 2.4, 2.4 Hz), 6.29 (1H, dd, *J* = 8.4, 3.0 Hz), 6.00 (1H, br s), 5.88 (1H, ddd, *J* = 7.5, 2.1, 2.1), 4.89 (1H, br. d, *J* = 7.8 Hz), 4.68 (1H, dd, *J* = 8.4, 1.2 Hz), 3.66 (1H, d, *J* = 13.8 Hz), 2.97 (1H, d, *J* = 13.8 Hz), 2.64 (1H, d, *J* = 15.0 Hz), 2.36 (3H, s), 2.20 (3H, s), 2.13 (3H, s), 1.82 (1H, ddd, *J* = 15.3, 2.1, 2.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1, 165.6, 164.4, 139.7, 137.3, 133.5, 130.9, 128.7, 127.9, 109.1, 105.5, 71.4, 69.9, 68.0, 61.7, 46.4, 39.6, 21.2, 14.5, 14.0; $[\alpha]_D^{27}$ = −178 (c = 0.556, $CHCl_3$) (Lit. $[\alpha]_D$ = −102 (*c* = 0.4, $CHCl_3$)); HRMS (ESI) *m/z*: calcd. for $C_{22}H_{24}N_2NaO_5S_2$ [M+Na$^+$] 483.1019, found 483.0996. The spectral data were identical with those reported in the literature [13].

*4.40 AllomCl (**26**)* [20]

and paraformaldehyde (19.0 g, 0.633 mol) was added anhydrous hydrogen chloride generated from H_2SO_4 and NaCl at room temperature. After stirred for 30 min at room temperature, the mixture was heated by oil bath at 150 °C for 2 h. The resulting mixture was diluted with hexanes, dried over magnesium sulfate, and the hexanes were removed under reduced pressure. The crude material was distilled from anhydrous calcium chloride to afford AllomCl (**26**) (25.0 g, 0.234 mol, 40%) as colorless oil.

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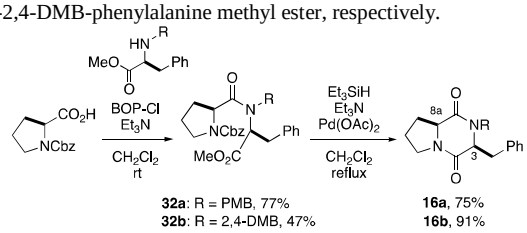
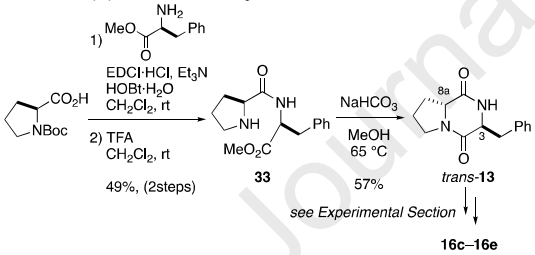
16. Compounds **16a** and **16b** with C3 (*S*) and C8a (*S*) stereochemistries were synthesized by the stepwise condensation of *N*-Cbz-L-proline and *N*-PMB-L-phenylalanine methyl ester or *N*-2,4-DMB-phenylalanine methyl ester, respectively.



17. Compounds **16c–e** were synthesized from *trans*-**13** with C3 (*S*) and C8a (*R*) stereochemistries, which was prepared by the stepwise condensation of *N*-Boc-L-proline and L-phenylalanine methyl ester. During the intramolecular condensation step, the C8a (*S*) stereochemistry was completely isomerized to give *trans*-**13** with C8a (*R*) stereochemistry.



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22. Specific rotations of synthetic **4** and **5** were significantly larger than those reported. According to our careful inspection, the reported ^{1}H NMR spectra of natural **5** should contain small amount of impurities, which presumably caused disagreement of the magnitude of the specific rotation.
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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: