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Total syntheses of chaetocin and *ent*-chaetocin

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ABSTRACT

The first total synthesis of chaetocin (**1**), a potent histone methyltransferase inhibitor, is described in detail. Key reactions were radical bromination for α-oxidation of the diketopiperazine ring, and reductive radical coupling for construction of the dimeric core structure. Stereoselective construction of the disulfide bridges was achieved via substitution reaction with H_2S. The total synthesis of **1** was accomplished in nine steps starting from known D-amino acid derivatives. Total synthesis of non-natural *ent*-chaetocin (*ent*-**1**) was also achieved via the established synthetic route, starting from L-amino acid derivatives.

1. Introduction

Chaetocin (**1**), a secondary metabolite isolated from fermentation broth of *Chaetomium minutum* in 1970,[1] belongs to a family of dimeric epidithiodiketopiperazine (ETP) alkaloids. Biological activities of **1**, such as antibacterial and cytostatic activities, have been known for a long time,[2] but recently, the potent inhibitory activity of **1** against lysine-specific histone methyltransferases has attracted increasing attention.[3] Histone methylation is involved in controlling gene expression patterns, in conjunction with DNA methylation and histone acetylation.[4] As for DNA methylation, 5-azacytidine (Vidaza™) has been developed as an anti-cancer drug that acts by controlling the level of DNA methylation.[5] Histone acetylation has also been well studied, and several inhibitors of the enzymes responsible for regulating the level of acetylation are approved (e.g., Zolinza™) or undergoing clinical trials for the treatment of critical diseases.[6] However, histone methylation is less well understood, compared to DNA methylation and histone acetylation.[7]

To clarify the molecular mechanism of histone methylation, the development of selective inhibitors would be useful. Furthermore, such selective inhibitors are expected to be candidate anti-cancer drugs, because dysfunction of histone methylation is considered to induce cancerous diseases.[8] However, only a few compounds are known that inhibit histone methyltransferases.[9] Among them, **1** is the only known naturally occurring inhibitor of lysine-specific histone methyltransferases. The structural features of **1** include a C_2 symmetric octacyclic ring system with eight stereogenic carbon centers and chemically sensitive disulfide bridges on the diketopiperazine (DKP) rings. Although more than 100 ETP alkaloids have been isolated from natural sources, only a few of them have been totally synthesized.[10] For example, Kishi and Fukuyama reported seminal work on the ETP alkaloids in 1970s, including total syntheses of gliotoxin and sporidesmines.[11] Quite recently, Overman et al. achieved the first total synthesis of gliocladine C.[12]

Fig. 1 shows the dimeric ETP alkaloids for which total syntheses have been achieved. Movassaghi and Kim reported an elegant total synthesis of 11,11′-dideoxyverticillin (**2**) in 2009.[13] However, **1** is considered to be one of the most challenging synthetic targets among dimeric ETP alkaloids, because of the additional presence of hydroxymethyl groups that may undergo facile β-elimination during synthetic manipulations. Early in 2010, we achieved the first total synthesis of chaetocin (**1**), *ent*-chaetocin (*ent*-**1**), and their sulfur-deficient analogues.[14] We also evaluated their histone methyltransferase-inhibitory activity and demonstrated the significance of the sulfur group for the inhibitory activity. Following our report, Movassaghi's group established a more general route to chaetocin (**1**) and related poly sulfur natural products.[15] In this article, we present full details of our chemical synthesis of **1**.

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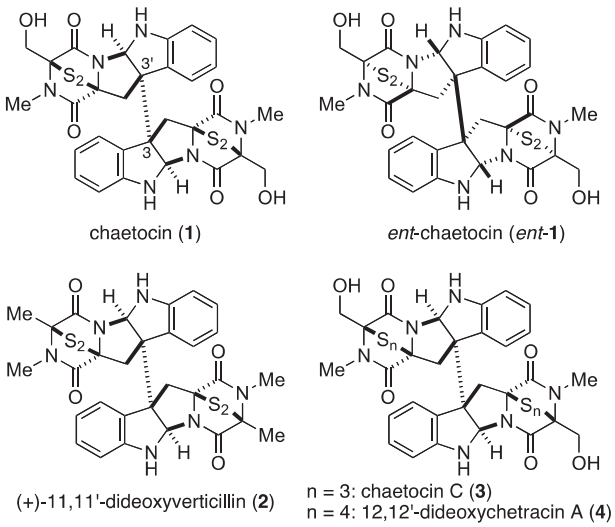


Fig. 1. Dimeric epidithiodiketopiperazine (ETP) alkaloids that have been chemically synthesized to date.

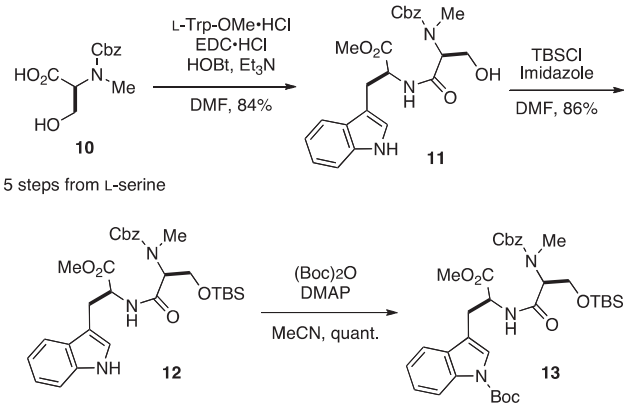
2. Results and discussion

2.1. Retrosynthesis of chaetocin

Our retrosynthetic analysis of chaetocin (**1**) is shown in Scheme 1. Since the disulfide bridge is extremely labile under oxidative, reductive, and basic conditions, we planned to carry out its construction at the last stage of the synthesis, under acidic conditions. We selected acid-sensitive protecting groups to protect the hydroxyl group (P^1) and the amino group (P^2), anticipating that such protecting groups could be removed simultaneously with construction of the disulfide. If substitution reaction is employed for this purpose, an appropriate leaving group (X) is required at the α-position of the DKP ring. The precursor **5** could be synthesized through dimeric octacyclic DKP **6** or monomeric tetracyclic DKP **7**. Basically, these routes differ in the order in which α-oxidation and dimerization reactions are performed. Compounds **6** and **7** are considered to be accessible from tetracyclic bromide **8**, which would be synthesized via bromocyclization of DKP **9**. Alternatively, compound **6** might also be accessible from the DKP **9** through a sequential oxidative dimerization–cyclization process. In route A and route B, the α-positions of the DKP rings are oxidized after the construction of the dimeric core structure. Such late-stage oxidation is proposed to occur in the biosynthesis.[16] On the contrary, route C starts from the α-oxidation of the tetracyclic compound **8**, followed by reductive dimerization of the resulting **7**. Since enolate chemistry seemed inappropriate, we planned to examine radical bromination reaction for the α-oxidation. We expected that these dimerization reactions of the bromide **7** or **8** would be feasible by using the Co(I)-mediated reductive coupling reaction reported by Movassaghi's group.[13,15,17,18] Because retention of the stereochemistry at the benzylic position is assured in the Co(I)-mediated reductive coupling reaction, the absolute stereochemistry would be directly transferred to the 3 and 3′ positions of **1**. Therefore, it is essential that bromocyclization of **9** should occur stereoselectively. Because the diastereoselectivity in this step was uncertain at the planning stage and because the newly generated absolute stereochemistry depends on that of the starting amino acids, the preparation of the bromide **8** was optimized using less expensive L-amino acid derivatives.

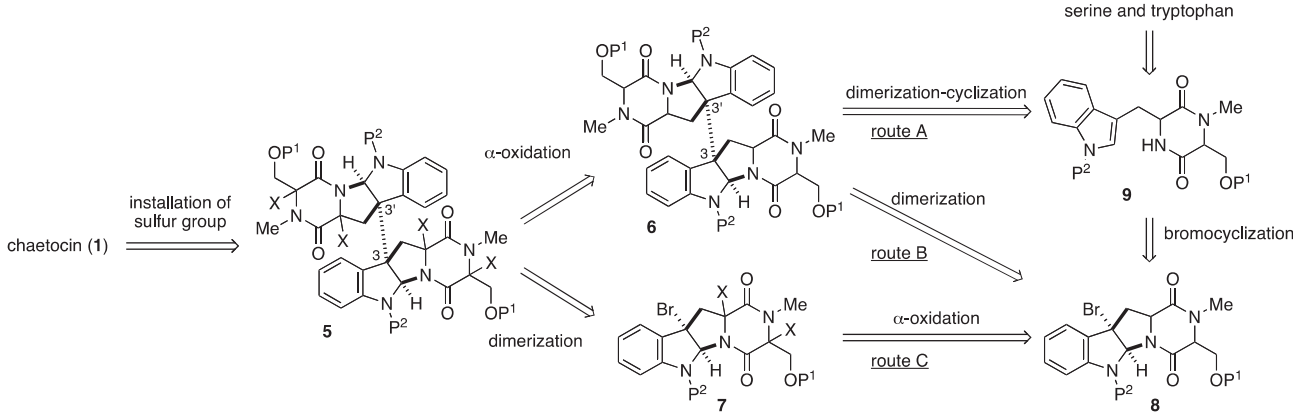
2.2. Synthesis of diketopiperazine

According to the synthetic plan shown in Scheme 1, we synthesized 2,5-diketopiperazines **9** as follows (Scheme 2). Based on Hughes's report, *N*-Cbz-protected *N*-methyl serine (**10**) was readily prepared in five steps.[19] Condensation of the obtained *N*-methyl-L-serine **10** with L-tryptophan methyl ester using EDC/HOBt method gave dipeptide **11**. The hydroxyl group and the nitrogen atom of the indole ring within **11** were protected with a TBS group and a Boc group, respectively.



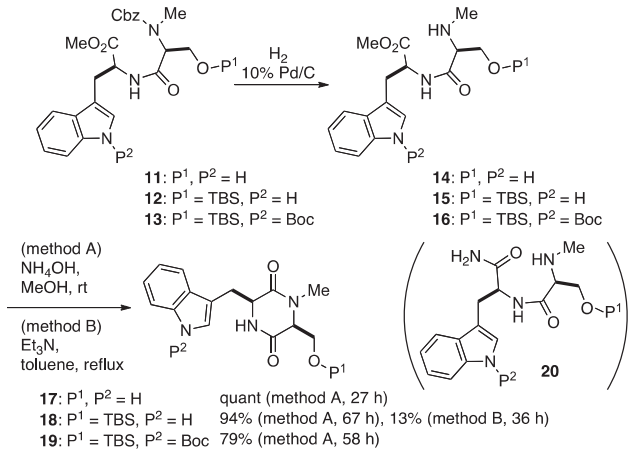
Scheme 2. Synthesis of L-Ser-Trp dipeptide **13**.

The resulting dipeptides **11**–**13** were subjected to hydrogenolysis to afford the desired amines **14**–**16** (Scheme 3). The



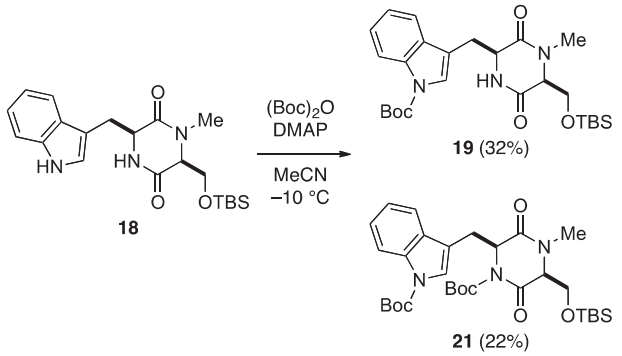
Scheme 1. Retrosynthetic analysis of chaetocin (**1**).

addition of a weak base is normally necessary for intramolecular condensation reaction between an ester and a secondary amine.[20] We first tried the reaction of **14**–**16** in the presence of ammonium hydroxide (method A). DKP **17**–**19** were obtained without difficulty, even though a trace amount of the epimer was obtained in each case. We also used triethylamine in place of ammonium hydroxide for amine **15**. Unfortunately, the cyclized compound **18** was obtained in only 13% yield (method B). The concentration of ammonium hydroxide should be kept under 7 vol %, otherwise amide **20** is produced in an appreciable amount.



Scheme 3. Syntheses of diketopiperazines.

The *N*-Boc-protected DKP **19** was also accessible from **18**, as shown in Scheme 4. However, di-Boc protection occurred concomitantly. Because the DKP ring is conformationally rigid, the nucleophilicity of the lactam might be higher than that of the acyclic amide.

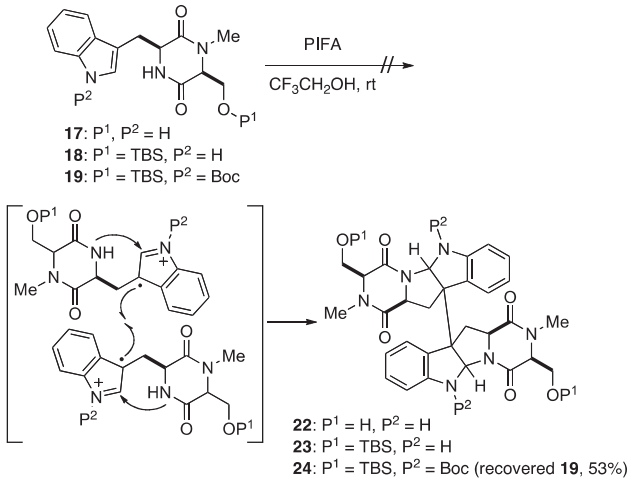


Scheme 4. Boc-protection of the indole ring of the DKP **18**.

2.3. Synthesis of the octacyclic compound and attempts at its α-oxidation

As shown in Scheme 1, we envisaged that single-electron transfer from the indole ring would give a radical cation intermediate, which might undergo radical homocoupling reaction and subsequent intramolecular nucleophilic attack of the amide on the resultant iminium ion (route A). This idea is supported by the findings by Hino and Nakagawa's group and more recently by Takayama's group.[21] Based on the original report, the synthesized diketopiperazines were treated with phenyliodine bis(trifluoroacetate) (PIFA) as an oxidant (Scheme 5).

Unfortunately, the reaction of **17** and **18** gave a complex mixture, and the desired compound was not detected. Movassaghi discussed a similar observation in their review article, in which they suggested that the complexity of the reaction arose from the instability

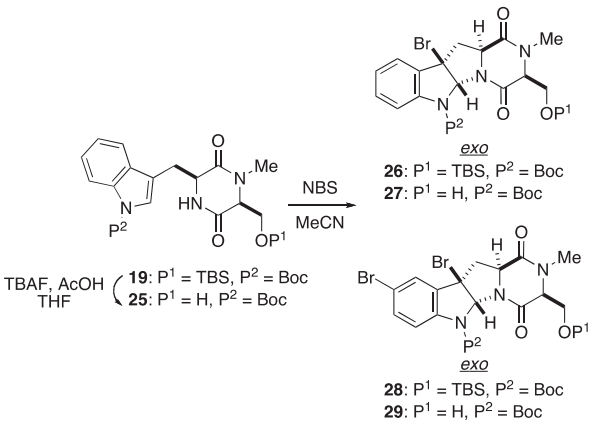


Scheme 5. Attempts at oxidative dimerization–cyclization of the DKPs.

of the starting material and the product under the oxidative conditions used.[22] We considered that it might be in part due to the weak electrophilicity of the imine or iminium ion intermediates (P^2=H). Therefore we next examined the reaction of the *N*-Boc-protected substrate **19**. However, the reaction of **19** did not afford the desired product, but instead the starting material was recovered in 53% yield. This may be with a result of the reduced electron density on the indole ring.

Anticipating that a stepwise procedure (route B or C) would be a more reliable approach, we next examined bromocyclization of **19**.[23] As shown in Table 1, **19** reacted smoothly with NBS at −30 °C to give tetracyclic compound **26** in 88% yield (entry 2). Interestingly, this bromocyclization reaction was highly stereoselective. The corresponding diastereomer was not detected even at higher temperatures, although the amount of over-brominated compound **28** was increased (entries 3 and 4). The bulky TBS group is considered unlikely to affect the stereoselectivity, since the reaction of deprotected **25** also proceeded in a stereoselective manner (entry 5).

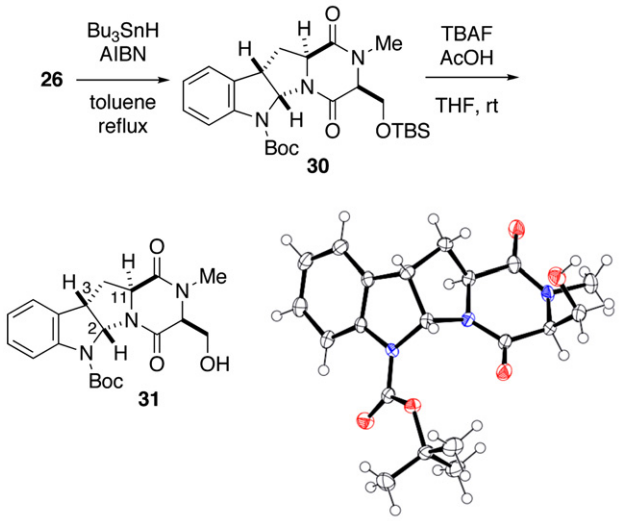
Table 1
Optimization of bromocyclization



Entry	Substrate	Temperature	Monobromide	Dibromide
1	**19**	−40 °C	**26**: 28%	**28**: —[a]
2	**19**	−30 °C	**26**: 88%	**28**: 6%
3	**19**	−20 °C	**26**: 32%	**28**: 24%
4	**19**	0 °C	**26**: 46%	**28**: 28%
5	**25**	−30 °C	**27**: 58%[b]	**29**: —[c]

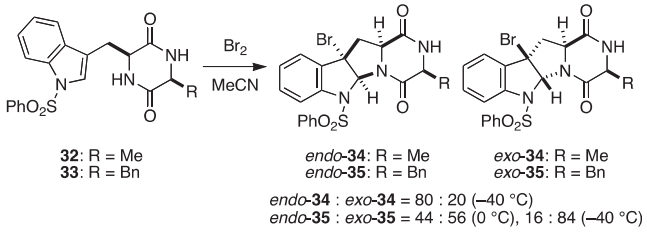
[a] Not detected.
[b] A trace amount of by-product assigned as isomeric *endo*-**27** was detected by LC/MS.
[c] A trace amount of by-product assigned as **29** was detected by LC/MS.

After the removal of the bromine atom and the TBS group, the structure of **31** was determined by X-ray analysis, which revealed that the bromine atom within **26** was positioned trans to the hydrogen atoms at the C_{11} position (Scheme 6). In this article, we refer to the reaction giving the *trans* product as *exo*-selective, and that giving the *cis* product as *endo*-selective.



Scheme 6. Conversion of **26** to **31**, and X-ray crystallographic structure of **31**.

Similar bromocyclization reactions were examined by Movassaghi's group in their total syntheses of (−)-ditryptophenaline (**2**)[17b] and (+)-11,11′-dideoxyverticillin (**4**).[13] The *endo*/*exo*-selectivity of the reactions varied depending on the size of the α-substituent on the DKP ring and the reaction temperature (Scheme 7).[24] It should be noted that DKP substrates without the *N*-methyl group were used in their work. Therefore, we speculated that the difference in the diastereoselectivity might be caused by the presence or absence of the *N*-methyl group.



Scheme 7. Halocyclization reaction of DKPs **32** and **33** reported by Movassaghi's group.[13,17b]

The excellent *exo*-selectivity observed in our reaction can be explained as follows. The conformations of the DKP rings are known to vary from planar to boat- or chair-like, depending on the substitution pattern. In the case of *N*-methyl DKPs, side chains would be preferentially located at the pseudo-axial position to avoid steric interaction with the *N*-methyl group.[25] Therefore, in the case of compound **19**, the TBS-oxymethyl group is expected to be located at the pseudo-axial position to minimize steric interaction with the *N*-methyl group (Fig. 2).

This speculation is supported by the X-ray structure of **31**. It seems that the reaction via transition state A proceeds without difficulty to afford *exo*-**26**. In contrast, the formation of the *endo*-oriented product is unfavorable, since the transition state B would be destabilized considerably due to the severe steric repulsion between the indole ring and the TBS-oxymethyl group.

As revealed by the X-ray analysis (Scheme 6), the absolute configuration at the C_2 and C_3 positions of **26** was not coincident

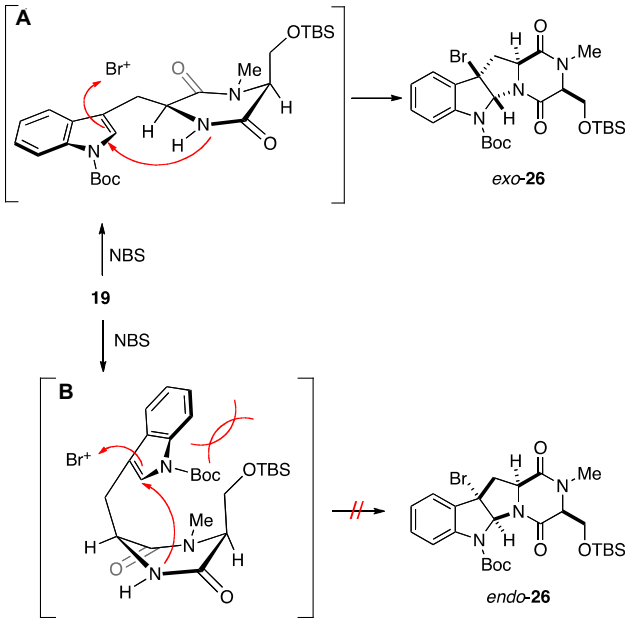
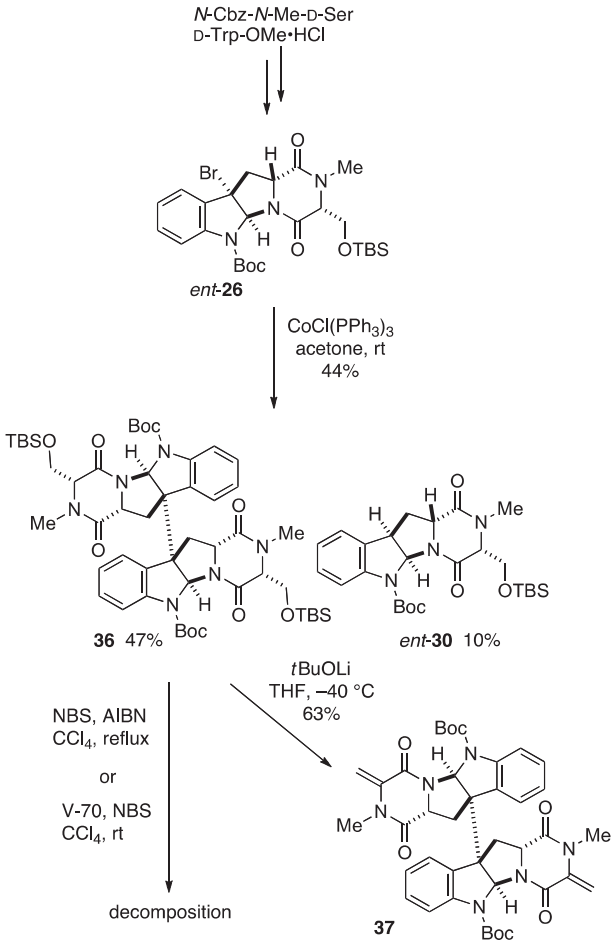


Fig. 2. Stereochemical model of bromocyclization.

with that of **1**. This indicates that the enantiomer of **1** (*ent*-chaetocin, *ent*-**1**) would be obtained starting from naturally abundant L-amino acid derivatives. Therefore, we prepared its enantiomer *ent*-**26** using the corresponding D-amino acid derivatives as starting materials (Scheme 8).

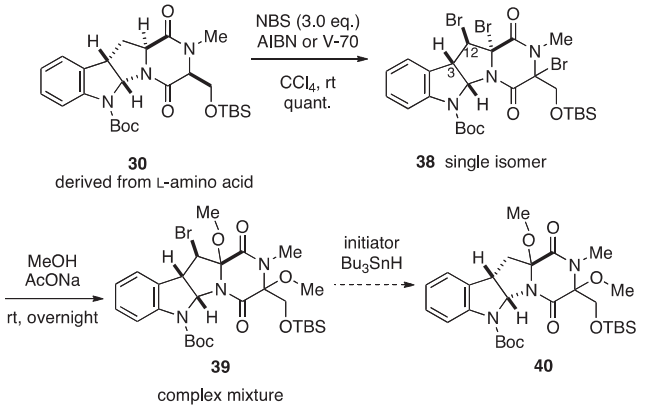


Scheme 8. Reductive dimerization and attempts at α-oxidation of the octacyclic core structure.

According to route B, we next examined the reductive radical coupling reaction. As shown in Scheme 8, the reductive coupling of *ent*-**26** was carried out based on Movassaghi's procedure. The reaction proceeded smoothly to give the desired dimeric compound **36** in 47% yield together with the reduced compound *ent*-**30** in 10% yield. For the introduction of the sulfur functionality onto the simple DKP rings, Schmidt et al. examined electrophilic sulfenylation using enolate chemistry.[26] However, the reactions of the octacyclic compound **36** with various bases, including LDA, LiHMDS, and KHMDS, led to complete decomposition, even at −78 °C, regardless of the presence or absence of electrophilic sulfur compounds. Although the reaction with ^{t}BuOLi was clean, β-elimination of the TBS-oxy group readily occurred to give *exo*-methylene compound **37** in 63% yield. Therefore, we next investigated the radical α-bromination reaction as planned in Scheme 1, expecting that the undesired β-elimination of the TBS-oxy group would be suppressed, because the formation of an oxy-radical species is energetically disfavored. Even though only non-substituted diketopiperazines derived from glycine or sarcosine were employed for the radical α-bromination reaction,[11,27] we tried the reaction of **36** with NBS. Unfortunately, the dimeric structure of **36** was extremely unstable under the radical conditions even at room temperature,[28] resulting in the formation of a complex mixture. Therefore, we had to abandon the late-stage oxidation of the dimeric core.

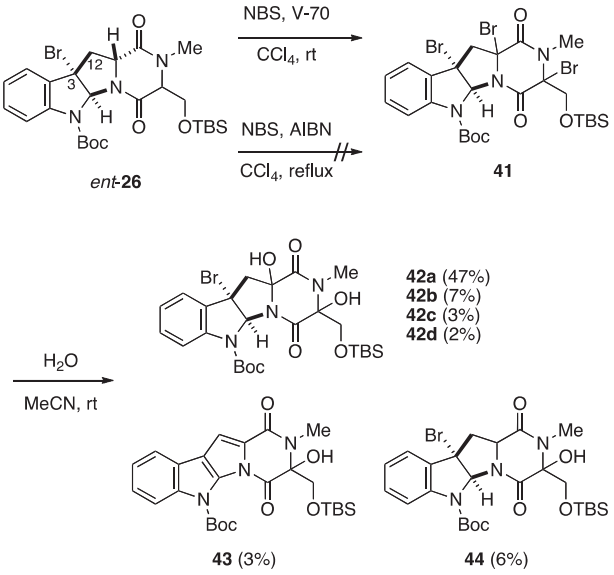
2.4. α-Oxidation of tetracyclic compound *ent*-26

To confirm the feasibility of α-bromination without β-elimination, we first studied a model reaction using compound **30** under standard reaction conditions using AIBN and NBS (Scheme 9).



Scheme 9. Radical bromination of **30** derived from L-amino acids.

Although the desired bromination proceeded smoothly, the C_{12} position was also brominated, affording tribromide **38** as a single stereoisomer. It is likely that the undesired bromination occurred quickly after the reactions at the α-positions, since the tribromide **38** was a major product even when only 2 equiv of NBS was used. However, the reaction gave many by-products. It is well-known that a hydrogen atom next to a bromine atom tends to be abstracted by a radical species to give a carbon radical, because the generated carbon radical is stabilized by positive interaction with the bonding orbital of the C–Br bond.[29] Accordingly, the second bromine atom would attack the carbon radical from the opposite side to the bromine atom already in the compound. Such stereoelectronic and steric effects are considered to result in selective bromination with trans stereochemistry. Although the obtained tribromide could be converted to the corresponding methyl ether **39**, the subsequent removal of the remaining bromine atom at the C_{12} position was found to be difficult. An analysis of the coupling constants in the ^{1}H NMR spectrum of **38** suggested that the hydrogen atom at the C_3 position and the bromine atom at the C_{12} position are *cis*-oriented. This led us to hypothesize that the undesired third bromination at the C_{12} position would be suppressed if the C_3 position carried a bulky group. We expected that the tetracyclic bromide *ent*-**26** would be a suitable compound for this purpose (Scheme 10). As we hoped, α-bromination occurred selectively to give the desired compound **41** almost quantitatively as a single stereoisomer, when the reaction was performed at room temperature using V-70[28] as a radical initiator. In contrast, *ent*-**26** decomposed under standard reflux conditions with AIBN. These results clearly indicate that the bulky bromine atom at the benzylic position played an important role in this reaction. Importantly, β-elimination of the silyloxy group was effectively suppressed by use of the radical reaction. On the other hand, the instability observed in the case of **36** may be associated with its dimeric structure. Due to its high reactivity, the obtained crude **41** was used directly in the next reaction after removal of precipitated succinimide by filtration.



Scheme 10. Successful α-oxidation of the tetracylic compound *ent*-**26** (two-step yield is given).

The obtained dibromide **41** was subjected to substitution reactions using various oxygen nucleophiles, including water, alcohol, and acetate anion. Among them, water was found to be the best nucleophile, affording hemiaminal **42**. Thus, the treatment of **41** with phosphate buffer gave the diol **42a** as a major stereoisomer, accompanied with the other three stereoisomers **42b**–**d** and two by-products (**43** and **44**). Since the completion of the radical bromination was confirmed by ^{1}H NMR, it is clear that the by-product **44** was formed from **41**, and not from partial bromination of *ent*-**26**. The stereochemistry of the major diastereomer **42a** was unequivocally determined by X-ray crystallographic analysis, while those of the minor diols remain unclear (Fig. 3).

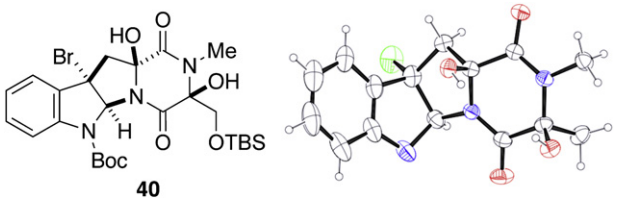
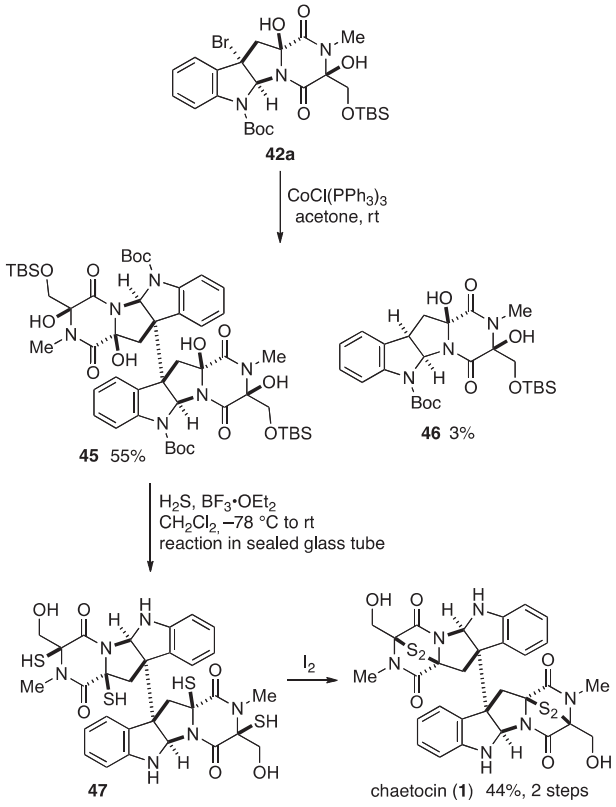


Fig. 3. X-ray crystallographic analysis of **42a** (protecting groups are omitted for clarity).

2.5. Completion of the total synthesis of chaetocin (1)

The final stage of the total synthesis is briefly summarized in Scheme 11. With the hemiaminal **42a** in hand, construction of the octacyclic framework was investigated using Movassaghi's reductive coupling reaction. Since the hemiaminal moiety within **42a** is likely to be unstable, we were afraid that **42a** would decompose under the reaction conditions. To our delight, however, the desired octacyclic tetraol **45** was obtained in 55% yield as a single isomer. As in the case of the synthesis of **36**, a small amount of reduced by-product **46** was isolated. As discussed later, the efficiency of this reaction was strongly influenced by the relative stereochemistry of the hemiaminal moiety.

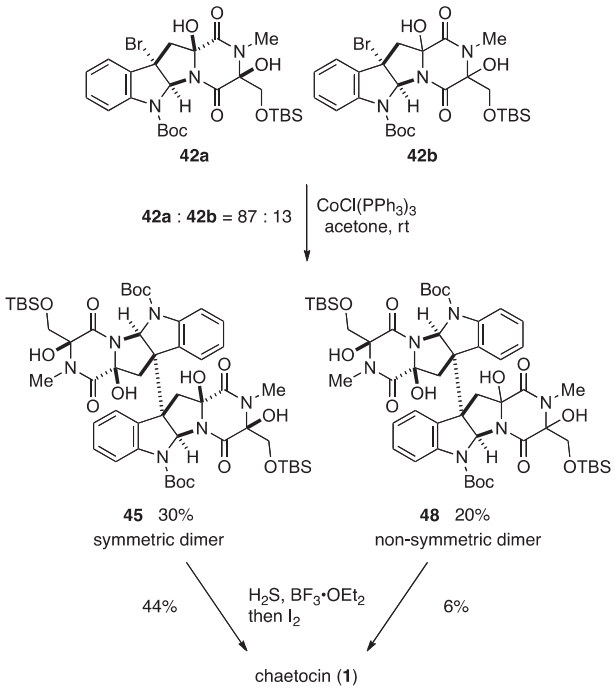


Scheme 11. Completion of the total synthesis of chaetocin (**1**).

Based on previous reports, in which hydrogen sulfide was reacted with a hemiaminal ether in the presence of $ZnCl_2$,[30] we examined the substitution reaction using Lewis acids. Because $BF_3 \cdot OEt_2$ is a widely used Lewis acid for the activation of hemiaminals and their ethers, we tested it in our case. Considering the intrinsic nature of boron as a hard Lewis acid, we expected that the resulting thiol would be sufficiently stable to $BF_3 \cdot OEt_2$. Thus, the reaction of **45** with condensed hydrogen sulfide (bp: −60.7 °C) was attempted in the presence of $BF_3 \cdot OEt_2$ in a sealed tube, and furnished the desired tetrathiol **47**. The crude tetrathiol **47** was subsequently oxidized with molecular iodine, and chaetocin (**1**) was obtained in 44% yield (two steps). The obtained compound was spectroscopically identical to a natural sample of **1**. It should be noted that the final step involved no less than 10 bond-forming and breaking events: (1) four substitution reactions, (2) the removal of four protecting groups (Boc and TBS groups), and (3) formation of two disulfide bonds. Using this established route, we also achieved the total synthesis of *ent*-chaetocin (*ent*-**1**) from L-amino acid derivatives as starting materials.

2.6. Effect of stereochemistry in the dimerization reaction

As mentioned above, the relative configuration of the hemiaminal moiety influenced the dimerization reaction. When a mixture of **42a** and its stereoisomer **42b** was treated with the Co(I) complex,[13,15,17,18] symmetric **45** and non-symmetric **48** were obtained in 30% and 20% yield, respectively (Scheme 12).[31] In this reaction, three isomers are potentially formed, but the homocoupling product of **42b** was not isolated. To confirm this, we tested the coupling reaction of the isolated **42b**. The reaction gave a complex mixture, but no homocoupling product was detected. It is likely that the symmetric **45** arose from the homocoupling reaction of **42a**, and non-symmetric **48** was formed via the heterocoupling reaction between **42a** and **42b**. We speculate that the switch of the stereochemistry at the α-position caused strong steric repulsion between the two tetracyclic ring systems, disfavoring their approach.



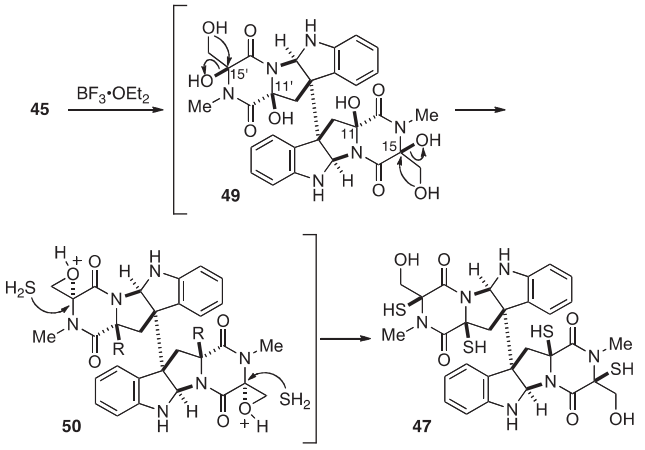
Scheme 12. Dimerization reaction using a diastereomeric mixture of diols **42a** and **42b**.

2.7. Stereochemical effects in the substitution reaction with H_2S

While symmetric **45** underwent substitution reaction with H_2S in 44% yield, **48** was less reactive, affording only 6% yield of the final product (Scheme 12). These results indicate that $BF_3 \cdot OEt_2$ could access the hydroxyl groups of **45**, and the substitution reaction could proceed smoothly. It is inferred that at least one hydroxyl group within **48** is oriented toward the inside of the core structure, thereby preventing its activation by the Lewis acid. This result also indicates the importance of the stereochemistry at the hemiaminal moiety for the substitution reaction.

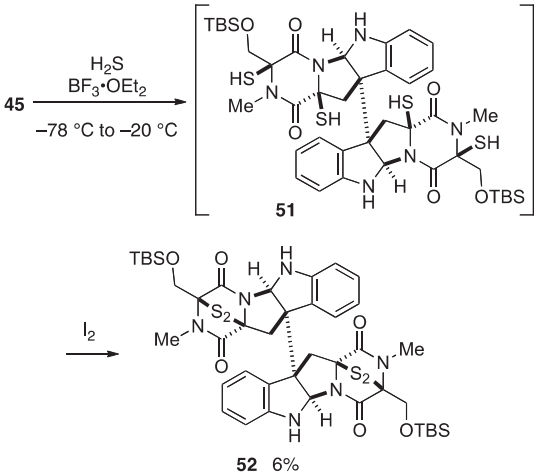
Examination of the ^1H NMR spectrum of the crude product **47** suggested that hydrogen sulfide attacked the putative iminium intermediate stereoselectively. Initially, we simply reasoned that the steric bias caused by the double-decker structure would favor the attack of hydrogen sulfide from the outside of the core structure. This idea may explain the stereochemical outcome at the C_{11} and $C_{11'}$ positions. However, a molecular modeling study suggested that the C_{15} and $C_{15'}$ positions are more accessible, so that H_2S can attack from the other side. Our alternative explanation is as follows

(Scheme 13): if the TBS group is removed before displacement, the resulting hydroxyl group may attack the generated iminium ion to form an epoxide with inversion of the stereochemistry, and re-opening with hydrogen sulfide would produce the desired stereochemistry.



Scheme 13. Alternative idea to explain the high stereoselectivity observed in the H_2S substitution reaction.

However, careful analysis of the reaction suggested that cleavage of the TBS group occurred after the substitution event. Namely, when the reaction was quenched at −20 °C, **52** was obtained with the TBS group remaining (Scheme 14). Although the yield of **52** was low, involvement of the hydroxyl group in the double inversion mechanism is unlikely. Instead, the TBS-oxy group might act as a bulky shielding group. Since the TBS-oxy group of **45** points toward the inside of the core structure, the reactive iminium ion might be formed with the TBS group keeping similar orientation. If this is the case, it appears that the TBS group effectively interferes with the attack of hydrogen sulfide from the inner surface of the core structure, so that hydrogen sulfide should attack preferentially from the outer surface of the core (Fig. 4).



Scheme 14. Substitution reaction of tetraol **45** below −20 °C.

Although further investigation, including computational structural analysis of **45** and its iminium forms, is required to elucidate the reaction mechanism, we believe that the stereoselectivity of this substitution reaction is controlled by its unique double-decker structure, as well as the orientation of the TBS groups.

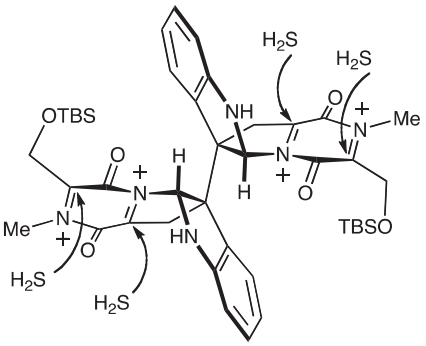


Fig. 4. Possible explanation for the stereoselectivity of the substitution reaction by hydrogen sulfide.

3. Conclusion

We have achieved the first total synthesis of chaetocin (**1**) and *ent*-chaetocin (*ent*-**1**) in only nine steps starting from known *N*-methyl-serine and tryptophan methyl ester. The key reactions were two radical reactions. Firstly, the α-oxidation of the tetracyclic DKP compound was successfully accomplished by radical bromination with NBS, followed by treatment with water. This transformation was useful to avoid undesired β-elimination of the oxygen functionality. Secondly, the obtained diol was subjected to radical dimerization using the Co(I) complex. Though the diol contained the relatively unstable hemiaminal moiety, the dimerization reaction was successfully conducted to give a symmetrical octacyclic carbon framework. The final disulfide bridge formation was achieved stereoselectively, and all the protective groups were removed in a single step. We have discussed the origin of the stereoselectivity observed in the stereoselective bromocyclization reaction, the radical bromination reaction, and the substitution reaction by hydrogen sulfide. The established synthetic route described in this paper should also be applicable to the syntheses of various derivatives, which will facilitate the development of molecular tools for epigenetic research. The results of a detailed structure–activity relationship study will be reported in due course.

4. Experimental section

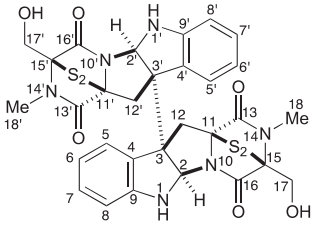
4.1. General

NMR spectra were recorded on a JEOL JNM-ECP500 spectrometer operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR or a JEOL JNM-ECP400 spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts are reported downfield from TMS (=0) or relative to the solvent signal as an internal reference for ^{1}H NMR. For ^{13}C NMR, chemical shifts are reported relative to the solvent signal as an internal reference. IR was measured on a Thermo Nicolet AVATAR 370 FTIR. Optical rotations were measured on a JASCO DIP-370 polarimeter. In some cases, purification was carried out using Yamazen medium-pressure liquid chromatography (MPLC) systems [pump, 580-D; UV-detector, prepUV-10VW; column, Yamazen HI-FLASH™ or Ultra Pack™ SI-40A or Kusano pre-packed SiO_2 column; eluent, *n*-hexane/ethyl acetate or chloroform/methanol]. Column chromatography was performed with silica gel 60 (40–100 μm) purchased from Kanto Chemical Co., Inc. Dehydrated *N*,*N*-dimethylformamide (DMF), acetonitrile, stabilizer-free tetrahydrofuran (THF), and dichloromethane were purchased from Kanto Chemical Co., Inc. Dehydrated acetone was purchased from Wako Pure Chemical Industries, Ltd. *N*-Bromosuccinimide was recrystallized from water and dried over P_2O_5 under vacuum before use. Other solvents and

reagents used in this paper were purchased and used as received. *N*-Benzyloxycarbonyl-*N*-methyl-D-serine (**7**) was synthesized from D-serine according to the reported procedure.[19] Tris(triphenylphosphine)cobalt(I) chloride ($CoCl(PPh_3)_3$) was freshly prepared according to the literature.[32] A natural sample of chaetocin (**1**) was purchased from Sigma–Aldrich.

4.2. Numbering system

Based on a numbering system employed in Movassaghi's paper,[13] we use the following numbering system in this paper. The numbers assigned to early synthetic intermediates to specify the positions of interest are in accord with the corresponding carbons within chaetocin.



(+)-Chaetocin

4.3. Synthesis

The following experimental procedures and characterization data are given for the synthesis of natural chaetocin (**1**). For the enantiomers of the synthetic intermediates, which were derived from L-amino acid derivatives, only optical rotations are provided.

*4.3.1. Synthesis of dipeptide ent-**11**.* To a solution of *ent*-**10** (14.3 g, 56.4 mmol), D-tryptophan methyl ester hydrochloride (14.4 g, 56.4 mmol), and triethylamine (7.9 mL, 56.7 mmol) in *N*,*N*-dimethylformamide (180 mL) were added 1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide hydrochloride (11.9 g, 62.1 mmol) and 1-hydroxybenzotriazole monohydrate (9.15 g, 67.7 mmol) at −20 °C. The reaction mixture was allowed to warm up to room temperature and then stirred overnight. After removal of the solvent in vacuo, the obtained residue was diluted with ethyl acetate (700 mL). The organic layer was washed with 5% aqueous sodium bicarbonate solution (4×500 mL), 10% aqueous citric acid solution (4×500 mL), and water (3×500 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. Further purification was performed by flash column chromatography (chloroform/methanol=99/1 to 95/5) to give *ent*-**11** (23.4 g, 91%) as a colorless gum. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C) δ: 2.59 (br s, 1H, OH), 2.65 (s, 3H, $C_{18}H$), 3.21 (dd, *J*=6.6 Hz, 14.9 Hz, 1H, $C_{12}H$), 3.29 (dd, *J*=5.3 Hz, 14.9 Hz, 1H, $C_{12}H$), 3.69 (s, 3H, OCH_3), 3.78 (br, 1H, $C_{17}H$), 3.95–4.00 (m, 1H, $C_{15}H$), 4.58 (br, 1H, $C_{17}H$), 4.83–4.87 (m, 1H, $C_{11}H$), 5.07 (br s, 2H, PhC*H*$_2$), 6.50 (br s, 1H, $N_{10}H$), 6.84 (s, 1H, C_2H), 7.08 (t, *J*=7.6 Hz, 1H, C_6H), 7.15 (t, *J*=7.6 Hz, 1H, C_7H), 7.28 (d, *J*=7.6 Hz, 1H, C_5H), 7.25–7.40 (m, 5H, *Ph*CH_2OCON), 7.80 (d, *J*=7.6 Hz, 1H, C_8H), 7.84 (br s, 1H, N_1H); ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C) δ: 27.6 (C_{12}), 31.8 (C_{18}), 52.5 (OCH_3), 52.8 (C_{11}), 60.6 (C_{15}), 61.1 (C_{17}), 67.9 (PhC*H*$_2$OCON), 109.9 (C_3), 111.5 (C_5), 118.5 (C_8), 119.9 (C_6), 122.5 (C_7), 123.0 (C_2), 127.5 (C_4), 128.1 (*Ph*CH_2OCON), 128.4 (*Ph*CH_2OCON), 128.7 (*Ph*CH_2OCON), 136.5 (C_9 and PhCH_2OCON), 170.3 (C_{16}), 172.2 (C_{13}); $[\alpha]_D$ +6.8 (*c* 1.0, $CHCl_3$, 25 °C); FTIR (neat) cm^{-1}: 3321 (br), 2953 (m), 1666 (s), 744 (s); LRMS (ESI) *m*/*z* 476 $[M+Na]^+$.

Compound **11**: $[\alpha]_D$ −9.5 (*c* 0.63, $CHCl_3$, 24 °C).

*4.3.2. Synthesis of dipeptide ent-**12**.* To a solution of *ent*-**11** (38.7 g, 85.2 mmol) and imidazole (13.9 g, 204 mmol) in dry *N*,*N*-dimethylformamide (0.4 M, 210 mL) was added *tert*-butyldimethylchlorosilane (15.4 g, 226 mmol) under a nitrogen atmosphere. After having been stirred overnight at room temperature, the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (400 mL), then washed with water (3×200 mL) and brine (150 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give crude *ent*-**12** (48.8 g, quant.) as a pale yellow gum. A small crude sample was further purified by GPC for spectroscopic analysis. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C) δ: 0.00 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.82 (9H, s, $SiC(CH_3)_3$), 2.72 (s, 3H, $C_{18}H$), 3.23 (dd, *J*=5.5 Hz, 11.9 Hz, 1H, $C_{12}H$), 3.31 (dd, *J*=5.5 Hz, 11.9 Hz, 1H, $C_{12}H$), 3.67 (s, 3H, OCH_3), 3.84 (br, 1H, $C_{17}H$), 4.03 (dd, *J*=6.4 Hz, 10.5 Hz, 1H, $C_{17}H$), 4.08 (br, 1H, $C_{15}H$), 4.88 (br, 1H, $C_{11}H$), 5.10 (br s, 2H, PhC*H*$_2$OCON), 6.89 (br, 1H, C_2H), 7.08 (t, *J*=7.5 Hz, 1H, C_6H), 7.16 (t, *J*=7.5 Hz, 1H, C_7H), 7.29 (d, *J*=7.5 Hz, 1H, C_5H), 7.24–7.34 (m, 5H, *Ph*CH_2OCON), 7.51 (br d, *J*=7.5 Hz, 1H, C_8H), 7.96 (br, 1H, N_1H); ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C) δ: −5.53 ($SiCH_3$), −5.45 ($SiCH_3$), 18.1 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 27.8 (C_{12}), 31.6 (C_{18}), 52.3 (OCH_3), 52.9 (C_{11}), 60.8 (C_{17}), 61.4 (C_{15}), 67.7 (PhCH_2OCON), 110.3 (C_4), 111.4 (C_5), 118.7 (C_8), 119.9 (C_6), 122.4 (C_7), 122.9 (C_2), 127.8 (*Ph*CH_2OCON), 128.1 (*Ph*CH_2OCON), 128.2 (*Ph*CH_2OCON), 128.7 (*Ph*CH_2OCON), 136.5 (C_9), 136.9 (PhCH_2OCON), 169.3 (C_{16}), 172.2 (C_{13}); $[\alpha]_D$ −8.2 (*c* 0.86, $CHCl_3$, 23 °C); FTIR (neat) cm^{-1}: 3338 (br), 2952 (m), 2930 (m), 1741 (s), 1690 (s), 1676 (m), 1154 (s), 1112 (s), 839 (s), 742 (s); LRMS (ESI) *m*/*z* 590 $[M+Na]^+$.

Compound **12**: $[\alpha]_D$ +10 (*c* 1.0, $CHCl_3$, 25 °C).

*4.3.3. Synthesis of dipeptide ent-**13**.* To a solution of *ent*-**12** (17.6 g, 30.9 mmol) in dry acetonitrile (80 mM, 390 mL) was added 4-dimethylaminopyridine (378 mg, 3.09 mmol) at 0 °C. Then di-*tert*-butyl dicarbonate (7.44 g, 34.0 mmol) in dry acetonitrile (30 mL) was added dropwise over 25 min. The reaction mixture was stirred at 0 °C for 5 h. Then additional di-*tert*-butyl dicarbonate (733 mg, 3.36 mmol) in dry acetonitrile (30 mL) was added dropwise. After further stirring for 90 min, the reaction mixture was concentrated in vacuo. Further purification by flash column chromatography (hexane/acetone=20/80) was carried out to give *ent*-**13** (19.9 g, 96%) as a white amorphous foam. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ: 0.00 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.81 (s, 9H, $SiC(CH_3)_3$), 1.66 (s, 9H, $(CH_3)_3COCON$), 2.80 (s, 3H, $C_{18}H$), 3.17 (dd, *J*=5.6, 14.6 Hz, 1H, $C_{12}H$), 3.26 (dd, *J*=5.6, 14.6 Hz, 1H, $C_{12}H$), 3.69 (s, 3H, OCH_3), 3.84 (br, 1H, $C_{17}H$), 4.05 (dd, *J*=6.6, 10.7 Hz, 1H, $C_{17}H$), 4.63 (br, 1H, $C_{15}H$), 4.90–4.92 (br m, 1H, $C_{11}H$), 5.07–5.12 (m, 2H, PhC*H*$_2$OCON), 7.00 (br, 1H, $N_{10}H$), 7.21 (t, *J*=7.7 Hz, 1H, C_6H), 7.27–7.36 (m, 7H, C_2H, C_7H, *Ph*CH_2OCON), 7.46 (br, 1H, C_5H), 8.10 (d, *J*=7.7 Hz, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.56 ($SiCH_3$), −5.50 ($SiCH_3$), 18.1 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 27.6 (C_{12}), 28.4 ($(CH_3)_3COCON$), 32.1 (C_{18}), 52.4 (OCH_3), 52.7 (C_{11}), 61.0 (C_{17}), 61.4 (C_{15}), 67.7 (PhCH_2OCON), 83.8 ($(CH_3)_3COCON$), 115.2 (C_3), 115.5 (C_5), 118.9 (C_8), 122.8 (C_6), 124.2 (C_2), 124.7 (C_7), 128.0 (*Ph*CH_2OCON), 128.1 (*Ph*CH_2OCON), 128.6 (*Ph*CH_2OCON), 130.7 (C_4), 135.6 (C_9), 136.7 (PhCH_2OCON), 149.7 ($(CH_3)_3COCON$), 169.4 (C_{16}), 171.8 (C_{13}); $[\alpha]_D$ −18 (*c* 1.0, $CHCl_3$, 26 °C); FTIR (neat) cm^{-1}: 3322 (br), 2953 (m), 2929 (m), 2856 (m), 1729 (s), 1691 (s), 1678 (s), 1255 (s), 1158 (s), 839 (s), 748 (s); LRMS (ESI) *m*/*z* 690 $[M+Na]^+$.

Compound **13**: $[\alpha]_D$ +16 (*c* 1.0, $CHCl_3$, 24 °C).

*4.3.4. Synthesis of dipeptides **14** and **15**.* Dipeptides **14** and **15** were synthesized according to the same protocol used for the synthesis of *ent*-**16** (vide infra). ^{1}H NMR data of each compound are summarized below.

Compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 2.35 (s, 3H), 3.01 (t, *J*=5.5 Hz, 1H), 3.28 (dd, *J*=5.9, 14.9 Hz, 1H), 3.35 (dd, *J*=5.9, 14.9 Hz, 1H), 3.61 (d, *J*=5.5, 11.2 Hz, 1H), 3.65 (dd, *J*=5.5, 11.2 Hz, 1H), 3.72 (s, 3H), 4.93 (ddd, *J*=5.9, 5.9, 8.4 Hz, 1H), 7.01 (app. d, *J*=2.2 Hz, 1H), 7.11 (t, *J*=7.7 Hz, 1H), 7.18 (t, *J*=7.7 Hz, 1H), 7.35 (d, *J*=7.7 Hz, 1H), 7.53 (d, *J*=7.7 Hz, 1H), 7.68 (d, *J*=8.4 Hz, 1H), 8.17 (br, 1H).

Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C) δ: 0.02 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 2.35 (s, 3H), 3.04 (dd, J=4.2, 7.7 Hz, 1H), 3.26 (dd, J=5.8, 14.8 Hz, 1H), 3.31 (dd, J=5.8, 14.8 Hz, 1H), 3.47 (dd, J=7.7, 10.0 Hz, 1H), 3.79 (d, J=4.2, 10.0 Hz, 1H), 4.93 (dt, J=5.8, 8.6 Hz, 1H), 7.01 (d, J=2.2 Hz, 1H), 7.10 (dt, J=0.8, 8.1 Hz, 1H), 7.18 (dt, J=0.8, 8.1 Hz, 1H), 7.34 (app. d, J=8.1 Hz, 1H), 7.55 (app. d, J=8.1 Hz, 1H), 7.86 (d, J=8.6 Hz, 1H), 8.04 (br s, 1H).

*4.3.5. Synthesis of dipeptide ent-**16**.* To a solution of *ent*-**13** (21.4 g, 32.1 mmol) in ethanol (100 mM, 320 mL) was added 10% Pd/C (3.39 g, 10 mol % Pd). After replacement of the inner gas with hydrogen (balloon), the resulting mixture was stirred for 5 h. The reaction mixture was diluted with ethyl acetate, then filtered through Celite® with ethyl acetate washing. Concentration in vacuo gave crude *ent*-**16** (18.9 g, quant.) as a colorless gum. A small crude sample was further purified by MPLC (column: Yamazen High Flash, chloroform/methanol=63/37 to 95/5) for spectroscopic analysis. ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ: 0.02 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 1.66 (s, 9H, $(CH_3)_3COCON$), 2.38 (s, 3H, $C_{18}H$), 3.05 (dd, J=4.2, 7.8 Hz, 1H, $C_{15}H$), 3.19 (dd, J=6.0, 14.8 Hz, 1H, $C_{12}H$), 3.22 (dd, J=6.0, 14.8 Hz, 1H, $C_{12}H$), 3.52 (dd, J=7.8, 10.1 Hz, 1H, $C_{17}H$), 3.67 (s, 3H, OCH_3), 3.81 (dd, J=4.2, 10.1 Hz, 1H, $C_{17}H$), 4.92 (dt, J=6.0, 8.3 Hz, 1H, $C_{11}H$), 7.21 (t, J=7.8 Hz, 1H, C_6H), 7.29 (t, J=7.8 Hz, 1H, C_7H), 7.39 (s, 1H, C_2H), 7.50 (d, J=7.8 Hz, 1H, C_5H), 7.86 (d, J=8.3 Hz, 1H, $N_{10}H$), 8.10 (d, J=7.8 Hz, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) δ: −5.40 ($SiCH_3$), −5.32 ($SiCH_3$), 18.3 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 27.9 (C_{12}), 28.3 ($(CH_3)_3COCON$), 35.3 (C_{18}), 52.1 (OCH_3), 52.3 (C_{11}), 63.2 (C_{17}), 66.9 (C_{15}), 83.6 ($(CH_3)_3COCON$), 115.4 (C_3 and C_8), 119.0 (C_5), 122.6 (C_6), 124.1 (C_2), 124.6 (C_7), 130.7 (C_4), 135.6 (C_9), 149.6 ($(CH_3)_3COCON$), 171.8 (C_{16}), 172.1 (C_{13}); $[\alpha]_D$ −22 (*c* 1.4, $CHCl_3$, 26 °C); FTIR (neat) cm^{-1}: 3348 (br), 2952 (m), 2931 (m), 2884 (m), 2857 (s), 1735 (s), 1372 (s), 1255 (s), 1158 (s), 1088 (s), 838 (s); LRMS (ESI) *m*/*z* 556 $[M+Na]^+$.

Compound **16**: $[\alpha]_D$ +24 (*c* 1.0, $CHCl_3$, 26 °C).

*4.3.6. Synthesis of diketopiperazine **17** (method A).* Compound **17** was synthesized according to the protocol used for the synthesis of *ent*-**19** (vide infra). The ^{1}H NMR data were as follows.

Compound **17**: ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C) δ: 2.34 (dd, J=4.0, 7.0 Hz, 1H), 3.00 (s, 3H), 3.27 (dd, J=9.5, 14.4 Hz, 1H), 3.49–3.56 (m, 2H), 3.83–3.88 (m, 2H), 4.28 (dt, J=2.8, 13.5 Hz, 1H), 5.96 (br s, 1H), 7.09 (d, J=2.4 Hz, 1H), 7.16 (dt, J=1.0, 8.0 Hz, 1H), 7.23 (dt, J=1.0, 8.0 Hz, 1H), 7.39 (dd, J=1.0, 8.0 Hz, 1H), 7.65 (dd, J=1.0, 8.0 Hz, 1H), 8.14 (br s, 1H).

*4.3.7. Synthesis of diketopiperazine **18** (method B).* To a solution of dipeptide **15** (26.1 mg, 60.2 μmol) in toluene (10 mM, 6.0 mL) was added triethylamine (0.5 mL, 3.60 mmol). The reaction mixture was refluxed for 18 h in an autoclave (0.04 MPa). After cooling to room temperature, the reaction mixture was concentrated in vacuo. The crude material was purified by preparative TLC (Merk TLC silica gel 60 F_{254}, 0.25 mm×20 cm×20 cm, developed twice with chloroform/methanol=98/2) to give diketopiperazine **18** (3.1 mg, 13%) as a colorless gum.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 0.11 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 3.02 (s, 3H, $C_{18}H$), 3.12 (dd, J=11.1, 14.0 Hz, 1H, $C_{12}H$), 3.63 (dd, J=2.0, 14.0 Hz, 1H, $C_{12}H$), 3.87 (app. s, 1H, $C_{15}H$), 3.96 (dd, J=2.3, 10.6 Hz, 1H, $C_{17}H$), 4.06 (dd, J=2.3, 10.6 Hz, 1H, $C_{17}H$), 4.15 (app. d, J=11.1 Hz, 1H, $C_{11}H$), 6.01 (s, 1H, $N_{10}H$), 7.01 (s, 1H, C_2H), 7.11 (t, J=7.7 Hz, 1H, C_6H), 7.20 (t, J=7.7 Hz, 1H, C_7H), 7.36 (d, J=7.7 Hz, 1H, C_5H), 7.64 (d, J=7.7 Hz, 1H, C_2H), 8.59 (s, 1H, N_1H); ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C) δ: −5.20 ($SiCH_3$), −5.17 ($SiCH_3$), 18.8 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 32.5 (C_{18}), 32.8 (C_{12}), 56.2 (C_{11}), 62.2 (C_{17}), 64.2 (C_{15}), 110.4 (C_3), 111.6 (C_5), 119.0 (C_8), 120.0 (C_6), 122.6 (C_7), 123.5 (C_2), 127.0 (C_4), 136.7 (C_9), 166.0 (C_{16}), 166.6 (C_{13}); $[\alpha]_D$ −86 (*c* 3.6, $CHCl_3$, 24 °C).

*4.3.8. Synthesis of diketopiperazine ent-**19** (method A).* To a solution of *ent*-**16** (184 mg, 345 μmol) in methanol (6 mM, 54 mL) was added 28% aqueous NH_4OH solution (2.0 mL) at room temperature. This was stirred for 27 h, additional 28% aqueous NH_4OH solution (2.0 mL) was added, and stirring was continued for an additional 31 h, after which time TLC indicated complete consumption of the starting material. The reaction mixture was concentrated in vacuo, and further purification by flash column chromatography (hexane/ethyl acetate=30/70 to 0/100) gave *ent*-**19** (136 mg, 79%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ: 0.13 (s, 6H, $Si(CH_3)_2$), 0.94 (s, 9H, $SiC(CH_3)_3$), 1.67 (s, 9H, $(CH_3)_3COCON$), 3.02 (s, 3H, $C_{18}H$), 3.07 (dd, J=11.0, 14.2 Hz, 1H, $C_{12}H$), 3.58 (dd, J=2.8, 14.2 Hz, 1H, $C_{12}H$), 3.86–3.87 (m, 1H, $C_{15}H$), 3.98 (dd, J=2.8, 10.6 Hz, 1H, $C_{17}H$), 4.08 (dd, J=2.3, 10.6 Hz, 1H, $C_{17}H$), 4.19–4.22 (m, 1H, $C_{11}H$), 5.95 (s, 1H, $N_{10}H$), 7.25 (dt, J=0.9, 8.1 Hz, 1H, C_6H), 7.33 (dt, J=0.9, 8.1 Hz, 1H, C_7H), 7.46 (s, 1H, C_2H), 7.61 (app. d, J=8.1 Hz, 1H, C_5H), 8.16 (app. d, J=8.1 Hz, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) δ: −5.20 ($SiCH_3$), −5.13 ($SiCH_3$), 18.8 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 28.3 ($(CH_3)_3COCON$), 32.5 (C_{18}), 32.8 (C_{12}), 55.7 (C_{11}), 62.3 (C_{17}), 64.4 (C_{15}), 84.0 ($(CH_3)_3COCON$), 115.4 (C_3), 115.7 (C_8), 119.3 (C_5), 123.0 (C_6), 124.7 (C_2), 125.1 (C_7), 129.8 (C_4), 136.1 (C_9), 149.5 ($(CH_3)_3COCON$), 165.8 (C_{16}), 166.2 (C_{13}); $[\alpha]_D$ +79 (*c* 1.7, $CHCl_3$, 26 °C); FTIR (neat) cm^{-1}: 3229 (br), 2931 (m), 2857 (m), 1732 (s), 1660 (s), 1158 (s), 1086 (s), 837 (s), 749 (s); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{39}N_3NaO_5Si$ $[M+Na]^+$ 524.25567, found: 524.25358.

Compound **19**: $[\alpha]_D$ −79 (*c* 1.0, $CHCl_3$, 25 °C).

*4.3.9. Synthesis of diketopiperazine **21**.* Compound **21** was obtained as a by-product in the synthesis of **19**. Refer to the synthesis of *ent*-**13** for the procedure. The analytical data were as follows.

Compound **21**: ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C) δ: 0.02 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.13 (s, 9H), 1.64 (s, 9H), 2.98 (s, 3H), 3.35 (dd, 1H, J=8.3, 14.6 Hz), 3.42 (dd, 1H, J=8.3, 14.6 Hz), 3.79 (dd, J=3.4, 10.9 Hz, 1H), 3.87 (dd, J=2.7, 10.9 Hz, 1H), 4.02 (app. t, J=3.4 Hz, 1H), 5.04 (dd, J=4.6, 8.1 Hz, 1H), 7.24–7.32 (m, 2H), 7.38 (s, 1H), 7.62 (d, J=7.8 Hz, 1H), 8.12 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) δ: −5.4, 18.7, 26.1, 27.4, 28.3, 32.1, 32.5, 58.8, 63.3, 64.4, 83.7, 84.3, 115.4, 115.6, 119.4, 123.0, 124.7, 124.8, 130.5, 135.6, 149.6, 149.7, 166.2, 166.5.

*4.3.10. Synthesis of diketopiperazine **25**.* To a solution of diketopiperazine **19** (300 mg, 598 μmol) in THF (0.1 M, 6.0 mL) were added acetic acid (0.34 mL, 6.0 mmol) and tetrabutylammonium fluoride (1 M THF solution, 1.2 mL, 1.2 mmol). The reaction mixture was heated to 60 °C and stirred for 2 h, then cooled to room temperature, and concentrated in vacuo. The residue was purified by flash column chromatography (chloroform/methanol=99/1) to give diketopiperazine **25** (257 mg, quant.) as a white solid.

Compound **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.51 (s, 9H, $CO_2C(CH_3)_3$), 2.99 (s, 3H, $C_{18}H$), 3.26 (dd, J=10.8, 14.2 Hz, 1H, $C_{12}H$), 3.45 (dd, J=2.8, 14.2 Hz, 1H, $C_{12}H$), 3.76–3.79 (m, 2H, $C_{15}H$, $C_{17}H$), 3.94 (dd, J=3.0, 12.9 Hz, 1H, $C_{17}H$), 4.14 (app. d, J=10.8 Hz, 1H, $C_{11}H$), 7.03 (br s, 1H, $N_{10}H$), 7.19 (t, J=7.4 Hz, 1H, C_6H), 7.26 (t, J=7.4 Hz, 1H, C_7H), 7.59, (s, 1H, C_2H), 7.59 (d, J=7.4 Hz, 1H, C_5H), 7.98 (br, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.9 ($CO_2C(CH_3)_3$), 31.9 (C_{18}), 32.3 (C_{12}), 55.4 (C_{11}), 60.2 (C_{17}), 64.2 (C_{15}), 84.1 ($CO_2C(CH_3)_3$), 115.1 (C_8), 115.3 (C_3), 119.0 (C_5), 122.7 (C_6), 124.5 (C_7), 125.0 (C_2), 130.1 (C_4), 135.3 (C_9), 149.8 ($CO_2C(CH_3)_3$), 166.3 (C_{13}), 166.9 (C_{16}); $[\alpha]_D$ −57 (*c* 1.0, $CHCl_3$, 26 °C); IR (neat) cm^{-1}: 3369 (br m), 2975 (s), 1731 (s), 1670 (s), 1652 (s).

*4.3.11. Synthesis of tetracyclic compound ent-**26**.* To a solution of *ent*-**19** (426 mg, 849 μmol) in acetonitrile (40 mM, 21 mL) was added *N*-bromosuccinimide (182 mg, 102 μmol) at −30 °C. The reaction mixture was stirred for 9.5 h at −30 °C, then diluted with dichloromethane (50 mL), and quenched with aqueous 5% sodium

bicarbonate (16 mL). The mixture was warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (20 mL), and then dried over anhydrous sodium sulfate. After concentration in vacuo, purification by flash column chromatography (chloroform), followed by purification by MPLC (column: Yamazen Ultra Pack, hexane/ethyl acetate=63/37) gave *ent*-**26** (211.8 mg, 88%, white amorphous foam) and dibromide *ent*-**28** (35.2 mg, 6%, white amorphous foam).

Compound *ent*-**26**: ^{1}H NMR (500 MHz, $CDCl_3$, 24 °C) δ: 0.11 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.57 (s, 9H, $(CH_3)_3COCON$), 2.83 (t, J=12.3 Hz, 1H, $C_{12}H$), 2.91 (s, 3H, $C_{18}H$), 3.12 (dd, J=4.1, 11.9 Hz, 1H, $C_{12}H$), 3.77 (dd, J=4.1, 12.3 Hz, 1H, $C_{11}H$), 3.92 (dd, J=2.8, 10.1 Hz, 1H, $C_{17}H$), 3.98 (app. s, 1H, $C_{15}H$), 4.27 (dd, J=1.0, 10.1 Hz, 1H, $C_{17}H$), 6.83 (s, 1H, C_2H), 7.09 (dt, J=0.9, 7.8 Hz, 1H, C_6H), 7.27 (dt, J=0.9, 7.8 Hz, 1H, C_7H), 7.40 (app. d, J=7.8 Hz, 1H, C_5H), 7.70 (br, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 26 °C) δ: −5.27 ($SiCH_3$), −5.12 ($SiCH_3$), 18.7 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 28.4 ($(CH_3)_3COCON$), 31.7 (C_{18}), 50.5 (C_{12}), 58.4 (C_{11}), 59.6 (C_3), 61.4 (C_{17}), 64.3 (C_{15}), 83.0 ($(CH_3)_3COCON$), 84.0 (C_2), 115.4 (C_8), 124.2 (C_6), 125.3 (C_5), 130.9 (C_7), 131.0 (C_4), 142.2 (C_9), 151.6 ($(CH_3)_3COCON$), 163.9 (C_{16}), 164.6 (C_{13}); $[\alpha]_D$ +132 (c 1.0, $CHCl_3$, 25 °C); FTIR (neat) cm^{-1}: 2953 (m), 2931 (m), 2886 (m), 2857 (m), 1717 (s), 1689 (s), 1668 (s), 1374 (s), 1152 (s), 754 (s); HRMS (ESI) m/z calcd for $C_{26}H_{38}BrN_3NaO_5Si$ $[M+Na]^+$ 602.16618, found: 602.16369.

Compound **26**: $[\alpha]_D$ −112 (c 1.0, $CHCl_3$, 25 °C).

Compound *ent*-**28**: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 0.11 (s, 6H), 0.90 (s, 9H), 1.56 (s, 9H), 2.82 (t, J=12.0 Hz, 1H), 2.92 (s, 3H), 3.09 (dd, J=4.4, 12.0 Hz, 1H), 3.78 (dd, J=4.4, 12.0 Hz, 1H), 3.92 (dd, J=2.6, 10.0 Hz, 1H), 3.98 (app. s, 1H), 4.27 (app. d, J=10.0 Hz, 1H), 6.81 (s, 1H), 7.37 (dd, J=2.1, 8.6 Hz, 1H), 7.52 (app. d, J=2.1 Hz, 1H), 7.61 (br, 1H).

*4.3.12. Synthesis of tetracyclic compound **27**.* Compound **27** was synthesized according to the protocol used for the synthesis of *ent*-**26**, but with DKP **25** as the starting material. The analytical data were as follows.

Compound **27**: ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C) δ: 1.59 (9H), 2.95 (t, J=12.4 Hz, 1H), 2.99 (s, 3H), 3.19 (dd, J=4.8, 12.1 Hz, 1H), 3.82 (dd, J=4.8, 12.1 Hz, 1H), 3.95 (br, 1H), 4.00 (br, 1H), 4.24 (br, 1H), 6.80 (s, 1H), 7.12 (t, J=7.2 Hz, 1H), 7.30 (app. dt, J=1.5, 7.2 Hz, 1H), 7.43 (d, J=7.2 Hz, 1H), 7.70 (br, 1H).

*4.3.13. Synthesis of **31**.* A solution of **26** (332 mg, 570 μmol), tri-*n*-butyltin hydride (180 μL, 690 μmol), and 2,2′-azobisisobutyronitrile (11.5 mg, 69 μmol) in toluene (5.8 mL) was heated to reflux for 3.5 h under a nitrogen atmosphere. The reaction mixture was concentrated in vacuo. The resulting residue was purified by flash column chromatography (chloroform) to give reduced **30** (261 mg, 91%) as a white solid.

To a solution of **30** (198 mg, 0.39 mmol) in dry THF (10 mM, 4 mL) were added acetic acid (60 μL, 1.0 mmol) and tetrabutylammonium fluoride (1 M THF solution, 800 μL, 0.8 mmol) at 0 °C. The reaction mixture was stirred for 4 h at room temperature under a nitrogen atmosphere, then concentrated in vacuo. The obtained residue was purified by column chromatography (chloroform/methanol=100/0 to 98/2) to give **31** (180 mg, quant.) as a white solid. Recrystallization from hexane/ethyl acetate afforded a crystal suitable for X-ray structural analysis.

Compound **30**: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.58 (s, 9H, $(CH_3)_3COCON$), 2.26 (ddd, J=8.3, 11.8, 11.8 Hz, 1H, $C_{12}H$), 2.45 (dd, J=4.8, 11.8 Hz, 1H, $C_{12}H$), 2.94 (s, 3H, $C_{18}H$), 3.89–3.95 (m, 3H, C_3H, $C_{11}H$, $C_{17}H$), 3.98 (app. s, 1H, $C_{15}H$), 4.26 (dd, J=1.4, 10.1 Hz, 1H, $C_{17}H$), 6.77 (d, J=7.8 Hz, 1H, C_2H), 7.02 (t, J=7.5 Hz, 1H, C_6H), 7.19 (d, J=7.5 Hz, 1H, C_5H), 7.22 (t, J=7.5 Hz, 1H, C_7H), 7.71 (br, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: −5.24 ($SiCH_3$), −5.21 ($SiCH_3$), 18.7 ($SiC(CH_3)_3$), 26.1 ($SiC(CH_3)_3$), 28.6 ($(CH_3)_3COCON$), 31.8 (C_{18}), 39.8 (C_{12}), 42.7 (C_3), 57.1 (C_{11}), 61.6 (C_{17}), 64.6 (C_{15}), 75.5 (C_2), 82.3 ($(CH_3)_3COCON$), 115.1 (C_8), 123.5 (C_6), 125.0 (C_5), 128.7 (C_7), 130.3 (C_4), 143.3 (C_9), 152.2 ($(CH_3)_3COCON$), 163.8 (C_{16}), 166.2 (C_{13}); $[\alpha]_D$ −95 (c 0.35, $CHCl_3$, 25 °C); FTIR (neat) cm^{-1}: 2949 (m), 2930 (m), 2857 (m), 1711 (s), 1678 (s), 1382 (s), 1149 (s), 836 (s); HRMS (ESI) m/z calcd for $C_{26}H_{39}N_3NaO_5Si$ $[M+Na]^+$ 524.25567, found: 524.25414.

Compound **31**: ^{1}H NMR (500 MHz, $CDCl_3$, 24 °C) δ: 1.58 (s, 9H, $(CH_3)_3COCON$), 2.30 (ddd, J=8.1, 11.9, 11.9 Hz, 1H, $C_{12}H$), 2.52 (dd, J=5.1, 11.9 Hz, 1H, $C_{12}H$), 2.57 (br s, 1H, OH), 3.00 (s, 3H, $C_{18}H$), 3.88–3.94 (m, 2H, $C_{11}H$ and $C_{17}H$), 4.00–4.03 (m, 2H, C_3H and $C_{15}H$), 4.23 (ddd, J=2.3, 6.9, 11.0 Hz, 1H, $C_{17}H$), 6.76 (d, J=7.8 Hz, 1H, C_2H), 7.03 (t, J=7.4 Hz, 1H, C_6H), 7.20 (d, J=7.4 Hz, 1H, C_7H), 7.22 (t, J=7.4 Hz, 1H, C_5H), 7.68 (br s, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 28.5 ($(CH_3)_3COCON$), 31.8 (C_{18}), 39.1 (C_{12}), 42.8 (C_3), 57.2 (C_{11}), 60.3 (C_{17}), 64.0 (C_{15}), 75.5 (C_2), 82.4 ($(CH_3)_3COCON$), 115.2 (C_8), 123.5 (C_6), 124.8 (C_5), 128.7 (C_7), 130.3 (C_4), 143.1 (C_9), 152.1 ($(CH_3)_3COCON$), 164.4 (C_{16}), 166.8 (C_{13}); $[\alpha]_D$ −125 (c 0.12, $CHCl_3$, 26 °C); FTIR (neat) cm^{-1}: 3408 (br), 2977 (m), 2927 (m), 1710 (s), 1659 (s), 1381 (s), 1149 (s), 753 (s); HRMS (ESI) m/z calcd for $C_{20}H_{25}N_3NaO_5$ $[M+Na]^+$ 410.16919, found: 410.17098.

*4.3.14. Synthesis of octacyclic compound **36**.* To a solution of *ent*-**26** (377 mg, 650 μmol) in dry acetone saturated with nitrogen was added $CoCl(PPh_3)_3$ (1.14 g, 1.29 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred for 3 h at room temperature, then water (20 mL) was added for quenching. The organic solvent was removed in vacuo. The obtained suspension was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water (50 mL) and brine (30 mL), and then dried over anhydrous sodium sulfate. After concentration in vacuo, purification by flash column chromatography (hexane/ethyl acetate=70/30) and GPC was carried out to give **36** (152 mg, 47%, white amorphous foam) and reduced by-product *ent*-**30** (31.2 mg, 10%, white amorphous foam).

Compound **36**: ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ: 0.10 (s, 6H, $SiCH_3$), 0.12 (s, 6H, $SiCH_3$), 0.91 (18H, s, $SiC(CH_3)_3$), 1.61 (s, 18H, $(CH_3)_3COCON$), 2.39 (t, J=11.9 Hz, 2H, $C_{12}H$), 2.81 (dd, J=4.9, 11.9 Hz, 2H, $C_{12}H$), 2.97 (s, 6H, $C_{18}H$), 3.82 (dd, J=4.9, 11.9 Hz, 2H, $C_{11}H$), 3.86 (app. br s, 2H, $C_{15}H$), 4.08 (dd, J=2.5, 11.0 Hz, 2H, $C_{17}H$), 4.28 (dd, J=2.8, 11.0 Hz, 2H, $C_{17}H$), 6.47 (s, 2H, C_2H), 6.83 (t, J=7.4 Hz, 2H, C_6H), 7.05 (t, J=7.4 Hz, 2H, C_7H), 7.23 (d, J=7.4 Hz, 2H, C_5H), 7.48 (d, J=7.4 Hz, 2H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ: −5.24 ($SiCH_3$), −5.00 ($SiCH_3$), 18.6 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 28.5 ($(CH_3)_3COCON$), 31.1(C_{18}), 38.8 (C_{12}), 58.4(C_{11}), 58.7(C_3), 61.7(C_{17}), 63.8(C_{15}), 78.5 (C_2), 82.5 ($(CH_3)_3COCON$), 116.1 (C_8), 122.7 (C_5), 123.4 (C_6), 129.8 (C_7), 130.1 (C_4), 143.4 (C_9), 151.4 ($(CH_3)_3COCON$), 162.6 (C_{16}), 166.2 (C_{13}); $[\alpha]_D$ +213 (c 1.8, $CHCl_3$, 25 °C); FTIR (neat) cm^{-1}: 2953 (m), 2931 (m), 2887 (m), 2857 (m), 1715 (s), 1678 (m), 1155 (s), 752 (s); HRMS (ESI) m/z calcd for $C_{52}H_{76}N_6NaO_{10}Si_2$ $[M+Na]^+$ 1023.50591, found: 1023.50647.

Compound *ent*-**30**: $[\alpha]_D$ +96 (c 1.3, $CHCl_3$, 26 °C).

*4.3.15. Synthesis of **37**.* To a solution of **36** (6.5 mg, 6.5 μmol) in THF was added 1.0 M lithium *tert*-butoxide in hexane solution (30 μL) at −40 °C. After having been stirred for 10 min, the reaction mixture turned orange, then the reaction was quenched with pH 7.0 phosphate buffer. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After concentration in vacuo, purification by flash column chromatography (chloroform/ethyl

acetate=5/1 to 3/1) was carried out to give **37** (3.0 mg, 63%) as a white solid.

Compound **37**: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 1.61 (s, 9H, $(CH_3)_3COCON$), 2.35 (t, J=11.9 Hz, 1H, $C_{12}H$), 2.77 (dd, J=5.2, 11.9 Hz, 1H, $C_{12}H$), 3.13 (s, 3H, $C_{18}H$), 3.95 (dd, J=5.2, 11.9 Hz, 1H, $C_{11}H$), 4.90 (s, 1H, $C_{17}H$), 5.79 (s, 1H, $C_{17}H$), 6.64 (s, 1H, C_2H), 6.89 (t, J=7.5 Hz, 1H, C_6H), 7.11 (t, J=7.5 Hz, 1H, C_7H), 7.21 (d, J=7.5 Hz, 1H, C_5H), 7.49 (br, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 28.3 ($(CH_3)_3CO$-CON), 29.9 (C_{18}), 38.7 (C_{12}), 58.0 (C_{11}), 58.1 (C_3), 78.6 (C_2), 82.7 ($(CH_3)_3COCON$), 103.8 (C_{17}), 116.4 (C_8), 123.3 (C_5), 123.4 (C_7), 129.4 (C_4), 129.9 (C_6), 138.3 (C_{15}), 143.2 (C_9), 151.3 ($(CH_3)_3COCON$), 156.2 (C_{15}), 163.9 (C_{13}); $[\alpha]_D$ −190 (*c* 5.2, $CHCl_3$, 23 °C).

*4.3.16. Synthesis of tribromide **38**.* To a solution of **30** (16.6 mg, 33.1 μmol) and *N*-bromosuccinimide (17.6 mg, 99.4 μmol) in carbon tetrachloride (1.1 mL, 30 mM) was added V-70 (2.1 mg, 6.8 μmol) at room temperature. The mixture was stirred for 2 h at room temperature, then precipitated succinimide was filtered off through a cotton plug and washed with carbon tetrachloride. Concentration in vacuo afforded crude **38** (single isomer) together with residual succinimide (27.8 mg).

Compound **38**: ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C) δ: 0.09 (s, 3H), 0.13 (s, 3H), 0.84 (9H, s), 1.73 (s, 9H), 3.16 (s, 3H), 4.10 (d, J=10.9 Hz, 1H), 4.67 (d, J=7.9 Hz, 1H), 4.70 (d, J=10.9 Hz, 1H), 5.31 (s, 1H), 7.03 (d, J=7.9 Hz, 1H), 7.09 (t, J=7.2 Hz, 1H), 7.26–7.34 (m, 2H), 7.79 (d, J=7.2 Hz, 1H).

*4.3.17. Synthesis of diol **42**.* To a solution of *ent*-**26** (2.02 g, 3.48 mmol) and *N*-bromosuccinimide (1.26 g, 7.06 mmol) in carbon tetrachloride (30 mM, 115 mL) was added V-70 (2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile), 255 mg, 0.83 mmol) at room temperature. After having been stirred for 5 h at room temperature, the reaction mixture was filtered through a cotton plug and the remaining solid was washed with carbon tetrachloride. After removal of the solvent in vacuo, crude tribromide **41** was obtained almost quantitatively.

The crude product **41** was dissolved in MeCN/10 mM pH 7.0 phosphate buffer=1/1 (140 mL, 25 mM) at room temperature. After having been stirred for 3 h, the reaction mixture was diluted with ethyl acetate (3×100 mL). The separated organic layer was washed with brine (100 mL) and then dried over anhydrous sodium sulfate. After concentration in vacuo, purification by flash column chromatography (chloroform/ethyl acetate=80/20) was carried out to give a mixture of two diastereomers **42a**, **42b** (**42a**/**42b**=87/13, 1.15 g, 54%, white solid). Recovered unpurified mixture of more polar compounds was subjected to MPLC (column: Yamazen High Flash, hexane/ethyl acetate=20/80 and Kusano pre-packed SiO_2 column, hexane/ethyl acetate=50/50) to give other diastereomers **42c** (53.4 mg, 3%), **42d** (39.3 mg, 2%), and by-products **43** (64.4 mg, 3%) and **44** (102 mg, 6%). Preparative chiral HPLC (Chiralpak IC (2 cm ϕ×25 cm), hexane/2-propanol=95/5, 6 mL/min) separated stereoisomers **42a** and **42b**. The major compound, **42a**, was obtained in 47% yield as a white solid, which was used in the following step.

Tribromide **41**: ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) δ: 0.09 (s, 3H), 0.13 (s, 3H), 0.85 (9H, s), 1.62 (s, 9H), 3.21 (s, 3H), 3.46 (d, J=15.0 Hz, 1H), 3.83 (d, J=15.0 Hz, 1H), 4.10 (d, J=10.9 Hz, 1H), 4.65 (d, J=10.9 Hz, 1H), 6.74 (s, 1H), 7.19 (t, J=7.7 Hz, 1H), 7.37 (t, J=7.7 Hz, 1H), 7.49 (d, J=7.7 Hz, 1H), 7.78 (d, J=7.7 Hz, 1H).

Diol **42a**: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 0.13 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.60 (s, 9H, $(CH_3)_3CO$-CON), 3.00 (s, 3H, $C_{18}H$), 3.18 (d, J=14.2 Hz, 1H, $C_{12}H$), 3.43 (d, J=14.2 Hz, 1H, $C_{12}H$), 3.82 (br s, 1H, OH), 4.09 (d, J=11.0 Hz, 1H, $C_{17}H$), 4.14 (d, J=11.0 Hz, 1H, $C_{17}H$), 4.57 (br s, 1H, $C_{15}OH$), 6.63 (s, 1H, C_2H), 7.14 (t, J=7.8 Hz, 1H, C_6H), 7.31 (dt, J=0.9, 7.8 Hz, 1H, C_7H), 7.44 (app. d, J=7.8 Hz, 1H, C_5H), 7.66 (d, J=7.8 Hz, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: −5.44 ($SiCH_3$), −5.24 ($SiCH_3$), 18.3 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 27.9 (C_{18}), 28.3 (($CH_3)_3COCON$), 51.7 (C_{12}), 58.3 (C_3), 63.2 (C_{17}), 83.1 ($(CH_3)_3COCON$), 85.4 (C_{15}), 85.5 (C_2), 87.6 (C_{11}), 117.3 (C_8), 124.1 (C_5), 124.6 (C_6), 130.5 (C_7), 134.3 (C_4), 141.0 (C_9), 152.1 ($(CH_3)_3COCON$), 163.7 (C_{16}), 167.9 (C_{13}); $[\alpha]_D$ +139 (*c* 1.0, $CHCl_3$, 25 °C); FTIR (neat) cm^{-1}: 3402 (br), 2954 (m), 2923 (m), 2883 (m), 2847 (m), 1710 (s), 1389 (s), 1155 (s), 842 (s); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{38}BrN_3NaO_7Si$ $[M+Na]^+$ 634.15601, found: 634.15453.

ent-Diol **42a**: $[\alpha]_D$ −134 (*c* 1.0, $CHCl_3$, 26 °C).

Diol **42b**: ^{1}H NMR (500 MHz, THF-d_8, 25 °C) δ: −0.27 (s, 3H, $SiCH_3$), −0.11 (s, 3H, $SiCH_3$), 0.59 (s, 9H, $SiC(CH_3)_3$), 1.58 (s, 9H, $(CH_3)_3COCON$), 2.84 (s, 3H, $C_{18}H$), 3.10 (d, J=15.1 Hz, 1H, $C_{12}H$), 3.56 (d, J=10.1 Hz, 1H, $C_{17}H$), 3.62 (d, J=15.1 Hz, 1H, $C_{12}H$), 4.08 (d, J=10.1 Hz, 1H, $C_{17}H$), 5.74 (br s, 1H, $C_{15}OH$), 6.47 (s, 1H, C_2H), 6.52 (s, 1H, $C_{11}OH$), 6.98 (dt, J=0.9, 7.8 Hz, 1H, C_7H), 7.16 (dt, J=1.4, 7.8 Hz, 1H, C_6H), 7.36 (dd, J=0.9, 7.8 Hz, 1H, C_5H), 7.62 (br, 1H, C_8H); ^{13}C NMR (125 MHz, THF-d_8, 25 °C) δ: −5.47 ($SiCH_3$), −5.02 ($SiCH_3$), 19.0 ($SiC(CH_3)_3$), 26.4 ($SiC(CH_3)_3$), 27.2 (C_{18}), 28.7 (($CH_3)_3COCON$), 51.7 (C_{12}), 60.0 (C_3), 65.1 (C_{17}), 82.7 ($(CH_3)_3COCON$), 86.6 (C_2), 87.7 (C_{11}), 87.7 (C_{15}), 118.1 (C_8), 125.1 (C_7), 125.6 (C_5), 131.1 (C_6), 136.0 (C_4), 141.7 (C_9), 152.3 ($(CH_3)_3COCON$), 166.4 (C_{16}), 167.7 (C_{13}); $[\alpha]_D$ +27 (*c* 1.3, $CHCl_3$, 26 °C); FTIR (neat) cm^{-1}: 3358 (br), 2953 (m), 2931 (m), 2883 (m), 2857 (m), 1710 (s), 1368 (s), 1156 (s), 841 (s); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{38}BrN_3NaO_7Si$ $[M+Na]^+$ 634.15601, found: 634.15722.

Diol **42c**: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: −0.11 (s, 3H, $SiCH_3$), −0.06 (s, 3H, $SiCH_3$), 0.75 (s, 9H, $SiC(CH_3)_3$), 1.62 (s, 9H, $(CH_3)_3CO$-CON), 2.98 (s, 3H, $C_{18}H$), 3.14 (dd, J=2.3, 13.8 Hz, 1H, $C_{12}H$), 3.49 (d, J=13.8 Hz, 1H, $C_{12}H$), 3.61 (d, J=10.6 Hz, 1H, $C_{17}H$), 3.76 (d, J=10.6 Hz, 1H, $C_{17}H$), 4.41 (d, J=2.3 Hz, 1H, $C_{11}OH$), 4.44 (s, 1H, $C_{15}OH$), 6.76 (s, 1H, C_2H), 7.13 (dt, J=0.9, 7.6 Hz, 1H, C_6H), 7.26 (dt, J=1.4, 7.6 Hz, 1H, C_7H), 7.45 (dd, J=1.4, 7.6 Hz, 1H, C_5H), 7.58 (br, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: −5.88 ($SiCH_3$), −5.75 ($SiCH_3$), 18.7 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 27.0 (C_{18}), 28.3 (($CH_3)_3COCON$), 51.3 (C_{12}), 58.3 (C_3), 65.9 (C_{17}), 82.9 ($(CH_3)_3COCON$), 84.7 (C_{15}), 85.2 (C_2), 88.0 (C_{11}), 117.2 (C_8), 124.3 (C_5), 124.7 (C_6), 130.1 (C_7), 134.6 (C_4), 140.6 (C_9), 151.8 ($(CH_3)_3COCON$), 164.9 (C_{13}), 166.3 (C_{16}); $[\alpha]_D$ +121 (*c* 1.2, $CHCl_3$, 24 °C); FTIR (neat) cm^{-1}: 3366 (br), 2953 (m), 2931 (m), 2884 (m), 2859 (m), 1719 (s), 1677 (s), 1389 (s), 1156 (s), 838 (s); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{38}BrN_3NaO_7Si$ $[M+Na]^+$ 634.15601, found: 634.15445.

Diol **42d**: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) δ: 0.16 (s, 6H, $Si(CH_3)_2$), 0.92 (s, 9H, $SiC(CH_3)_3$), 1.63 (s, 9H, $(CH_3)_3COCON$), 2.87 (s, 3H, $C_{18}H$), 3.32 (d, J=15.1 Hz, 1H, $C_{12}H$), 3.67 (d, J=15.1 Hz, 1H, $C_{12}H$), 3.70 (d, J=10.6 Hz, 1H, $C_{17}H$), 3.77 (d, J=10.6 Hz, 1H, $C_{17}H$), 4.04 (s, 1H, $C_{15}OH$), 5.28 (s, 1H, $C_{11}OH$), 6.57 (s, 1H, C_2H), 7.10 (t, J=7.4 Hz, 1H, C_6H), 7.28 (t, J=7.4 Hz, 1H, C_7H), 7.39 (d, J=7.4 Hz, 1H, C_5H), 7.64 (br, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: −5.49 ($SiCH_3$), −5.46 ($SiCH_3$), 18.8 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 27.0 (C_{18}), 28.4 (($CH_3)_3COCON$), 49.9 (C_{12}), 57.3 (C_3), 65.7 (C_{17}), 83.0 ($(CH_3)_3CO$-CON), 85.0 (C_{15}), 85.5 (C_2), 87.2 (C_{11}), 116.8 (C_8), 124.7 (C_5), 124.7 (C_6), 130.6 (C_7), 134.8 (C_4), 139.8 (C_9), 151.7 ($(CH_3)_3COCON$), 165.0 (C_{13}), 166.6 (C_{16}); $[\alpha]_D$ +21 (*c* 0.97, $CHCl_3$, 25 °C); IR (neat) cm^{-1}: 3344 (br), 2954 (m), 2932 (m), 2886 (m), 2859 (m), 1725 (s), 1687 (s), 1391 (s), 1158 (s), 838 (s); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{38}BrN_3NaO_7Si$ $[M+Na]^+$ 634.15601, found: 634.15600.

Compound **43**: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C) δ: −0.14 (s, 3H, $SiCH_3$), −0.04 (s, 3H, $SiCH_3$), 0.60 (s, 9H, $SiC(CH_3)_3$), 1.68 (s, 9H, $(CH_3)_3COCON$), 3.11 (s, 3H, $C_{18}H$), 3.87 (d, J=10.3 Hz, 1H, $C_{17}H$), 4.09 (d, J=10.3 Hz, 1H, $C_{17}H$), 5.61 (br s, 1H, $C_{15}OH$), 7.09–7.10 (m, 1H, $C_{12}H$), 7.12–7.19 (m, 2H, C_6H, C_7H), 7.34–7.35 (m, 1H, C_5H), 7.82 (d, J=8.3 Hz, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: −5.76 ($SiCH_3$), −5.64 ($SiCH_3$), 17.8 ($SiC(CH_3)_3$), 25.5 ($SiC(CH_3)_3$), 26.6 (C_{18}), 28.2 (($CH_3)_3COCON$), 64.7 (C_{17}), 85.3 (($CH_3)_3COCON$), 87.5 (C_{15}), 110.0 (C_{12}), 115.5 (C_8), 115.6 (C_2), 119.6 (C_5), 121.3 (C_4), 123.6 (C_6),

124.9 (C_7), 125.4 (C_3), 134.4 (C_{11}), 140.2 (C_9), 148.7 ((CH_3)$_3$COCON), 157.9 (C_{13}), 163.5 (C_{16}); $[\alpha]_D$ +1.2 (*c* 1.00, $CHCl_3$, 24 °C); IR (neat) cm^{-1}: 3260 (br m), 2932 (m), 1741 (s); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{35}N_3NaO_6Si$ $[M+Na]^+$ 536.21928, found: 536.21851.

Compound **44**: ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 0.13 (s, 6H, Si(CH_3)$_2$), 0.91 (s, 9H, SiC(CH_3)$_3$), 1.60 (s, 9H, (CH_3)$_3$COCON), 2.84 (t, *J*=12.2 Hz, 1H, $C_{12}H$), 2.96 (s, 3H, $C_{18}H$), 3.24 (dd, *J*=4.8, 12.2 Hz, 1H, $C_{12}H$), 3.46 (br s, 1H, $C_{15}OH$), 3.81 (d, *J*=9.6 Hz, 1H, $C_{17}H$), 3.91 (dd, *J*=4.8, 12.2 Hz, $C_{11}H$), 4.05 (d, *J*=9.6 Hz, 1H, $C_{17}H$), 6.73 (s, 1H, C_2H), 7.13 (t, *J*=7.4 Hz, 1H, C_6H), 7.31 (dt, *J*=0.93, 7.4 Hz, 1H, C_7H), 7.43 (app. d, *J*=7.4 Hz, 1H, C_5H), 7.67 (br, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: −5.31 (SiCH_3), −5.19 (SiCH_3), 18.5 (Si*C*(CH_3)$_3$), 26.0 (SiC(*C*H_3)$_3$), 27.2 (C_{18}), 28.3 ((*C*H_3)$_3$COCON), 49.0 (C_{12}), 58.3 (C_{11}), 58.9 (C_3), 64.7 (C_{17}), 83.2 ((CH_3)$_3$*C*OCON), 84.3 (C_2), 85.9 (C_{15}), 116.0 (C_8), 124.5 (C_6), 124.9 (C_5), 131.0 (C_7), 131.1 (C_4), 142.1 (C_9), 151.6 ((CH_3)$_3$COCON), 164.6 (C_{16}), 165.1 (C_{13}); $[\alpha]_D$ +132 (*c* 0.95, $CHCl_3$, 26 °C); FTIR (neat) cm^{-1}: 3365 (br), 2949 (m), 2931 (m), 2883 (m), 2857 (m), 1711 (s), 1374 (s), 1153 (s), 842 (s); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{38}BrN_3NaO_6Si$ $[M+Na]^+$ 618.16109, found: 618.15806.

*4.3.18. Synthesis of tetraol **45**.* Freshly prepared tris(triphenylphosphine)cobalt chloride ($CoCl(PPh_3)_3$, 509 mg, 578 μmol) was quickly added as a solid to a degassed (nitrogen bubbling for 10 min) solution of **42a** (182 mg, 300 μmol) in dry acetone (3.0 mL) at room temperature under a nitrogen atmosphere. After 90 min, the reaction mixture was diluted with dichloromethane (10 mL) and quenched with saturated aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine (10 mL) and then dried over anhydrous sodium sulfate. After removal of the solvent in vacuo, purification by flash column chromatography (chloroform/ethyl acetate=80/20 to 70/30) gave a crude mixture of **45** and **46** (2.4 mg, 3%). The obtained crude compound was subjected to purification with MPLC system (column: High Flash M, hexane/ethyl acetate=70/30 to 50/50) to give pure **45** (86.6 mg, 55%) as a white solid.

Compound **45**: ^1H NMR (400 MHz, $CDCl_3$, 55 °C) δ: 0.17 (s, 6H, SiCH_3), 0.18 (s, 6H, SiCH_3), 0.94 (s, 18H, SiC(CH_3)$_3$), 1.66 (s, 18H, (CH_3)$_3$COCON), 2.83 (d, *J*=14.1 Hz, 2H, $C_{12}H$), 2.91 (d, *J*=14.1 Hz, 2H, $C_{12}H$), 3.08 (s, 6H, $C_{18}H$), 3.37 (s, 2H, $C_{11}OH$), 4.15 (d, *J*=11.0 Hz, 2H, $C_{17}H$), 4.22 (d, *J*=11.0 Hz, 2H, $C_{17}H$), 4.28 (s, 2H, $C_{15}OH$), 6.89 (dt, *J*=1.0, 7.4 Hz, 2H, C_6H), 7.10 (dt, *J*=1.1, 7.4 Hz, 2H, C_7H), 7.26 (app. d, *J*=7.4 Hz, 2H, C_5H), 7.51 (app. d, *J*=7.4 Hz 2H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: −5.57 (SiCH_3), −5.14 (SiCH_3), 18.4 (SiC(CH_3)$_3$), 25.9 (SiC(CH_3)$_3$), 27.9 (C_{18}), 28.1 ((CH_3)$_3$COCON), 42.6 (C_{12}), 56.7 (C_3), 62.5 (C_{17}), 79.7 (C_{15}), 82.7 ((CH_3)$_3$*C*OCON), 85.4 (C_2), 86.8 (C_{11}), 117.0 (C_8), 122.4 (C_5), 123.3 (C_6), 129.7 (C_7), 131.6 (C_4), 141.7 (C_9), 151.2 ((CH_3)$_3$*C*OCON), 163.1 (C_{13}), 169.1 (C_{16}); $[\alpha]_D$ +182 (*c* 1.0, $CHCl_3$, 24 °C); IR (neat) cm^{-1}: 3367 (br), 2954 (m), 2932 (m), 2890 (m), 2858 (m), 1717 (s), 1390 (s), 1367 (s), 1157 (s), 841 (s); HRMS (ESI) *m*/*z* calcd for $C_{52}H_{76}N_6NaO_{14}Si_2$ $[M+Na]^+$ 1087.48557, found: 1087.48134.

Compound *ent*-**45**: $[\alpha]_D$ −217 (*c* 1.0, $CHCl_3$, 25 °C).

Reduced by-product **46**: ^1H NMR (500 MHz, $CDCl_3$, 23 °C) δ: 0.06 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3), 0.85 (s, 9H, SiC(CH_3)$_3$), 1.56 (s, 9H, (CH_3)$_3$COCON), 2.47 (dd, *J*=7.8, 13.8 Hz, 1H, $C_{12}H$), 2.67 (d, *J*=13.8 Hz, 1H, $C_{12}H$), 2.94 (s, 3H, $C_{18}H$), 3.84 (d, *J*=10.4 Hz, 1H, $C_{17}H$), 3.99 (t, *J*=7.8 Hz, 1H, C_3H), 4.09 (s, 1H, $C_{11}OH$), 4.23 (d, *J*=10.4 Hz, 1H, $C_{17}H$), 5.00 (s, 1H, $C_{15}OH$), 6.60 (d, *J*=7.8 Hz, 1H, C_2H), 7.01 (t, *J*=7.8 Hz, 1H, C_6H), 7.18 (d, *J*=7.8 Hz, 1H, C_5H), 7.21 (t, *J*=7.8 Hz, 1H, C_7H), 7.68 (d, *J*=7.8 Hz, 1H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: −5.50 (SiCH_3), −5.27 (SiCH_3), 18.3 (Si*C*(CH_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 27.7 (C_{18}), 28.3 ((*C*H_3)$_3$COCON), 41.6 (C_3), 42.3 (C_{12}), 63.5 (C_{17}), 77.5 (C_2), 82.3 ((CH_3)$_3$*C*OCON), 86.0 (C_{15}), 87.6 (C_{11}), 116.6 (C_8), 123.6 (C_6), 123.8 (C_5), 128.3 (C_7), 132.9 (C_4), 142.2 (C_9), 152.4 ((CH_3)$_3$*C*OCON), 163.9 (C_{16}), 168.5 (C_{13}); $[\alpha]_D$ +99 (*c* 0.59, $CHCl_3$, 25 °C); IR (neat) cm^{-1}: 3256 (br), 2953 (m), 2931 (m), 2883 (m), 2857 (m), 1710 (s), 1391 (s), 1156 (s), 839 (s); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{39}N_3NaO_7Si$ $[M+Na]^+$ 556.24550, found: 556.24623.

Compound *ent*-**46**: $[\alpha]_D$ −86 (*c* 0.64, $CHCl_3$, 24 °C).

*4.3.19. Synthesis of chaetocin (**1**).* Hydrogen sulfide (bp −60 °C, ca. 1 mL) was condensed at −78 °C in a sealed tube capped with a rubber septum. A solution of **45** (20.0 mg, 18.8 μmol) in dichloromethane (0.76 mL) and boron trifluoride diethyl ether complex (23 μL, 186 μmol) were added to the liquid hydrogen sulfide. Then the rubber septum was replaced with a stopper, and the mixture was allowed to warm to room temperature. The reaction apparatus was placed behind a blast shield in a fume hood. The reaction mixture was stirred for 90 min at room temperature, then cooled to −78 °C again, and the stopper was replaced with a rubber septum having a needle connected to two traps arranged linearly, filled with 20% aqueous sodium hydroxide. The cooling bath was removed, and the solution was warmed to room temperature. After purging with nitrogen gas, the reaction mixture was diluted with ethyl acetate (3 mL) and washed with saturated aqueous ammonium chloride (2 mL). The separated aqueous layer was extracted with ethyl acetate (3×2 mL). To the combined organic layers was added a solution of 2 equiv of I_2 in ethyl acetate (50 mM, 0.73 mL) at room temperature. The organic solution turned red immediately. It was stirred for 1 min, then 10% aqueous sodium thiosulfate solution was added for quenching. The separated aqueous phase was further extracted with ethyl acetate (3×3 mL) and the combined organic phase was dried over anhydrous sodium sulfate. After concentration in vacuo, purification by preparative TLC (Merck HPTLC Diol F_{254s}, 0.25 mm×10 cm×10 cm, ethyl acetate) gave (+)-chaetocin (**1**) (5.8 mg, 44%) as a white solid.

(+)-Chaetocin (**1**): ^1H NMR (500 MHz, $CDCl_3$, 24 °C) δ: 2.74 (d, *J*=15.1 Hz, 2H, $C_{12}H$), 3.08 (s, 6H, $C_{18}H$), 3.29 (dd, *J*=6.0, 9.2 Hz, 2H, $C_{17}OH$), 3.84 (d, *J*=15.1 Hz, 2H, $C_{12}H$), 4.18 (dd, *J*=9.2, 12.8 Hz, 2H, $C_{17}H$), 4.25 (dd, *J*=6.0, 12.8 Hz, 2H, $C_{17}H$), 5.25 (s, 2H, C_2H), 5.25 (s, 2H, N_1H), 6.74 (app. d, *J*=7.5 Hz, 2H, C_5H), 6.92 (dt, *J*=0.9, 7.5 Hz, 2H, C_6H), 7.25 (dt, *J*=1.4, 7.5 Hz, 2H, C_7H), 7.42 (app. d, *J*=7.5 Hz, 2H, C_8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.5 (C_{18}), 39.4 (C_{12}), 60.0 (C_3), 60.7 (C_{17}), 73.5 (C_{11}), 76.0 (C_{15}), 80.7 (C_2), 110.9 (C_5), 120.5 (C_6), 125.4 (C_8), 127.6 (C_4), 130.6 (C_7), 149.3 (C_9), 163.0 (C_{16}), 165.8 (C_{13}); $[\alpha]_D$ +537 (c 0.20, $CHCl_3$, 26 °C); IR (neat) cm^{-1}: 3374 (br), 2928 (m), 1677 (s), 751 (s); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{28}N_6NaO_6S_4$ $[M+Na]^+$ 719.08508, found: 719.08494.

ent-Chaetocin (*ent*-**1**): $[\alpha]_D$ −527 (*c* 0.20, $CHCl_3$, 24 °C).

Chaetocin (**1**, from *C. minutum*): ^1H NMR (500 MHz, $CDCl_3$, 24 °C) δ: 2.74 (d, *J*=15.2 Hz, 2H, $C_{12}H$), 3.08 (s, 6H, $C_{18}H_3$), 3.26 (dd, *J*=6.0, 9.6 Hz, 2H, $C_{17}OH$), 3.84 (d, *J*=15.1 Hz, 2H, $C_{12}H$), 4.18 (dd, *J*=9.6, 12.8 Hz, 2H, $C_{17}H$), 4.25 (dd, *J*=6.0, 12.8 Hz, 2H, $C_{17}H$), 5.23 (s, 2H, N_1H), 5.25 (s, 2H, C_2H), 6.74 (d, *J*=7.8 Hz, 2H, C_5H), 6.92 (t, *J*=7.8 Hz, 2H, C_6H), 7.25 (t, *J*=7.8 Hz, 2H, C_7H), 7.42 (d, *J*=7.8 Hz, 2H, C_8H); $[\alpha]_D$ +530 (*c* 0.04, $CHCl_3$, 26 °C).

*4.3.20. Synthesis of asymmetric dimer **48**.* Asymmetric dimer **48** was synthesized according to the method used for **45**. The analytical data were as follows.

Compound **48**: ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ: −0.54 (s, 3H), −0.41 (s, 3H), 0.15 (s, 3H), 0.18 (s, 3H), 0.59 (s, 9H), 0.94 (s, 9H), 1.59 (s, 9H), 1.69 (s, 9H), 2.85 (s, 3H), 2.89 (app. dd, *J*=1.9, 14.2 Hz, 1H), 3.01 (s, 3H), 3.08 (d, *J*=14.2 Hz, 1H), 3.35 (d, *J*=14.7 Hz, 1H), 3.57 (d, *J*=10.4 Hz, 1H), 3.73 (d, *J*=10.6 Hz, 1H), 3.80 (d, *J*=10.4 Hz, 1H), 3.89 (d, *J*=14.7 Hz, 1H), 4.37 (d, *J*=10.6 Hz, 1H), 4.67 (s, 1H), 5.81 (br s, 1H), 6.07 (s, 1H), 6.54 (s, 1H), 6.57 (br s, 1H), 6.75 (app. dt, *J*=1.0, 7.8 Hz, 1H), 6.84 (app. dt, *J*=0.9, 7.8 Hz, 1H), 6.94 (app. dt, *J*=1.0, 8.3 Hz, 1H), 6.96–6.99 (m, 2H), 7.10 (d, *J*=7.3 Hz, 1H), 7.14 (s, 1H), 7.30 (d, *J*=7.4 Hz, 1H), 7.32 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 26 °C)

δ: −6.34, −6.08, −5.63, −5.11, 18.2, 18.6, 25.9, 26.0, 27.1, 27.4, 28.1, 28.5, 41.7, 44.9, 56.7, 56.9, 62.7, 65.8, 79.7, 80.1, 82.0, 84.2, 85.1, 85.9, 86.7, 86.9, 115.7, 116.2, 122.0, 122.6, 123.4, 123.8, 128.7, 129.2, 131.5, 133.4, 139.4, 141.9, 151.1, 152.8, 162.7, 165.7, 170.1; $[\alpha]_D$ −118 (*c* 0.75, $CHCl_3$, 24 °C); FTIR (neat) cm^{-1}: 3361 (br m), 2927 (m), 1711 (m), 1657 (s).

*4.3.21. Synthesis of chaetocin analogue **52**.* Chaetocin analogue **52** was synthesized according to the method used for chaetocin (**1**). The analytical data were as follows.

Compound **52**: ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 0.13 (s, 3H), 0.14 (s, 3H), 0.91 (s, 9H), 2.64 (d, *J*=14.9 Hz, 1H), 3.13 (s, 3H), 3.75 (d, *J*=14.9 Hz, 1H), 4.28 (d, *J*=12.1 Hz, 1H), 4.36 (d, *J*=12.1 Hz, 1H), 5.28 (s, 1H), 5.36 (s, 1H), 6.69 (d, *J*=8.0 Hz, 1H), 6.88 (t, *J*=8.0 Hz, 1H), 7.21 (t, *J*=8.0 Hz, 1H), 7.38 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: −5.59, −5.30, 18.4, 25.8, 28.2, 29.8, 39.9, 60.2, 60.8, 74.0, 80.9, 110.7, 120. 0, 125.5, 128.0, 130.0, 149.6, 161.9, 165.8.

4.4. Crystallography

CCDC-764669 contains the supplementary crystallographic data for **31** and CCDC-819081 contains the supplementary crystallographic data for **42a**.

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