Studies Directed toward Synthesis of the Structure Proposed for Stereocalpin A

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Some synthetic efforts directed to the proposed structure of stereocalpin A are disclosed. The stereogenic centers in the aldol unit were installed using the method of Evans and the intermediates obtained through a reliable route helped to reveal that the spectroscopic data reported earlier in the literature for the same structures were either erroneous or irrelevant.

Keywords peptide, natural product, aldol reaction, amino acid, condensation

Introduction

Stereocalpin A was first reported in 2008 by Oh and coworkers[1] as a natural cyclic depsipeptide (**1**, Figure 1) with significant antitumoral activity. In an effort to confirm the assigned structure, also as a natural extension of our studies in aldol related synthesis of natural products, we began a synthetic investigation targeting at **1** soon after the Oh's publication fell to our sight. Then, in 2009, while our work was still under going, Ghosh *et al.*[2] published their synthesis of compound **1** and showed that the NMR data of the synthetic **1** were not compatible with those for the natural product. As this in fact already put an end for compound **1** as a natural product, we were about to discontinue the work along this line. However, a more recent publication[3] reporting on the aldol subunit of **1**, which gave spectroscopic data substantially different from ours, prompted us to disclose our own results detailed below.

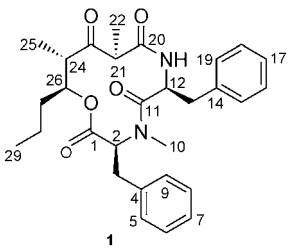
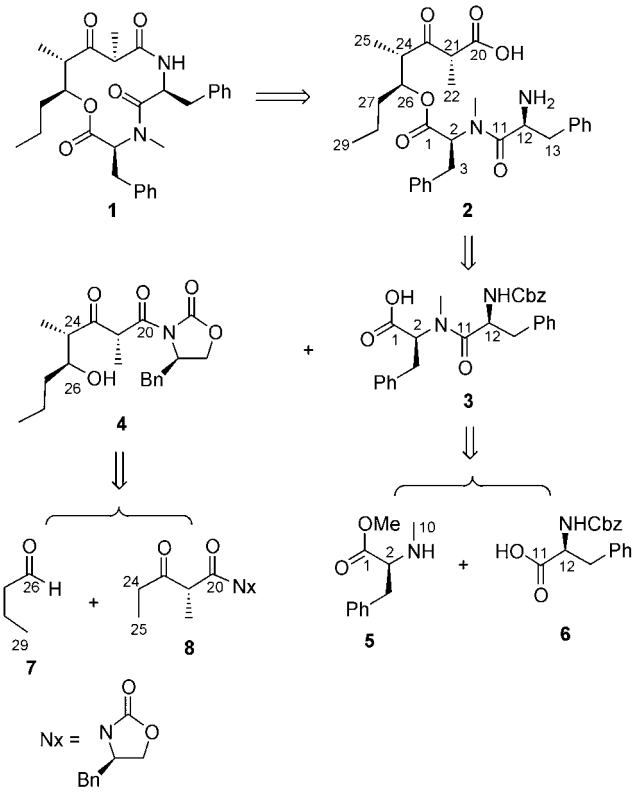


Figure 1 Structure proposed for the natural stereocalpin A (**1**).

Results and discussion

Our general plan, in a form of retrosynthetic analysis, is shown in Scheme 1. The initial bond disconnection was arranged at the amido bond between C-20 and the amino group at C-12, which related to structure **2**. And this linear intermediate can be further disconnected into the dipeptide fragment **3** and the aldol subunit **4**. The former **3** is a straightforward condensation product of phenylalanine derivatives **5** and **6**, while the latter **4**,

Scheme 1



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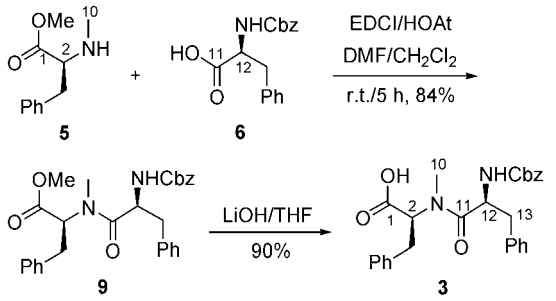
should be possible to be derived from aldol reaction between **7** and **8**.

In execution of the synthetic plan, the commercially available phenylalanine derivatives **5** and **6** were condensed with each other to give the desired dipeptide fragment **3** (Scheme 2). Initially, this was attempted under the most traditional conditions using DCC (dicyclohexylcarbodiimide) as the condensing agent. However, the product was very difficult to separate from the dicyclohexylurea generated in the reaction. Replacing DCC with EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) and performing the reaction under otherwise the same conditions (with CH_2Cl_2 as the solvent) did eliminate the separation problem. However, the yield was still rather low. Using pyBOP [(Benzotriazol-1-yl-oxy)tripyrrolidinophosphonium hexafluorophosphate] gave a higher yield (70%), but the reagent was substantially more expensive. Finally, we were pleased to observe that addition[4] of some DMF (dimethylformamide) to the EDCI system in the presence of HOAt (1-hydroxy-7-azabenzotriazole) could raise the yield of **9** to 84% and thus provided a satisfactory means to access the desired dipeptide. Further treatment of **9** with LiOH in THF led to smooth hydrolysis of the methyl ester, giving the corresponding acid **3** in 90% yield.

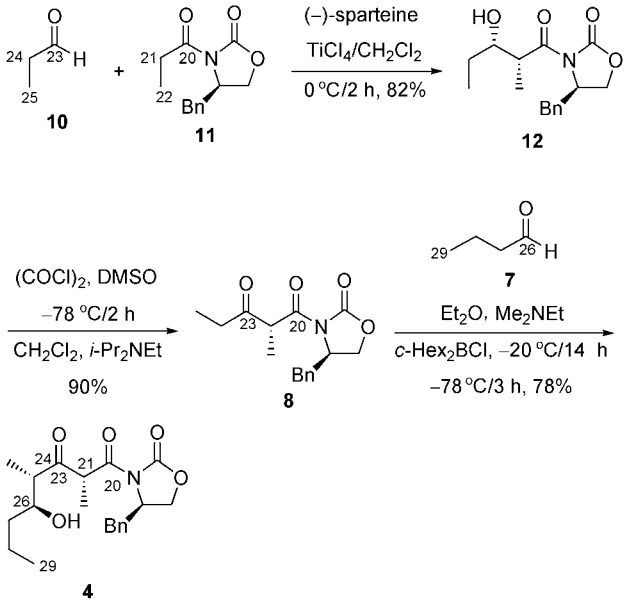
Scheme 2



It is noteworthy that both the ^1H and ^{13}C NMR of **9** contained "additional" signals, which seemingly suggested presence of configurational isomer(s), a problem occurs from time to time to peptide synthesis in general. However, repeated careful HPLC separation of **9** failed to show any isomer(s). Also, when recording at higher temperature (80 ℃ in DMSO-d_6) complete signals degeneration occurred to both the ^1H and ^{13}C NMR—the "extra" signals in the spectra acquired at ambient temperature all disappeared. Then we also noticed that similar phenomena of "extra" signals had been observed in some literature cases,[5] where the amido NH in normal peptides was methylated (NMe).

The aldol fragment **4** was synthesized using the route shown in Scheme 3. Starting from the commercially available aldehyde **10** and *N*-acyloxazolidinone **11** through an asymmetric aldol reaction under the conditions developed by Crimmins *et al.*[6] the aldol **12**[7] was obtained in 82% isolated yield.

Scheme 3



Oxidation of **12** into **8** was realized with SO_3-py in the original report[8a,8b] of Evans *et al*. However, in our hands the yield fluctuated significantly from run to run regardless of the source (from several different commercial suppliers) of the oxidant. This problem later was solved by using Swern oxidation. Under such conditions the ketone **8** could be obtained in high yields with high reproducibility. Subjection of ketone **8** to the Evans' asymmetric aldol reaction conditions[8a] led to formation of fragment **4** in 78% yield.

It should be noted here that in their original report, Evans and coworkers[8a] mentioned that direct reaction (Scheme 4) of **11** with propionyl chloride could lead to **8'** (not **8**). Therefore, an indirect two-step sequence (*i.e.*, aldol reaction followed by oxidation) was proposed for the preparation of compound **8**. Although a recent publication[3] claimed acquisition of **8** rather than **8'** through the same reaction under slightly modified conditions (no $MgBr_2$ and fast addition of propionyl chloride), the accompanying data for the **8'** (including optical rotation and ^1H as well as ^{13}C NMR) therein were not only incompatible with those[8a] of Evans' **8'**, but also exactly the same as those[8a] for the **8** reported by Evans. In comparison, our **8** was identical to that of Evans' **8** in all respects, with additional support from single crystal X-ray analysis[8c] (Figure 2). All these manifest that the aldol reaction followed by oxidation was (and still is to date) indeed necessary for the synthesis of **8** and the structure as well as configuration of the **8** employed in the present investigation was secured with full confidence.

Then, we were in a position to scrutinize the incompatibility between the data for the aldol subunit **4** syn-

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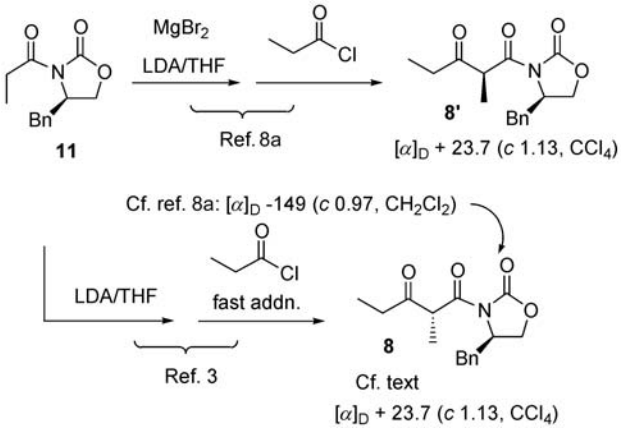
Scheme 4



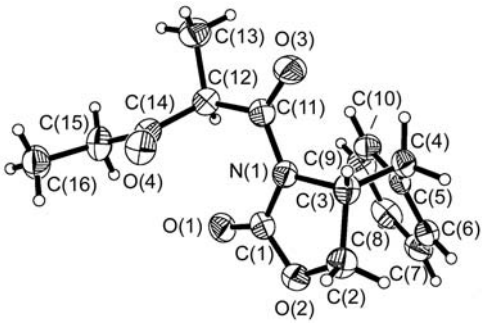


Figure 2 The ORTEP presentation for **8**.

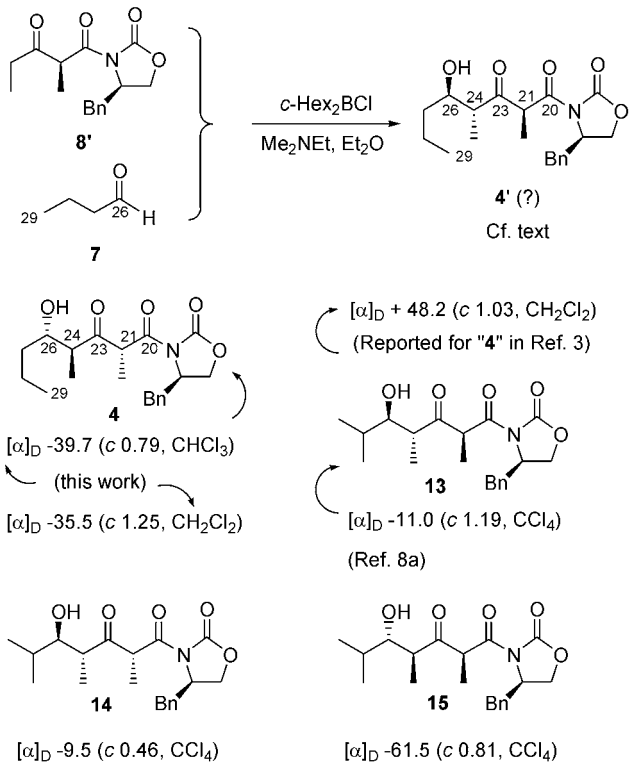


Figure 3 Configuration of the product **4'** that might be derived from **8'** according to the rule in Ref. 7 and three configurational isomers along with their optical rotations mentioned in Ref. 7.

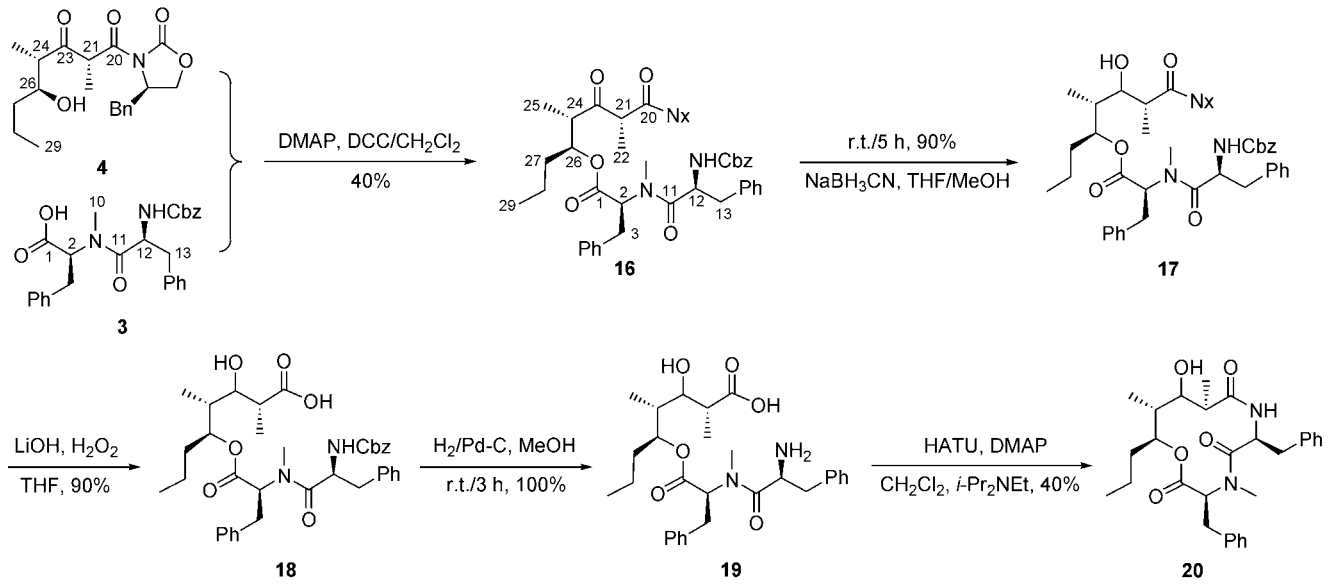
thesized in this work and that reported in the literature.[3] As the identity of our **8** was established beyond any doubts and the subsequent aldol reaction was performed exactly under the Evans' conditions (with the aldehyde being essentially the same: propionaldehyde in Evans' case and butyraldehyde in ours), the relative as well as absolute configuration of our **4** therefore should be the same as those reported for the congener of **4** (with only one less CH_2 in the alkyl chain compared with **4**) by Evans. Under the same reaction conditions, the corresponding aldol product in the earlier paper[3] (Figure 3), where the starting **8** was reported to have all the spectroscopic data identical to those for **8'**, is expected to afford the diastereomer **4'** (instead of **4**) according to the rule established by Evans.[8] However, while it is impossible to confirm this possibility on the basis of the available NMR data, its specific rotation {$[\alpha]_D$ +48.2 (*c* 1.03, CH_2Cl_2)[3]} does not seem to be compatible with a closely related compound {**13**, $[\alpha]_D$ −11.0 (*c* 1.19, CCl_4[8a])}. We noticed that all the other possible diastereomers[8a] in the literature also showed negative rotations.

The coupling of the aldol fragment and the dipeptide one was executed as shown in Scheme 5. An initial attempt under the Yamaguchi conditions was unsuccessful, with the ketone carbonyl group apparently enolized. Then, the union of the two fragments was performed using DCC as the condensing agent, which led to the desired coupling product in 40% yield. Having noticed the great tendency for enolization (and consequently, racemization) at the C-21, we next opted to reduce the ketone carbonyl to the corresponding alcohol before further elaborations on the carboxylic as well as the amino terminals of the substrate. To this end, the mild $NaBH(OAc)_3$ was first examined, which failed to give any reduction product. $NaBH_4$ was potent enough to reduce the ketone completely, but the chiral auxiliary was also cleaved with the C-20 concurrently transformed to the corresponding alcohol. Finally, $NaBH_3(CN)$, which was usually unable to reduce ketones, was found to be a suitable reductant for the desired transformation, affording a clean[9] reduction of the C-23 ketone.

The chiral auxiliary was then cleaved under the classic $LiOH/H_2O_2$[10] conditions. The resulting acid (**18**) was treated with atmospheric H_2 over Pd-C at ambient temperature to cleave the Cbz (benzyloxycarbonyl) protecting group. The newly formed amino acid **19** was then cyclized into **20** with the aid of HATU [2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate].

Up to this point, the structure (**20**) was already very similar to that of **1**. It seems that only one step of oxidation of the C-23 alcohol into the corresponding ketone would finish the whole synthesis. However, such a usually rather simple transformation turned out to be extremely difficult here. We tried several protocols in-

Scheme 5



cluding Swern, SO_3-py, and Dess-Martin oxidation. Unfortunately, they all led to a mixture containing a component with the C-23 ketone enolized, strongly suggesting that the structure **1** enolizes very easily. Because by that time Ghosh[2] already published their work, where the original spectra for the natural product were disclosed for the first time and the possibility for **1** being the natural product had been completely excluded, we did not make any further attempts to convert **20** into **1**.

Conclusion

In an attempt to synthesize the structure originally assigned for the natural stereocalpin A, the aldol subunit of the target structure was constructed efficiently using the Evans asymmetric aldol reaction, with the absolute configurations of all stereogenic centers established without any ambiguity. The present results also show that the spectroscopic data previously reported for the corresponding aldol intermediates were either erroneous or irrelevant.

Experimental

Dry THF was distilled over Na/Ph_2CO under N_2 prior to use. Dry CH_2Cl_2 and dry DMF were distilled over CaH_2 under N_2 prior to use. Addition of air/moisture sensitive reagents was done using syringe techniques. PE (for chromatography) stands for petroleum ether (b.p. 60—90 ℃). Column chromatography was performed on silica gel (300—400 mesh) under slightly positive pressure. NMR spectra were recorded on a Varian Mercury Bruker Avance NMR spectrometer operating at 300 MHz for ^1H with Me_4Si as the internal standard. IR spectra were measured on a Nicolet 380 infrared spectrometer. ESI-MS data were acquired on a Shimadzu LCMS-2010EV mass spectrometer. HRMS data were obtained with a Bruker APEXIII 7.0 Tesla FT-MS spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter.

(4*R*)-3-[(2*R*,3*S*)-3-Hydroxy-2-methyl-pentanoyl]-4-benzyl-oxazolidine-2-one (12) To a solution of the *N*-acyl oxazolidinone **11** (4.66 g, 20 mmol) in dry CH_2Cl_2 (130 mL) stirred at 0 ℃ under N_2 (balloon) were added dropwise $TiCl_4$ (2.3 mL, 21 mmol) and (5 min later) (−)-sparteine (7.5 mL, 50 mmol). The dark red-brown mixture was stirred at the same temperature for 30 min. Propionaldehyde (2.18 mL, 30 mmol) was added slowly. Stirring was continued at 0 ℃ for 2 h before aqueous saturate NH_4Cl (20 mL) was added. The mixture was filtered through Celite. The filtrate was washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (EtOAc/PE, V∶V=1∶4) on silica gel gave aldol **12** as a colorless oil (4.77 g, 16.4 mmol, 82%) which solidified on standing. m.p. 82—83 ℃ (Lit.[7] m.p. 78—79 ℃). $[\alpha]_D^{25}$ −38.9 (*c* 1.07, $CHCl_3$) [Lit.[7] $[\alpha]_D^{25}$ −39.8 (*c* 1.09, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.36—7.19 (m, 5H), 4.70 (m, 1H), 4.19 (m, 2H), 3.86 (m, 1H), 3.79 (dq, J=7.0, 2.8 Hz, 1H), 3.25 (dd, J=13.4, 3.3 Hz, 1H), 2.92 (d, J=3.2 Hz, 1H), 2.79 (dd, J=9.4, 13.4Hz, 1H), 1.53 (m, 2H), 1.25 (d, J=7.0 Hz, 3H), 0.98 (t, J=7.4 Hz, 3H).

(4*R*)-3-[(2*R*)-2-Methyl-3-oxo-pentanoyl]-4-benzyl-oxazolidine-2-one (8) To a solution of $(COCl)_2$ (6.76 mL, 8 mmol) in dry CH_2Cl_2 (20 mL) stirred at −78 ℃ under N_2 (balloon) were added dropwise dry DMSO (1.1 mL, 16 mmol) and **12** (1.16 g, 4 mmol, added *ca*. 5 min later). The mixture was stirred at the same temperature for 30 min. Dry *i*-Pr_2NEt (2.8 mL, 20 mmol) was introduced. The cooling bath was allowed to warm slowly to ambient temperature. The reaction mixture

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was partitioned between water and CH_2Cl_2. The organic layer was washed with aqueous saturated NH_4Cl, aqueous saturated $NaHCO_3$ and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (EtOAc/PE, V∶V=1∶8) on silica gel gave ketone **8** as a colorless oil (1.04 g, 3.6 mmol, 90%), which solidified on standing. m.p. 76—77 ℃ (Lit.[8a] 76—77 ℃); $[\alpha]_D^{25}$ −144 (*c* 1.2, CH_2Cl_2) [Lit.[8a] $[\alpha]_D^{25}$ −149 (*c* 0.97, CH_2Cl_2)]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.36—7.18 (m, 5H), 4.74 (m, 1H), 4.60 (q, J=7.5 Hz, 1H), 4.20 (m, 2H), 3.30 (dd, J=13.4, 3.2 Hz, 1H), 2.77 (dd, J=13.4, 9.6 Hz, 1H), 2.65 (m, 2H), 1.43 (d, J=7.3 Hz, 3H), 1.07 (t, J=7.2 Hz, 3H).

(4*R*)-3-[(2*R*,5*S*)-2,4-Dimethyl-3-oxo-5-hydroxyoctanoyl]-4-benzyl-oxazolidine-2-one (4) To a solution of **8** (2.89 g, 10 mmol) in dry Et_2O (100 mL) stirred at 0 ℃ under N_2 (balloon) were added *c*-Hex_2BCl (1.0 mol•L^{-1}, in hexanes, 12 mL, 12 mmol) and Me_2NEt (1.6 mL, 15 mmol). The stirring was continued at the same temperature for 1 h and the temperature of the cooling bath was lowered to −78 ℃. Butyraldehyde (1.35 g, 30 mmol) was added to the milky-yellowish mixture. Stirring was continued at −78 ℃ for 3 h and then at −20 ℃ for 14 h. The mixture was diluted with Et_2O (100 mL). A pH 7 buffer (100 mL) was added, followed by 30% H_2O_2 (50 mL). The mixture was stirred at ambient temperature for 1 h. The phases were separated. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (EtOAc/PE, V∶V=1∶4) on silica gel afforded aldol **4** as a colorless oil (2.82 g, 7.8 mmol, 78%). $[\alpha]_D^{25}$ −39.7 (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34—7.18 (m, 5H), 4.89 (q, J=7.3 Hz, 1H), 4.76—4.68 (m, 1H), 4.27—4.08 (m, 2H), 3.62—3.54 (m, 1H), 3.29—3.26 (m, 1H), 2.85—2.74 (m, 2H), 1.48—1.44 (m, 3H), 1.34 (d, J=6.6 Hz, 1H), 1.18 (d, J=7.1 Hz, 2H), 1.09 (t, J=7.4 Hz, 1H), 0.96 (t, J=7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 212.2, 170.5, 153.5, 135.0, 129.3, 128.9, 127.4, 73.3, 66.4, 55.3, 52.4, 49.7. 37.9, 36.5, 18.5, 14.1, 13.9, 12.8; FT-IR (film) *v*: 2959, 2865, 1781, 1694, 1683 cm^{-1}; ESI-MS *m/z*: 362.3 ($[M+H]^+$); ESI-HRMS calcd for $C_{23}H_{21}N_3O_7Na$ ($[M+Na]^+$) 384.1780, found 384.1786.

Methyl (*S*)-2-[(*S*)-2-(benzyloxycarbonylamino)-*N*-methyl-3-phenylpropanamido]-3-phenylpropanoate (9) A solution of the methyl ester **5** (1.74 g, 9 mmol), acid **6** (1.8 g, 6 mmol), EDCI (2.3 g, 12 mmol) and HOAt (1.22 g, 9 mmol) in dry CH_2Cl_2 (50 mL) and dry DMF (10 mL) was stirred first at 0 ℃ for 2 h then at ambient temperature for 5 h. EtOAc (100 mL) was added. The mixture was washed with aqueous saturated $NaHCO_3$ and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (EtOAc/PE, V∶V=1∶3) on silica gel afforded dipeptide **9** as a colorless oil (2.38 g, 5 mmol, 84%). $[\alpha]_D^{25}$ +19.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34—7.12 (m, 15H), 5.92—5.90 (m, 1H), 5.18—5.16 (m, 1H), 5.05—4.97 (m, 3H), 4.95—4.79 (m, 1.5H), 3.68 (s, 3H), 3.36—3.31 (m, 15H), 3.05—2.59 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.6, 172.7, 155.6, 136.7, 135.9, 129.4, 129.2, 129.1, 129.0, 128.7, 128.6, 128.4, 127.9, 127.5, 126.9, 126.8, 126.7, 67.2, 66.8, 66.7, 59.3, 52.4, 52.1, 51.0, 38.8, 38.3, 37.5, 34.9, 34.5, 34.3, 33.6, 33.2, 30.2; FT-IR (film) *v*: 2959, 2865, 1781, 1694, 1683 cm^{-1}; ESI-MS *m/z*: 497.3 ($[M+H]^+$); ESI-HRMS calcd for $C_{28}H_{30}N_2O_7Na$ ($[M+Na]^+$) 497.2061, found 497.2052.

(*S*)-2-[(*S*)-2-(Benzyloxycarbonylamino)-*N*-methyl-3-phenylpropanamido]-3-phenylpropanoic acid (3) A solution of **9** (4.74 g, 10 mmol) and LiOH (0.50 g, 12 mmol) in water (5 mL) and THF (35 mL) was stirred at 0 ℃ for 2 h. The mixture was acidified to pH 3 with 1 N HCl and extracted with EtOAc (100 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (EtOAc/PE, V∶V=2∶1) on silica gel afforded acid **3** as a colorless oil (4.27 g, 9 mmol, 90%). $[\alpha]_D^{25}$ +16.7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 12.1 (br s OH), 7.34—7.12 (m, 15H), 5.92—5.90 (m, 1H), 5.18—5.16 (m, 1H), 5.05—4.97 (m, 3H), 4.95—4.79 (m, 1.5H), 3.36—3.31 (m, 1.5H), 3.05—2.59 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.6, 172.7, 155.6, 136.7, 135.9, 129.4, 129.2, 129.1, 129.0, 128.7, 128.6, 128.4, 127.9, 127.5, 126.9, 126.8, 126.7, 67.2, 66.8, 66.7, 59.3, 52.4, 52.1, 51.0, 38.8, 38.3, 37.5, 34.9, 34.5, 34.3, 33.6, 33.2, 30.2; FT-IR (film) *v*: 3345, 2959, 2865, 1781, 1694, 1683 cm^{-1}; ESI-MS *m/z*: 483.2 ($[M+H]^+$); ESI-HRMS calcd for $C_{27}H_{28}N_2O_5Na$ ($[M+Na]^+$) 483.1889, found 483.1895.

(*S*)-(4*S*,5*S*,7*R*)-8-[(*R*)-4-Benzyl-oxazolidin-2-on-3-yl]-5,7-dimethyl-6,8-dioxo-octan-4-yl 2-(*S*)-2-(benzyloxycarbonylamino)-*N*-methyl-3-phenylpropanamido)-3-phenylpropanoate (16) A solution of acid **3** (460 mg, 1.0 mmol), DCC (466 mg, 2.0 mmol), DMAP (0.1 mg) in dry CH_2Cl_2 (5 mL) was stirred at 0 ℃ for 1 h. Aldol **4** (361 mg, 1.0 mmol) was added. The stirring was continued at ambient temperature for 2 h before being diluted with EtOAc (20 mL), washed with aqueous saturated $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (EtOAc/PE, V∶V=1∶2) on silica gel afforded **16** as a colorless oil (320 mg, 0.4 mmol, 40%). $[\alpha]_D^{25}$ +16.7 (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34—7.12 (m, 20H), 5.92—5.90 (m, 1H), 5.18—5.16 (m, 1H), 5.05—4.97 (m, 3H), 4.95—4.79 (m, 3.5H), 4.76—4.68 (m, 1H), 4.27—4.08 (m, 2H), 3.62—3.54 (m, 2H), 3.36—3.26 (m, 2.5H), 3.05—2.59 (m, 6H), 1.48—1.44 (m, 3H), 1.34 (d, J=6.6 Hz, 1H), 1.18 (d, J=7.1 Hz, 2H), 1.09 (t, J=7.4 Hz, 1H), 0.96 (t, J=7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 212.2, 173.6, 172.7, 171.5, 152.8, 155.6, 136.7, 135.9, 129.4, 129.2, 129.1, 129.0, 128.7, 128.6, 128.4, 127.9, 127.5, 126.9, 126.8, 126.7, 67.2, 66.8, 66.7, 59.3, 52.4, 52.1, 51.0, 38.8, 38.3, 37.5, 34.9,

34.5, 34.3, 33.6, 33.2, 30.2, 14.9, 14.1, 12.2; FT-IR (film) *v*: 2959, 2865, 1781, 1694, 1683 cm^{-1}; ESI-MS *m/z*: 826.3 ($[M + H]^+$); ESI-HRMS calcd for $C_{47}H_{53}N_3O_9Na$ ($[M+Na]^+$) 826.3681, found 826.3679.

(*S*)-(4*S*,5*S*,7*R*)-8-[(*R*)-4-Benzyl-oxazolidin-2-on-3-yl]-5,7-dimethyl-6-hydroxy-8-oxo-octan-4-yl 2-(*S*)-2-(benzyloxycarbonylamino)-*N*-methyl-3-phenylpropanamido)-3-phenylpropanoate (17) A solution of ketone **16** (400 mg, 0.5 mmol) and $NaBH_3CN$ (31 mg, 0.5 mmol) in MeOH (1 mL) and THF (1 mL) was stirred at ambient temperature for 5 h before being diluted with EtOAc (30 mL), washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (EtOAc/PE, $V:V=3:1$) on silica gel afforded **17** as a colorless oil (360 mmg, 9 mmol, 90%). $[\alpha]_D^{25}$ +25.8 (*c* 1.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.36—7.10 (m, 20H), 5.92—5.90 (m, 1H), 5.18—5.16 (m, 1H), 5.05—4.97 (m, 3 H), 4.95—4.79 (m, 4H), 4.76—4.68 (m, 1H), 4.27—4.08 (m, 2H), 3.62—3.54 (m, 2H), 3.36—3.25 (m, 4 H), 3.07—2.59 (m, 6H), 1.48—1.44 (m, 3H), 1.35 (d, $J=6.6$ Hz, 1H), 1.19 (d, $J=7.1$ Hz, 2H), 1.08 (t, $J=7.4$ Hz, 1H), 0.96 (t, $J=7.4$ Hz, 2H); FT-IR (film) *v*: 3345, 2959, 2865, 1781, 1694, 1683 cm^{-1}; ESI-MS *m/z*: 828.4 ($[M+Na]^+$); ESI-HRMS calcd for $C_{47}H_{55}N_3O_9Na$ ($[M+Na]^+$) 828.3681, found 828.3681.

(*S*)-(4*S*,5*S*,7*R*)-8-Carboxy-5,7-dimethyl-6-hydroxy-8-oxo-octan-4-yl 2-(*S*)-2-(benzyloxycarbonylamino)-*N*-methyl-3-phenylpropanamido)-3-phenylpropanoate (18) A solution of **17** (200 mg, 0.25 mmol) and LiOH (13 mg, 0.3 mmol) in THF (1 mL) and water (0.1 mL) was stirred at 0 ℃ for 2 h. The mixture was acidified to pH 3 with diluted HCl before being diluted with EtOAc (30 mL), washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (EtOAc/PE, $V:V=8:1$) on silica gel afforded acid **18** as a colorless oil (145 mg, 0.22 mmol, 90%). $[\alpha]_D^{24}$ +23.1 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 12.1 (br s, 1H), 7.36—7.15 (m, 15H), 5.18—5.16 (m, 1H), 5.00—4.97 (m, 1H), 4.95—4.79 (m, 3H), 4.76—4.68 (m, 1H), 3.62—3.54 (m, 3H), 3.36—3.25 (m, 4 H), 3.07—2.59 (m, 7H), 1.48—1.44 (m, 3H), 1.35 (d, $J=6.6$ Hz, 1H), 1.19 (d, $J=7.1$ Hz, 2H), 1.08 (t, $J=7.4$ Hz, 1H), 0.96 (t, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.6, 172.7, 168.2, 155.6, 136.7, 135.9, 129.4, 129.2, 129.1, 129.0, 128.7, 128.6, 128.4, 127.9, 127.5, 126.9, 126.8, 126.7, 67.2, 66.8, 66.7, 59.3, 52.4, 52.1, 51.0, 34.3, 33.6, 33.2, 30.2, 15.9, 14.1, 12.0; FT-IR (film) *v*: 3345, 2959, 2865, 1781, 1694, 1683 cm^{-1}; ESI-MS *m/z*: 647.8 ($[M + Na]^+$); ESI-HRMS calcd for $C_{37}H_{46}N_2O_8Na$ ($[M+Na]^+$) 669.7590, found 669.7581.

(*S*)-(4*S*,5*S*,7*R*)-8-Carboxy-5,7-dimethyl-6-hydroxy-8-oxo-octan-4-yl 2-(*S*)-2-amino-*N*-methyl-3-phenylpropanamido)-3-phenylpropanoate (19) The above obtained **18** (145 mg, 0.22 mmol) and Pd-C (10%, 10 mg) were stirred in MeOH (2 mL) at ambient temperature under H_2 (1.01×10^5 Pa) for 3 h. The solids were filtered off. The filtrate was concentrated on a rotary evaporator to give amino acid **19** as a yellowish oil (100%). $[\alpha]_D^{24}$ +18.8 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.28—7.15 (m, 10H), 5.19—5.16 (m, 1H), 5.00—4.97 (m, 1H), 4.95—4.79 (m, 1H), 4.76—4.68 (m, 1H), 3.62—3.54 (m, 3H), 3.36—3.25 (m, 4H), 3.07—2.59 (m, 9H), 1.48—1.44 (m, 3H), 1.35 (d, $J=6.6$ Hz, 1H), 1.20 (d, $J=7.1$ Hz, 2H), 1.08 (t, $J=7.4$ Hz, 1H), 0.98 (t, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.6, 172.7, 155.6, 136.7, 135.9, 129.4, 129.2, 129.1, 129.0, 128.7, 128.6, 128.4, 127.9, 127.5, 126.9, 126.8, 126.7, 67.2, 66.8, 66.7, 59.3, 52.4, 52.1, 51.0, 38.8, 38.3, 37.5, 34.9, 34.5, 34.3, 33.6, 33.2, 30.2, 15.9, 14.1, 12.0; FT-IR (film) *v*: 3345, 2959, 2865, 1781, 1694, 1683 cm^{-1}; ESI-MS *m/z*: 535.3 ($[M+Na]^+$); ESI-HRMS calcd for $C_{29}H_{40}N_2O_6Na$ ($[M + Na]^+$) 535.2782, found 535.2789.

(3*S*,6*S*,9*R*,11*R*,12*S*)-3,6-Dibenzyl-10-hydroxy-4,9,11-trimethyl-12-propyl-1-oxa-4,7-diazacyclododecane-2,5,8-trione (20) A solution of amino acid **19** (460 mg, 1.0 mmol), HATU (766 mg, 2.0 mmol), DMAP (0.1 mg), *i*-Pr_2NEt (0.28 mL, 2.0 mmol) was stirred at 0 ℃ for 5 h before being diluted with EtOAc (30 mL), washed with aqueous saturated $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (EtOAc/PE, $V:V=1:2$) on silica gel afforded **20** as a colorless oil (320 mg, 0.4 mmol, 40%). $[\alpha]_D^{24}$ +27.7 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.27—7.15 (m, 10H), 5.18—5.16 (m, 1H), 5.00—4.97 (m, 1 H), 4.95—4.79 (m, 1H), 4.76—4.68 (m, 2H), 3.62—3.54 (m, 3H), 3.36—3.25 (m, 4H), 3.07—2.59 (m, 7H), 1.48—1.44 (m, 3H), 1.36 (d, $J=6.6$ Hz, 1H), 1.21 (d, $J=7.1$ Hz, 2H), 1.10 (t, $J=7.4$ Hz, 1H), 0.98 (t, $J=7.4$ Hz, 2H); FT-IR (film) *v*: 3326, 2929, 2857, 1702, 1698, 1471, 1416 cm^{-1}; ESI-MS *m/z*: 493.2 ($[M+H]^+$); ESI-HRMS calcd for $C_{29}H_{38}N_2O_5Na$ ($[M + Na]^+$) 517.2672, found 517.2669.

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