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On the Synthesis of Stereocalpin A: Partial Retraction/ Correction of Previous Results and Rationalization of the Hidden Difficulties

Zhiwei Zhao,[a,b] Yikang Wu,*[,b] and Yan Li*[,a]

[a] *Hubei Collaborative Innovation Center for Advanced Organic Chemical Materials and Ministry-of-Education Key Laboratory for Synthesis and Application of Organic Functional Molecules, Hubei University, Wuhan, Hubei 430062, China*

[b] *State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

In continuation/checking of a previous synthesis directed toward the literature structure of stereocalpin A it was found that the data for a substantial part of the intermediates reported before were incorrect. Some of the transformations were not successfully reproduced and the failures were shown to be consequences of the presence of the N-Me and the particular location of the ester linkage. The origins of the "extra/minor" signals in the NMR for most of the intermediates, which tend to be mistaken as signs for the presence of impurity/isomers, are also discussed.

Keywords peptide, natural product, aldol reaction, cyclization, condensation

Introduction

Stereocalpin A (**1**) is an antitumor depsipeptide isolated[1] from the MeOH extract of the Antarctic lichen *Stereocaulon alpinum*. In 2009, Ghosh (A. Ghosh) and Xu reported the first synthesis of the assigned structure using a ring-closure strategy with a macrolactamization at the -NHMe (Figure 1, disconnection a).[2] In a previous report[3] (under the title "Studies Directed toward Synthesis of the Structure Proposed for Stereocalpin A") by Huang and Wu (one of us), a different macrolactamization approach (disconnection a, Figure 1) was also described, where the ring-closure occurred at the -NH_2 rather than the -HNMe group (disconnection b) as in the Ghosh's[2] route. S. Ghosh and coworkers also made extensive efforts in synthesis of **1**.[4] Their attempts to employ the strategy of macrolactamization at the primary -NH_2 did not succeed. In the end, their synthesis of 12-*epi*-**1** was completed using the same strategy of ring-closure at the -NHMe developed[2] by A. Ghosh.

In a recent effort to check the results of the above[3] mentioned report, it was found that a substantial part of that study was, regrettably, not reproduced; some physical and spectroscopic data were proven incorrect, while the condensation of the aldol subunit with the dipeptide one and the macrolactamization did not lead to the expected products as described before. Therefore, we feel obliged[5] to retract part of the previous results to terminate any confusion that might have already been caused by the previous report and clarify the transformations involved therein through the new results. Some hidden difficulties and so far unexplained phenomena in the synthesis of stereocalpin A will also be discussed.

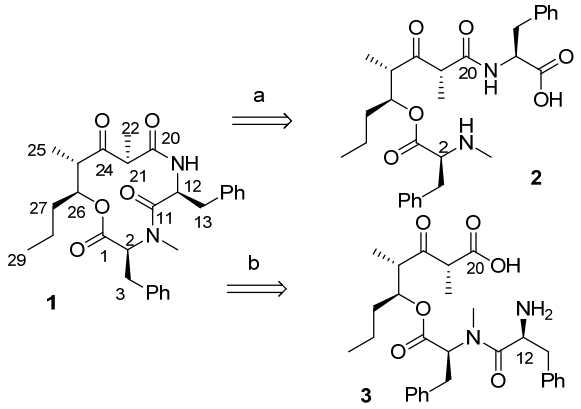

Figure 1 The structure assigned for stereocalpin A (**1**) and the two retrosynthetic disconnections for the macrolactamization.

Results and Discussion

The dipeptide subunit was prepared as described before (Scheme 1). Condensation of the known **4**[6] and **5**[7] led to **6**, which on saponification gave free acid **7**.

* E-mail: yikangwu@sioc.ac.cn
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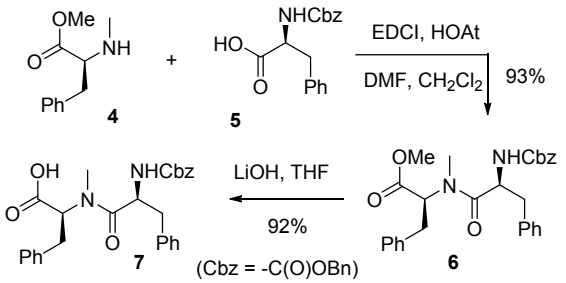
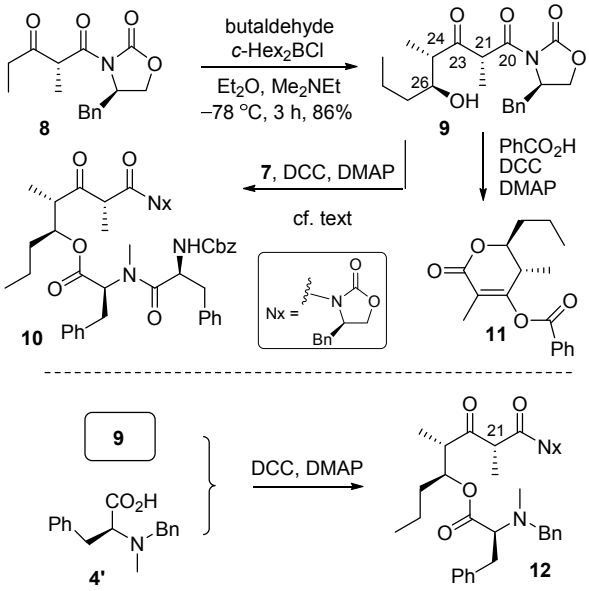
Scheme 1



The previously published ^{1}H and ^{13}C NMR data for **7** (compound **3** therein) were more or less compatible with those for the sample gained in this work. However, subsequent condensation of **7** with aldol subunit **9** (prepared as described before, Scheme 2) did not occur as reported[3] before. The reaction mixture was very complex. Although the presence of traces of **10** could not be excluded, the yield for **10** was definitely impossible to exceed 10%. In a control experiment using sterically less hindered/more reactive benzoic acid to replace acid **7** led to mainly **11** (Scheme 2), which suggested that the failure of direct condensation of **7** and **9** was most likely caused by the undesired lactonization.

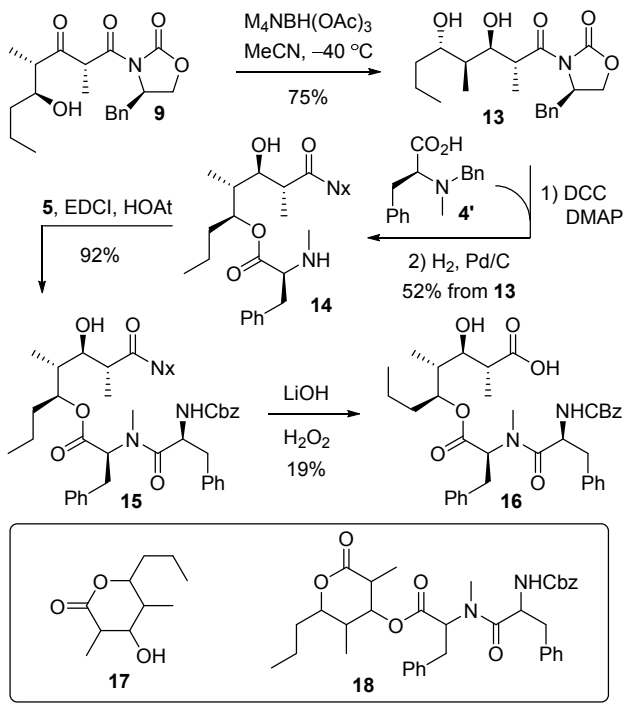
Scheme 2



To this end, the C-23 ketone carbonyl group in **9** was setereoselectively reduced with $Me_4NB(OAc)_3H$[8] to afford **13** (Scheme 3). Treatment of diol **13** with **4'** in the presence of EDCI/HOAt followed by hydrogenolysis over Pd/C under H_2 (1 atm) afforded **14** in 52% yield over 2 steps (from **13**). The second amino acid residue was then introduced by a condensation of **14** with **5**.

Without interference of any side reactions leading to 6-membered lactone or lactam, the reaction occurred smoothly, giving desired **15** in 92% isolated yield. Subsequent cleavage of the Evans auxiliary under the standard $LiOH/H_2O_2$ conditions could afford the desired acid **16**, but the yield was too low to provide sufficient quantity for full characterization. The other two isolable side products appeared to possess the gross structures **17** and **18**, while the starting **15** was fully consumed.

Scheme 3



To gain sufficient amounts of **16** for full characterization, the route in Scheme 4 was then employed. The chiral auxiliary Nx was cleaved at an earlier stage to avoid complications encountered in the final step in Scheme 3. Masking the primary OH and introduction of two amino acid residues were performed using the similar strategy in Scheme 3. And finally, deprotection of the primary OH followed by oxidation provided acid **16**.

Removal of the Cbz protecting group was unexpectedly complicated. Treatment of **16** (or **15**) with H_2 (1 atm) in the presence of 10% Pd/C or Pd $(OH)_2$ (with or without added NH_4CO_2H[4]) could not afford the desired **3** at all. In all runs the only separable products turned out to be **25**—**27** (Scheme 5), which presumably occurred via the intramolecular attack of the newly freed NH_2 on the C-1 ester carbonyl group. It is noteworthy that ketone **10**, an intermediate in Scheme 2, was obtained by a Swern oxidation of **15**. The spectroscopic data for **10** were thus made available.

At first sight such unexpected results were hard to understand, because similar operations had many successful precedents in peptide syntheses. However, if one looks into the particular structural features of this unique molecule, *i.e*, a methylated amino group and the location of the fragile ester bond, the observed phenomenon is still understandable: The presence of the methyl group on the amino group made the chain more easily adopt a "bent" conformation than otherwise, so that the free amino group generated by the cleavage of

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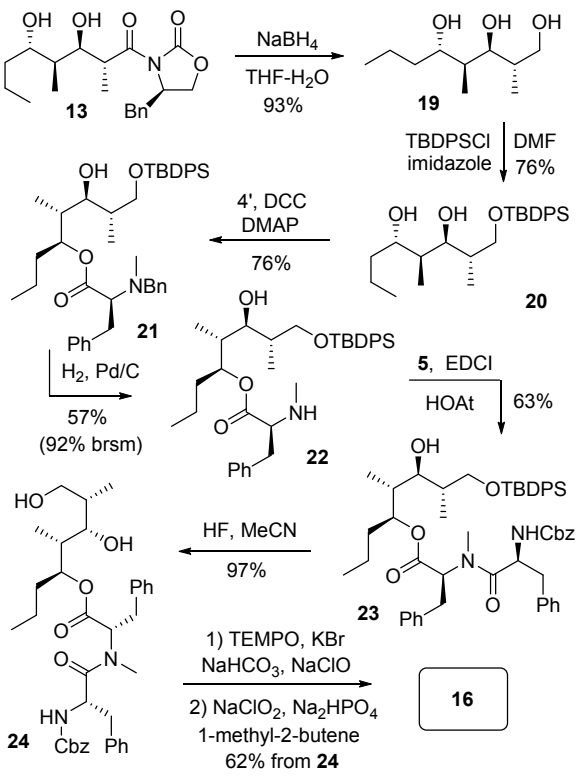
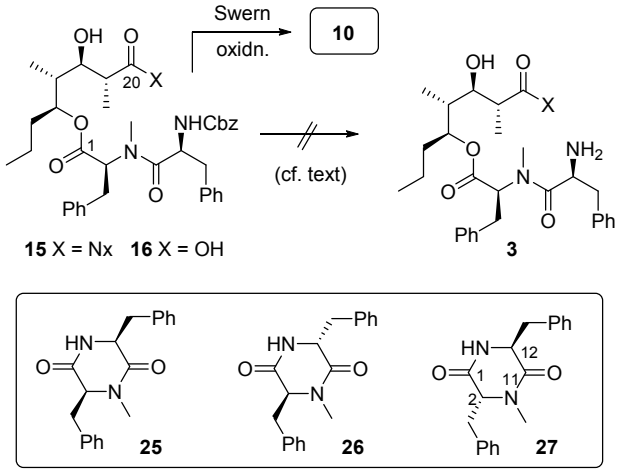
the Cbz group had better chance to approach the C-1 carbonyl group.

Scheme 4



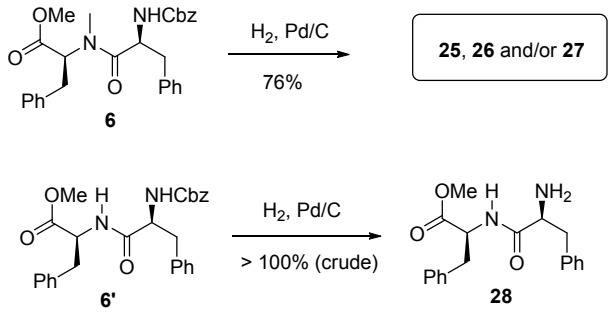
Scheme 5



As cleavage of an ester bond with concurrent formation of a new lactam bond is a thermodynamically favorable process, the aldol subunit was readily cleaved regardless what substituent was installed at the C-20 carbonyl group. Indeed, under the same conditions intermediate **15** also gave exactly the same results as **16**, proving that formation of **25**—**27** was an inevitable outcome. This also explains why only (A.) Ghosh's[2] macrolactmization could be accomplished—the possibility to form a similar (undesired) six-memebred lactam or lactone simply did not exist.

To demonstrate the role of the methyl group on the amino group we also performed the reactions in Scheme 6, which clearly show the critical influence of the N-Me on the cyclization and the effects of Cbz on the NMR: no cyclization (*i.e.*, formation of analogues of **25**—**27**) occurred and the crude product (without any purification/material loss) showed clean ^{1}H and ^{13}C NMR (without any "redundant" signals).

Scheme 6



It is noteworthy that the ^{1}H and ^{13}C NMR for **13** were more complicated than one may presume. Some of the ^{1}H NMR signals showed similar ones of lower intensity in the close vicinity, seemingly suggesting co-existence of isomers. However, because raising the temperature at which the NMR spectra were recorded clearly showed simplification of the spectra, the complication of the spectra appeared to be mainly caused by the partial double bond nature of the C-N in the Cbz group. Indeed, nearly all compounds[9] that contained a Cbz masked amino group showed similar phenomena in NMR spectra, including the simplest ones **5** and **6**. And variable temperature NMR did show simplified spectra at higher temperatures.

The above rationalization that part of the "minor species" in the ^{1}H NMR was caused by the presence of the Cbz was experimentally proven in the case of **5**: Conversion of **5** into its methyl ester followed by hydrogenolysis to remove the Cbz group led to pure phenylglycine methyl ester (without any discernible minor species in the ^{1}H NMR).

Conclusions

In repetition/continuation of the previously published synthesis directed toward stereocalpin A, it was found that a substantial part of the reported[3] data were incorrect. The connection of the aldol subunit (corresponding to **9** of this work) with the dipeptide (corresponding to **7** of this work) moiety and the final macrolactamization were not successfully reproduced; the corresponding steps in the previous[3] report (in the previous report from condensation of **3** with **4** to afford **16** and the subsequent steps) thus must be retracted along with the reported data. The physical and spectroscopic data for all attainable intermediates mentioned in the previous work (*i.e.*, compounds **16**, **17** and **18**, in the

previous report, corresponding to **10**, **15** and **16**) were carefully acquired through alternative routes to eliminate any potential confusion caused by their counterparts in the previous report.[3] The hidden causes for the failures of those steps that were not successfully reproduced in this work were explored and the unexpected products from these reactions were identified. The ultimate cause for the predominating formation of the six-membered lactams, which decided no macrolactamization would occur, was attributed to the presence of the *N*-methyl group and the particular location of an ester linkage. This conclusion also explains why Ghosh's[2] macrolactamization occurred smoothly. The almost inevitable complications in the appearance of NMR spectra for compounds containing Cbz, which tend to be mistaken for isomers or impurities, were also explored carefully. Although the previously[1] assigned target structure **1** had been proven[2] incorrect, the difficulties in the synthetic studies of this compound may well be encountered in syntheses of other peptides and related compounds. The knowledge gained herein may help to avoid undesired side reactions and understand the "unclean" NMR spectra.

Experimental

The NMR spectra were recorded on either an Agilent 500/54 NMR spectrometer (operating at 500 MHz for ^{1}H) or an Agilent 400/54 instrument (operating at 400 MHz for ^{1}H). IR spectra were measured on a Nicolet 380 Infrared spectrophotometer. ESI-MS data were acquired on a Shimadzu LCMS-2010EV mass spectrometer. ESI-HRMS data were obtained with a Bruker APEX III 7.0 Tesla FF-MS spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. Melting points were uncorrected (measured on a hot stage melting point apparatus equipped with a microscope). CH_2Cl_2 was dried with activated 4 Å MS (molecular sieves). All chemicals were reagent grade and used as purchased. Column chromatography was performed on silica gel (300−400 mesh) under slightly positive pressure. Petroleum ether (chromatography eluent) refers to the fraction boiling between 60 and 90 ℃. EDCI＝1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide hydrochloride, HOAt＝3-hydroxytriazolo[4,5-*b*]pyridine, HATU ＝ 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate, DCC＝dicyclohexylcarbodiimide.

(*S*)-Methyl 2-((*S*)-2-(((benzyloxy)carbonyl)-amino)-*N*-methyl-3-phenylpropanamido)-3-phenylpropanoate (6)

EDCI (406 mg, 2.12 mmol) was added to a solution of amine **4** (226 mg, 1.17 mmol) and acid **5** (317 mg, 1.06 mmol) in dry DMF-CH_2Cl_2 (1∶5, *V*/*V*, 10 mL) stirred in an ice-water bath under N_2 (balloon), followed by HOAt (159 mg, 1.17 mmol). The mixture was stirred at ambient temperature for 24 h. EtOAc (20 mL) was added. The phases were separated. The organic layer was washed with aq. sat. $NaHCO_3$ (10 mL) and brine (3 ×10 mL) and then dried over anhydrous Na_2SO_4. Filtration and rotary evaporation left a crude oil, which on purification by column chromatography (2∶1, PE/EtOAc, *V*/*V*) on silica gel gave **6** as a colorless oil (468 mg, 0.986 mmol, 93% from **5**). $[\alpha]_D^{25}$ −63.9 (*c* 0.85, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41−7.26 (m, 5H), 7.25−7.03 (m, 10H), 5.30 (d, *J*＝9.0 Hz, NH), 5.27 (dd, *J*＝10.0, 5.9 Hz, 1H), 5.05 (d, *J*＝12.4 Hz, 1H), 5.03 (d, *J*＝12.4 Hz, 1H), 4.78 (br q, *J*＝7.5 Hz, 1H), 3.72, 3.68 and 3.63 (three singlets, with 3.68 being the main signal, 3H altogether), 3.32 (dd, *J*＝14.5, 5.8 Hz, 1H), 3.02 (dd, *J*＝13.4, 7.8 Hz, 1H), 2.93 (dd, *J*＝9.9, 4.5 Hz, 1H), 2.88 (dd, *J*＝13.4, 5.9 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.83, 170.72, 155.41, 136.59, 136.39, 136.03, 129.53, 128.84, 128.49, 128.44, 128.41, 128.09, 127.89, 126.86, 126.74, 66.73, 58.48, 52.25, 51.96, 39.22, 34.62, 32.53; FT-IR (film) *v*: 3305, 3030, 2951, 2360, 1739, 1717, 1646, 1497, 1455, 1246, 1048, 750, 699 cm^{-1}. ESI-MS *m/z* 475.6 ([M＋H]$^+$); ESI-HRS calcd for $C_{28}H_{30}N_2NaO_5$ ([M＋Na]$^+$) 497.2047, found 497.2053.

(*S*)-2-((*S*)-2-(((Benzyloxy)carbonyl)amino)-*N*-methyl-3-phenylpropanamido)-3-phenylpropanoic acid (7)

A mixture of ester **6** (56 mg, 0.118 mmol) and LiOH (monohydrate, 6.0 mg, 0.14 mmol) in THF (0.41 mL) and H_2O (0.06 mL) was stirred in an ice-water bath for 4 h. The mixture was acidified with 1 mol/L HCl to pH 3 and extracted with EtOAc (10 mL). The organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4. The drying agent and the solvent were removed by filtration and rotary evaporation. The residue was purified by column chromatography (1∶5∶0.002, PE/EtOAc/AcOH, *V*/*V*/*V*) on silica gel to give acid **7** (50 mg, 0.108 mmol, 92%) as a colorless oil. $[\alpha]_D^{25}$ −62.4 (*c* 0.85, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34−7.03 (m, 15H), 6.00, 5.88, 5.84, 5.79 and 5.74 (five doublets, with 5.74 being the main signal, *J*＝9.0 Hz, 1H altogether, NH), 5.11 (dd, *J*＝10.3, 5.3 Hz, 1H), 5.06 −4.96 (m, 2H), 4.80 (br dd, *J*＝15.4, 7.5 Hz, 1H), 3.35 (br dd, *J*＝14.5, 5.1 Hz, 1H), 3.02 (dd, *J*＝13.4, 7.7 Hz, 0.9H), 2.98−2.93 (m, 1H), 2.88 (dd, *J*＝13.7, 6.7 Hz, 0.9H), 2.77, 2.74 and 2.73 (three singlets of different intensities, with the most intense line at 2.73, 3H altogether), 2.51 (dd, *J*＝14.1, 9.3 Hz, 0.1H), 2.00 (dd, *J*＝14.1, 4.7 Hz, 0.1H) (because of the co-existence of several conformers, the number of protons for each signal is imprecise, for reference only); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.66, 172.56, 155.65, 136.58, 136.38, 135.99, 129.53, 128.79, 128.52, 128.50, 128.47, 128.05, 127.83, 126.93, 126.78, 66.77, 59.67, 52.17, 38.92, 34.33, 33.51; FT-IR (film) *v*: 3307, 3029, 2937, 1718, 1647, 1497, 1454, 1249, 748, 699 cm^{-1}. ESI-MS *m/z* 459.0 ([M−H]$^-$); ESI-HRS calcd for $C_{27}H_{30}N_2NaO_3$ ([M＋Na]$^+$) 483.1890, found 483.1896.

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(2*R*,4*S*,5*S*)-1-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-hydroxy-2,4-dimethyloctane-1,3-dione (9)

A solution of *c*-Hex_2BCl (1.0 mol/L, in hexanes, 13.33 mL, 13.33 mmol) was added to a solution of **8** (3.211 g, 11.10 mmol) in dry Et_2O (40 mL) stirred in an ice-water bath under N_2 (balloon), followed by dry Me_2NEt (1.6 mL, 15 mmol). The resulting greenish-yellow mixture was stirred at the same temperature for 3 h. The ice-water bath was replaced with a –78 ℃ one (acetone-dry ice). Butyraldehyde (4.89 mL g, 55.55 mmol) was introduced dropwise via a syringe. Stirring was then continued at –78 ℃ for 5 h before sequential addition of H_2O (7 mL), H_2O_2 (7 mL) and MeOH (7 mL). The mixture was then stirred in an ice-water bath. Aq. sat. Na_2SO_3 (25 mL) was added dropwise. The mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with aq. sat. Na_2SO_3 (25 mL) and brine (50 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (3∶1, PE/EtOAc, *V*/*V*) on silica gel afforded aldol **9** as a colorless oil (3.450 g, 9.55 mmol, 86%). $[\alpha]_D^{25}$ –58.1 (*c* 0.97, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.38－7.18 (m, 5H), 4.90 (q, *J*＝7.3 Hz, 1H), 4.79－4.73 (m, 1H), 4.25 (t, *J*＝8.5 Hz, 1H), 4.18 (dd, *J*＝9.1, 2.8 Hz, 1H), 3.72 (dt, *J*＝13.6, 2.5 Hz, 1H), 3.29 (dd, *J*＝13.4, 3.2 Hz, 1H), 2.82 (dq, *J*＝7.9, 7.2 Hz, 1H), 2.78 (dd, *J*＝13.4, 9.6 Hz, 1H), 2.35 (br s, 1H, OH), 1.58－1.50 (m, 2H), 1.47 (d, *J*＝7.3 Hz, 3H), 1.43－1.32 (m, 1H), 1.19 (d, *J*＝7.1 Hz, 3H), 0.92 (t, *J*＝6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.10, 170.61, 153.50, 135.09, 129.40, 128.96, 127.39, 73.32, 66.42, 55.35, 52.48, 49.82, 37.92, 36.54, 18.58, 14.14, 13.99, 12.84. FT-IR (film) *v*: 3523, 3028, 2959, 2874, 1780, 1717, 1693, 1455, 1391, 1360, 762, 703 cm^{-1}. ESI-MS *m/z* 362.2 ($[M+H]^+$); ESI-HRS calcd for $C_{20}H_{27}NNaO_5$ ($[M+Na]^+$) 384.1781, found 384.1778.

(2*S*,3*S*)-2-Eethyl-3,5-dimethyl-6-oxo-3,6-dihydro-2*H*-pyran-4-yl benzoate (11)

A solution of **9** (25 mg, 0.07 mmol), benzoic acid (9.0 mg, 0.07 mmol) and DCC (29 mg, 0.14 mmol) in dry CH_2Cl_2 (0.15 mL) was stirred at ambient temperature for 1 h. TLC showed that the added **9** was not fully consumed yet. DMAP (2 mg, 0.02 mmol) was added. The mixture was stirred for another 3 h and filtered through a short pad of silica gel (eluting with 4∶1 PE/EtOAc). The filtrate was concentrated and purified by column chromatography (4∶1, PE/EtOAc, , *V*/*V*) on silica gel to give **11** as a colorless oil (10 mg, 0.035 mmol, 50%): $[\alpha]_D^{25}$ –14.4 (*c* 0.60, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 8.12 (d, *J*＝7.4 Hz, 2H), 7.68 (s, 1H), 7.53 (br t, *J*＝7.7 Hz, 2H), 4.22 (dt, *J*＝7.8, 4.0 Hz, 1H), 2.89 (d quint, *J*＝1.5, 7.1 Hz, 1H), 1.83 (d, *J*＝1.3 Hz, 3H), 1.81－1.72 (m, 2H), 1.66－1.56 (m, 1H), 1.56 －1.45 (m, 1H), 1.18 (d, *J*＝7.1 Hz, 3H), 0.97 (t, *J*＝7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.94, 163.09, 161.73, 134.27, 130.23, 128.86, 128.14, 116.13, 81.61, 35.78, 35.01, 18.29, 14.50, 13.83, 10.37. FT-IR (film) *v*: 2961, 2932, 2361, 1736, 1719, 1151, 1058, 1021, 760, 707 cm^{-1}; ESI-MS *m/z* 289.2 $[M+H]^+$; ESI-HRS calcd for $C_{17}H_{20}O_4Na$ $[M+Na]^+$ 311.1254, found 311.1260.

(*S*)-(4*S*,5*S*,7*R*)-8-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-5,7-dimethyl-6,8-dioxooctan-4-yl 2-(benzyl(methyl)-amino)-3-phenylpropanoate (12)

A solution of **4'** (112 mg, 0.417 mmol), DCC (87 mg, 0.417 mmol) and DMAP (1.7 mg, 0.014 mmol) in dry CH_2Cl_2 (1.8 mL) was stirred in an ice-water bath under N_2 (balloon) for 0.5 h before a solution of **9** (50 mg, 0.138 mmol) in dry CH_2Cl_2 (1 mL) was introduced dropwise. The mixture was then stirred at ambient temperature for 4 h. Petroleum ether (PE, 5.6 mL) was added. The mixture was stirred for 0.5 min. The solids were filtered off through a short pad of silica gel (washing with 10∶1 PE/EtOAc, 10 mL). The filtrate was concentrated on a rotary evaporator. The residue was purified by column chromatography (10∶1, PE/EtOAc, *V*/*V*) on silica gel to afford **12** as a colorless oil (58 mg, 0.094 mmol, 68%). Data for **12**: $[\alpha]_D^{22}$ –50.0 (*c* 0.40, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.42－7.10 (m, 15H), 5.21－5.09 (an unresolved m, 1H), 4.82 (q, *J*＝6.9 Hz, 1H), 4.75 (br tt, *J*＝8.5, 3.0 Hz, 1H), 4.31 (t, *J*＝8.5 Hz, 1H), 4.18 (dd, *J*＝8.9, 2.6 Hz, 1H), 3.82 (br d, *J*＝13.6 Hz, 1H), 3.61 and 3.59 (two unresolved doublets for an AB system, *J*＜10.5 Hz, 2H altogether), 3.29 (dd, *J*＝13.4, 3.2 Hz, 1H), 3.06 (dd, *J*＝13.3, 8.6 Hz, 1H), 3.02－2.94 (m, 1H), 2.89－2.82 (m, 1H), 2.79 (dd, *J*＝13.4, 9.6 Hz, 1H), 2.32 (s, 3H), 1.52－1.42 (m, 1H), 1.43 (d, *J*＝7.2 Hz, 3H), 1.41－1.31 (m, 1H), 1.32 －1.22 (m, 2H), 0.92 (br d, *J*＝6.5 Hz, 3H), 0.89 (br t, *J*＝6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.04, 171.61, 170.57, 153.62, 139.19, 138.04, 135.11, 129.38, 129.22, 128.95, 128.55, 128.31, 128.17, 127.38, 126.93, 126.44, 73.81, 67.43, 66.46, 58.60, 55.37, 51.48, 51.42, 47.23, 37.98, 36.04, 31.29, 18.81, 13.78, 12.77, 10.46. FT-IR (film) *v*: 3028, 2959, 2874, 1779, 1720, 1359, 1212, 739, 699 cm^{-1}. ESI-MS *m/z* 613.9 ($[M+H]^+$); ESI-HRS calcd for $C_{37}H_{44}N_2NaO_6$ ($[M+Na]^+$) 635.3092, found 635.3087.

(*R*)-4-Benzyl-3-((2*R*,3*S*,4*S*,5*S*)-3,5-dihydroxy-2,4-dimethylheptanoyl)oxazolidin-2-one (13)

A mixture of **9** (500 mg, 1.38 mmol) and $Me_4NBH(OAc)_3$ (1.378 g, 5.24 mmol) in AcOH (6.4 mL) and MeCN (6.4 mL) was stirred first in an –40 ℃ (MeCN-liquid N_2) bath for 1 h, in an ice-water bath for 1 h and finally at ambient temperature for 1 h. The mixture was partitioned between CH_2Cl_2 (10 mL) and aq. sat. $NaHCO_3$ (15 mL). The phases were separated. The aqueous layer was back-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (1∶1, PE/EtOAc, *V*/*V*) on silica gel gave **13** as a white solid (378 mg, 1.04 mmol, 75%). M.p. 109－110 ℃. $[\alpha]_D^{25}$

–55.4 (*c* 1.05, $CDCl_3$); ^1H NMR (500 MHz,$CDCl_3$) δ: 7.37－7.19 (m, 5H), 4.78－4.70 (m, 1H), 4.31 (dd, *J*= 9.7, 1.8 Hz, 1H), 4.22 (d, *J*=8.1 Hz, 1H), 4.16 (dd, *J*= 9.0, 2.7 Hz, 1H), 4.01 (dq, *J*=9.6, 6.9 Hz, 1H), 3.67 (dt, *J*=8.6, 4.2 Hz, 1H), 3.26 (dd, *J*=13.4, 3.2 Hz, 1H), 2.79 (dd, *J*=13.4, 9.5 Hz, 1H), 2.69－2.50 (a lump, 2H, including an OH), 1.71－1.65 (m, 1H), 1.64－1.59 (m, H), 1.59－1.54 (m, 1H), 1.54－1.47 (m, 1H), 1.41－1.31 (m, 1H), 1.13 (d, *J*=6.9 Hz, 3H), 1.05 (d, *J*=7.1 Hz, 3H), 0.96 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.74, 153.47, 135.25, 129.43, 128.93, 127.35, 76.04, 73.31, 66.24, 55.35, 41.08, 38.02, 37.72, 37.61, 19.32, 14.29, 14.12, 10.54. FT-IR (film of a solution in $CHCl_3$) *v*: 3438 2960, 2933, 2872, 1697, 1451, 1693, 1455, 1389, 1350, 1211, 966, 762, 748, 702 cm^{-1}; ESI-MS *m/z* 386.4 ($[M+Na]^+$); ESI-HRS calcd for $C_{20}H_{29}NNaO_5$ ($[M+Na]^+$) 386.1938, found 386.1942.

(*S*)-(4*S*,5*S*,7*R*)-8-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-5,7-dimethyl-6,8-dioxooctan-4-yl 2-(methylamino)-3-phenylpropanoate (14)

A solution of acid **4'** (364 mg, 1.35 mmol), DCC (279 mg, 1.35 mmol) and DMAP (3 mg, 0.024 mmol) in dry CH_2Cl_2 (4.4 mL) was stirred at ambient temperature for 1 h. A solution of **13** (98 mg, 0.27 mmol) in dry CH_2Cl_2 (1 mL) was then introduced. The resulting milky mixture was stirred for another 3 h. Solids were filtered off through a short pad of silica gel (eluting with 3∶1, PE/EtOAc, 10 mL). The filtrate was concentrated and purified by column chromatography (3∶1, PE/EtOAc, *V*/*V*) on silica gel to give the *N*-protected **14** (**13'**) as a colorless oil (113 mg, 0.184 mmol, 68%). Data for **13'**: $[\alpha]_D^{25}$ –40.8 (*c* 0.50, $CDCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37－7.14 (m, 15H), 4.90 (ddd, *J*= 9.0, 6.1, 3.2 Hz, 1H), 4.77－4.70 (m, 1H), 4.30 (t, *J*= 8.3 Hz, 1H), 4.17 (dd, *J*=8.8, 2.1 Hz, 1H), 4.02 (dq, *J*=7.2, 6.7 Hz, 1H), 3.84 (br d, *J*=11.9 Hz, 1H), 3.70 －3.59 (unresolved m, 3H), 3.25 (dd, *J*=13.4, 3.2 Hz, 1H), 3.09 (dd, *J*=13.6, 8.4 Hz, 1H), 3.06－3.03 (unresolved m, 1H), 2.84－2.80 (m, 2H), 2.35 (br s, 1H), 1.74－1.66 (m, 1H), 1.53－1.44 (m, 2H), 1.41－1.28 (m, 2H), 1.21 (d, *J*=6.9 Hz, 3H), 0.91 (t, *J*=7.3 Hz, 3H), 0.80 (br d, *J*=5.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.71, 172.53, 153.45, 139.19, 138.15, 135.33, 129.44, 129.17, 128.93, 128.56, 128.36, 128.18, 127.35, 126.94, 126.41, 76.03, 73.58, 67.46, 66.32, 58.63, 55.35, 39.77, 38.79, 38.01, 37.88, 35.96, 32.60, 29.70, 18.80, 14.79, 13.92, 9.34. FT-IR (film) *v*: 3430, 2961, 1781, 1636, 1454, 1385, 1350, 737 cm^{-1}. ESI-MS *m/z* 614.7 ($[M+H]^+$); ESI-HRS calcd for $C_{37}H_{46}N_2NaO_6$ ($[M+Na]^+$) 637.3248, found 637.3242.

The above obtained oil (**13'**, 113 mg) was dissolved in MeOH (2 mL) and AcOH (0.5 mL). 10% Pd/C (11 mg) was added. The mixture was stirred under H_2 (1 atm) at ambient temperature for 6 h. Solids were filtered off (washing with 15 mL of EtOAc). The filtrate was concentrated and purified by column chromatography (1∶1, PE/EtOAc, *V*/*V*) to give **14** as a colorless oil (74 mg, 0.141 mmol, 77%). $[\alpha]_D^{25}$ –27.3 (*c* 0.57, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.40－7.11 (m, 15H), 4.89 (ddd, *J*=9.1, 5.5, 3.3 Hz, 1H), 4.74－4.64 (m, 1H), 4.24 (t, *J*=8.3 Hz, 1H), 4.14 (dd, *J*=8.9, 2.2 Hz, 1H), 4.02 (dq, *J*=7.2, 7.0 Hz, 1H), 3.73 (dd, *J*=7.7, 4.1 Hz, 1H), 3.45 (br t, *J*=6.9 Hz, 1H), 3.23 (dd, *J*=13.4, 3.1 Hz, 1H), 2.99 (dd, *J*=13.7, 6.5 Hz, 1H), 2.93 (dd, *J*=13.7, 7.4 Hz, 1H), 2.80 (dd, *J*=13.3, 9.5 Hz, 1H), 2.36 (s, 3H), 1.77－1.67 (m, 1H), 1.65－1.54 (m, 1H), 1.52－1.44 (m, 1H), 1.36－1.23 (m, 2H), 1.21 (d, *J*=6.9 Hz, 3H), 0.90 (t, *J*=7.4 Hz, 3H), 0.86 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.69, 174.68, 153.43, 137.04, 135.34, 129.44, 129.18, 128.90, 128.57, 127.31, 126.81, 76.54, 73.44, 66.31, 64.92, 55.31, 39.82, 39.39, 38.87, 37.95, 34.82, 32.65, 18.79, 14.79, 13.86, 9.59; FT-IR (film) *v*: 3445, 2961, 2932, 2874, 1698, 1604, 1497, 1455, 1388, 1350, 1211, 967, 761, 747, 701 cm^{-1}. ESI-MS *m/z* 525.6 ($[M+H]^+$); ESI-HRS calcd for $C_{30}H_{41}N_2O_6$ ($[M+H]^+$) 525.2959, found 525.2964.

(*S*)-(4*S*,5*S*,6S,7*R*)-8-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-5,7-dimethyl-6-hydroxy-8-oxooctan-4-yl 2-((S)-2-(((benzyloxy)carbonyl)amino)-*N*-methyl-3-phenylpropanamido)-3-phenylpropanoate (15)

A mixture of **14** (300 mg, 0.572 mmol), **5** (223 mg, 0.744 mmol), HATU (435 mg, 1.144 mmol) and *i*-Pr_2NEt (0.76 mL, 4.576 mmol) in dry CH_2Cl_2 (1.5 mL) was stirred at ambient temperature for 24 h. The mixture (initially pale yellow but darkened gradually with time; evetually became yellow-brown) was diluted with EtOAc (30 mL), washed with aq. $KHSO_4$ (0.5 N, 10 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (2∶1, PE/EtOAc, *V*/*V*) on silica gel gave **15** as a colorless oil (422 mg, 0.524 mmol, 92% from **14**). $[\alpha]_D^{25}$ –67.3 (*c* 0.44, $CDCl_3$), of 97% pure as shown by HPLC analysis on an Eclipse XDB-C18 (250×4.6 mm, particle size 5 μmol/L) column eluting at 25 ℃ with MeCN/H_2O (85∶15, *V*/*V*) at a flow rate of 1.0 mL/min with the UV detector set to 220 nm. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37－6.93 (m, 20H), 5.71 and 5.48 (two doublets, *J*=9.0 Hz, 1H altogether), 5.02 (d, *J*=12.2 Hz, 1H), 5.01 (d, *J*=12.3 Hz, 1H), 4.95－4.86 (m, 2H), 4.79 (dq, *J*=7.0 Hz, 1H), 4.71－4.63 (m, 1H), 4.13－4.02 (m, 3H), 3.90 and 3.76 (two doublets, *J*=8.6, 2.6 Hz, 1H altogether), 3.34 (dd, *J*=14.4, 5.6 Hz, 1H), 3.21 (br dd, *J*=13.0, 1.8 Hz, 1H), 3.08－3.03 (m, 2H), 2.86 (dd, *J*=13.6, 6.6 Hz, 1H), 2.82 (s, 3H), 2.81－2.77 (m, 1H), 1.84－1.80 (m, 1H), 1.57－1.53 (m, 2H), 1.33－1.23 (m, 2H), 1.20 (d, *J*=6.9 Hz, 3H), 0.93 (d, *J*=6.9 Hz, 3H), 0.88 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.56, 171.51, 170.80, 155.51, 153.37, 136.89, 136.34, 136.20, 135.27, 129.53, 129.41, 128.86, 128.79, 128.47, 128.44, 128.43, 128.02, 127.86, 127.28, 126.84, 126.70, 77.10, 72.41, 66.70, 66.11, 60.85, 55.25, 52.03, 40.17, 38.90, 38.40, 37.89, 34.59, 34.37, 33.32, 18.48, 14.50, 13.89, 9.32. FT-IR (film) *v*: 3430, 1781, 1697, 1644, 1496, 1454, 1388, 749, 700 cm^{-1}. ESI-MS

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m/z 806.7 ([M+H]$^+$); ESI-HRS calcd for $C_{47}H_{55}N_3NaO_9$ ([M+Na]$^+$) 828.3831, found 828.3836.

(2*R*,3*S*,4*R*,5*S*)-5-{[(2*S*)-2-[(2*S*)-2-{[(benzyloxy)carbonyl]amido}-*N*-methyl-3-phenylpropanamido]-3-phenylpropanoyl]oxy}-2,4-dimethyl-3-hydrox-octanoic acid (16, obtained by removal of the chiral auxiliary in 15)

A mixture of H_2O_2 (21 μL, 0.20 mmol) and LiOH (monohydrate, 3 mg, 0.075 mmol) in THF-H_2O (3∶1, *V*/*V*, 0.3 mL) was stirred in an ice-water bath for 1 h. A solution of ester **15** (20 mg, 0.025 mmol) in THF-H_2O (3∶1, *V*/*V*, 0.3 mL) was added. Stirring was continued at the same temperature for 3 h. The mixture was diluted with EtOAc (2 mL). Aq. Na_2SO_3 (0.5 mol/L, 0.4 mL) was added. The mixture was then acidified with 1 mol/L HCl to pH 4 and extracted with EtOAc (3×5 mL). The organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4. The drying agent and the solvent were removed by filtration and rotary evaporation. The residue was purified by column chromatography (1∶3, PE/EtOAt, *V*/*V*) on silica gel to give acid **16** (3.0 mg, 0.00464 mmol, 19%) as a colorless oil. Data for **16**: Cf below (prepared by oxidation of **24**).

(2*S*,3*R*,4*S*,5*S*)-2,4-Dimethyloctane-1,3,5-triol (19)

A mixture of **13** (41 mg, 0.113 mmol) and $NaBH_4$ (13 mg, 0.344 mmol) in THF (0.38 mL) and H_2O (0.08 mL) was stirred at ambient temperature for 3 h. NaOH (20 mg, 0.50 mmol) was added. The mixture was stirred for 2 h and concentrated to dryness by rotary evaporation. The residue was purified by column chromatography (8∶1, PE/EtOAc, *V*/*V*) on silica gel to give triol **19** as a colorless oil (20 mg, 0.105 mmol, 93%). $[\alpha]_D^{25}$ +22.2 (*c* 0.65, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.95 (dd, *J*=9.6, 1.6 Hz, 1H), 3.75−3.58 (m, 3H), 3.24 (br s, 3H, OH), 1.93−1.85 (m, 1H), 1.69−1.61 (m, 1H), 1.60−1.57 (m, 1H), 1.55−1.50 (m, 1H), 1.50−1.43 (m, 1H), 1.40−1.29 (m, 1H), 1.04 (d, *J*=7.1 Hz, 3H), 0.96 (t, *J*=7.2 Hz, 3H), 0.73 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 77.20, 76.60, 69.27, 38.10, 37.71, 37.10, 19.36, 14.08, 13.13, 10.72. FT-IR (film) *v*: 3373, 2960, 2932, 2874, 1461, 1027, 967 cm^{-1}; ESI-MS *m/z* 191.3 ([M+H]$^+$); ESI-HRS calcd for $C_{10}H_{22}NaO_3$ ([M+Na]$^+$) 213.1461, found 213.1463.

(2*S*,3*R*,4*S*,5*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethyloctane-3,5-diol (20)

A solution of triol **19** (135 mg, 0.71 mmol), imidazole (97 mg, 1.42 mmol) and TBDPSCl (0.22 mL, 0.85 mmol) in dry DMF (1.4 mL) was stirred at ambient temperature for 5 h. EtOAc (2 mL) was added. The mixture was washed with H_2O (5 mL), aq. HCl (2%, 5 mL) and brine (5 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (10∶1 PE/EtOAc) on silica gel gave **20** as a colorless oil (233 mg, 0.543 mmol, 76%). $[\alpha]_D^{25}$ +18.5 (*c* 0.55, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.74−7.65 (m, 4H), 7.50−7.36 (m, 6H), 4.00 (dd, *J*=9.4, 2.1 Hz, 1H), 3.75 (dd, *J*=10.2, 4.1 Hz, 1H), 3.67 (dd, *J*=10.1, 8.8 Hz, 1H), 3.59 (dt, *J*=8.5, 4.3 Hz, 1H), 2.00−1.85 (m, 1H), 1.68−1.59 (m, 1H), 1.59−1.55 (m, 2H), 1.53−1.46 (m, 1H), 1.44−1.29 (m, 1H), 1.05 (s, 9H), 1.04 (d, *J*=7.0 Hz, 3H), 0.96 (t, *J*=7.1 Hz, 3H), 0.65 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 135.59, 135.57, 132.71, 132.59, 129.96, 129.93, 127.85, 127.83, 76.47, 75.87, 70.46, 38.24, 38.17, 37.27, 26.79, 19.53, 19.06, 14.25, 12.66, 10.46. FT-IR (film) *v*: 3440, 2959, 2930, 2858, 1463, 1427, 1112, 822 cm^{-1}; ESI-MS *m/z* 451.5 ([M+Na]$^+$); ESI-HRS calcd for $C_{26}H_{40}NaO_3Si$ ([M+Na]$^+$) 451.2639, found 451.2642.

(*S*)-(4*S*,5*R*,6*R*,7*S*)-8-((*tert*-Butyldiphenylsilyl)oxy)-6-hydroxy-5,7-dimethyloctan-4-yl 2-(benzyl(methyl)-amino)-3-phenylpropanoate (21)

A mixture of **20** (191 mg, 0.446 mmol), acid **4'** (235 mg, 0.892 mmol), DCC (276 mg, 1.34 mmol) and DMAP (11 mg, 0.09 mmol) in dry CH_2Cl_2 (2.2 mL) was stirred at ambient temperature for 8 h. Petroleum ether (PE, 8 mL) was added. Solids were filtered off through a short pad of silica gel (eluting with 10∶1 PE/EtOAc, 10 mL). The filtrate was concentrated and purified by column chromatography (12∶1, PE/EtOAc, *V*/*V*) on silica gel to give **21** as a colorless oil (232 mg, 0.341 mmol, 76%). $[\alpha]_D^{25}$ –9.0 (*c* 0.72, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.69−7.05 (m, 20H), 4.96 (dt, *J*=3.3, 7.9 Hz, 1H), 3.84 (br d, *J*=13.2 Hz, 1H), 3.74−3.67 (m, 2H), 3.65 (d, *J*=5.2 Hz, 1H), 3.63 (d, *J*=5.2 Hz, 1H), 3.30 (d, *J*=8.9 Hz, 1H), 3.14−3.08 (m, 1H), 2.98 (s, 2H), 2.34 (s, 3H), 1.78−1.64 (m, 3H), 1.56−1.53 (m, 1H), 1.47−1.26 (m, 2H), 1.06 (s, 9H), 0.93 (t, *J*=7.3 Hz, 3H), 0.79−0.76 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 170.20, 139.34, 138.30, 135.60, 135.56, 133.35, 133.28, 129.71, 129.31, 129.22, 128.54, 128.20, 128.16, 127.71, 127.69, 126.88, 126.31, 73.41, 68.27, 67.44, 58.64, 38.16, 37.84, 35.74, 33.71, 29.69, 26.86, 19.20, 18.48, 14.05 13.58, 8.84, 8.43. FT-IR (film) *v* 3504, 2959, 2930, 2857, 1723, 1637, 1455, 1112, 823, 738 cm^{-1}; ESI-MS *m/z* 680.4 ([M+H]$^+$); ESI-HRS calcd for $C_{43}H_{58}NO_4Si$ ([M+H]$^+$) 680.4130, found 680.4132.

(*S*)-(4*S*,5*R*,6*R*,7*S*)-8-((*tert*-Butyldiphenylsilyl)oxy)-6-hydroxy-5,7-dimethyloctan-4-yl 2-((S)-2-(((benzyloxy)carbonyl)amino)-*N*-methyl-3-phenylpropanamido)-3-phenylpropanoate (23)

A mixture of **21** (218 mg, 0.321 mmol) and 10% Pd/C (28 mg) in EtOAc (1 mL) was stirred under H_2 (1 atm) at ambient temperature for 18 h. Solids were filtered off. The filtrate was concentrated by rotary evaporation and purified by column chromatography (4∶1, PE/EtOAc, *V*/*V*) to give **22** as a colorless oil (107 mg, 0.182 mmol, 57%) along with recovered **21** (77 mg, 0.113 mmol, 35%).

A mixture of the above obtained **22** (125 mg, 0.212 mmol), **5** (95 mg, 0.317 mmol), EDCI (81 mg, 0.423 mmol) and HOAT (43 mg, 0.316 mmol, addition of

which led to a yellow-green color) in dry DMF (0.15 mL) and dry CH_2Cl_2 (0.92 mL) was stirred first in an ice-water bath for 1 h and then at ambient temperature for 24 h. EtOAc (25 mL) was added. The mixture was washed with H_2O (5 mL) and brine (5 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (6∶1, PE/EtOAc, *V*/*V*) on silica gel gave **23** as a colorless oil (116 mg, 0.133 mmol, 63%). Data for **23**: $[\alpha]_D^{24}$ –35.1 (*c* 0.47, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79−6.96 (m, 25H), 5.38 and 5.28 (two doublets, J=8.9 Hz, 1H altogether), 5.15 (dd, J=9.8, 5.7 Hz, 1H), 5.09−4.93 (m, 3H), 4.75 (dt, J=8.8, 6.6 Hz, 1H), 3.79 (dd, J=10.0, 4.5 Hz, 1H), 3.71 (dd, J=9.9, 5.9 Hz, 1H), 3.53 and 3.37 (two doublets, J=9.2, 1.6 Hz, 1H altogether), 3.33 and 3.26 (two doublets, J=14.5, 5.7 Hz, 1H altogether), 3.01−2.93 (m, 2H), 2.78 (s, 3H), 2.81−2.76 (m, 1H), 1.82−1.72 (m, 2H), 1.69−1.59 (m, 1H), 1.56−1.45 (m, 1H), 1.32−1.18 (m, 2H), 1.06 (s, 9H), 0.89 (t, J=7.2 Hz, 3H), 0.88 (d, J=6.9 Hz, 3H), 0.81 (d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.59, 170.53, 155.39, 136.72, 136.05, 135.56, 125.53, 133.33, 133.20, 129.76, 129.74, 129.49, 128.80, 128.44, 128.40, 128.38, 128.03, 127.87, 127.75, 127.73, 126.83, 126.70, 77.53, 73.02, 68.25, 66.66, 59.27, 51.98, 38.86, 38.56, 37.73, 34.58, 33.93, 26.89, 19.25, 18.39, 14.00, 13.57, 8.74. FT-IR (film) *v*: 3502, 2961, 2931, 1781, 1717, 1454, 1388, 1239, 1249, 749, 700 cm^{-1}; ESI-MS *m*/*z*: 871.7 ([M + Na]$^+$); ESI-HRS calcd for $C_{53}H_{66}N_2O_7NaSi$ ([M+H]$^+$) 893.4532, found 893.4533.

(*S*)-(4*S*,5*R*,6*R*,7*S*)-6,8-Dihydroxy-5,7-dimethyloctan-4-yl 2-((S)-2-(((benzyloxy)carbonyl)amino)-*N*-methyl-3-phenylpropanamido)-3-phenylpropanoate (24)

Aq. HF (48%, 0.16 mL) was added to a mixture of **23** (110 mg, 0.126 mmol) in MeCN (1.26 mL) stirred in a plastic tube. The mixture was stirred at ambient temperature for 10 h. The excess HF was neutralized with 15% aq. K_2CO_3. The mixture was diluted with CH_2Cl_2 (10 mL). Phases were separated. The aq. layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1∶1, PE/EtOAc, *V*/*V*) on silica gel gave **24** as a colorless oil (77 mg, 0.122 mmol, 97%). $[\alpha]_D^{25}$ –60.2 (*c* 0.72, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37−7.28 (m, 6H), 7.26−7.13 (m, 7H), 7.02 and 6.98 (two doublets, J=7.0 Hz, 2H altogether), 5.58 and 5.40 (two doublets, J=9.0 Hz, 1H), 5.07 (d, J=12.3 Hz, 1H), 4.99 (d, J=12.3 Hz, 1H), 4.93 (dt, J=3.2, 8.5 Hz, 1H), 4.88−4.77 (m, 1H), 4.69 (dd, J=9.2, 6.0 Hz, 1H), 3.76 (dd, J=10.8, 2.9 Hz, 1H), 3.61−3.55 (m, 2H), 3.35 (dd, J=14.2, 6.0 Hz, 1H), 3.07−2.98 (m, 2H), 2.84 (dd, J=13.7, 6.9 Hz, 1H), 2.82 (s, 3H), 2.71 (br s, 2H, OH), 1.86−1.80 (m, 1H), 1.78−1.71 (m, 1H), 1.68−1.59 (m, 1H), 1.59−1.47 (m, 1H), 1.34−1.19 (m, 2H), 0.90 (d, J=6.9 Hz, 3H), 0.89 (t, J=7.4 Hz, 3H), 0.80 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.86, 170.96, 155.60, 136.94, 136.31, 136.12, 129.46, 128.89, 128.58, 128.53, 128.47, 128.06, 127.90, 126.96, 126.86, 77.69, 73.92, 68.17, 66.85, 62.11, 52.15, 38.89, 38.80, 37.08, 35.22, 34.63, 34.28, 18.48, 13.91, 13.59, 9.11. FT-IR (film) *v*: 3424, 2960, 1716, 1643, 1497, 1455, 1249, 1080, 1029, 749, 699 cm^{-1}. ESI-MS *m*/*z* 655.6 ([M+Na]$^+$); ESI-HRS calcd for $C_{37}H_{48}N_2NaO_7$ ([M+Na]$^+$) 655.3354, found 655.3356.

(5*S*,8*S*,11*S*,12*R*,13*S*,14*R*)-5,8-Dibenzyl-13-hydroxy-7,12,14-trimethyl-3,6,9-trioxo-1-phenyl-11-propyl-2,10-dioxa-4,7-diazapentadecan-15-oic acid (16 from 24)

A solution of TEMPO (0.05 mol/L, in CH_2Cl_2, 35 μL) was added to a solution of **24** (55 mg, 0.087 mmol) in dry CH_2Cl_2 (0.87 mL) stirred in an ice-water bath, followed by aq. KBr (0.5 mol/L, 17.4 μL, 0.0087 mmol) and $KHCO_3$ (131 mg, 1.31 mmol) and aq. NaOCl (14.5%, 82 μL). The mixture was stirred at the same temperature for 90 min. H_2O (0.5 mL) and aq. Na_2SO_3 (20%, 5 mL) were added in turn. Phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation left a yellowish oil (53 mg, 0.084 mmol, 97%), which was directly dissolved in *t*-BuOH (4.35 mL) and H_2O (0.44 mL) and stirred at ambient temperature. To this solution were added in turn a solution of 2-methyl-2-butene (0.73 mL, 8.7 mmol) in THF (3.65 mL), NaH_2PO_4 (31 mg, 0.258 mmol) and NaClO (16 mg, 0.177 mmol). The mixture was stirred at ambient temperature for 30 min. Et_2O (10 mL) and aq. sodium citrate (0.5 mol/L, 6 mL) were added. Phases were separated. Aqueous layer was extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Removal of solvents by rotary evaporation and column chromatography (1∶3∶0.002, PE/EtOAc/AcOH, *V*/*V*/*V*) on silica gel gave **16** as a colorless oil (35 mg, 0.054 mmol, 62% over 2 steps from **24**). Data for **16**: $[\alpha]_D^{27}$ –42.4 (*c* 0.67, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37−6.94 (m, 15H), 5.70 and 5.52 (two doublets, J=8.7 Hz, 1H altogether), 5.05 (d, J=12.5 Hz, 1H), 4.93 (d, J=12.3 Hz, 1H), 4.97−4.91 (m, 1H), 4.83−4.71 (m, 2H), 3.88 and 3.61 (two br doublets, J=8.7 Hz, 1H altogether), 3.32 and 3.23 (two doublets, J=14.2, 5.2 Hz, 1H altogether), 3.06−2.94 (m, 2H), 2.88−2.82 (m, 1H), 2.81 (s, 3H), 2.64−2.56 (m, 1H), 1.85−1.75 (m, 1H), 1.66−1.48 (m, 2H), 1.25−1.18 (m, 2H), 1.14 (d, J=6.7 Hz, 3H), 0.91−0.87 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.95, 171.85, 170.83, 155.58, 136.79, 136.23, 136.07, 129.46, 128.83, 128.61, 128.55, 128.47, 128.07, 127.90, 126.98, 126.88, 70.94, 66.86, 62.29, 52.10, 42.19, 38.83, 38.45, 35.45, 34.55, 34.20, 29.70, 18.31, 13.91, 13.66, 8.89. FT-IR (film) *v*: 3430, 2959, 2931, 1716, 1644, 1455, 1253, 750, 699 cm^{-1}. ESI-MS *m*/*z* 647.8 ([M+H]$^+$); ESI-HRS calcd for $C_{37}H_{46}N_2NaO_8$ ([M+Na]$^+$) 669.3146, found

669.3148.

(3*S*,6*S*)-3,6-Dibenzyl-1-methylpiperazine-2,5-dione (25), (3*R*,6*S*)-3,6-dibenzyl-1-methylpiperazine-2,5-dione (26) and/or (3*S*,6*R*)-3,6-dibenzyl-1-methylpiperazine-2,5-dione (27)

A mixture of **6** (18 mg, 0.038 mmol) and 10% Pd/C (3.6 mg) in EtOAc (1 mL) was stirred under H_2 (1 atm) at ambient temperature for 24 h. Solids were filtered off. The filtrate was concentrated by rotary evaporation and purified by column chromatography (1∶1, PE/EtOAc, *V*/*V*) to give **25**－**27** as a white solid (9 mg, 0.029 mmol, 76%). Data for **25**: $[\alpha]_D^{26}$ –157.4 (*c* 0.56, $CHCl_3$). M.p.: 160－161 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.43－7.18 (m, 10H), 5.59 (s, 1H), 4.22 (t, *J*＝3.9 Hz, 1H), 3.87 (d, *J*＝11.5 Hz, 1H), 3.29 (dd, *J*＝14.1, 3.6 Hz, 1H), 3.17 (dd, *J*＝12.9, 3.1 Hz, 1H), 3.14 (s, 3H), 2.91 (dd, *J*＝13.5, 2.7 Hz, 1H), 0.78 (dd, *J*＝13.3, 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 165.62, 165.33, 136.08, 134.79, 130.40, 129.13, 129.04, 128.94, 127.76, 127.15. 63.05, 56.77, 40.55, 36.56, 33.16; FT-IR (film of a solution in $CHCl_3$) *v*: 3479, 3226, 2931, 1658, 1454, 1338, 1249, 746, 701 cm^{-1}; ESI-MS *m/z* 309.3 ([M＋H]$^+$); ESI-HRS calcd for $C_{19}H_{20}N_2NaO_2$ ([M＋Na]$^+$) 331.1417, found 331.1419.

Data for **26**: $[\alpha]_D^{26}$ –71.8 (*c* 0.83, $CHCl_3$). M.p.: 210－211 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.35－6.35 (s, 10H), 5.45 (s, 1H), 4.13 (t, *J*＝4.0 Hz, 1H), 3.30 (dd, *J*＝13.9, 3.1 Hz, 1H), 3.24 (dd, *J*＝13.9, 3.6 Hz, 1H), 3.14 (dd, *J*＝13.9, 4.5 Hz, 1H), 3.07 (s, 3H), 2.59 (dd, *J*＝10.7, 3.1 Hz, 1H), 2.51 (dd, *J*＝13.9, 10.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 167.54, 166.26, 135.63, 134.49, 129.96, 129.08, 128.88, 128.80, 127.78, 127.41, 64.01, 53.74, 38.20, 36.74, 32.94; FT-IR (film of a solution in $CHCl_3$) *v*: 3241, 1680, 1643, 1454, 1444, 1345, 699 cm^{-1}. ESI-MS *m/z*: 309.1 ([M＋H]$^+$); ESI-HRS calcd for $C_{19}H_{20}N_2NaO_2$ ([M＋Na]$^+$) 331.1417 , found 331.1407.

(*S*)-Methyl 2-((*S*)-2-amino-3-phenylpropanamido)-3-phenylpropanoate (28)

A mixture of **6'** (10 mg, 0.021 mmol) and 10% Pd/C (3.6 mg) in EtOAc (0.5 mL) was stirred under H_2 (1 atm) at ambient temperature for 24 h. Solids were filtered off. The filtrate was concentrated by rotary evaporation to give **28** as a colorless oil (8 mg, 0.024 mmol, 114% crude yield). Data for **28**: $[\alpha]_D^{27}$ –7.2 (*c* 0.33, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.70－7.04 (m, 10H), 4.87 (dt, *J*＝8.2, 6.3 Hz, 1H), 3.70 (s, 3H), 3.67 (dd, *J*＝8.8, 4.4 Hz, 1H), 3.16 (dd, *J*＝13.9, 4.4 Hz, 1H), 3.12 (dd, *J*＝14.4, 6.5 Hz, 1H) 3.06 (dd, *J*＝13.8, 6.6 Hz, 1H), 2.66 (dd, *J*＝13.7, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 173.74, 171.89, 137.58, 135.91, 129.29, 129.19, 128.64, 128.40, 126.96, 126.79, 56.13, 52.63, 52.17, 40.67, 38.05. FT-IR (film) *v*: 3326, 3028, 2951, 2925, 2360, 2342, 1743, 1670, 1507, 1497, 1213, 1178 , 745, 701 cm^{-1}. ESI-MS *m/z* 327.1 ([M＋H]$^+$); ESI-HRS calcd for $C_{19}H_{23}N_2O_3$ ([M＋H]$^+$) 327.1703, found 327.1707.

(*S*)-(4*S*,5*S*,7*R*)-8-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-5,7-dimethyl-6,8-dioxooctan-4-yl 2-((S)-2-(((benzyloxy)carbonyl)amino)-*N*-methyl-3-phenylpropanamido)-3-phenylpropanoate (10, by oxidation of 15)

Dry DMSO (0.24 mL, 3.44 mmol) was added slowly to a solution of $(COCl)_2$ (0.15 mL, 1.72 mmol) in dry CH_2Cl_2 (2 mL) stirred at –78 ℃ under argon (balloon). After completion of the addition the mixture was stirred at the same temperature for 45 min. A solution of **15** (69 mg, 0.086 mmol) in dry CH_2Cl_2 (1 mL) was then introduced. Stirring was continued at –78 ℃ for 1 h beofre Et_3N (0.60 mL, 4.30 mmol) was added slowly. The mixture was stirred for another 30 min. Water (3 mL) was then added, followed by EtOAc (15 mL). The phases were saparated. The organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was purified by column chromatography (3∶1, PE/EtOAc, *V*/*V*) on silica gel to give **10** as a colorless oil (53 mg, 0.065 mmol, 76%), along with recovered **15** (6.0 mg, 0.007 mmol, 9%).

Data for **10**: $[\alpha]_D^{22}$ –62.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.36－7.10 (m, 20H), 5.47 (d, *J*＝9.3 Hz, 0.3H), 5.25 (d, *J*＝9.0 Hz, 0.7H), 5.15 (dt, *J*＝3.9, 7.1 Hz, 1H), 5.04－4.97 (four doublets of different intensities, a part of an AB system from different conformers, *J*＝12.5 Hz, 2H altogether), 4.97 (dd, *J*＝9.4, 5.5 Hz, 0.1H), 4.85 (q, *J*＝7.2 Hz, 0.9H), 4.78 (dt, *J*＝7.3, 6.8 Hz, 0.8H), 4.74－4.69 (m, 1H), 4.42 (br t, *J*＝8.4 Hz, 1H), 4.14 (dd, *J*＝9.0, 2.7 Hz, 1H), 3.29 (dd, *J*＝14.3, 5.6 Hz, 1H), 3.26 (dd, *J*＝13.5, 3.1 Hz, 1H), 3.05－2.89 (m, 3H), 2.81 (s, 3H), 2.79－2.72 (m, 2H), 1.53－1.42 (m, 5H), 1.33－1.27 (m, 1H), 1.24－1.18 (m, 1H), 1.13 (d, *J*＝7.1 Hz, 3H), 0.87 (t, *J*＝7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 171.54, 170.47, 169.70, 155.40, 153.58, 136.76, 136.40, 136.08, 135.07, 129.44, 129.39, 128.97, 128.85, 128.48, 128.47, 128.43, 128.07, 127.86, 127.41, 127.30, 126.88, 126.77, 75.33, 66.67, 66.44, 59.68, 55.34, 51.93, 51.63, 47.17, 38.86, 37.95, 34.62, 32.14, 18.24, 13.88, 13.88, 13.85, 12.88, 11.96. FT-IR (film) *v*: 3304, 3029, 2690, 1778, 1719, 1649, 1454, 1215, 1050, 753, 700 cm^{-1}. ESI-MS *m/z* 826.6 ([M＋Na]$^+$), 804.6 ([M＋H]$^+$); ESI-HRS calcd for $C_{47}H_{53}N_3NaO_9$ ([M＋Na]$^+$) 826.3674, found 826.3677.

References

[1] Seo, C.; Yim, J. H.; Lee, H. K.; Park, S. M.; Sohn, J. H.; Oh, H. *Tetrahedron Lett*. **2008**, *49*, 29.
[2] Ghosh, A. K.; Xu, C. X. *Org. Lett*. **2009**, *11*, 1963.
[3] Huang, Y.-X.; Wu, Y.-K. *Chin. J. Chem*. **2011**, *29*, 1185.
[4] Reddy, K. M.; Shashidhar, J.; Pottireddygari, G. R.; Ghosh, S. *Tetrahedron Lett*. **2011**, *52*, 5987.
[5] One of us (Y.-K. Wu) apologizes for the failure to detect those problems in ref 3 in time and all the confusion/inconvenience that may have already been caused by the publication of that work. Those data/results in ref 3 that were different from their counterparts reported in this work should be ignored altogether.

[6] Park, J. D.; Lee, K. J.; Kim, D. H. *Bioorg*. *Med*. *Chem*. **2011**, *9*, 237.
[7] Piloto, A. M.; Rovira, D.; Costa, S. P. G.; Gonçalves, S. T. *Tetrahedron* **2006**, *62*, 11955.
[8] Czuba, I. R.; Zammit, S.; Rizzacasa, A. A. *Org*. *Biomol*. *Chem*. **2003**, *1*, 2044.
[9] Nishimura, T.; Yamada, K.; Takebe, T.; Yokoshima, S.; Fukuyama, T. *Org*. *Lett*. **2008**, *10*, 2601.
[10] Chen, H.; He, M. M.; Wang, Y. Y.; Zhai, L. H.; Cui, Y. B.; Li, Y. Y.; Li, Y.; Zhou, H. B.; Hong, X. C.; Deng, Z. X. *Green Chem*. **2011**, *13*, 2723.

(Zhao, X.)