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Synthesis and biological activity evaluation of dolastatin 10 analogues with N-terminal modifications

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ABSTRACT

We have described the synthesis of the two complex units (2*R*,3*R*,4*S*)-dolaproine (Dap) and (3*R*,4*S*,5*S*)-dolaisoleuine (Dil) of dolastatin 10 from natural amino acids. The stereoselective syntheses of *N*-Boc-Dap (**4a**) and *N*-Boc-(2*S*)-*iso*-Dap (**4b**) were performed by employing crotylation of *N*-Boc-L-prolinal as a key step. Barbier-type allylation of *N*-Boc-L-isoleucinal provided a mild and convenient approach for the synthesis of *N*-Boc-Dil (**5a**) and *N*-Boc-(3*S*)-*iso*-Dil (**5b**). Ten dolastatin 10 analogues have been designed and synthesized with N-terminal modifications based on the known compound monomethylauristatin F (MMAF, **3**). In comparison with MMAF (**3**), four of the compounds showed enhanced potency against HCT 116 human colon cancer cells *in vitro*.

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1. Introduction

The marine natural product dolastatin 10 (**1**) (Fig. 1) was originally isolated from the Indian Ocean sea hare *Dolabella auricularia* by Pettit and co-workers in 1987,[1] and its absolute configuration was ascertained by total synthesis.[2] Dolastatin 10 (**1**) is a pentapeptide that exhibits remarkable antineoplastic activity.[1] Despite satisfactory preclinical results, dolastatin 10 as a single agent was dropped from Phase II human cancer clinical trials due to toxic side effects.[3] Thus, structure modification of dolastatin 10 (**1**) has been gaining focus. Several dolastatin 10 analogues, termed "auristatins," have been designed and synthesized to investigate structure–activity relationships.[4] Miyazaki et al. discovered that removal of one methyl group from the N-terminal amine of dolastatin 10 to give monomethylauristatin D (MMAD, **2**; Fig. 1) did not compromise the *in vivo* antitumor activity.[4a] On this basis, Doronina et al. reported the replacement of the C-terminal thiazole of MMAD (**2**) with a carboxylic group to give monomethylauristatin F (MMAF, **3**; Fig. 1), which was subsequently applied in antibody–drug conjugates.[4d,5] Additionally, Maderna et al. have found that N-terminal modification of dolastatin 10 by replacement of the *N*,*N*-dimethylvaline unit with amino acids bearing α,α-disubstituted carbon atoms, which allows the removal of both *N*-methyl groups, leads to excellent antitumor activity.[4f]

Although the introduction of the charged carboxylic group in MMAF (**3**) caused a loss of *in vitro* potency due to impaired membrane translocation capabilities, the activities of MMAF (**3**) were enhanced approximately 2200-fold once it was attached to an antibody through a linker.[4d] On the contrary, the introduction of the carboxylic group could accelerate the metabolism of the free drug and contribute to lower toxicity.[4d] We were interested in determining whether N-terminal modification of MMAF (**3**) by replacement of the secondary amine with a primary amine would lead to other auristatin analogues that retain the potency, as well as lower toxicity, for the design of optimally active compounds.

The unusual amino acids (2*R*,3*R*,4*S*)-dolaproine (Dap) and (3*R*,4*S*,5*S*)-dolaisoleuine (Dil) are the two most complex units of dolastatin 10 and its analogues. Several research groups have made great efforts to synthesize these two key units.[6] However, there were only few reports about the synthesis of their stereoisomers.[4a,6j,7] We aimed to develop a more efficient route for the synthesis of both *N*-Boc-Dap (**4a**) and *N*-Boc-Dil (**5a**) and their stereoisomers.

Herein, we report our results for the preparation of the two complex units *N*-Boc-Dap (**4a**) and *N*-Boc-Dil (**5a**) and their

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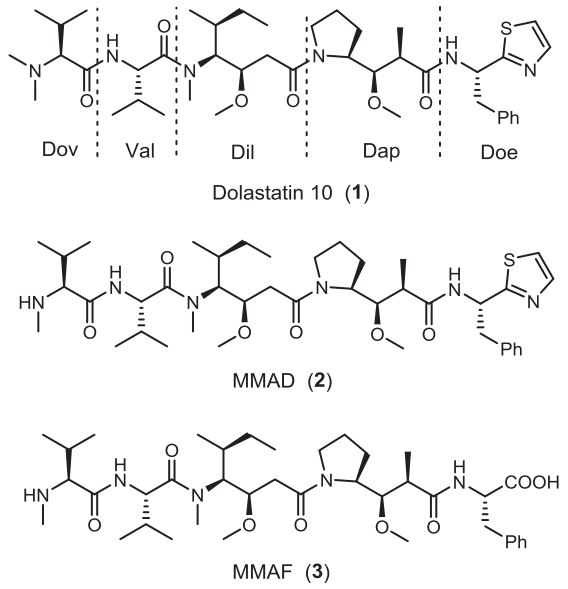


Fig. 1. Structures of dolastatin 10 and its synthetic analogues MMAD and MMAF.

diastereoisomers *N*-Boc-(2*S*)-*iso*-Dap (**4b**) and *N*-Boc-(3*S*)-*iso*-Dil (**5b**; Fig. 2). We also describe the synthesis and antitumor activity evaluation of auristatin analogues with N-terminal modifications by varying the substituent at the α-carbon atom of the N-terminal amino acid and three chiral isomers of compound **19a**, with reversal of configuration at the side chain of either the Dil unit or the Dap unit.

2. Results and discussion

Stefani et al. disclosed a mild approach by employing crotylation of *N*-Boc-prolinal (**7**) with potassium (*Z*)-2-butenyltrifluoroborate as a key step for the stereoselective synthesis of the *N*-Boc-Dap (**4a**) unit.[6i] We anticipated that the stereoselective synthesis of *N*-Boc-(2*S*)-*iso*-Dap (**4b**) could be achieved by employing potassium (*E*)-2-butenyltrifluoroborate with the addition of *N*-Boc-prolinal (**7**).

For the synthesis of *N*-Boc-Dil (**5a**), chain elongation of the α-aminocarbaldehyde was required. The Barbier reaction has been reported as an effective method for allylation of aldehydes or ketones.[8] We hypothesized that a Barbier-type reaction of *N*-Boc-L-isoleucinal (**11**) with allyl halide would allow the synthesis of either the *syn* or *anti* vicinal amino alcohols, which could be used as key intermediates for the synthesis of *N*-Boc-Dil (**5a**) or *N*-Boc-(3*S*)-*iso*-Dil (**5b**).

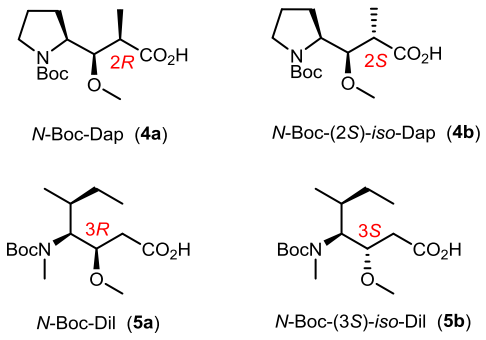


Fig. 2. Structures of two key units of dolastatin 10 and their stereoisomers.

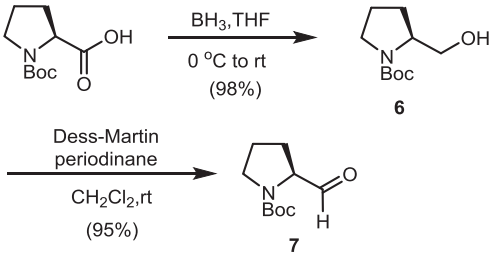
The synthesis began with the preparation of building blocks *N*-Boc-Dap (**4a**) and *N*-Boc-Dil (**5a**). In accordance with the approach reported by Stefani, we employed crotylation of *N*-Boc-L-prolinal (**7**) as a key step for the synthesis of *N*-Boc-Dap (**4a**).[6i] The synthesis began with reduction of commercially available *N*-Boc-L-proline to *N*-Boc-L-prolinol (**6**), with BH_3 as the reducing agent (Scheme 1). Alcohol (**6**) was then oxidized under standard Dess-Martin oxidation conditions to give *N*-Boc-L-prolinal (**7**) in 95% yield.[9]

From the reaction of *N*-Boc-L-prolinal (**7**) with potassium (*Z*)-2-butenyltrifluoroborate in the presence of a catalytic amount of *n*-Bu_4NBr in dichloromethane and water, the desired addition product *syn*-(2*R*,3*R*)-**8a** was obtained in 87% yield with a diastereomeric ratio (dr) > 95:5. Afterwards, the amino alcohol **8a** was converted into *O*-methylated product **9a** by treatment with NaH and MeI in DMF. Finally, oxidative cleavage of the olefin **9a** to the corresponding carboxylic acid was carried out in a two-step procedure, with a catalytic amount of OsO_4 for dihydroxylation and $NaIO_4$ for cleavage of the vicinal diols to furnish the *N*-Boc-Dap (**4a**) unit (Scheme 2).

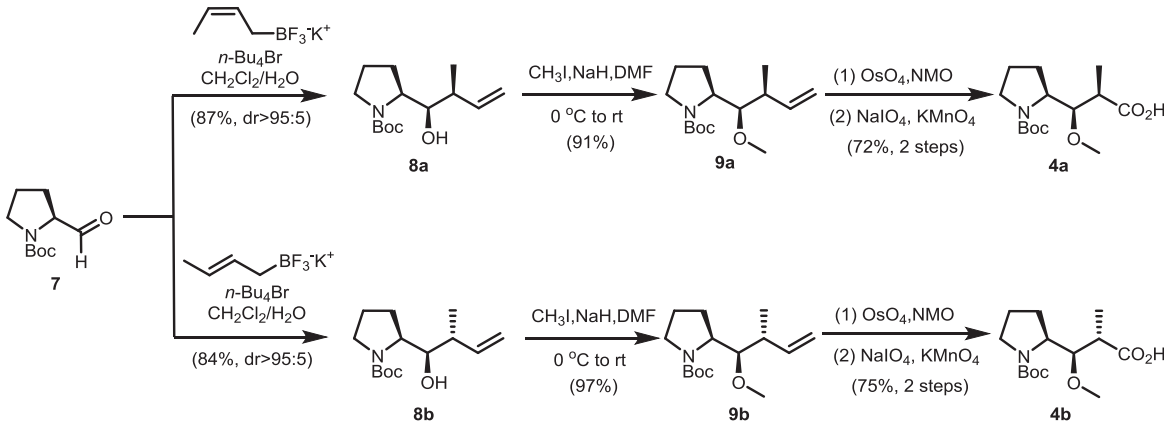
For the synthesis of *N*-Boc-(2*S*)-*iso*-Dap (**4b**; Scheme 2), when *N*-Boc-L-prolinal (**7**) was treated with potassium (*E*)-2-butenyltrifluoroborate, we were pleased to find that the required product *anti*-(2*S*,3*R*)-**8b** was obtained in 84% yield with dr > 95:5. Similarly to the synthesis of *N*-Boc-Dap (**4a**), subsequent O-methylation and oxidative cleavage of the double bond gave *N*-Boc-(2*S*)-*iso*-Dap (**4b**) with an overall yield of 73%. The ^1H and ^{13}C NMR spectroscopy data and optical rotation of $[\alpha]^{25}_D$ 92.2° (*c* 1.0, $CHCl_3$) were in agreement with literature data.[7b]

Next, both *N*-Boc-Dil (**5a**) and *N*-Boc-(3*S*)-*iso*-Dil (**5b**) were prepared from *N*-Boc-L-isoleucinal (**11**; Scheme 4). Aldehyde **11** was obtained in two steps in a manner analogous to that used to convert *N*-Boc-L-proline into *N*-Boc-L-prolinal (**7**) by starting from commercially available *N*-Boc-L-isoleucine (Scheme 3). When *N*-Boc-L-isoleucinal (**11**) was subjected to Barbier-type reaction conditions with allyl bromide in the presence of Zn and NH_4Cl in tetrahydrofuran,[10] an inseparable 1:2 mixture of *anti*-(3*R*,4*S*)-**12** and *syn*-(3*S*,4*S*)-**12** was obtained in 93% yield. *O*- and N-methylation of the mixture was achieved upon treatment with NaH and MeI. To our delight, the two diastereoisomers could be easily separated on a silica gel chromatography column to give *anti*-(3*R*,4*S*)-**13a** in 31% yield and *syn*-(3*S*,4*S*)-**13b** in 58% yield. Advancement of **13a** and **13b** to *N*-Boc-Dil (**5a**) and *N*-Boc-(3*S*)-*iso*-Dil (**5b**) was achieved by a two-step sequence similar to the synthesis of *N*-Boc-Dap (**4a**) from **9a**. Oxidative cleavage of the double bond of compounds **13a** and **13b** provided the targets *N*-Boc-Dil (**5a**) and *N*-Boc-(3*S*)-*iso*-Dil (**5b**), respectively. ^1H and ^{13}C NMR spectrometry data of **5a** and **5b** were consistent with those reported in the literature.[6b,7a]

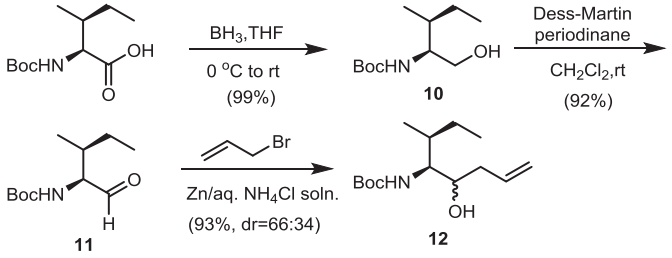
With the two building blocks *N*-Boc-Dap (**4a**) and *N*-Boc-Dil (**5a**) in hand, we initiated the preparation of the dolastatin 10 analogues by following the literature-reported method for the synthesis of dolastatin 10.[11] Phenylalanine was used as the C-terminus instead



Scheme 1. Synthesis of *N*-Boc-L-prolinal **7**.



Scheme 2. Synthesis of *N*-Boc-Dap **4a** and *N*-Boc-(2*S*)-*iso*-Dap **4b**.



Scheme 3. Synthesis of compound **12**.

of the dolaphenine (Doe) unit. Trifluoroacetic acid (TFA) was generally used to remove the Boc groups for deprotection; diethyl phosphorocyanidate (DEPC) was mainly used for coupling, with the exception of valine (Val) residue coupling to the tripeptide fragment.[11]

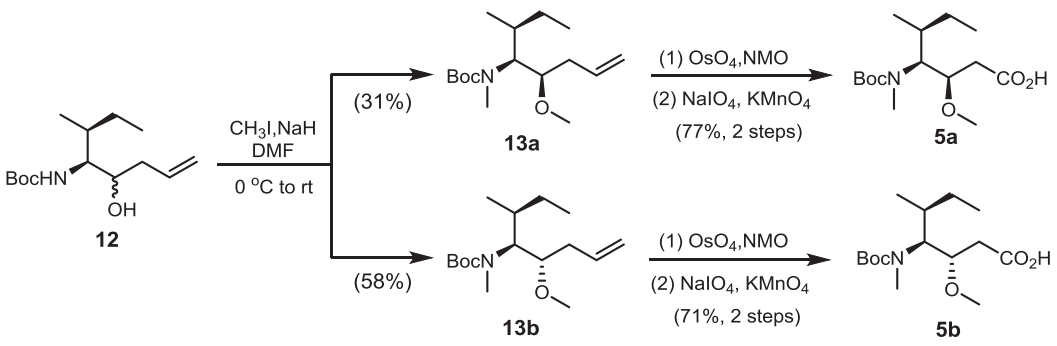
By starting from commercially available methyl L-phenylalaninate hydrochloride, the construction of the linear pentapeptide was achieved sequentially from the C-terminus to the N-terminus. Condensation of L-phenylalaninate hydrochloride with *N*-Boc-Dap (**4a**) was carried out in the presence of DEPC and *iso*-Pr_2NEt (DIPEA), which gave an excellent yield of 90% for the dipeptide **14a**. Amine deprotection of dipeptide **14a** with TFA provided a free amine species, which was then subjected to coupling with the *N*-Boc-Dil (**5a**) unit under the same conditions as those for the synthesis of the dipeptide to give the tripeptide **15a** in 85% yield. After deprotection of tripeptide **15a**, (trisdimethylamino) phosphonium hexafluorophosphate (Brop) was selected for coupling of the *N*-Me-amine species with the *N*-Boc-valine unit.[6b] Upon treatment with Brop and DIPEA, the reaction proceeded smoothly at room temperature for 24 h and furnished the key tetrapeptide **16a** in 71% yield (Scheme 5).

Tetrapeptide **16a** was considered as a common intermediate for the synthesis of all of the dolastatin 10 analogues. A series of amino acids (mainly natural amino acids) was then selected as the last fragments for coupling with tetrapeptide **16a** to provide pentapeptides **18a**–**g**, which have different substituent groups attached at the α-carbon atom of the N-terminal amino acid. All coupling reactions were carried out with moderate yields by employing DEPC as the coupling agent. Upon treatment with $LiOH\cdot H_2O$ in MeOH, hydrolysis of the methyl ester group of the pentapeptide afforded the free acid species; subsequent removal of Boc or Cbz groups afforded the target auristatin analogues **19a**–**g** (Scheme 6).

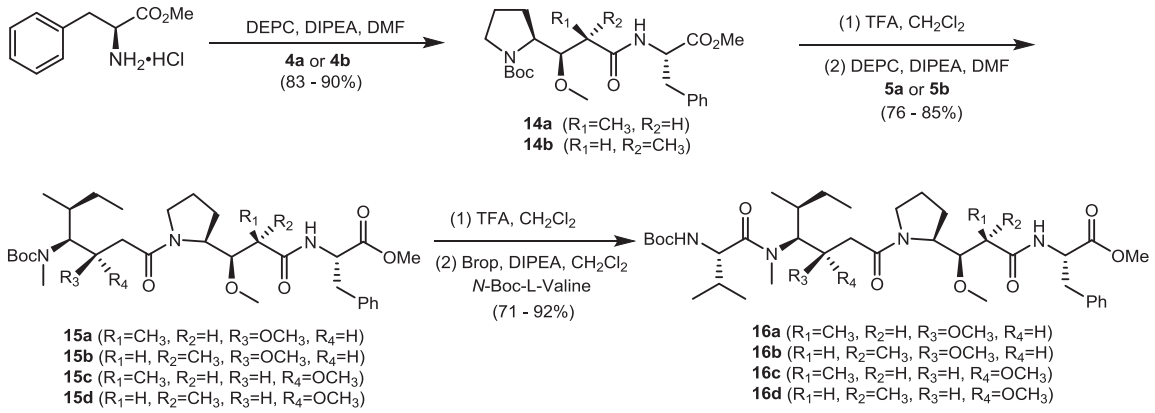
Since we have successfully prepared both *N*-Boc-(2*S*)-*iso*-Dap (**4b**) and *N*-Boc-(3*S*)-*iso*-Dil (**5b**) units, three chiral isomers of compound **19a** were synthesized to probe the impact of stereochemistry at the C6 and C15 positions on the antitumor activity (Scheme 7). All the reaction conditions for deprotection and coupling were the same as those for the synthesis of auristatin analogues **19a**–**g** described above. Relative to compound **19a**, replacement of Dap with (2*S*)-*iso*-Dap formed isomer **19h**, replacement of Dil with (3*S*)-*iso*-Dil formed isomer **19i**, and replacement of both the Dap and Dil units with the (2*S*)-*iso*-Dap and (3*S*)-*iso*-Dil units, respectively, formed isomer **19j**.

3. Biological activity

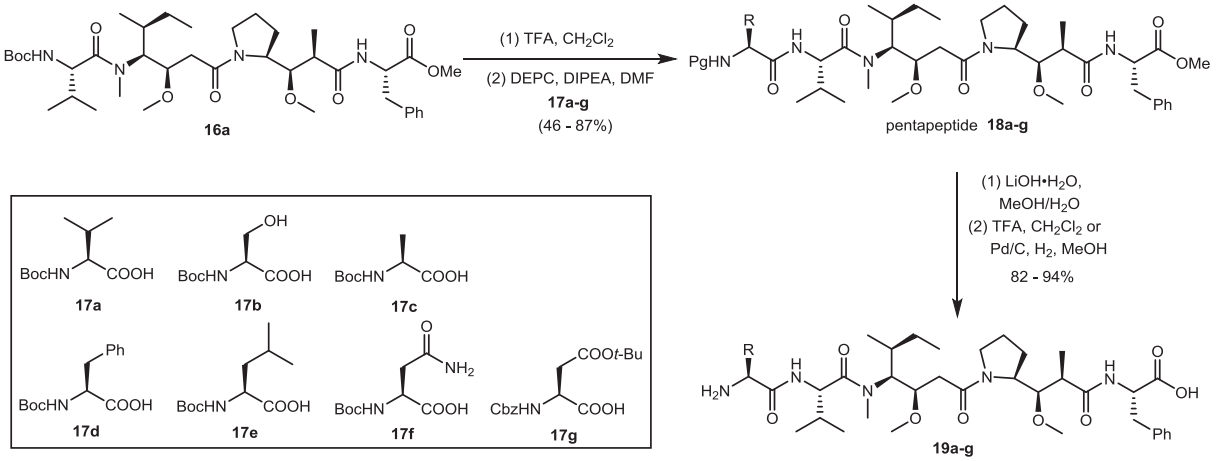
To evaluate the antitumor activity, we measured the half-maximal inhibitory concentration (IC_{50}) values for the final compounds **19a**–**j** against the HCT 116 tumor cell line. The results are



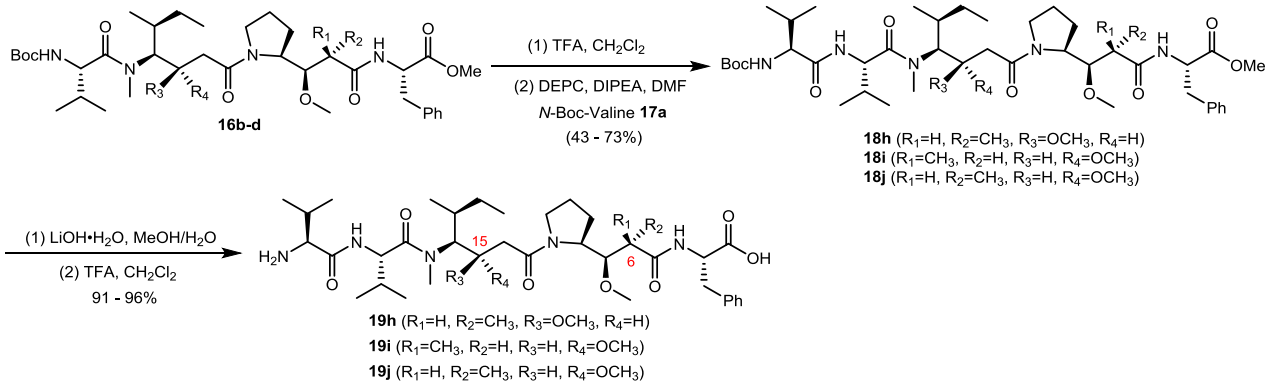
Scheme 4. Synthesis of *N*-Boc-Dil **5a** and *N*-Boc-(3*S*)-*iso*-Dil **5b**.



Scheme 5. Synthesis of tetrapeptide **16a-d**.



Scheme 6. Synthesis of compounds **19a-g**.



Scheme 7. Synthesis of compounds **19h-j**.

summarized in Table 1. Compound **19a** with L-valine as the N-terminal amino acid exhibited the most effective potency with an IC_{50} value of 0.25 μM and was 10-fold more potent than MMAF (**3**). Compound **19c** with L-alanine, compound **19d** with L-phenylalanine, and compound **19e** with L-leucine as the N-terminal amino acids, respectively, also showed enhanced potency with IC_{50} values of 0.3–0.62 μM. Compounds **19b**, **19f**, and **19g** with polar functional groups at the α-carbon atom of the N-terminal amino acid had lower potency (5.39–11.13 μM). The three chiral isomers **19h**–**j** of compound **19a**, with inversion of configuration of the methoxy group in the Dil unit or the methyl group in the Dap unit, all showed a loss of potency (11.13–17.96 μM). The results suggested the importance of the configuration at the C6 and C15 positions.

4. Conclusions

In conclusion, the synthesis of *N*-Boc-Dap (**4a**) and *N*-Boc-Dil (**5a**) and their diastereoisomers *N*-Boc-(2*S*)-*iso*-Dap (**4b**) and *N*-Boc-(3*S*)-*iso*-Dil (**5b**) was achieved, and each compound was a useful synthetic intermediate for dolastatin 10 and its analogues.

Table 1
In vitro cytotoxicity of MMAF **3** and compound **19a-j.**

Entry	Compound	IC_{50}(μM)
1	MMAF	2.88
2	**19a**	0.25
3	**19b**	5.39
4	**19c**	0.30
5	**19d**	0.30
6	**19e**	0.62
7	**19f**	11.13
8	**19g**	6.21
9	**19h**	12.71
10	**19i**	11.13
11	**19j**	17.96

The use of a Barbier-type allylation of *N*-Boc-isoleucinal (**11**) as a key step provided a mild and convenient approach for the synthesis of *N*-Boc-Dil (**5a**) and *N*-Boc-(3*S*)-*iso*-Dil (**5b**). The method therefore represents an effective supplement to the existing procedures for the synthesis of the Dil unit. We have described N-terminal modifications of MMAF (**3**) with replacement of the terminal tertiary amine by a primary amine. By varying the substituent at the α-carbon atom of the N-terminal amino acid, we were able to prepare a series of auristatin analogues for bioactivity evaluation. All of the new analogues display only moderate IC_{50} values in the range of 0.25–17.96 μM. However, in comparison with MMAF (**3**), most of the new analogues show comparable inhibitory potencies against HCT 116 cells *in vitro*. Evaluation of inhibitory potencies against other types of tumors and the toxicity is currently underway and will be reported in due course.

5. Experimental section

5.1. General experimental

All chemicals were of reagent grade quality purchased from commercial sources and used without further purification. HRMS (ESI) Mass spectra were recorded on Bruker microTOF-Q 10198 mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker Ascend-400 MHz spectrometer, 400 MHz for ^{1}H and 100 MHz for ^{13}C. Optical rotations were recorded on an Autopol VI polarimeter.

5.2. N-Boc-L-prolinol (*6*)

1 To a solution of *N*-Boc-L-proline (10.75 g, 50 mmol) in THF (100 mL) was added dropwise 1 M BH_3·THF (65 mL, 65 mmol) at 0 °C over 20 min under argon atmosphere. After stirring at 0 °C for another 30 min, the reaction was allowed to warm to room temperature and stirred for 5 h. The mixture was cooled to 0 °C again, quenched by dropwise addition of water. Removing most of the THF under reduced pressure, then ethyl acetate (150 mL) and water (50 mL) was added to the residue. The mixture was separated and the organic layer was washed with water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give **6** (9.85 g, 98%) as a colorless oil. The compound was used for next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 1H), 3.84 (d, J = 39.0 Hz, 1H), 3.53 (d, J = 8.2 Hz, 2H), 3.37 (dt, J = 13.5, 6.9 Hz, 1H), 3.24 (dd, J = 17.1, 6.9 Hz, 1H), 1.93 (dt, J = 13.7, 7.0 Hz, 1H), 1.75 (ddd, J = 19.2, 12.2, 6.0 Hz, 2H), 1.56–1.45 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 79.2, 66.5, 59.1, 46.5, 27.6, 27.4, 23.0; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{10}H_{19}NO_3Na$ 224.1257, found 224.1269.

5.3. N-Boc-L-prolinal (*7*)

To a solution of *N*-Boc-L-prolinol **6** (9.05 g, 45 mmol) in CH_2Cl_2 (100 mL) was added Dess-Martin periodinane (20 g, 47.25 mmol) in portions over 10 min. The resulting suspension was stirred at room temperature for 2 h and filtered through a pad of celite. The filtrate was washed with saturated aqueous solution of sodium bicarbonate (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give **7** (8.5 g, 95%) as a colorless oil. The compound was used for next step without further purification. $[\alpha]^{25}_D$ −67.7° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63–9.39 (m, 1H), 4.11 (ddd, J = 14.1, 10.1, 4.3 Hz, 1H), 3.51 (ddq, J = 24.6, 13.7, 6.7 Hz, 2H), 2.10 (ddd, J = 23.4, 13.2, 6.9 Hz, 1H), 2.02–1.93 (m, 1H), 1.88 (dt, J = 13.6, 6.7 Hz, 2H), 1.46 (d, J = 20.1 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 200.5, 80.6, 80.2, 65.0, 64.9, 46.8, 46.7, 28.4, 28.3, 28.0, 26.7, 24.6, 24.0; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{10}H_{17}NO_3Na$ 222.1101, found 222.1037.

5.4. tert-Butyl (S)-2-((1R,2S)-1-hydroxy-2-methylbut-3-en-1-yl) pyr-rolidine-1-carboxylate (*8a*)

To a solution of **7** (5.97 g, 30 mmol) and *n*-Bu_4NBr (0.97 g, 3 mmol) in CH_2Cl_2 (50 mL) and H_2O (25 mL) was added potassium (*Z*)-2-butenyltrifluoroborate (5.10 g, 31.5 mmol). The biphasic reaction mixture was stirred at room temperature for 30 min and then separated. The aqueous layer was extracted with CH_2Cl_2 (25 mL) and the combined organic fractions were washed with saturated brine (30 mL), and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (with 1/10 ethyl acetate/hexane as eluent) to give **8a** (6.66 g, 87%) as a white solid. $[\alpha]^{25}_D$ −62.9° (c 0.73, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H), 5.02 (dd, J = 21.8, 13.7 Hz, 2H), 3.88 (s, 2H), 3.55 (s, 1H), 3.25 (dt, J = 10.6, 7.0 Hz, 1H), 2.19 (dd, J = 14.7, 7.5 Hz, 1H), 1.91 (dd, J = 20.3, 12.1 Hz, 4H), 1.78–1.60 (m, 1H), 1.47 (s, 9H), 1.12 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 140.9, 114.7, 79.6, 74.7, 60.8, 47.6, 41.9, 28.5, 24.9, 24.5, 17.5; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{14}H_{25}NO_3Na$ 278.1727, found 278.1706.

5.5. tert-Butyl (S)-2-((1R,2S)-1-methoxy-2-methylbut-3-en-1-yl) pyr-rolidine-1-carboxylate (*9a*)

NaH (60% dispersion in mineral oil, 1.5 g, 37.5 mmol) and CH_3I (3.22 mL, 50 mmol) were added to DMF (60 mL) successively, a solution of **8a** (6.37 g, 25 mmol) in DMF (15 mL) was added dropwise to the suspension at 0 °C over 10 min under argon atmosphere. The stirring was maintained at 0 °C for 30 min, then warmed to room temperature and stirred for 3 h. The reaction was then quenched with water at 0 °C. After extraction with ethyl acetate (2 × 100 mL), the combined organic layer was washed with water (60 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (with 1/20 ethyl acetate/hexane as eluent) to give **9a** (6.12 g, 91%) as a colorless oil. $[\alpha]^{25}_D$ −61.7° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85–5.59 (m, 1H), 5.11–4.89 (m, 2H), 3.88 (d, J = 23.7 Hz, 1H), 3.69–3.51 (m, 1H), 3.51–3.36 (m, 4H), 3.31–3.19 (m, 1H), 2.21–2.09 (m, 1H), 2.02–1.61 (m, 5H), 1.48 (d, J = 10.2 Hz, 9H), 1.09 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 154.3, 140.9, 114.5, 114.5, 86.0, 84.2, 79.3, 78.9, 61.1, 60.9, 59.4, 59.2, 47.3, 46.8, 42.7, 42.3, 41.9, 28.6, 27.0, 25.3, 25.0, 24.7, 24.4, 24.2, 17.8, 17.7; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{15}H_{27}NO_3Na$ 292.1883, found 292.1910.

5.6. (2R, 3R)-3-((S)-1-(tert-butoxycarbonyl)pyrroliodin-2-yl)-3-meth-oxy-2-methylpropanoic acid (**4a**)

To a stirred solution of **9a** (5.38 g, 20 mmol) in acetone (50 mL) was added water (25 mL) followed by *N*-methylmorpholine-*N*-oxide (4.68 g, 40 mmol) and OsO_4 (0.25 g, 1 mmol). The reaction mixture was stirred at room temperature for 6 h and quenched by addition of Na_2SO_3. Most of the acetone was removed under reduced pressure, then ethyl acetate (100 mL) and water (50 mL) was added to the residue. The mixture was separated and the organic layer was washed with water, the solvent was removed under reduced pressure. The obtained residue was suspended in a mixture of ethyl acetonitrile (50 mL) and water (25 mL), followed by addition of $KMnO_4$ (0.16 g, 1 mmol) and $NaIO_4$ (8.56 g, 40 mmol) at 0 °C. After stirring at 0 °C for 6 h, the reaction mixture was quenched by addition of Na_2SO_3 and then filtered through a pad of celite. The filtrate was extracted with ethyl acetate (2 × 50 mL), the combined organic layer was washed with water (30 mL) and saturated brine (30 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (with 1/30 MeOH/CH_2Cl_2 as eluent) to give **4a** (4.13 g, 72% over 2 steps) as a colorless oil. $[\alpha]^{25}_D$ −55.7° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 8.7 Hz, 1H), 3.92 (d, J = 13.3 Hz, 1H), 3.80 (s, 1H), 3.57 (s, 1H), 3.43 (d, J = 9.6 Hz, 3H), 3.30–3.18 (m, 1H), 2.51 (d, J = 5.7 Hz, 1H), 2.05–1.82 (m, 3H), 1.80–1.68 (m, 1H), 1.45 (d, J = 19.6 Hz, 9H), 1.28 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 179.3, 154.9, 154.5, 83.0, 81.8, 80.0, 79.5, 61.1, 60.8, 59.6, 47.1, 46.6, 43.0, 29.7, 28.5, 26.1, 25.5, 24.4, 24.0, 13.6; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{25}NO_5Na$ 310.1625, found 310.1658.

5.7. tert-Butyl (S)-2-((1R, 2R)-1-hydroxy-2-methylbut-3-en-1-yl)-pyr-rolidine-1-carboxylate (**8b**)

Compound **8b** was synthesized from **7** and potassium (*E*)-2-butenyltrifluoroborate according the same procedure described for **8a**, a white solid (2.14 g, 84%). $[\alpha]^{25}_D$ −84.6° (c 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (d, J = 7.0 Hz, 1H), 5.07 (d, J = 15.2 Hz, 2H), 3.98 (d, J = 35.6 Hz, 1H), 3.77 (d, J = 6.3 Hz, 1H), 3.47 (s, 1H), 3.24 (s, 1H), 2.21 (dd, J = 13.6, 6.7 Hz, 1H), 1.91 (s, 4H), 1.75 (d, J = 6.3 Hz, 1H), 1.47 (s, 9H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 141.0, 114.5, 79.5, 75.4, 60.4, 47.7, 41.3, 29.7, 28.5, 25.8, 24.4, 18.0; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{25}NO_3Na$ 287.1727, found 287.1706.

5.8. tert-Butyl (S)-2-((1R, 2R)-1-methoxy-2-methylbut-3-en-1-yl)-pyr-rolidine-1-carboxylate (**9b**)

Compound **9b** was synthesized from **8b** according the same procedure described for **9a**, a colorless oil (2.09 g, 97%). $[\alpha]^{25}_D$ −82.7° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, J = 17.6, 10.2, 7.7 Hz, 1H), 5.02 (dd, J = 19.5, 13.0 Hz, 2H), 3.90 (d, J = 31.9 Hz, 1H), 3.70–3.51 (m, 1H), 3.47–3.40 (m, 1H), 3.37 (s, 3H), 3.32–3.18 (m, 1H), 2.30–2.17 (m, 1H), 2.09–1.87 (m, 2H), 1.88–1.76 (m, 1H), 1.76–1.62 (m, 1H), 1.48 (d, J = 9.0 Hz, 9H), 1.02 (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 154.2, 141.7, 141.4, 113.9, 86.3, 84.5, 79.3, 78.9, 60.8, 60.8, 59.2, 59.0, 47.1, 46.6, 41.4, 41.0, 28.6, 25.6, 24.8, 24.3, 16.7, 16.6; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{15}H_{27}NO_3Na$ 292.1883, found 292.1910.

5.9. (2S, 3R)-3-((S)-1-(tert-butoxycarbonyl) pyrrolidin-2-yl)-3-meth-oxy-2-methylpropanoic acid (**4b**)

Compound **4b** was synthesized from **9b** according the same procedure described for **4a**, a white solid (1.51 g, 75% over 2 steps). $[\alpha]^{25}_D$ −92.2° (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 3.86 (dd, J = 16.5, 6.5 Hz, 2H), 3.46–3.41 (m, 1H), 3.30 (s, 3H), 3.20–3.14 (m, 1H), 2.33 (dq, J = 14.2, 6.9 Hz, 1H), 1.96–1.76 (m, 3H), 1.76–1.64 (m, 1H), 1.46 (s, 9H), 1.07 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ13C NMR (101 MHz, DMSO) δ 175.9, 175.8, 153.3, 153.1, 83.0, 81.3, 78.5, 78.3, 60.1, 59.8, 57.7, 57.6, 46.7, 46.4, 43.1, 28.1, 24.7, 24.3, 23.9, 23.7, 14.1, 13.9; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{14}H_{25}NO_5Na$ 310.1625, found 310.1658.

5.10. N-Boc-L-isoleucinol (**10**)

To a solution of *N*-Boc-L-isoleucine (13.86 g, 60 mmol) in THF (150 mL) was added dropwise 1 M BH_3·THF (90 mL, 90 mmol) at 0 °C over 20 min under argon atmosphere. After stirring at 0 °C for another 30 min, the reaction was allowed to warm to room temperature and stirred for 5 h. The mixture was cooled to 0 °C again, quenched by dropwise addition of water. Removing most of the THF under reduced pressure, then ethyl acetate (180 mL) and water (60 mL) was added to the residue. The mixture was separated and the organic layer was washed with water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give **6** (12.89 g, 99%) as a colorless oil. The compound was used for next step without further purification. $[\alpha]^{25}_D$ −14.8° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (dd, J = 48.3, 13.9 Hz, 1H), 3.73–3.55 (m, 2H), 3.48 (s, 1H), 3.37 (s, 1H), 1.58 (d, J = 14.5 Hz, 1H), 1.56–1.48 (m, 1H), 1.45 (s, 10H), 1.23–1.05 (m, 1H), 0.91 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 79.3, 63.4, 56.8, 35.9, 28.4, 25.3, 15.5, 11.4; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{11}H_{23}NO_3Na$ 240.1570, found 240.1530.

5.11. N-Boc-L-isoleucinal (**11**)

To a solution of *N*-Boc-L-isoleucinol **10** (11.94 g, 55 mmol) in CH_2Cl_2 (150 mL) was added *Dess-Martin* periodinane (28 g, 66 mmol) in portions over 15 min. The resulting suspension was stirred at room temperature for 2 h and filtered through a pad of celite. The filtrate was washed with saturated aqueous solution of sodium bicarbonate (75 mL) and saturated brine (75 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give **11** (10.88 g, 92%) as a colorless oil. The compound was used for next step without further purification. $[\alpha]^{25}_D$ −2.5° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 5.42 (d, J = 6.3 Hz, 1H), 4.27 (s, 1H), 2.03 (s, 1H), 1.58–1.34 (m, 10H), 1.34–1.21 (m, 1H), 1.06–0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 155.6, 79.5, 64.0, 36.1, 28.1, 25.1, 15.5, 11.6; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{11}H_{21}NO_3Na$ 238.1414, found 238.1379.

5.12. tert-Butyl ((3S, 4S)-5-hydroxy-3-methyloct-7-en-4-yl) carbamate (**12**)

To a solution of *N*-Boc-L-isoleucinal **11** (10.54 g, 49 mmol) in THF (100 mL) was added 3-bromopropene (11.86 g, 98 mmol) followed by a saturated aqueous solution of NH_4Cl (50 mL). The mixture was cooled to 0 °C, and zinc dust (6.37 g, 98 mmol) was added in one portion. The ice bath was then removed and the resulting suspension was stirred at room temperature for 1 h. The mixture was separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layer was washed with saturated brine (60 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The obtained pale yellow oil was purified by silica gel column chromatography (with 1/6 ethyl acetate/hexane as eluent) to give a mixture of two diastereoisomers **12** (11.71 g, 93%) as a colorless oil.

5.13. tert-Butyl ((3S, 4S,5R)-5-methoxy-3-methyloct-7-en-4-yl) (meth-yl)carbamate (**13a**) and tert-Butyl ((3S,4S,5S)-5-methoxy-3-methyl-oct-7-en-4-yl)(methyl)carbamate (**13b**)

NaH (60% dispersion in mineral oil, 2.7 g, 67.5 mmol) and CH_3I (3.22 mL, 90 mmol) were added to DMF (100 mL) successively, a solution of **12** (11.57 g, 45 mmol) in DMF (25 mL) was added dropwise to the suspension at 0 °C over 10 min under argon atmosphere. The stirring was maintained at 0 °C for 30 min, then warmed to room temperature and stirred for 4 h. The reaction was then quenched with water at 0 °C. After extraction with ethyl acetate (2 × 150 mL), the combined organic layer was washed with water (90 mL) and saturated brine (90 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (with 1/50 ethyl acetate/hexane as eluent) to give **13a** (3.97g, 31%) as a colorless oil $[\alpha]^{25}_D$ −14.4° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99–5.76 (m, 1H), 5.08 (dd, J = 19.1, 9.5 Hz, 2H), 3.94 (s, 1H), 3.37 (s, 4H), 2.71 (s, 3H), 2.43–2.29 (m, 1H), 2.28–2.12 (m, 1H), 1.81 (s, 1H), 1.45 (s, 10H), 1.06 (ddd, J = 19.9, 12.7, 8.3 Hz, 1H), 1.00–0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 135.4, 134.6, 117.1, 116.6, 81.3, 81.0, 79.5, 78.9, 57.2, 35.4, 35.2, 28.4, 28.4, 25.8, 25.6, 16.3, 16.2, 11.5, 11.4; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{16}H_{31}NO_3Na$ 308.2196, found 308.2230, and **13b** (7.44 g, 58%) as a colorless oil; $[\alpha]^{25}_D$ −18.1° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93–5.67 (m, 1H), 5.15–4.87 (m, 2H), 3.86–3.53 (m, 1H), 3.50–3.14 (m, 4H), 2.70 (d, J = 14.1 Hz, 3H), 2.36–2.19 (m, 1H), 2.08 (dd, J = 13.5, 6.6 Hz, 1H), 1.89 (dd, J = 20.7, 13.6 Hz, 1H), 1.52–1.12 (m, 10H), 1.07–0.90 (m, 1H), 0.79 (ddd, J = 24.6, 12.6, 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 156.6, 135.3, 135.1, 116.8, 116.8, 81.9, 81.6, 79.3, 78.8, 61.6, 60.8, 58.4, 58.1, 35.5, 35.0, 32.2, 31.0, 30.4, 28.4, 25.4, 25.4, 15.8, 15.7, 10.9, 10.6; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{16}H_{31}NO_3Na$ 308.2196, found 308.2230.

5.14. (3R,4S,5S)-4-((tert-butoxycarbonyl)(methyl)amino)-3-methoxy-5-methylheptanoic acid (**5a**)

To a stirred solution of **13a** (3.42 g, 12 mmol) in acetone (30 mL) was added water (15 mL) followed by *N*-methylmorpholine-*N*-oxide (2.81 g, 24 mmol) and OsO_4 (0.15 g, 0.6 mmol). The reaction mixture was stirred at room temperature for 4 h and quenched by addition of Na_2SO_3. Most of the acetone was removed under reduced pressure, then ethyl acetate (80 mL) and water (30 mL) was added to the residue. The mixture was separated and the organic layer was washed with water, the solvent was removed under reduced pressure. The obtained residue was suspended in a mixture of ethyl acetonitrile (30 mL) and water (15 mL), followed by addition of $KMnO_4$ (0.09 g, 0.6 mmol) and $NaIO_4$ (5.14 g, 24 mmol) at 0 °C. After stirring at 0 °C for 6 h, the reaction mixture was quenched by addition of Na_2SO_3 and then filtered through a pad of celite. The filtrate was extracted with ethyl acetate (2 × 30 mL), the combined organic layer was washed with water (20 mL) and saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (with 1/15 MeOH/CH_2Cl_2 as eluent) to give **5a** (2.80 g, 77% over 2 steps) as a colorless oil; $[\alpha]^{25}_D$ −8.8° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16–3.78 (m, 2H), 3.48–3.33 (m, 3H), 2.69 (s, 3H), 2.62–2.46 (m, 2H), 1.78 (s, 1H), 1.56–1.35 (m, 10H), 1.10 (tt, J = 14.8, 7.5 Hz, 1H), 0.95 (t, J = 8.0 Hz, 3H), 0.90 (dt, J = 7.2, 4.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 176.5, 156.6, 156.5, 80.2, 79.6, 78.2, 60.7, 57.8, 57.6, 37.2, 36.9, 34.5, 28.4, 28.4, 25.9, 25.7, 16.2, 16.1, 11.3; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{15}H_{29}NO_5Na$ 326.1938, found 326.1928.

5.15. (3S,4S,5S)-4-((tert-butoxycarbonyl)(methyl)amino)-3-methoxy-5-methylheptanoic acid (**5b**)

Compound **5b** was synthesized from **13b** according the same procedure described for **5a**, a colorless oil (2.58 g, 71% over 2 steps); $[\alpha]^{25}_D$ −24.3° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04–3.91 (m, 1H), 3.88–3.69 (m, 1H), 3.35 (d, J = 6.9 Hz, 3H), 2.78 (d, J = 3.9 Hz, 3H), 2.60 (td, J = 16.9, 5.5 Hz, 1H), 2.45 (ddd, J = 15.4, 12.7, 6.9 Hz, 1H), 1.97 (dd, J = 10.0, 6.3 Hz, 1H), 1.42 (t, J = 15.0 Hz, 9H), 1.38–1.27 (m, 1H), 1.09–0.76 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 175.7, 157.6, 156.7, 80.0, 79.9, 78.3, 77.7, 62.0, 61.5, 58.2, 58.1, 36.7, 35.3, 32.0, 31.9, 31.1, 30.4, 28.4, 28.3, 25.6, 25.5, 15.8, 15.7, 10.6, 10.3; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{15}H_{29}NO_5Na$ 326.1938, found 326.1928.

5.16. General procedure for the deprotection of N-Boc peptides with trifluoroacetic acid

To a solution of the *N*-Boc peptide in dichloromethane was added trifluoroacetic acid (10 equiv). The reaction mixture was stirred at room temperature for about 8 h and then concentrated under reduced pressure to give the amine trifluoroacetate that is used in the next synthetic step without further purification.

5.17. N-Boc-Dap-Phe-OMe (**14a**)

To a solution of *N*-Boc-Dap **4a** (2.87 g, 10 mmol) and methyl L-phenylalaninate hydrochloride (2.48 g, 11.5 mmol) in DMF (30 mL) was added DIPEA (5.16 g, 40 mmol). The mixture was cooled to 0 °C, and DEPC (1.96 g, 12 mmol) was added dropwise under argon atmosphere. The stirring was maintained at 0 °C for 30 min, then warmed to room temperature and stirred for 5 h. Water (30 mL) and ethyl acetate (80 mL) were added to the reaction mixture. The phases were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic fractions were combined, washed successively with 10% citric acid (40 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (with 1/1 ethyl acetate/hexane as eluent) to give **14** (4.03 g, 90%) as a white solid; $[\alpha]^{25}_D$ −51.6° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.03 (m, 5H), 4.93–4.66 (m, 1H), 3.77 (t, J = 31.2 Hz, 4H), 3.55 (d, J = 5.0 Hz, 1H), 3.37 (s, 3H), 3.17 (dd, J = 14.0, 5.2 Hz, 2H), 3.10–2.97 (m, 1H), 2.34 (dd, J = 31.4, 6.3 Hz, 1H), 1.76 (s, 2H), 1.61 (d, J = 25.7 Hz, 2H), 1.49 (s, 9H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 173.6, 172.3, 154.7, 154.3, 136.4, 136.0, 129.1, 128.6, 127.1, 126.9, 83.5, 81.8, 79.7, 79.2, 60.7, 60.6, 58.9, 58.6, 53.5, 52.9, 52.3, 46.9, 46.5, 43.9, 37.7, 37.5, 28.6, 25.7, 25.1, 24.7, 24.2, 14.0; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{24}H_{36}N_2O_6Na$ 471.2466, found 471.2474.

5.18. N-Boc-(9S)-Dap-Phe-OMe (**14b**)

Compound **14b** was synthesized from *N*-Boc-(2*S*)-*iso*-Dap **4b** and methyl L-phenyl-alaninate hydrochloride according the same procedure described for **14a**, a white solid (0.64 g, 83%); $[\alpha]^{25}_D$ −70.5° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.09 (m, 5H), 6.77 (d, J = 6.2 Hz, 1H), 6.25 (d, J = 6.7 Hz, 1H), 4.90–4.78 (m, 1H), 3.86 (t, J = 23.3 Hz, 2H), 3.71 (d, J = 6.5 Hz, 3H), 3.61–3.38 (m, 1H), 3.32 (d, J = 5.2 Hz, 3H), 3.26–3.12 (m, 2H), 3.07 (dd, J = 13.3, 6.0 Hz, 1H), 2.33–2.07 (m, 1H), 1.94–1.79 (m, 2H), 1.72 (dt, J = 24.5, 12.0 Hz, 2H), 1.48 (d, J = 14.6 Hz, 9H), 1.11 (dd, J = 30.9, 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 174.0, 172.2, 172.0, 154.6, 154.2, 136.4, 136.0, 129.3, 128.5, 127.1, 126.9, 83.3, 82.3, 79.7, 79.3, 61.0, 60.9, 59.2, 58.6, 53.4, 53.3, 52.2, 52.1, 47.0, 46.6, 44.6, 44.1, 37.8, 28.5, 25.1, 24.8, 24.7, 24.3, 15.0, 14.6; HRMS (ESI; m/z) $[M+Na]^+$ calcd for

$C_{24}H_{36}N_2O_6Na$ 471.2466, found 471.2488.

5.19. N-Boc-Dil-Dap-Phe-OMe (**15a**)

To an ice-cooled solution of *N*-Boc-Dil **5a** (2.67 g, 8.8 mmol) and the deprotected dipeptide from **14a** (3.58 g, 8 mmol) in DMF (25 mL) was added DIPEA (3.61 g, 28 mmol). DEPC (1.96 g, 12 mmol) was added dropwise under argon atmosphere at 0 °C. The stirring was maintained at 0 °C for 30 min, then warmed to room temperature and stirred for 5 h. Water (30 mL) and ethyl acetate (75 mL) were added to the reaction mixture. The phases were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic fractions were combined, washed successively with 10% citric acid (40 mL) and saturated brine (40 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (with 1/1 ethyl acetate/hexane as eluent) to give **15a** (4.31g, 85%) as a colorless oil; $[\alpha]^{25}_D$ −34.5° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.17 (m, 5H), 4.96–4.71 (m, 1H), 4.17–4.05 (m, 4H), 3.89 (s, 1H), 3.78–3.67 (m, 3H), 3.47–3.40 (m, 1H), 3.40–3.31 (m, 6H), [3.19 (d, J = 5.3 Hz) and 3.16 (d, J = 4.9 Hz), 1H], 3.12–3.00 (m, 1H), 2.78–2.63 (m, 2H), 2.49–2.30 (m, 2H), 2.23 (s, 1H), 1.93 (d, J = 7.5 Hz, 1H), 1.87–1.60 (m, 4H), 1.46 (d, J = 6.6 Hz, 9H), 1.34 (td, J = 7.1, 1.0 Hz, 4H), 1.17 (d, J = 7.0 Hz, 3H), 1.01–0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 174.2, 172.4, 170.6, 170.2, 156.6, 136.6, 129.2, 128.6, 128.5, 126.9, 81.7, 81.7, 79.7, 79.2, 78.3, 63.7, 63.6, 60.5, 59.0, 58.1, 57.9, 53.8, 53.7, 52.2, 47.5, 43.7, 37.9, 37.7, 37.4, 34.5, 28.5, 28.4, 25.8, 25.0, 24.8, 24.7, 16.2, 16.1, 14.0, 11.4, 11.0; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{34}H_{55}N_3O_8Na$ 656.3881, found 656.3872.

5.20. N-Boc-(9S)-Dil-Dap-Phe-OMe (**15b**)

Compound **15b** was synthesized from 1**4b** and *N*-Boc-Dil **5a** according the same procedure described for **15a**, a colorless oil (0.18 g, 79%); $[\alpha]^{25}_D$ −56.3° (c 0.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.21 (m, 5H), 4.97–4.63 (m, 1H), 4.28–4.10 (m, 2H), 3.97–3.56 (m, 5H), 3.55–3.26 (m, 7H), 3.23–2.99 (m, 2H), 2.81 (d, J = 12.9 Hz, 2H), 2.43–2.39 (m, 2H), 2.04–1.61 (m, 5H), 1.55–1.35 (m, 9H), 1.35–1.23 (m, 2H), 1.23–1.10 (m, 3H), 1.05–0.95 (m, 3H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 174.0, 172.4, 172.3, 170.9, 170.5, 162.5, 156.9, 156.4, 136.8, 136.4, 129.2, 129.1, 128.5, 128.4, 126.9, 126.8, 81.7, 81.6, 79.5, 78.8, 78.7, 78.2, 65.2, 63.6, 61.6, 60.6, 60.4, 59.5, 59.0, 59.0, 58.6, 53.9, 53.6, 52.2, 52.1, 52.0, 47.8, 47.2, 43.7, 43.6, 38.9, 37.5, 37.3, 36.9, 36.4, 32.1, 32.0, 31.3, 31.2, 30.4, 29.6, 28.5, 28.4, 25.6, 25.4, 25.1, 24.9, 24.8, 24.6, 16.0, 15.9, 15.9, 14.0, 13.8, 10.8, 10.3; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{34}H_{55}N_3O_8Na$ 656.3881, found 656.3867.

5.21. N-Boc-(18S)-Dil-Dap-Phe-OMe (**15c**)

Compound **15c** was synthesized from **14** and *N*-Boc-(3*S*)-Dil **5b** according the same procedure described for **15a**, a white solid (0.23 g, 83%); $[\alpha]^{25}_D$ −57.2° (c 0.53, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.05 (m, 5H), 4.84 (dd, J = 12.2, 6.1 Hz, 1H), 4.28–4.22 (m, 2H), 4.12–4.06 (m, 2H), 3.98–3.84 (m, 1H), 3.72 (d, J = 7.6 Hz, 3H), 3.48–3.41 (m, 1H), 3.41–3.24 (m, 6H), [3.21 (d, J = 5.2 Hz) and 3.17 (d, J = 4.9 Hz), 1H], [3.08 (d, J = 7.1 Hz) and 3.05 (d, J = 7.1 Hz), 1H], 2.71 (d, J = 11.2 Hz, 2H), 2.49–2.21 (m, 3H), 1.91–1.75 (m, 5H), [1.46 (s) and 1.45 (s), 9H], 1.26 (t, J = 9.5 Hz, 2H), 1.21–1.03 (m, 4H), 1.02–0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.9, 172.3, 172.2, 170.5, 170.1, 162.5, 156.6, 136.4, 136.3, 129.2, 128.5, 128.4, 126.9, 82.1, 82.0, 79.6, 79.1, 78.3, 65.2, 63.6, 60.8, 60.3, 59.1, 59.0, 58.2, 58.0, 53.3, 52.1, 47.6, 44.1, 44.0, 38.0, 37.7, 36.4, 34.5, 31.4, 29.6, 28.4, 28.4, 25.7, 25.0, 24.8, 24.5, 24.4, 16.1, 16.0, 15.0, 14.9, 14.2, 11.4, 11.0; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{34}H_{55}N_3O_8Na$ 656.3881, found 656.3860.

5.22. N-Boc-(9S, 18S)-Dil-Dap-Phe-OMe (**15d**)

Compound **15d** was synthesized from **14b** and *N*-Boc-(3*S*)-Dil **5b** according the same procedure described for **15a**, a colorless oil (0.13 g, 76%); $[\alpha]^{25}_D$ −70.7° (c 0.3, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–6.99 (m, 5H), 4.91–4.75 (m, 1H), 4.30–4.20 (m, 2H), 3.88–3.57 (m, 5H), 3.54–3.43 (m, 1H), 3.37 (t, J = 11.3 Hz, 5H), 3.32–3.26 (m, 2H), [3.20 (d, J = 4.9 Hz) and 3.16 (d, J = 5.3 Hz), 1H], [3.08 (d, J = 7.5 Hz) and 3.05 (d, J = 7.2 Hz), 1H], 2.88–2.72 (m, 3H), 2.61–2.17 (m, 3H), 1.99 (d, J = 33.1 Hz, 3H), 1.84–1.65 (m, 2H), [1.45 (s) and 1.42 (s), 9H], 1.35–1.24 (m, 3H), 1.22–1.07 (m, 3H), 1.00 (t, J = 6.9 Hz, 3H), 0.87 (dd, J = 12.8, 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.8, 173.6, 172.4, 172.1, 171.9, 170.7, 170.6, 169.4, 156.8, 156.4, 136.6, 136.3, 129.3, 129.2, 128.5, 128.4, 128.4, 127.1, 126.9, 126.8, 82.2, 81.9, 79.5, 78.8, 78.8, 78.5, 78.3, 65.2, 63.6, 61.5, 61.3, 61.0, 60.8, 59.4, 59.2, 59.2, 58.8, 58.7, 58.4, 53.5, 53.4, 53.2, 52.3, 52.1, 52.1, 48.0, 47.3, 44.6, 44.2, 43.5, 38.8, 37.8, 37.7, 37.1, 32.1, 31.1, 30.4, 29.6, 28.4, 28.4, 25.6, 25.5, 25.4, 25.0, 24.9, 24.6, 24.3, 16.1, 16.1, 15.9, 15.9, 15.1, 14.9, 10.8, 10.6, 10.3; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{34}H_{55}N_3O_8Na$ 656.3881, found 656.3874.

5.23. N-Boc-Val-Dil-Dap-Phe-OMe (**16a**)

To a solution of *N*-Boc-L-valine (3.47 g, 16 mmol) and the deprotected tripeptide from **15a** (4.11 g, 6.5 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added DIPEA (3.02 g, 23.4 mmol) followed by Brop (4.04 g, 10.4 mmol). The reaction mixture was shielded from light and stirred at 0 °C for 30 min, then warmed to room temperature and stirred for 24 h. Water (30 mL) and CH_2Cl_2 (50 mL) were added to the reaction mixture. The phases were separated, and the organic layer was washed successively with 10% citric acid (30 mL), saturated aqueous solution of sodium bicarbonate (30 mL) and saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (with 2/1 ethyl acetate/hexane as eluent) to give **16a** (3.38 g, 71%) as a white solid; $[\alpha]^{25}_D$ −40.1° (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.09 (m, 5H), 4.91–4.52 (m, 2H), 4.33 (dd, J = 9.2, 6.8 Hz, 1H), 4.25–3.93 (m, 2H), 3.89–3.76 (m, 1H), [3.69 (d, J = 13.2 Hz) and 3.63 (d, J = 6.3 Hz), 3H], 3.40–3.33 (m, 1H), 3.30–3.24 (m, 5H), 3.14–2.98 (m, 2H), 2.95 (d, J = 12.2 Hz, 2H), 2.44–2.20 (m, 3H), 2.00–1.80 (m, 3H), 1.79–1.54 (m, 4H), [1.35 (s) and 1.34 (s), 9H], 1.13–1.08 (m, 3H), 1.01–0.77 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 173.9, 173.7, 172.5, 170.3, 170.2, 156.1, 155.7, 136.6, 129.2, 128.9, 128.6, 128.5, 127.2, 126.9, 85.6, 81.8, 81.7, 79.4, 79.2, 78.3, 60.6, 60.4, 60.3, 59.1, 59.0, 58.2, 58.0, 55.6, 53.7, 53.6, 52.5, 52.2, 47.6, 43.9, 37.8, 37.6, 37.4, 33.8, 33.6, 32.9, 31.9, 31.0, 29.7, 29.3, 28.3, 28.3, 25.8, 24.9, 24.7, 23.6, 22.7, 19.5, 17.5, 16.3, 16.0, 14.1, 11.1, 10.8; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{39}H_{64}N_4O_9Na$ 755.4566, found 755.4601.

5.24. N-Boc-(9S)-Val-Dil-Dap-Phe-OMe (**16b**)

Compound **16b** was synthesized from **15b** and *N*-Boc-L-valine according the same procedure described for **16a**, a colorless oil (0.103 g, 92%); $[\alpha]^{25}_D$ −52.8° (c 0.4, MeOH); ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.34–7.16 (m, 5H), 5.91–5.83 (m, 1H), 4.77–4.72 (m, 2H), 4.34 (t, J = 8.2 Hz, 1H), 4.23–4.01 (m, 2H), 3.92 (dd, J = 8.0, 2.3 Hz, 1H), 3.67 (s, 3H), 3.64–3.57 (m, 1H), 3.54–3.41 (m, 1H), 3.40–3.34 (m, 1H), 3.32–3.22 (m, 5H), 3.19–3.06 (m, 4H), 3.06–2.96 (m, 1H), 2.62–2.39 (m, 3H), 2.10–1.92 (m, 4H), 1.85–1.71 (m, 2H), 1.40 (s, 9H), 1.30 (d, J = 5.6 Hz, 3H), 1.04–0.80 (m, 15H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 175.2, 172.8, 170.8, 156.8, 138.1, 130.2,

129.2, 127.5, 82.7, 79.6, 79.2, 60.8, 59.4, 58.4, 58.0, 57.1, 54.5, 52.3, 48.3, 44.4, 38.3, 38.1, 33.9, 32.6, 31.7, 31.3, 28.6, 26.6, 25.5, 25.2, 23.3, 19.7, 18.5, 16.5, 14.9, 14.4, 11.2; HRMS (ESI; *m/z*) $[M+Na]^+$ calcd for $C_{39}H_{64}N_4O_9Na$ 755.4566, found 755.4560.

5.25. N-Boc-(18S)-Val-Dil-Dap-Phe-OMe (**16c**)

Compound **16c** was synthesized from **15c** and *N*-Boc-L-valine according the same procedure described for **16a**, a colorless oil (0.121 g, 82%); $[\alpha]^{25}_D$ −78.7° (c 0.4, MeOH); ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.66 (d, J = 7.9 Hz, 1H), 7.40–7.10 (m, 5H), 4.75–4.69 (m, 1H), 4.50–4.17 (m, 3H), 4.09–3.98 (m, 1H), 3.80–3.48 (m, 5H), 3.43–3.28 (m, 4H), 3.27–3.06 (m, 6H), 3.06–2.91 (m, 2H), 2.72–2.50 (m, 1H), 2.50–2.19 (m, 2H), 2.08–1.74 (m, 5H), 1.65–1.53 (m, 1H), 1.40 (s, 9H), 1.34–1.23 (m, 3H), 1.11–0.78 (m, 15H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 175.2, 174.9, 173.3, 170.4, 156.6, 138.5, 130.2, 130.0, 129.2, 127.4, 83.0, 79.1, 78.7, 61.1, 60.5, 59.7, 58.5, 56.5, 54.3, 52.4, 47.8, 44.1, 38.2, 37.1, 32.7, 32.6, 31.2, 28.6, 26.1, 25.9, 25.2, 20.9, 20.3, 18.5, 16.5, 14.6, 13.8, 10.8; HRMS (ESI; *m/z*) $[M+Na]^+$ calcd for $C_{39}H_{64}N_4O_9Na$ 755.4566, found 755.4545.

5.26. N-Boc-(9S, 18S)-Val-Dil-Dap-Phe-OMe (**16d**)

Compound **16d** was synthesized from **15d** and *N*-Boc-L-valine according the same procedure described for **16a**, a colorless oil (0.093 g, 83%); $[\alpha]^{25}_D$ −65.8° (c 0.33, MeOH); ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.83 (d, J = 7.9 Hz, 1H), 7.36–7.13 (m, 5H), 5.84 (d, J = 9.2 Hz, 1H), 4.74 (dt, J = 13.8, 7.1 Hz, 1H), 4.51–4.33 (m, 2H), 4.28–4.11 (m, 2H), 3.81 (dd, J = 7.2, 3.3 Hz, 1H), 3.67 (s, 3H), 3.37 (d, J = 7.8 Hz, 3H), 3.28 (d, J = 4.2 Hz, 3H), 3.22 (s, 1H), 3.15 (d, J = 7.1 Hz, 3H), 3.06–2.96 (m, 1H), 2.65 (dd, J = 16.2, 5.4 Hz, 1H), 2.56–2.44 (m, 1H), 2.08–1.90 (m, 5H), 1.89–1.68 (m, 2H), 1.52–1.34 (m, 9H), 1.32–1.27 (m, 3H), 1.07–0.77 (m, 15H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 175.4, 174.9, 172.8, 170.8, 170.2, 156.6, 138.1, 130.2, 129.2, 127.5, 83.1, 82.9, 79.2, 78.5, 78.2, 61.0, 60.9, 59.4, 58.7, 58.6, 56.5, 54.5, 52.4, 48.3, 48.0, 44.1, 38.3, 37.5, 32.7, 32.5, 32.2, 31.2, 30.7, 28.6, 25.6, 25.4, 25.4, 23.3, 20.2, 18.3, 16.3, 15.9, 15.0, 14.4, 11.1, 10.9; HRMS (ESI; *m/z*) $[M+Na]^+$ calcd for $C_{39}H_{64}N_4O_9Na$ 755.4566, found 755.4556.

5.27. N-Boc-Val-Val-Dil-Dap-Phe-OMe (**18a**)

To an ice-cooled solution of *N*-Boc-valine (43.4 mg, 0.6 mmol) and the deprotected tetrapeptide from **16a** (146 mg, 0.2 mmol) in DMF (2.5 mL) was added DIPEA (129 mg, 1 mmol). A solution of DEPC (19 mg, 0.3 mmol) in DMF (0.5 mL) was added dropwise under argon atmosphere at 0 °C. The stirring was maintained at 0 °C for 30 min, then warmed to room temperature and stirred for 3 h. Water (10 mL) and ethyl acetate (20 mL) were added to the reaction mixture. The phases were separated, and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic fractions were combined, washed successively with saturated aqueous solution of sodium bicarbonate (10 mL) and saturated brine (10 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (with 1/30 MeOH/CH_2Cl_2 as eluent) to give **18a** (135 mg, 81%) as a white solid; $[\alpha]^{25}_D$ −31.7° (c 0.42, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.15 (m, 5H), 7.09 (d, J = 6.8 Hz, 1H), 7.01 (d, J = 7.1 Hz, 1H), 6.72–6.63 (m, 1H), 5.18–5.01 (m, 1H), 4.94–4.85 (m, 1H), 4.80–4.68 (m, 2H), 4.23–4.09 (m, 2H), 4.02–3.91 (m, 1H), 3.87 (ddd, J = 13.8, 7.4, 2.2 Hz, 1H), 3.81–3.75 (m, 1H), 3.70 (d, J = 5.7 Hz, 2H), 3.47–3.38 (m, 1H), 3.35 (dd, J = 13.4, 7.5 Hz, 6H), 3.21–3.07 (m, 2H), 3.02 (d, J = 8.5 Hz, 2H), 2.51–2.30 (m, 3H), 2.14–1.66 (m, 8H), 1.44 (s, 9H), 1.38–1.32 (m, 2H), 1.20–1.15 (m, 3H), 1.04–0.78 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 172.5, 171.5, 170.1, 155.7, 136.6, 135.9, 129.2, 128.9, 128.6, 128.4, 127.2, 126.9, 114.0, 85.6, 81.7, 79.6, 78.2, 63.6, 63.6, 61.5, 60.4, 59.9, 59.1, 58.1, 58.0, 54.1, 54.1, 53.7, 52.5, 52.2, 47.6, 46.6, 44.5, 43.9, 37.6, 37.4, 33.4, 31.9, 31.3, 31.1, 29.7, 29.3, 28.3, 27.5, 25.8, 24.9, 24.7, 23.6, 22.7, 19.4, 19.2, 19.1, 17.9, 17.7, 17.2, 16.1, 16.1, 15.9, 14.1, 10.9, 10.5; HRMS (ESI; *m/z*) $[M+Na]^+$ calcd for $C_{44}H_{73}N_5O_{10}Na$ 854.5250, found 854.5225.

5.28. N-Boc-Ser-Val-Dil-Dap-Phe-OMe (**18b**)

Compound **18b** was synthesized from **16a** and *N*-Boc-L-serine according the same procedure described for **18a**, a white solid (55 mg, 87%); $[\alpha]^{25}_D$ −32.0° (c 0.15, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.14 (m, 5H), 4.90–4.60 (m, 3H), 4.23–4.11 (m, 3H), 3.90 (dd, J = 21.0, 7.4 Hz, 2H), 3.79–3.69 (m, 3H), 3.62–3.52 (m, 1H), 3.48–3.26 (m, 8H), 3.23–3.10 (m, 2H), 3.04 (dt, J = 30.4, 13.3 Hz, 3H), 2.60–2.25 (m, 5H), 2.10–1.88 (m, 3H), 1.87–1.62 (m, 4H), 1.44 (s, 9H), 1.16 (d, J = 7.0 Hz, 3H), 1.07–0.80 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 172.5, 172.2, 171.6, 170.2, 155.6, 136.5, 135.8, 129.2, 128.9, 128.7, 128.5, 127.2, 126.9, 114.1, 85.6, 81.7, 80.1, 78.3, 63.2, 61.6, 60.5, 59.2, 58.1, 55.0, 53.6, 53.4, 52.6, 52.2, 47.6, 46.6, 44.5, 43.9, 37.6, 37.6, 37.4, 33.4, 31.9, 31.4, 30.6, 30.4, 29.7, 29.3, 28.3, 26.9, 25.8, 25.7, 24.9, 24.7, 23.6, 22.7, 20.1, 20.0, 19.7, 19.5, 17.6, 17.5, 17.3, 16.6, 16.5, 16.0, 14.1, 14.0, 12.2, 11.5, 10.9; HRMS (ESI; *m/z*) $[M+Na]^+$ calcd for $C_{42}H_{69}N_5O_{11}Na$ 842.4886, found 842.4868.

5.29. N-Boc-Ala-Val-Dil-Dap-Phe-OMe (**18c**)

Compound **18c** was synthesized from **16a** and *N*-Boc-L-alanine according the same procedure described for **18a**, a white solid (50 mg, 46%); $[\alpha]^{25}_D$ −10.3° (c 0.3, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.09 (m, 5H), 5.12–5.02 (m, 1H), 4.85–4.79 (m, 1H), 4.67 (dt, J = 20.9, 9.9 Hz, 2H), 4.18–4.07 (m, 3H), 3.81 (d, J = 7.6 Hz, 1H), [3.70 (d, J = 8.1 Hz) and 3.63 (d, J = 5.9 Hz), 3H], 3.40–3.24 (m, 8H), 3.12–2.87 (m, 5H), 2.43–2.18 (m, 4H), 2.01–1.83 (m, 3H), 1.80–1.72 (m, 1H), 1.70–1.55 (m, 3H), 1.36 (s, 10H), 1.09 (d, J = 7.0 Hz, 3H), 0.98–0.72 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 172.6, 172.5, 170.5, 155.2, 139.2, 136.6, 129.2, 128.9, 128.6, 128.4, 127.2, 126.9, 114.0, 85.6, 81.7, 79.8, 78.2, 60.4, 59.1, 58.1, 58.0, 54.2, 53.7, 52.2, 47.6, 46.6, 44.5, 43.8, 37.7, 37.4, 33.8, 33.5, 31.9, 31.5, 31.2, 30.1, 29.7, 29.5, 29.3, 29.1, 28.9, 28.3, 25.9, 25.8, 24.9, 24.7, 23.6, 22.7, 19.5, 18.5, 17.4, 15.9, 14.1, 11.0, 10.6; HRMS (ESI; *m/z*) $[M+H]^+$ calcd for $C_{42}H_{70}N_5O_{10}Na$ 804.5117, found 804.5145.

5.30. N-Boc-Phe-Val-Dil-Dap-Phe-OMe (**18d**)

Compound **18d** was synthesized from **16a** and *N*-Boc-L-phenylalanine according the same procedure described for **18a**, a white solid (61 mg, 64%); $[\alpha]^{25}_D$ −18.4° (c 0.35, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.13 (m, 10H), 5.04–4.83 (m, 2H), 4.79–4.68 (m, 2H), 4.38 (s, 1H), 4.16 (s, 1H), 3.88 (dd, J = 7.6, 1.7 Hz, 1H), 3.77 (d, J = 14.9, 1H), 3.70 (d, J = 8.9, 2H),3.50–3.22 (m, 8H), 3.20–2.93 (m, 6H), 2.48–2.25 (m, 3H), 2.16 (ddd, J = 20.2, 15.0, 7.4 Hz, 2H), 1.99 (ddd, J = 19.0, 12.3, 7.4 Hz, 3H), 1.91–1.54 (m, 5H), 1.39 (s, 9H), 1.16 (d, J = 7.0 Hz, 3H), 1.03–0.93 (m, 6H), 0.93–0.81 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 172.7, 172.5, 171.1, 170.2, 155.3, 139.3, 136.6, 129.4, 129.4, 129.2, 128.9, 128.7, 128.5, 128.5, 127.2, 126.9, 126.8, 114.1, 106.8, 85.6, 81.7, 80.0, 78.2, 60.5, 59.2, 58.2, 58.1, 55.6, 54.2, 53.7, 52.6, 52.2, 47.6, 44.6, 43.9, 37.7, 37.5, 33.8, 33.5, 31.9, 31.5, 31.4, 31.3, 30.2, 30.1, 29.7, 29.6, 29.5, 29.4, 29.2, 28.9, 28.2, 25.9, 24.9, 24.7, 23.6, 22.7, 19.6, 17.3, 17.0, 16.0, 14.1, 14.1, 11.1, 10.8; HRMS (ESI; *m/z*) $[M+Na]^+$ calcd for $C_{48}H_{73}N_5O_{10}Na$ 902.5250, found 902.5264.

5.31. N-Boc-Leu-Val-Dil-Dap-Phe-OMe (**18e**)

Compound **18e** was synthesized from **16a** and *N*-Boc-L-leucine according the same procedure described for **18a**, a white solid (48 mg, 65%); $[\alpha]^{25}_{D}$ −36.1° (c 0.21, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.10 (m, 5H), 5.09–4.94 (m, 1H), 4.90–4.57 (m, 3H), 4.09 (d, *J* = 13.8 Hz, 2H), 3.91 (d, *J* = 6.7 Hz, 1H), 3.84–3.77 (m, 1H), 3.71 (d, *J* = 9.4 Hz, 1H), 3.63 (d, *J* = 6.2 Hz, 2H), 3.40–3.20 (m, 8H), 3.16–2.89 (m, 5H), 2.46–2.14 (m, 4H), 2.03–1.80 (m, 3H), 1.80–1.56 (m, 5H), 1.36 (s, 9H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.99–0.69 (m, 22H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.7, 171.9, 171.5, 171.2, 170.5, 169.2, 154.6, 138.24, 135.6, 134.9, 128.2, 127.9, 127.7, 127.5, 127.5, 126.2, 125.9, 113.1, 84.6, 80.7, 78.7, 77.2, 60.6, 59.4, 58.2, 58.1, 57.1, 57.0, 53.1, 52.7, 51.6, 51.3, 51.2, 46.6, 45.6, 43.5, 42.9, 36.8, 36.7, 36.5, 36.4, 32.8, 32.4, 30.9, 30.4, 28.7, 28.3, 28.1, 27.3, 24.8, 24.0, 23.8, 23.7, 22.6, 21.7, 18.4, 16.6, 16.6, 15.0, 14.9, 14.5, 14.4, 13.1, 10.4, 10.3, 9.9, 9.6; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{45}H_{75}N_5O_{10}Na$ 868.5406, found 868.5387.

5.32. N-Boc-Asn-Val-Dil-Dap-Phe-OMe (**18f**)

Compound **18f** was synthesized from **16a** and *N*-Boc-L-asparagine according the same procedure described for **18a**, a white solid (55 mg, 65%); $[\alpha]^{25}_{D}$ −17.1° (c 0.39, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.1 Hz, 1H), 7.33–7.16 (m, 5H), 6.09 (d, *J* = 7.6 Hz, 1H), 5.90 (s, 1H), 4.81–4.64 (m, 2H), 4.47 (s, 1H), 4.15 (s, 2H), 3.87 (dd, *J* = 7.5, 1.6 Hz, 1H), 3.77 (d, *J* = 10.3 Hz, 1H), 3.70 (d, *J* = 4.8 Hz, 2H), 3.49–3.25 (m, 8H), 3.22–2.92 (m, 5H), 2.64–2.30 (m, 5H), 2.10–1.88 (m, 3H), 1.88–1.60 (m, 4H), 1.43 (s, 9H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.05–0.77 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 173.5, 172.8, 172.5, 172.2, 171.1, 170.9, 170.7, 170.2, 169.8, 155.6, 139.3, 136.5, 136.4, 135.8, 129.2, 128.9, 128.6, 128.5, 128.5, 127.2, 126.9, 114.1, 85.6, 81.9, 81.7, 80.2, 78.3, 61.5, 60.4, 59.1, 58.6, 58.1, 54.6, 53.7, 52.5, 52.2, 51.3, 47.6, 46.6, 44.5, 43.9, 37.8, 37.6, 37.4, 37.0, 33.6, 31.9, 31.4, 31.1, 30.2, 29.7, 29.3, 29.1, 28.3, 25.8, 24.9, 24.7, 23.6, 22.7, 19.7, 19.5, 17.4, 17.2, 16.7, 16.5, 16.1, 14.1, 14.1, 12.2, 11.1; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{43}H_{70}N_6O_{11}Na$ 869.4995, found 869.5112.

5.33. N-Cbz-Asp-Val-Dil-Dap-Phe-OMe (**18g**)

Compound **18g** was synthesized from **16a** and **17g** according the same procedure described for **18a**, a white solid (55 mg, 65%); $[\alpha]^{25}_{D}$ −11.2° (c 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (ddd, *J* = 27.1, 16.0, 5.5 Hz, 10H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 6.9 Hz, 1H), 6.09–6.00 (m, 1H), 5.20–5.05 (m, 2H), 4.91–4.69 (m, 2H), 4.54 (d, *J* = 4.8 Hz, 1H), 4.19–4.07 (m, 2H), 3.88 (d, *J* = 7.3 Hz, 1H), 3.76 (d, *J* = 11.3 Hz, 1H), 3.69 (d, *J* = 10.6 Hz, 2H), 3.47–3.24 (m, 8H), 3.21–2.84 (m, 6H), 2.64–2.54 (m, 1H), 2.50–2.34 (m, 2H), 2.22–2.10 (m, 1H), 2.05–1.87 (m, 2H), 1.86–1.58 (m, 4H), 1.42 (s, 9H), 1.18 (dd, *J* = 15.8, 7.0 Hz, 3H), 1.10–0.74 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 172.5, 171.0, 170.7, 170.2, 156.0, 136.6, 136.1, 129.2, 128.9, 128.7, 128.6, 128.5, 128.2, 127.2, 126.9, 85.6, 81.7, 78.2, 67.2, 60.4, 59.1, 58.2, 58.1, 54.4, 53.7, 52.6, 52.2, 51.4, 47.6, 44.5, 43.8, 43.6, 37.7, 37.6, 37.4, 37.2, 33.6, 31.4, 29.7, 28.0, 25.9, 25.0, 24.7, 23.6, 19.8, 19.6, 17.2, 16.9, 16.4, 16.0, 14.1, 11.1, 10.8; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{50}H_{75}N_5O_{12}Na$ 960.5304, found 960.5323.

5.34. N-Boc-(9S)-Val-Val-Dil-Dap-Phe-OMe (**18h**)

Compound **18h** was synthesized from **16b** and *N*-Boc-L-valine according the same procedure described for **18a**, a white solid (49 mg, 47%); $[\alpha]^{25}_{D}$ −81.4° (c 0.24, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.03 (m, 5H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.69–6.49 (m, 1H), 5.12–5.05 (m, 1H), 4.93–4.65 (m, 2H), 4.17 (d, *J* = 33.5 Hz, 2H), 4.00–3.80 (m, 2H), 3.73 (d, *J* = 13.4 Hz, 3H), 3.47–3.39 (m, 1H), 3.38–3.22 (m, 6H), [3.20 (d, *J* = 5.6 Hz) and 3.17 (d, *J* = 5.4 Hz), 3H], [3.08 (d, *J* = 7.0 Hz) and 3.05 (d, *J* = 7.0 Hz), 3H], 2.99 (s, 2H), 2.48–2.17 (m, 3H), 2.11–1.84 (m, 4H), 1.83–1.63 (m, 3H), 1.44 (s, 9H), 1.26 (s, 2H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.90 (ddd, *J* = 31.7, 20.1, 6.9 Hz, 19H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 172.3, 171.5, 170.1, 155.7, 136.3, 129.3, 128.4, 126.9, 108.2, 82.1, 81.9, 79.7, 78.2, 60.8, 60.0, 59.1, 58.1, 54.1, 53.3, 52.2, 47.7, 44.1, 37.8, 33.4, 31.9, 31.3, 31.2, 31.0, 29.7, 28.3, 25.8, 25.0, 24.8, 24.4, 19.4, 19.1, 17.9, 17.6, 17.6, 15.9, 14.9, 10.9; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{44}H_{73}N_5O_{10}Na$ 854.5250, found 854.5252.

5.35. N-Boc-(18S)-Val-Val-Dil-Dap-Phe-OMe (**18i**)

Compound **18i** was synthesized from **16c** and *N*-Boc-L-valine according the same procedure described for **18a**, a white solid (40 mg, 43%); $[\alpha]^{25}_{D}$ −90.2° (c 0.44, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.9 Hz, 1H), 7.36–7.13 (m, 5H), 6.95 (d, *J* = 9.1 Hz, 1H), 5.13 (d, *J* = 9.2 Hz, 1H), 4.89 (dd, *J* = 17.1, 8.8 Hz, 2H), 4.30–4.22 (m, 3H), 4.06–3.94 (m, 1H), 3.72 (s, 3H), 3.44–3.37 (m, 2H), 3.32 (dd, *J* = 7.5, 4.6 Hz, 2H), 3.23–3.12 (m, 3H), 3.08 (d, *J* = 11.9 Hz, 3H), 3.04–2.95 (m, 1H), 2.55–2.38 (m, 2H), 2.26 (dd, *J* = 16.1, 6.4 Hz, 1H), 2.18–2.07 (m, 2H), 2.06–1.90 (m, 3H), 1.86 (d, *J* = 11.9 Hz, 2H), 1.75–1.62 (m, 1H), 1.43 (s, 9H), 1.26 (s, 2H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.08–0.82 (m, 17H), 0.76 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 173.3, 173.2, 171.7, 170.0, 155.7, 136.7, 129.2, 128.5, 126.9, 82.2, 79.5, 77.7, 60.6, 60.0, 59.8, 58.6, 54.0, 53.2, 52.4, 46.8, 42.5, 38.1, 36.7, 32.6, 31.8, 31.5, 31.2, 29.7, 28.3, 25.5, 24.3, 20.0, 19.3, 17.8, 17.7, 16.1, 12.2, 10.2; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{44}H_{73}N_5O_{10}Na$ 854.5250, found 854.5233.

5.36. N-Boc-(9S, 18S)-Val-Val-Dil-Dap-Phe-OMe (**18j**)

Compound **18j** was synthesized from **16d** and *N*-Boc-L-valine according the same procedure described for **18a**, a white solid (51 mg, 73%); $[\alpha]^{25}_{D}$ −109.1° (c 0.20, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (ddd, *J* = 23.7, 15.4, 6.7 Hz, 5H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.48 (d, *J* = 8.7 Hz, 1H), 5.09 (d, *J* = 8.7 Hz, 1H), 4.92–4.77 (m, 2H), 4.40–4.16 (m, 3H), 3.96–3.78 (m, 2H), 3.70 (s, 3H), 3.46 (dd, *J* = 15.7, 7.3 Hz, 1H), 3.38 (s, 3H), 3.29 (s, 3H), 3.18 (dd, *J* = 13.7, 5.7 Hz, 1H), 3.08 (s, 3H), 2.34 (tdd, *J* = 19.6, 16.1, 5.2 Hz, 3H), 2.12–1.85 (m, 6H), 1.83–1.65 (m, 2H), 1.43 (s, 9H), 1.26 (s, 2H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.07–0.99 (m, 6H), 0.92 (dd, *J* = 15.8, 6.6 Hz, 11H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 172.8, 172.3, 171.4, 170.0, 155.7, 136.5, 129.3, 128.4, 126.9, 82.0, 79.7, 60.9, 60.8, 60.1, 59.3, 59.1, 53.6, 53.5, 52.2, 47.5, 43.9, 38.3, 37.8, 32.2, 31.8, 31.4, 31.1, 29.7, 28.3, 25.4, 25.0, 24.6, 19.9, 19.1, 17.9, 17.4, 16.0, 15.0, 10.6; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{44}H_{73}N_5O_{10}Na$ 854.5250, found 854.5266.

5.37. N-H-Val-Val-Dil-Dap-Phe-OH (**19a**)

$LiOH\cdot H_2O$ (5 mg, 0.12 mmol) was added to a solution of **18a** (30 mg, 0.06 mmol) in MeOH (2 mL) and water (1 mL) at room temperature. After stirring at room temperature for 3 h, the reaction mixture was concentrated *in vacuo* and the obtained residue was redissolved in water (5 mL). The mixture was acidified to pH = 4–5 by addition of 1 N HCl and a white precipitate was formed. The solid was collected and dried to afford the free acid species as a white solid. The obtained solid was dissolved in CH_2Cl_2 (2.5 mL), TFA (68 mg, 0.6 mmol) was added and the reaction mixture was stirred at room temperature for about 5 h and then concentrated under reduced pressure. The crude residue was purified by preparative HPLC (SB-C18 column, 5 μm, 9.4 × 250 mm, 40% CH_3CN/60% H_2O) to yield the desired product (24 mg, 93% over 2 steps) as a white solid; $[\alpha]^{25}_{D}$ −23.8° (c 0.39, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.19–7.09 (m, 5H), 4.71–4.51 (m, 2H),

4.10–3.92 (m, 1H), 3.73–3.64 (m, 1H), 3.60–3.52 (m, 1H), 3.46–3.38 (m, 1H), 3.34–3.15 (m, 10H), 2.83 (dd, J = 24.8, 11.5 Hz, 1H), 2.39–2.33 (m, 2H), 2.23–1.94 (m, 4H), 1.84–1.59 (m, 3H), 1.58–1.37 (m, 2H), 1.37–1.15 (m, 4H), 1.09 (dd, J = 11.1, 6.8 Hz, 3H), 1.02 (d, J = 6.4 Hz, 1H), 0.98–0.66 (m, 18H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.1, 176.6, 175.1, 174.9, 172.1, 171.9, 169.3, 138.8, 138.7, 130.2, 129.9, 129.7, 129.5, 127.8, 127.7, 86.9, 83.1, 79.8, 79.2, 62.1, 61.5, 60.8, 60.6, 59.3, 59.2, 58.5, 58.3, 57.8, 56.9, 56.7, 54.6, 53.7, 45.3, 38.0, 36.7, 35.8, 33.8, 33.5, 33.0, 28.1, 27.1, 26.5, 25.9, 25.4, 24.5, 23.8, 19.9, 19.3, 19.2, 19.0, 18.9, 17.9, 16.8, 16.3, 16.0, 15.6, 15.2, 15.1, 14.5, 14.3, 11.5, 10.9, 10.9; HRMS (ESI; m/z) $[M+H]^+$ calcd for $C_{38}H_{64}N_5O_8$ 718.4749, found 718.4743.

5.38. N-H-Ser-Val-Dil-Dap-Phe-OH (**19b**)

Compound **19b** was synthesized from **18b** according the same procedure described for **19a**, a white solid (20 mg, 87% over 2 steps); $[\alpha]^{25}_D$ −24.0° (c 0.2, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.34–7.09 (m, 5H), 4.81–4.66 (m, 2H), 4.17–3.86 (m, 3H), 3.78–3.62 (m, 2H), 3.60–3.39 (m, 2H), 3.36–3.28 (m, 8H), 3.21 (s, 1H), 3.18–3.05 (m, 2H), 2.95 (dd, J = 25.3, 14.9 Hz, 1H), 2.57–2.09 (m, 4H), 1.96–1.78 (m, 3H), 1.73–1.38 (m, 3H), 1.32 (d, J = 17.0 Hz, 3H), 1.20 (d, J = 8.7 Hz, 3H), 1.13–0.84 (m, 13H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.5, 176.6, 174.8, 174.6, 172.1, 168.1, 138.8, 138.5, 131.1, 130.9, 130.8, 130.2, 129.9, 129.7, 129.5, 127.8, 127.8, 126.3, 104.9, 86.9, 82.9, 79.9, 79.2, 64.2, 62.1, 61.9, 61.8, 61.7, 61.0, 60.7, 58.6, 58.3, 57.0, 56.9, 56.0, 54.6, 53.6, 45.3, 38.0, 37.9, 36.7, 33.9, 33.6, 33.1, 32.9, 31.7, 31.5, 30.8, 30.8, 30.6, 30.5, 30.3, 30.3, 28.1, 26.9, 26.5, 26.0, 25.9, 25.3, 24.5, 23.8, 20.1, 19.9, 19.5, 18.8, 18.5, 16.6, 16.5, 16.0, 15.6, 15.4, 14.5, 11.7, 10.9; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{36}H_{59}N_5O_9Na$ 728.4205, found 728.4194.

5.39. N-H-Ala-Val-Dil-Dap-Phe-OH (**19c**)

Compound **19c** was synthesized from **18c** according the same procedure described for **19a**, a white solid (24 mg, 94% over 2 steps); $[\alpha]^{25}_D$ −25.0° (c 0.12, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.33–7.13 (m, 5H), 4.77 (d, J = 7.2 Hz, 1H), 4.66 (dd, J = 17.4, 8.2 Hz, 1H), 4.18–3.96 (m, 2H), 3.67 (s, 1H), 3.59–3.40 (m, 2H), 3.34 (d, J = 14.7 Hz, 8H), 3.23 (s, 2H), 3.14 (s, 1H), 3.02–2.83 (m, 1H), 2.67–2.39 (m, 2H), 2.38–2.00 (m, 4H), 1.95–1.72 (m, 3H), 1.71–1.50 (m, 3H), 1.50–1.43 (m, 3H), 1.31 (s, 3H), 1.24–1.15 (m, 3H), 1.14–0.84 (m, 14H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.6, 174.9, 172.1, 170.8, 138.8, 138.7, 131.1, 130.9, 130.8, 130.2, 129.9, 129.7, 129.5, 128.6, 127.8, 127.73, 126.3, 117.5, 86.9, 83.1, 79.8, 79.2, 64.2, 62.1, 61.5, 60.9, 60.6, 58.6, 58.34, 57.7, 56.9, 56.7, 45.3, 38.0, 36.8, 36.6, 33.8, 33.5, 33.1, 33.0, 31.7, 31.5, 30.8, 30.8, 30.6, 30.5, 30.5, 30.3, 30.3, 28.1, 26.9, 26.9, 26.5, 25.9, 25.4, 24.5, 23.8, 22.1, 20.0, 19.4, 19.0, 18.7, 17.8, 17.7, 16.7, 16.4, 16.0, 15.6, 15.2, 14.5, 10.8, 10.7; HRMS (ESI; m/z) $[M+H]^+$ calcd for $C_{36}H_{60}N_5O_8$ 690.4436, found 690.4411.

5.40. N-H-Phe-Val-Dil-Dap-Phe-OH (**19d**)

Compound **19d** was synthesized from **18d** according the same procedure described for **19a**, a white solid (28 mg, 83% over 2 steps); $[\alpha]^{25}_D$ −22.5° (c 0.31, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.45–6.96 (m, 10H), 4.72–4.52 (m, 2H), 4.13–3.91 (m, 2H), 3.54 (d, J = 18.5 Hz, 2H), 3.40 (d, J = 14.5 Hz, 1H), 3.34–3.00 (m, 13H), 2.88–2.73 (m, 2H), 2.40 (d, J = 14.4 Hz, 1H), 2.28–1.89 (m, 3H), 1.87–1.62 (m, 3H), 1.58–1.38 (m, 2H), 1.21 (d, J = 16.7 Hz, 3H), 1.15–0.69 (m, 16H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.6, 174.8, 172.1, 169.6, 138.8, 138.7, 135.5, 130.9, 130.8, 130.6, 130.6, 130.2, 130.1, 129.9, 129.7, 129.5, 128.9, 127.9, 127.7, 97.3, 86.9, 83.3, 79.3, 62.1, 61.5, 60.7, 60.7, 58.6, 58.4, 57.9, 56.9, 56.7, 55.4, 54.6, 53.7, 45.3, 38.6, 38.0, 36.8, 33.9, 33.6, 33.1, 33.0, 31.8, 31.6, 30.8, 30.6, 30.5, 30.3, 30.3, 28.2, 27.1, 26.5, 25.9, 25.5, 24.5, 23.8, 20.1, 19.5, 18.8, 18.5, 16.4, 16.0, 15.6, 15.1, 14.5, 11.0, 11.0; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{42}H_{63}N_5O_8Na$ 788.4569, found 788.4570.

5.41. N-H-Leu-Val-Dil-Dap-Phe-OH (**19e**)

Compound **19e** was synthesized from **18e** according the same procedure described for **19a**, a white solid (21 mg, 93% over 2 steps); $[\alpha]^{25}_D$ −25.7° (c 0.23, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.21–7.02 (m, 5H), 4.67 (d, J = 8.2 Hz, 1H), 4.54 (d, J = 8.9 Hz, 1H), 4.10–3.92 (m, 1H), 3.91–3.80 (m, 1H), 3.76 (d, J = 9.3 Hz, 1H), 3.59–3.55 (m, 1H), 3.48–3.38 (m, 1H), 3.34–3.15 (m, 11H), 3.11 (s, 2H), 3.02 (s, 1H), 2.89–2.76 (m, 1H), 2.48–2.28 (m, 2H), 2.24–1.90 (m, 3H), 1.84–1.64 (m, 3H), 1.63–1.47 (m, 4H), 1.20 (t, J = 7.0 Hz, 3H), 1.09 (dd, J = 13.9, 6.7 Hz, 3H), 1.03–0.72 (m, 20H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.0, 176.5, 175.1, 174.8, 172.1, 171.9, 170.5, 138.9, 131.1, 130.9, 130.81, 130.2, 129.9, 129.7, 129.5, 127.8, 127.7, 126.3, 93.7, 86.9, 83.3, 79.7, 79.2, 62.1, 61.5, 60.8, 60.6, 58.6, 58.4, 57.8, 56.9, 56.7, 52.7, 52.6, 45.3, 43.5, 42.0, 38.1, 38.0, 36.8, 36.6, 33.8, 33.5, 33.1, 33.0, 31.8, 31.7, 30.8, 30.8, 30.6, 30.5, 30.3, 30.3, 28.1, 26.9, 26.5, 25.9, 25.4, 25.3, 24.5, 23.8, 23.2, 23.2, 23.1, 22.2, 22.1, 19.9, 19.3, 19.1, 18.9, 16.4, 16.0, 15.6, 15.1, 14.5, 11.6, 10.9, 10.9; HRMS (ESI; m/z) $[M+H]^+$ calcd for $C_{39}H_{66}N_5O_8$ 732.4906, found 732.4902.

5.42. N-H-Asn-Val-Dil-Dap-Phe-OH (**19f**)

Compound **19f** was synthesized from **18f** according the same procedure described for **19a**, a white solid (16 mg, 82% over 2 steps); $[\alpha]^{25}_D$ −22.8° (c 0.17, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.21–6.99 (m, 5H), 4.67 (d, J = 6.5 Hz, 1H), 4.53 (d, J = 7.9 Hz, 1H), 4.17 (td, J = 9.4, 3.8 Hz, 1H), 4.01 (d, J = 34.0 Hz, 1H), 3.63–3.51 (m, 1H), 3.46–3.37 (m, 1H), 3.33–3.29 (m, 1H), 3.23 (d, J = 15.3 Hz, 10H), 3.11 (s, 2H), 3.01 (s, 1H), 2.88–2.71 (m, 2H), 2.63–2.52 (m, 1H), 2.38 (d, J = 6.1 Hz, 2H), 2.23–2.07 (m, 2H), 1.93 (d, J = 5.3 Hz, 1H), 1.83–1.62 (m, 3H), 1.60–1.42 (m, 2H), 1.36–1.30 (m, 1H), 1.20 (d, J = 7.2 Hz, 3H), 1.08 (dd, J = 17.1, 6.6 Hz, 3H), 1.01 (d, J = 6.5 Hz, 2H), 0.97–0.86 (m, 8H), 0.79 (dd, J = 13.7, 6.8 Hz, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.5, 175.1, 173.6, 172.1, 169.5, 169.4, 138.9, 130.9, 130.8, 130.2, 129.9, 129.7, 129.5, 127.8, 127.7, 126.3, 86.9, 83.4, 79.8, 79.3, 64.3, 62.06, 61.5, 60.8, 60.7, 58.6, 58.4, 57.0, 56.9, 51.0, 51.0, 45.3, 38.1, 38.0, 36.8, 36.5, 36.1, 33.8, 33.6, 33.1, 32.9, 31.6, 31.4, 30.9, 30.6, 30.5, 30.3, 30.2, 28.1, 26.9, 26.5, 25.9, 25.5, 24.5, 23.8, 20.1, 19.5, 18.7, 18.4, 16.5, 16.1, 15.6, 15.0, 14.5, 11.0; HRMS (ESI; m/z) $[M+Na]^+$ calcd for $C_{37}H_{60}N_6O_9Na$ 755.4314, found 755.4290.

5.43. N-H-Asp-Val-Dil-Dap-Phe-OH (**19g**)

$LiOH\cdot H_2O$ (3 mg, 0.07 mmol) was added to a solution of **18g** (33 mg, 0.035 mmol) in MeOH (2 mL) and water (1 mL) at room temperature. After stirring at room temperature for 10 h, the reaction mixture was concentrated *in vacuo* and the obtained residue was redissolved in water (5 mL). The mixture was acidified to pH = 4–5 by addition of 1 N HCl and a white precipitate was formed. The solid was collected and dried to afford the free acid species as a white solid. The obtained solid was dissolved in MeOH (2.5 mL), 10% palladium on carbon (4 mg) was added to the solution, followed by stirring at room temperature for 5 h under hydrogen atmosphere. The reaction mixture was filtered, concentrated *in vacuo* to give **19g** (22 mg, 87%) as a white solid; $[\alpha]^{25}_D$ −35.8° (c 0.43, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.27–7.17 (m, 5H), 4.80 (d, J = 5.6 Hz, 1H), 4.75–4.64 (m, 1H), 4.26–4.01 (m, 2H), 3.89–3.79 (m, 1H), 3.73–3.51 (m, 2H), 3.46–3.25 (m, 9H), 3.19 (s, 2H), 3.11 (s, 1H), 3.02–2.71 (m, 3H), 2.67–2.43 (m, 2H), 2.38–2.07 (m, 2H), 1.99–1.71 (m, 3H), 1.66–1.60 (m, 1H), 1.58–1.39 (m, 3H), 1.30 (s, 2H), 1.19 (dd, J = 17.1, 6.3 Hz, 3H),

1.13–0.74 (m, 14H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.5, 176.3, 176.2, 175.2, 173.2, 172.3, 172.1, 171.7, 169.9, 169.8, 139.1, 130.3, 130.0, 129.6, 129.5, 127.7, 127.6, 86.9, 83.4, 79.6, 79.1, 64.3, 62.7, 62.1, 61.5, 60.7, 58.7, 58.4, 57.8, 56.7, 55.3, 54.4, 52.9, 51.8, 45.4, 38.4, 38.2, 37.7, 36.8, 35.8, 34.0, 33.6, 33.1, 33.0, 31.8, 31.6, 30.8, 30.5, 27.0, 26.5, 25.9, 25.5, 24.6, 20.2, 20.1, 20.1, 19.6, 19.0, 18.7, 18.5, 18.2, 16.5, 16.1, 15.7, 15.1, 14.5, 14.3, 11.0, 10.9; HRMS (ESI; *m*/*z*) $[M+Na]^+$ calcd for $C_{37}H_{59}N_5O_{10}Na$ 756.4154, found 756.4163.

5.44. N-H-(9S)-Val-Val-Dil-Dap-Phe-OH (**19h**)

Compound **19h** was synthesized from **18h** according the same procedure described for **19a**, a white solid (23 mg, 96% over 2 steps); $[\alpha]^{25}_D$ −52.3° (c 0.19, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.28–7.21 (m, 5H), 4.83–4.67 (m, 2H), 4.18 (s, 1H), 4.09 (d, J = 4.5 Hz, 1H), 3.96 (d, J = 9.5 Hz, 1H), 3.78–3.73 (m, 1H), 3.66–3.58 (m, 1H), 3.50–3.45 (m, 1H), 3.32 (d, J = 5.0 Hz, 3H), 3.29–3.20 (m, 4H), 3.14 (s, 3H), 3.03–2.91 (m, 1H), 2.61–2.28 (m, 3H), 2.24–1.94 (m, 5H), 1.82 (s, 3H), 1.29 (d, J = 9.2 Hz, 3H), 1.14–0.80 (m, 23H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.1, 176.9, 175.1, 174.7, 174.5, 172.4, 172.2, 172.0, 169.3, 138.5, 130.4, 129.4, 127.8, 86.2, 83.2, 83.0, 81.7, 79.8, 61.4, 61.3, 60.2, 60.1, 59.2, 58.4, 56.8, 54.8, 45.5, 45.2, 38.6, 38.2, 33.8, 33.1, 31.9, 31.7, 30.8, 30.8, 30.3, 28.1, 27.1, 25.9, 25.1, 24.6, 23.8, 19.9, 19.5, 19.2, 19.2, 18.9, 17.9, 16.8, 16.3, 15.0, 14.5, 10.9; HRMS (ESI; *m*/*z*) $[M+H]^+$ calcd for $C_{38}H_{64}N_5O_8$ 718.4749, found 718.4744.

5.45. N-H-(18S)-Val-Val-Dil-Dap-Phe-OH (**19i**)

Compound **19i** was synthesized from **18i** according the same procedure described for **19a**, a white solid (17 mg, 91% over 2 steps); $[\alpha]^{25}_D$ −55.6° (c 0.45, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.34–7.10 (m, 5H), 4.82 (d, J = 7.3 Hz, 1H), 4.73 (dd, J = 10.9, 4.1 Hz, 1H), 4.40 (d, J = 10.8 Hz, 1H), 4.31–4.16 (m, 1H), 3.92 (d, J = 5.2 Hz, 1H), 3.82 (d, J = 6.8 Hz, 1H), 3.71–3.60 (m, 2H), 3.41–3.36 (m, 3H), 3.33 (s, 2H), 3.28 (s, 3H), 3.17 (s, 3H), 2.99–2.87 (m, 1H), 2.56 (dd, J = 15.2, 7.5 Hz, 1H), 2.41–2.25 (m, 2H), 2.24–2.09 (m, 2H), 2.07–1.85 (m, 3H), 1.77 (dt, J = 12.6, 6.7 Hz, 1H), 1.69–1.59 (m, 1H), 1.49–1.40 (m, 1H), 1.29 (d, J = 9.0 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H), 1.11–0.81 (m, 21H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.9, 176.5, 174.9, 174.7, 174.3, 172.0, 169.4, 138.9, 138.8, 130.2, 129.5, 127.9, 127.7, 87.3, 83.3, 79.9, 79.5, 62.4, 62.1, 61.7, 60.8, 60.4, 60.1, 59.7, 59.3, 56.0, 54.6, 45.5, 45.2, 39.3, 38.3, 38.1, 33.2, 32.8, 31.8, 31.7, 26.7, 25.9, 25.5, 24.4, 23.7, 20.3, 20.1, 19.1, 18.5, 17.8, 17.7, 16.3, 16.2, 15.0, 14.5, 11.6, 11.3; HRMS (ESI; *m*/*z*) $[M+H]^+$ calcd for $C_{38}H_{64}N_5O_8$ 718.4749, found 718.4733.

5.46. N-H-(9S, 18S)-Val-Val-Dil-Dap-Phe-OH (**19j**)

Compound **19j** was synthesized from **18j** according the same procedure described for **19a**, a white solid (25 mg, 94% over 2 steps); $[\alpha]^{25}_D$ −62.7° (c 0.23, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (dd, J = 22.3, 7.2 Hz, 5H), 4.77 (t, J = 8.1 Hz, 1H), 4.70 (dd, J = 9.1, 5.0 Hz, 1H), 4.33 (d, J = 10.6 Hz, 1H), 4.30–4.23 (m, 1H), 4.19 (s, 1H), 3.96 (d, J = 9.0 Hz, 1H), 3.78 (d, J = 5.1 Hz, 1H), 3.68 (d, J = 7.5 Hz, 1H), 3.38 (s, 3H), 3.31 (d, J = 14.5 Hz, 3H), 3.25 (s, 3H), 3.18 (s, 3H), 2.97 (dd, J = 13.8, 9.3 Hz, 1H), 2.62 (dd, J = 15.7, 7.2 Hz, 1H), 2.46–2.32 (m, 1H), 2.22–1.93 (m, 6H), 1.84 (s, 2H), 1.31 (s, 3H), 1.08–0.83 (m, 23H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.0, 174.6, 174.5, 172.0, 169.2, 138.6, 130.9, 130.8, 130.4, 129.4, 127.8, 83.1, 79.0, 62.4, 61.5, 60.3, 59.4, 59.3, 56.1, 54.8, 45.4, 39.3, 38.6, 33.3, 33.1, 32.9, 31.7, 31.7, 28.1, 26.9, 26.7, 25.9, 25.2, 23.7, 20.1, 18.9, 18.6, 17.8, 16.3, 15.0, 14.5, 11.2; HRMS (ESI; *m*/*z*) $[M+H]^+$ calcd for $C_{38}H_{64}N_5O_8$ 718.4749, found 718.4749.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.03.006.

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