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ARTICLE

A Practical Approach to Asymmetric Synthesis of Dolastatin 10

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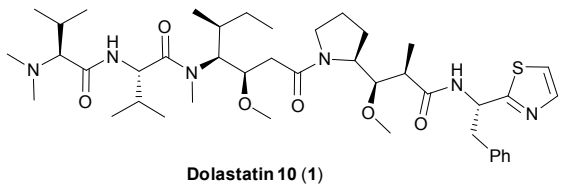
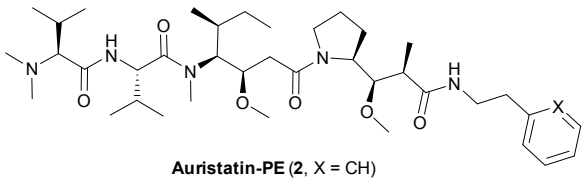
Dolastatin 10, an antineoplastic agent for cancer chemotherapy, is a linear peptide possessing *N,N*-dimethyl Val-OH, *L*-valine, (*3R,4S,5S*)-dolaisoleucine, (*2R,3R,4S*)-dolaproine and (*S*)-dolaphenine. Our efficient synthesis includes the following three key features: 1) SmI_2-induced cross-coupling was employed to couple aldehyde **11** with (*S*)-*N*-*tert*-butanesulfinyl imine **12** to generate the required stereocenters of Dap (**7**); 2) Asymmetric addition of chiral *N*-sulfinyl imine **10** provided a straightforward approach to protected Doe ((*S,S*)-**8**); 3) A practical method to the key subunit Val-Dil (**24a**) has been established as an alternative synthetic route for synthesis of this challenging chemical structure.

Introduction

Linear small peptides,[1] an interesting family of peptidic secondary metabolites, displaying a variety of physiological activities, including antimicrobial, antimalarial, antifungal, cytotoxic and neurotoxic properties, are a class of promising compounds for drug discovery. Due to their important bioactivities and attractive structures, the linear peptides have attracted significant attention in recent years. Dolastatin 10 (**1**), named as star molecule which was isolated from Indian ocean sea hare *Dolabella auricularia* by Pettit in 1987,[2] is a highly cytotoxic compound that inspired the design of auristatin as the potent 'warhead' component of antibody conjugates (ADC)



Dolastatin 10 (**1**)



Auristatin-PE (**2**, X = CH)

Auristatin-PYE (**3**, X = N)

Figure 1. The structures of dolastatin 10 and its analogues.

that have been approved as antineoplastic agents for cancer chemotherapy.[3] Dolastatin 10 shows antitumor activity in sub-nanomolar concentrations against a wide range of tumor cell lines, and was evaluated in clinical trials.[4] It functions through a unique mode of action, which are different from paclitaxel, vinblastine and the epothilones, and exhibits more potent activity against a variety of cancers.[5] As a result, the divergent synthesis of **1** has attracted significant attention[6] and a few analogues (For example, **2** and **3**) have entered clinical trials.[7]

As continuation of our interests in developing divergent syntheses of natural products[8] isolated from cyanobacteria and investigating their structure-activity relationships, we decided to develop an asymmetric synthesis of dolastatin 10 (**1**) and its analogues. Herein, we present an effective approach to dolastatin 10 (**1**).

Results and discussion

The retrosynthetic analysis of dolastatin 10 (**1**) led to five subunits (Figure 2): *N,N*-dimethyl valine (**4**, Dov), *L*-valine (**5**, Val), (*3R,4S,5S*)-dolaisoleucine (**6**, Dil), (*2R,3R,4S*)-dolaproine (**7**, Dap) and protected (*S*)-dolaphenine ((*S,S*)-**8**, protected Doe) fragments. As for the syntheses of five units, (*S*)-dolaphenine (Doe) could be prepared by asymmetric addition of lithium thiazole to chiral *N*-*tert*-butanesulfinyl imines.[9] (*2R,3R,4S*)-Dolaproine (Dap) could be obtained through SmI_2-induced cross-coupling [10] of aldehyde with (*S*)-*N*-*tert*-butanesulfinyl imine, which was established in early years and successfully used in asymmetric synthesis of natural products.[11] (*3R,4S,5S*)-dolaisoleucine (Dil) could be prepared by asymmetric reduction of ketone which was derived from isoleucine.[12] Importantly, dolastatin 10 (**1**) was effectively synthesized through an alternative condensation sequence of the five subunits.

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Due to its limitation from natural sources and high demand in preclinical and clinical chemotherapeutics studies, dolastatin 10 and its analogues have attracted considerable

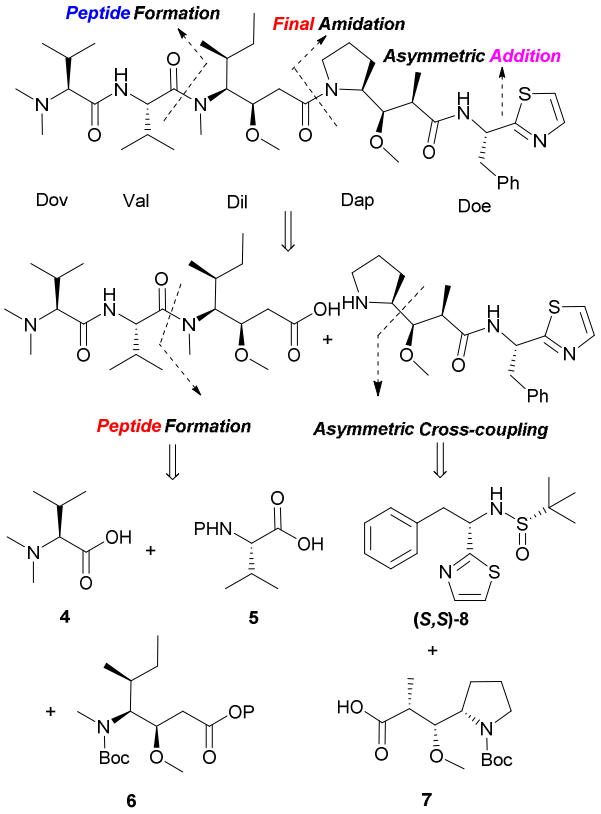
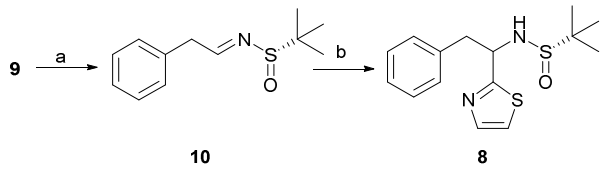


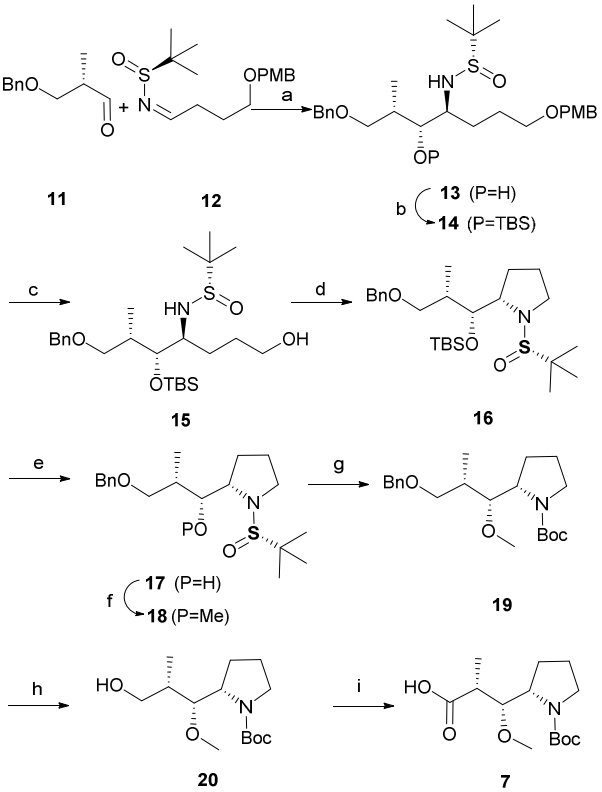
Figure 2. Our initial strategy to access dolastatin 10.

research interests and tremendous efforts have been devoted to the development of several synthetic approaches. Among them, several known approaches to dolaphenine (Doe) seem to be not very efficient.[6f,13] In recent years, one of our research interests is to utilize Ellman's chiral auxiliaries[14] in asymmetric synthesis of natural products.[8g,15] As a result, we were interested in developing a straightforward approach to the synthesis of dolaphenine (Doe). As shown in Scheme 1, chiral *N*-sulfinyl imine **10** was first prepared through the following sequence. The commercially available phenylacetaldehyde **9** was condensed with sulfinamide in presence of anhydrous cupric sulphate to afford the desired chiral *N*-sulfinyl imine **10** in 80% yield. Then 2-thiazole lithium[13b], which was obtained from the treatment of 2-bromothiazole with *n*-butyllithium (*n*-BuLi) at -78 °C for 30 min, reacted with *N*-sulfinyl imine (**10**) to give desired amine ((*S,S*)-**8**) in 53% yield and its diastereoisomer ((*R,S*)-**8**) in 27% yield.



Scheme 1 The preparation of protected Doe fragment ((*S,S*)-**8**). Reagents and conditions: a. (*S*)-*tert*-butanesulfinamide, $CuSO_4$, PPTS, DCM, rt, 36 h, 80%; b. 2-bromothiazole, *n*-BuLi, toluene, -78 °C, 3 h, 53% (complete yield 80%), *dr* = 2:1.

Next, we turned our attention to prepare the key (*2R,3R,4S*)-dolaproine subunit **7** (Dap) of dolastatin 10 (Scheme 2). The chiral aldehyde **11** and (*R*)-*N*-(4-(4-methoxybenzyloxy)butylidene)-2-methylpropane-2-sulfinamide **12** were prepared according to our previous methods.[11] The SmI_2-induced cross-coupling of **11** and **12** gave desired vicinal *β*-amino alcohol **13** with high diastereoselectivity (*dr* > 99:1) in 75% yield. Treatment of **13** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) generated silyl ether **14** in 88% yield. After the following two sequential steps, removal of PMB group (DDQ)[16] and mesylation (MsCl, TEA), the cyclization took place under potassium *tert*-butoxide conditions to give **16** in 50% overall yield. Upon the deprotection of TBS group with tetrabutylammonium fluoride[17] (TBAF), the alcohol **17** was converted to methyl ether **18**, using methyl methanesulfonate, in 58% overall yield. The chiral auxiliary was cleaved using HCl/dioxane, and the resulting secondary amine was converted to **19** in 79% overall yield. Hydrogenation (Pd/C, H_2) and oxidation with Dess-Martin periodinane[18] gave crude aldehyde, which was subjected to Pinnick oxidation[19] ($NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$) to give free acid **7** in 54% overall yield.



Scheme 2 The preparation of Dap fragment (**7**). *Reagents and conditions:* a. SmI_2, *t*-BuOH, THF, -78 °C, 5 h, 75% (*dr* > 99:1); b. TBSOTf, 2,6-lutidine, DCM, 0 °C to rt, 4 h, 88%; c. DDQ, DCM/H_2O, 0 °C, 30 min, 68%; d. (1). MsCl, TEA, DCM, 0 °C, 15 min; (2). *t*-BuOK, THF, 0 °C, 15 min, for two steps 73%; e. TBAF, THF, 0 °C to rt, 4 h, 61%; f. LiHMDS, HMPA, THF, -78 °C, 30 min, then MeOTf, -15 °C, 15 min, 95%; g. (1). HCl/dioxane, MeOH, 0 °C, 30 min; (2).

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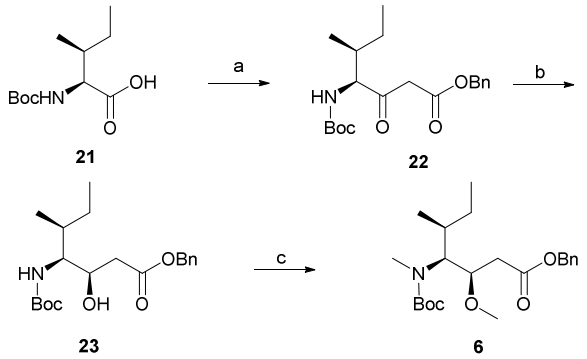
Boc_2O, TEA, DCM, rt, 12 h, for two steps 79%; h. Pd/C, H_2, MeOH, 5 h, 72%; i. (1). DMP, DCM, rt, 30 min; (2). $NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$, 2-methyl-2-butene/*t*-BuOH, rt, 8 h, for two steps 75%.

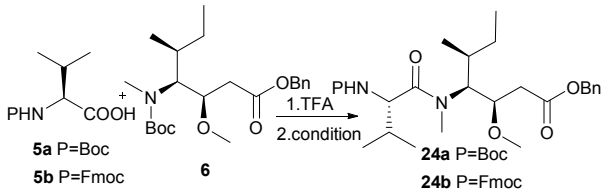
The (*3R,4S,5S*)-dolaisoleucine (**6**, Dil) of **3a** was prepared from (*S*)-*N*-Boc-isoleucine (**21**) according to a simple process[20] (Scheme 3). Activation of **21** with carbonyldiimidazole and subsequent reaction with benzyl acetate gave ketone **22** in 80% overall yield. Reduction (KBH_4, MeOH) of ketone **22** gave secondary alcohol **23** with high diastereoselectivity (*dr* > 99:1) in 78% yield. Methylation of **23** with methyl trifluoromethanesulfonate (MeOTf)[6f] in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) generated the desired compound **6** in 90% yield.



Scheme 3 The preparation of Dil fragment (**6**). *Reagents and conditions:* a. carbonyldiimidazole, THF, rt, 2 h, then LDA, benzyl acetate, THF, rt, 3 h, 80%; b. KBH_4, MeOH, -78 °C, 10 min, then -15 °C, 35 min, 78% (*dr* > 99:1); c. LiHMDS, HMPA, THF, -78 °C, 30 min, then MeOTf, -15 °C, 15 min, 90%.

The peptide formation of intermediate **24** (Dil-Val) involved the coupling of **6** (Dil) and Val-OH moiety **5a** or **5b**. When 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU)[21] was used, the yield of desired **24a** was only 15% yield (Table 1, entry 1). Other reagents, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBoP)[22] and bis(2-oxooxazolidin-3-yl)phosphinic chloride (BOP-Cl)[23] also led to limited yield of **24a** (Table 1, entries 2-3). Bromotris(dimethylamino)phosphonium hexafluophosphate (BrOP)[24] could slightly improve the yield of **24a** (Table 1, entry 4). Additional coupling reagents, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI),[25]

Table 1. The peptide formation of subunit **24** (Dil-Val).

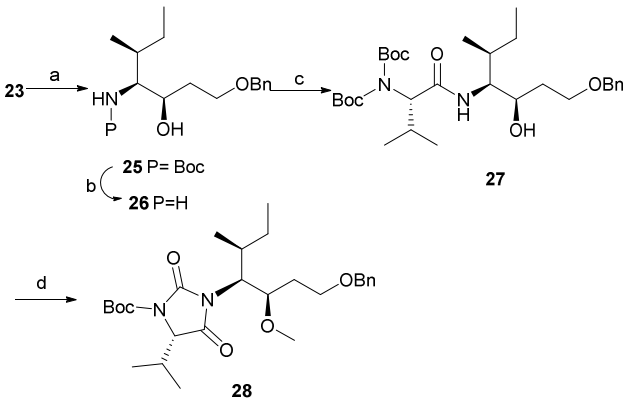


Entries[a]	5	Reagents	base	solvent	Yield %[b]
1	**a**	HATU	DIPEA	DCM	15
2	**a**	PyBOP	DIPEA	MeCN	18
3	**a**	BOP-Cl	DIPEA	DCM	16
4	**a**	BrOP	DIPEA	DCM	20
5	**a**	EDCI/HOBt	NMM	DMF	10
6	**b**	FDPP	DIPEA	MeCN	trace
7	**b**	CDMT	NMM	2-MeTHF	trace

[a] The reaction was performed with **6** (1.0 mmol), **5** (1.0 mmol), coupling reagent (1.1 mmol), base (6.0 mmol) in solvent (4.0 mL) overnight after **6** was deprotected with TFA; [b] Isolated yield.

pentafluorophenyl diphenylphosphinate (FDPP)[26] and 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT)[27] were also screened, and the results indicated that these classic reagents were not very effective in our case (Table 1, entries 5-7).

Considering the ester group and *N*-Me of **6** affected the amidation[28], compound **25** was prepared (Scheme 4). Removal of the Bn group in **23** and reduction of mixed anhydride ($NaBH_4$) afforded a diol, in which the primary alcohol was regioselective protected by Bn group to give desired product **25** in 62% overall yield. Removal of the Boc group in **25** and subsequent amidation (HATU, HOAt)[29] with *N*,*N*-bis[(1,1-dimethylethoxy)carbonyl]-*L*-Val-OH gave **27** in 52% overall yield. However, when **27** was subjected to methylation using LiHMDS and methyl trifluoromethanesulfonate (MeOTf)[6f], a cyclic by-product **28** was generated in 62% overall yield.



Scheme 4 *Reagents and conditions:* a.(1) Pd/C, H_2, MeOH, rt, 2 h; (2) Isobutyl chloroformate, THF, 30 min, then $NaBH_4$, H_2O, rt, overnight; (3) BnBr, NaH, DMF, 0 °C to rt, overnight, for three steps 62%; b. TFA, DCM, 0 °C, 2 h; c. *N*,*N*-bis[(1,1-dimethylethoxy)carbonyl]-*L*-Valine, HATU, HOAt, DIPEA, DCM, rt, overnight, for two steps 52%; d. LiHMDS, HMPA, THF, -78 °C, 30 min, then MeOTf, -15 °C, 15 min, 62%.

To establish an efficient approach to synthesize dolastatin 10, the retrosynthetic analysis of **34** was modified to use reduction alkylation instead of condensention with *N,N*-dimethyl valine (**4**, Dov) (Figure 3). As the *N*-Me in Dil fragment was introduced before coupling with Val fragment, the condensation of *N*-Me amine in fragment **29** with *N*-Boc-*L*-valine **5a** became an essential step.

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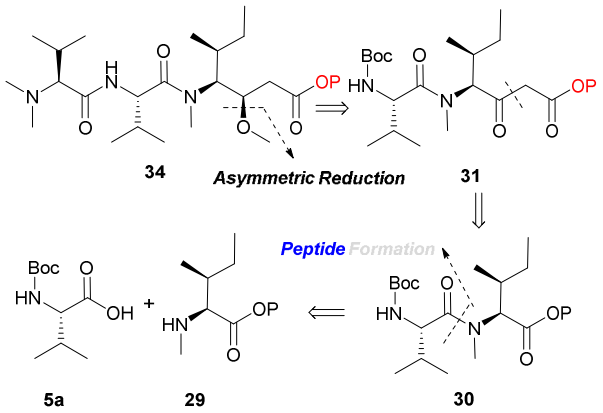
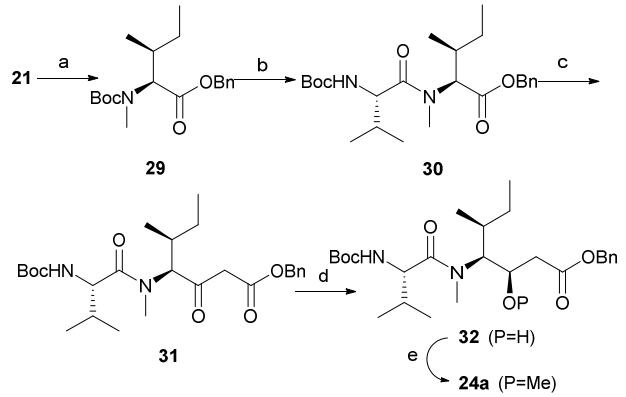


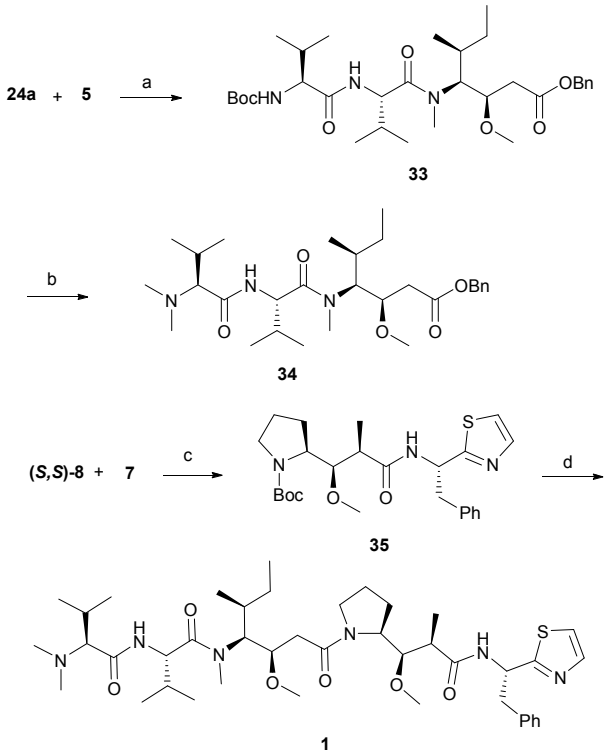
Figure 3. Our second strategy to access **34**.

The synthesis of subunit **24a** is shown in Scheme 5. Methylation (NaH, MeI) of (*S*)-Boc-isoleucine (**21**) and subsequent protection (BnBr, K_2CO_3) gave ester **29** in 55% overall yield.[30] Once the Boc group in **29** was removed using TFA, the crude salt was used directly to react with *N*-Boc-*L*-Val-OH in presence of HATU and HOAt[29] to give desired coupled product **30** in 82% yield. Then **30** was treated with carbonyldiimidazole and benzyl acetate in the presence of LDA[31] to produce ketone **31** in 80% yield. Reduction (KBH_4) of **31** and subsequent methylation (LiHMDS, MeOTf)[6f] generated the desired Val-Dil fragment **24a** in 47% yield.



Scheme 5 The preparation of Val-Dil fragment (**24a**). *Reagents and conditions:* a. (1). NaH, MeI, THF, rt, 48 h; (2). BnBr, K_2CO_3, DMSO, rt, overnight, for two steps 55%; b. (1), TFA, DCM, rt, 2 h; (2). *N*-Boc-*L*-Valine, HATU, HOAt, DIPEA, DCM, rt, overnight, for two steps 82%; c. (1) Pd/C, H_2, rt, 5 h; (2) carbonyldiimidazole, THF, rt, 2 h, then LDA, benzyl acetate, THF, -78 °C, 3 h, for two steps 80%; d. KBH_4, MeOH, -78 °C, 10 min, then -15 °C, 35 min, 78% (*dr* > 99:1); e. LiHMDS, HMPA, THF, -78 °C, 30 min, then MeOTf, -15 °C, 15 min, 60%.

With fragments (*S,S*)-**8** (protected Doe), **7** (Dap) and **24a** (Val-Dil) in hand, we turned our attention to final assembly of Dolastatin 10 (**3a**) through successive coupling reactions (Scheme 6). The crude amine salt, prepared by removal of Boc group in **24a** (TFA), was directly coupled with **5** (HATU, HOAt) to generate **33** in 85% yield. Upon the deprotection of Boc in **33**, the subsequent dimethylation[32] (40% HCHO, $Na(BH_3)CN$) gave the fragment **34** (Dov-Val-Dil) in 82% yield. The crude amine salt through the removal of Boc group in (*S,S*)-**8** (TFA) was coupled with **7** (HATU, HOAt)[29] to give desired compound **35** in 80% yield. Finally, the crude amine salt and acid, which were obtained from the removal of Boc group (TFA) in **35** and Bn group (Pd/C, H_2) of **34**, were coupled in the presence of HATU and HOAt[29] to give Dolastatin 10 (**1**) as a viscous liquid, which was further treated with acetone/hexane to give white powder {$[\alpha]_D^{23}$ = -63.3 (*c* 1.00, MeOH), lit.[2] $[\alpha]_D^{29}$ = -69 (*c* 0.01, MeOH), lit.[6f] $[\alpha]_D^{24}$ = -57.5 (*c* 1.07, MeOH)} in 60% isolated yield. The spectroscopic and physical data of the synthetic Dolastatin 10 (**1**) were identical to the reported data.[2,6f]



Scheme 6 The final synthesis of Dolastatin 10 (**3a**). *Reagents and conditions:* a. (1). TFA, DCM, 0 °C, 2 h; (2). HATU, HOAt, DIPEA, DCM, rt, overnight, for two steps 85%; b. (1). TFA, DCM, rt, 2 h; (2). 40% HCHO, $Na(BH_3)CN$, CH_3CN, rt, 18 h, for two steps 82%; c. (1). HCl/dioxane, MeOH, 0 °C, 30 min; (2). HATU, HOAt, DIPEA, DCM, rt, overnight, for two steps 80%; d. (1). TFA, DCM, 0 °C, 2 h; (2). **34**, Pd/C, H_2, MeOH, 2 h; (3). HATU, HOAt, DIPEA, DCM, rt, 24 h, for three steps 60%.

Conclusions

In summary, a practical approach to natural dolastatin 10 (**1**) has been established using SmI_2-induced cross-coupling of aldehyde with (*S*)-*N*-*tert*-butanesulfinyl imine to generate the required stereocenters of Dap (**7**). The alternative strategy for the preparation of the key subunit Val-Dil (**24a**) and a straightforward approach through asymmetric addition of chiral *N*-sulfinyl imine **10** to dolaphenine (Doe) were also developed to give dolastatin 10.

Experimental

General

THF was distilled from sodium/benzophenone. DCM was distilled from phosphorus pentoxide. Reactions were

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monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with fluorescent indicator. Flash chromatography was performed on silica gel (300-400 mesh). Optical rotations were measured on a polarimeter with a sodium lamp. HRMS were measured on a Thermo Scientific LTQ Orbitrap XL apparatus. IR spectra were recorded using film on a Fourier Transform Infrared Spectrometer. NMR spectra were recorded at 400 MHz or 600 MHz, and chemical shifts are reported in δ (ppm) referenced to the appropriate residual solvent peaks unless otherwise noted.

(*S*)-2-Methyl-*N*-((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)propane-2-sulfinamide 8. To a solution of **9** (5.00 g, 41.61 mmol) in DCM (150 mL) was added (*S*)-*tert*-butanesulfinamide (5.55 g, 45.77 mmol), $CuSO_4$ (13.28 g, 83.22 mmol) and PPTS (1.05 g, 4.16 mmol), after being stirred for 36 h, the reaction mixture was filtrated, concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 20:1) to give imine **10** in 80% yield. To a cooled (-78 ^{o}C) solution of 2-bromothiazole (2.42 mL, 26.87 mmol) in toluene (90 mL) was added *n*-butyllithium (1.6 M in hexane, 22.39 mmol) slowly, after being stirred for 30 min, another solution of **10** (5.00 g, 22.39 mmol) in toluene (10 mL) was added dropwise, after 3 h of stirring, the mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (80 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 2:1 to 1:1) to give the major product (*S,S*)-**8** (3.66 g, 53%) and the minor product (*R,S*)-**8** (1.83 g, 27%). (*S,S*)-**8** is a colorless oil, $[\alpha]_D^{27}$ = +31.6 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3205, 2956, 2924, 2864, 1668, 1604, 1497, 1455, 1363, 1056, 748, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 3.2 Hz, 1H), 7.28-7.26 (m, 2H), 7.25-7.21 (m, 2H), 7.13-7.10 (m, 2H), 4.96 (dd, *J* = 14.4, 7.2 Hz, 1H), 4.26 (d, *J* = 7.2 Hz, 1H), 3.30-3.27 (m, 2H), 1.12 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 142.6, 136.7, 129.8, 128.6, 127.0, 119.4, 58.9, 56.6, 43.9, 22.6 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{21}N_2OS_2^+$: 309.1090, Found: 309.1086. (*R,S*)-**8**, ^1H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J* = 3.2 Hz, 1H), 7.28-7.21 (m, 4H), 7.12-7.09 (m, 2H), 5.10 (dd, *J* = 12.4, 6.0 Hz, 1H), 3.94 (d, *J* = 6.4 Hz, 1H), 3.54-3.48 (m, 1H), 3.43-3.38 (m, 1H), 1.21 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 173.4, 143.3, 135.3, 130.4, 128.8, 127.3, 119.4, 58.3, 56.6, 43.2, 22.7 ppm.

(*S*)-*N*-((2*S*,3*R*,4*S*)-1-(Benzyloxy)-3-hydroxy-7-((4-methoxybenzyl)oxy)-2-methylheptan-4-yl)-2-methylpropane-2-sulfinamide 13. To a cooled (-78 ^{o}C) solution of **11** (2.50 g, 14.00 mmol), **12** (4.36 g, 14.00 mmol) and *t*-BuOH (5.36 mL, 56.00 mmol) in THF (280 mL) was added a freshly prepared solution of samarium diiodide (0.2 M in THF, 56.00 mmol), after being stirred for 5 h, the mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 1:1) to give **13** (5.16 g, 75%) as a colorless oil. $[\alpha]_D^{26}$ = +37.1 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3406, 2957, 2926, 2858, 1612, 1513, 1454, 1363, 1247, 1094, 1035, 822, 771, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.38-7.28 (m, 5H), 7.27-7.22 (m, 2H), 6.89-6.84 (m, 2H), 4.52-4.48 (m, 2H), 4.44-4.40 (m, 2H), 3.84-3.80 (m, 0.5H), 3.80-3.78 (m, 3H), 3.66-3.62 (m, 0.5H), 3.55-3.53 (m, 1H), 3.53-3.47 (m, 3H), 3.45-3.41 (m, 1H), 3.33-3.26 (m, 1H), 2.07-1.99 (m, 1H), 1.97-1.74 (m, 3H), 1.74-1.63 (m, 2H), 1.20-1.17 (m, 9H), 1.04-0.98 (m, 1.5H), 0.93-0.89 (m, 1.5H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 159.3, 138.1(138.3), 130.8 (130.8), 129.5 (129.5), 128.7 (128.7), 128.0, 128.0 (127.9), 114.0, 78.5 (76.7), 74.3 (74.9), 73.7 (73.6), 72.8 (72.8), 70.0 (70.1), 59.2 (58.9), 56.0 (56.1), 55.5, 35.4 (34.9), 26.3 (27.4), 25.6 (25.7), 23.0 (23.0), 14.5 (11.9) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{42}NO_5S^+$: 492.2778, Found: 492.2777.

(*S*)-*N*-((2*S*,3*R*,4*S*)-1-(Benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2-methylheptan-4-yl)-2-methylpropane-2-sulfinamide 14. To a cooled (0 ^{o}C) solution of **13** (10.00 g, 20.34 mmol) and 2,6-lutidine (11.84 mL, 101.70 mmol) in DCM (80 mL) was carefully treated with TBSOTf (11.68 mL, 50.85 mmol) for 4 h. Then, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 10:1) to give **14** (10.85 g, 88%) as a colorless oil. $[\alpha]_D^{25}$ = +33.6 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3449, 3296, 2955, 2928, 2856, 1610, 1513, 1455, 1362, 1248, 1093, 1067, 1049, 836, 774 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.34-7.24 (m, 7H), 6.89-6.84 (m, 2H), 4.46-4.41 (m, 4H), 4.24 (d, *J* = 6.2 Hz, 0.5H), 4.13 (d, *J* = 6.2 Hz, 0.5H), 3.79 (s, 3H), 3.71-3.60 (m, 2H), 3.49-3.43 (m, 2H), 3.24-3.18 (m, 2H), 2.35-2.22 (m, 1H), 1.90-1.82 (m, 2H), 1.65-1.55 (m, 2H), 1.13-1.09 (m, 9H), 0.95-1.90 (m, 3H), 0.88 (s, 6H), 0.11 (s, 3H), 0.08 (s, 1.5H), 0.03 (s, 1.5H) ppm; ^{13}C NMR ($CDCl_3$, 100MHz, rotamers) δ 159.2, 138.3 (138.3), 130.8 (130.8), 129.4 (129.4), 128.5, 127.8 (127.9), 127.7 (127.7), 113.8, 79.3 (78.5), 73.2 (73.3), 72.7 (72.6), 71.7 (71.6), 69.9 (70.0), 60.7 (60.1), 55.8 (55.8), 55.4, 35.8 (35.3), 28.6 (27.7), 26.7 (26.5), 26.3, 23.0 (22.9), 18.5, 16.6 (16.4), 1.0, -3.2, -3.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{33}H_{56}NO_5SSi^+$: 606.3643, Found: 606.3643.

(*S*)-N-((2*S*,3*R*,4*S*)-1-(Benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-2-methylheptan-4-yl)-2-methylpropane-2-sulfinamide 15. To a cooled (0 ^{o}C) solution of **14** (1.00 g, 1.65 mmol) in DCM (10 mL) and H_2O (1 mL) was added DDQ (749 mg, 3.30 mmol) for three times. After being stirred for 30 min, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and extracted with DCM (60 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 1:1) to give **15** (545 mg, 68%) as a colorless oil. $[\alpha]_D^{24}$ = +24.4 (*c* 2.00, $CHCl_3$); IR (film) ν_{max} 3387, 3302, 2956, 2928, 2857, 1472, 1455, 1363, 1252, 1093, 1048, 835, 774, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.25 (m, 5H), 4.52-4.43 (m, 2H), 4.09 (d, *J* = 7.2 Hz, 1H), 3.70-3.58 (m, 4H), 3.34-3.26 (m,

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1H), 3.23 (dd, *J* = 9.2, 4.8 Hz, 1H), 2.21-2.14 (m, 1H), 1.88-1.72 (m, 2H), 1.70-1.54 (m, 2H), 1.16 (s, 9H), 0.98-0.95 (m, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3, 128.5, 127.8, 127.7, 78.5, 73.2, 71.7, 62.7, 61.1, 56.0, 36.1, 29.3, 28.7, 26.2, 23.0, 18.5, 16.3, -3.3, -4.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{48}NO_4SSi^+$: 486.3068, Found: 486.3067.

(*S*)-2-((1*R*,2*S*)-3-(Benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-1-((*S*)-tert-butylsulfinyl)pyrrolidine 16. To a solution of **15** (7.00 g, 14.41 mmol) in DCM (58 mL) was added TEA (16.00 mL, 115.28 mmol) followed by MsCl (3.35 mL, 43.23mmol), after being stirred for 15 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated to give a crude residue, which was dissolved in THF (58 mL), and carefully treated with *t*-BuOK (3.23 g, 28.82 mmol), after being stirred for 15 min, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 6:1) to give **16** (4.92 g, 73%, two steps) as a colorless oil. $[\alpha]_D^{26}$ = +52.1 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2956, 2928, 2856, 1472, 1455, 1361, 1252, 1072, 947, 836, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.37-7.24 (m, 5H), 4.53-4.43 (m, 2H), 3.95-3.92 (m, 0.75H), 3.82-3.79 (m, 0.25H), 3.76-3.71 (m, 1H), 3.68-3.61 (m, 1H), 3.50-3.42 (m, 1H), 3.37-3.31 (m, 0.75H), 3.25-3.20 (m, 0.25H), 2.72-2.63 (m, 1H), 2.12-1.96 (m, 1.75H), 1.90-1.80 (m, 1.25H), 1.76-1.66 (m, 2H), 1.21 (s, 2.25H), 1.17 (s, 6.75H), 0.95-0.91 (m, 3H), 0.90-0.87 (m, 9H), 0.11-0.01 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 138.7 (138.7), 128.4, 127.5, 75.3, 73.2 (72.9), 72.8 (72.7), 68.3 (69.6), 57.3 (57.6), 42.6 (42.3), 39.2 (37.7), 27.7 (26.8), 26.2 (26.7), 26.1, 24.0 (24.2), 18.4 (18.5), 13.5 (11.9), -4.0 (-3.7), -4.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{46}NO_3SSi^+$: 468.2962, Found: 468.2963.

(1*R*,2*S*)-3-(Benzyloxy)-1-((*S*)-1-((*S*)-*tert*-butylsulfinyl)pyrrolidin-2-yl)-2-methylpropan-1-ol 17. To a cooled (0 °C) solution of **16** (4.60 g, 9.84 mmol) in THF (40 mL) was added TBAF (19.68 mL, 19.68 mmol) dropwise, after being stirred for 4 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (60 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 1:1) to give **17** (2.12 g, 61%) as a white solid, m.p. 84-86 °C. $[\alpha]_D^{25}$ = +94.8 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3441, 2964, 2915, 2857, 1453, 1359, 1068, 1039, 955, 749, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.26 (m, 5H), 4.57-4.50 (m, 2H), 3.82-3.73 (m, 2H), 3.63-3.59 (m, 1H), 3.58-3.53 (m, 2H), 2.99-2.95 (m, 1H), 2.78-2.70 (m, 1H), 1.94-1.88 (m, 1H), 1.86-1.77 (m, 3H), 1.74-1.64 (m, 1H), 1.22 (s, 9H), 0.98-0.94 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 128.5, 127.8, 127.7, 75.1, 74.2, 73.4, 68.1, 57.3, 42.8, 36.5, 27.1, 23.9, 23.9, 13.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{32}NO_3S^+$: 354.2097, Found: 354.2097.

(*S*)-2-((1*R*,2*S*)-3-(Benzyloxy)-1-methoxy-2-methylpropyl)-1-((*S*)-*tert*-butylsulfinyl)pyrrolidine 18. To a cooled (-78 °C) solution of **17** (2.00 g, 5.66 mmol) and HMPA (1.49 mL, 8.50 mmol) in THF (24 mL) was added LiHMDS (1 M in THF, 8.50 mmol) dropwise, after being stirred for 30 min, the reaction was warmed to -15 °C and added MeOTf (1.28 mL, 11.32 mmol), after being stirred for 15 min, it was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (60 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 5:1) to give **18** (1.98 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ = +65.6 (*c* 2.00, $CHCl_3$); IR (film) ν_{max} 2961, 2924, 2868, 1454, 1361, 1095, 1071, 1028, 949, 737, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.39-7.23 (m, 5H), 4.55-4.47 (m, 2H), 3.84-3.76 (m, 1H), 3.74-3.67 (m, 1H), 3.51-3.45 (m, 1.5H), 3.43-3.41 (m, 3H), 3.36-3.28 (m, 1.5H), 2.78-2.71 (m, 1H), 1.93-1.82 (m, 3H), 1.81-1.67 (m, 2H), 1.22 (s, 9H), 1.01-0.93 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 138.6 (138.5), 128.4, 127.6, 127.5, 85.3 (84.0), 73.2 (73.1), 72.4 (73.0), 68.0 (68.7), 60.2 (60.8), 57.3 (57.6), 42.7 (42.2), 36.8 (36.3), 27.6 (26.9), 25.1 (26.3), 24.1 (24.1), 14.5 (12.3) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{34}NO_3S^+$: 368.2254, Found: 368.2255.

***tert*-Butyl (*S*)-2-((1*R*,2*S*)-3-(benzyloxy)-1-methoxy-2-methylpropyl)pyrrolidine-1-carboxylate 19.** To a cooled (0 °C) solution of **18** (1.90 g, 5.17 mmol) in MeOH (20 mL) was added HCl/dioxane (2.00 mL) dropwise, after being stirred for 30 min, the reaction was concentrated. The resulted mixture was diluted with DCM (20 mL), and added Boc_2O (1.35 g, 6.20 mmol) and TEA (4.30 mL, 31.02 mmol), after being stirred for 12 h, the mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (60 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 10:1) to give **19** (1.48 g, 79%, two steps) as a colorless oil. $[\alpha]_D^{26}$ = +45.2 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2972, 2931, 2878, 1693, 1454, 1398, 1365, 1250, 1166, 1100, 735, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.38-7.24 (m, 5H), 4.55-4.46 (m, 2H), 4.02-3.84 (m, 1H), 3.70-3.65 (m, 0.33H), 3.64-3.59 (m, 1H), 3.58-3.46 (m, 2H), 3.42-3.36 (m, 0.67H), 3.35 (s, 3H), 3.31-3.22 (m, 1H), 1.99-1.89 (m, 2H), 1.86-1.65 (m, 3H), 1.49-1.46 (m, 9H), 1.04-0.99 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 154.4 (154.5), 138.9, 128.4, 127.7, 127.5, 83.1 (82.2), 79.5 (79.1), 73.1, 72.7 (73.0), 61.0 (60.8), 59.0 (59.1), 46.8 (47.3), 37.4 (37.6), 28.7, 25.3 (25.0), 24.5 (24.7), 14.8 (14.5) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{34}NO_4^+$: 364.2482, Found: 364.2482.

***tert*-Butyl (*S*)-2-((1*R*,2*S*)-3-hydroxy-1-methoxy-2-methylpropyl)pyrrolidine-1-carboxylate 20.**

A solution of **19** (1.40 g, 3.85 mmol) and 10% Pd/C (1.40 g) were stirred in MeOH (100 mL) for 5 h under H_2

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atmosphere. Then, the mixture was filtrated, concentrated and purified by flash chromatography on silica gel (PE/EA = 2:1) to give **20** (758 mg, 72%) as a colorless oil. $[\alpha]_D^{25}$ = +71.4 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3453, 2972, 2931, 2878, 1693, 1673, 1403, 1366, 1166, 1110, 1039, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 4.01-3.82 (m, 1H), 3.81-3.75 (m, 0.5H), 3.69-3.62 (m, 1H), 3.61-3.51 (m, 2.5H), 3.48-3.41 (m, 3.5H), 3.32-3.24 (m, 1H), 3.18-3.03 (m, 0.5H), 2.06-1.99 (m, 1H), 1.99-1.92 (m, 1H), 1.89-1.66 (m, 3H), 1.50-1.45 (m, 9H), 1.06-0.86 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 154.9 (154.3), 85.4 (87.9), 79.5 (79.7), 67.3 (67.6), 65.8, 60.3 (61.2), 58.5 (59.3), 47.1 (46.9), 38.4 (38.9), 38.0, 28.6 (28.7), 25.3 (25.7), 25.0 (24.3), 13.5 (14.6) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{28}NO_4^+$: 274.2013, Found: 274.2012.

(2*R*,3*R*)-3-((*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl)-3-methoxy-2-methylpropanoic acid 7. To a cooled (0 °C) solution of **20** (600 mg, 2.19 mmol) in DCM (10 mL) was slowly added DMP (1.12 g, 2.63 mmol), after being stirred for 30 min, the reaction mixture was carefully quenched with a saturated aqueous solution of $NaHCO_3$ and solid $Na_2S_2O_3$, extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated without further purification to give a crude aldehyde. A solution of above aldehyde in *t*-BuOH/2-methyl-2-butene (5/5 mL) was treated with a solution of $NaClO_2$ (594 mg, 6.57 mmol) and $NaH_2PO_4 \bullet 2H_2O$ (1.02 g, 6.57 mmol) in water (5 mL), after being stirred for 8 h, the reaction mixture was extracted with EtOAc (30 mL × 3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 30:1) to give **7** (472 mg, 75%, two steps) as a colorless oil. $[\alpha]_D^{24}$ = -57.2 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3180, 2977, 2934, 2882, 1735, 1696, 1671, 1401, 1367, 1166, 1099, 865, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 4.01-3.85 (m, 1H), 3.83-3.77 (m, 1H), 3.62-3.46 (m, 1H), 3.45 (s, 3H), 3.28-3.20 (m, 1H), 2.58-2.48 (m, 1H), 2.01-1.84 (m, 3H), 1.80-1.70 (m, 1H), 1.50-1.45 (m, 9H), 1.30-1.26 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz, rotamers) δ 179.4 (178.5), 153.8 (154.3), 82.4 (81.1), 79.3 (78.9), 60.6 (60.2), 58.9 (58.7), 46.0 (46.5), 42.2, 27.9, 25.5 (24.9), 23.4 (23.8), 12.9 (12.8) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{26}NO_5^+$: 288.1806, Found: 288.1805.

Benzyl (*4S*,*5S*)-4-((*tert*-butoxycarbonyl)amino)-5-methyl-3-oxoheptanoate 22. A solution of **21** (5.00 g, 21.62 mmol) in THF was added carbonyldiimidazole (3.51 g, 21.62 mmol) and stirred at room temperature for 2 h to give a crude imidazolide for preparation. To a suspension of bencyl acetate (9.85 mL, 69.18 mmol) in THF was added LDA (2M in THF, 64.86 mmol), after stirred for 30 min, the above solution of crude imidazolide previously prepared in THF was added dropwise, and the reaction mixture was allowed to stir for 3 h at -78 °C, quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (80 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=15:1) to give **22** (6.29 g, 80%) as a colorless oil. $[\alpha]_D^{22}$ = +3.0 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3358, 2967, 2932, 2876, 1748, 1712, 1499, 1366, 1249, 1166, 1012, 747, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.38-7.34 (m, 5H), 5.22-5.13 (m, 3H), 5.03 (d, *J* = 8.4 Hz, 1H), 4.32 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.62-3.58 (m, 2H), 1.99-1.88 (m, 1H), 1.08-0.99 (m, 1H), 0.98-0.95 (m, 2H), 0.93-0.90 (m, 1H), 0.88-0.83 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 202.3, 166.7 (172.5), 155.9 (155.4), 135.4 (135.8), 128.7, 128.6, 128.5, 80.2 (80.0), 67.4 (66.2), 64.5 (58.4), 47.4, 36.4 (37.2), 28.4 (28.5), 24.2 (24.9), 16.2 (15.8), 11.7 (11.6) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{29}NO_5^+$: 364.2119, Found: 364.2116.

Benzyl (3*R*,4*S*,5*S*)-4-((*tert*-butoxycarbonyl)amino)-3-hydroxy-5-methylheptanoate 23. To a cooled (-78 °C) solution of **22** (6.00 g, 16.51 mmol) in MeOH (66 mL) was added KBH_4 (3.12 g, 57.79 mmol) for 3 times, after being stirred for 10 min, the reaction was warmed to -15°C and stirred for another 35 min, then CH_3COOH was added to adjust pH ranging from 9 to 10. The reaction mixture was evaporated, extracted with EtOAc (80 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=7:1) to give **23** (4.71 g, 78%) as a white solid, m.p. 74-76 °C; $[\alpha]_D^{25}$ = +5.1 (*c* 2.00, $CHCl_3$); IR (film) ν_{max} 3441, 3370, 2965, 2932, 2876, 1714, 1697, 1500, 1366, 1251, 1169, 1068, 751, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.40-7.30 (m, 5H), 5.16 (brs, 2H), 4.47-4.28 (m, 1H), 4.10-3.90 (m, 1H), 3.62-3.45 (m, 1H), 3.42-3.15 (m, 1H), 2.76-2.58 (m, 1H), 2.56-2.43 (m, 1H), 1.84-1.74 (m, 1H), 1.63-1.49 (m, 1H), 1.45-1.42 (m, 9H), 1.04-0.95 (m, 1H), 0.94-0.89 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 173.1, 156.6, 135.7, 128.7, 128.4, 128.4, 79.7, 69.1, 66.7, 59.1, 38.5, 34.8, 28.5, 23.5, 16.4, 11.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{32}NO_5^+$: 366.2275, Found: 366.2274.

Benzyl (3*R*,4*S*,5*S*)-4-((*tert*-butoxycarbonyl)(methyl)amino)-3-methoxy-5-methylheptanoate 6. To a cooled (-78 °C) solution of **23** (2.00 g, 5.47 mmol) in HMPA (2.11 mL, 12.04 mmol) and THF (20 mL) was added a solution of LiHMDS (1M in THF, 10.94 mmol) slowly, after being stirred for 30 min, the reaction was warmed to -15 °C and MeOTf (2.48 mL, 21.88 mmol) was added, then the mixture was stirred for an additional 15 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (60 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=10:1) to give **6** (1.94 g, 90%) as a colorless oil. $[\alpha]_D^{22}$ = -17.9 (*c* 2.00, $CHCl_3$); IR (film) ν_{max} 2968, 2932, 2876, 1736, 1691, 1455, 1391, 1365, 1328, 1161, 1100, 771, 749, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.37-7.31 (m, 5H), 5.18-5.10 (m, 2H), 4.17-3.82 (m, 2H), 3.50-3.33 (m, 3H), 2.70-2.65 (m, 3H), 2.57-2.51 (m, 2H), 1.81-1.65 (m, 1H), 1.53-1.46 (m, 1H), 1.45-1.43 (m, 9H), 1.13-1.05 (m, 1H), 0.97-0.94 (m, 3H), 0.91-0.86 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 171.8 (172.1), 156.6 (156.4), 135.9 (136.0), 128.6, 128.5, 128.4 (128.3), 79.3 (79.9),

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78.5 (60.8), 66.6 (66.5), 58.0 (57.8), 37.8 (37.4), 34.9 (30.6), 34.4, 28.5 (28.5), 26.0 (25.9), 16.2 (16.4), 11.3(11.3) ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{22}H_{36}NO_5^+$: 393.2588, Found: 393.2588.

***tert*-Butyl ((3*R*,4*S*,5*S*)-1-(benzyloxy)-3-hydroxy-5-methylheptan-4-yl)carbamate 25.** A solution of **23** (2.00 g, 5.47 mmol) and 10% Pd/C (2.00 g) were stirred in MeOH (100 mL) for 2 h under H_2 atmosphere. Then, the mixture was filtrated to give a crude acid without further purification. To a cooled (0 °C) solution of above alcohol was added isobutyl chloroformate (725 μL, 5.74 mmol) in THF (20 mL), after stirred for 30 min, the reaction mixture was added $NaBH_4$ (414 mg, 10.94 mmol) in water (2 mL) slowly, after being stirred overnight, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (60 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=1:1) to give a crude alcohol without further purification. To a cooled (0 °C) solution of above alcohol (1.00 g, 3.83 mmol) was added NaH (153 mg, 60%, 3.83 mmol) and BnBr (455 μL, 3.83 mmol) in DMF (5 mL), after being stirred overnight, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (60 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=6:1) to give **25** (1.20 g, 62%, three steps) as a colorless oil. $[\alpha]_D^{26}$ = +9.3 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3449, 3344, 2962, 2927, 2875, 1697, 1500, 1454, 1391, 1366, 1171, 1088, 737, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.25 (m, 5H), 4.57-4.42 (m, 3H), 3.85-3.78 (m, 1H), 3.73-3.57 (m, 3H), 3.57-3.46 (m, 0.5H), 3.45-3.42 (m, 0.5H), 1.92-1.73 (m, 3H), 1.45-1.41 (m, 9H), 1.40-1.31 (m, 1H), 1.25-1.14 (m, 1H), 0.94-0.89 (m, 3H), 0.88-0.80 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4, 137.9, 128.6, 127.9, 127.8, 79.3, 73.5, 72.7, 69.7, 57.2, 34.0, 33.2, 28.5, 27.3, 13.6, 11.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{20}H_{34}NO_4^+$: 352.2482, Found: 352.2481.

Di*tert*-butyl ((*S*)-1-(((3*R*,4*S*,5*S*)-1-(benzyloxy)-3-hydroxy-5-methylheptan-4-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate 27. To a cooled (0 °C) solution of **25** (907 mg, 2.58 mmol) in DCM (10 mL) was added TFA (2 mL) slowly, after being stirred for 2 h, the mixture was concentrated under reduced pressure. The residue was dissolved in DCM (10 mL), HATU (1.18 g, 3.10 mmol), HOAt (422 mg, 3.10 mmol), DIPEA (2.70 mL, 15.48 mmol) and *N*,*N*-bis[(1,1-dimethylethoxy) carbonyl]-*L*-Valine (984 mg, 3.10 mmol) were added, after being stirred overnight, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=5:1) to give **27** (739 mg, 52%, two steps) as a colorless oil. $[\alpha]_D^{25}$ = +22.6 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 3445, 3336, 2965, 2922, 2875, 2851, 1742, 1697, 1368, 1333, 1236, 1167, 1129, 851, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.27 (m, 5H), 7.16 (d, *J* = 9.2 Hz, 1H), 4.56-4.48 (m, 2H), 4.14 (d, *J* = 10.8 Hz, 1H), 3.98-3.91 (m, 1H), 3.85-3.79 (m, 1H), 3.78-3.71 (m, 1H), 3.68-3.62 (m, 1H), 3.58 (d, *J* = 4.0 Hz, 1H), 2.48-2.37 (m, 1H), 1.95-1.87 (m, 1H), 1.84-1.79 (m, 1H), 1.78-1.75 (m, 1H), 1.50 (s, 18H), 1.32-1.25 (m, 1H), 1.17-1.09 (m, 1H), 1.03-1.00 (m, 3H), 0.92-0.88 (m, 6H), 0.87-0.84 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.1, 153.9, 138.1, 128.6, 127.8, 127.8, 83.5, 73.5, 72.2, 69.6, 68.4, 55.9, 34.2, 33.1, 28.0, 27.4, 27.3, 20.8, 19.9, 13.6, 11.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{30}H_{51}N_2O_7^+$: 551.3691, Found: 551.3691.

***tert*-Butyl (*S*)-3-((3*R*,4*S*,5*S*)-1-(benzyloxy)-3-methoxy-5-methylheptan-4-yl)-5-isopropyl-2,4-dioxoimidazolidine-1-carboxylate 28.** To a cooled (-78 °C) solution of **27** (700 mg, 1.27 mmol) in HMPA (488 μL, 2.79 mmol) and THF (5 mL) was added a solution of LiHMDS (1M in THF, 2.54 mmol) slowly, after being stirred for 30 min, the reaction was warmed to -15 °C and MeOTf (575 mL, 5.08 mmol) was added, then the mixture was stirred for an additional 15 min. The reation was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=10:1) to give **28** (386 mg, 62%) as a colorless oil. $[\alpha]_D^{25}$ = -24.8 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 2966, 2932, 2880, 2853, 1813, 1794, 1730, 1367, 1318, 1156, 1104, 794, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.36-7.29 (m, 5H), 4.56-4.51 (m, 1H), 4.47-4.42 (m, 1H), 4.32-4.08 (m, 2H), 3.96-3.66 (m, 1H), 3.56-3.52 (m, 2H), 3.37-3.32 (m, 3H), 3.31-3.28 (m, 1H), 2.55-2.42 (m, 2H), 2.14-1.96 (m, 1H), 1.54 (s, 9H), 1.52-1.42 (m, 2H), 1.21-1.17 (m, 3H), 0.95-0.87 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz, rotamers) δ 171.4, 153.2 (153.7), 148.7, 138.8, 128.5, 127.7, 127.6, 84.1, 72.9, 66.7, 64.0 (63.2), 58.4 (59.3), 57.9, 57.1, 57.0, 31.8 (32.4), 31.5 (31.3), 29.8 (30.1), 28.2, 26.3 (26.0), 18.5 (18.3), 16.4, 16.3 (16.8), 16.2 (16.0), 10.5 (10.9) ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ Calcd for $C_{27}H_{43}N_2O_6^+$: 491.3116, Found: 491.3116.

Benzyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-isoleucinate 29. To a cooled (0 °C) solution of **21** (10.00 g, 43.24 mmol) in THF (170 mL) was added NaH (8.65 g, 60%, 216.20 mmol) for three times, after being stirred for 30 min, MeI (18.84 mL, 302.68 mmol) was added slowly. After being stirred for 48 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated to give a crude acid without further purification. To a solution of the above acid in DMSO (50 mL) was treated with K_2CO_3 (11.95 g, 86.48 mmol) and BnBr (4.11 mL, 47.56 mmol), after being stirred overnight, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=40:1) to give **29** (7.98 g, 55%, two steps) as a colorless oil. $[\alpha]_D^{25}$ = -64.3 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2969, 2932, 2880, 1739, 1698,

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1456, 1367, 1312, 1256, 1177, 1144, 750, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.40-7.27 (m, 5H), 5.19-5.10 (m, 2H), 4.60 (d, *J* = 10.8 Hz, 0.5H), 4.29 (d, *J* = 10.8 Hz, 0.5H), 2.84-2.76 (m, 3H), 2.07-1.91 (m, 1H), 1.46-1.41 (m, 10H), 1.14-1.03 (m, 1H), 0.92-0.86 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 171.2 (171.6), 155.7 (156.3), 135.8 (136.0), 128.7 (128.6), 128.4, 128.2 (128.1), 80.4 (80.1), 66.4 (66.3), 63.5 (62.1), 33.6 (33.7), 30.5 (30.3), 28.4, 25.1 (25.1), 16.0 (15.9), 10.4 (10.8) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{30}NO_4^+$: 336.2169, Found: 336.2169.

Benzyl *N*-((*tert*-butoxycarbonyl)-*L*-valyl)-*N*-methyl-*L*-isoleucinate 30. To a cooled (0 °C) solution of **29** (7.80 g, 23.25 mmol) in DCM (90 mL) was added TFA (10 mL) slowly, after being stirred for 2 h, the mixture was concentrated under reduced pressure. The residue was dissolved in DCM (90 mL), HATU (9.72 g, 25.58 mmol), DIPEA (24.30 mL, 139.50 mmol), and *N*-Boc-*L*-Valine (5.56 g, 25.58 mmol) were added, after being stirred overnight, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA 8:1) to give **30** (8.29 g, 82%, two steps) as a colorless oil. $[\alpha]_D^{25}$ = -77.0 (*c* 2.00, $CHCl_3$); IR (film) ν_{max} 3431, 2966, 2932, 2876, 1736, 1706, 1647, 1498, 1456, 1366, 1255, 1175, 1013, 750, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.28 (m, 5H), 5.21 (d, *J* = 12.0 Hz, 1H), 5.18-5.13 (m, 1H), 5.09 (d, *J* = 6.8 Hz, 1H), 5.05 (d, *J* = 8.4 Hz, 1H), 4.35 (dd, *J* = 9.6, 7.2 Hz, 1H), 2.98 (s, 3H), 2.05-1.97 (m, 1H), 1.88-1.80 (m, 1H), 1.42 (s, 9H), 1.38-1.30 (m, 1H), 1.06-0.98 (m, 1H), 0.97-0.94 (m, 3H), 0.88-0.81 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.6, 170.8, 156.1, 135.6, 128.7, 128.6, 128.5, 79.6, 66.7, 60.5, 55.5, 33.2, 31.4, 31.2, 28.4, 24.8, 19.4, 17.7, 16.0, 10.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{39}N_2O_5^+$: 435.2854, Found: 435.2852.

Benzyl (4*S*,5*S*)-4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-*N*,3-dimethylbutanamido)-5-methyl-3-oxoheptanoate 31. A solution of **30** (8.00 g, 18.41 mmol) and 10% Pd/C (800 mg) were stirred in MeOH (500 mL) for 5 h under H_2 atmosphere. Then, the mixture was filtrated to give a crude acid without further purification. To a solution of above acid in THF (70 mL) was added carbonyldiimidazole (2.99 g, 18.41 mmol) and stirred at room temperature for 2 h to give a crude imidazolide for preparation. To a suspension of bencyl acetate (8.43 mL, 58.91 mmol) in THF (70 mL) was added LDA (2M in THF, 55.23 mmol) at -78 °C, after stirred for 30 min, the above solution of crude imidazolide previously prepared in THF (10 mL) was added dropwise, and the reaction mixture was allowed to stir for 3 h at -78 °C, quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=8:1) to give **31** (7.02 g, 80%, two steps) as a colorless oil. $[\alpha]_D^{26}$ = -210.9 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3344, 2966, 2930, 2876, 1748, 1715, 1642, 1498, 1367, 1254, 1170, 1102, 750, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.38-7.32 (m, 5H), 5.25-5.10 (m, 3H), 5.06-4.85 (m, 1H), 4.39 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.55-3.43 (m, 2H), 3.10 (s, 0.33H), 2.89 (s, 2.67H), 2.09-1.99 (m, 1H), 1.97-1.89 (m, 1H), 1.42 (s, 9H), 1.32-1.26 (m, 1H), 1.01-0.94 (m, 1H), 0.93-0.89 (m, 6H), 0.88-0.79 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 198.9, 174.1, 166.7, 156.0, 135.3, 128.7, 128.6, 128.6, 128.5, 128.2, 79.9, 67.3, 65.3, 55.6, 48.0, 31.0, 30.9, 30.8, 28.4, 24.2, 19.7, 17.7, 15.8, 10.6 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{41}N_2O_6^+$: 477.2959, Found: 477.2960.

Benzyl (3*R*,4*S*,5*S*)-4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-*N*,3-dimethylbutanamido)-3-hydroxy-5-methylheptanoate 32. To a cooled (-78 °C) solution of **31** (6.50 g, 13.64 mmol) in MeOH (55 mL) was added KBH_4 (2.58 g, 47.74 mmol) for 3 times, after being stirred for 10 min, the reaction was warmed to -15°C and stirred for another 35 min, then CH_3COOH was added to adjust pH ranging from 9 to 10. The reation mixture was evaporated, extracted with EtOAc (80 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=5:1) to give **32** (5.09 g, 78%) as a colorless oil. $[\alpha]_D^{24}$ = -21.7 (*c* 2.00, $CHCl_3$); IR (film) ν_{max} 3375, 2966, 2932, 2876, 1709, 1626, 1498, 1456, 1366, 1254, 1170, 1102, 750, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.39-7.26 (m, 5H), 5.19-5.05 (m, 3H), 4.46-4.31 (m, 2H), 4.29-4.20 (m, 0.5H), 3.19-3.05 (m, 3H), 2.55-2.27 (m, 2H), 2.14-2.03 (m, 0.5H), 2.02-1.87 (m, 1H), 1.43-1.34 (m, 9H), 1.03-0.95 (m, 6H), 0.94-0.87 (m, 4H), 0.87-0.76 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 174.0 (173.6), 156.1, 135.7, 128.7, 128.5, 128.4, 128.3, 79.7, 67.8 (67.7), 66.6, 59.6 (55.7), 39.2, 32.2 (31.6), 30.9 (31.4), 28.4 (30.7), 25.5 (28.3), 20.0 (19.9), 15.8 (17.6), 15.6 (17.3), 10.9 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{43}N_2O_6^+$: 479.3116, Found: 479.3115.

Benzyl (3*R*,4*S*,5*S*)-4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-*N*,3-dimethylbutanamido)-3-methoxy-5-methylheptanoate 24a. To a cooled (-78 °C) solution of **32** (1.00 g, 2.09 mmol) in HMPA (4.02 mL, 2.30 mmol) and THF (8 mL) was added a solution of LiHMDS (1M in THF, 2.09 mmol) slowly, after being stirred for 30 min, the reaction was warmed to -15 °C and MeOTf (473 μL, 4.18 mmol) was added, then the mixture was stirred for an additional 15 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (60 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=8:1) to give **24a** (618 mg, 60%) as a colorless oil. $[\alpha]_D^{25}$ = -22.4 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3329, 2965, 2929, 2876, 1735, 1172, 1639, 1497, 1366, 1251, 1167, 1102, 751, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.37-7.31 (m, 5H), 5.18-5.14 (m, 1.33H), 5.11-5.05 (m, 1.67H), 4.45-4.40 (m, 1H), 4.39-4.32 (m, 1H), 4.13-4.07 (m, 1H), 3.29-3.27 (m, 3H), 3.07-3.04 (m, 3H), 2.51-2.44 (m, 1H), 2.41-2.34 (m, 1H), 2.04-1.88 (m, 2.67H), 1.66-1.60 (m, 0.33H), 1.42-1.36 (m, 9H), 1.30-1.25 (m, 1H), 0.99-0.97 (m, 3H), 0.96-0.93 (m, 3H), 0.92-0.89 (m, 3H), 0.83-0.75 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz,

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rotamers) δ 174.1 (173.9), 171.8 (172.1), 156.1, 135.9 (136.0), 128.6, 128.5, 128.4, 128.3, 77.8 (79.5), 66.6 (66.5), 60.1 (59.8), 58.6 (58.7), 55.4 (55.6), 37.1 (36.6), 32.1 (32.0), 31.8 (31.6), 31.0 (30.9), 28.4, 25.3 (25.8), 20.0 (19.9), 17.4 (17.6), 15.9 (15.8), 10.8 (10.8) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{45}N_2O_6^+$: 493.3272, Found: 493.3270.

Benzyl (6*S*,9*S*,12*S*,13*R*)-12-((*S*)-sec-butyl)-6,9-diisopropyl-13-methoxy-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate 33. To a cooled (0 °C) solution of **24a** (1.50 g, 3.04 mmol) in DCM (12 mL) was added TFA (1 mL) slowly, after being stirred for 2 h, the mixture was concentrated under reduced pressure. The residue was dissolved in DCM (12 mL), HATU (1.12 g, 3.65 mmol), HOAt (497 mg, 3.65 mmol), DIPEA (3.18 mL, 18.24 mmol), and **5** (793 mg, 3.65 mmol) were added, after being stirred overnight, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=5:1) to give **33** (1.53 g, 85%, two steps) as a colorless oil. $[\alpha]_D^{25}$ = -23.5 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3295, 2965, 2931, 2875, 1736, 1694, 1630, 1523, 1366, 1246, 1165, 1101, 754, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.36-7.32 (m, 5H), 6.54-6.36 (m, 1H), 5.19-5.15 (m, 0.5H), 5.09-5.04 (m, 2.5H), 4.83-4.78 (m, 1H), 4.38-4.32 (m, 1H), 4.11-4.06 (m, 1H), 3.94-3.78 (m, 1H), 3.29-3.26 (m, 3H), 3.05-3.02 (m, 3H), 2.52-2.39 (m, 1H), 2.37-2.24 (m, 1H), 2.06-1.98 (m, 2H), 1.97-1.88 (m, 1.5H), 1.66-1.59 (m, 0.5H), 1.43-1.41 (m, 9H), 1.24-1.11 (m, 1H), 0.98-0.95 (m, 3H), 0.95-0.92 (m, 3H), 0.89-0.86 (m, 6H), 0.81-0.79 (m, 3H), 0.78-0.75 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 173.1 (172.9), 171.6 (171.8), 171.6 (171.5), 155.8, 135.9 (135.8), 128.7 (128.6), 128.7 (128.5), 128.6 (128.4), 79.7 (79.8), 77.7 (59.9), 66.6 (66.7), 60.1 (60.1), 58.6 (58.7), 54.1 (53.8), 36.9 (36.7), 32.1, 31.5 (31.7), 31.4 (31.3), 31.1 (31.2), 28.4, 25.7 (25.4), 20.0 (20.1), 19.4 (19.3), 17.9, 17.4 (17.3), 15.9 (15.8), 10.7 (10.7) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{32}H_{54}N_3O_7^+$: 592.3956, Found: 592.3956.

Benzyl (3*R*,4*S*,5*S*)-4-((*S*)-2-((*S*)-2-(dimethylamino)-3-methylbutanamido)-*N*,3-dimethylbutanamido)-3-methoxy-5-methylheptanoate 34. To a cooled (0 °C) solution of **33** (1.40 g, 2.37 mmol) in DCM (9 mL) was added TFA (1 mL) slowly, after being stirred for 2 h, the mixture was concentrated under reduced pressure, which was dissolved in CH_3CN (9 mL), added 40% HCHO (4 mL, 18.96 mmol) and $Na(BH_3)CN$ (447 mg, 7.11 mmol), after being stirred for 18 h, the reaction mixture was evaporated and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA/NH_4OH=1:1:0.01) to give **34** (1.01 g, 82%, two steps) as a colorless oil. $[\alpha]_D^{25}$ = -20.4 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3303, 2963, 2932, 2874, 2830, 1737, 1633, 1620, 1456, 1164, 1101, 751, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.41-7.29 (m, 5H), 6.87 (d, *J* = 9.2 Hz, 0.5H), 6.78 (d, *J* = 9.2 Hz, 0.5H), 5.20-5.16 (m, 0.5H), 5.10-5.07 (m, 1.5H), 4.89-4.83 (m, 1H), 4.40-4.34 (m, 1H), 4.12-4.09 (m, 1H), 3.30-3.23 (m, 3H), 3.10-3.06 (m, 3H), 2.53-2.39 (m, 2H), 2.38-2.30 (m, 1H), 2.25 (s, 3H), 2,19 (s, 3H), 2.10-1.91 (m, 3.5H), 1.68-1.59 (m, 0.5H), 1.30-1.18 (m, 1H), 1.03-1.00 (m, 3H), 0.99-0.96 (m, 4.5H), 0.95-0.91 (m, 6H), 0.88-0.86 (m, 1.5H), 0.80-0.75 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 172.6, 170.9 (171.2), 170.8, 135.1 (135.2), 127.9, 127.8, 127.6, 76.5 (77.0), 75.9 (75.7), 65.9 (65.7), 59.2 (59.2), 57.9 (57.9), 52.5 (52.9), 42.2 (42.1), 36.3 (35.9), 31.3 (31.4), 30.9 (30.8), 30.3 (30.0), 27.0 (26.9), 24.6 (25.0), 19.5 (19.6), 19.5, 17.2 (17.4), 16.9 (17.1), 15.0 (15.2), 9.9 (9.9) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{50}N_3O_5^+$: 520.3745, Found: 520.3745.

***tert*-Butyl (*S*)-2-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)pyrrolidine-1-carboxylate 35.** To a cooled (0 °C) solution of **8** (484 mg, 1.57 mmol) in MeOH (6 mL) was added HCl/dioxane (500 µL) slowly, after being stirred for 30 min, the mixture was concentrated under reduced pressure. The residue was dissolved in DCM (6 mL), HATU (581 mg, 1.88 mmol), HOAt (256 mg, 1.88 mmol), DIPEA (1.64 mL, 9.42 mmol), and **7** (450 mg, 1.57 mmol) were added, after being stirred overnight, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH=100:1) to give **35** (595 mg, 80%, two steps) as a white solid, m.p. 121-123 °C; $[\alpha]_D^{24}$ = -66.4 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3456, 3288, 2974, 2931, 2873, 1655, 1535, 1454, 1404, 1365, 1168, 1104, 772, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.76-7.73 (m, 1H), 7.28-7.26 (m, 1H), 7.24-7.10 (m, 5.5H), 6.50-6.46 (m, 0.5H), 5.66-5.55 (m, 1H), 3.94-3.85 (m, 0.5H), 3.81-3.74 (m, 0.5H), 3.73-3.70 (m, 0.5H), 3.57-3.47 (m, 1H), 3.42-3.39 (m, 0.5H), 3.37-3.35 (m, 3H), 3.30-3.11 (m, 2.5H), 2.45-2.35 (m, 0.5H), 2.31-2.25 (m, 0.5H), 2.17-2.08 (m, 0.5H), 1.84-1.76 (m, 1H), 1.76-1.64 (m, 2H), 1.62-1.55 (m, 1H), 1.50-1.46 (m, 9H), 1.18-1.12 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 173.4 (174.0), 171.2 (171.7), 154.4 (154.9), 142.6, 136.6 (137.0), 129.5, 129.4, 128.6, 127.1 (126.9), 119.0 (118.9), 83.6 (81.9), 79.9 (79.5), 60.9 (60.7), 58.7 (59.0), 52.0 (52.6), 46.6 (47.0), 44.3 (43.9), 41.5, 28.7, 25.7 (25.1), 24.4 (24.8), 14.2 (13.9) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{36}N_3O_4S^+$: 474.2421, Found: 474.2422.

Dolastatin 10 (1). A solution of **34** (608 mg, 1.17 mmol) and 10% Pd/C (600 mg) were stirred in MeOH (50 mL) for 2 h under H_2 atmosphere. Then, the mixture was filtrated to give a crude acid without further purification. To a cooled (0 °C) solution of **35** (500 mg, 1.06 mmol) in DCM (4 mL) was added TFA (1 mL) slowly, after being stirred for 2 h, the mixture was concentrated. The residue was dissolved in DCM (4 mL), HATU (392 mg, 1.27 mmol), HOAt (173 mg, 1.27 mmol), DIPEA (1.11 mL, 6.36 mmol), and the above crud acid were added, after being stirred for 24 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated. The

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residue was purified by flash chromatography on silica gel (DCM/MeOH=100:1 to 25:1) to give **1** (500 mg, 60%, three steps) as a viscous liquid, which was further treated with acetone /hexane to give white powder, m.p. 89-90 °C, [lit.[4b] 102-106 °C]. $[\alpha]_D^{23}$ = -63.3 (*c* 1.00, MeOH); IR (film) ν_{max} 3443, 3295, 2966, 2932, 2875, 2831, 1634, 1537, 1498, 1454, 1100, 1033, 753, 696, 663 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, rotamers) δ 7.74 (dd, *J* = 7.2, 3.0 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 0.5H), 7.31 (d, *J* = 7.8 Hz, 0.5H), 7.28-7.18 (m, 6H), 6.99-6.91 (m, 1H), 5.62-5.55 (m, 1H), 4.92 (dd, *J* = 9.0, 6.0 Hz, 0.5H), 4.85 (dd, *J* = 9.0, 4.8 Hz, 0.5H), 4.39-4.27 (m, 2H), 4.15-4.05 (m, 1H), 3.89 (dd, *J* = 7.2, 2.4 Hz, 0.5H), 3.79 (dd, *J* = 7.2, 3.0 Hz, 0.5H), 3.47-3.39 (m, 1.5H), 3.39 (s, 1.5H), 3.38-3.36 (m, 0.5H), 3.35 (s, 1.5H), 3.34-3.31 (m, 1H), 3.31 (s, 1.5H), 3.31-3.29 (m, 0.5H), 3.29 (s, 1.5H), 3.28-3.26 (m, 0.5H), 3.13-3.11 (m, 2.5H), 2.49-2.46 (m, 0.5H), 2.46-2.40 (m, 2H), 2.35-2.30 (m, 1H), 2.29 (s, 3H), 2.26 (s, 3H), 2.14-2.00 (m, 4H), 1.98-1.94 (m, 1H), 1.92-1.82 (m, 1H), 1.82-1.75 (m, 1H), 1.74-1.62 (m, 2H), 1.26-1.18 (m, 1H), 1.16-1.11 (m, 3H), 1.10-1.04 (m, 3H), 1.04-0.99 (m, 6H), 0.96-0.92 (m, 6H), 0.80-0.75 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz, rotamers) δ 173.9 (174.2), 173.0 (173.4), 172.0, 171.7 (171.6), 170.5 (170.2), 142.5 (142.5), 137.2 (137.3), 129.6 (129.5), 128.5 (128.5), 126.9 (126.8), 118.9, 81.9 (81.8), 77.6 (76.5), 76.7, 60.7 (60.9), 60.5 (60.6), 59.2, 59.2 (59.3), 53.8 (53.5), 52.7, 47.6 (47.4), 43.9 (43.8), 43.2, 42.9, 41.3 (41.0), 38.4 (38.1), 32.1 (32.4), 32.0 (31.8), 31.2 (30.0), 27.7 (27.7), 26.0 (25.5), 25.2 (25.1), 24.9 (24.6), 20.4 (20.6), 20.3 (20.2), 18.1 (18.1), 17.9 (17.2), 16.1 (15.9), 13.9 (13.6), 10.8(10.6) ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{42}H_{69}N_6O_6S^+$: 785.4994, Found: 785.4996.

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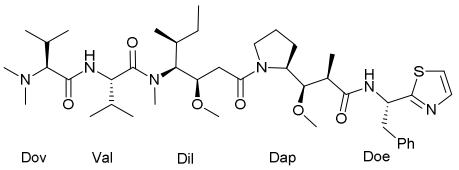
Dolastatin 10 has been effectively synthesized through SmI_2-induced cross-coupling for Dap, asymmetric addition for Doe and an alternative method to Val-Dil.



Dolastatin 10