ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

Cite this: *Org. Chem. Front.*, 2020, **7**, 76

A diastereoselective approach to amino alcohols and application for divergent synthesis of dolastatin 10†

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Received 22nd October 2019,
Accepted 12th November 2019

DOI: 10.1039/c9qo01292c

rsc.li/frontiers-organic

A diastereoselective approach to obtain amino alcohols **10** through SmI_2-induced radical addition of chiral imine **8** with 2-(benzyloxymethylsulfonyl)pyridine **9** is described. This approach was easily used for the synthesis of non-natural amino acid **15**, a flexible key fragment whose utility was demonstrated in the divergent synthesis of dolastatin 10 (**1**) and its nine analogues **31a**, **31c**, **31d**, **31e**, **31f**, **31g**, **40a**, **40b** and **40c** were obtained.

Introduction

Bioactive small peptides derived from peptidic secondary metabolites are a promising class of compounds for drug discovery,[1] due to their interesting biological activities, including antimalarial, antifungal, antimicrobial, cytotoxic and neurotoxic properties.[2] Among them, linear peptides displaying a variety of physiological activities and possessing attractive structures have attracted significant attention in recent years.[3] Several of these bioactive peptides or cyclodepsipeptides were selected as novel pharmaceuticals and are currently being evaluated in human clinical trials for cancer treatment.[4] As a prime instance, dolastatins, a large family of compounds named star molecules, were gradually isolated from the marine mollusk *Dolabella auricularia* over the last 30 years.[5] Among the family, several are of the linear peptide form[6] and several are of the cyclodepsipeptide form (Fig. 1).[7] Most of them exhibit strong activity against a variety of cancers, and the mechanism of action is through a unique mode of action, which is different from that of paclitaxel, vinblastine and epothilones.[8]

Dolastatin 10 (**1**) is one of the star molecules of its family compounds, which shows strong antitumor activity in subnanomolar concentrations against a wide range of tumor cell lines.[9] Structurally, dolastatin 10 (**1**) led to five subunits (Fig. 2): *N*,*N*-dimethyl valine (Dov), L-valine (Val), (3*R*,4*S*,5*S*)-dolaisoleucine (Dil), (2*R*,3*R*,4*S*)-dolaproine (Dap) and protected (*S*)-dolaphenine (Doe) fragments. Due to the extensive biological activity against a variety of cancers and easily modified chemical structures, the synthetic dolastatin 10 (**1**) and its analogues have attracted significant attention and several important synthetic methods have been achieved.[10] But most of the modifications of dolastatin 10 are focused on the Doe and Dov units. As a result, dolastatin 10 (**1**) and its analogues have

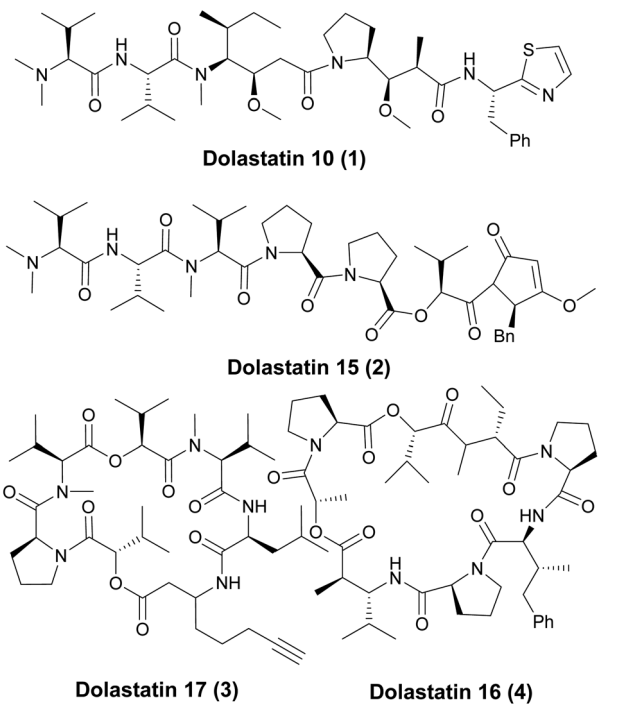

Fig. 1 Several structures of dolastatins.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c9qo01292c

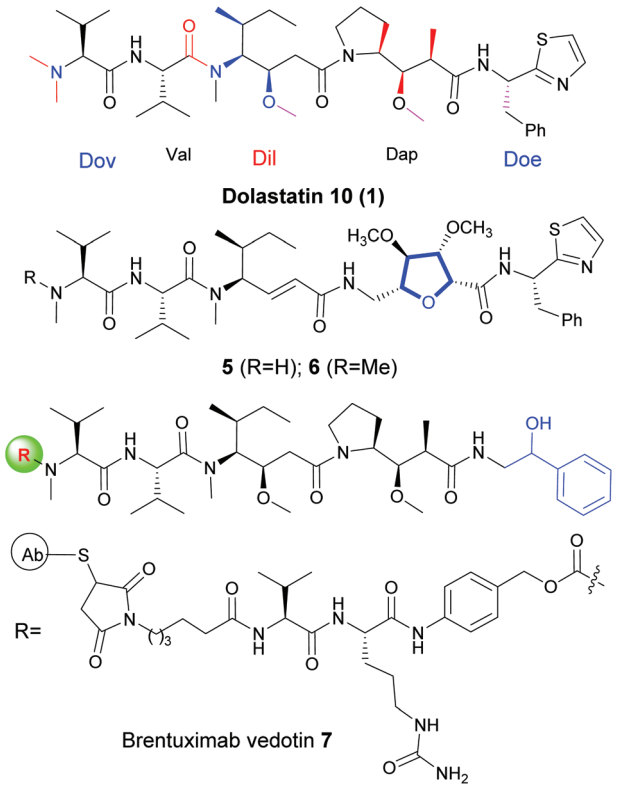


Fig. 2 The structures of dolastatin 10 and its analogues.

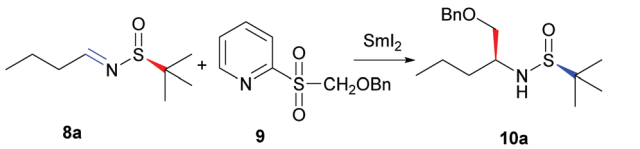
inspired the design of auristatin as the potent 'warhead' component of antibody–drug conjugates (ADC) which has been approved as the antineoplastic agent for cancer chemotherapy and was evaluated in clinical trials in recent years.[11] There are also a few modifications for Dap fragments.[12] However, to the best of our knowledge, structural modifications for the Dil unit are not well studied, and the main reason is that the Dil fragment is difficult to synthesize. Moreover, another tricky reason for the synthesis of dolastatin 10 is the effective condensation between the Dil and Dov-Val fragments.[10c]

In recent years, we have been focusing on the divergent synthesis of bioactive secondary metabolites,[13] and very recently, we have established a diverse approach to obtain dolastatin 10 through a SmI_2-induced cross-coupling process to obtain the Dap fragment.[13d] As a continuation of our interest in developing the divergent synthesis of dolastatins and investigating their structure–activity relationships, herein, we present an asymmetric approach to obtain the Dil fragment and divergent synthesis of more analogues of dolastatin 10 (**1**).

Results and discussion

As shown in Table 1, our investigation started with an effective method to obtain the Dil subunit of dolastatin 10. Commercialized chiral *N-tert*-butanesulfinamide has been undoubtedly one of the most efficient classes of auxiliaries in the past decade,[14] and we decided to investigate an asymmetric process through the SmI_2-induced radical addition of chiral imine **8a** with 2-(benzyloxymethylsulfonyl)pyridine **9**. The imine **8a** was easily prepared through oxidation and following condensation with *N-tert*-butanesulfinamide,[15] and 2-(benzyloxymethylsulfonyl)pyridine **9** was synthesized through a known procedure.[16] When a mixture of **8a** (0.5 mmol) and 2-(benzyloxymethylsulfonyl)pyridine **9** (0.75 mmol) was treated with newly prepared SmI_2 (0.1 M in THF), the desired product **10a** was not produced (Table 1, entry 1). Even when the amount of **9** (1.0 mmol) or SmI_2 was increased, the results were still fruitless (Table 1, entries 2 and 3). When a solution of 2-(benzyloxymethylsulfonyl)pyridine **9** in THF was dropped into the mixture of imine **8a** with SmI_2 and stirred for 30 min, the desired product was obtained in 42% yield with high diastereoselectivity (Table 1, entry 4). Different amounts of 2-(benzyloxymethylsulfonyl)pyridine **9** and SmI_2 were screened, and the results are summarized in Table 1 (Table 1, entries 5–8). Although the best yield is 67%, the diastereoselectivity is excellent (Table 1, entry 6).

Table 1 Optimization of reaction conditions

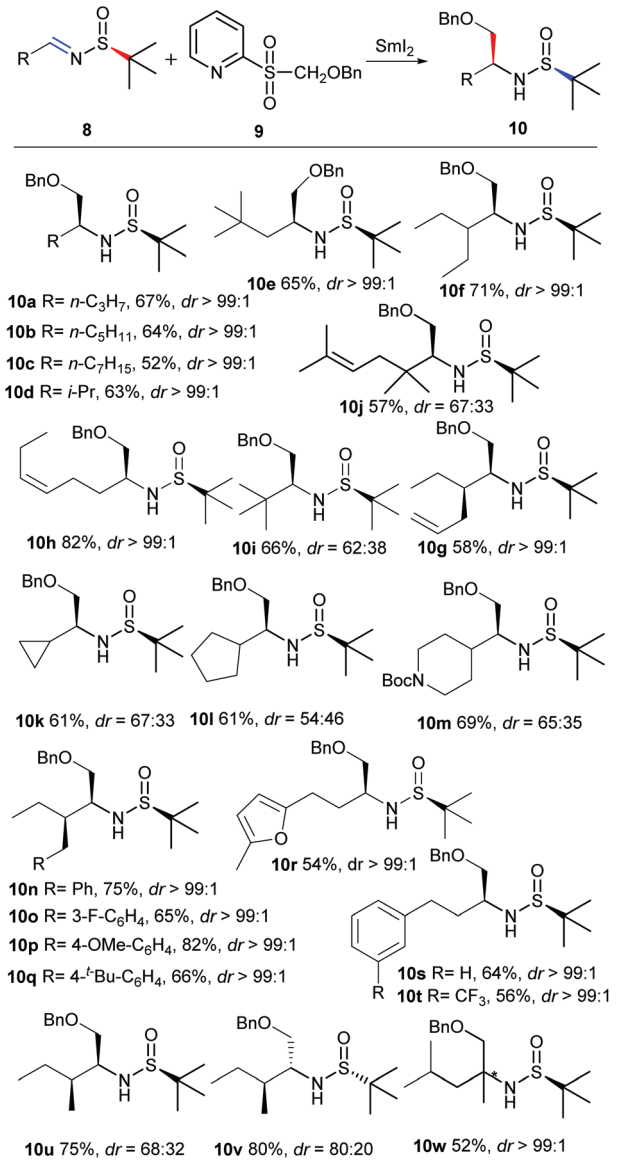


8a 9 10a

Entry[a]	SmI_2 (equiv.)	**9** (equiv.)	Yield[b] (%)	dr[c]
1[d]	4.0	1.5	Trace	—
2[d]	4.0	3.0	Trace	—
3[d]	6.0	3.0	Trace	—
4	4.0	1.5	42	99 : 1
5	4.0	3.0	47	99 : 1
6	6.0	3.0	67	99 : 1
7	6.0	2.0	45	99 : 1
8	6.0	2.5	56	99 : 1

[a] 2-(Benzyloxymethylsulfonyl)pyridine **9** (in THF) was dropped into the mixture of imine **8a** (0.5 mmol) with SmI_2, and then stirred for 30 min at room temperature. [b] Isolated yield. [c] dr values were determined by ^1H NMR of crude products. [d] The new prepared SmI_2 (0.1 M in THF) was dropped into a mixture of **8a** with 2-(benzyloxymethylsulfonyl)pyridine **9**.

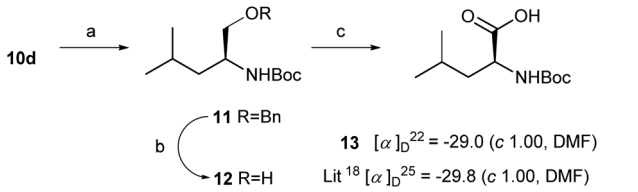
Next, we turned to investigate the scope and limitation of this asymmetric radical addition of imines **8b–8w** with 2-(benzyloxymethylsulfonyl)pyridine **9**. Different substituted linear alkyl imines **8a–8h** were surveyed under the optimal conditions, as summarized in Scheme 1. In general, the reactions with various substituted linear alkyl imines **8a–8h** proceeded smoothly in moderate yields with excellent diastereoselectivities (dr > 99 : 1). When *tert*-butyl type imines **8i** and **8j** were investigated, the results showed that the desired **10i–10j** could be produced in moderate yields with low diastereoselectivities. Cyclic alkyl substituted imines **8k–8m** were also studied, and it was found that the diastereoselectivities of **10k–10m** are still low. Several aryl including furan substituted linear alkyl imines **8n–8t** were also examined, affording the desired products in moderate yields with excellent diastereo-



Scheme 1 The addition of imines **8** with 2-(benzyloxymethylsulfonyl) pyridine **9**. The reactions were performed with **8** (0.5 mmol), **9** (1.5 mmol) and SmI_2 (3.0 mmol, 0.1 M in THF) in dry THF (2 mL) at room temperature for 30 min. Isolated yield. dr values were determined by ^1H NMR of crude products or column chromatography.

selectivities. When **8u**, a compound containing chiral α-methyl imine, was investigated, the desired **10u** was obtained with low diastereoselectivity. To confirm the effect of different chiral auxiliaries in imine, **8v** was also studied and the result suggested that the chiral sulfinamide moiety determined the stereocontrol of this addition process in this example (**10v**). Imine **8w** derived from a ketone was also examined, and the desired product **10w** was obtained in moderate yield with high diastereoselectivity. Despite our great efforts to determine the stereochemistry of the newly generated chiral center, the result is fruitless.

To confirm the stereochemistry of **10a–10v**, compound **10d** was easily transformed to the known **13**. The treatment of **10d** with HCl/dioxane in methanol and subsequent protection

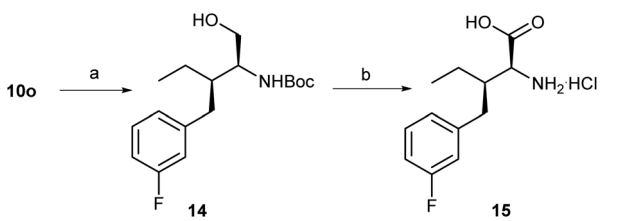


Scheme 2 The synthesis of known compound **13**. Reagents and conditions: a. (1) HCl/dioxane, MeOH, 30 min; (2) Boc_2O, TEA, DCM, overnight, 67%, two steps; b. Pd/C, H_2, MeOH, rt, 4 h, 81%; c. (1) Dess–Martin periodinane, DCM, rt, 30 min; (2) $NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$, 2-methyl-2-butene/*t*-BuOH, rt, 8 h, 70%, two steps.

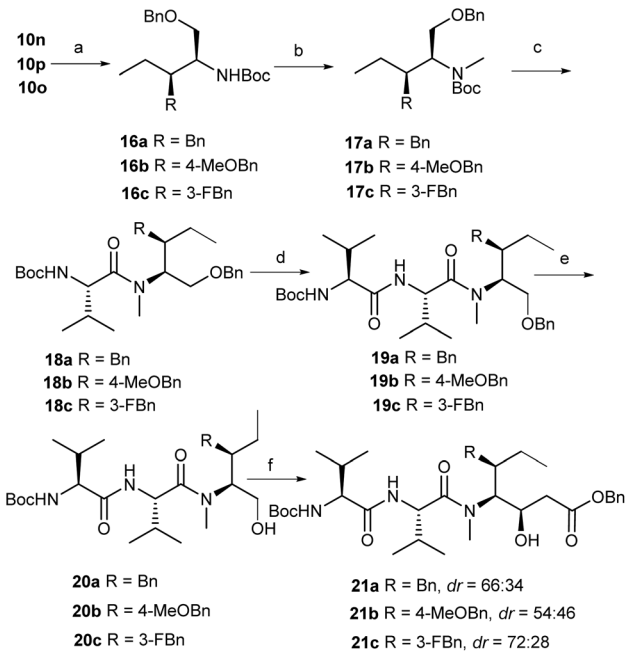
(Boc_2O) afforded ester **11** in 67% overall yield (Scheme 2). The deprotection (Pd/C, H_2) of **11** gave alcohol **12** in 81% yield. Dess–Martin oxidation[17] and subsequent Pinnick oxidation ($NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$)[18] gave the known **13** {$[\alpha]_D^{22}$ = −29.0 (*c*, 1.00, DMF), lit.[19] $[\alpha]_D^{25}$ = −29.8 (*c* 1.00, DMF)} in 70% overall yield. The spectroscopic and physical data of the synthetic **13** were identical to the reported data.[19] Thus the new stereochemistry of product **10d** was unambiguously determined as the *S*-form.

With **10o** in hand, another non-natural amino acid **15** was considered as shown in Scheme 3. The removal of the chiral auxiliary (HCl/dioxane) of **10o** and protection (Boc_2O) gave an ester, which was deprotected with hydrogen (H_2) in the presence of Pd/C to obtain alcohol **14** in 88% overall yield (Scheme 3). Dess–Martin oxidation and subsequent Pinnick oxidation ($NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$) generated a crude acid without further purification, which was treated with dry hydrogen chloride in methanol to obtain the desired amino acid hydrochloride **15** {$[\alpha]_D^{25}$ = −33.6 (*c* 0.50, MeOH)} in 66% overall yield.

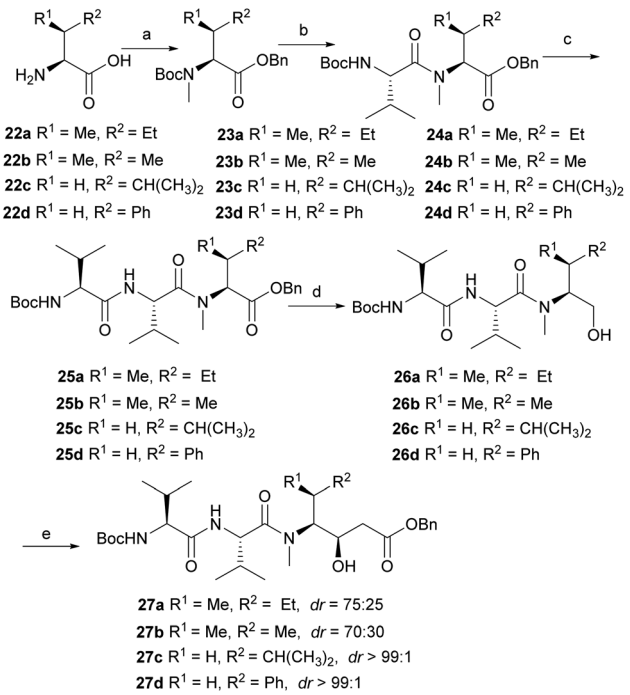
We turned our attention to utilize this diastereoselective approach in the synthesis of Dov-Val–Dil fragments of dolastatin 10 (**1**) analogues (Scheme 4). The deprotection (HCl/dioxane) of **10n** and subsequent protection (Boc_2O/TEA) gave ester **16a** in 65% yield. The methylation of **16a** with methyl trifluoromethanesulfonate (MeOTf)[10c] in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) produced the desired compound **17a** in 81% yield. The deprotection (TFA/DCM) of **17a** and condensation (HATU/DIPEA) with *N*-Boc-L-Val-OH gave the desired amide **18a** in 94% yield. The crude amine salt, pre-



Scheme 3 The synthesis of non-natural amino acid **15**. Reagents and conditions: a. (1) HCl/dioxane, MeOH, 30 min; (2) Boc_2O, TEA, DCM, overnight; (3) Pd/C, H_2, MeOH, 4 h, 88%, three steps; b. (1) Dess–Martin periodinane, DCM, rt, 30 min; (2) $NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$, 2-methyl-2-butene/*t*-BuOH, rt, 8 h; (3) HCl/MeOH (3 M), 2 h, 66%, three steps.



Scheme 4 The synthesis of Dov-Val–Dil fragment precursors **21a**, **21b**, and **21c**. Reagents and conditions: a. (1) HCl/dioxane, MeOH, 30 min; (2) Boc_2O, TEA, DCM, overnight, 65% for **16a**, 75% for **16b**, 76% for **16c**, two steps; b. LiHMDS, HMPA, THF, −78 °C, 30 min, and then MeOTf, −15 °C, 20 min, 81% for **17a**, 95% for **17b**, 93% for **17c**; c. (1) TFA, DCM, rt, 3 h; (2) *N*-Boc-L-Val-OH, HATU, DIPEA, DCM, rt, 7 h, 94% for **18a**, 80% for **18b**, 85% for **18c**; d. (1) TFA, DCM, rt, 3 h; (2) *N*-Boc-L-Val-OH, HATU, DIPEA, DCM, rt, 7 h, 87% for **19a**, 86% for **19b**, 88% for **19c**; e. Pd/C, H_2, MeOH, 4 h, 82% for **20a**, 80% for **20b**, 83% for **20c**; f. (1) Dess–Martin periodinane, DCM, rt, 30 min; (2) LDA, benzyl acetate, THF, −78 °C, 30 min, 53% for **21a** (dr = 66 : 34), 61% for **21b** (dr = 54 : 46), 72% for **21c** (dr = 72 : 28), two steps.

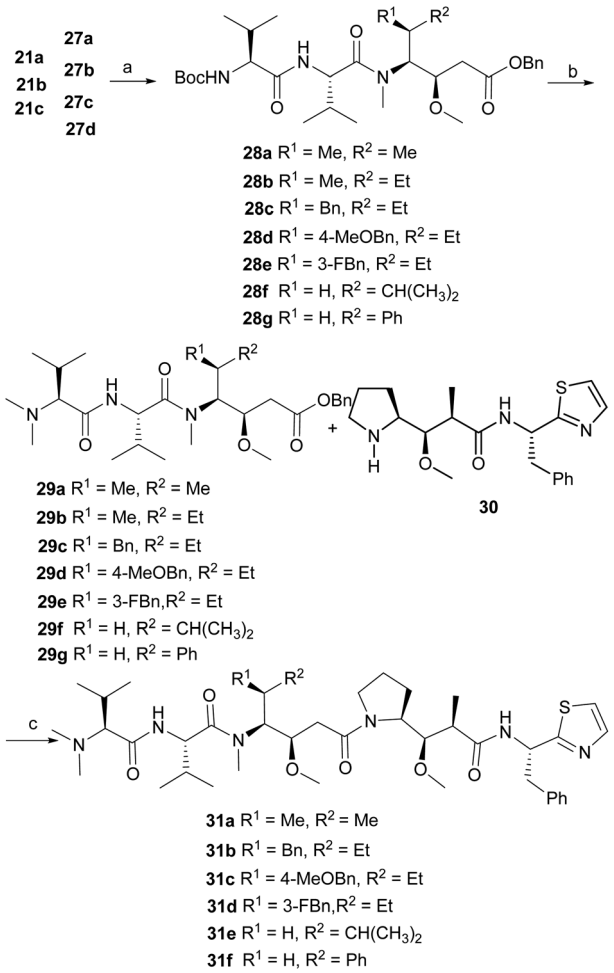


Scheme 5 The synthesis of Dov-Val–Dil fragment precursors **27a**, **27b**, **27c**, and **27d**. Reagents and conditions: a. (1) Boc_2O, NaOH, H_2O/dioxane, overnight; (2) NaH, MeI, THF, rt, 48 h; (3). BnBr, K_2CO_3, DMSO, rt, overnight, 40% for **23a**, 42% for **23b**, 41% for **23c**, 40% for **23d**, three steps; b. (1) TFA, DCM, rt, 3 h; (2) *N*-Boc-L-Val-OH, HATU, DIPEA, DCM, rt, 7 h, 82% for **24a**, 70% for **24b**, 77% for **24c**, 68% for **24d**, two steps; c. (1) TFA, DCM, rt, 3 h; (2) *N*-Boc-L-Val-OH, HATU, DIPEA, DCM, rt, 7 h, 94% for **25a**, 92% for **25b**, 90% for **25c**, 87% for **25d**, two steps; d. $LiHBEt_3$, THF, 0 °C–rt., 90% for **26a**, 90% for **26b**, 60% for **26c**, 59% for **26d**; e. (1) Dess–Martin periodinane, DCM, rt, 30 min; (2) LDA, benzyl acetate, THF, −78 °C, 30 min, 63% for **27a** (dr = 75 : 25), 57% for **27b** (dr = 70 : 30), 65% for **27c** (dr > 99 : 1), 71% for **27d** (dr > 99 : 1), two steps.

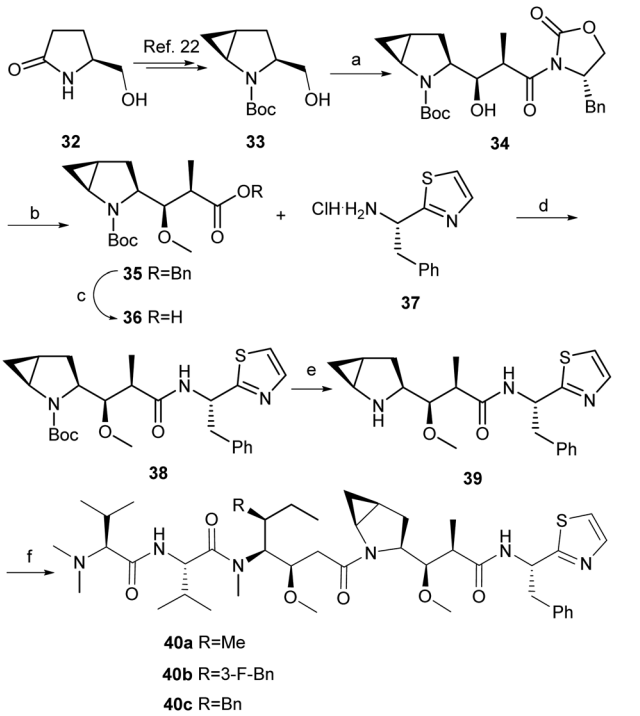
pared by the removal of the Boc group in **18a** (TFA), was directly coupled with *N*-Boc-L-Val-OH (HATU/DIPEA) to give tripeptide **19a** in 87% yield. The hydrogenation (Pd/C, H_2) of **19a** gave alcohol **20a** in 82% yield. Upon the Dess–Martin oxidation of the hydroxy group in **20a**, the subsequent addition with benzyl acetate in the presence of lithium diisopropylamide (LDA) gave the desired alcohol **21a** in 73% yield with low diastereoselectivity (dr = 66 : 34). Following the similar synthetic sequence described above, two analogues of Dov-Val–Dil fragment precursors **21b** and **21c** (dr = 54 : 46 for **21b**, dr = 72 : 28 for **21c**) in 24% and 32% respective overall yields were successfully achieved in parallel.

To obtain more diverse fragments of Dov-Val–Dil, several commercial amino acids **22a**, **22b**, **22c** and **22d** were also selected as the starting material. As shown in Scheme 5, continuous sequential protection of amino acids gave esters **23a**, **23b**, **23c** and **23d** in 40%, 42%, 41%, and 40% respective yields. Then through the key condensation and asymmetric addition as described in Scheme 4, four other analogues of Dov-Val–Dil fragment precursors **27a–27d** (dr = 75 : 25 for **27a**, dr = 70 : 30 for **27b**, dr > 99 : 1 for **27c**, dr > 99 : 1 for **27d**) in 44%, 33%, 27%, 25% respective overall yields were also successfully obtained in parallel.

With a series of Dov-Val–Dil fragment precursors in hand, we then turned our attention to synthesize the dolastatin 10 (**1**) analogues. As shown in Scheme 6, **27b** was firstly methylated with methyl trifluoromethanesulfonate (MeOTf) in the presence of bis(trimethylsilyl)amine lithium (LiHMDS) to give protected dipeptide **28a** in 55% yield. The removal (TFA/DCM) of Boc in **28a** and subsequent dimethylation[20] (40% HCHO, $Na(BH_3)CN$) gave Dov-Val–Dil fragment **29a** in 70% yield. Upon the hydrogenation (Pd/C, H_2) of Bn in **29a**, the crude acid was directly amidated with our previously prepared Dap–Doe amine **30**[13d] in the presence of HATU and DIPEA to give dolastatin 10 analogue **31a** as a viscous liquid, which was further treated with acetone/hexane to give a white powder {mp 94–95 °C; $[\alpha]_D^{22}$ = −214.4 (*c* 0.125, $CHCl_3$)} in 50% isolated yield. Finally, following a similar synthetic sequence described above, five other analogues of dolastatin 10 **31b** {$[\alpha]_D^{26}$ = −39.2 (*c* 0.25, $CHCl_3$)}, **31c** {$[\alpha]_D^{26}$ = −35.2 (*c* 0.25, $CHCl_3$)}, **31d** {$[\alpha]_D^{26}$ = −41.5 (*c* 1.00, $CHCl_3$)}, **31e** {$[\alpha]_D^{23}$ = −5.6 (*c* 0.50, $CHCl_3$)}, and **31f** {$[\alpha]_D^{23}$ = −26.4 (*c* 0.125, $CHCl_3$)}were successfully achieved in 25%, 22%, 27%, 14%, and 12% respective overall yields in parallel. The structures of analogues **31a**, **31b**, **31c**, **31d**, **31e** and **31f** were overall confirmed by spectroscopic data.



Scheme 6 The divergent synthesis of dolastatin 10 (**1**). Reagents and conditions: a. LiHMDS, HMPA, THF, −78 °C, 30 min, and then MeOTf, −15 °C, 15 min, 55% for **28a**, 53% for **28b**, 77% for **28c**, 73% for **28d**, 67% for **28e**, 50% for **28f**, 44% for **28g**; b. (1) TFA, DCM, rt, 2 h; (2) 40% HCHO, $Na(BH_3)CN$, MeCN, rt, 10 h, 70% for **29a**, 70% for **29b**, 77% for **29c**, 89% for **29d**, 91% for **29e**, 65% for **29f**, 60% for **29g**, two steps; c. (1) Pd/C, H_2, MeOH, 4 h; (2) HATU, DIPEA, DCM, rt, 12 h, 50% for **31a**, 42% for **31b**, 34% for **31c**, 45% for **31d**, 42% for **31e**, 45% for **31f**, two steps.



Scheme 7 The synthesis of three analogues **40a**, **40b**, and **40c**. Reagents and conditions: a. (1) Dess–Martin periodinane, DCM, rt, 30 min; (2) Bu_2BOTf, TEA, DCM, −78 °C to rt, 60%, two steps; b. (1) LiOH, H_2O_2, THF/H_2O; (2) BnBr, K_2CO_3, DMF; (3) LiHMDS, HMPA, MeOTf, THF, 81%, three steps; c. Pd/C, H_2, MeOH, 4 h; d. HATU, DIPEA, DCM, rt, 7 h, 75%; e. TFA, DCM, 2 h; f. (1) **29b**, **29c**, **29e**, Pd/C, H_2, MeOH, 4 h; (2) HATU, DIPEA, DCM, rt, 12 h, 31% for **40a**, 28% for **40b**, 45% for **40c**.

In light of our interest in diversity-oriented synthesis,[21] we decided to prepare several analogues of dolastatin 10 containing a cyclopropane skeleton. As shown in Scheme 7, the cyclopropanated amino alcohol **33** was easily prepared from the commercialized (*S*)-(+)-5-hydroxymethyl-2-pyrrolidinone **32** by a known procedure.[22] The hydroxy group in **33** was oxidized to the corresponding aldehyde without further purification, which was directly converted to compound **34** with two stereocenters according to a known procedure using the well-established Evans' asymmetric aldol methodology[23] in 60% yield with excellent diastereoselectivity (dr > 99 : 1). Hydrolysis (LiOH, H_2O_2), protection ($BnBr/K_2CO_3$) and following methylation (MeOTf/LiHMDS) produced the protected ether **35** in 81% yield. The hydrogenation (Pd/C, H_2) of **35** gave crude acid **36** without further purification, which was directly coupled with our previously prepared chiral salt **37** [13d] in the presence of HATU and DIPEA to generate **38** in 75% yield. Upon the deprotection (TFA, DCM) of Boc in **38**, the crude amine was directly condensed separately with free acids of **29b**, **29c** and **29e** to obtain three analogues of dolastatin 10 **40a** $\{[\alpha]_D^{24} = -38.0$ (*c* 0.10, $CHCl_3)\}$, **40b** $\{[\alpha]_D^{26} = -22.0$ (*c* 0.25, $CHCl_3)\}$, and **40c** $\{[\alpha]_D^{24} = -30.2$ (*c* 0.50, $CHCl_3)\}$ in 31%, 28%, and 45% respective yields in parallel. The structures of analogues **40a**, **40b** and **40c** were overall confirmed by spectroscopic data.

Conclusions

In summary, a diastereoselective approach to obtain amino alcohols **10** which were easily converted to non-natural amino acids through SmI_2-induced radical addition of chiral imines **8** with 2-(benzyloxymethylsulfonyl)pyridine **9** has been developed. Moreover, this novel approach was used to prepare the key fragment-Dil of dolastatin 10 analogues. Using this strategy, nine dolastatin 10 analogues **31a**, **31b**, **31c**, **31d**, **31e**, **31f**, **40a**, **40b** and **40c** have been synthesized. It is worth mentioning that several analogues containing divergent Dil subunits have been synthesized for the first time. Further chemistry and related biological data will be published in due course.

Experimental

General

THF was distilled from sodium/benzophenone. The reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with a 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 an LTQ-Orbitrap-XL apparatus. IR spectra were recorded using a 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.

General procedure for the synthesis of 8a–8u

To a solution of (*S*)-2-methyl-2-propane-sulfinamide (606 mg, 5.00 mmol) and aldehyde (5.00 mmol) in DCM (100 mL) was added anhydrous cupric sulfate (1.59 g, 10 mmol) and PPTS (63 mg, 0.25 mmol) in one portion, and the mixture was stirred for 24 h. The resulting mixture was filtered, and the filtrate was concentrated to give the crude product, which was purified by flash chromatography on silica gel (PE/EA = 15 : 1) to give the title product (**8a–8u**).

(*S*,*E*)-*N*-Butylidene-2-methylpropane-2-sulfinamide (8a)

Colorless oil (572 mg, 65%); $[\alpha]_D^{25}$ +267 (*c* 1.00, $CHCl_3$), lit.[24]{$[\alpha]_D^{20}$ +303.5 (*c* 1.00, $CHCl_3$)}; IR (film): ν_{max} 2961, 1622, 1363, 1085, 587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 5.2, 4.4 Hz, 1H), 2.53–2.48 (m, 2H), 1.71–1.65 (m, 2H), 1.20 (s, 9H), 1.00 (t, *J* = 7.6 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.6, 56.5, 38.0, 22.3, 18.9, 13.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_8H_{18}NOS^+$, 176.1104, found: 176.1102.

(*S*,*E*)-*N*-Hexylidene-2-methylpropane-2-sulfinamide (8b)

Colorless oil (755 mg, 74%); $[\alpha]_D^{25}$ +282 (*c* 1.00, $CHCl_3$), lit.[25]{$[\alpha]_D$ +240.3 (*c* 1.00, $CHCl_3$)}; IR (film): ν_{max} 2957, 1622, 1363, 1087, 583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10–8.03 (m, 1H), 2.55–2.47 (m, 2H), 1.67–1.58 (m, 2H), 1.37–1.32 (m, 4H), 1.20 (s, 9H), 0.94–0.86 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 56.6, 36.2, 31.5, 25.3, 22.5, 14.0 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{22}NOS^+$, 204.1417, found: 204.1419.

(*S*,*E*)-2-Methyl-*N*-octylidenepropane-2-sulfinamide (8c)

Colorless oil (720 mg, 62%); $[\alpha]_D^{25}$ +207 (*c* 1.00, $CHCl_3$), lit.[24]{$[\alpha]_D^{20}$ +177.0 (*c* 1.00, $CHCl_3$)}; IR (film): ν_{max} 2926, 1621, 1455, 1087, 583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 5.2, 4.4 Hz, 1H), 2.54–2.49 (m, 2H), 1.67–1.57 (m, 2H), 1.38–1.26 (m, 8H), 1.20 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 56.5, 36.2, 31.7, 29.3, 29.1, 25.6, 22.7, 22.4, 14.1 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{26}NOS^+$, 232.1730, found: 232.1730.

(*S*,*E*)-2-Methyl-*N*-(3-methylbutylidene)propane-2-sulfinamide (8d)

Colorless oil (789 mg, 83%); $[\alpha]_D^{25}$ +282 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2959, 1621, 1363, 1085, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 5.2, 4.4 Hz, 1H), 2.44–2.38 (m, 2H), 2.13–2.01 (m, 1H), 1.21 (s, 9H), 1.02–1.00 (m, 3H), 1.00–0.98 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 56.5, 45.0, 26.2, 22.6, 22.5, 22.4 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_9H_{20}NOS^+$, 190.1260, found: 190.1262.

(*S*,*E*)-*N*-(3,3-Dimethylbutylidene)-2-methylpropane-2-sulfinamide (8e)

Colorless oil (887 mg, 87%); $[\alpha]_D^{25}$ +267 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2958, 1619, 1364, 1092, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.45–2.38 (m, 2H), 1.23–1.19 (m, 9H), 1.05–1.01 (m, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.0, 56.7, 49.9, 31.5, 29.9, 22.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{22}NOS^+$, 204.1417, found: 204.1416.

(*S*,*E*)-*N*-(2-Ethylbutylidene)-2-methylpropane-2-sulfinamide (8f)

Colorless oil (898 mg, 88%); $[\alpha]_D^{25}$ +279 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2963, 1619, 1458, 1086, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 6.0, 2.0 Hz, 1H), 2.42–2.33 (m, 1H), 1.64–1.57 (m, 4H), 1.23–1.21 (m, 9H), 0.94–0.89 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 56.5, 48.8, 24.6, 22.5, 11.7, 11.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{22}NOS^+$, 204.1417, found: 204.1416.

(*S*,*E*)-*N*-((*R*)-2-Ethylpent-4-enylidene)-2-methylpropane-2-sulfinamide (8g)

Colorless oil (799 mg, 74%); $[\alpha]_D^{25}$ +270 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2963, 1619, 1363, 1086, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96–7.90 (m, 1H), 5.81–5.68 (m, 1H), 5.12–5.01 (m, 2H), 2.60–2.49 (m, 1H), 2.40–2.27 (m, 2H), 1.66–1.58 (m, 2H), 1.20 (s, 9H), 0.94 (t, *J* = 7.6 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.4, 135.4, 117.0, 56.5, 46.7, 35.8, 24.5, 22.4, 11.4 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{22}NOS^+$, 216.1417, found: 216.1415.

(*S*,*E*)-*N*-((*Z*)-Hept-4-enylidene)-2-methylpropane-2-sulfinamide (8h)

Colorless oil (929 mg, 86%); $[\alpha]_D^{25}$ +247 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2961, 1622, 1456, 1086, 583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09–8.04 (m, 1H), 5.48–5.39 (m, 1H), 5.38–5.28 (m, 1H), 2.62–2.55 (m, 2H), 2.40–2.33 (m, 2H), 2.10–2.01 (m, 2H), 1.21–1.18 (m, 9H), 1.00–0.94 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.2, 133.4, 126.9, 56.6, 36.3, 23.2, 22.4, 20.7, 14.3 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{22}NOS^+$, 216.1417, found: 216.1414.

(*S*,*E*)-*N*-(2,2-Dimethylpropylidene)-2-methylpropane-2-sulfinamide (8i)

Colorless oil (799 mg, 84%); $[\alpha]_D^{25}$ +287 (*c* 1.00, $CHCl_3$), lit.[26]{$[\alpha]_D$ +267.1 (*c* 0.70, $CHCl_3$)}; IR (film): ν_{max} 2963, 1620,

1474, 1363, 1086, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (brs, 1H), 1.18 (s, 9H), 1.16 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.6, 56.4, 37.9, 26.7, 22.3 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_9H_{20}NOS^+$, 190.1260, found: 190.1262.

(*S*,*E*)-2-Methyl-*N*-(2,2,5-trimethylhex-4-enylidene)propane-2-sulfinamide (8j)

Colorless oil (781 mg, 64%); $[\alpha]_D^{25}$ +212 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2965, 1619, 1385, 1089, 588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93–7.90 (m, 1H), 5.15–5.07 (m, 1H), 2.23–2.16 (m, 2H), 1.70–1.68 (m, 3H), 1.62–1.60 (m, 3H), 1.20–1.18 (m, 9H), 1.14–1.12 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.7, 134.5, 119.6, 56.6, 42.1, 38.5, 26.1, 24.6, 24.3, 22.4, 18.0 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{26}NOS^+$, 244.1730, found: 244.1731.

(*S*,*E*)-*N*-(Cyclopropylmethylene)-2-methylpropane-2-sulfinamide (8k)

Colorless oil (714 mg, 82%); $[\alpha]_D^{25}$ +410 (*c* 1.00, $CHCl_3$), lit.[27]{$[\alpha]_D$ +332 (*c* 0.50, CH_2Cl_2)}; IR (film): ν_{max} 2960, 1616, 1363, 1080, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 1H), 2.02–1.96 (m, 1H), 1.19 (s, 9H), 1.12–1.07 (m, 2H), 0.98–0.94 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.8, 56.7, 22.3, 17.6, 8.6, 8.5 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_8H_{16}NOS^+$, 174.0947, found: 174.0945.

(*S*,*E*)-*N*-(Cyclopentylmethylene)-2-methylpropane-2-sulfinamide (8l)

Colorless oil (717 mg, 71%); $[\alpha]_D^{25}$ +261 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2956, 1619, 1474, 1084, 584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01–7.98 (m, 1H), 2.99–2.92 (m, 1H), 1.94–1.85 (m, 2H), 1.73–1.65 (m, 6H), 1.20–1.18 (m, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.6, 56.5, 45.7, 30.0, 29.9, 25.6, 25.6, 22.4 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{20}NOS^+$, 202.1260, found: 202.1262.

(*S*,*E*)-*tert*-Butyl 4-((2-methylpropan-2-ylsulfinamido)methyl) piperidine-1-carboxylate (8m)

Colorless oil (1.14 g, 72%); $[\alpha]_D^{25}$ +138 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3444, 2975, 1692, 1423, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 4.0 Hz, 1H), 4.15–4.02 (m, 2H), 2.94–2.82 (m, 2H), 2.67–2.56 (m, 1H), 1.92–1.84 (m, 2H), 1.59–1.49 (m, 2H), 1.46 (s, 9H), 1.19 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 154.8, 79.8, 56.7, 42.2, 28.5, 28.4, 22.4 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{29}N_2O_3S^+$, 317.1893, found: 317.1899.

(*S*)-*N*-((*R*,*E*)-2-Benzylbutylidene)-2-methylpropane-2-sulfinamide (8n)

Colorless oil (1.16 g, 87%); $[\alpha]_D^{25}$ +143 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2961, 1620, 1495, 1363, 1124, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97–7.88 (m, 1H), 7.30–7.21 (m, 2H), 7.19–7.12 (m, 3H), 2.93–2.81 (m, 3H), 1.68–1.56 (m, 2H), 1.06–0.99 (m, 9H), 0.99–0.91 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.2, 139.2, 129.1, 128.5, 126.3, 56.6, 48.9, 38.1, 25.0, 22.3, 11.6 ppm; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{24}NOS^+$, 266.1573, found: 266.1576.

(*S*)-*N*-((*R*,*E*)-2-(3-Fluorobenzyl)butylidene)-2-methylpropane-2-sulfinamide (8o)

Colorless oil (1.16 g, 82%); $[\alpha]_D^{25}$ +141 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2963, 1619, 1589, 1488, 1363, 1083, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 5.6 Hz, 1H), 7.25–7.16 (m, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.91–6.83 (m, 2H), 2.91–2.78 (m, 3H), 1.69–1.57 (m, 2H), 1.05 (s, 9H), 0.95 (t, *J* = 7.6 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.8, 163.0 (d, *J* = 244.3 Hz), 141.9 (d, *J* = 7.2 Hz), 130.0 (d, *J* = 8.3 Hz), 124.8 (d, *J* = 2.2 Hz), 116.0 (d, *J* = 20.9 Hz), 113.3 (d, *J* = 20.9 Hz), 56.7, 48.7, 37.8, 25.1, 22.3, 11.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.6 ppm; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{23}FNOS^+$, 284.1479, found: 284.1480.

(*S*)-*N*-((*R*,*E*)-2-(4-Methoxybenzyl)butylidene)-2-methylpropane-2-sulfinamide (8p)

Colorless oil (1.23 g, 83%); $[\alpha]_D^{25}$ +130 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3447, 2960, 1698, 1661, 1513, 1363, 1247, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 5.6 Hz, 1H), 7.10–7.05 (m, 2H), 6.82–6.77 (m, 2H), 3.77 (s, 3H), 2.88–2.80 (m, 1H), 2.80–2.73 (m, 2H), 1.65–1.55 (m, 2H), 1.05 (s, 9H), 0.94 (t, *J* = 7.6 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.5, 158.3, 131.3, 130.1, 114.1, 56.7, 55.4, 49.2, 37.4, 25.0, 22.4, 11.7 ppm; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{26}NO_2S^+$, 296.1679, found: 296.1680.

(*S*,*E*)-*N*-((*R*)-2-(4-*tert*-Butylbenzyl)butylidene)-2-methylpropane-2-sulfinamide (8q)

Colorless oil (1.21 g, 75%); $[\alpha]_D^{25}$ +104 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2961, 1620, 1363, 1086, 589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.87 (m, 1H), 7.28–7.24 (m, 2H), 7.12–7.07 (m, 2H), 2.84–2.81 (m, 3H), 1.66–1.58 (m, 2H), 1.28 (s, 9H), 0.99 (s, 9H), 0.95 (t, *J* = 7.6 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.4, 149.1, 136.0, 128.8, 125.4, 56.5, 49.0, 37.8, 34.4, 31.4, 25.3, 22.3, 11.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{32}NOS^+$, 322.2199, found: 322.2203.

(*S*,*E*)-2-Methyl-*N*-(3-(5-methylfuran-2-yl)propylidene)propane-2-sulfinamide (8r)

Yellow oil (944 mg, 78%); $[\alpha]_D^{25}$ +208 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2957, 1623, 1363, 1086, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 4.0, 3.2 Hz, 1H), 5.90–5.87 (m, 1H), 5.84–5.82 (m, 1H), 2.96–2.92 (m, 2H), 2.88–2.84 (m, 2H), 2.23 (s, 3H), 1.16 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.3, 152.2, 150.7, 106.2, 106.0, 56.7, 34.5, 23.9, 22.3, 13.5 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{20}NO_2S^+$, 242.1209, found: 242.1211.

(*S*,*E*)-2-Methyl-*N*-(3-phenylpropylidene)propane-2-sulfinamide (8s)

Colorless oil (964 mg, 81%); $[\alpha]_D^{25}$ +196 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2958, 1622, 1453, 1079, 699 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) δ 8.13–8.08 (m, 1H), 7.30–7.25 (m, 2H), 7.22–7.17 (m, 3H), 2.99–2.94 (m, 2H), 2.88–2.83 (m, 2H), 1.12 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.5, 140.3, 128.6, 128.4, 126.3, 56.6, 37.5, 31.4, 22.3 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{20}NOS^+$, 238.1260, found: 238.1261.

(*S*,*E*)-2-Methyl-*N*-(3-(3-(trifluoromethyl)phenyl)propylidene) propane-2-sulfinamide (8t)

Colorless oil (1.03 g, 67%); $[\alpha]_D^{25}$ +145 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2961, 1623, 1328, 1124, 1075, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–8.08 (m, 1H), 7.50–7.45 (m, 2H), 7.43–7.38 (m, 2H), 3.08–3.04 (m, 2H), 2.94–2.89 (m, 2H), 1.11 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.8, 141.4, 131.9, 131.0 (d, *J* = 31.9 Hz), 129.1, 125.2 (d, *J* = 3.6 Hz), 124.2 (d, *J* = 270.7 Hz), 123.3 (d, *J* = 3.5 Hz), 56.7, 37.0, 31.0, 22.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{19}F_3NOS^+$, 306.1134, found: 306.1130.

(*S*,*E*)-2-Methyl-*N*-((*S*)-2-methylbutylidene)propane-2-sulfinamide (8u)

Colorless oil (865 mg, 91%); $[\alpha]_D^{25}$ +296 (*c* 1.00, $CHCl_3$), lit.[28]{$[\alpha]_D^{27}$ +208.7 (*c* 1.00, $CHCl_3$)}; IR (film): ν_{max} 2964, 2929, 1620, 1457, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.89 (m, 1H), 2.53–2.45 (m, 1H), 1.65–1.57 (m, 1H), 1.47–1.37 (m, 1H), 1.13 (s, 9H), 1.08–1.05 (m, 3H), 0.91–0.86 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 56.5, 41.6, 26.7, 22.3, 16.5, 11.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_9H_{20}NOS^+$, 190.1260, found: 190.1261.

(*R*,*E*)-2-Methyl-*N*-((*S*)-2-methylbutylidene)propane-2-sulfinamide (8v)

To a solution of (*S*)-(−)-2-methyl-1-butanol (176 mg, 2.00 mmol) in DCM (8 mL) was added Dess–Martin periodinane (1.70 g, 4.00 mmol). After being stirred for 30 min, the reaction mixture was carefully quenched with a saturated aqueous solution of $NaHCO_3$ and solid $Na_2S_2O_3$. The resulting mixture was extracted with DCM (20 mL × 3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a crude aldehyde without further purification. To a solution of the crude aldehyde in DCM (10 mL) was added (*R*)-2-methyl-2-propane-sulfinamide (266 mg, 2.20 mmol), anhydrous cupric sulfate (636 mg, 4.00 mmol) and PPTS (25 mg, 0.10 mmol), and after being stirred for 24 h, the reaction mixture was filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 15 : 1) to give the imine **8v**. Colorless oil (282 mg, 75%, two steps); $[\alpha]_D^{25}$ −268 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2964, 2875, 1621, 1086, 587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.2, 4.4 Hz, 1H), 2.58–2.50 (m, 1H), 1.71–1.64 (m, 1H), 1.52–1.47 (m, 1H), 1.21–1.19 (m, 9H), 1.16–1.13 (m, 3H), 0.97–0.92 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.5, 56.5, 41.7, 26.7, 22.4, 16.5, 11.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_9H_{20}NOS^+$, 190.1260, found: 190.1261.

(*S*,*E*)-2-Methyl-*N*-(4-methylpentan-2-ylidene)propane-2-sulfinamide (8w)

To a solution of 4-methyl-2-pentanone (350 mg, 5 mmol) in THF (14 mL) was added (*S*)-2-methyl-2-propane-sulfinamide (462 mg, 3.85 mmol) and $Ti(OEt)_4$ (1.45 mL, 7.00 mmol). After the mixture was refluxed for 12 h, water was added. The resulting mixture was extracted with EtOAc (60 mL × 3), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 15 : 1) to give the imine **8w**. Colorless oil (504 mg, 50%); $[\alpha]_D^{25}$ +160 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2957, 1620, 1463, 1387, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33–2.30 (m, 3H), 2.29–2.27 (m, 1H), 2.15–2.08 (m, 1H), 1.25 (s, 9H), 1.01–0.97 (m, 1H), 0.97–0.95 (m, 3H), 0.95–0.93 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.2, 56.2, 52.5, 25.7, 23.3, 22.6, 22.5, 22.2 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{22}NOS^+$, 204.1417, found: 204.1419.

General procedure for the synthesis of 10a–10u

A solution of 2-(benzyloxymethylsulfonyl)-pyridine **9** (395 mg, 1.50 mmol) in THF (1 ml) was dropped into the mixture of imine **8** (0.50 mmol) with SmI_2 (30 ml, 3.00 mmol, 0.1 M in THF) at room temperature under an Ar atmosphere. The reaction mixture was quenched with H_2O (0.2 ml), then the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 3 : 1) to give **10a–10u**.

(*S*)-*N*-((*S*)-1-(Benzyloxy)pentan-2-yl)-2-methylpropane-2-sulfinamide (10a)

Colorless oil (99 mg, 67%); $[\alpha]_D^{20}$ +45.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2956, 2869, 1589, 1454, 1387, 1362, 1114, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 3.67–3.62 (m, 2H), 3.56–3.48 (m, 1H), 3.47–3.36 (m, 1H), 1.63–1.53 (m, 1H), 1.52–1.44 (m, 1H), 1.43–1.28 (m, 2H), 1.22 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 128.5, 127.9, 127.8, 73.4, 73.2, 55.9, 55.8, 35.2, 22.8, 22.7, 19.1, 14.1 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{28}NO_2S^+$, 298.1835, found: 298.1836.

(*S*)-*N*-((*S*)-1-(Benzyloxy)heptan-2-yl)-2-methylpropane-2-sulfinamide (10b)

Colorless oil (104 mg, 64%); $[\alpha]_D^{21}$ +43.5 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2954, 2928, 2859, 1454, 1362, 1098, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.65–4.45 (m, 2H), 3.68–3.60 (m, 1H), 3.56–3.48 (m, 1H), 3.46–3.32 (m, 2H), 1.73–1.61 (m, 1H), 1.60–1.48 (m, 1H), 1.42–1.37 (m, 1H), 1.35–1.26 (m, 5H), 1.22–1.20 (m, 9H), 0.93–0.83 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 138.2, 128.5, 127.9, 127.8, 73.4, 73.2, 56.6, 55.9, 55.8, 33.0, 32.8, 31.8, 25.7, 25.5, 22.8, 22.7, 22.6, 22.5, 14.2 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{32}NO_2S^+$, 326.2148, found: 326.2150.

(*S*)-*N*-((*S*)-1-(Benzyloxy)nonan-2-yl)-2-methylpropane-2-sulfinamide (10c)

Colorless oil (92 mg, 52%); $[\alpha]_D^{21}$ +40.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2924, 2855, 1454, 1362, 1113, 1057, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 3.53–3.43 (m, 2H), 3.42–3.39 (m, 1H), 3.38–3.33 (m, 1H), 1.71–1.59 (m, 2H), 1.33–1.25 (m, 10H), 1.20 (s, 9H), 0.91–0.84 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 128.5, 127.8, 73.4, 73.3, 56.6, 55.9, 32.8, 31.9, 29.6, 29.3, 26.1, 22.8, 22.7, 14.2 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{36}NO_2S^+$, 354.2461, found: 354.2462.

(*S*)-*N*-((*S*)-1-(Benzyloxy)-4-methylpentan-2-yl)-2-methylpropane-2-sulfinamide (10d)

Colorless oil (98 mg, 63%); $[\alpha]_D^{20}$ +35.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2955, 2927, 2867, 1587, 1454, 1386, 1114, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$,) δ 7.39–7.28 (m, 5H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 3.69–3.64 (m, 1H), 3.64–3.59 (m, 1H), 3.55–3.48 (m, 1H), 3.47–3.44 (m, 1H), 1.84–1.65 (m, 1H), 1.62–1.46 (m, 2H), 1.23–1.18 (m, 9H), 0.94–0.86 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 128.5, 127.9, 127.8, 74.0, 73.4, 73.3, 56.0, 54.6, 42.5, 41.7, 24.6, 23.3, 23.1, 22.8, 22.7, 22.3, 22.0 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{30}NO_2S^+$, 312.1992, found: 312.1993.

(*S*)-*N*-((*S*)-1-(Benzyloxy)-4,4-dimethylpentan-2-yl)-2-methylpropane-2-sulfinamide (10e)

Colorless oil (105 mg, 65%); $[\alpha]_D^{21}$ +48.6 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2953, 1587, 1474, 1454, 1388, 1117, 1069, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5H), 4.60 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 3.74–3.69 (m, 1H), 3.69–3.64 (m, 1H), 3.53–3.46 (m, 2H), 1.51–1.46 (m, 1H), 1.46–1.39 (m, 1H), 1.23–1.19 (m, 9H), 0.96–0.91 (m, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 128.5, 127.9, 127.8, 127.7, 75.4, 74.9, 73.3, 73.2, 55.8, 53.6, 53.0, 47.2, 45.6, 30.5, 30.1, 30.0, 22.8, 22.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{32}NO_2S^+$, 326.2148, found: 326.2149.

(*S*)-*N*-((*S*)-1-(Benzyloxy)-3-ethylpentan-2-yl)-2-methylpropane-2-sulfinamide (10f)

Colorless oil (115 mg, 71%); $[\alpha]_D^{21}$ +26.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2960, 2927, 1591, 1454, 1362, 1074, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 3.67–3.62 (m, 2H), 3.60 (d, *J* = 8.0 Hz, 1H), 3.46–3.37 (m, 1H), 1.57–1.49 (m, 1H), 1.46–1.38 (m, 2H), 1.36–1.26 (m, 2H), 1.24 (s, 9H), 0.90–0.82 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 128.5, 127.9, 127.8, 73.2, 71.2, 57.6, 56.1, 42.8, 22.9, 21.9, 21.7, 11.7, 11.5 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{32}NO_2S^+$, 326.2148, found: 326.2148.

(*S*)-*N*-((2*S*,3*R*)-1-(Benzyloxy)-3-ethylhex-5-en-2-yl)-2-methylpropane-2-sulfinamide (10g)

Colorless oil (98 mg, 58%); $[\alpha]_D^{21}$ +37.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2958, 1638, 1454, 1100, 911, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.36–7.29 (m, 5H), 5.88–5.67 (m, 1H), 5.10–5.04 (m, 1H), 5.03–4.97 (m, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 3.67–3.62 (m, 0.7H), 3.60–3.56 (m, 0.3H), 3.53–3.48 (m, 3H), 2.26–2.16 (m, 1H), 2.15–2.07 (m, 1H), 1.83–1.76 (m, 0.7H), 1.74–1.69 (m, 0.3H), 1.59–1.49 (m, 1H), 1.46–1.35 (m, 1H), 1.24–1.18 (m, 9H), 0.97–0.89 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 138.2, 137.2, 137.1, 128.5, 127.9, 127.8, 116.8, 116.5, 73.3, 73.2, 71.9, 71.0, 57.9, 57.5, 56.1, 56.0, 41.3, 41.2, 34.0, 33.9, 22.9, 22.7, 22.1, 11.7, 11.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{32}NO_2S^+$, 338.2148, found: 338.2149.

(*S*)-*N*-((*S*,*Z*)-1-(Benzyloxy)oct-5-en-2-yl)-2-methylpropane-2-sulfinamide (10h)

Colorless oil (138 mg, 82%); $[\alpha]_D^{20}$ +41.4 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2959, 2929, 1454, 1362, 1069, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.26 (m, 5H), 5.42–5.34 (m, 1H), 5.33–5.25 (m, 1H), 4.65–4.57 (m, 0.6H), 4.57–4.53 (m, 0.4H), 4.53–4.49 (m, 0.4H), 4.49–4.45 (m, 0.6H), 3.71–3.66 (m, 1H), 3.65–3.64 (m, 0.4H), 3.57–3.53 (m, 0.6H), 3.53–3.51 (m, 0.4H), 3.50–3.45 (m, 0.6H), 3.44–3.37 (m, 1H), 2.19–2.04 (m, 2H), 2.04–1.96 (m, 2H), 1.78–1.70 (m, 1H), 1.66–1.56 (m, 1H), 1.24–1.19 (m, 9H), 0.95 (t, *J* = 7.6 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 138.2, 132.7, 132.6, 128.5, 128.2, 127.9, 127.8, 73.4, 73.3, 73.2, 56.2, 55.9, 55.8, 33.4, 32.7, 23.8, 23.6, 22.8, 22.7, 20.7, 14.4 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{32}NO_2S^+$, 338.2148, found: 338.2149.

(*S*)-*N*-((*S*)-1-(Benzyloxy)-3,3-dimethylbutan-2-yl)-2-methylpropane-2-sulfinamide (10i)

Colorless oil (64 mg, 66%, dr = 62 : 38); $[\alpha]_D^{21}$ +36.2 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2955, 2868, 1586, 1474, 1388, 1115, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 3.95 (d, *J* = 8.0 Hz, 1H), 3.83–3.77 (m, 1H), 3.72–3.63 (m, 1H), 3.10–2.96 (m, 1H), 1.25 (s, 9H), 0.94 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.4, 128.4, 127.7, 127.6, 73.3, 71.1, 64.4, 56.4, 35.3, 27.4, 23.0 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{30}NO_2S^+$, 312.1992, found: 312.1997.

(*S*)-*N*-((*R*)-1-(Benzyloxy)-3,3-dimethylbutan-2-yl)-2-methylpropane-2-sulfinamide ((1*R*)-10i)

Colorless oil (39 mg, 25%); $[\alpha]_D^{21}$ +22.4 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2955, 2867, 1473, 1454, 1364, 1117, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 4.56–4.47 (m, 2H), 3.63–3.57 (m, 1H), 3.55–3.50 (m, 1H), 3.50–3.45 (m, 1H), 3.64–3.57 (m, 1H), 3.56–3.50 (m, 1H), 3.18–3.09 (m, 1H), 1.24–1.18 (m, 7H), 1.05–0.99 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.5, 127.7, 73.3, 71.6, 64.7, 56.3, 34.3, 27.4, 22.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{30}NO_2S^+$, 312.1992, found: 312.1998.

(*S*)-*N*-((*S*)-1-(Benzyloxy)-3,3,6-trimethylhept-5-en-2-yl)-2-methylpropane-2-sulfinamide (10j)

Colorless oil (70 mg, 57%, dr = 67 : 33); $[\alpha]_D^{20}$ +33.6 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 2960, 2923, 1587, 1453, 1385, 1180,

1113, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 5.15 (dd, J = 8.0, 7.2 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 4.44 (d, J = 11.8 Hz, 1H), 3.96 (d, J = 8.8 Hz, 1H), 3.83–3.77 (m, 1H), 3.67 (dd, J = 9.8, 4.2 Hz, 1H), 3.15–3.07 (m, 1H), 2.00–1.95 (m, 2H), 1.73–1.69 (m, 3H), 1.57–1.53 (m, 3H), 1.25 (s, 9H), 0.93–0.88 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.5, 133.6, 128.5, 127.8, 127.6, 120.5, 73.4, 71.2, 63.1, 56.4, 39.0, 38.1, 26.3, 24.9, 24.4, 23.1, 18.1 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{21}H_{36}NO_2S^+$, 366.2461, found: 366.2467.

(*S*)-*N*-((*R*)-1-(Benzyloxy)-3,3,6-trimethylhept-5-en-2-yl)-2-methylpropane-2-sulfinamide ((1*R*)-10j)

Colorless oil (34 mg, 19%); $[\alpha]_D^{22}$ +20.4 (c 0.25, $CHCl_3$); IR (film): ν_{max} 2917, 2849, 1649, 1454, 1386, 1180, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 5.26–5.15 (m, 1H), 4.50–4.48 (m, 2H), 3.64–3.59 (m, 2H), 3.54–3.49 (m, 1H), 3.25–3.20 (m, 1H), 2.06–2.00 (m, 2H), 1.73–1.70 (m, 3H), 1.59–1.57 (m, 3H), 1.19 (s, 9H), 1.00–0.98 (m, 3H), 0.98–0.96 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 128.5, 127.8, 127.7, 120.4, 73.3, 71.7, 63.8, 56.2, 38.1, 37.9, 26.3, 25.4, 24.9, 22.8, 18.2 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{21}H_{36}NO_2S^+$, 366.2461, found: 366.2465.

(*S*)-*N*-((*S*)-2-(Benzyloxy)-1-cyclopropylethyl)-2-methylpropane-2-sulfinamide (10k)

Colorless oil (60 mg, 61%, dr = 67 : 33); $[\alpha]_D^{20}$ +54.3 (c 1.00, $CHCl_3$); IR (film): ν_{max} 2923, 2862, 1587, 1454, 1387, 1117, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.60 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 3.91 (d, J = 2.8 Hz, 1H), 3.69 (dd, J = 9.1, 3.6 Hz, 1H), 3.53 (dd, J = 9.1, 8.2 Hz, 1H), 2.81–2.74 (m, 1H), 1.23 (s, 9H), 0.82–0.73 (m, 1H), 0.66–0.59 (m, 1H), 0.50–0.43 (m, 2H), 0.24–0.14 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.1, 128.6, 127.8, 73.4, 73.0, 59.2, 55.4, 22.7, 13,1, 4.6, 2.3 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{16}H_{26}NO_2S^+$, 296.1679, found: 296.1676.

(*S*)-*N*-((*R*)-2-(Benzyloxy)-1-cyclopropylethyl)-2-methylpropane-2-sulfinamide ((1*R*)-10k)

Colorless oil (30 mg, 20%); $[\alpha]_D^{20}$ +34.2 (c 0.50, $CHCl_3$); IR (film): ν_{max} 2923, 1594, 1454, 1387, 1362, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 4.58 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 3.64–3.58 (m, 3H), 2.60–2.53 (m, 1H), 1.21 (s, 9H), 1.10–1.03 (m, 1H), 0.67–0.59 (m, 2H), 0.46–0.40 (m, 1H), 0.36–0.27 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.5, 127.8, 127.7, 73.8, 73.4, 61.8, 55.8, 22.7, 14.3, 4.6, 4.4 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{16}H_{26}NO_2S^+$, 296.1679, found: 296.1682.

(*S*)-*N*-((*S*)-2-(Benzyloxy)-1-cyclopentylethyl)-2-methylpropane-2-sulfinamide (10l)

Colorless oil (53 mg, 61%, dr = 54 : 46); $[\alpha]_D^{20}$ +19.4 (c 0.50, $CHCl_3$); IR (film): ν_{max} 2952, 1587, 1454, 1387, 1071, 735.6, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.62 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 3.78 (d, J = 8.4 Hz, 1H), 3.69 (dd, J = 9.5, 3.8 Hz, 1H), 3.63 (dd, J = 9.5, 3.2 Hz, 1H), 3.19–3.11 (m, 1H), 2.21–2.06 (m, 1H), 1.85–1.71 (m, 1H), 1.62–1.56 (m, 2H), 1.56–1.50 (m, 2H), 1.24 (s, 9H), 1.22–1.20 (m, 1H), 1.20–1.10 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.4, 128.5, 127.9, 127.8, 73.4, 72.8, 61.6, 56.2, 42.8, 30.3, 29.8, 25.6, 25.4, 22.9 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{30}NO_2S^+$, 324.1992, found: 324.1993.

(*S*)-*N*-((*R*)-2-(Benzyloxy)-1-cyclopentylethyl)-2-methylpropane-2-sulfinamide ((1*R*)-10l)

Colorless oil (46 mg, 28%); $[\alpha]_D^{22}$ +43.6 (c 0.25, $CHCl_3$); IR (film): ν_{max} 2952, 2920, 2865, 1650, 1453, 1362, 1066, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 4.58–4.44 (m, 2H), 3.63–3.46 (m, 3H), 3.25–3.14 (m, 1H), 2.26–2.10 (m, 1H), 1.97–1.81 (m, 1H), 1.80–1.70 (m, 1H), 1.60–1.50 (m, 3H), 1.43–1.29 (m, 2H),1.29–1.25 (m, 1H), 1.23–1.19 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.5, 127.9, 127.8, 76.8, 73.4, 73.3, 61.1, 56.0, 41.8, 30.2, 25.7, 25.3, 22.9, 22.8 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{30}NO_2S^+$, 324.1992, found: 324.1994.

***tert*-Butyl-4-((*S*)-2-(benzyloxy)-1-(((*S*)-*tert*-butylsulfinyl)amino) ethyl)piperidine-1-carboxylate (10m)**

Colorless oil (101 mg, 69%, dr = 67 : 33); $[\alpha]_D^{20}$ +10.1 (c 1.00, $CHCl_3$); IR (film): ν_{max} 3439, 2922, 1691, 1423, 1364, 1172, 1071, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 4.58 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 4.25–3.97 (m, 2H), 3.73–3.60 (m, 3H), 3.18–3.02 (m, 1H), 2.72–2.54 (m, 2H), 1.86–1.73 (m, 2H), 1.56 (d, J = 11.2 Hz, 1H), 1.45 (s, 9H), 1.23 (s, 9H), 1.19–1.04 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.9, 138.0, 128.6, 128.0, 127.9, 79.5, 77.5, 77.2, 76.8, 73.5, 71.0, 56.2, 38.6, 28.9, 28.6, 22.7 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{23}H_{39}N_2O_4S^+$, 439.2625, found: 439.2624.

***tert*-Butyl-4-((*R*)-2-(benzyloxy)-1-(((*S*)-*tert*-butylsulfinyl)amino) ethyl)piperidine-1-carboxylate ((1*R*)-10m)**

Colorless oil (50 mg, 23%); $[\alpha]_D^{20}$ +27.1 (c 1.00, $CHCl_3$); IR (film): ν_{max} 3259, 2922, 1691, 1453, 1364, 1170, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 4.55 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.26–4.08 (m, 2H), 3.61–3.55 (m, 1H), 3.54–3.45 (m, 2H), 3.24–3.10 (m, 1H), 2.76–2.58 (m, 2H), 1.97–1.79 (m, 2H), 1.67–1.61 (m, 1H), 1.47 (s, 9H), 1.36–1.23 (m, 2H), 1.20 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 138.0, 128.6, 128.0, 127.9, 79.5, 73.5, 71.0, 56.2, 38.6, 28.9, 28.6, 22.7 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{23}H_{39}N_2O_4S^+$, 439.2625, found: 439.2626.

(*S*)-*N*-((2*S*,3*R*)-3-Benzyl-1-(benzyloxy)pentan-2-yl)-2-methylpropane-2-sulfinamide (10n)

Colorless oil (145 mg, 75%); $[\alpha]_D^{22}$ +12.5 (c 1.00, $CHCl_3$); IR (film): ν_{max} 2958, 2925, 2870, 1637, 1454, 1362, 1100, 1071, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.40–7.24 (m, 7H), 7.23–7.12 (m, 3H), 4.57–4.39 (m, 2H), 3.66–3.63 (m, 1H), 3.61–3.60 (m, 0.28H), 3.55–3.52 (m, 1H), 3.52–3.47 (m, 0.72H), 2.81–2.73 (m, 1H), 2.58–2.42 (m, 1H),

2.11–2.05 (m, 0.28H), 2.04–1.94 (m, 0.72H), 1.58–1.46 (m, 0.28H), 1.45–1.33 (m, 1H), 1.33–1.26 (m, 0.72H), 1.26–1.12 (m, 9H), 0.94–0.86 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 141.3, 138.2, 129.3, 129.2, 128.5, 127.9, 127.8, 127.7, 126.0, 73.3, 73.1, 71.8, 71.0, 57.3, 56.6, 56.1, 44.0, 43.6, 36.1, 36.0, 22.9, 22.7, 22.1, 11.7, 11.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + Na]^+$ calcd for $C_{23}H_{33}NO_2SNa^+$, 410.2124, found: 410.2129.

(*S*)-*N*-((2*S*,3*R*)-1-(Benzyloxy)-3-(3-fluorobenzyl)pentan-2-yl)-2-methylpropane-2-sulfinamide (10o)

Colorless oil (131 mg, 65%); $[\alpha]_D^{22}$ +12.2 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2959, 1587, 1453, 1362, 1068, 743, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.39–7.27 (m, 5H), 7.27–7.18 (m, 1H), 6.98–6.82 (m, 3H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 3.66–3.59 (m, 2.5H), 3.57–3.51 (m, 0.5H), 3.49–3.40 (m, 1H), 2.70 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.47 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.98 (d, *J* = 6.0 Hz, 1H), 1.46–1.35 (m, 1H), 1.35–1.27 (m, 1H), 1.25 (s, 7.5H), 1.18 (s, 1.5H), 0.89 (t, *J* = 7.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 163.0 (d, *J* = 243.9 Hz), 143.9 (d, *J* = 2.0 Hz), 138.1, 129.9 (d, *J* = 8.2 Hz), 127.9, 127.8, 124.9, 115.9 (d, *J* = 20.7 Hz), 112.9 (d, *J* = 20.9 Hz), 73.4, 73.2, 71.7, 70.9, 57.2, 56.6, 56.1, 43.9, 43.5, 35.9, 35.8, 22.9, 22.7, 22.0, 11.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.0 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{33}FNO_2S^+$, 406.2211, found: 406.2214.

(*S*)-*N*-((2*S*,3*R*)-1-(Benzyloxy)-3-(4-methoxybenzyl)pentan-2-yl)-2-methylpropane-2-sulfinamide (10p)

Colorless oil (170 mg, 82%); $[\alpha]_D^{20}$ +14.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2957, 1611, 1512, 1246, 1179, 1071, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.38–7.26 (m, 5H), 7.10–7.01 (m, 2H), 6.87–6.77 (m, 2H), 4.56–4.40 (m, 2H), 3.78 (s, 3H), 3.70–3.54 (m, 2H), 3.63–3.46 (m, 1.67H), 3.42–3.38 (m, 0.33H), 2.75–2.60 (m, 1H), 2.53–2.36 (m, 1H), 2.03–1.87 (m, 1H), 1.55–1.48 (m, 0.33H), 1.44–1.34 (m, 1H), 1.34–1.27 (m, 0.67H), 1.27–1.20 (m, 6H), 1.17–1.15 (m, 3H), 0.96–0.84 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 158.0, 157.9, 138.2, 133.2, 132.6, 130.2, 130.1, 128.5, 127.9, 127.8, 127.7, 113.9, 73.3, 73.1, 71.9, 71.1, 57.3, 56.6, 56.1, 56.0, 55.4, 44.2, 43.7, 35.1, 35.0, 22.9, 22.7, 22.6, 22.0, 11.8, 11.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{36}NO_3S^+$, 418.2410, found: 418.2412.

(*S*)-*N*-((2*S*,3*R*)-1-(Benzyloxy)-3-(4-(*tert*-butyl)benzyl)pentan-2-yl)-2-methylpropane-2-sulfinamide (10q)

Colorless oil (145 mg, 66%); $[\alpha]_D^{22}$ +7.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2959, 1587, 1455, 1363, 1073, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 7H), 7.10–7.04 (m, 2H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 3.65–3.62 (m, 1H), 3.59 (d, *J* = 8.4 Hz, 1H), 3.54–3.48 (m, 1H), 2.79–2.60 (m, 1H), 2.56–2.37 (m, 1H), 2.07–1.89 (m, 1H), 1.45–1.36 (m, 1H), 1.31 (s, 9H), 1.24 (s, 9H), 1.20–1.19 (m, 1H), 1.15–1.13 (m, 1H), 0.95–0.86 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.8, 138.2, 138.1, 128.9, 128.5, 127.9, 127.8, 127.7, 125.4, 73.1, 71.1, 56.7, 56.1, 44.2, 35.5, 34.5, 31.5, 22.9, 22.7, 22.4, 11.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{42}NO_2S^+$, 444.2931, found: 444.2932.

(*S*)-*N*-((*S*)-1-(Benzyloxy)-4-(5-methylfuran-2-yl)butan-2-yl)-2-methylpropane-2-sulfinamide (10r)

Colorless oil (98 mg, 54%); $[\alpha]_D^{21}$ +33.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2922, 1570, 1454, 1362, 1072, 1021, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.28 (m, 5H), 5.92–5.88 (m, 0.37H), 5.85–5.81 (m, 1.63H), 4.62–4.46 (m, 2H), 3.71–3.65 (m, 1H), 3.59–3.52 (m, 1H), 3.51–3.39 (m, 2H), 2.78–2.67 (m, 1H), 2.67–2.53 (m, 1H), 2.24 (s, 3H), 2.09–1.92 (m, 1H), 1.91–1.87 (m, 1H), 1.24–1.19 (m, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 153.5, 153.3, 150.6, 138.2, 128.5, 127.9, 127.8, 106.2, 106.0, 105.9, 73.4, 73.3, 56.1, 56.0, 55.8, 31.8, 24.6, 22.8, 22.7, 13.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{30}NO_3S^+$, 364.1941, found: 364.1944.

(*S*)-*N*-((*S*)-1-(Benzyloxy)-4-phenylbutan-2-yl)-2-methylpropane-2-sulfinamide (10s)

Colorless oil (114 mg, 64%); $[\alpha]_D^{20}$ +30.8 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 2924, 1602, 1454, 1363, 1071, 745, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.30 (m, 5H), 7.30–7.27 (m, 2H), 7.20–7.13 (m, 3H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 3.73 (d, *J* = 7.6 Hz, 1H), 3.68 (dd, *J* = 9.4, 4.2 Hz, 1H), 3.56 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.47–3.40 (m, 1H), 2.75–2.68 (m, 1H), 2.66–2.56 (m, 1H), 1.96–1.80 (m, 2H), 1.26–1.23 (m, 7.6H), 1.20–1.19 (m, 1.4H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 141.8, 138.2, 128.7, 128.6, 128.5, 128.0, 126.1, 73.4, 73.3, 56.1, 55.8, 35.2, 32.2, 22.9, 22.8, 22.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{30}NO_2S^+$, 360.1992, found: 360.1996.

(*S*)-*N*-((*S*)-1-(Benzyloxy)-4-(3-(trifluoromethyl)phenyl)butan-2-yl)-2-methylpropane-2-sulfinamide (10t)

Colorless oil (119 mg, 56%); $[\alpha]_D^{19}$ +31.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2921, 1454, 1328, 1163, 1123, 1073, 799, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.47–7.39 (m, 3H), 7.39–7.36 (m, 1H), 7.35–7.28 (m, 5H), 4.63–4.55 (m, 0.68H), 4.53–4.52 (m, 0.32H), 4.52–4.50 (m, 0.32H), 4.49–4.45 (m, 0.68H), 3.79–3.69 (m, 1H), 3.68–3.66 (m, 0.32H), 3.60–3.56 (m, 0.68H), 3.54–3.45 (m, 1H), 3.44–3.36 (m, 1H), 2.89–2.83 (m, 0.32H), 2.81–2.73 (m, 1H), 2.71–2.61 (m, 0.68H), 2.08–1.95 (m, 1H), 1.94–1.86 (m, 1 H), 1.26 (s, 6H), 1.21 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 142.7, 142.5, 138.1, 132.0 (d, *J* = 23.6 Hz), 130.8 (d, *J* = 31.8 Hz), 129.0, 128.6, 127.9 (d, *J* = 5.6 Hz), 125.2 (d, *J* = 3.5 Hz), 123.0, 73.4, 73.3, 73.2, 56.2, 56.1, 56.0, 55.9, 34.9, 34.3, 32.1, 22.8, 22.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{29}F_3NO_2S^+$, 428.1866, found: 428.1867.

(*S*)-*N*-((2*S*,3*S*)-1-(Benzyloxy)-3-methylpentan-2-yl)-2-methylpropane-2-sulfinamide (10u)

Colorless oil (79 mg, 75%, dr = 68 : 32); $[\alpha]_D^{20}$ +41.4 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2959, 2924, 2874, 1591, 1454, 1362,

1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 4.59 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 3.69 (d, J = 7.2 Hz, 1H), 3.65–3.61 (m, 2H), 3.29–3.17 (m, 1H), 1.83–1.72 (m, 1H), 1.57–1.48 (m, 1H), 1.23 (s, 9H), 1.15–1.05 (m, 1H), 0.97–0.88 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 128.5, 127.9, 127.8, 73.2, 70.7, 59.9, 56.0, 36.5, 25.5, 22.9, 15.1, 11.5 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{30}NO_2S^+$, 312.1992, found: 312.1997.

(*S*)-*N*-((2*R*,3*S*)-1-(Benzyloxy)-3-methylpentan-2-yl)-2-methylpropane-2-sulfinamide ((2*R*)-10u)

Colorless oil (37 mg, 24%); $[\alpha]_D^{21}$ +44.2 (c 1.00, $CHCl_3$); IR (film): ν_{max} 2959, 2926, 2872, 1590, 1454, 1362, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 4.54 (d, J = 12 Hz, 1H), 4.48 (d, J = 12 Hz, 1H), 3.52–3.44 (m, 2H), 3.43–3.38 (m, 1H), 3.30 (d, J = 6.0 Hz, 1H), 1.83–1.78 (m, 1H), 1.62–1.47 (m, 1H), 1.31–1.26 (m, 1H), 1.19 (s, 9H), 0.96–0.88 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.5, 127.8, 73.3, 72.0, 59.4, 56.0, 36.4, 26.2, 22.7, 14.6, 11.8 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{30}NO_2S^+$, 312.1992, found: 312.1993.

(*R*)-*N*-((2*R*,3*S*)-1-(Benzyloxy)-3-methylpentan-2-yl)-2-methylpropane-2-sulfinamide (10v)

A solution of 2-(benzyloxymethylsulfonyl)-pyridine **9** (395 mg, 1.50 mmol) in THF was dropped into the mixture of imine **8v** (94 mg, 0.50 mmol) with SmI_2 (30 ml, 3.00 mmol, 0.1 M in THF) at room temperature under an Ar atmosphere. The reaction mixture was quenched with H_2O (0.20 ml), then the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 3 : 1) to give **10v**. Colorless oil (99 mg, 80%, dr = 80 : 20); $[\alpha]_D^{20}$ −38.4 (c 1.00, $CHCl_3$); IR (film): ν_{max} 2959, 2924, 2873, 1454, 1362, 1067, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 4.57 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 3.69–3.62 (m, 1H), 3.62–3.57 (m, 1H), 3.49 (d, J = 8.0 Hz, 1H), 3.40–3.30 (m, 1H), 1.79–1.68 (m, 1H), 1.50–1.42 (m, 1H), 1.23 (s, 9H), 1.17–1.10 (m, 1H), 0.91–0.85 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 128.5, 127.9, 127.8, 73.3, 71.5, 59.6, 56.2, 36.7, 26.1, 22.9, 14.9, 11.8 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{30}NO_2S^+$, 312.1992, found: 312.1995.

(*R*)-*N*-((2*S*,3*S*)-1-(Benzyloxy)-3-methylpentan-2-yl)-2-methylpropane-2-sulfinamide ((2*S*)-10v)

Colorless oil (25 mg, 16%); $[\alpha]_D^{20}$ −26.4 (c 1.00, $CHCl_3$); IR (film): ν_{max} 2959, 2924, 2873, 1454, 1362, 1067, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 4.53 (d, J = 12.2 Hz, 1H), 4.49 (d, J = 12.2 Hz, 1H), 3.55–3.47 (m, 2H), 3.44 (d, J = 6.4 Hz, 1H), 3.30–3.25 (m, 1H), 1.84–1.76 (m, 1H), 1.63–1.51 (m, 1H), 1.20 (s, 9H), 1.18–1.12 (m, 1H), 0.98–0.86 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.5, 127.8, 73.4, 71.6, 60.4, 56.0, 37.2, 25.6, 22.7, 15.5, 11.6 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{30}NO_2S^+$, 312.1992, found: 312.1995.

(*S*)-*N*-(1-(Benzyloxy)-2,4-dimethylpentan-2-yl)-2-methylpropane-2-sulfinamide (10w)

A solution of 2-(benzyloxymethylsulfonyl)-pyridine **9** (395 mg, 1.50 mmol) in THF was dropped into the mixture of imine **8w** (102 mg, 0.50 mmol) with SmI_2 (30 ml, 3.00 mmol, 0.1 M in THF) at room temperature under an Ar atmosphere. The reaction mixture was quenched with H_2O (0.20 ml), then the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 3 : 1) to give **10w**. Colorless oil (84 mg, 52%); $[\alpha]_D^{23}$ +36.0 (c 0.25, $CHCl_3$); IR (film): ν_{max} 2955, 1455, 1362, 1200, 1099, 919, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 4.61 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 3.72–3.69 (m, 1H), 3.45–3.68 (m, 2H), 1.75–1.70 (m, 1H), 1.52–1.42 (m, 2H), 1.34–1.30 (m, 3H), 1.20 (s, 9H), 0.96–0.88 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.6, 127.5, 126.8, 126.7, 77.5, 72.5, 57.8, 54.7, 47.1, 24.3, 24.2, 22.7, 21.9, 21.5 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{32}NO_2S^+$, 326.2148, found: 326.2149.

***tert*-Butyl (*S*)-(1-(benzyloxy)-4-methylpentan-2-yl)carbamate (11)**

A cooled (0 °C) solution of **10d** (1.00 g, 3.22 mmol) in MeOH (14 mL) was treated with a solution of HCl/dioxane (2.80 mL). After being stirred for 30 min, the reaction mixture was concentrated. The resulting mixture was diluted with DCM (13 mL), and Boc_2O (1.18 g, 6.44 mmol) and TEA (1.80 mL, 12.88 mmol) were added. After being stirred overnight, the 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 $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 10 : 1) to give **11**. Colorless oil (662 mg, 67%, two steps); $[\alpha]_D^{23}$ −34.6 (c 1.00, $CHCl_3$); IR (film): ν_{max} 3348, 2956, 1713, 1498, 1365, 1171, 1101, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.67 (d, J = 7.6 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 3.89–3.77 (m, 1H), 3.50–3.41 (m, 2H), 1.68–1.56 (m, 1H), 1.44 (s, 9H), 1.42–1.35 (m, 2H), 0.94–0.89 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.7, 138.5, 128.5, 127.7, 127.6, 79.1, 73.3, 72.6, 48.7, 41.4, 28.6, 25.0, 23.1, 22.5 ppm; HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{18}H_{29}NO_3Na^+$, 330.2040, found: 330.2038.

***tert*-Butyl (*S*)-(1-hydroxy-4-methylpentan-2-yl)carbamate (12)**

Compound **11** (500 mg, 1.52 mmol) and 10% Pd/C (50 mg) were stirred in MeOH (50 mL) for 4 h under a H_2 atmosphere. Then the mixture was filtered to give a crude alcohol, which was purified by flash chromatography on silica gel (PE/EA = 4 : 1) to give **12**. Colorless oil (267 mg, 81%); $[\alpha]_D^{23}$ −20.3 (c 1.00, $CHCl_3$); IR (film): ν_{max} 3348, 2956, 1713, 1171, 1101, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68–4.53 (m, 1H), 3.77–3.62 (m, 1H), 3.67–3.60 (m, 1H), 3.54–3.42 (m, 1H), 2.83–2.60 (m, 1H), 1.68–1.62 (m, 1H), 1.44 (s, 9H), 1.34–1.27 (m, 2H), 0.97–0.87

(m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.7, 79.8, 66.7, 51.2, 40.7, 28.5, 24.9, 23.2, 22.3 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{24}NO_3^+$, 218.1681, found: 218.1685.

(*tert*-Butoxycarbonyl)-L-leucine (13)

To a cooled (0 °C) solution of **12** (180 mg, 0.83 mmol) in DCM (4 mL) was slowly added Dess–Martin periodinane (880 mg, 2.08 mmol). After being stirred for 30 min, the reaction mixture was carefully quenched with a saturated aqueous solution of $NaHCO_3$ and solid $Na_2S_2O_3$. The resulting mixture was extracted with DCM (20 mL × 3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a crude aldehyde without further purification. A solution of the above crude aldehyde in *t*-BuOH/2-methyl-2-butene (1/3 mL) was treated with a solution of $NaClO_2$ (224 mg, 2.49 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (388 mg, 2.49 mmol) in water (3 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 $MgSO_4$, filtered and concentrated to give a crude acid. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 100 : 1–50 : 1) to give **13**. Colorless oil (134 mg, 70%, two steps); $[\alpha]_D^{22}$ −29.0 (*c* 1.00, DMF); IR (film): ν_{max} 3387, 2956, 1714, 1649, 1251, 1019, 750, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94–4.79 (m, 1H), 4.35–4.25 (m, 1H), 1.79–1.63 (m, 2H), 1.57–1.50 (m, 1H), 1.44 (s, 9H), 0.98–0.91 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.7, 155.9, 80.4, 52.1, 41.4, 28.4, 24.9, 23.0, 21.9 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{22}NO_4^+$, 232.1543, found: 232.1549.

tert-Butyl ((2*S*,3*R*)-1-(benzyloxy)-3-(3-fluorobenzyl)pentan-2-yl) carbamate (14)

To a cooled (0 °C) solution of **10o** (1.90 g, 4.69 mmol) in MeOH (20 mL) was added dropwise a solution of HCl/dioxane (4.00 mL). After being stirred for 30 min, the reaction mixture was concentrated. The resulting mixture was diluted with DCM (20 mL), and then Boc_2O (2.04 g, 9.38 mmol) and TEA (2.6 ml, 18.76 mmol) were added. After stirring overnight, the mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a crude middle compound without further purification. Above crude middle compound and 10% Pd/C (190 mg) were stirred in MeOH (100 mL) for 4 h under a H_2 atmosphere, and filtered to give a crude alcohol, which was purified by flash chromatography on silica gel (PE/EA = 4 : 1) to give **14**. Colorless oil (1.28 g, 88%, three steps); $[\alpha]_D^{22}$ −6.4 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3356, 2967, 1689, 1589, 1488, 1366, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.19 (m, 1H), 6.98–6.93 (m, 1H), 6.91–6.85 (m, 2H), 4.84–4.63 (m, 1H), 3.77–3.68 (m, 1H), 3.67–3.59 (m, 2H), 2.75 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.70–2.64 (m, 0.3H), 2.60 (d, *J* = 6.8 Hz, 1H), 2.57–2.42 (m, 0.7H), 1.90–1.79 (m, 1H), 1.45 (s, 9H), 1.40–1.28 (m, 2H), 0.97–0.88 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.0 (d, *J* = 243.9 Hz), 156.8, 143.6, 129.9 (d, *J* = 8.0 Hz), 124.8 (d, *J* = 8.1 Hz), 115.9 (d, *J* = 20.7 Hz), 113.0 (d, *J* = 20.9 Hz), 79.9, 64.5, 54.5, 54.3, 43.2, 42.5, 36.5, 35.9, 28.5, 22.6, 11.8, 10.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + Na]^+$ calcd for $C_{17}H_{26}FNO_3Na^+$ $(M + Na)^+$, 334.1789, found: 334.1789.

(2*S*,3*R*)-2-Amino-3-(3-fluorobenzyl)pentanoic acid hydrochloride (15)

Dess–Martin periodinane (2.05 g, 4.83 mmol) was carefully added to a cooled (0 °C) solution of **14** (600 mg, 1.93 mmol) in DCM (8 mL) and stirred for 30 min. Then the reaction mixture was carefully quenched with a saturated aqueous solution of $NaHCO_3$ and solid $Na_2S_2O_3$. The mixture was extracted with DCM (30 mL × 3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a crude aldehyde without further purification. The above aldehyde was dissolved in *t*-BuOH/2-methyl-2-butene (2.3/7.0 mL) and $NaClO_2$ (589 mg, 5.79 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (902 mg, 5.79 mmol) in water (7 mL) was added dropwise. After stirring for 8 h, the reaction mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a crude acid without further purification. The above crude acid was dissolved in MeOH (8 mL) and treated with a solution of HCl/MeOH (2.00 mL, 3 M) for 2 h. The mixture was directly concentrated to give a crude salt, which was recrystallized to give **15**. White solid (287 mg, 66%, three steps); mp 103.6–105.6 °C; $[\alpha]_D^{20}$ −33.6 (*c* 0.50, MeOH); IR (film): ν_{max} 3421, 2966, 1732, 1589, 1489, 1253, 784, 691 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.41–7.31 (m, 1H), 7.14–7.07 (m, 1H), 7.07–6.95 (m, 2H), 3.8–3.82 (m, 1H), 2.87–2.67 (m, 2H), 2.32–2.12 (m, 1H), 1.65–1.48 (m, 1H), 1.43–1.30 (m, 1H), 1.07–0.95 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, CD_3OD) δ 171.0, 164.4 (d, *J* = 243.3 Hz), 143.3 (d, *J* = 7.1 Hz), 131.5 (d, *J* = 8.3 Hz), 126.2, 117.0 (d, *J* = 21.5 Hz), 113.2 (d, *J* = 21.2 Hz), 55.3, 44.8, 44.5, 36.7, 36.6, 23.4, 23.0, 12.1, 11.9 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{17}FNO_2^+$, 226.1238, found: 226.1239.

General procedure for the synthesis of 16a, 16b and 16c

A cooled (0 °C) solution of **10n**/**10o**/**10p** (10.12 mmol) in MeOH (40 mL) was treated with a solution of HCl/dioxane (8.00 mL) for 30 min. The reaction mixture was concentrated and the resulting mixture was dissolved in DCM (40 mL). Boc_2O (4.41 g, 20.24 mmol) and TEA (5.63 mL, 40.48 mmol) were added. After being stirred overnight, 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 $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 10 : 1) to give the title product (**16a**, **16b** and **16c**).

tert-Butyl ((2*S*,3*R*)-3-benzyl-1-(benzyloxy)pentan-2-yl)carbamate (16a)

Colorless oil (2.52 g, 65%, two steps); $[\alpha]_D^{23}$ −9.1 (*c* 3.00, $CHCl_3$); IR (film): ν_{max} 3446, 2965, 1699, 1496, 1365, 1170,

699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.31 (m, 2H), 7.31–7.22 (m, 5H), 7.19–7.13 (m, 3H), 4.79–4.65 (m, 1H), 4.52–4.36 (m, 2H), 3.97–3.78 (m, 1H), 3.57–3.41 (m, 2H), 2.85–2.74 (m, 0.3H), 2.70–2.60 (m, 0.7H), 2.58–2.48 (m, 0.7H), 2.44–2.37 (m, 0.3H), 2.03–1.85 (m, 1H), 1.44 (s, 9H), 1.38–1.20 (m, 2H), 0.95–0.78 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 156.0, 155.8, 141.3, 138.3, 129.2, 129.1, 128.4, 128.3, 127.8, 127.7, 125.9, 79.1, 73.2, 73.0, 70.8, 70.4, 51.7, 51.5, 43.2, 42.4, 36.7, 35.8, 28.5, 22.3, 11.5, 10.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{34}NO_4^+$, 384.2533, found: 384.2536.

tert-Butyl ((2*S*,3*R*)-1-(benzyloxy)-3-(4-methoxybenzyl)pentan-2-yl)carbamate (16b)

Colorless oil (3.13 g, 75%, two steps); $[\alpha]_D^{23}$ −12.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3344, 2964, 1635, 1512, 1246, 1173, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.26 (m, 5H), 7.12–7.05 (m, 2H), 7.85–7.78 (m, 2H), 4.79–4.65 (m, 0.8H), 4.53–4.51 (m, 0.2H), 4.50–4.36 (m, 2H), 3.92–3.80 (m, 1H), 3.78 (s, 3H), 3.57–3.42 (m, 2H), 2.77–2.71 (m, 0.2H), 2.63–2.52 (m, 0.8H), 2.52–2.45 (m, 0.8H), 2.42–2.30 (m, 0.2H), 1.95–1.82 (m, 1H), 1.44 (s, 9H), 1.34–1.17 (m, 2H), 0.98–0.81 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 157.9, 156.0, 155.8, 138.3, 133.3, 130.2, 130.1, 128.5, 127.7, 113.8, 79.2, 73.3, 73.1, 70.8, 70.5, 55.4, 51.4, 43.4, 35.7, 34.9, 28.6, 22.3, 11.6, 10.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{36}NO_4^+$, 414.2639, found: 414.2641.

tert-Butyl ((2*S*,3*R*)-1-(benzyloxy)-3-(3-fluorobenzyl)pentan-2-yl) carbamate (16c)

Colorless oil (3.25 g, 76%, two steps); $[\alpha]_D^{22}$ −8.3 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3447, 2964, 1699, 1614, 1488, 1390, 1248, 1099, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.36–7.25 (m, 5H), 7.25–7.19 (m, 1H), 6.97–6.84 (m, 3H), 4.78–4.70 (m, 0.75H), 4.54–4.41 (m, 0.25H), 4.51–4.38 (m, 2H), 3.92–3.76 (m, 1H), 3.59–3.43 (m, 2H), 2.86–2.73 (m, 0.25H), 2.72–2.59 (m, 0.75H), 2.59–2.45 (m, 0.75H), 2.46–2.39 (m, 0.25H), 2.00–1.89 (m, 1H), 1.45 (s, 9H), 1.33–1.20 (m, 2H), 0.94–0.84 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 162.5 (d, J = 243.7 Hz), 156.0, 155.8, 144.1, 138.2, 129.7 (d, J = 8.3 Hz), 128.5, 127.8 (d, J = 4.0 Hz), 125.0, 124.8, 116.0 (d, J = 20.6 Hz), 112.8 (d, J = 20.9 Hz), 79.3, 73.3, 73.2, 70.7, 70.3, 51.8, 51.5, 43.1, 42.4, 36.5, 35.7, 29.8, 28.5, 22.3, 11.6, 10.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.1 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + Na]^+$ calcd for $C_{24}H_{32}FNO_3Na^+$, 424.2258, found: 424.2258.

General procedure for the synthesis of 17a, 17b and 17c

Compounds **16a**/**16b**/**16c** (6.50 mmol) were stirred in HMPA (1.35 ml, 7.80 mmol) and THF (28 mL) at −78 °C, and then a solution of LiHMDS (7.80 ml, 7.80 mmol, 1 M in THF) was slowly added dropwise and stirred for 30 min. The reaction mixture was allowed to warm to −15 °C and MeOTf (1.47 ml, 13.00 mmol) was added. The resulting mixture was stirred for an additional 15 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (40 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 10 : 1) to give the desired product (**17a**, **17b** and **17c**).

tert-Butyl ((2*S*,3*R*)-3-benzyl-1-(benzyloxy)pentan-2-yl)(methyl) carbamate (17a)

Colorless oil (2.09 g, 81%); $[\alpha]_D^{23}$ +4.8 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3444, 2970, 1688, 1454, 1365, 1149, 737, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.28 (m, 5H), 7.27–7.23 (m, 2H), 7.20–7.12 (m, 3H), 4.62–4.48 (m, 1H), 4.46–4.41 (m, 0.5H), 4.41–4.38 (m, 0.5H), 4.38–4.02 (m, 1H), 3.68–3.56 (m, 2H), 2.84–2.73 (m, 3H), 2.72–2.63 (m, 1H), 2.55–2.38 (m, 1H), 2.17–1.93 (m, 1H), 1.49–1.42 (m, 9H), 1.31–1.17 (m, 2H), 0.90–0.79 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 156.9, 156.5, 141.2, 140.7, 138.6, 138.4, 129.1, 128.5, 128.4, 127.7, 127.6, 126.0, 125.9, 125.8, 79.6, 79.4, 79.3, 72.9, 70.4, 70.2, 69.7, 69.5, 56.4, 56.1, 39.8, 39.4, 39.2, 36.0, 35.7, 35.6, 30.5, 29.8, 28.7, 28.6, 21.6, 21.2, 9.3, 8.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{36}NO_3^+$, 398.2690, found: 398.2688.

tert-Butyl ((2*S*,3*R*)-1-(benzyloxy)-3-(4-methoxybenzyl)pentan-2-yl)(methyl)carbamate (17b)

Colorless oil (2.64 g, 95%); $[\alpha]_D^{24}$ +5.1 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3448, 2966, 1680, 1512, 1246, 1149, 1037, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.39–7.25 (m, 5H), 7.10–7.01 (m, 2H), 6.85–6.75 (m, 2H), 4.65–4.50 (m, 1H), 4.47–4.33 (m, 1H), 4.37–3.96 (m, 1H), 3.79 (s, 3H), 3.67–3.66 (m, 2H), 2.85–2.71 (m, 3H), 2.68–2.57 (m, 1H), 2.47–2.35 (m, 1H), 2.12–1.83 (m, 1H), 1.49–1.41 (m, 9H), 1.27–1.16 (m, 2H), 0.91–0.81 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 157.9, 156.5, 138.6, 138.4, 133.1, 132.7, 129.9, 128.5, 128.4, 127.7, 127.6, 113.8, 79.6, 79.2, 72.9, 70.4, 69.7, 55.4, 39.5, 39.3, 35.0, 34.6, 28.7, 28.6, 21.5, 21.1, 21.0, 9.3, 8.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{38}NO_4^+$, 428.2795, found: 428.2796.

tert-Butyl-((2*S*,3*R*)-1-(benzyloxy)-3-(3-fluorobenzyl)pentan-2-yl) (methyl)carbamate (17c)

Colorless oil (2.51 g, 93%); $[\alpha]_D^{25}$ +1.3 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3445, 2969, 1689, 1452, 1365, 1251, 1142, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.38–7.26 (m, 5H), 7.24–7.16 (m, 1H), 6.97–6.78 (m, 3H), 4.62–4.48 (m, 1H), 4.47–4.35 (m, 1H), 4.37–4.00 (m, 1H), 3.68–3.53 (m, 2H), 2.85–2.70 (m, 3H), 2.68–2.5 8 (m, 1H), 2.56–2.37 (m, 1H), 2.17–1.98 (m, 1H), 1.49–1.42 (m, 9H), 1.32–1.15 (m, 2H), 0.92–0.78 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 163.0 (d, J = 243.8 Hz), 156.4, 156.3, 144.3, 143.8, 143.4, 138.4 (d, J = 19.1 Hz), 129.7, 128.5, 128.4, 127.7 (d, J = 7.3 Hz), 124.8, 115.9 (d, J = 20.6 Hz), 112.9 (d, J = 19.9 Hz), 79.7, 79.5, 79.3, 73.0, 70.5, 70.2, 69.7, 58.6, 56.3, 39.7, 39.3, 39.2, 35.8, 35.7, 35.4, 30.6, 29.8, 28.6, 21.5, 21.4, 21.2, 9.3, 8.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{35}FNO_3^+$, 416.2596, found: 416.2596.

General procedure for the synthesis of 18a, 18b, 18c, 24a, 24b, 24c and 24d

Compounds **17a**/**17b**/**17c**/**23a**/**23b**/**23c**/**23d** (5.00 mmol) were stirred in DCM (20 mL) at 0 °C and were treated with TFA (4.00 mL) for 2 h. The mixture was concentrated under reduced pressure and the residue was dissolved in DCM (20 mL). HATU (2.85 g, 7.50 mmol), DIPEA (2.61 mL, 15.00 mmol), and *N*-Boc-L-Val-OH (1.19 g, 5.50 mmol) were added in turn and the resulting mixture was stirred overnight. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 8 : 1) to give the desired product (**18a**, **18b**, **18c**, **24a**, **24b**, **24c** and **24d**).

***tert*-Butyl-((*S*)-1-(((2*S*,3*R*)-3-benzyl-1-(benzyloxy)pentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (18a)**

Colorless oil (2.33 g, 94%, two steps); $[\alpha]_D^{23}$ +10.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3434, 2966, 1636, 1495, 1171, 739, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.30 (m, 2H), 7.30–7.23 (m, 5H), 7.20–7.06 (m, 3H), 5.41–5.15 (m, 1H), 4.84–4.66 (m, 1H), 4.59–4.50 (m, 1H), 4.47–4.36 (m, 2H), 3.66–3.52 (m, 2H), 3.13–2.98 (m, 3H), 2.83–2.80 (m, 0.5H), 2.72–2.67 (m, 0.5H), 2.56–2.45 (m, 1H), 2.21–2.07 (m, 1H), 2.03–1.87 (m, 1H), 1.45–1.40 (m, 9H), 1.31–1.26 (m, 1H), 1.22–1.12 (m, 1H), 0.93–0.85 (m, 6H), 0.79 (t, *J* = 7.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.4, 156.2, 140.8, 138.1, 129.1, 128.5, 128.4, 128.0, 127.9, 127.8, 126.1, 79.5, 73.2, 73.1, 69.8, 55.7, 38.8, 38.3, 35.9, 35.4, 31.3, 31.1, 28.5, 28.4, 21.5, 20.5, 19.7, 17.7, 17.0, 9.4, 8.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{45}N_2O_4^+$, 497.3374, found: 497.3370.

***tert*-Butyl-((*S*)-1-(((2*S*,3*R*)-1-(benzyloxy)-3-(4-methoxybenzyl)pentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (18b)**

Colorless oil (2.10 g, 80%, two steps); $[\alpha]_D^{24}$ +8.0 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3438, 2965, 1636, 1512, 1365, 1247, 1175, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.38–7.23 (m, 5H), 7.13–7.01 (m, 2H), 6.87–6.77 (m, 2H), 5.42–5.13 (m, 1H), 4.83–4.69 (m, 0.76H), 4.56–4.53 (m, 0.24H), 4.52–4.43 (m, 1H), 4.43–4.27 (m, 2H), 3.78 (s, 3H), 3.65–3.50 (m, 2H), 3.13–2.89 (m, 3H), 2.81–2.78 (m, 0.24H), 2.68–2.59 (m, 0.76H), 2.54–2.42 (m, 1H), 2.19–1.88 (m, 2H), 1.41 (s, 9H), 1.24–1.13 (m, 2H), 0.96–0.83 (m, 6H), 0.82–0.74 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.4, 157.9, 156.2, 138.1, 132.7, 130.0, 128.5, 128.4, 128.0, 127.9, 127.8, 113.8, 79.4, 73.1, 69.7, 55.7, 55.3, 38.9, 34.8, 31.1, 28.5, 28.4, 21.3, 19.6, 17.7, 9.5 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{31}H_{47}N_2O_5^+$, 527.3480, found: 527.3480.

***tert*-Butyl ((*S*)-1-(((2*S*,3*R*)-1-(benzyloxy)-3-(3-fluorobenzyl)pentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (18c)**

Colorless oil (2.18 g, 85%, two steps); $[\alpha]_D^{26}$ +6.7 (*c* 1.00, $CHCl_3$, rotamers); IR (film): ν_{max} 3320, 2965, 1708, 1637, 1488, 1390, 1172, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 7.26–7.23 (m, 1H), 6.94–6.82 (m, 3H), 5.40–5.14 (m, 1H), 4.83–4.66 (m, 0.7H), 4.56–4.53 (m, 0.3H), 4.50–4.42 (m, 1H), 4.42–4.29 (m, 2H), 3.63–3.48 (m, 2H), 3.13–2.96 (m, 3H), 2.83–2.81 (m, 0.3H), 2.73–2.65 (m, 0.7H), 2.58–2.48 (m, 1H), 2.20–2.06 (m, 1H), 2.02–1.87 (m, 1H), 1.41 (s, 9H), 1.27–1.14 (m, 2H), 0.97–0.87 (m, 6H), 0.85–0.75 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.3, 162.9 (d, *J* = 244.0 Hz), 156.0, 143.3 (d, *J* = 7.0 Hz), 137.8, 129.7 (d, *J* = 8.1 Hz), 128.4, 128.3, 127.9, 127.7, 127.6, 124.6, 115.7 (d, *J* = 20.6 Hz), 112.9 (d, *J* = 20.8 Hz), 79.4, 73.1, 69.7, 55.6, 38.6, 35.5, 31.0, 28.4, 28.3, 21.3, 19.5, 17.6, 9.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{44}FN_2O_4^+$, 515.3280, found: 515.3281.

Benzyl *N*-((*tert*-butoxycarbonyl)-L-valyl)-*N*-methyl-L-isoleucinate (24a)[13d]

Colorless oil (1.78 g, 82%, two steps).

Benzyl *N*-((*tert*-butoxycarbonyl)-L-valyl)-*N*-methyl-L-valinate (24b)

Colorless oil (1.47 g, 70%, two steps); $[\alpha]_D^{23}$ −80.8 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2965, 1736, 1654, 1497, 1366, 1175, 1130, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.31 (m, 5H), 5.25–5.20 (m, 1H), 5.17–5.13 (m, 1H), 5.07–5.03 (m, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 4.35 (dd, *J* = 9.2, 6.8 Hz, 1H), 2.99–2.96 (m, 3H), 2.27–2.17 (m, 1H), 1.88–1.78 (m, 1H), 1.41 (s, 9H), 1.03–1.00 (m, 3H), 0.98–0.88 (m, 1H), 0.86–0.82 (m, 8H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 170.8, 156.1, 135.6, 128.7, 128.6, 128.6, 79.6, 66.8, 61.6, 55.5, 31.4, 31.2, 28.4, 27.2, 20.0, 19.4, 18.7, 17.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{37}N_2O_5^+$, 421.2697, found: 421.2694.

Benzyl *N*-((*tert*-butoxycarbonyl)-L-valyl)-*N*-methyl-L-leucinate (24c)

Colorless oil (1.67 g, 77%, two steps); $[\alpha]_D^{23}$ −39.9 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2960, 1738, 1711, 1498, 1456, 1367, 1265, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 5.43 (dd, *J* = 10.8, 5.2 Hz, 1H), 5.20–5.05 (m, 3H), 4.39 (dd, *J* = 9.2, 6.4 Hz, 1H), 2.99–2.95 (m, 3H), 1.95–1.87 (m, 1H), 1.80–1.70 (m, 2H), 1.52–1.45 (m, 1H), 1.42 (s, 9H), 0.94–0.88 (m, 9H), 0.87–0.84 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 173.5, 171.7, 156.1, 135.5, 128.7, 128.6, 79.6, 67.2, 55.4, 54.6, 37.0, 31.3, 31.1, 28.4, 24.8, 23.4, 21.5, 19.5, 17.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{39}N_2O_5^+$, 435.2854, found: 435.2849.

Benzyl *N*-((*tert*-butoxycarbonyl)-L-valyl)-*N*-methyl-L-phenylalaninate (24d)

Colorless oil (1 g, 68%, two steps); $[\alpha]_D^{23}$ −72.4 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2968, 1741, 1649, 1498, 1407, 1366, 1012, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.32 (m, 3H), 7.31–7.28 (m, 2H), 7.25–7.16 (m, 5H), 5.41 (dd, *J* = 9.6, 5.6 Hz, 1H), 5.22–5.18 (m, 1H), 5.11–5.06 (m, 1H), 5.06–5.02 (m, 1H), 4.32 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.40 (dd, *J* = 14.4, 5.6 Hz, 1H),

2.99 (dd, J = 14.4, 10.0 Hz, 1H), 2.90–2.86 (m, 3H), 1.90–1.80 (m, 1H), 1.40 (s, 9H), 0.90–0.86 (m, 3H), 0.84–0.80 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.9, 170.6, 155.8, 136.9, 135.4, 129.0, 128.7, 128.6, 128.6, 126.9, 79.5, 67.3, 58.4, 55.1, 34.7, 32.8, 31.3, 28.5, 19.6, 17.2 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{27}H_{37}N_2O_5^+$, 469.2697, found: 469.2692.

General procedure for the synthesis of 19a, 19b, 19c, 25a, 25b, 25c and 25d

Compounds **18a**/**18b**/**18c**/**24a**/**24b**/**24c**/**24d** (3.20 mmol) were dissolved in DCM (16 mL) at 0 °C and treated with TFA (3.20 mL) for 2 h. The mixture was concentrated under reduced pressure and the residue was dissolved in DCM (16 mL). HATU (1.82 g, 4.8 mmol), DIPEA (1.67 ml, 9.6 mmol), and *N*-Boc-L-Val-OH (0.76 g, 3.52 mmol) were added in turn and the resulting mixture was stirred overnight. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 3 : 1) to give the desired product (**19a**, **19b**, **19c**, **25a**, **25b**, **25c** and **25d**).

tert-Butyl ((*S*)-1-(((*S*)-1-(((2*S*,3*R*)-3-benzyl-1-(benzyloxy)pentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (19a)

Colorless oil (1.66 g, 87%, two steps); $[\alpha]_D^{23}$ −6.4 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3444, 2963, 1633, 1517, 1454, 1174, 739, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.35–7.29 (m, 3H), 7.29–7.24 (m, 5H), 7.19 (d, J = 7.2 Hz, 1H), 7.15–7.10 (m, 2H), 6.69–6.55 (m, 1H), 5.13–5.08 (m, 0.7H), 4.94–4.87 (m, 0.3H), 4.79–4.75 (m, 1H), 4.53–4.47 (m, 0.3H), 4.45–4.30 (m, 1.7H), 3.99–3.84 (m, 1H), 3.69–362 (m, 0.3H), 3.60–3.52 (m, 1.7H), 3.16–2.97 (m, 3H), 2.84–2.76 (m, 0.3H), 2.75–2.64 (m, 0.7H), 2.59–2.48 (m, 1H), 2.25–2.17 (m, 0.3H), 2.10–1.97 (m, 2.7H), 1.45–1.43 (m, 9H), 1.04–0.94 (m, 2H), 0.92–0.85 (m, 12H), 0.75 (t, J = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 172.4, 171.5, 155.8, 140.7, 138.0, 129.0, 128.5, 128.4, 128.0, 127.8, 126.1, 79.8, 73.3, 73.2, 69.6, 63.2, 60.1, 58.6, 54.2, 38.7, 35.8, 31.5, 31.3, 30.9, 28.4, 21.5, 19.6, 19.3, 17.7, 9.3 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{35}H_{54}N_3O_5^+$, 596.4058, found: 596.4059.

tert-Butyl ((*S*)-1-(((*S*)-1-(((2*S*,3*R*)-1-(benzyloxy)-3-(4-methoxybenzyl)pentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (19b)

Colorless oil (1.72 g, 86%, two steps); $[\alpha]_D^{23}$ −4.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3325, 2962, 1650, 1512, 1455, 1247, 1176, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.36–7.26 (m, 5H), 7.07–6.98 (m, 2H), 6.82–6.77 (m, 2H), 6.62–6.47 (m, 1H), 5.13–5.03 (m, 1H), 4.77 (dd, J = 8.8, 6.8 Hz, 1H), 4.52–4.43 (m, 1H), 4.40–4.32 (m, 1H), 3.98–3.86 (m, 1H), 3.78 (s, 3H), 3.65–3.51 (m, 2H), 3.15–2.97 (m, 2.7H), 2.84–2.79 (m, 0.3H), 2.76–2.70 (m, 0.3H), 2.66–2.59 (m, 0.7H), 2.54–2.41 (m, 1H), 2.20–1.96 (m, 3H), 1.45–1.42 (m, 9H), 1.15–0.95 (m, 2H), 0.93–0.85 (m, 12H), 0.82–0.72 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 172.4, 171.5, 158.0, 155.8, 138.1, 132.6, 130.0, 128.5, 128.4, 127.9, 127.8, 113.9, 79.8, 73.1, 69.6, 60.2, 55.4, 54.2, 38.8, 34.8, 31.5, 31.3, 28.4, 21.4, 20.1, 19.6, 19.3, 18.0, 17.7 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{36}H_{56}N_3O_6^+$, 626.4164, found: 626.4164.

tert-Butyl ((*S*)-1-(((*S*)-1-(((2*S*,3*R*)-1-(benzyloxy)-3-(3-fluorobenzyl)pentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (19c)

Colorless oil (1.73 g, 88%, two steps); $[\alpha]_D^{26}$ −11.2 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3296, 2962, 1693, 1630, 1524, 1417, 1249, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.26 (m, 5H), 7.26–7.24 (m, 1H), 7.23–7.17 (m, 1H), 6.94–6.81 (m, 3H), 6.63–6.48 (m, 1H), 5.10–5.06 (m, 0.7H), 4.79–4.70 (m, 1.3H), 4.50–4.34 (m, 2H), 3.98–3.87 (m, 1H), 3.68–3.48 (m, 2H), 3.14–3.01 (m, 2.7H), 2.85–2.81 (m, 0.3H), 2.81–2.72 (m, 0.3H), 2.71–2.61 (m, 0.7H), 2.57–2.45 (m, 1H), 2.22–2.15 (m, 0.3H), 2.14–1.98 (m, 2.7H), 1.45–1.42 (m, 9H), 1.27–1.04 (m, 2H), 0.93–0.85 (m, 12H), 0.82–0.71 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 172.6, 172.4, 171.5, 163.0 (d, J = 243.9 Hz), 155.8, 143.3 (d, J = 6.8 Hz), 137.9, 129.9, 129.8 (d, J = 8.0 Hz), 128.5, 128.4, 128.0, 127.9, 127.8, 124.7, 115.8 (d, J = 20.8 Hz), 113.0 (d, J = 20.8 Hz), 79.8, 73.2, 69.7, 60.1, 54.1, 38.5, 35.6, 31.5, 31.3, 28.4, 21.4, 20.5, 20.1, 19.6, 19.3, 18.0, 17.7, 17.2, 9.2, 8.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.0 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{35}H_{53}FN_3O_5^+$, 614.3964, found: 614.3967.

Benzyl *N*-(*tert*-butoxycarbonyl)-L-valyl-L-valyl-*N*-methyl-L-isoleucinate (25a)

Colorless oil (1.60 g, 94%, two steps); $[\alpha]_D^{22}$ −88.1 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3322, 2964, 1738, 1690, 1525, 1179, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 5H), 6.50–6.43 (m, 1H), 5.22–5.04 (m, 4H), 4.75–4.69 (m, 1H), 3.93–3.88 (m, 1H), 3.00–2.97 (m, 3H), 2.08–1.97 (m, 2H), 1.96–1.88 (m, 1H), 1.45–1.42 (m, 9H), 1.30–1.24 (m, 1H), 1.03–0.96 (m, 1H), 0.95–0.93 (m, 3H), 0.92–0.88 (m, 6H), 0.85–0.80 (m, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.6, 171.6, 170.8, 155.8, 135.6, 128.7, 128.7, 128.6, 79.9, 66.8, 60.5, 60.1, 54.0, 33.1, 31.5, 31.4, 31.2, 28.4, 24.9, 19.4, 19.2, 18.0, 17.8, 15.9, 10.8 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{29}H_{48}N_3O_6^+$, 534.3538, found: 534.3531.

Benzyl *N*-(*tert*-butoxycarbonyl)-L-valyl-L-valyl-*N*-methyl-L-valinate (25b)

Colorless oil (1.53 g, 92%, two steps); $[\alpha]_D^{23}$ −92.0 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3322, 2964, 1738, 1692, 1525, 1366, 1178, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 5H), 6.53–6.40 (m, 1H), 5.24–5.18 (m, 1H), 5.08–5.02 (m, 2H), 4.98 (d, J = 10.4 Hz, 1H), 4.71 (dd, J = 8.8, 7.2 Hz, 1H), 3.94–3.88 (m, 1H), 2.97 (brs, 3H), 2.26–2.18 (m, 1H), 2.08–2.00 (m, 1H), 1.95–1.86 (m, 1H), 1.43 (s, 9H), 1.01–0.99 (m, 3H), 0.97–0.92 (m, 1H), 0.90–0.87 (m, 5H), 0.85–0.82 (m, 6H), 0.80–0.77 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)

δ 172.5, 171.5, 170.5, 155.7, 135.4, 128.6, 128.5, 128.5, 79.8, 66.7, 61.5, 60.0, 53.9, 31.3, 31.3, 31.0, 28.3, 27.0, 19.8, 19.3, 19.2, 18.6, 17.8, 17.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{46}N_3O_6^+$, 520.3381, found: 520.3377.

Benzyl *N*-(*tert*-butoxycarbonyl)-L-valyl-L-valyl-*N*-methyl-L-leucinate (25c)

Colorless oil (1.54 g, 90%, two steps); $[\alpha]_D^{21}$ −53.6 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3321, 2959, 1739, 1689, 1525, 1367, 1179, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.29 (m, 5H), 6.53–6.46 (m, 1H), 5.42 (dd, *J* = 10.8, 5.2 Hz, 1H), 5.17–5.05 (m, 3H), 4.76 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.91 (dd, *J* = 8.4, 6.8 Hz, 1H), 2.97–2.95 (m, 3H), 2.09–2.02 (m, 1H), 2.02–1.96 (m, 1H), 1.79–1.67 (m, 2H), 1.43 (s, 9H), 1.41–1.35 (m, 1H), 0.92–0.88 (m, 12H), 0.87–0.84 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.5, 171.5, 171.4, 155.7, 135.3, 128.6, 128.5, 79.8, 67.1, 60.0, 54.4, 53.8, 36.8, 31.3, 31.1, 31.1, 28.3, 24.7, 23.3, 21.3, 19.4, 19.1, 17.9, 17.5 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{29}H_{48}N_3O_6^+$, 534.3538, found: 534.3530.

Benzyl *N*-(*tert*-butoxycarbonyl)-L-valyl-L-valyl-*N*-methyl-L-phenylalaninate (25d)

Colorless oil (1.58 g, 87%, two steps); $[\alpha]_D^{23}$ −66.2 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 3321, 2963, 1739, 1525, 1366, 1247, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 3H), 7.31–7.28 (m, 2H), 7.25–7.20 (m, 2H), 7.19–7.14 (m, 3H), 6.41–6.36 (m, 1H), 5.48 (dd, *J* = 10.4, 5.6 Hz, 1H), 5.19–5.09 (m, 2H), 5.02–4.98 (m, 1H), 4.66 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.84 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.42 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.98 (dd, *J* = 14.8, 10.4 Hz, 1H), 2.89–2.87 (m, 3H), 2.00–1.88 (m, 2H), 1.44–1.43 (m, 9H), 0.90–0.87 (m, 3H), 0.85–0.79 (m, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.0, 171.4, 170.5, 155.8, 136.6, 135.4, 128.8, 128.7, 128.6, 128.6, 127.0, 79.9, 67.4, 60.1, 58.0, 53.6, 34.5, 32.5, 31.5, 31.1, 28.4, 19.7, 19.4, 18.0, 17.2 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{32}H_{46}N_3O_6^+$, 568.3381, found: 568.3377.

General procedure for the synthesis of 20a, 20b and 20c

Compounds **19a**/**19b**/**19c** (2.60 mmol) and 10% Pd/C (800 mg) were stirred in MeOH (50 mL) for 4 h under a H_2 atmosphere. Then, the mixture was filtered to give a crude alcohol, which was purified by flash chromatography on silica gel (PE/EA = 1 : 1) to give the title product (**20a**, **20b** and **20c**).

***tert*-Butyl ((*S*)-1-(((*S*)-1-(((2*S*,3*R*)-3-benzyl-1-hydroxypentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (20a)**

Colorless oil (1.08 g, 82%); $[\alpha]_D^{24}$ −11.1 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3434, 2965, 1625, 1496, 1417, 1300, 1247, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.84–7.70 (m, 0.5H), 7.38–7.24 (m, 3H), 7.23–7.16 (m, 2H), 7.15–7.08 (m, 1H), 7.07–6.87 (m, 0.5H), 5.25–5.05 (m, 1H), 4.87–4.67 (m, 1H), 4.67–4.47 (m, 1H), 4.27–4.15 (m, 0.5H), 4.15–4.02 (m, 0.5H), 4.02–3.91 (m, 1H), 3.72–3.46 (m, 1H), 3.16–2.93 (m, 3H), 2.85–2.78 (m, 0.5H), 2.75–2.70 (m, 0.5H), 2.58–2.53 (m, 0.5H), 2.51–2.33 (m, 0.5H), 2.11–1.96 (m, 3H), 1.42 (s, 9H), 1.26–1.06 (m, 2H), 1.00–0.84 (m, 12H), 0.83–0.68 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 174.0, 173.6, 172.2, 171.8, 140.6, 140.5, 129.5, 129.0, 128.7, 128.5, 126.2, 79.9, 61.8, 61.3, 59.8, 58.9, 58.7, 55.2, 54.6, 39.1, 38.7, 35.9, 35.6, 32.0, 31.6, 31.5, 31.2, 31.3, 28.4, 21.5, 19.9, 19.4, 19.3, 18.4, 18.1, 17.9, 9.1, 8.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{48}N_3O_5^+$, 506.3589, found: 506.3590.

***tert*-Butyl-((*S*)-1-(((*S*)-1-(((2*S*,3*R*)-1-hydroxy-3-(4-methoxybenzyl)pentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (20b)**

Colorless oil (1.11 g, 80%); $[\alpha]_D^{23}$ −13.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3326, 2963, 1624, 1513, 1466, 1366, 1246, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.17–7.09 (m, 1H), 7.09–7.01 (m, 2H), 6.90–6.84 (m, 0.5H), 6.84–6.80 (m, 2H), 6.75–6.69 (m, 0.5H), 5.18–5.07 (m, 1H), 4.83–4.70 (m, 1H), 4.60–4.54 (m, 0.5H), 4.49–4.42 (m, 0.5H), 4.07–4.03 (m, 0.5H), 4.00–3.95 (m, 0.5H), 3.93–3.85 (m, 1H), 3.79 (s, 3H), 3.69–3.59 (m, 1H), 3.14–3.01 (m, 3H), 2.70–2.59 (m, 1H), 2.56–2.50 (m, 1H), 2.38–2.32 (m, 0.5H), 2.12–2.08 (m, 0.5H), 2.06–1.96 (m, 2H), 1.45–1.42 (m, 9H), 1.25–1.08 (m, 2H), 0.97–0.88 (m, 12H), 0.85–0.77 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.9, 173.6, 172.2, 171.8, 158.0, 155.9, 132.4, 132.3, 130.5, 129.9, 114.0, 79.9, 61.9, 61.3, 59.9, 58.7, 55.4, 55.2, 54.6, 39.2, 38.8, 34.9, 34.6, 31.7, 31.3, 31.1, 28.4, 20.5, 19.9, 19.5, 19.4, 18.0, 17.9, 9.2, 8.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{29}H_{50}N_3O_6^+$, 536.3694, found: 536.3695.

***tert*-Butyl ((*S*)-1-(((*S*)-1-(((2*S*,3*R*)-3-(3-Fluorobenzyl)-1-hydroxypentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (20c)**

Colorless oil (1.13 g, 83%); $[\alpha]_D^{26}$ −12.4 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3292, 2964, 1623, 1525, 1417, 1366, 1173, 779 cm^{-1};^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.46–7.27 (m, 1H), 7.26–7.18 (m, 1H), 7.04–6.83 (m, 3H), 6.83–6.60 (m, 1H), 5.19–4.95 (m, 1H), 4.87–4.67 (m, 1H), 4.64–4.39 (m, 1H), 4.16–3.94 (m, 1H), 3.93–3.83 (m, 1H), 3.74–3.51 (m, 1H), 3.15–3.01 (m, 3H), 2.77–2.65 (m, 1H), 2.58–2.45 (m, 1H), 2.13–2.03 (m, 2H), 2.02–1.81 (m, 1H), 1.47–1.41 (m, 9H), 1.25–1.06 (m, 2H), 1.03–0.91(m, 12H), 0.76 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.6, 171.8, 169.1, 163.0 (d, *J* = 245.4 Hz), 155.9, 143.1, 130.0 (d, *J* = 8.1 Hz), 124.7, 115.8 (d, *J* = 20.6 Hz), 113.2 (d, *J* = 21.0 Hz), 80.0, 62.0, 61.4, 60.0, 59.5, 54.7, 38.9, 35.7, 32.2, 31.8, 31.4, 31.1, 28.4, 21.5, 19.3, 18.0, 9.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{47}FN_3O_5^+$, 524.3494, found: 524.3497.

General procedure for the synthesis of 21a, 21b, 21c, 27a, 27b, 27c and 27d

Compounds **20a**/**20b**/**20c**/**26a**/**26b**/**26c**/**26d** (1.50 mmol) in DCM (8 mL) were added to Dess–Martin periodinane (672 mg,

3.00 mmol) and stirred for 30 min at room temperature. The mixture was carefully quenched with a solution of saturated aqueous $NaHCO_3$ and solid $Na_2S_2O_3$. The resulting mixture was extracted with DCM (30 mL × 3), and the combined organic layers were washed with brine, and then dried and concentrated to give the aldehyde without further purification. To a solution of benzyl acetate (0.51 ml, 3.60 mmol) in THF was added dropwise a solution of LDA (1.73 ml, 3.45 mmol, 2 M in THF) at −78 °C and stirred for 30 min. The solution of the above aldehyde in THF (2 ml) was added dropwise, and the reaction mixture was stirred for 30 min at −78 °C. The mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 2 : 1) to give the title product (**21a**, **21b**, **21c**, **27a**, **27b**, **27c** and **27d**).

Benzyl (6*S*,9*S*,12*S*,13*R*)-13-hydroxy-6,9-diisopropyl-2,2,11-trimethyl-4,7,10-trioxo-12-((*R*)-1-phenylbutan-2-yl)-3-oxa-5,8,11-triazapentadecan-15-oate (21a)

Colorless oil (519 mg, 53%, dr = 66 : 34, two steps); $[\alpha]_D^{24}$ −10.6 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3439, 2963, 1636, 1496, 1390, 1301, 1167, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5H), 7.31–7.27 (m, 1H), 7.27–7.22 (m, 2H), 7.20–7.14 (m, 3H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.16–5.11 (m, 2H), 5.08 (d, *J* = 8.4 Hz, 1H), 4.78 (dd, *J* = 8.0, 7.2 Hz, 1H), 4.46–4.39 (m, 1H), 3.97 (dd, *J* = 8.0, 7.2 Hz, 1H), 3.10–3.01 (m, 3H), 2.96–2.87 (m, 1H), 2.57–2.48 (m, 3H), 2.35–2.21 (m, 1H), 2.07–1.98 (m, 2H), 1.44 (s, 9H), 1.38–1.26 (m, 2H), 1.14–1.04 (m, 1H), 1.02–0.96 (m, 3H), 0.98–0.87 (m, 9H), 0.76 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$,) δ 173.3, 172.3, 171.7, 155.9, 140.8, 135.7, 129.1, 128.7, 128.6, 128.5, 128.4, 126.1, 79.9, 69.5, 66.8, 60.2, 54.3, 40.3, 39.2, 36.2, 31.3, 31.2, 28.4, 22.2, 19.9, 19.4, 18.0, 17.6, 10.1 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{37}H_{56}N_3O_7^+$, 654.4113, found: 654.4114.

Benzyl(6*S*,9*S*,12*S*,13*R*)-13-hydroxy-6,9-diisopropyl-12-((*R*)-1-(4-methoxyphenyl)butan-2-yl)-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (21b)

Colorless oil (625 mg, 61%, dr = 54 : 46, two steps); $[\alpha]_D^{24}$ −10.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3433, 2963, 1626, 1512, 1366, 1247, 1173, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 5H), 7.20–7.10 (m, 1H), 7.10–7.02 (m, 2H), 6.88–6.81 (m, 1H), 6.81–6.69 (m, 2H), 5.15–5.12 (m, 2H), 5.11–5.00 (m, 1H), 4.78 (dd, *J* = 7.2, 6.4 Hz, 1H), 4.47–4.39 (m, 1H), 4.42–3.95 (m, 1H), 3.78 (s, 3H), 3.10–2.98 (m, 3H), 2.90–2.79 (m, 1H), 2.57–2.48 (m, 2H), 2.48–2.40 (m, 1H), 2.26–2.14 (m, 1H), 2.10–1.96 (m, 2H), 1.44 (s, 9H), 1.37–1.22 (m, 2H), 1.12–1.03 (m, 1H), 1.02–0.96 (m, 3H), 0.93–0.85 (m, 9H), 0.78–0.75 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.4, 172.3, 171.7, 158.0, 155.8, 135.7, 132.7, 130.0, 128.7, 128.5, 128.4, 113.9, 79.9, 69.5, 66.8, 60.1, 58.6, 55.3, 54.3, 40.4, 39.1, 35.2, 31.3, 31.2, 28.4, 22.2, 19.9, 19.3, 18.6, 18.1, 17.6, 10.1 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{38}H_{58}N_3O_8^+$, 684.4218, found: 684.4219.

Benzyl(6*S*,9*S*,12*S*,13*R*)-12-((*R*)-1-(3-fluorophenyl)butan-2-yl)-13-hydroxy-6,9-diisopropyl-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (21c)

Colorless oil (725 mg, 72%, dr = 72 : 28, two steps); $[\alpha]_D^{26}$ −11.8 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3323, 2963, 1626, 1524, 1386, 1169, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (m, 5H), 7.25–7.17 (m, 1H), 6.99–6.95 (m, 1H), 6.94–6.82 (m, 2H), 6.61 (d, *J* = 8.8 Hz, 1H), 5.18–5.11 (m, 2H), 5.05 (d, *J* = 8.4 Hz, 1H), 4.77 (dd, *J* = 7.2, 6.4 Hz, 1H), 4.42–4.32 (m, 1H), 3.99–3.88 (m, 1H), 3.09–3.01 (m, 3H), 2.98–2.87 (m, 1H), 2.56–2.51 (m, 2H), 2.51–2.44 (m, 1H), 2.37–2.20 (m, 1H), 2.07–2.00 (m, 2H), 1.41 (s, 9H), 1.39–1.27 (m, 2H), 1.16–1.04 (m, 1H), 1.01–0.94 (m, 3H), 0.94–0.83 (m, 9H), 0.77 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.2, 172.4, 171.7, 162.5 (d, *J* = 243.7 Hz), 155.9, 135.6, 129.8 (d, *J* = 8.3 Hz), 128.7, 128.6, 128.5, 124.8, 115.9 (d, *J* = 20.7 Hz), 113.0 (d, *J* = 20.8 Hz), 80.0, 69.5, 66.9, 60.2, 54.3, 40.4, 39.3, 36.0, 31.3, 31.1, 28.4, 22.2, 20.0, 19.4, 18.0, 17.5, 10.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{37}H_{55}FN_3O_7^+$, 672.4019, found: 672.4017.

Benzyl(6*S*,9*S*,12*S*,13*R*)-12-((*S*)-*sec*-butyl)-13-hydroxy-6,9-diisopropyl-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (27a)

Colorless oil (545 mg, 63%, dr = 75 : 25, two steps); $[\alpha]_D^{23}$ −21.4 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3302, 2964, 1693, 1525, 1417, 1297, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.32 (m, 5H), 7.34–7.30 (m, 1H), 6.87–6.71 (m, 1H), 5.17–5.12 (m, 2H), 5.10–5.05 (m, 1H), 4.77 (d, *J* = 9.2, 7.2 Hz, 1H), 4.40–4.32 (m, 1H), 4.03–3.94 (m, 1H), 3.73–3.48 (m, 1H), 3.04–3.02 (m, 2.7H), 2.79–2.78 (m, 0.3H), 2.58–2.52 (m, 2H), 2.07–1.99 (m, 2H), 1.96–1.85 (m, 1H), 1.44–1.42 (m, 9H), 1.42–1.36 (m, 2H), 1.00–0.97 (m, 6H), 0.92–0.88 (m, 9H), 0.83 (t, *J* = 7.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.6, 172.3, 171.7, 155.8, 135.7, 128.7, 128.5, 128.5, 128.4, 79.9, 69.8, 66.8, 60.0, 54.3, 39.2, 33.6, 31.4, 31.3, 28.4, 26.1, 19.8, 19.3, 18.1, 18.0, 17.7, 17.5, 16.2, 11.1 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{31}H_{52}N_3O_7^+$, 578.3800, found: 578.3796.

Benzyl (6*S*,9*S*,12*S*,13*R*)-13-hydroxy-6,9,12-triisopropyl-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (27b)

Colorless oil (481 mg, 57%, dr = 70 : 30, two steps); $[\alpha]_D^{23}$ +4.0 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 2971, 2920, 1668, 1396, 1202, 1135, 936, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 5H), 7.34–7.31 (m, 1H), 5.21–5.13 (m, 3H), 4.79 (dd, *J* = 8.8, 7.2 Hz, 1H), 4.36 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.10–3.95 (m, 1H), 3.08–3.03 (m, 3H), 2.59–2.50 (m, 2H), 2.25–2.11 (m, 1H), 2.20–1.98 (m, 3H), 1.45–1.43 (m, 9H), 1.04–1.01 (m, 3H), 1.00–0.98 (m, 3H), 0.95–0.92 (m, 3H), 0.91–0.88 (m, 6H), 0.86–0.83 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.7, 172.2, 155.9, 135.7, 128.7, 128.5, 128.5, 128.4, 80.0, 69.8, 66.8, 60.1, 54.5, 39.3, 31.3, 31.2, 28.4, 27.4, 20.5, 20.4, 19.7, 19.3, 18.2, 17.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{50}N_3O_7^+$, 564.3643, found: 564.3646.

Benzyl(6*S*,9*S*,12*S*,13*R*)-13-hydroxy-12-isobutyl-6,9-diisopropyl-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (27c)

Colorless oil (563 mg, 65%, two steps); $[\alpha]_D^{23}$ −31.6 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3319, 2961, 1690, 1525, 1417, 1172, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5H), 6.69–6.58 (m, 1H), 5.15–5.11 (m, 2H), 5.10–5.04 (m, 1H), 4.87–4.74 (m, 2H), 4.09–4.01 (m, 1H), 3.96–3.91 (m, 1H), 3.08–3.04 (m, 2H), 3.00–2.99 (m, 1H), 2.53–2.49 (m, 1H), 2.12–2.00 (m, 3H), 1.78–1.58 (m, 2H), 1.44–1.43 (m, 9H), 1.40–1.34 (m, 1H), 1.03–0.99 (m, 2H), 0.98–0.95 (m, 3H), 0.94–0.93 (m, 2H), 0.91–0.88 (m, 9H), 0.84–0.81 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.1, 198.9, 173.3, 172.8, 172.7, 172.6, 171.8, 171.6, 155.8, 135.6, 128.7, 128.5, 128.5, 128.4, 80.0, 79.9, 70.4, 66.8, 63.3, 60.1, 54.2, 54.0, 38.9, 37.4, 35.1, 34.5, 33.3, 31.5, 31.4, 31.3, 31.3, 31.1, 28.4, 25.0, 24.9, 24.0, 23.4, 21.6, 19.9, 19.8, 19.6, 19.3, 18.0, 17.8, 17.6, 17.5 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{31}H_{52}N_3O_7^+$, 578.3800, found: 578.3795.

Benzyl(6*S*,9*S*,12*S*,13*R*)-12-benzyl-13-hydroxy-6,9-diisopropyl-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (27d)

Colorless oil (651 mg, 71%, two steps); $[\alpha]_D^{23}$ −32.8 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3333, 2959, 1633, 1533, 1180, 937, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 5H), 7.26–7.10 (m, 5H), 6.61–6.48 (m, 1H), 5.18–5.09 (m, 2H), 5.08–5.02 (m, 1H), 4.63–4.54 (m, 1H), 4.32–4.10 (m, 2H), 3.94–3.83 (m, 1H), 3.34–3.12 (m, 1H), 3.08–2.96 (m, 1H), 2.94–2.74 (m, 3H), 2.57–2.42 (m, 2H), 2.03–1.95 (m, 1H), 1.91–1.81 (m, 1H), 1.45–1.40 (m, 9H), 0.92–0.88 (m, 3H), 0.87–0.78 (m, 9H), 0.48–0.34 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.7, 172.7, 172.6, 172.3, 171.6, 171.5, 155.8, 138.3, 138.2, 135.6, 135.5, 129.4, 128.9, 128.9, 128.7, 128.7, 128.6, 128.5, 128.4, 128.4, 127.7, 127.1, 126.9, 126.6, 79.9, 70.1, 69.6, 66.9, 66.8, 63.6, 60.2, 60.0, 54.0, 53.1, 39.0, 34.1, 32.6, 31.1, 30.7, 30.4, 29.2, 28.4, 20.2, 19.3, 18.0, 17.9, 17.0, 16.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{34}H_{50}N_3O_7^+$, 612.3643, found: 612.3645.

General procedure for the synthesis of 23a, 23b, 23c and 23d

Compounds **22a**/**22b**/**22c**/**22d** (20.00 mmol) were stirred in H_2O/dioxane (35 ml/30 ml), then NaOH (1.60 g, 40.00 mmol) and Boc_2O (4.80 g, 22.00 mmol) were added and the mixture was stirred overnight at room temperature. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (50 mL × 1). The water phase was acidified with hydrochloric acid to pH = 2–3 and the resulting mixture was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a crude acid without further purification. To a cooled (0 °C) solution of the above crude acid in THF (70 mL) was added NaH (1.23 g, 51.30 mmol) three portions and stirred for 30 min. MeI (4.36 mL, 70.00 mmol) was slowly added dropwise and stirred for 48 h. The mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a crude acid without further purification. A solution of the above acid in DMSO (70 mL) was treated with K_2CO_3 (4.24 g, 40.00 mmol) and BnBr (2.37 mL, 20.00 mmol) 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 and brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 15 : 1) to give the desired product (**23a**, **23b**, **23c** and **23d**).

Benzyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-isoleucinate (23a)[13d]

Colorless oil (2.68 g, 40%, three steps).

Benzyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-valinate (23b)

Colorless oil (2.70 g, 42%, three steps); $[\alpha]_D^{23}$ −67.3 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2967, 1739, 1455, 1392, 1258, 1144, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.38–7.28 (m, 5 H), 5.19–5.11 (m, 2H), 4.51 (d, *J* = 10.4 Hz, 0.5 H), 4.15 (d, *J* = 10.4 Hz, 0.5 H), 2.85–2.76 (m, 3H), 2.25–2.13 (m, 1H), 1.46–1.41 (m, 9H), 0.97–0.94 (m, 3H), 0.91–0.87 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 171.5, 171.1, 156.4, 155.8, 136.0, 135.8, 128.7, 128.6, 128.4, 128.2, 128.1, 80.4, 80.1, 66.5, 66.3, 65.2, 63.4, 30.7, 30.6, 28.5, 27.9, 27.7, 20.1, 19.9, 19.2, 18.9 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{28}NO_4^+$, 322.2013, found: 322.2009.

Benzyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucinate (23c)

Colorless oil (2.75 g, 41%, three steps); $[\alpha]_D^{21}$ −29.3 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 2959, 1698, 1455, 1391, 1367, 1151, 972, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.31 (m, 5H), 5.16–5.13 (m, 2H), 4.93 (dd, *J* = 8.8, 7.2 Hz, 0.5H), 4.63 (dd, *J* = 10.8, 4.8 Hz, 0.5H), 2.80–2.74 (m, 3H), 1.78–1.67 (m, 2H), 1.60–1.51 (m, 1H), 1.46–1.40 (m, 9H), 0.96–0.91 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, rotamers) δ 172.5, 172.3, 156.4, 155.8, 136.0, 135.8, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 80.4, 80.0, 66.7, 66.6, 57.4, 56.2, 38.0, 37.5, 30.6, 30.5, 28.5, 28.4, 25.0, 24.7, 23.4, 23.4, 21.4, 21.3 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{30}NO_4^+$, 336.2169, found: 336.2162.

Benzyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-phenylalaninate (23d)

Colorless oil (2.95 g, 40%, three steps); $[\alpha]_D^{23}$ −47.5 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 1743, 1693, 1455, 1142, 849, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.36–7.31 (m, 5H), 7.29–7.26 (m, 1.5H), 7.24–7.15 (m, 3.5H), 5.22–5.12 (m, 2H), 4.95 (dd, *J* = 10.4, 5.2 Hz, 0.5H), 4.62 (dd, *J* = 10.8, 4.4 Hz, 0.5H), 3.37–3.26 (m, 1H), 3.08–2.99 (m, 1H), 2.72–2.67 (m, 3H), 1.37–1.29 (m, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 171.4, 171.1, 155.9, 155.1, 137.7, 137.5, 135.8, 135.6, 129.1, 129.1, 128.7, 128.7, 128.5, 128.3, 128.2, 126.8, 126.6, 80.4, 80.1, 67.0, 66.9, 61.7, 59.9, 35.6, 35.1, 32.6, 32.3, 28.4, 28.3 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{28}NO_4^+$, 370.2013, found: 370.2007.

General procedure for the synthesis of 26a, 26b, 26c and 26d

To a solution of **25a**/**25b**/**25c**/**25d** (2.70 mmol) in THF (11 ml) was added dropwise $LiHBEt_3$ (8.10 ml, 8.10 mmol, 1 M in THF) at 0 °C before gradually warming to room temperature, and the reaction mixture was stirred overnight. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 1 : 1) to give the title product (**26a**, **26b**, **26c** and **26d**).

***tert*-Butyl-((*S*)-1-(((*S*)-1-(((2*S*,3*S*)-1-hydroxy-3-methylpentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (26a)**

Colorless oil (1.04 g, 90%); $[\alpha]_D^{23}$ −30.6 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 3290, 2964, 1693, 1366, 1175, 1016, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.49–7.44 (m, 0.75H), 6.77–6.73 (m, 0.25H), 5.15–5.12 (m, 0.75H), 5.01–4.97 (m, 0.25H), 4.83–4.77 (m, 1H), 4.36–4.28 (m, 1H), 4.17–4.11 (m, 1H), 3.97–3.82 (m, 2H), 3.61–3.50 (m, 1H), 3.02–3.01 (m, 2.25H), 2.94–2.87 (m, 1H), 2.78–2.77 (m, 0.75H), 2.09–2.01 (m, 2H), 1.69–1.62 (m, 1H), 1.59–1.47 (m, 1H), 1.44–1.42 (m, 9H), 1.02–1.00 (m, 3H), 0.94–0.91 (m, 12H), 0.80 (t, *J* = 7.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.7, 171.8, 155.9, 79.9, 64.5, 61.5, 61.3, 60.3, 59.8, 54.6, 54.2, 53.6, 35.4, 32.8, 31.9, 31.7, 31.4, 30.9, 28.4, 27.6, 25.7, 20.3, 19.4, 19.3, 19.2, 18.4, 18.2, 18.1, 16.3, 15.9, 11.9, 10.5 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{44}N_3O_5^+$, 430.3276, found: 430.3273.

***tert*-Butyl-((*S*)-1-(((*S*)-1-(((*S*)-1-hydroxy-3-methylbutan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (26b)**

Colorless oil (1.01 g, 90%); $[\alpha]_D^{20}$ −37.9 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3302, 2964, 1693, 1533, 1367, 1247, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.74–7.65 (m, 0.76H), 7.10–7.03 (m, 0.24H), 5.23–5.02 (m, 1H), 4.84–4.74 (m, 1H), 4.36–4.28 (m, 0.76H), 4.25–4.19 (m, 0.76H), 4.02–3.96 (m, 0.24H), 3.91–3.84 (m, 1H), 3.75–3.68 (m, 0.24H), 3.59–3.40 (m, 1H), 3.24–3.10 (m, 1H), 3.04–3.02 (m, 2.24H), 2.80–2.79 (m, 0.76H), 2.16–2.06 (m, 0.76H), 2.03–1.94 (m, 1.24H), 1.86–1.76 (m, 1H), 1.44–1.41 (m, 9H), 1.04–1.01 (m, 3H), 0.98–0.90 (m, 13H), 0.81–0.79 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.8, 173.2, 172.8, 171.9, 155.9, 80.1, 79.8, 65.4, 62.8, 61.3, 60.5, 60.2, 59.7, 54.6, 54.2, 32.0, 31.7, 31.5, 31.0, 30.9, 28.6, 28.4, 27.5, 27.0, 21.2, 21.0, 20.3, 20.1, 20.0, 19.3, 19.2, 19.2, 18.5, 18.2, 18.1 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{42}N_3O_5^+$, 416.3119, found: 416.3120.

***tert*-Butyl-((*S*)-1-(((*S*)-1-(((*S*)-1-hydroxy-4-methylpentan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (26c)**

Colorless oil (695 mg, 60%); $[\alpha]_D^{22}$ −24.5 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3293, 2959, 1696, 1535, 1468, 1366, 1173, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.65–7.57 (m, 0.73H), 6.90–6.82 (m, 0.27H), 5.20–5.15 (m, 0.73H), 5.07–5.01 (m, 0.27H), 4.88–4.70 (m, 2H), 4.27–4.12 (m, 1H), 4.00–3.84 (m, 0.27H), 3.68–3.56 (m, 1H), 3.54–3.41 (m, 1H), 3.25–3.03 (m, 0.73H), 2.98–2.97 (m, 2.27H), 2.79–2.78 (m, 0.73H), 2.11–2.05 (m, 0.73H), 2.04–1.96 (m, 1.27H), 1.93–1.74 (m, 0.73H), 1.62–1.56 (m, 0.27H), 1.44–1.41 (m, 9H), 1.39–1.36 (m, 1H), 1.21–1.11 (m, 1H), 1.02–1.00 (m, 2H), 0.99–0.95 (m, 3H), 0.95–0.93 (m, 3H), 0.92–0.87 (m, 7H), 0.87–0.84 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.6, 172.8, 172.7, 171.7, 155.8, 80.0, 79.7, 63.1, 62.4, 60.0, 59.6, 57.2, 54.5, 54.3, 54.0, 39.1, 36.6, 31.9, 31.7, 31.3, 30.9, 29.7, 28.3, 26.9, 24.9, 24.8, 23.5, 23.3, 22.8, 22.0, 19.7, 19.2, 19.0, 18.4, 18.2, 18.1, 17.9 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{44}N_3O_5^+$, 430.3276, found: 430.3277.

***tert*-Butyl-((*S*)-1-(((*S*)-1-(((*S*)-1-hydroxy-3-phenylpropan-2-yl)(methyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (26d)**

Colorless oil (738 mg, 59%); $[\alpha]_D^{23}$ −57.8 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3310, 2965, 1686, 1523, 1366, 1247, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.32–7.27 (m, 1H), 7.25–7.22 (m, 1H), 7.21–7.15 (m, 3H), 7.01–6.95 (m, 0.5H), 6.77–6.72 (m, 0.5H), 5.13–5.08 (m, 0.5H), 5.05–5.02 (m, 0.5H), 4.72–4.64 (m, 1H), 4.51–4.46 (m, 0.5H), 4.43–4.36 (m, 0.5H), 4.06–3.99 (m, 0.5H), 3.95–3.88 (m, 0.5H), 3.73–3.69 (m, 1.5H), 3.61–3.52 (m, 0.5H), 3.16–3.03 (m, 1H), 2.97–2.96 (m, 1.5H), 2.91–2.90 (m, 1.5H), 2.89–2.83 (m, 1H), 2.81–2.77 (m, 1H), 2.03–1.95 (m, 1H), 1.68–1.58 (m, 1H), 1.44–1.41 (m, 9H), 0.97–0.94 (m, 1.5H), 0.92–0.89 (m, 4.5H), 0.88–0.86 (m, 3H), 0.78–0.75 (m, 1.5H), 0.48–0.45 (m, 1.5H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.0, 172.8, 172.8, 171.7, 155.9, 137.8, 137.7, 129.2, 129.0, 128.9, 128.6, 127.1, 126.7, 80.2, 79.9, 62.7, 62.4, 61.3, 60.2, 59.9, 59.7, 54.6, 54.2, 36.0, 34.5, 32.7, 31.6, 31.3, 30.9, 30.8, 28.4, 28.4, 19.7, 19.4, 19.3, 19.2, 18.2, 18.0, 17.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{42}N_3O_5^+$, 464.3119, found: 464.3117.

General procedure for the synthesis of 28a, 28b, 28c, 28d, 28e, 28f and 28g

Compounds **21a**/**21b**/**21c**/**27a**/**27b**/**27c**/**27d** (0.49 mmol) and HMPA (94 μL, 0.54 mmol) were stirred in THF (2 mL) at −78 °C, then a solution of LiHMDS (0.49 ml, 0.49 mmol, 1 M in THF) was slowly added dropwise and stirred for 30 min. The reaction mixture was warmed to −15 °C and MeOTf (111 μL, 0.98 mmol) was added and stirred for an additional 15 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 2 : 1) to give the title product (**28a**, **28b**, **28c**, **28d**, **28e**, **28f** and **28g**).

Benzyl-(6*S*,9*S*,12*S*,13*R*)-6,9,12-triisopropyl-13-methoxy-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (28a)

Colorless oil (156 mg, 55%); $[\alpha]_D^{23}$ −40.0 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 3288, 2964, 1739, 1525, 1417, 1390, 1170, 698 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.33 (m, 5H), 6.56–6.49 (m, 1H), 5.20–5.08 (m, 3H), 4.78–4.64 (m, 2H), 3.97–3.90 (m, 2H), 3.33–3.29 (m, 3H), 2.99–2.76 (m, 3H), 2.60–2.44 (m, 2H), 2.07–1.99 (m, 2H), 1.43 (s, 9H), 1.01–0.97 (m, 6H), 0.93–0.88 (m, 9H), 0.83–0.79 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 172.4, 170.9, 170.9, 155.1, 135.1, 127.9, 127.8, 127.7, 79.1, 77.8, 77.3, 66.1, 66.0, 63.8, 59.3, 57.8, 57.6, 57.3, 53.5, 52.8, 36.6, 36.1, 31.0, 30.6, 30.6, 30.5, 27.7, 26.3, 20.2, 19.8, 19.4, 19.3, 18.9, 18.5, 17.2, 17.0, 15.9 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{31}H_{52}N_3O_7^+$, 578.3800, found: 578.3799.

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 (28b)[13d]

Colorless oil (153 mg, 53%).

Benzyl-(6*S*,9*S*,12*S*,13*R*)-6,9-diisopropyl-13-methoxy-2,2,11-trimethyl-4,7,10-trioxo-12-((*R*)-1-phenylbutan-2-yl)-3-oxa-5,8,11-triazapentadecan-15-oate (28c)

Colorless oil (252 mg, 77%); $[\alpha]_D^{23}$ −9.7 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3322, 2964, 1626, 1455, 1390, 1367, 1169, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5H), 7.28–7.25 (m, 2H), 7.25–7.22 (m, 1H), 7.20–7.13 (m, 3H), 6.49 (d, *J* = 8.8 Hz, 1H), 5.18–5.08 (m, 2H), 5.08–5.05 (m, 1H), 5.02–4.90 (m, 1H), 4.80–4.72 (m, 1H), 4.12–3.97 (m, 1H), 3.97–3.85 (m, 1H), 3.35–3.32 (m, 3H), 3.02–2.96 (m, 3H), 2.80–2.72 (m, 1H), 2.61–2.42 (m, 3H), 2.09–1.95 (m, 3H), 1.44 (s, 9H), 1.16–1.02 (m, 1H), 1.02–0.95 (m, 3H), 0.92–0.85 (m, 9H), 0.76 (t, *J* = 7.0 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$,) δ 172.8, 171.6, 171.5, 155.8, 140.5, 135.8, 129.1, 128.7, 128.5, 126.2, 79.9, 78.0, 66.8, 60.1, 58.0, 54.2, 39.9, 37.4, 35.9, 31.3, 31.2, 28.4, 22.1, 19.8, 19.3, 18.0, 17.5, 9.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{38}H_{58}N_3O_7^+$, 668.4269, found: 668.4268.

Benzyl (6*S*,9*S*,12*S*,13*R*)-6,9-diisopropyl-13-methoxy-12-(1-(4-methoxyphenyl)butan-2-yl)-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (28d)

Colorless oil (249 mg, 73%); $[\alpha]_D^{24}$ −7.5 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3322, 2961, 1636, 1512, 1455, 1247, 1095, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 7.09–7.04 (m, 2H), 6.83–6.77 (m, 2H), 6.48 (d, *J* = 8.4 Hz, 1H), 5.19–5.08 (m, 2H), 5.08–5.03 (m, 1H), 5.01–4.85 (m, 1H), 4.76 (dd, *J* = 7.6, 6.8 Hz, 1H), 4.08–3.94 (m, 1H), 3.91 (dd, *J* = 7.6, 6.8 Hz, 1H), 3.78 (s, 3H), 3.34–3.31 (m, 3H), 2.99–2.96 (m, 3H), 2.72–2.63 (m, 1H), 2.60–2.41 (m, 3H), 2.08–1.94(m, 3H), 1.43 (s, 9H), 1.30–1.02 (m, 1H), 1.02–0.96 (m, 3H), 0.93–0.85 (m, 9H), 0.76 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.8, 171.5, 158.1, 155.8, 135.8, 132.4, 130.0, 128.7, 128.5, 113.9, 79.9, 78.0, 66.8, 60.2, 58.0, 55.4, 54.2, 40.1, 37.4, 34.9, 31.3, 28.5, 22.0, 19.8, 19.3, 18.0, 17.5, 9.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{39}H_{60}N_3O_8^+$, 698.4375, found: 698.4376.

Benzyl (6*S*,9*S*,12*S*,13*R*)-12-((*R*)-1-(3-fluorophenyl)butan-2-yl)-6,9-diisopropyl-13-methoxy-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (28e)

Colorless oil (225 mg, 67%); $[\alpha]_D^{26}$ −14.4 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3314, 2963, 1635, 1488, 1390, 1249, 1168, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 7.21 (dd, *J* = 14.0, 6.8 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.90–6.83 (m, 2H), 6.50 (d, *J* = 8.8 Hz, 1H), 5.20–5.09 (m, 2H), 5.08–5.03 (m, 1H), 4.99–4.84 (m, 1H), 4.76 (dd, *J* = 7.2, 6.4 Hz, 1H), 4.06–3.95 (m, 1H), 3.92 (dd, *J* = 8.0, 7.2 Hz, 1H), 4.06–3.96 (m, 1H), 3.34–3.32 (m, 3H), 3.01–2.98 (m, 3H), 2.79–2.71 (m, 1H), 2.59–2.46 (m, 3H), 2.08–1.97 (m, 3H), 1.43 (s, 9H), 1.16–1.02 (m, 1H), 1.00–0.94 (m, 3H), 0.90–0.87 (m, 9H), 0.76 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.9, 171.6, 171.5, 163.0 (d, *J* = 243.8 Hz), 155.8, 143.2, 135.8, 129.9 (d, *J* = 8.4 Hz), 128.7, 128.5, 124.8, 115.9 (d, *J* = 20.7 Hz), 113.1 (d, *J* = 20.9 Hz), 79.9, 78.0, 66.8, 60.2, 58.0, 54.2, 40.0, 37.6, 35.8, 31.3, 31.2, 28.4, 22.1, 19.8, 19.3, 18.0, 17.5, 10.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{38}H_{57}FN_3O_7^+$, 686.4175, found: 686.4179.

Benzyl(6*S*,9*S*,12*S*,13*R*)-12-isobutyl-6,9-diisopropyl-13-methoxy-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (28f)

Colorless oil (145 mg, 50%); $[\alpha]_D^{23}$ −74.8 (*c* 0.25, $CHCl_3$); IR (film) ν_{max} 3319, 2960, 1690, 1525, 1416, 1247, 1173, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.37–7.33 (m, 5H), 6.52–6.45 (m, 1H), 5.17–5.09 (m, 2H), 5.10–5.04 (m, 1H), 4.78–4.73 (m, 1H), 3.98–3.84 (m, 1.33H), 3.70–3.55 (m, 1H), 3.45–3.36 (m, 0.67H), 3.33–3.31 (m, 3H), 2.97–2.94 (m, 3H), 2.58–2.40 (m, 2H), 2.12–1.90 (m, 3H), 1.44 (s, 9H), 1.39–1.34 (m, 1H), 0.97–0.94 (m, 3H), 0.91–0.88 (m, 10H), 0.87–0.84 (m, 3H), 0.82–0.79 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 172.5, 171.6, 171.6, 171.5, 155.8, 135.8, 128.7, 128.6, 128.5, 128.5, 128.0, 127.9, 80.1, 79.9, 66.7, 60.1, 58.5, 54.1, 31.3, 28.4, 24.8, 24.0, 23.9, 21.7, 21.5, 19.9, 19.6, 19.2, 18.0, 17.8, 17.6, 17.5 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{32}H_{54}N_3O_7^+$, 592.3956, found: 592.3953.

Benzyl (6*S*,9*S*,12*S*,13*R*)-12-benzyl-6,9-diisopropyl-13-methoxy-2,2,11-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (28g)

Colorless oil (135 mg, 44%); $[\alpha]_D^{22}$ −25.3 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3320, 2964, 1735, 1497, 1246, 1164, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.32 (m, 5H), 7.34–7.29 (m, 1H), 7.23–7.18 (m, 2H), 7.16–7.10 (m, 3H), 6.43–6.35 (m, 1H), 5.16–5.13 (m, 2H), 5.04–4.98 (m, 1H), 4.55 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.01–3.80 (m, 2H), 3.40–3.36 (m, 3H), 3.16 (dd, *J* = 14.8, 4.0 Hz, 1H), 2.93–2.75 (m, 3H), 2.66–2.51 (m, 2H), 2.03–1.92 (m, 1H), 1.90–1.81 (m, 1H), 1.44–1.41 (m, 9H), 0.99–0.92 (m, 1H), 0.91–0.88 (m, 3H), 0.85–0.80 (m, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.5, 171.8, 171.2, 155.7, 138.1, 137.6, 135.7, 129.3, 128.8, 128.6, 128.5, 128.4, 128.4, 126.9, 126.5, 125.6, 79.9, 79.7, 79.5, 79.5, 66.7, 66.6, 62.6, 60.0, 59.9, 58.7, 58.5, 53.7, 53.0, 37.0, 33.8, 32.0, 31.1, 30.7, 30.4, 29.7, 28.3,

20.1, 19.5, 19.3, 19.2, 17.9, 17.8, 16.8, 16.3 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{35}H_{52}N_3O_7^+$, 626.3800, found: 626.3798.

General procedure for the synthesis of 29a, 29b, 29c, 29d, 29e, 29f and 29g

A cooled (0 °C) solution of **28a**/**28b**/**28c**/**28d**/**28e**/**28f**/**28g** (0.21 mmol) in DCM (1 mL) was treated with TFA (0.20 mL) for 2 h. The mixture was concentrated under reduced pressure and the residue was dissolved in CH_3CN (1 mL), then a solution of 40% HCHO (354 μL, 1.68 mmol) and $Na(BH_3)CN$ (40 mg, 0.63 mmol) was added. After being stirred for 10 h, the reaction mixture was evaporated and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH/NH_4OH = 50 : 1 : 0.01) to give the title product (**29a**, **29b**, **29c**, **29d**, **29e**, **29f** and **29g**).

Benzyl (3*R*,4*S*)-4-((*S*)-2-((*S*)-2-(dimethylamino)-3-methylbutanamido)-*N*,3-dimethylbutanamido)-3-methoxy-5-methylhexanoate (29a)

Colorless oil (74 mg, 70%, two steps); $[\alpha]_D^{23}$ −25.4 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 2961, 1738, 1517, 1455, 1163, 1098, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.38–7.34 (m, 5H), 6.93–6.87 (m, 1H), 5.20–5.09 (m, 2H), 4.77–4.68 (m, 2H), 3.98–3.89 (m, 1H), 3.36–3.28 (m, 4H), 3.04–3.00 (m, 3H), 2.56–2.49 (m, 1H), 2.45–2.41 (m, 1H), 2.25–2.23 (m, 6H), 2.10–1.99 (m, 2H), 1.90–1.80 (m, 1H), 1.02–0.98 (m, 9H), 0.97–0.94 (m, 3H), 0.93–0.90 (m, 3H), 0.83–0.79 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rotamers) δ 173.6, 172.0, 171.7, 135.9, 128.7, 128.5, 128.5, 78.0, 76.7, 66.8, 58.2, 58.0, 54.0, 43.1, 43.0, 37.3, 31.9, 31.0, 27.8, 27.0, 20.3, 20.2, 20.1, 19.8, 18.3, 17.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{48}N_3O_5^+$, 506.3589, found: 506.3586.

Benzyl (3*R*,4*S*,5*S*)-4-((*S*)-2-((*S*)-2-(dimethylamino)-3-methylbutanamido)-*N*,3-dimethylbutanamido)-3-methoxy-5-methylheptanoate (29b)[13d]

Colorless oil (76 mg, 70%, two steps).

Benzyl (3*R*,4*S*,5*R*)-5-benzyl-4-((*S*)-2-((*S*)-2-(dimethylamino)-3-methylbutanamido)-*N*,3-dimethylbutanamido)-3-methoxyheptanoate (29c)

Colorless oil (96 mg, 77%, two steps); $[\alpha]_D^{25}$ −9.4 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3336, 2961, 1623, 1454, 1164, 1084, 750, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5H), 7.29–7.24 (m, 2H), 7.20–7.14 (m, 3H), 6.92 (d, *J* = 9.2 Hz, 1H), 5.15 (d, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 5.06–4.91 (m, 1H), 4.79 (dd, *J* = 8.8, 6.4 Hz, 1H), 4.08–3.94 (m, 1H), 3.35–3.31 (m, 3H), 3.04–2.98 (m, 3H), 2.79–2.70 (m, 1H), 2.62–2.47 (m, 3H), 2.43 (d, *J* = 6.4 Hz, 1H), 2.24–2.21 (m, 6H), 2.12–1.98 (m, 3H), 1.33–1.27 (m, 1H), 1.16–1.05 (m, 1H), 1.03–0.97 (m, 6H), 0.97–0.88 (m, 6H), 0.75 (t, *J* = 6.6 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$,) δ 173.3, 171.8, 171.5, 140.5, 135.9, 129.1, 128.7, 128.5, 126.1, 70.1, 66.8, 58.0, 53.8, 43.1, 37.4, 35.9, 31.0, 27.8, 22.0, 20.3, 20.0, 17.9, 9.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{35}H_{54}N_3O_5^+$, 596.4059, found: 596.4060.

Benzyl (3*R*,4*S*,5*R*)-4-((*S*)-2-((*S*)-2-(dimethylamino)-3-methylbutanamido)-*N*,3-dimethylbutanamido)-3-methoxy-5-(4-methoxybenzyl)heptanoate (29d)

Colorless oil (117 mg, 89%, two steps); $[\alpha]_D^{25}$ −7.3 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3446, 2960, 1657, 1512, 1247, 1084, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 7.11–7.04 (m, 2H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.83–6.77 (m, 2H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 5.02–4.91 (m, 1H), 4.79 (dd, *J* = 6.8, 6.0 Hz, 1H), 4.11–3.93 (m, 1H), 3.78 (s, 3H), 3.44–3.38 (m, 1H), 3.35–3.32 (m, 3H), 3.05–2.98 (m, 3H), 2.75–2.63 (m, 1H), 2.58–2.48 (m, 2H), 2.46–2.43 (m, 1H), 2.29–2.19 (m, 6H), 2.12–1.96 (m, 3H), 1.77–1.69 (m, 2H), 1.03–0.97 (m, 6H), 0.96–0.89 (m, 6H), 0.79–0.71 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 171.6, 158.0, 135.9, 132.4, 130.0, 128.7, 128.5, 113.9, 78.0, 76.6, 70.8, 66.8, 58.0, 55.4, 53.8, 43.0, 37.4, 34.9, 31.0, 27.8, 26.7, 22.0, 20.3, 20.0, 17.9, 9.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{36}H_{56}N_3O_6^+$, 626.4164, found: 626.4165.

Benzyl (3*R*,4*S*,5*R*)-4-((*S*)-2-((*S*)-2-(dimethylamino)-3-methylbutanamido)-*N*,3-dimethylbutanamido)-5-(3-fluorobenzyl)-3-methoxyheptanoate (29e)

Colorless oil (117 mg, 91%, two steps); $[\alpha]_D^{25}$ −12.5 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3443, 2962, 1624, 1454, 1124, 1084, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 7.23–7.16 (m, 1H), 6.97–6.87 (m, 3H), 6.87–6.83 (m, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 5.00–4.85 (m, 1H), 4.78 (dd, *J* = 6.8, 6.0 Hz, 1H), 4.07–3.87 (m, 1H), 3.36–3.29 (m, 3H), 3.07–3.00 (m, 3H), 2.78–2.70 (m, 1H), 2.58–2.47 (m, 3H), 2.44 (d, *J* = 6.4 Hz, 1H), 2.28–2.22 (m, 6H), 2.10–1.97 (m, 3H), 1.34–1.27 (m, 1H), 1.17–1.08 (m, 1H), 1.04–0.97 (m, 6H), 0.97–0.88 (m, 6H), 0.75 (t, *J* = 6.8 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 171.8, 171.5, 163.0 (d, *J* = 243.9 Hz), 143.3 (d, *J* = 7.1 Hz), 135.8, 129.9 (d, *J* = 8.3 Hz), 128.7, 128.5, 124.8, 115.9 (d, *J* = 20.7 Hz), 113.0 (d, *J* = 20.9 Hz), 78.1, 76.6, 66.8, 58.0, 53.8, 43.1, 35.8, 30.9, 27.8, 22.1, 20.3, 20.0, 17.9, 9.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.6 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{35}H_{53}FN_3O_5^+$, 614.3964, found: 614.3967.

Benzyl (3*R*,4*S*)-4-((*S*)-2-((*S*)-2-(dimethylamino)-3-methylbutanamido)-*N*,3-dimethylbutanamido)-3-methoxy-6-methylheptanoate (29f)

Colorless oil (71 mg, 65%, two steps); $[\alpha]_D^{25}$ −60.0 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 2959, 1738, 1456, 1197, 1103, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.32 (m, 5H), 6.92–6.87 (m, 1H), 5.15–5.12 (m, 2H), 4.86–4.66 (m, 2H), 3.77–3.63 (m, 1H), 3.33–3.30 (m, 3H), 3.06–3.02 (m, 1H), 3.01–2.96 (m, 3H), 2.55–2.47 (m, 2H), 2.45–2.43 (m, 1H), 2.25–2.22 (m, 6H), 2.11–2.05 (m, 1H), 2.01–1.94 (m, 1H), 1.65–1.55 (m, 1H), 1.38–1.32 (m, 1H), 1.00–0.97 (m, 6H), 0.94–0.90 (m, 6H), 0.88–0.86 (m, 3H), 0.80–0.77 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR

(100 MHz, $CDCl_3$) δ 172.8, 171.7, 171.5, 135.7, 128.6, 128.4, 80.0, 76.5, 66.6, 58.4, 53.6, 53.4, 42.8, 37.7, 30.9, 27.7, 24.6, 24.6, 24.0, 21.3, 20.1, 19.9, 17.8, 17.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{29}H_{50}N_3O_5^+$, 520.3745, found: 520.3744.

Benzyl-(3*R*,4*S*)-4-((*S*)-2-((*S*)-2-(dimethylamino)-3-methylbutanamido)-*N*,3-dimethylbutanamido)-3-methoxy-5-phenylpentanoate (29g)

Colorless oil (70 mg, 60%, two steps); $[\alpha]_D^{23}$ −21.2 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 2970, 1732, 1544, 1456, 1202, 936, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.42–7.31 (m, 6H), 7.23–7.11 (m, 5H), 5.17–5.14 (m, 2H), 4.71–4.50 (m, 1H), 3.97–3.60 (m, 2H), 3.45–3.37 (m, 3H), 3.18–3.11 (m, 1H), 2.98–2.76 (m, 10H), 2.73–2.42 (m, 3H), 2.21–1.84 (m, 2H), 1.13–1.05 (m, 3H), 0.96–0.83 (m, 6H), 0.79–0.66 (m, 2H), 0.54–0.34 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rotamers) δ 171.9, 171.4, 171.2, 166.5, 166.5, 162.2, 162.0, 138.1, 135.7, 135.7, 129.3, 129.0, 128.8, 128.7, 128.6, 127.1, 126.6, 117.1, 115.2, 80.0, 79.7, 72.0, 66.9, 66.8, 63.1, 59.0, 58.6, 53.9, 53.6, 36.9, 33.9, 29.6, 29.6, 28.9, 28.2, 28.1, 20.4, 20.1, 19.4, 19.4, 19.3, 17.0, 16.1 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{32}H_{48}N_3O_5^+$, 554.3589, found: 554.3583.

General procedure for the synthesis of 31a, 31b, 31c, 31d, 31e and 31f

Compounds **29a**/**29c**/**29d**/**29e**/**29f**/**29g** (0.12 mmol) and 10% Pd/C (40 mg) were stirred in MeOH (10 mL) for 4 h under a H_2 atmosphere. Then, the mixture was filtered and concentrated to give a crude acid without further purification. HATU (68 mg, 0.18 mmol), DIPEA (63 μL, 0.36 mmol), and **30** (49 mg, 0.13 mmol) were added in turn. After being stirred for 12 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel to give the title product (**31a**, **31b**, **31c**, **31d**, **31e** and **31f**) as a viscous liquid, which was further treated with acetone/hexane to give a white powder.

(*S*)-2-((*S*)-2-(Dimethylamino)-3-methylbutanamido)-*N*-((3*S*,4*R*)-4-methoxy-6-((*S*)-2-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)pyrrolidin-1-yl)-2-methyl-6-oxohexan-3-yl)-*N*,3-dimethylbutanamide (31a)

White powder (46 mg, 50%, three steps), mp 94–95 °C; $[\alpha]_D^{22}$ −214.4 (*c* 0.125, $CHCl_3$); IR (film) ν_{max} 3292, 2965, 1622, 1498, 1100, 830, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.78–7.74 (m, 1H), 7.26–7.16 (m, 6H), 7.12–7.06 (m, 1H), 5.68–5.51 (m, 1H), 4.86–4.64 (m, 2H), 4.21–4.02 (m, 2H), 3.92–3.86 (m, 1H), 3.81–3.53 (m, 1H), 3.44–3.37 (m, 3H), 3.36–3.31 (m, 6H), 3.29–3.23 (m, 1H), 3.18 (s, 1H), 3.05 (s, 2H), 2.74–2.65 (m, 1H), 2.50–2.41 (m, 2H), 2.40–2.36 (m, 6H), 2.25–2.19 (m, 1H), 2.14–2.07 (m, 2H), 2.05–1.99 (m, 1H), 1.97–1.86 (m, 2H), 1.83–1.71 (m, 2H), 1.68–1.60 (m, 1H), 1.50–1.43 (m, 3H), 1.29–1.20 (m, 2H), 1.17–1.11 (m, 3H), 1.03–1.00 (m, 6H), 0.98–0.95 (m, 2H), 0.92–0.90 (m, 2H), 0.84–0.81 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rotamers) δ 174.1, 173.4, 173.3, 171.9, 170.4, 170.1, 142.6, 137.0, 136.5, 129.5, 129.2, 128.8, 128.6, 127.2, 127.0, 119.4, 119.0, 85.7, 81.8, 78.5, 76.0, 64.6, 61.7, 60.6, 60.5, 59.3, 59.0, 58.7, 58.7, 58.2, 58.1, 55.8, 54.2, 53.6, 51.4, 47.8, 46.7, 44.9, 44.0, 43.8, 42.9, 42.8, 41.4, 41.3, 37.9, 36.3, 32.1, 31.1, 30.7, 29.8, 27.8, 27.2, 26.9, 25.9, 25.1, 24.8, 23.8, 20.8, 20.8, 20.4, 20.2, 20.1, 20.1, 19.8, 19.6, 18.4, 18.3, 17.9, 17.8, 15.4, 14.1, 12.7 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{41}H_{67}N_6O_6S^+$, 771.4837, found: 771.4836.

(*S*)-*N*-((3*R*,4*S*,5*R*)-5-Benzyl-3-methoxy-1-((*S*)-2-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)pyrrolidin-1-yl)-1-oxoheptan-4-yl)-2-((*S*)-2-(dimethylamino)-3-methylbutanamido)-*N*,3-dimethylbutanamide (31b)

White powder (43 mg, 42%, three steps), mp 73.6–75.6 °C; $[\alpha]_D^{26}$ −39.2 (*c* 0.25, $CHCl_3$); IR (film): ν_{max} 3290, 2960, 1622, 1497, 1098, 749, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.71(m, 1H), 7.26–7.21 (m, 5H), 7.20–7.04 (m, 6H), 7.00–6.92 (m, 1H), 5.63–5.53 (m, 1H), 5.02–4.86 (m, 1H), 4.82 (dd, *J* = 6.4, 5.6 Hz, 1H), 4.34–4.19 (m, 1H), 4.12–4.04 (m, 1H), 3.89 (d, *J* = 6.8 Hz, 1H), 3.44–3.42 (m, 1H), 3.38–3.36 (m, 2H), 3.33–3.33 (m, 2H), 3.30–3.28 (m, 1H), 3.21–3.17 (m, 1H), 3.08–3.05 (m, 2H), 2.83–2.76 (m, 1H), 2.53–2.41 (m, 4H), 2.28–2.22 (m, 6H), 2.12–2.00 (m, 4H), 1.95–1.90 (m, 1H), 1.84–1.74 (m, 2H), 1.68–1.64 (m, 6H), 1.44–1.32 (m, 2H), 1.15–1.12 (m, 3H), 1.04–0.98 (m, 6H), 0.96–0.92 (m, 6H), 0.77 (t, *J* = 7.0 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 173.9, 173.3, 171.7, 170.1, 142.6, 140.8, 137.1, 130.0, 129.2, 129.1, 128.8, 129.0, 128.4, 127.2, 126.9, 126.0, 119.4, 118.9, 85.7, 81.9, 60.5, 59.3, 58.3, 53.8, 52.7, 51.4, 47.7, 46.7, 43.9, 43.1, 41.5, 41.3, 40.3, 38.2, 35.7, 32.3, 31.0, 29.8, 27.8, 25.9, 25.1, 24.8, 23.8, 22.0, 20.4, 18.0, 13.9, 10.1 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{48}H_{73}N_6O_6S^+$, 861.5307, found: 861.5306.

(*S*)-2-((*S*)-2-(Dimethylamino)-3-methylbutanamido)-*N*-((3*R*,4*S*,5*R*)-3-methoxy-1-((*S*)-2-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)pyrrolidin-1-yl)-5-(4-methoxybenzyl)-1-oxoheptan-4-yl)-*N*,3-dimethylbutanamide (31c)

White powder (36 mg, 34%), mp 72.5–74.5 °C; $[\alpha]_D^{26}$ −35.2 (*c* 0.25, $CHCl_3$); IR (film): ν_{max} 3290, 2962, 2874, 1623, 1512, 1453, 1247, 1100, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.71 (m, 1H), 7.25–7.17 (m, 6H), 7.12–7.07 (m, 2H), 7.08–6.94 (m, 1H), 6.82–6.77 (m, 2H), 5.63–5.51 (m, 1H), 5.16–4.87 (m, 1H), 4.86–4.76 (m, 1H), 4.32–4.15 (m, 1H), 4.12–4.02 (m, 1H), 3.93–3.84 (m, 1H), 3.77 (s, 3H), 3.76–3.71 (m, 1H), 3.46–3.39 (m, 2H), 3.38–3.35 (m, 3H), 3.32–3.30 (m, 3H), 3.28–3.23 (m, 2H), 3.21–3.16 (m, 1H), 3.09–3.01 (m, 3H), 2.77–2.70 (m, 1H), 2.49–2.42 (m, 3H), 2.34–2.22 (m, 6H), 2.15–2.02 (m, 3H), 2.02–1.88 (m, 2H), 1.85–1.79 (m, 1H), 1.43–1.29 (m, 1H), 1.28–1.24 (m, 2H), 1.17–1.12 (m, 3H), 1.06–1.10 (m, 6H), 0.97–0.93 (m, 6H), 0.81–0.72 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 173.9, 173.5, 171.8, 170.1,

157.9, 142.6, 137.1, 132.7, 130.1, 130.0, 129.6, 129.2, 128.8, 128.5, 126.9, 119.4, 118.9, 113.8, 85.7, 81.9, 70.8, 60.5, 59.3, 58.6, 58.3, 55.3, 53.8, 53.6, 52.7, 47.7, 44.9, 43.9, 43.1, 41.3, 38.2, 34.7, 31.0, 27.8, 25.1, 24.8, 23.7, 22.0, 20.3, 18.6, 18.0, 13.9, 10.1 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{49}H_{75}N_6O_7S^+$, 891.5413, found: 891.5415.

(*S*)-2-((*S*)-2-(Dimethylamino)-3-methylbutanamido)-*N*-((3*R*,4*S*,5*R*)-5-(3-fluorobenzyl)-3-methoxy-1-((*S*)-2-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)pyrrolidin-1-yl)-1-oxoheptan-4-yl)-*N*,3-dimethylbutanamide (31d)

White powder (47 mg, 45%), mp 86.5–88.5 °C; $[\alpha]_D^{26}$ −41.5 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3291, 2963, 1636, 1488, 1251, 1141, 1098, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.71 (m, 1H), 7.26–7.17 (m, 6H), 7.12–7.05 (m, 1H), 7.02–6.96 (m, 2H), 6.92–6.83 (m, 2H), 5.61–5.54 (m, 1H), 4.94–4.84 (m, 1H), 4.80 (dd, *J* = 8.4, 7.6 Hz, 1H), 4.27–4.19 (m, 1H), 4.11–4.04 (m, 1H), 3.89 (d, *J* = 7.2 Hz, 1H), 3.44–3.42 (m, 1H), 3.37–3.35 (m, 3H), 3.34–3.32 (m, 3H), 3.31–3.29 (m, 1H), 3.28–3.24 (m, 1H), 3.18–3.17 (m, 1H), 3.08–3.05 (m, 2H), 2.82–2.75 (m, 1H), 2.54–2.40 (m, 4H), 2.34–2.26 (m, 6H), 2.16–2.02 (m, 4H), 1.96–1.88 (m, 2H), 1.84–1.73 (m, 2H), 1.72–1.61 (m, 2H), 1.43–1.33 (m, 1H), 1.28–1.24 (m, 1H), 1.17–1.13 (m, 3H), 1.06–1.00 (m, 6H), 0.97–0.93 (m, 6H), 0.82–0.72 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 173.8, 173.2, 171.7, 170.3, 170.0 169.7, 162.9 (d, *J* = 243.8 Hz), 143.5, 142.6, 137.1, 136.6, 129.8 (d, *J* = 8.1 Hz), 129.5, 129.2, 128.8, 128.5, 127.2, 126.9, 124.9, 119.4, 118.9, 115.9 (d, *J* = 20.7 Hz), 113.0 (d, *J* = 20.9 Hz), 85.7, 81.9, 61.7, 60.5, 59.2, 58.9, 58.5, 58.3, 52.7, 51.4, 47.7, 46.7, 43.8, 43.1, 41.3, 40.4, 38.4, 35.6, 30.8, 27.8, 25.9, 25.1, 24.8, 23.7, 22.1, 20.3, 19.9, 18.0, 13.9, 10.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.9 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{48}H_{72}FN_6O_6S^+$, 879.5213, found: 879.5212.

(*S*)-2-((*S*)-2-(Dimethylamino)-3-methylbutanamido)-*N*-((3*R*,4*S*)-3-methoxy-1-((*S*)-2-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)pyrrolidin-1-yl)-6-methyl-1-oxoheptan-4-yl)-*N*,3-dimethylbutanamide (31e)

White powder (40 mg, 42%), mp 108–110 °C; $[\alpha]_D^{23}$ −5.6 (*c* 0.50, $CHCl_3$); IR (film) ν_{max} 2914, 1959, 1682, 1453, 1200, 936, 870 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81–7.77 (m, 1H), 7.53–7.43 (m, 1H), 7.36–7.29 (m, 1H), 7.25–7.09 (m, 6H), 5.87–5.62 (m, 1H), 4.90–4.72 (m, 2H), 3.97–3.75 (m, 4H), 3.46–3.37 (m, 2H), 3.36–3.26 (m, 8H), 3.19–3.12 (m, 1H), 3.06–2.88 (m, 8H), 2.59–2.45 (m, 1H), 2.34–2.28 (m, 1H), 2.28–2.16 (m, 2H), 2.15–2.06 (m, 1H), 2.03–1.92 (m, 1H), 1.92–1.77 (m, 2H), 1.75–1.65 (m, 1H), 1.63–1.56 (m, 1H), 1.29–1.23 (m, 2H), 1.15–1.10 (m, 6H), 1.01–0.98 (m, 3H), 0.98–0.94 (m, 3H), 0.93–0.90 (m, 6H), 0.81–0.68 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 172.5, 166.6, 162.3, 162.1, 161.8, 130.5, 129.5, 129.3, 128.8, 128.7, 127.3, 127.2, 125.8, 117.2, 115.3, 81.8, 81.6, 72.2, 51.6, 47.8, 47.7, 47.6, 47.6, 47.5, 47.3, 47.2, 44.4, 44.3, 44.3, 44.2, 44.1, 30.7, 29.9, 28.1, 27.9, 26.9, 26.0, 25.3, 24.1, 24.0, 23.9, 21.2, 21.1, 18.9, 18.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{42}H_{69}N_6O_6S^+$, 785.4994, found: 785.4999.

(*S*)-2-((*S*)-2-(Dimethylamino)-3-methylbutanamido)-*N*-((2*S*,3*R*)-3-methoxy-5-((*S*)-2-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)pyrrolidin-1-yl)-5-oxo-1-phenylpentan-2-yl)-*N*,3-dimethylbutanamide (31f)

White powder (44 mg, 45%), mp 112–114 °C.; $[\alpha]_D^{23}$ −26.4 (*c* 0.125, $CHCl_3$); IR (film) ν_{max} 2916, 1957, 1650, 1453, 1203, 936, 919, 870 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, rotamers) δ 7.88–7.83 (m, 1H), 7.43–7.37 (m, 1H), 7.25–7.10 (m, 11H), 5.76–5.66 (m, 1H), 5.26–5.03 (m, 1H), 4.67–4.58 (m, 1H), 3.90–3.72 (m, 4H), 3.42–3.38 (m, 3H), 3.35–3.33 (m, 1H), 3.33–3.31 (m, 2H), 3.31–3.28 (m, 2H), 3.27–3.21 (m, 1H), 3.16–3.10 (m, 1H), 3.03–2.87 (m, 10H), 2.56–2.46 (m, 1H), 2.45–2.20 (m, 3H), 2.16–2.10 (m, 1H), 2.07–1.88 (m, 3H), 1.84–1.76 (m, 1H), 1.74–1.66 (m, 1H), 1.63–1.55 (m, 1H), 1.17–1.04 (m, 7H), 0.97–0.93 (m, 3H), 0.91–0.86 (m, 3H), 0.78–0.73 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, rotamers) δ 175.0, 173.5, 173.0, 171.5, 166.2, 161.8, 161.5, 161.2, 135.9, 129.4, 129.4, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 127.3, 126.7, 120.5, 118.7, 116.7, 114.8, 81.8, 72.1, 72.0, 61.7, 61.0, 60.6, 59.9, 59.6, 59.1, 54.5, 54.5, 54.4, 54.3, 51.7, 47.8, 47.8, 44.1, 41.2, 30.8, 29.9, 29.7, 29.7, 29.5, 28.2, 28.0, 27.9, 25.2, 25.1, 25.1, 24.5, 24.3, 20.4, 20.1, 19.0, 18.9, 17.1, 17.0, 15.5, 14.5, 14.3, 14.0 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{45}H_{67}N_6O_6S^+$, 818.4759, found: 818.4755.

***tert*-Butyl(1*S*,3*S*,5*S*)-3-((1*R*,2*R*)-3-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-1-hydroxy-2-methyl-3-oxopropyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (34)**

Compound **33** (1.74 g, 8.16 mmol) was stirred in DCM (30 ml). Then Dess–Martin periodinane (8.6 g, 20.4 mmol) was added and the resulting mixture was stirred for 30 min at room temperature. The reaction mixture was carefully quenched with a solution of saturated aqueous $NaHCO_3$ and solid $Na_2S_2O_3$. The mixture was extracted with DCM (50 mL × 3), and the combined organic layers were washed with brine, and dried and concentrated to give the aldehyde without further purification. To a stirred solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one (2.13 g, 8.98 mmol) in DCM (20 mL) at 0 °C was added dropwise *n*-Bu_2BOTf (9.8 mL, 9.79 mmol, 1 M in DCM) and stirred for 10 min. TEA (1.47 mL, 10.61 mmol) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. Then a solution of the above crude aldehyde in DCM was added dropwise, and the reaction mixture was stirred at −78 °C for 2 h before gradually warming to room temperature. Then the mixture was quenched with a solution of 30% aqueous H_2O_2 (15 mL) and MeOH (5 mL) at 0 °C. The resulting mixture was stirred at room temperature for additional 4 h and extracted with DCM (80 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 4 : 1) to give **34**. Colorless oil (2.17 g, 60%, two steps); $[\alpha]_D^{24}$ −29.1 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3443, 2976, 1782, 1617, 1405, 1211, 1117, 702 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 7.36–7.25 (m, 3H), 7.22–7.17 (m, 2H), 4.72–4.60 (m, 1H), 4.30–4.15 (m, 3H), 4.12–3.95 (m, 1H), 3.84–3.78 (m, 1H), 3.52–3.42 (m, 1H), 3.23 (dd, J = 13.2, 3.2 Hz, 1H), 2.77 (dd, J = 13.6, 9.6 Hz, 1H), 2.24–2.13 (m, 2H), 1.50 (s, 9H), 1.46–1.41 (m, 1H), 1.35–1.24 (m, 4H), 0.89–0.83 (m, 1H), 0.72–0.64 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.4, 155.4, 152.8, 135.2, 129.6, 129.1, 127.5, 66.2, 55.2, 40.8, 38.6, 37.9, 28.7, 27.5 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{24}H_{33}N_2O_6^+$, 445.2333, found: 445.2337.

tert-Butyl-(1*S*,3*S*,5*S*)-3-((1*R*,2*R*)-3-(benzyloxy)-1-methoxy-2-methyl-3-oxopropyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (35)

Compound **34** (0.95 g, 4.80 mmol) was dissolved in a mixture of THF and H_2O (80 mL v/v = 3 : 1). Then a solution of 30% H_2O_2 (4 mL, 38.4 mmol) and $LiOH{\cdot}H_2O$ (604 mg, 14.4 mmol) was added in one portion. After being stirred for 7 h, the mixture was acidified with hydrochloric acid to pH = 2–3 and the resulting mixture was extracted with EtOAc (100 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a crude compound, which was dissolved in DMF (20 mL). Then K_2CO_3 (950 mg, 9.6 mmol) and BnBr (0.57 mL, 4.8 mmol) were added. After being stirred for 4 h, the reaction mixture was diluted with water and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water and brine respectively, then dried over $MgSO_4$, filtered and concentrated to give the crude secondary alcohol. To a cooled (−78 °C) solution of the secondary alcohol in HMPA (926 μL, 5.3 mmol) and THF (20 mL) was added a solution of LiHMDS (4.8 ml, 4.8 mmol, 1 M in THF) dropwise. After being stirred for 30 min, the reaction mixture was warmed to −15 °C and MeOTf (1.08 mL, 9.6 mmol) was added, and then the mixture was stirred for an additional 15 min. The reaction mixture 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 $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 5 : 1) to give **35**. Colorless oil (1.51 g, 81%, three steps); $[\alpha]_D^{23}$ +4.8 (c 0.50, $CHCl_3$); IR (film): ν_{max} 3443, 2075, 1637, 1404, 1172, 1088, 582 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.42–7.30 (m, 5H), 5.18–5.01 (m, 2H), 4.18–4.07 (m, 0.5H), 4.04–3.90 (m, 1H), 3.76–3.71 (m, 0.5H), 3.54–3.48 (m, 0.5H), 3.38–3.34 (m, 3.5H), 2.50–2.39 (m, 1H), 2.18–2.08 (m, 1H), 2.02–1.90 (m, 1H), 1.50–1.44 (m, 9H), 1.41–1.37 (m, 1H), 1.25–1.20 (m, 3H), 0.84 (d, J = 13.6 Hz, 1H), 0.70–0.60 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 174.4, 154.7, 135.9, 128.7, 128.4, 82.4, 81.2, 80.2, 79.5, 66.5, 63.6, 63.4, 61.0, 60.6, 43.4, 38.8, 38.5, 31.6, 30.3, 28.7, 28.0, 27.2, 14.0, 13.8 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{22}H_{32}NO_5^+$, 390.2275, found: 390.2278.

tert-Butyl-(1*S*,3*S*,5*S*)-3-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (38)

Compound **35** (1.48 g, 3.80 mmol) and 10% Pd/C (148 mg) were stirred in MeOH (60 mL) for 4 h under a H_2 atmosphere. The mixture was filtered and concentrated to give a crude acid, which was dissolved in DCM (16 mL). HATU (2.17 g, 5.70 mmol), DIPEA (1.98 mL, 11.40 mmol), and **37** (912 mg, 3.80 mmol) were added and 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 $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 1 : 1) to give **38**. Colorless oil (1.38 g, 75%, two steps); $[\alpha]_D^{23}$ −39.2 (c 1.00, $CHCl_3$); IR (film): ν_{max} 3443, 2975, 2076, 1646, 1408, 1175, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.77–7.72 (m, 1H), 7.25–7.15 (m, 5H), 6.92–6.86 (m, 0.5H), 6.26–6.19 (m, 0.5H), 5.67–5.58 (m, 1H), 4.09–4.03 (m, 0.5H), 3.87–3.77 (m, 0.5H), 3.74–3.68 (m, 0.5H), 3.66–3.61 (m, 0.5H), 3.54–3.44 (m, 0.5H), 3.40–3.33 (m, 3H), 3.32–3.28 (m, 2H), 3.27–3.18 (m, 1.5H), 2.28–2.22(m, 0.5H), 2.14–2.05 (m,0.5H), 2.00–1.90 (m, 0.5H), 1.88–1.86 (m, 0.5H), 1.82–1.74 (m, 1H), 1.50 (s, 9H), 1.37–1.32 (m, 1H), 1.16–1.09 (m, 3H), 0.81–0.74 (m, 1H), 0.67–0.62 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 173.7, 173.2, 171.6, 171.0, 154.8, 142.6, 137.0, 136.6, 129.5, 129.4, 128.7, 128.6, 127.2, 127.0, 119.1, 118.9, 82.4, 81.1, 80.3, 79.7, 63.2, 62.9, 60.5, 52.4, 44.8, 44.4, 41.5, 38.9, 38.3, 28.7, 27.7, 26.5, 15.0, 14.6, 14.2, 13.9, 13.7 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{26}H_{36}N_3O_4S^+$, 486.2421, found: 486.2427.

General procedure for the synthesis of 40a, 40b and 40c

Compound **29b**/**29c**/**29e** (0.1 mmol) and 10% Pd/C were stirred in MeOH (10 mL) for 4 h under a H_2 atmosphere. The mixture was filtered and concentrated to give a crude acid without further purification. Compound **38** (53.4 mg, 0.11 mmol) and TFA (0.2 mL) were stirred in DCM (1 mL) for 2 h at 0 °C and the mixture was directly concentrated. The residue was dissolved in DCM (1 mL), HATU (57 mg, 0.15 mmol), and DIPEA (52 μL, 0.3 mmol) and the above crude acid was added. After being stirred for 12 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated, and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 100 : 1 to 25 : 1) to give the title product (**40a**, **40b** and **40c**) as a viscous liquid, which was further treated with acetone/hexane to give a white powder.

(*S*)-2-((*S*)-2-(Dimethylamino)-3-methylbutanamido)-*N*-((3*R*,4*S*,5*S*)-3-methoxy-1-((1*S*,3*S*,5*S*)-3-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)-2-azabicyclo[3.1.0]hexan-2-yl)-5-methyl-1-oxoheptan-4-yl)-*N*,3-dimethylbutanamide (40a)

White powder (25 mg, 31%), mp 92.5–94.5 °C; $[\alpha]_D^{24}$ −38.0 (c 0.10, $CHCl_3$); IR (film): ν_{max} 3344, 2965, 1634, 1454, 1210, 1096, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.72 (m, 1H), 7.24–7.18 (m, 5H), 7.13–7.06 (m, 1H), 5.61–5.51 (m, 1H), 4.93–4.72 (m, 2H), 4.40–4.32 (m, 1H), 4.24–4.13 (m, 1H), 3.89 (d, J = 8.0 Hz, 1H), 3.43–3.35 (m, 2H), 3.35–3.31 (m, 3H), 3.29–3.26 (m, 3H), 3.26–3.21 (m, 1H), 3.20–3.09 (m, 2H),

3.07–3.00 (m, 3H), 2.67–2.57 (m, 1H), 2.51–2.40 (m, 2H), 2.27–2.22 (m, 6H), 2.15–2.07 (m, 1H), 2.06–1.93 (m, 3H), 1.92–1.85 (m, 1H), 1.44–1.31 (m, 3H), 1.12–1.09 (m, 3H), 1.04–1.00 (m, 6H), 0.98–0.95 (m, 6H), 0.93–0.91 (m, 3H), 0.84–0.82 (m, 3H), 0.79–0.64 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 173.6, 171.9, 165.5, 163.1, 158.4, 156.5, 142.6, 137.1, 132.4, 129.9, 129.6, 128.6, 127.0, 122.0, 121.9, 118.9, 118.8, 80.1, 63.3, 60.0, 58.0, 53.9, 53.3, 52.7, 52.5, 44.4, 43.0, 41.3, 38.3, 38.1, 33.4, 31.1, 27.8, 25.8, 20.2, 17.9, 16.4, 14.3 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{43}H_{69}N_6O_6S^+$, 797.4994, found: 797.4999.

(*S*)-2-((*S*)-2-(Dimethylamino)-3-methylbutanamido)-*N*-((3*R*,4*S*,5*R*)-5-(3-fluorobenzyl)-3-methoxy-1-((1*S*,3*S*,5*S*)-3-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)-2-azabicyclo[3.1.0]hexan-2-yl)-1-oxoheptan-4-yl)-*N*,3-dimethylbutanamide (40b)

White powder (25 mg, 28%), mp 87.5–89.5 °C; $[\alpha]_D^{26}$ −22.0 (*c* 0.25, $CHCl_3$); IR (film): ν_{max} 3291, 2928, 1639, 1453, 1252, 1096, 774, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.72 (m, 1H), 7.23–7.18 (m, 5H), 7.04–6.96 (m, 3H), 6.94–6.83 (m, 3H), 5.61–5.52 (m, 1H), 4.95–4.75 (m, 2H), 4.40–4.32 (m, 1H), 4.32–4.23 (m, 1H), 3.93–3.86 (m, 1H), 3.38–3.35 (m, 3H), 3.29–3.26 (m, 3H), 3.11–3.07 (m, 3H), 2.80–2.62 (m, 3H), 2.53–2.42 (m, 3H), 2.31–2.23 (m, 6H), 2.12–1.98 (m, 5H), 1.91–1.84 (m, 1H), 1.53–1.47 (m, 2H), 1.39–1.36 (m, 1H), 1.29–1.24 (m, 3H), 1.13–1.10 (m, 3H), 1.05–0.99 (m, 6H), 0.96–0.91 (m, 6H), 0.82–0.77 (m, 3H), 0.76–0.68 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 173.5, 171.9, 169.5, 163.0 (d, *J* = 243.6 Hz), 143.6, 142.6, 137.0, 129.8 (d, *J* = 7.7 Hz), 129.5, 128.6, 127.0, 124.9, 118.9, 116.0 (d, *J* = 20.6 Hz), 112.9 (d, *J* = 20.9 Hz), 80.2, 63.3, 60.0, 58.0, 53.8, 52.6, 44.3, 43.1, 41.4, 40.7, 38.6, 38.3, 35.8, 30.9, 27.8, 25.7, 20.3, 18.0, 16.4, 14.3, 10.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.9 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{49}H_{72}FN_6O_6S^+$, 891.5213, found: 891.5211.

(*S*)-*N*-((3*R*,4*S*,5*R*)-5-Benzyl-3-methoxy-1-((1*S*,3*S*,5*S*)-3-((1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-(((*S*)-2-phenyl-1-(thiazol-2-yl)ethyl)amino)propyl)-2-azabicyclo[3.1.0]hexan-2-yl)-1-oxoheptan-4-yl)-2-((*S*)-2-(dimethylamino)-3-methylbutanamido)-*N*,3-dimethylbutanamide (40c)

White powder (39 mg, 45%), mp 76.5–78.5 °C; $[\alpha]_D^{24}$ −30.2 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3423, 2930, 1637, 1535, 1454, 1096, 750, 700, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.71 (m, 1H), 7.26–7.22 (m, 4H), 7.22–7.15 (m, 8H), 7.08 (d, *J* = 6.8 Hz, 1H), 6.95 (d, *J* = 9.2 Hz, 1H), 5.57 (dd, *J* = 14.0, 8.0 Hz, 1H), 5.02–4.86 (m, 1H), 4.83 (dd, *J* = 6.8, 6.0 Hz, 1H), 4.40–4.33 (m, 1H), 4.32–4.26 (m, 1H), 3.88 (d, *J* = 7.6 Hz, 1H), 3.48–3.38 (m, 1H), 3.37–3.35 (m, 3H), 3.32–3.28 (m, 1H), 3.28–3.26 (m, 3H), 3.10–3.07 (m, 3H), 2.82–2.75 (m, 1H), 2.72–2.58 (m, 1H), 2.55–2.49 (m, 1H), 2.44 (d, *J* = 6.4 Hz, 1H), 2.42–2.27 (m, 1H), 2.26–2.23 (m, 6H), 2.10–1.97 (m, 4H), 1.91–1.86 (m, 1H), 1.54–1.46 (m, 1H), 1.44–1.37 (m, 1H), 1.12–1.09 (m, 3H), 1.04–0.98 (m, 6H), 0.97–0.94 (m, 3H), 0.93–0.91 (m, 3H), 0.90–0.87 (m, 2H), 0.78 (t, *J* = 7.0 Hz, 3H), 0.75–0.67 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 173.6, 173.3, 171.9, 171.7, 169.5, 142.6, 140.9, 137.0, 129.5, 129.2, 128.6, 128.4, 118.9, 80.1, 76.7, 63.3, 60.0, 58.0, 53.8, 52.6, 44.3, 43.1, 41.3, 38.4, 38.3, 35.9, 31.0, 29.8, 27.8, 25.7, 22.2, 20.3, 19.9, 18.0, 17.9, 16.4, 14.4, 10.3 ppm; HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{49}H_{73}N_6O_6S^+$, 873.5307, found: 873.5309.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (21772027 to B.-G. Wei, and 21702032 to C.-M. Si) and the Open Research Fund Program of Beijing Key Lab of Plant Resource Research and Development, BTBU (No. PRRD-2018-ZD1) for financial support.

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