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Total synthesis of dolastatin 10 through ruthenium-catalyzed asymmetric hydrogenations

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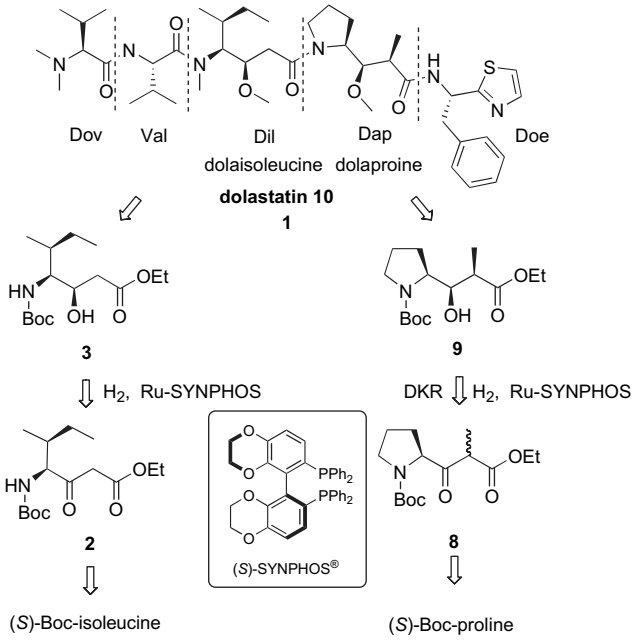
Abstract—A total synthesis of dolastatin 10, a potent inhibitor of microtubule assembly, which displayed remarkable antineoplastic activity, is reported. Our synthetic approach was based upon ruthenium-promoted asymmetric hydrogenation of β-keto esters derived from (*S*)-Boc-proline and (*S*)-Boc-isoleucine for the construction of the two key units: (2*R*,3*R*)-Boc-dolaproine (Dap) and (3*R*)-Boc-dolaisoleucine (Dil).

1. Introduction

The marine natural product dolastatin 10 originally isolated from the sea hare *Dolabella auricularia* and structurally defined in 1987 by Pettit and co-workers[1] is a member of a whole family of cytotoxic antimitotic peptides.[2]

Total syntheses of dolastatin 10[3–10] have been reported as well as the preparation of the three unique key units: (2*R*,3*R*,4*S*)-dolaproine (Dap),[11–16] (3*R*,4*S*,5*S*)-dolaisoleucine (Dil)[17–22] and (*S*)-dolaphenine (Doe)[23] fragments. In our retrosynthetic approach, the target compound dolastatin 10 was envisioned as potentially being derived from the union of the two key subunits, dolaisoleucine (Dil) and dolaproine (Dap), which could be prepared by catalytic hydrogenation[24] of β-keto esters promoted by ruthenium-catalysts (Scheme 1). To the best of our knowledge, no synthetic approach towards dolastatin 10 was based upon asymmetric hydrogenations as key steps to furnish the key intermediates dolaisoleucine (Dil) and dolaproine (Dap). In our continuous interest[25] in the synthesis of challenging bioactive molecules, we report in this paper full experimental details regarding the total synthesis of dolastatin 10 by using ruthenium-SYNPHOS[26] catalyzed asymmetric hydrogenations.



Scheme 1. Retrosynthetic analysis of dolastatin 10.

2. Results and discussion

Our approach began with the synthesis of β-keto ester **2** (Scheme 2) from the commercially available (*S*)-Boc-isoleucine in reaction either with carbonyldiimidazole and the magnesium enolate of ethyl hydrogen malonate, which proceeded in 62% yield or with monoethyl monopotassium malonate, magnesium chloride and triethylamine in THF with an increased yield of 88%. Next, the amine hydrochloride salt **3** was prepared quantitatively from the corresponding β-keto ester **2** in a single step with gaseous HCl in ethanol at 0 °C for 2 h. Under these conditions, no work

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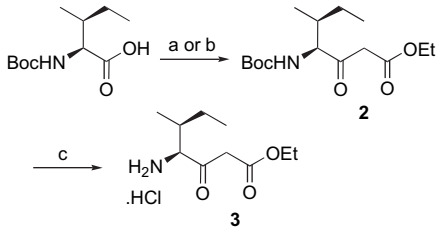
up was necessary and simple evaporation of the solvent afforded the required β-keto ester **3**.



Scheme 2. *Reagents and conditions*: (a) carbonyldiimidazole, THF, 0 °C, then $Mg(O_2CCH_2CO_2Et)_2$, THF/Et_2O, rt, 96 h, 62%; (b) carbonyldiimidazole, THF, 0 °C, then $KO_2CCH_2CO_2Et$, NEt_3, $MgCl_2$, THF, rt, 39 h, 88%; (c) HCl gas, EtOH, 0 °C, quant.

Afterwards, hydrogenation reactions of keto esters **2** and **3** were conducted under mild conditions (12 bar, 50 °C in EtOH) with both Ru-SYNPHOS and Ru-MeO-BIPHEP catalysts as shown in Scheme 3. Under these standard sets of conditions, complete conversions were observed in all cases, at a substrate/catalyst ratio (S/C)=100. The hydrogenation of **2** was first performed by using the in situ generated [$RuBr_2$((*S*)-SYNPHOS)] catalyst prepared by using our convenient procedure,[27] leading to good enantiofacial discrimination (Table 1, entry 1, dr 92:8 (3*R*)-**4**/(3*S*)-**5**). Comparable results were obtained when (*R*)-SYNPHOS ligand was used to perform the hydrogenation (entry 2, dr 2:98 (3*R*)-**4**/(3*S*)-**5**). Based on our previous results,[28] we studied the hydrogenation of the hydrochloride salt **3** (entries 3–5).

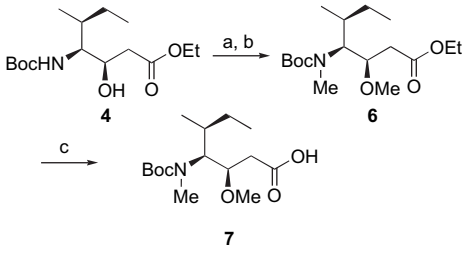
By using the in situ generated [$RuBr_2$((*S*)-MeO-BIPHEP)] catalyst, a comparable diastereoselectivity (entry 3, dr 94:6 (3*R*)-**4**/(3*S*)-**5**) was observed in a shorter reaction time (24 h). Finally, we were pleased to find that an excellent diastereoselectivity (entry 5, dr 98:2 (3*R*)-**4**/(3*S*)-**5**) was reached by using in situ prepared [$RuBr_2$((*S*)-SYNPHOS)]. The synthesis of Boc-(3*R*)-Dil **7** was completed in two subsequent steps (Scheme 4). First, N-methylation and O-methylation of **4** afforded the corresponding compound **6** (74% yield), which was treated with sodium hydroxide to furnish the corresponding (3*R*,4*S*,5*S*)-dolaisoleucine (Dil) **7** (81% yield) whose spectroscopic data were in agreement with those reported in the literature.[6,7,21]

Next, the synthesis of Dap[11–16] subunit **11** started with the hydrogenation reaction of β-keto ester **8** through dynamic kinetic resolution (DKR).[29] The latter was performed under newly optimized conditions at 50 °C under 130 bar of hydrogen pressure for 117 h in the presence of 3 mol % of in situ

Table 1. Asymmetric hydrogenation of β-keto esters **2** and **3** derived from Boc-Ile

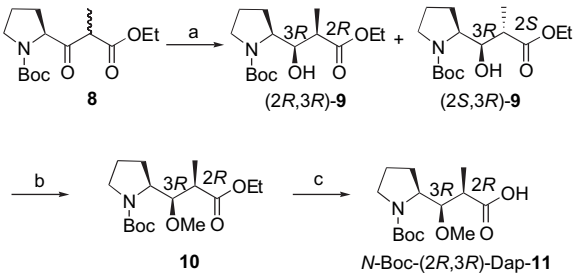
Entry	Substrate[a]	P×P	Time[b]	dr[c] (3*R*)/(3*S*)
1	**2**	(*S*)-SYNPHOS	72	92:8
2	**2**	(*R*)-SYNPHOS	66	2:98
3	**3**	(*S*)-MeO-BIPHEP	24	94:6
4	**3**	(*R*)-MeO-BIPHEP	24	8:92
5	**3**	(*S*)-SYNPHOS	24	98:2

[a] Reactions were conducted on 1 mmol scale.
[b] Reaction time was not optimized.
[c] Diastereomeric ratio was measured by ^{1}H NMR (400 MHz).



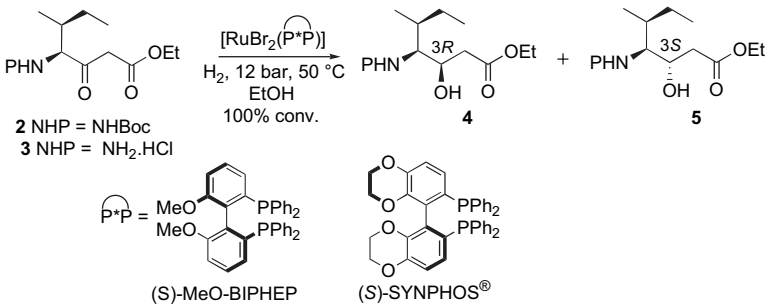
Scheme 4. *Reagents and conditions*: (a) LiHMDS, HMPA, THF, −78 °C, 25 min; (b) MeOTf, −20 °C, 25 min, 74%; (c) NaOH aq, EtOH, 0 °C to rt, 16 h, 81%.

Ru-SYNPHOS catalyst prepared by mixing [$RuCl_2$(*p*-cymene)]$_2$ with (*S*)-SYNPHOS (Scheme 5). An unseparable mixture of *syn* (2*R*,3*R*)-**9** and *anti* (2*S*,3*R*)-**9** diastereoisomers was isolated in a dr 2:1 with 55% yield after chromatography on silica gel.

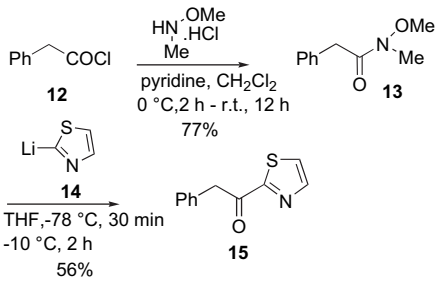


Scheme 5. *Reagents and conditions*: (a) [Ru]/(P×P)=3 mol %, [$RuCl_2$(*p*-cymene)]$_2$/(*S*)-SYNPHOS, H_2, 130 bar, 50 °C, 117 h, 55% yield; (b) LiHMDS, HMPA, THF, −78 °C, 25 min, then MeOTf, −20 °C, 15 min, 45% yield; (c) LiOH, EtOH/H_2O, overnight, 59% yield.

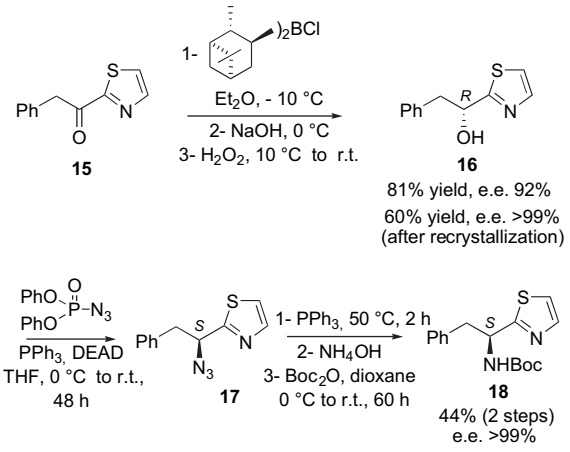
The *syn* (2*R*,3*R*)-**9** and *anti* (2*S*,3*R*)-**9** β-hydroxy esters were subjected to the next synthetic steps of O-methylation with LiHMDS in HMPA–THF and MeOTf. At this point, the *syn* (2*R*,3*R*)-**10** and *anti* (2*S*,3*R*)-**10** were separated and the



Scheme 3.



Scheme 6.



Scheme 7.

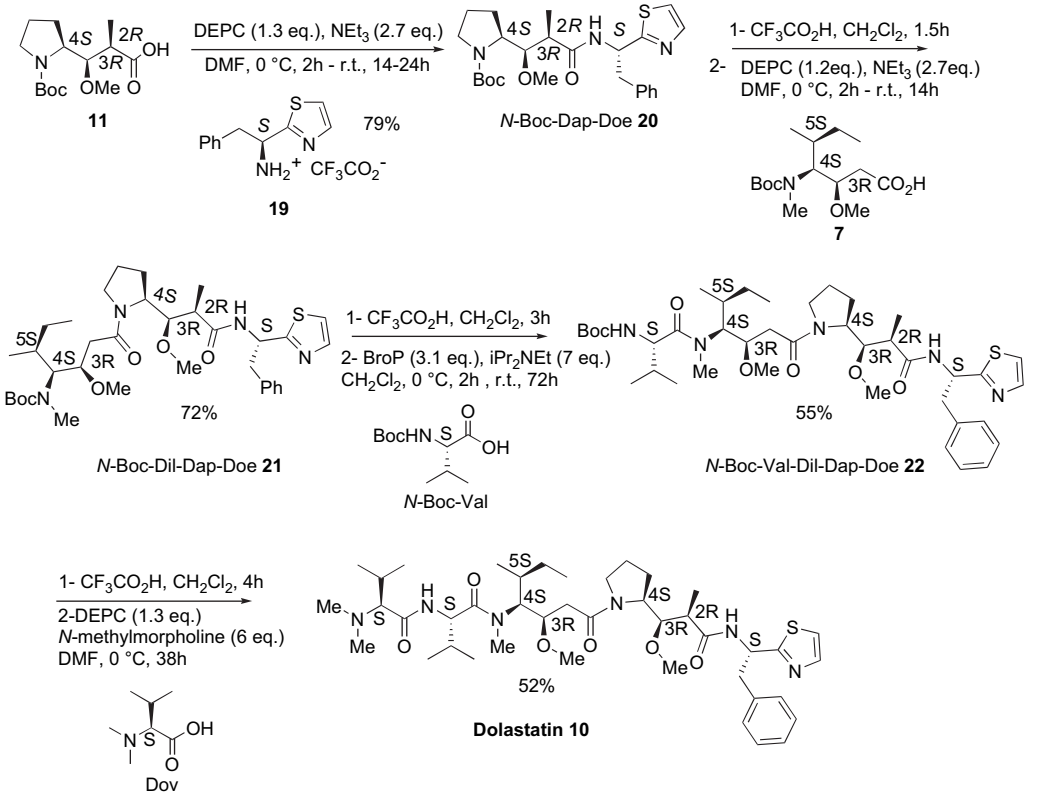
syn (2*R*,3*R*)-**10** was isolated with 45% yield. After saponification of (2*R*,3*R*)-**10** with LiOH, the naturally occurring *N*-Boc-(2*R*,3*R*)-Dap **11** was obtained with 59% yield in an enantiomerically pure form.

The C-terminal Doe unit *N*-Boc-(*S*)-dolaphenine ((*S*)-2-phenyl-1-(2-thiazolyl)ethylamine) **18** was prepared according to a modified procedure reported by Hamada and co-workers.[23b] Phenylacetyl chloride **12** was condensed with *N*-methoxy-*N*-methylamine hydrochloride in a mixture of pyridine/CH_2Cl_2 to give the amide **13** with 77% yield. Reaction of **13** with thiazolyllithium **14** obtained from 2-bromothiazole and *n*-butyllithium led to the benzyl thiazolyl ketone **15** (Scheme 6).

The asymmetric reduction of **15** was carried out by using Brown's reagent (Ipc_2BCl) (Scheme 7) affording the (*R*)-alcohol **16** with 60% yield and enantiomeric excess >99% measured by HPLC analysis after recrystallization.

The alcohol **16** was then treated under classical Mitsunobu reaction in the presence of triphenylphosphine, diethyl azodicarboxylate and diphenyl phosphorazidate to lead to the azide compound **17**, which was successively treated with triphenylphosphine, aqueous ammonia and Boc_2O to obtain optically pure Boc-(*S*)-dolaphenine **18**[23] (44%, two steps).

Having prepared the three key units required for the synthesis of dolastatin 10, the construction of **1** started from the C-terminal Doe unit *N*-Boc-(*S*)-dolaphenine. Thus, diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$) and trifluoroacetic acid were mainly used for the coupling and deprotection (Scheme 8). Trifluoroacetate salt of dolaphenine



Scheme 8.

19, prepared in dichloromethane from **18** and TFA, was condensed with **11** to afford *N*-Boc-Dap-Doe **20** with 79% yield.

Attachment of *N*-Boc-Dil **7** with the dipeptide *N*-Boc-Dap-Doe **20** was accomplished by using trifluoroacetic acid and DEPC to afford *N*-Boc-Dil-Dap-Doe **21** with 72% yield. Next, coupling of *N*-Boc-valine with tripeptide fragment *N*-Boc-Dil-Dap-Doe **21** was carried out by using TFA and (trisdimethylamino)phosphonium hexafluorophosphate (BroP) in the presence of diisopropylethylamine to provide *N*-Boc-Val-Dil-Dap-Doe **22** with 55% yield. Last coupling of (*S*)-dolavaline with *N*-Boc-Val-Dil-Dap-Doe **22** fragment in the presence of TFA and diethyl phosphorocyanidate provided the naturally occurring dolastatin 10 with spectroscopic data in agreement with those reported previously for this compound.[1,6,7]

3. Conclusion

In summary, a total synthesis of dolastatin 10 has been achieved. In this approach, three stereogenic centres were successfully set by catalytic hydrogenation reactions of β-keto esters by using ruthenium-SYNPHOS complexes with a good control of the stereochemistry of the natural product. This versatile approach could be applied to the synthesis of analogues.

4. Experimental

4.1. General methods

Dichloromethane was distilled from calcium hydride, and tetrahydrofuran and diethyl ether from sodium/benzophenone. Acetone for the catalyst preparation was distilled over potassium carbonate. Other solvents were used without any purification. Triethylamine was distilled from potassium hydroxide. All air and/or water sensitive reactions were carried out under an argon atmosphere unless otherwise noted. ^{1}H NMR spectra were recorded on an Avance 300 at 300 MHz or an Avance 400 at 400 MHz; ^{13}C NMR spectra were recorded on an Avance 300 at 75 MHz or an Avance 400 at 100 MHz. Chemical shifts (δ) are reported in parts per million downfield relative to internal Me_4Si. Coupling constants (J) are reported in hertz and refer to apparent peak multiplicities (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; qu, quintet; o, octet; m, multiplet; and br, broad). Mass spectra were determined on a Nermag R10-10C instrument. Ionization was obtained by chemical ionization with ammonia (DCI/NH_3) or by electrospray (on an API 3000 PE Sciex instrument). Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 589 nm (sodium lamp). GC analyses of compounds **9** were performed on a Agilent 6850 series equipped with an HP01 column capillary column (30 m, ∅ 0.25 μm): 70–210 °C, 5 °C/min, flow: 4 mL/min (He).

4.2. General procedure for asymmetric hydrogenation of β-keto esters 2 and 3

(*R*) or (*S*)-SYNPHOS® (7.7 mg, 0.012 mmol) and (COD)-Ru(2-methylallyl)$_2$ (3.2 mg, 0.01 mmol, commercially available from Acros) were placed in a round-bottomed tube, degassed by three vacuum/argon cycles at room temperature and dissolved in degassed acetone (1 mL). To this suspension was added at room temperature a 0.15 N methanolic HBr solution (147 μL, 0.022 mmol) and the mixture was stirred at 25 °C for 30 min. After evaporation of the solvent under vacuum, a solution of β-keto ester (2 mmol) in EtOH (2 mL) was added to the ruthenium catalyst. The resulting mixture was placed under the desired hydrogen pressure and temperature for 24 h. After removal of the solvent, the residue was purified by flash chromatography on silica gel to afford the β-hydroxyesters **4** and **5**.

4.3. Ethyl (4*S*,5*S*)-4-(*N*-*tert*-butoxycarbonylamino)-5-methyl-3-oxoheptanoate 2

Procedure A: a solution of (*S*)-*N*-Boc-isoleucine (86.5 mmol, 20 g) in tetrahydrofuran (120 mL) was cooled to 0 °C, and *N*,*N*′-carbonyldiimidazole (95.15 mmol, 1.1 equiv, 15.43 g) was added in small portions under vigorous stirring. After evolution of gas, the mixture was stirred at room temperature for 4 h, then cooled to −10 °C. In a 2 L three-necked reactor equipped with a mechanical stirrer and argon inlet, a solution of ethyl hydrogen malonate (173 mmol, 2 equiv, 22.85 g) in tetrahydrofuran (120 mL) was cooled to −10 °C. A solution of isopropylmagnesium bromide in diethyl ether (346 mmol, 4 equiv, 169 mL of a 2.05 M solution) was added dropwise, the temperature of the reaction mixture being kept below 5 °C. The resulting slurry was stirred at room temperature for 3 h, then recooled again to −10 °C before adding dropwise the solution of imidazolide, the temperature of the reaction mixture being kept below 5 °C. The homogeneous reaction mixture was vigorously stirred at room temperature for 96 h. The reaction mixture was quenched at 0 °C with 10% citric acid and acidified to pH 3 (500 mL). The mixture was extracted with ethyl acetate/toluene (4:1). The combined organic layers were washed with water (200 mL), saturated aqueous sodium hydrogen carbonate (2×150 mL) and saturated aqueous sodium chloride (150 mL), dried over sodium sulfate and concentrated under reduced pressure to give a yellow oil. The residue was purified by silica gel column chromatography using cyclohexane/ethyl acetate (9:1) as eluent to give the β-keto ester **2** (16 g, 62% yield) as a pale yellow oil.

Procedure B: a solution of (*S*)-*N*-Boc-isoleucine (27.4 mmol, 6.34 g) in tetrahydrofuran (50 mL) was cooled to 0 °C, and *N*,*N*′-carbonyldiimidazole (27.4 mmol, 4.45 g) was added in small portions under vigorous stirring. After evolution of gas, the mixture was stirred at room temperature for 3 h and then cooled in an ice bath. To a suspension of monoethyl malonate potassium salt (60.0 mmol, 10.22 g) in THF (100 mL) at 5 °C was added Et_3N (86 mmol, 13.4 mL) followed by anhydrous $MgCl_2$ (75 mmol, 7.15 g). The mixture was stirred at room temperature for 3 h, then cooled to 0 °C and the above solution of the activated ester previously prepared in THF was added dropwise over 35 min. The mixture was allowed to stir for 39 h at room temperature, quenched with aqueous citric acid and extracted with ethyl acetate. The organic layers were washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4) and concentrated in vacuo to give the β-keto ester **2** (7.30 g, 88%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 200 MHz, 24 °C): δ 5.04 (m, 1H), 4.32 (m, 1H), 4.22 (q, J=7.1 Hz, 2H), 3.53 (s, 2H), 1.7–2.0 (m, 1H), 1.44 (s, 9H), 1.28 (t, J=7.1 Hz, 3H), 1.0–1.3 (m, 2H), 0.98 (d, J=6.8 Hz, 3H), 0.90 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 202.1, 166.5, 155.5, 79.7, 64.0, 61.1, 47.0, 36.0, 28.0, 23.9, 15.8, 13.8, 11.3. MS (DCI, NH_3): m/z 319 (100%, $[M+NH_4]^+$), 302 (42%, $[M+H]^+$), 263 (96%, $[M-C_4H_8+NH_4]^+$), 246 (25%, $[M-C_4H_8+H]^+$). $[\alpha]_D^{21}$ −41 (c 1.0, EtOH).

4.4. Ethyl (3*R*,4*S*,5*S*)-4-(*N*-*tert*-butoxycarbonylamino)-3-hydroxy-5-methyl-heptanoate (3*R*)-4

A solution of ethyl (4*S*,5*S*)-4-(*N*-*tert*-butoxycarbonylamino)-5-methyl-3-oxo-heptanoate **2** (0.5 mmol, 150 mg) in absolute ethanol (2 mL) was degassed by three vacuum–argon cycles at room temperature and added via *cannula* to the catalyst [Ru(*S*)-SYNPHOS®Br_2] (0.05 mmol prepared according to the general procedure). The Schlenk vessel was then placed under argon in a 250 mL stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 12 bar. The autoclave was heated at 50 °C and stirring was maintained for 72 h. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude β-hydroxy ester as a brown oil. The crude product was purified by silica gel column chromatography using cyclohexane/ethyl acetate (9:1) as eluent to give the β-hydroxy ester (3*R*)-**4** (125 mg, 83% yield) as a white solid. ^{1}H NMR analysis of the crude product showed a dr 92:8, (3*R*)-**4**/(3*S*)-**5** diastereoisomers. Mp 50 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.41 (d, J=9.8 Hz, 1H, N), 4.15 (q, J=7.1 Hz, 2H), 3.98 (m, 1H), 3.55 (m, 1H), 2.55 (dd, J=2.8, 16.3 Hz, 1H), 2.43 (dd, J=8.9, 16.3 Hz, 1H), 1.79 (m, 1H), 1.53 (m, 1H), 1.28 (s, 9H), 1.26 (t, J=7.1 Hz, 3H), 0.99 (m, 1H), 0.92 (d, J=6.8 Hz, 3H), 0.90 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 173.2, 156.4, 79.5, 69.0, 60.7, 58.9, 38.3, 34.6, 28.3, 23.3, 16.2, 14.1, 11.7. MS (DCI, NH_3): m/z 304 (100%, $[M+H]^+$), 265 (14%, $[M-C_4H_8+NH_4]^+$), 248 (51%, $[M-C_4H_8+H]^+$). $[\alpha]_D^{21}$ +10 (c 1.02, MeOH) ($[\alpha]_D^{24}$ (lit.)[6] +10.3 (c 0.98, MeOH)).

4.5. Ethyl (3*R*,4*S*,5*S*)-4-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)-3-methoxy-5-methyl-heptanoate (3*R*)-6

To a solution of LiHMDS (1 M in THF, 5.2 mmol, 2.6 equiv, 5.2 mL) and HMPA (6 mmol, 3 equiv, 1.05 mL) in tetrahydrofuran (3 mL) at −78 °C was added a solution of ethyl (3*R*,4*S*,5*S*)-4-(*N*-*tert*-butoxycarbonylamino)-3-hydroxy-5-methyl-heptanoate (3*R*)-**4** (2 mmol, 606 mg) in tetrahydrofuran (6 mL). The stirring was maintained for 25 min at −78 °C before the addition of MeOTf (12 mmol, 6 equiv, 1.36 mL) at −20 °C. The reaction was then quenched with saturated aqueous ammonium chloride at −10 °C. After extraction with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (9:1) as eluent to give (3*R*)-**6** (493 mg, 74% yield) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, 54 °C): δ 4.17 (q, J=7.1 Hz, 2H), 3.89 (m, 2H), 3.38 (s, 3H), 2.72 (s, 3H), 2.50 (m, 2H), 1.80 (m, 1H), 1.51 (m, 1H), 1.47 (s, 9H), 1.27 (t, J=7.2 Hz, 3H), 1.10 (m, 1H), 0.99 (d, J=6.9 Hz, 3H), 0.91 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ (conformers) 172.1 and 171.8, 156.4 and 156.3, 79.7 and 79.2, 78.4, 60.6 and 60.5, 57.8, 57.6, 37.7 and 37.0, 34.9, 34.4, 28.4, 25.8, 16.2 and 16.1, 14.2, 11.3. MS (DCI, NH_3): m/z 332 (100%, $[M+H]^+$), 293 (3%, $[M-C_4H_8+NH_4]^+$), 276 (7%, $[M-C_4H_8+H]^+$). $[\alpha]_D^{21}$ −16 (c 1.4, MeOH).

4.6. (3*R*,4*S*,5*S*)-4-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-3-methoxy-5-methyl-heptanoic acid (3*R*)-7

To an ice-cooled solution of ethyl (3*R*,4*S*,5*S*)-4-(*N*-*tert*-butoxycarbonylamino)-3-methoxy-5-methyl-heptanoate (3*R*)-**6** (1.18 mmol, 390 mg) in ethanol (3 mL) was added 1 N sodium hydroxide (1.24 mmol, 1.05 equiv, 1.24 mL). The mixture was then stirred overnight at room temperature. The resulting solution was acidified to pH 4 with 1 N aqueous hydrochloric acid and then extracted (3×20 mL) with ethyl acetate. The combined organic layers were washed with 1 M aqueous potassium hydrogen sulfate, then saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure to give the desired *N*-Boc-dolaisoleucine (3*R*)-**7** as a colourless viscous oil (290 mg, 81% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, 54 °C): δ 3.80–4.02 (m, 2H), 3.41 (s, 3H), 2.70 (br s, 3H), 2.54 (m, 2H), 1.78 (m, 1H), 1.49 (m, 1H), 1.45 and 1.44 (s, 9H), 1.08 (m, 1H), 0.96 (d, J=6.8 Hz, 3H), 0.89 (t, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ (conformers) 176.4, 156.6 and 156.3, 80.1 and 79.6, 78.2, 60.2 (br), 57.7 and 57.6, 37.1 and 36.8, 35.0, 34.5, 28.4, 25.9 and 25.8, 16.2 and 16.1, 11.3. MS (DCI, NH_3): m/z 304 (100%, $[M+H]^+$), 265 (12%, $[M-C_4H_8+NH_4]^+$), 248 (23%, $[M-C_4H_8+H]^+$). $[\alpha]_D^{21}$ −13 (c 0.95, MeOH) ($[\alpha]_D^{23}$ (lit.)[6] −10.5 (c 0.97, MeOH)).

4.7. Ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*R*,3*R*)-9

A solution of ethyl (4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-oxo-2-methyl-propanoate **8** (3 mmol, 897 mg) in absolute ethanol (6 mL) was degassed by three vacuum–argon cycles at room temperature and added via *cannula* to the mixture (3 mol %) $[RuCl_2(p\text{-cymene})]_2$ (27 mg) and (*S*)-SYNPHOS® (63 mg). The Schlenk vessel was then placed under argon in a 250 mL stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 130 bar. The autoclave was heated at 50 °C and stirring was maintained for 117 h. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude β-hydroxy ester as a brown oil. The crude product was purified by silica gel column chromatography using cyclohexane/ethyl acetate (9:1) as eluent to give the β-hydroxy ester (500 mg, 55% yield) as a slightly yellow oil. GC analysis showed a 2:1 mixture of (2*R*,3*R*)-**9**/(2*S*,3*R*)-**9** diastereoisomers (t_R (2*R*,3*R*) 21.8 min, t_R (2*S*,3*R*) 21.9 min). ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 5.01 (br s, 1H), 4.14 (q, J=7.1 Hz, 2H), 3.99 (app t, J=4.9 Hz, 1H), 3.95 (m, 1H), 3.50 (m, 1H), 3.25 (m, 1H), 2.54 (m, 1H), 1.71–1.97 (m, 4H), 1.46 (s, 9H), 1.25 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ broad peaks (conformers) 175.6, 155

(br), 79.9 (br), 73.8 (br), 60.5, 59.4, 47.3, 42.1, 28.5, 25.2, 24.3, 14.6, 14.1. MS (DCI, NH_3): *m/z* 302 (100%, $[M+H]^+$), 263 (4%, $[M-C_4H_8+NH_4]^+$), 246 (13%, $[M-C_4H_8+H]^+$). $[\alpha]_D^{21}$ −47.7 (*c* 1.0, $CHCl_3$).

4.8. Ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (2*R*,3*R*)-10

A solution of ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*R*,3*R*)-**9** (2 mmol, 602 mg) in tetrahydrofuran (6 mL) was added to a solution of LiHMDS (1 M in THF, 2.8 mmol, 1.4 equiv, 2.8 mL) in HMPA (3.2 mmol, 1.6 equiv, 557 μL) and tetrahydrofuran (3.2 mL) at −78 °C. The stirring was maintained for 25 min at −78 °C before the addition of MeOTf (6.0 mmol, 3.0 equiv, 679 μL) at −20 °C. The mixture was stirred at −20 °C for an additional 15 min. The reaction was then quenched with saturated aqueous ammonium chloride. After extraction with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (9:1) as eluent to give (2*R*,3*R*)-**10** (282 mg, 45% yield) as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.14 (br q, 2H, *J*=7.1 Hz), 3.70–3.95 (m, 2H), 3.53 (m, 1H), 3.41 (s, 3H), 3.22 (m, 1H), 2.47 (m, 1H), 1.80–2.05 (m, 3H), 1.65–1.77 (m, 1H), 1.49 (m, 9H), 1.25 (t, *J*=7.1 Hz, 3H), 1.23 (d, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 174.6, 154.4 (br), 83.4, 79.6 (br), 61.0 (br), 60.4, 59.6 (br), 46.6 (br), 43.1, 28.5, 26.2 (br), 24.0 (br), 14.2, 13.6. MS (DCI, NH_3): *m/z* 333 (7%, $[M+NH_4]^+$), 316 (100%, $[M+H]^+$), 277 (7%, $[M-C_4H_8+NH_4]^+$), 260 (34%, $[M-C_4H_8+H]^+$). $[\alpha]_D^{21}$ −50.8 (*c* 1.2, $CHCl_3$).

4.9. (2*R*,3*R*,4*S*)-3-(*N*-*tert*-Butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methylpropanoic acid Boc-(2*R*,3*R*)-dolaproine 11

To an ice-cooled solution of ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate **10** (0.78 mmol, 247 mg) in a mixture of ethanol (5 mL) and water (1 mL) was added lithium hydroxide monohydrate (2.35 mmol, 3 equiv, 99 mg). The mixture was then stirred overnight at room temperature. After evaporation of the solvent, the residue was diluted with dichloromethane and washed with water. The aqueous layer was acidified to pH 4 by adding 1 N aqueous hydrochloric acid and then extracted with ethyl acetate followed by dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give the desired product **11** as a colourless viscous oil (132 mg, 59% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C): δ 4.11 (m, 1H), 3.62 (m, 1H), 3.47 (s, 3H), 3.44–3.51 (m, 1H), 3.06 (m, 1H), 2.65 (m, 1H), 1.89–1.96 (m, 2H), 1.76–1.88 (m, 2H), 1.47 (s, 9H), 1.26 (d, *J*=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 179.8 (br), 154.3 (br), 83.0, 79.9, 61.2, 59.4, 46.6, 42.8, 28.5, 26.1, 24.0, 13.5. MS (DCI, NH_3): *m/z* 305 (4%, $[M+NH_4]^+$), 288 (100%, $[M+H]^+$), 249 (14%, $[M-C_4H_8+NH_4]^+$), 232 (30%, $[M-C_4H_8+H]^+$). HRMS (DCI^+), *m/z* calcd for $C_{14}H_{26}O_5N$: 288.1811, found: 288.1804. $[\alpha]_D^{24}$ −60.0 (*c* 1.03, MeOH).

4.10. *N*-Methoxy-*N*-methylphenylacetamide 13

To an ice-cooled solution of *N*,*O*-dimethylhydroxylamine hydrochloride (51.2 mmol, 1.1 equiv, 5 g) and 2-phenylacetyl chloride (46.5 mmol, 1 equiv, 6.15 mL) in dichloromethane (200 mL) was added pyridine (102.3 mmol, 2.2 equiv, 8.3 mL). After 2 h at 0 °C, the reaction mixture was stirred overnight at room temperature. After evaporation of the solvents, the residue was diluted with a 1:1 mixture of dichloromethane and diethyl ether, filtered on a Celite pad and then washed with saturated aqueous sodium chloride (2×70 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using cyclohexane/ethyl acetate (9:1 to 5:5) as eluent to give the amide **13** (6.40 g, 77% yield) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 54 °C): δ 7.25–7.32 (m, 5H), 3.77 (s, 2H), 3.60 (s, 3H), 3.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 172.2, 134.9, 129.3, 128.5, 126.7, 61.3, 39.4, 32.2.

4.11. 2-Phenyl-1-(2-thiazolyl)ethanone 15

To a solution of *n*-butyllithium (2.5 M in hexane, 40.2 mmol, 1.2 equiv, 16.1 mL) and TMEDA (40.2 mmol, 1.2 equiv, 6.48 mL) in tetrahydrofuran (80 mL) at −78 °C was added dropwise 2-bromothiazole (40.2 mmol, 1.2 equiv, 3.62 mL). The reaction mixture was stirred at −78 °C for 2 h prior to the addition of a solution of *N*-methoxy-*N*-methylphenylacetamide **13** (33.5 mmol, 6 g) in tetrahydrofuran (40 mL). After 0.5 h at −78 °C and 2 h at −10 °C, the reaction mixture was quenched with 1 M aqueous potassium hydrogen sulfate. After extraction with diethyl ether (2×200 mL), the combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography using cyclohexane/ethyl acetate (95:5 to 9:1) as eluent to give the ketone **15** as a white solid (5.07 g, 75% yield). ^{1}H NMR ($CDCl_3$, 300 MHz, 54 °C): δ 8.04 (d, *J*=3.0 Hz, 1H), 7.68 (d, *J*=3.0 Hz, 1H), 7.26–7.39 (m, 5H), 4.47 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 191.0, 166.7, 144.8, 133.6, 129.9, 128.6, 127.0, 126.7, 44.8.

4.12. (*S*)-2-Phenyl-1-(2-thiazolyl)ethanol 16

To an ice-cooled solution of (+)-di-*iso*-pinocamphenylchloroborane (44.33 mmol, 3 equiv, 14.22 g) in diethyl ether (10 mL) was added a solution of 2-phenyl-1-(2-thiazolyl)-ethanone **15** (14.78 mmol, 3 g) in diethyl ether (60 mL). The reaction mixture was stirred for 23 h at 0 °C before the addition of 10% aqueous sodium hydroxide. Then 30% aqueous hydrogen peroxide was added at 10 °C and the resulting mixture was stirred for 5 h at room temperature. After dilution with water, the aqueous layer was saturated with potassium carbonate and extracted with diethyl ether three times. The combined organic layers were then washed with saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated under reduced pressure to give the crude alcohol as a white solid. The residue was purified by silica gel column chromatography using cyclohexane/ethyl acetate (8:2) as eluent to give the alcohol **16** as a white solid (2.45 g, 81% yield, ee 92%). The pure product was recrystallized in a 1:1 mixture of diethyl ether and *n*-hexane as

colourless crystals (1.82 g, 60% yield, ee >99%). ^{1}H NMR ($CDCl_3$, 300 MHz, 54 °C): δ 7.75 (d, J=3.3 Hz, 1H), 7.22–7.33 (m, 6H), 5.25 (dd, J=4.2, 8.4 Hz, 1H), 3.36 (dd, J=4.2, 13.5 Hz, 1H), 3.28 (br s, 1H, O), 3.10 (dd, J=8.4, 13.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 174.4, 142.1, 136.9, 129.7, 128.7, 127.1, 119.1, 72.8, 44.6. $[\alpha]_D^{24}$ −56.2 (c 1.6, MeOH). HPLC: Chiralcel OD-H, 95:5 hexane/*iso*-propanol, 1.0 mL/min, λ=254 nm, t_R (*S*) 14.8 min, t_R (*R*) 16.3 min.

4.13. (*S*)-2-Phenyl-1-(2-thiazolyl)ethylazide 17

To an ice-cooled solution of (*S*)-2-phenyl-1-(2-thiazolyl)-ethanol **16** (8.29 mmol, 1.7 g) in tetrahydrofuran (80 mL) was added triphenylphosphine (9.12 mmol, 1.1 equiv, 2.39 g) followed by diethyl azodicarboxylate (DEAD, 9.12 mmol, 1.1 equiv, 1.79 mL) and diphenyl azidophosphate (DPPA, 9.12 mmol, 1.1 equiv, 2.51 g). The resulting mixture was then stirred for 60 h at room temperature. After concentration under reduced pressure, the residue was purified by silica gel column chromatography using cyclohexane/ethyl acetate (8:2) as eluent to give the azide **17** as an orange oil in a mixture with DPPA (1.70 g, 89% yield). This mixture was used without any other purification in the next synthetic step. ^{1}H NMR ($CDCl_3$, 300 MHz, 54 °C): δ 7.82 (d, J=3.2 Hz, 1H), 7.22–7.42 (m, 6H), 5.02 (dd, J=5.1, 8.8 Hz, 1H), 3.42 (dd, J=5.1, 13.9 Hz, 1H), 3.17 (dd, J=8.8, 13.9 Hz, 1H).

4.14. (*S*)-Boc-Dolaphenine 18

To a solution of triphenylphosphine (8.42 mmol, 1.2 equiv, 2.21 g) in tetrahydrofuran (15 mL) was added a solution of (*S*)-2-phenyl-1-(2-thiazolyl)ethylazide **17** (6.96 mmol, 1.6 g) in tetrahydrofuran (20 mL). The reaction mixture was then heated at 50 °C for 3 h. Then 28% aqueous ammonium hydroxide (19.3 mL) was added and the stirring was continued for additional 3 h at 50 °C. The reaction mixture was diluted with water (100 mL) and extracted with diethyl ether (3×150 mL). The combined organic layers were washed with 1 N aqueous hydrochloric acid (148 mL). The aqueous layer was then cooled to 0 °C and adjusted to pH 14 with 10% aqueous sodium hydroxide. The aqueous layer was then extracted with dichloromethane (3×100 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was then dissolved in dioxane (20 mL) and cooled to 0 °C. Di-*tert*-butyl dicarbonate (11.2 mmol, 1.6 equiv, 2.46 g) was then added and the reaction mixture was stirred at room temperature overnight. After dilution with water, the mixture was extracted twice with diethyl ether. The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure to give the crude product **18**, which was purified by silica gel column chromatography using cyclohexane/ethyl acetate (8:2) as eluent to give the *N*-Boc-(*S*)-dolaphenine **18** as a white solid (1.12 g, 44% yield over two steps). The pure (*S*)-dolaphenine was recrystallized in acetone/*n*-hexane (ee>99%). Mp 82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 54 °C): δ 7.76 (d, J=3.3 Hz, 1H), 7.21–7.27 (m, 4H), 7.10 (m, 2H), 5.30 (br s, 1H), 3.30 (m, 2H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 172.0, 154.0, 142.2, 136.4, 129.4, 128.4, 126.8, 118.8, 80.1, 51.6, 41.9, 28.3. $[\alpha]_D^{21}$ −25.4 (c 0.56, $CHCl_3$) ($[\alpha]_D^{24.5}$ (lit.)[23b] −25.5 (c 0.60, $CHCl_3$)). HPLC: Chiralcel OD-H, 95:5 hexane/*iso*-propanol, 1.0 mL/min, λ=254 nm, t_R (*S*) 9.6 min, t_R (*R*) 11.0 min.

4.15. General procedure for the deprotection of *N*-Boc derivatives with trifluoroacetic acid

To a solution of the *N*-Boc amino acid or peptide in dichloromethane (2.5 mL/mmol) was added trifluoroacetic acid (11.6 equiv). After being stirred at room temperature for 2–24 h, the reaction mixture was concentrated under reduced pressure to give the crude deprotected product that is used immediately in the next synthetic step without any purification.

4.16. *N*-Boc-Dap-Doe 20

To an ice-cooled solution of the carboxylic acid *N*-Boc-Dap **11** (0.252 mmol, 72.3 mg, 1 equiv) and the deprotected (*S*)-Doe **19** (0.35 mmol, 1.44 equiv) in dimethylformamide (3 mL/mmol) was added DEPC (0.328 mmol, 55 μL, 1.3 equiv) followed by triethylamine (0.68 mmol, 95 μL, 2.7 equiv). After 2 h at 0 °C, the stirring was continued at room temperature for 14 h. The reaction mixture was then diluted with a 2:1 mixture of ethyl acetate and toluene, washed with 1 M aqueous potassium hydrogen sulfate, water, saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The crude dipeptide was purified by silica gel column chromatography using cyclohexane/ethyl acetate (5:5). *N*-Boc-Dap-Doe **20** was obtained as a white solid (94 mg, 79% yield). ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 7.72 (d, J=3.2 Hz, 1H), 7.13–7.27 (m, 6H), 6.42 (br d, 1H, N), 5.60 (m, 1H), 3.70–3.90 (m, 2H), 3.49 (m, 1H), 3.38 (m+s, 4H), 3.15–3.26 (m, 2H), 2.25–2.40 (m, 1H), 1.59–1.78 (m, 4H), 1.47 (m, 9H), 1.14 (m, 3H). ^{13}C NMR (C_6D_6, 100 MHz, 24 °C): δ (conformers) 174.0 and 173.4, 171.6 and 171.1, 154.8 and 154.4, 142.5, 137.0 and 136.6, 129.3, 128.6, 127.0 and 126.8, 118.9, 81.9, 79.8 and 79.4, 60.9 and 60.6, 59.0 and 58.7, 52.5 and 51.9, 46.9 and 46.6, 44.3 and 43.9, 41.4, 28.7, 25.7 and 25.1, 24.8 and 24.3, 14.1 and 13.9. MS (DCI, NH_3): m/z 474 (100%, $[M+H]^+$). $[\alpha]_D^{21}$ −75.0 (c 1.24, MeOH) ($[\alpha]_D^{24}$ (lit.)[6] −76.5 (c 0.96, MeOH)).

4.17. *N*-Boc-Dil-Dap-Doe 21

To an ice-cooled solution of the carboxylic acid (*N*-Boc-Dil, 1.1 equiv) and the deprotected dipeptide Dap-(*S*)-Doe **20** (1 equiv) in dimethylformamide (3 mL/mmol) was added DEPC (1.2 equiv) followed by triethylamine (2.7 equiv). After being stirred at 0 °C for 2 h, the stirring was continued at room temperature for 14 h. The reaction mixture was then diluted with a 2:1 mixture of ethyl acetate and toluene, washed with 1 N aqueous potassium hydrogen sulfate, water, saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The crude dipeptide was purified by silica gel column chromatography using cyclohexane/ethyl acetate (5:5). *N*-Boc-Dil-Dap-Doe **21** was obtained from the deprotected dipeptide Dap-(*S*)-Doe **20** (0.123 mmol) and *N*-Boc-Dil (3*R*)-**7** (0.136 mmol, 41 mg) according to the general procedure using DEPC

(0.15 mmol, 25 μL) and triethylamine (0.33 mmol, 46 μL), as a colourless viscous oil (58.2 mg, 72% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C): δ 7.71 (d, J=3.2 Hz, 1H), 7.16–7.24 (m, 6H), 5.60 (m, 1H), 4.13 (m, 2H), 3.90 (m, 2H), 3.38 (s, 3H), 3.34 (s, 3H), 3.32–3.44 (m, 4H), 2.70 (s, 3H), 2.44 (m, 3H), 1.50–2.00 (m, 6H), 1.47 (m, 9H), 1.16 (d, J=7.0 Hz, 3H), 1.12 (m, 1H), 0.99 (d, J=6.7 Hz, 3H), 0.91 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, 24 °C): δ 173.9, 171.8, 170.7 and 170.2, 156.7, 142.5, 137.1, 129.5, 128.5, 126.8, 118.8, 81.8 and 81.7, 79.8 and 79.3, 78.4 (br), 60.5, 59.2 and 59.1, 58.1 and 58.0, 52.7, 47.6, 43.9 and 43.8, 41.2, 38.0 and 37.8, 34.6, 28.6, 25.9, 25.1, 24.8 and 24.7, 16.2, 14.0 and 13.9, 11.5 and 11.1. MS (DCI, NH_3): m/z 659 (100%, $[M+H]^+$). $[\alpha]_D^{21}$ −66.7 (c 1.14, MeOH) ($[\alpha]_D^{23}$ (lit.)[6] −71.0 (c 0.12, MeOH)).

4.18. *N*-Boc-Val-Dil-Dap-Doe 22

To a solution of the deprotected tripeptide Dil-Dap-Doe **21** (0.0745 mmol, 49 mg) in dichloromethane (500 μL), shielded from light, was added diisopropylethylamine (0.13 mmol, 1.8 equiv, 21.5 μL) followed by *N*-Boc-(*S*)-Val (0.149 mmol, 2 equiv, 32.3 mg). Additional diisopropylethylamine (0.13 mmol, 1.8 equiv, 21.5 μL) was added and the resulting mixture was cooled to 0 °C before the addition of BroP (0.116 mmol, 1.56 equiv, 45.1 mg). The mixture was allowed to come back to room temperature and stirring was continued for 24 h. All the reactants were added once more to the mixture and then stirred for additional 48 h. The resulting mixture was extracted with ethyl acetate, washed with 10% aqueous sodium carbonate, dried over sodium sulfate and concentrated under reduced pressure. The crude tetrapeptide was purified by silica gel column chromatography using cyclohexane/ethyl acetate (5:5 to 0:100) as eluent to afford the desired product **22** as a colourless oil (31 mg, 55% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C): δ 7.72 (d, J=3.3 Hz, 1H), 7.20 (d, J=3.3 Hz, 1H), 7.16–7.26 (m, 7H, N), 5.57 (br q, J=6.0 Hz, 1H), 5.21 (d, J=9.5 Hz, 1H), 4.39 (br t, J=7.9 Hz, 1H), 3.95–4.20 (m, 2H), 3.88 (dd, J=2.0, 7.7 Hz, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 3.27–3.40 (m, 4H), 2.78 and 3.01 (s, 3H), 2.30–2.45 (m, 3H), 1.54–2.02 (m, 6H), 1.42 (m, 9H), 1.12 (d, J=7.0 Hz, 3H), 1.15 (m, 1H), 0.98 (d, J=6.6 Hz, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.93 (d, J=6.7 Hz, 3H), 0.84 (t, J=7.3 Hz, 3H). MS (DCI, NH_3): m/z 758 (100%, $[M+H]^+$). HRMS (DCI^+), m/z calcd for $C_{40}H_{64}N_5O_7S$: 758.4526, found: 758.4520. $[\alpha]_D^{21}$ −57.3 (c 0.62, MeOH) ($[\alpha]_D^{23.5}$ (lit.)[6] −64.6 (c 0.50, MeOH)).

4.19. Dolastatin 10

To a solution of the deprotected tetrapeptide Val-Dil-Dap-Doe **22** (0.0264 mmol, 20 mg) in dimethylformamide (500 μL) was added *N*-methylmorpholine (0.158 mmol, 6 equiv, 17 μL) and then stirring was maintained for 15 min before the addition of *N*,*N*-dimethyl-(*S*)-valine (0.158 mmol, 6 equiv, 23 mg). The resulting mixture was then cooled down to 0 °C and DEPC (0.0343 mmol, 1.3 equiv, 5.2 μL) was added. After 38 h at 0 °C, the mixture was diluted with ethyl acetate (10 mL) and 1 M sodium carbonate was added (3 mL). The resulting mixture was extracted with ethyl acetate, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane/acetone (75:25 to 5:5) as eluent to give the dolastatin 10 as a white powder (10.7 mg, 52% yield). ^{1}H NMR (CD_2Cl_2, 400 MHz, 24 °C): δ 7.71 (d, J=3.3 Hz, 1H), 7.18–7.27 (m, 7H), 6.80 (br d, 1H), 5.52 (m, 1H), 4.75 (dd, J=6.4, 9.0 Hz, 1H), 4.10 (m, 1H), 3.96 (m, 1H), 3.84 (dd, J=1.9, 8.2 Hz, 1H), 3.31 (s, 6H), 3.18–3.40 (m, 5H), 3.01 (s, 3H), 2.23 (s, 6H), 2.21–2.44 (m, 3H), 1.58–2.14 (m, 7H), 1.26–1.40 (m, 1H), 1.08 (d, J=7.0 Hz, 3H), 1.00 (d, J=7.0 Hz, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.95 (d, J=7.2 Hz, 3H), 0.93 (d, J=7.2 Hz, 3H), 0.90 (d, J=6.7 Hz, 3H), 0.81 (t, J=7.3 Hz, 3H). ^{13}C NMR (CD_2Cl_2, 100 MHz, 24 °C): δ 173.2, 171.7, 170.8, 169.8, 142.1, 137.0, 129.0, 128.0, 126.3, 118.4, 81.2, 78.0, 76.2, 60.2, 59.1, 57.4, 53.6, 53.4, 52.3, 47.3, 44.0, 42.3, 40.7, 37.2, 32.8, 30.6, 30.2, 27.3, 25.4, 24.7, 24.2, 19.5, 19.0, 17.3, 15.3, 13.8, 10.1. ESI-MS (MS^+): m/z 785.7 (100%, $[M+H]^+$). ESI-MS (MS^-): m/z 783.9 (100%, $[M-H]^-$). FABMS (FAB^+): m/z 785 (100%, $[M+H]^+$). HRMS (DCI^+), m/z calcd for $C_{42}H_{69}N_6O_6S$: 785.4999, found: 785.4980. $[\alpha]_D^{24}$ −57.5 (c 1.07, MeOH) ($[\alpha]_D^{23}$ (lit.)[6] −59.8 (c 0.035, MeOH)).

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