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The total synthesis and reassignment of stereochemistry of dragonamide

Hongliang Chen,[a,c] Yaqing Feng,[a] Zhengshuang Xu[b,c,*] and Tao Ye[c,*]

[a]*School of Chemical Engineering, Tianjin University, Tianjin 300072, China*
[b]*Laboratory of Chemical Genomics, The Shenzhen Graduate School of Peking University, Shenzhen 518055, China*
[c]*Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong, China*

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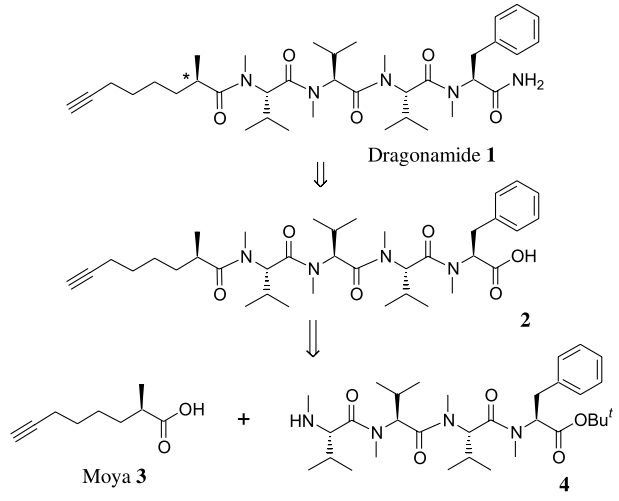
Abstract—The first total synthesis of dragonamide is reported. The synthesis has led to a reassignment of the configuration at the stereogenic centre on the alkyne-bearing fragment of the molecule.

1. Introduction

The marine cyanobacteria have provided chemists and biologists with a plethora of natural products, with a wide array of structures and functional groups.[1–4] They have been a fertile source for new bioactive molecules, and many possess potent activity, across a broad spectrum of targets. Their diversity in both biological activity and in chemical complexity has made these secondary metabolites the focus of much work in recent years. We have had a great deal of interest in products isolated from marine cyanobacteria,[5] and given its cytotoxicity against several cell lines it was decided to undertake the synthesis of dragonamide **1** (Scheme 1 and Fig. 1).

Dragonamide **1** was isolated from the marine cyanobacterium *Lyngbya majuscula*, collected at Boca del Drago Beach, Panama, and its structure was determined.[6] It is a structurally unusual natural product insofar as it has the 2-substituted alkynoate unit. The stereochemistry of this unit was assigned by degradation of the peptide chain, isolation and hydrogenation of the acid and correlation to previous work (centre marked * is (*R*) as reported). We would now like to amend the stereochemistry of the alkynoate fragment.



Scheme 1.

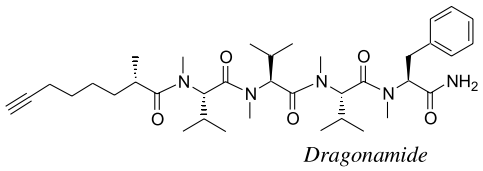


Figure 1.

2. Results and discussion

In our retrosynthetic analysis, dragonamide **1** was deconstructed into two parts: the moya **3** and the protected tetrapeptide **4** (Scheme 1).

Keywords: Stereochemistry; Dragonamide; Tetrapeptide.
* Corresponding authors. Tel.: +86 75526035351 (Z.X.); tel.: +852 27664173; fax: 852 22641912 (T.Y.);
e-mail addresses: xuzs@szpku.edu.cn; bctaoye@inet.polyu.edu.hk

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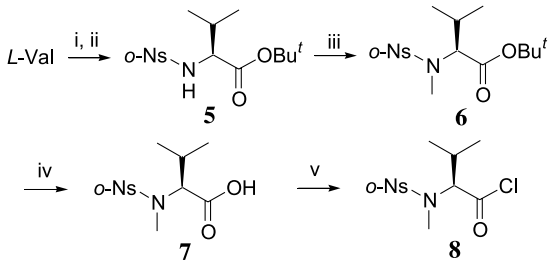
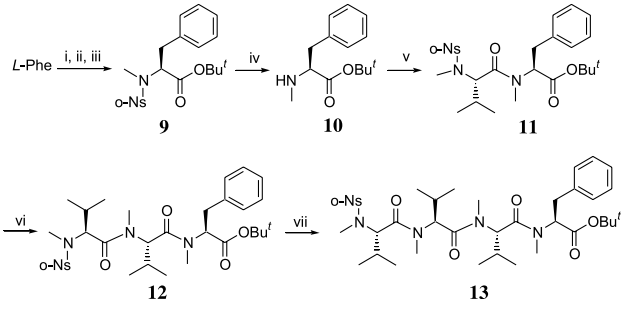
2.1. Synthesis of tetrapeptide 4

The synthesis started with (*S*)-valine, which was converted into its *t*-butyl ester using *tert*-butyl acetate and perchloric acid (Scheme 2).[7] It was then successively protected as its 2-nitrobenzenesulfonamide **5**, by treating it with *o*-nitrobenzenesufonyl chloride in the presence of base.[8] This method of protection was chosen as it allows the nitrogen to be alkylated under mild conditions, and it is readily removable. The alkylation was performed by treating **5** with methyl iodide in DMF with potassium carbonate as base,[9] to furnish **6**. Once the alkylation had been performed, **6** was treated with TFA to produce the free acid **7**, which was readily converted into its acyl chloride **8** by reacting it with oxalyl chloride and DMF in dichloromethane.



Scheme 2. Reagents and conditions: (i) AcOBu^t, $HClO_4$, 91%; (ii) 2-nitrobenzenesufonyl chloride, Et_3N, CH_2Cl_2, 91%; (iii) CH_3I, K_2CO_3, DMF, 77%; (iv) TFA–CH_2Cl_2; (v) $(COCl)_2$, CH_2Cl_2, DMF.

(*S*)-phenylalanine was treated in an analogous manner to (*S*)-valine above and was converted into, sequentially, its *t*-butyl ester, 2-nitrobenzenesulfonamide and *N*-methyl derivative **9**, with all steps proceeding smoothly (Scheme 3). The sulfonamide group was readily removed at this stage by treating **9** with mercaptoacetic acid in DMF under basic conditions, to give amino ester **10**.[10]

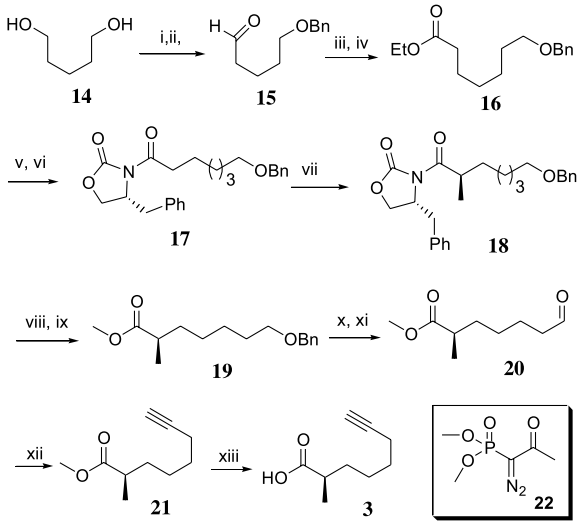


Scheme 3. Reagents and conditions: (i) AcOBu^t, $HClO_4$, 90%; (ii) *o*-nitrobenzenesufonyl chloride, Et_3N, CH_2Cl_2, 93%; (iii) CH_3I, K_2CO_3, DMF, 66%; (iv) LiOH, $HSCH_2COOH$, DMF, 90%; (v) **8**, Et_3N, CH_2Cl_2, 93%; (vi) repeat iv and v, 69%; (vii) repeat iv and v, 79% over two steps.

Fragments **8** and **10** were coupled under mild conditions to yield the protected dipeptide **11**. Compound **11** was then subjected to the same conditions for removal of the 2-nitrobenzenesulfonamide group as compound **9** and the product was coupled with **8** to give tripeptide **12**. Further iteration of this deprotection/coupling procedure led to compound **13** being obtained. These completed the main peptidic portion of the molecule. Our attention then turned towards the novel substituted alkynoate fragment.

2.2. Synthesis of moya 3

This fragment was synthesized via the route shown in Scheme 4. The monoprotection of 1,5-pentanediol **14** was effected by treatment with sodium hydride and benzyl bromide in THF,[11] and Swern oxidation of the remaining alcohol functionality produced aldehyde **15**. This aldehyde was readily olefinated using the commercially available (carbethoxymethylene) triphenylphosphorane to furnish the unsaturated ester in high yield. Hydrogenation using H_2, Pd/C in the presence of Na_2CO_3 in methanol afforded ester **16**.[12] After hydrolysis with LiOH in aqueous THF, **16** was converted into the acyl chloride with oxalyl chloride and DMF in dichloromethane, followed by treatment with (*R*)-4-benzyl-2-oxazolidinone, DMAP and triethylamine to give imide **17**.[13] The α-methylation was smoothly accomplished following the methodology of Evans,[14–15] to give the *R*-configuration at the newly formed centre in **18**. The chiral auxiliary was removed by treating **18** with hydrogen peroxide in aqueous THF, followed by acidification to give an excellent yield of the acid,[16] which was esterified by reacting it with freshly prepared diazomethane to give ester **19**. Cleavage of the benzyl protecting group through catalytic hydrogenation with Pd/C, followed by Swern oxidation produced aldehyde **20**. This was converted to the alkyne **21** in reasonable yield using the Ohira–Bestmann reagent **22**,[17–18] Saponification of alkyne **21** liberated the free acid **3**.

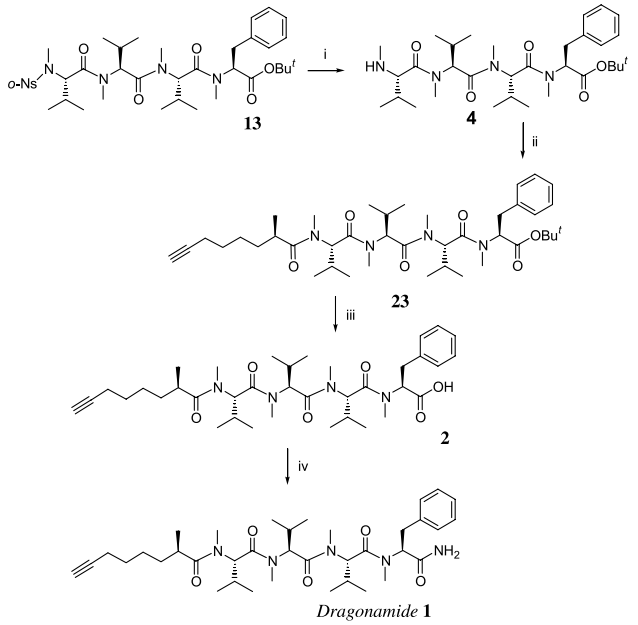


Scheme 4. Reagents and conditions: (i) NaH, BnBr, THF, 83%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 81%; (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 91%; (iv) H_2, Pd/C, Na_2CO_3, MeOH, 77%; (v) LiOH, THF–H_2O, 89%; (vi) (a) $(COCl)_2$, DMF, CH_2Cl_2; (b) (*R*)-4-benzyl-2-oxazolidinone, DMAP, Et_3N, CH_2Cl_2, 85% (over two steps); (vii) NaHMDS, MeI, THF, 87%; (viii) LiOH, H_2O_2, THF–H_2O, 91%; (ix) CH_2N_2, Et_2O, 99%; (x) H_2, Pd/C, MeOH, 99%; (xi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 84%; (xii) Ohira–Bestmann reagent **22**, K_2CO_3, MeOH, 78%; (xiii) LiOH, THF–H_2O, 92%.

2.3. Completion of the total synthesis of 1

With fragments **13** and **3** in hand, we next focused on the completion of the synthesis. The sulfonamide was cleaved by treating **13** with mercaptoacetic acid under basic conditions to form the free amine **4**, and it was then coupled with the acid **3** activated by BOPCl to produce **23** in

moderate yield. The final two steps involved cleavage of the *t*-butyl ester of **23** using TFA and formation of the primary amide, which was achieved by activation with PyBOP and treatment with ammonia,[19–20] to produce dragonamide **1**, or so it was assumed (Scheme 5).



Scheme 5. Reagents and conditions: (i) LiOH, $HSCH_2COOH$, DMF; (ii) **3**, BOPCl, DIPEA, CH_2Cl_2, 36% (two steps); (iii) TFA, CH_2Cl_2; (iv), PyBOP, DIPEA, THF, then NH_3 and NH_4OH, 32%.

The material we had made had the same stereochemistry as that reported in the isolation paper; however, both the NMR and optical rotation data of the synthetic material did not match. The main source of doubt about the true structure was the configuration of the novel alkynoate fragment, and it was here that we focused our attention.

Using exactly the same procedure, but this time with (*S*)-4-benzyl-2-oxazolidinone it was possible to make the enantiomer of the substituted alkynoic acid, (*S*)-**3**. This was used to complete the synthesis in exactly the same manner, and it was indeed found that the data for the newly synthesized material was an excellent match for the literature data on dragonamide. Consequently, we can now report that the correct structure for dragonamide is (*S*,*S*,*S*,*S*,*S*) (Fig. 1).

3. Conclusion

The marine cyanobacteria secondary metabolite dragonamide has been synthesized. As a result, the configuration of the moya fragment has been amended.

4. Experimental

4.1. General

All non-aqueous reactions were run under an inert atmosphere (nitrogen) with rigid exclusion of moisture from reagents, and all reaction vessels were oven-dried. Solvents were distilled prior to use: THF from Na/benzophenone; dichloromethane, DMF, triethylamine and diisopropylethylamine from CaH_2; methanol from iodine and magnesium. NMR spectra were recorded on Bruker AV 400 MHz spectrometers. Chemical shifts are reported in parts per million (ppm), relative to the signals due to the solvent. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), coupling constants and integration. High resolution mass spectra were obtained using a Finnigan MAT 95 mass spectrometer, while ESI mass spectra were obtained with a MicroMass Q-Tof-2^{TM} spectrometer. Optical rotations were recorded on a Perkin Elmer 343 Polarimeter. TLC was carried out using precoated sheets (Merck silica gel 60-F_{254}, 0.2 mm) which, after development, were visualized at 254 nm, and/or staining in *para*-anisole, ninhydrin or phosphomolybdic acid solution followed by heating. Flash column chromatography was performed using the indicated solvents (with R_f=0.15–0.20 for the desired component) on E. Merck silica gel 60 (230–400 mesh ASTM).

4.2. Synthesis of tetrapeptide

4.2.1. L-Valine *tert*-butyl ester. To a solution of L-valine (5.89 g, 50.0 mmol) in *tert*-butyl acetate (120 mL) at 0 °C, was added $HClO_4$ (6.5 mL, 75 mmol) slowly. The reaction mixture was stirred at room temperature for 12 h then washed with H_2O (250 mL) and 1.0 mol/L hydrochloric acid (150 mL). The resultant aqueous solution was adjusted to pH 9 by addition of 10% K_2CO_3 solution, and then extracted with dichloromethane (3×50 mL). The combined organic phases were dried with anhydrous sodium sulfate, filtered and concentrated to give an oil. This was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/1) as eluent, to give the title compound (7.9 g, 91%) as a yellow oil. $[\alpha]_D^{20}$ +20.6 (*c* 5.3, EtOAc); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.92 (d, J=7.0 Hz, 3H), 1.00 (d, J=7.0 Hz, 3H), 1.50 (s, 9H), 1.54 (s, 2H), 2.01–2.03 (m, 1H), 3.18 (d, J=4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 16.4, 18.6, 27.4, 31.5, 59.6, 79.8, 174.1; HR-ESIMS calcd for $C_9H_{20}NO_2$ $[M+H]^+$ 174.1494, found 174.1509.

4.2.2. *N-o*-Nitro-benzosulfonyl-L-valine *tert*-butyl ester 5. To a solution of L-valine *tert*-butyl ester (6.3 g, 36.0 mmol) in dichloromethane (120 mL) at 0 °C, was added triethylamine (6.0 mL, 39.6 mmol) and *o*-nitrobenzene-sulfonyl chloride (10.5 g, 45.0 mmol). The reaction mixture was stirred at room temperature overnight and then washed with H_2O (3×15 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/4) as eluent, to produce the title compound (11.7 g, 91%) as a yellow oil. $[\alpha]_D^{20}$ −108.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.94 (d, J=6.9 Hz, 3H), 1.03 (d, J=6.7 Hz, 3H), 1.20 (s, 9H), 2.11–2.17 (m, 1H), 3.88 (q, J=5.0 Hz, 1H), 6.06 (d, J=9.8 Hz, 1H), 7.70–7.73 (m, 1H), 7.86–7.94 (m, 2H), 8.06–8.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.3, 19.0, 27.6, 31.6, 62.6, 82.35, 125.5, 130.4, 132.8, 133.5, 134.4, 136.5, 169.6; HR-ESIMS calcd for $C_{15}H_{22}N_2O_6SNa$ $[M+Na]^+$ 381.1096, found 381.1121.

4.2.3. *N*-*o*-Nitro-benzosulfonyl-*N*-methyl-L-valine *tert*-butyl ester 6. K_2CO_3 (7.7 g, 55.2 mmol) was added to a solution of **5** (9.9 g, 27.6 mmol) in DMF (60.0 mL) at 0 °C under a protective flow of N_2. After 10 min, iodomethane (7.0 mL, 110.4 mmol) was introduced via a syringe. The reaction mixture was then stirred at room temperature overnight prior to being quenched by the addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with benzene–ethyl acetate (1/3, v/v) (3×80 mL). The combined organic extracts were washed with 0.5 mol/L HCl (2×50 mL) and brine (2×50 mL), dried (Na_2SO_4) and concentrated. The residue was subjected to flash chromatography on silica gel, using ethyl acetate–hexane (1/3) as eluent, affording the title compound (7.9 g, 77%) as a yellow oil. $[\alpha]_D^{20}$ −12.3 (*c* 3.5, $CH_3CO_2C_2H_5$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.98 (d, J=6.8 Hz, 3H), 1.02 (d, J=6.6 Hz, 3H), 1.31 (s, 9H), 2.17–2.23 (m, 1H), 3.08 (s, 3H), 4.04 (d, J=10.1 Hz, 1H), 7.63–7.66 (m, 1H), 7.70–7.76 (m, 2H), 8.04–8.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 19.0, 19.1, 27.5, 27.8, 30.6, 65.5, 81.7, 123.7, 130.8, 131.4, 132.8, 133.4, 147.9, 168.8; HR-ESIMS calcd for $C_{16}H_{24}N_2O_6SNa$ $[M+Na]^+$ 395.1253, found 395.1270.

4.2.4. (2*S*)-3-Methyl-2-(*o*-nitro-benzenesulfonyl-methyl-amino)-butyryl chloride 8. To a solution of **6** (980 mg, 2.6 mmol) in dichloromethane (10 mL) at 0 °C was added TFA (5.0 mL, 67.3 mmol) dropwise and with stirring at 0 °C. The reaction was monitored by TLC and after the starting material had disappeared, the reaction mixture was concentrated to give a dark red oil (**7**).

To a solution of **7** in dichloromethane (10 mL) at 0 °C was added $(COCl)_2$ (0.56 mL, 6.5 mmol) and DMF (20 μL, 0.3 mmol). The reaction was monitored by TLC and after the starting material had disappeared, the reaction mixture was concentrated to give a brown-yellow oil (**8**).

4.2.5. L-Phenylalanine *tert*-butyl ester. This compound was prepared in an analogous manner to compound L-valine *tert*-butyl ester on a 50.0 mmol scale. The yield for the title compound was 90%. $[\alpha]_D^{20}$ +25.1 (*c* 2.8, EtOAc); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.31 (s, 11H), 2.70 (dd, J=7.7, 13.5 Hz, 1H), 2.89 (dd, J=5.8, 13.5 Hz, 1H), 3.47 (dd, J=5.8, 7.7 Hz, 1H), 7.09–7.19 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 27.7, 41.1, 56.1, 80.7, 126.4, 128.2, 129.2, 137.4, 174.1; HR-ESIMS calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$ 222.1494, found 222.1490.

4.2.6. *N*-*o*-Nitro-benzosulfonyl-L-phenylalanine *tert*-butyl ester. This compound was prepared according to the procedures for compound **5** on a 45.1 mmol scale, with a yield of 93%. $[\alpha]_D^{20}$ +88.7 (*c* 3.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.19 (s, 9H), 3.07–3.09 (m, 2H), 4.31–4.36 (m, 1H), 6.06 (d, J=9.0 Hz, 1H), 7.15–7.24 (m, 5H), 7.65–7.70 (m, 1H), 7.82–7.84 (m, 2H), 7.89–8.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 27.4, 39.3, 58.0, 82.6, 125.1, 127.0, 128.3, 129.3, 130.2 132.9, 133.5, 135.0, 136.7, 147.4, 169.1; HR-ESIMS calcd for $C_{19}H_{22}N_2O_6SNa$ $[M+Na]^+$ 429.1096, found 429.1108.

4.2.7. *N*-*o*-Nitro-benzosulfonyl-*N*-methyl-L-phenylalanine *tert*-butyl ester 9. Compound **9** was prepared on a 41.9 mmol scale using the same procedures for compound **6**, with a yield of 66%. $[\alpha]_D^{20}$ +88.5 (*c* 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.35 (s, 9H), 3.00 (dd, J=9.2, 14.2 Hz, 1H), 3.06 (s, 3H), 3.36 (dd, J=6.5, 14.2 Hz, 1H), 4.88 (dd, J=6.5, 9.2 Hz, 1H), 7.21–7.27 (m, 5H), 7.53–7.57 (m, 1H), 7.61–7.63 (m, 2H), 7.73–7.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 27.3, 30.4, 35.4, 61.0, 81.9, 123.6, 126.5, 128.1, 128.7, 130.2, 131.4, 132.2, 133.2, 136.1, 147.5, 168.5; HR-ESIMS calcd for $C_{20}H_{24}N_2O_6SNa$ $[M+Na]^+$ 443.1253, found 443.1254.

4.2.8. *N*-Methyl-L-phenylalanine *tert*-butyl ester 10. Compound **9** (550 mg, 1.3 mmol) was dissolved in DMF (15 mL) at 0 °C and $LiOH\cdot H_2O$ (570 mg, 13.1 mmol) was added, followed by mercaptoacetic acid (0.19 mL, 2.6 mol). After 2 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (5 mL) and extracted with benzene–ethyl acetate (1/3, v/v) (3×20 mL). The combined organic phase was washed with saturated $NaHCO_3$ (2×60 mL) and brine (2×60 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/3) as eluent, to produce the title compound (280 mg, 90%) as a yellow oil. $[\alpha]_D^{20}$ +22.7 (*c* 3.3, $CH_3CO_2C_2H_5$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.24 (s, 9H), 1.82 (s, 1H), 2.24 (s, 3H), 2.72–2.75 (m, 1H), 2.82 (dd, J=6.4, 13.5 Hz, 1H), 3.17–3.21 (m, 1H), 7.04–7.15 (m, 5H); HR-ESIMS calcd for $C_{14}H_{22}NO_2$ $[M+H]^+$ 236.1651, found 236.1652.

4.2.9. Ns-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu 11. To a solution of **10** (280 mg, 1.2 mmol) in dichloromethane (3 mL) at 0 °C was added Et_3N (0.84 mL, 6 mmol) and **8** (503 mg, 1.5 mmol) dissolved in dichloromethane (3 mL). The reaction mixture was stirred at room temperature overnight, and was washed with 5% HCl (2×30 mL), saturated $NaHCO_3$ (2×30 mL), brine (2×30 mL), dried (Na_2SO_4) and then concentrated. The crude oil was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/2) as eluent, to give the title compound (0.58 g, 92.7%) as a yellow oil. $[\alpha]_D^{20}$ −108.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.66 (d, J=6.6 Hz, 3H), 0.98 (d, J=6.3 Hz, 3H), 1.48 (s, 9H), 2.24–2.31 (m, 1H), 2.98 (dd, J=7.1, 14.3 Hz, 1H), 3.02 (s, 3H), 3.12 (s, 3H), 3.34 (dd, J=5.9, 14.3 Hz, 1H), 4.53 (d, J=10.7 Hz, 1H), 5.31 (dd, J=5.9, 7.1 Hz, 1H), 7.21–7.37 (m, 5H), 7.59–7.72 (m, 3H), 7.91–7.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 18.6, 18.6, 27.9, 28.8, 30.6, 32.8, 34.6, 59.1, 59.3, 81.9, 124.0, 126.5, 128.4, 129.0, 129.8, 131.6, 133.2, 133.3, 137.2, 148.0, 169.6, 170.6; HR-ESIMS calcd for $C_{26}H_{35}N_3O_7SNa$ $[M+Na]^+$ 556.2093, found 556.2007.

4.2.10. (*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu. To a solution of **11** (6.68 g, 12.5 mmol) in DMF (120 mL) at 0 °C was added solid $LiOH\cdot H_2O$ (5.42 g, 125.2 mmol) and mercaptoacetic acid (1.78 mL, 25.0 mol). The reaction mixture was stirred at room temperature for 2 h, quenched by the addition of a saturated NH_4Cl (20 mL) and extracted with benzene–ethyl acetate (1/3, v/v) (3×120 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2×100 mL) and brine (2×100 mL), dried (Na_2SO_4) and concentrated to give the desired secondary amine as a yellow oil (4.18 g, 96%), which was used in next step without further purification.

4.2.11. Ns-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu 12. To a solution of (*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu (4.18 g, 12 mmol) in dichloromethane (30 mL) at 0 °C was added Et_3N (8.4 mL, 60 mmol), followed by a solution of **8** (5.02 g, 15 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature overnight and then concentrated to dryness. The residue was dissolved in EtOAc (150 mL) and washed with 5% HCl (2×60 mL), saturated $NaHCO_3$ (2×60 mL) and brine (2×60 mL). After being dried (Na_2SO_4), this solution was concentrated to a crude oil, which was subjected to chromatographic purification on silica gel, using ethyl acetate–hexane (1/2) as eluent. The title compound was obtained as a yellow oil (5.60 g, 69.2%, over two steps). $[\alpha]_D^{20}$ −513.8 (*c* 2.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.50 (d, J=6.7 Hz, 3H), 0.55 (d, J=6.7 Hz, 3H), 0.76 (d, J=6.8 Hz, 3H), 0.88 (d, J=6.6 Hz, 3H), 1.39 (s, 9H), 2.03–2.08 (m, 1H), 2.24–2.27 (m, 1H), 2.74 (s, 3H), 2.85 (s, 3H), 2.88 (dd, J=11.2, 15.0 Hz, 1H), 3.06 (s, 3H), 3.30 (dd, J=5.0, 15.0 Hz, 1H), 4.34 (d, J=10.6 Hz, 1H), 5.06 (d, J=10.7 Hz, 1H), 5.36 (dd, J=5.0, 11.2 Hz, 1H), 7.10–7.18 (m, 5H), 7.51–7.54 (m, 1H), 7.59–7.63 (m, 2H), 7.84–7.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.5, 18.4, 18.5, 19.6, 27.4, 27.8, 28.4, 30.0, 30.5, 31.7, 34.1, 57.7, 59.4, 64.0, 81.6, 123.8, 126.4, 128.2, 128.4, 129.7, 131.4, 132.6, 133.4, 136.9, 147.7, 169.4, 170.1, 170.7; HR-ESIMS calcd for $C_{32}H_{46}N_4O_8SNa$ $[M+Na]^+$ 669.2934, found 669.2908.

4.2.12. (*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu. To a solution of **12** (370 mg, 0.57 mmol) in DMF (3 mL) at 0 °C was added solid $LiOH\cdot H_2O$ (0.25 g, 5.7 mmol), followed by mercaptoacetic acid (81 μL, 1.14 mol). The reaction mixture was stirred at room temperature for 2 h and was then quenched by pouring it into saturated NH_4Cl (5 mL) and extracting with benzene–ethyl acetate (1/3, v/v) (3× 5 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2×10 mL), brine (2×10 mL), dried (Na_2SO_4) and concentrated to give the title compound as a yellow oil, which was used in next steps without further purification.

4.2.13. Ns-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu 13. To a solution of (*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu (1.64 g, 3.6 mmol) in dichloromethane (6 mL) at 0 °C was added Et_3N (3 mL, 21.4 mmol), followed by addition of a solution of **8** (1.34 g, 4 mmol) in dichloromethane (6 mL). The reaction mixture was stirred at room temperature overnight and was then concentrated to dryness. The residue was dissolved in EtOAc (150 mL) and was successively washed with 5% HCl (2×30 mL), saturated $NaHCO_3$ (2×30 mL) and brine (2×30 mL), dried (Na_2SO_4) and concentrated. The resultant residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/1) as eluent, to produce the title compound (2.14 g, 79%, over the last two steps) as a yellow oil. $[\alpha]_D^{20}$ −288.6 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.58 (d, J=6.6 Hz, 3H), 0.67 (d, J=6.8 Hz, 3H), 0.70 (d, J=6.5 Hz, 3H), 0.83 (d, J=6.6 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.5 Hz, 3H), 1.46 (s, 9H), 2.18–2.29 (m, 3H), 2.60 (s, 3H), 2.87 (s, 3H), 2.92 (dd, J=11.8, 14.9 Hz, 1H), 3.15 (s, 3H), 3.17 (s, 3H), 3.37 (dd, J=4.7, 14.9 Hz, 1H), 4.53 (d, J=10.7 Hz, 1H), 5.02 (d, J=10.8 Hz, 1H), 5.08 (d, J=10.6 Hz, 1H), 5.44 (dd, J=11.8, 4.7 Hz, 1H), 7.14–7.32 (m, 5H), 7.58–7.60 (m, 1H), 7.65–7.71 (m, 2H), 7.93–7.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.6, 18.1, 18.6, 18.6, 19.6, 19.7, 25.6, 27.0, 27.7, 28.0, 29.9, 30.5, 30.8, 30.9, 31.8, 34.2, 57.8, 57.9, 58.1, 59.7, 81.9, 124.0, 126.7, 128.4, 128.7, 130.1, 131.5, 133.0, 133.5, 137.0, 147.9, 169.6, 169.9, 170.4, 171.4; HR-ESIMS calcd for $C_{38}H_{57}N_5O_9SNa$ $[M+Na]^+$ 782.3775, found 782.3776.

4.3. Synthesis of moya

4.3.1. 5-Benzyloxy-pentan-1-ol. To a flask charged with NaH (80% in mineral oil, 0.96 g, 32.0 mmol) at 0 °C, was added pentane-1,5-diol (**14**) (11.0 mL, 105.0 mmol) slowly. After stirring for 6 h at room temperature, the reaction mixture was cooled in an ice-water bath and benzyl bromide (5.0 mL, 42.0 mmol) was added dropwise via a syringe and stirring was continued overnight. The reaction was quenched by slow addition of saturated NH_4Cl (30 mL) and the mixture was extracted with ether (3×30 mL). The combined organic extracts were washed with brine (60 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/2) as eluent, to provide the title compound (6.8 g, 83%) as a clear oil. ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.47–1.54 (m, 2H), 1.59–1.66 (m, 2H), 1.68–1.75 (m, 2H), 3.52–3.55 (m, 2H), 3.60–3.64 (m, 2H), 4.16 (s, 1H), 4.54 (s, 2H), 7.31–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 22.0, 29.0, 32.0, 61.8, 70.0, 72.5, 127.1, 127.3, 128.0, 138.1; HR-ESIMS calcd for $C_{12}H_{19}O_2$ $[M+H]^+$ 195.1385, found 195.1369.

4.3.2. 5-Benzyloxy-pentanal 15. To a solution of $(COCl)_2$ (0.86 mL, 10.0 mmol) in dichloromethane (20 mL) at −78 °C was added DMSO (1.42 mL, 20 mmol) in dichloromethane (5 mL). After 10 min, a pre-cooled solution of 5-benzyloxy-pentan-1-ol (0.97 g, 5 mmol) in dichloromethane (5 mL) was added dropwise. The reaction was kept at −78 °C for 1 h before Et_3N (5.6 mL, 39.8 mmol) was added. The reaction mixture was allowed to warm to −60 °C within 1 h then quenched by slow addition of saturated NH_4Cl. The volatiles were removed under reduced pressure and the remaining solution was extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (60 mL), brine (60 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, to give the title compound (0.78 g, 81%) as a clear oil. ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.52–1.57 (m, 2H), 1.59–1.65 (m, 2H), 2.32–2.36 (m, 2H), 3.38 (t, J=6.1 Hz, 2H), 4.38 (s, 2H), 7.17–7.24 (m, 5H), 9.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 18.8, 29.0, 43.5, 69.6, 72.8, 127.4, 127.5, 128.3, 138.3, 202.4; HR-ESIMS calcd for $C_{12}H_{16}O_2Na$ $[M+Na]^+$ 215.1048, found 215.1077.

4.3.3. 7-Benzyloxy-hept-2-enoic acid ethyl ester. (Carbethoxymethylene)triphenylphosphorane (3.69 g, 10.6 mmol) was dissolved in dichloromethane (50 mL) at 0 °C and to this was added aldehyde (**15**) (1.94 g, 10.1 mmol) in dichloromethane (10 mL), and the reaction was stirred at room temperature overnight. The triphenylphosphine oxide was removed simply by filtering the reaction mixture

through a pad of silica gel. The filtrate was concentrated to dryness, and the residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, to give the title compound (2.42 g, 91%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.17 (t, J=7.15 Hz, 3H), 1.43–1.57 (m, 4H), 2.07–2.13 (m, 2H), 3.36 (t, J= 6.2 Hz, 2H), 4.07 (q, J=7.1 Hz, 2H), 4.38 (s, 2H), 5.69–5.74 (m, 1H), 6.82–6.89 (m, 1H), 7.15–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 14.0, 24.5, 29.0, 31.7, 59.8, 69.6, 72.7, 121.3, 127.3, 127.3, 128.1, 138.3, 148.6, 166.3; HR-ESIMS calcd for $C_{16}H_{23}O_3$ $[M+H]^+$ 263.1647, found 263.1636.

4.3.4. 7-Benzyloxy-heptanoic acid methyl ester 16. 7-Benzyloxy-hept-2-enoic acid ethyl ester (0.64 g, 2.4 mmol) and Na_2CO_3 (0.77 g, 7.3 mmol) were placed in a 100 mL round-bottom flask and dissolved in methanol (50 mL). The flask was flushed with nitrogen. A catalytic amount of (10%) Pd/C was added; the flask was sealed tightly and then purged with hydrogen. The reaction mixture was stirred vigorously under a hydrogen atmosphere for 4 h, then filtered through a plug of celite and concentrated. The resultant residue was dissolved in ethyl acetate (150 mL) and washed with brine (30 mL). The solution was then dried (Na_2SO_4) and concentrated to leave a crude oil, which was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1:10) as eluent, to produce the title compound (0.47 g, 77%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.15–1.26 (m, 4H), 1.43–1.51 (m, 4H), 2.13 (t, J=7.5 Hz, 2H), 3.29 (t, J=6.5 Hz, 2H), 3.47 (s, 3H), 4.32 (s, 2H), 7.06–7.17 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 24.3, 25.4, 28.4, 29.1, 33.3, 50.6, 69.7, 72.2, 126.8, 126.9, 127.7, 138.2, 173.2; HR-ESIMS calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found 251.1654.

4.3.5. 7-Benzyloxy-heptanoic acid. To a solution of **16** (0.47 g, 1.9 mmol) in THF–water (8 mL/2 mL) at 0 °C was added solid $LiOH\cdot H_2O$ (130 mg, 2.9 mmol). The reaction mixture was stirred at room temperature for 12 h then extracted with EtOAc (5 ml). The organic layer was discarded. The aqueous phase was acidified to pH 2 with 5%$KHSO_4$ in the presence of EtOAc (20 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (3×20 mL). The combined organic extracts was washed with brine (50 mL), dried (Na_2SO_4) and concentrated to give the title compound (0.39 g, 89%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.23–1.29 (m, 4H), 1.45–1.53 (m, 4H), 2.18 (t, J=7.5 Hz, 2H), 3.33 (t, J= 6.6 Hz, 2H), 4.36 (s, 2H), 7.10–7.20 (m, 5H), 10.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 24.3, 25.5, 28.5, 29.2, 33.7, 69.9, 72.5, 127.2, 127.4, 128.0, 138.2, 179.4; HR-ESIMS calcd for $C_{14}H_{21}O_3$ $[M+H]^+$ 237.1491, found 237.1482.

4.3.6. (4*R*)-3-(7-Benzyloxy-1-oxoheptyl)-4-(benzyl)-2-oxazolidinone 17. To the solution of 7-benzyloxy-heptanoic acid (2.45 g, 10.4 mmol) in dichloromethane (80 mL) at 0 °C, was added $(COCl)_2$ (4.47 mL, 52.1 mmol), followed by DMF (100.5 μL, 1.3 mmol). The reaction was monitored with TLC and after the starting material had been consumed, the mixture was concentrated to provide the corresponding acylchloride as a dark red oil. Meanwhile, in another reaction vessel, (*R*)-4-benzyl-2-oxazolidinone (4.61 g, 26.0 mmol) and DMAP (0.16 g, 1.29 mmol) were dissolved in dichloromethane (80 mL). The solution was cooled to 0 °C and Et_3N (5.48 mL, 39 mmol) added, followed by a solution of the above acylchloride in dichloromethane (10 ml). The reaction was stirred at room temperature for 12 h and concentrated under reduced pressure and the residue was dissolved in EtOAc (100 mL). The solution was successively washed with 3% HCl (100 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated. The residue, after being purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, provided the desired compound (3.48 g, 84.9%) as a clear oil. $[\alpha]_D^{20}$ −91.1 (*c* 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.33–1.35 (m, 4H), 1.55–1.64 (m, 4H), 2.68 (dd, J=9.6, 13.3 Hz, 1H), 2.82–2.89 (m, 2H), 3.21 (dd, J=2.8, 13.3 Hz, 1H), 3.40 (t, J=6.5 Hz, 2H), 4.06–4.12 (m, 2H), 4.42 (s, 2H), 4.56–4.60 (m, 1H), 7.11–7.27 (m, 10H); ^{130}C NMR ($CDCl_3$, 100 Hz) δ ppm: 24.1, 25.9, 28.9, 29.5, 35.4, 37.9, 55.1, 66.1, 70.3, 72.8, 127.3, 127.4, 127.6, 128.3, 128.9, 129.4, 135.3, 138.6, 153.4, 173.3; HR-ESIMS calcd for $C_{24}H_{30}NO_4$ $[M+H]^+$ 396.2175, found 396.2166.

4.3.7. (2′*R*),4*R*]-3-(7-Benzyloxy-2-methyl-1-oxoheptyl)-4-(benzyl)-2-oxazolidinone 18. To NaHMDS (sodium bis-(trimethylsilyl)amide) (5.8 mL, 9.9 mmol, 1.71 M solution in THF) in THF (70 mL) at −78 °C was added a pre-cooled solution of **17** (3.25 g, 8.22 mmol) in THF (10 mL). After 45 min, iodomethane (2.56 mL, 41.12 mmol) was added slowly via a syringe. After stirring at ×78 °C for 4 h, the reaction mixture was quenched by adding saturated NH_4Cl (50 mL). Volatiles were removed under reduced pressure and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic extracts were successively washed with 5% $KHSO_4$ (100 mL), saturated $Na_2S_2O_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, to give the title compound (2.92 g, 87%) as a clear oil. $[\alpha]_D^{20}$ −75.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.24 (d, J= 6.9 Hz, 3H), 1.33–1.48 (m, 5H), 1.61–1.68 (m, 2H), 1.77–1.81 (m, 1H), 2.79 (dd, J=9.5, 13.3 Hz, 1H), 3.24–3.27 (m, 1H), 3.48 (t, J=6.5 Hz, 2H), 3.71–3.76 (m, 1H), 4.13–4.16 (m, 2H), 4.51 (s, 2H), 4.65–4.68 (m, 1H), 7.21–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.2, 26.0, 26.9, 29.4, 33.0, 37.4, 37.6, 55.0, 65.7, 70.1, 72.6, 127.1, 127.2, 127.4, 128.1, 128.7, 129.2, 135.1, 138.5, 152.8, 176.9; HR-ESIMS calcd for $C_{25}H_{32}NO_4$ $[M+H]^+$ 410.2331, found 410.2316.

4.3.8. (2*R*)-7-Benzyloxy-2-methyl-heptanoic acid. To a solution of **18** (2.7 g, 6.5 mmol) in THF–water (80 mL/25 mL) at 0 °C was added H_2O_2 (5.3 mL, 52.2 mmol) and after 10 min, $LiOH\cdot H_2O$ (0.56 g, 13.1 mmol) was added. The reaction mixture was stirred at room temperature for 12 h and then cooled to 0 °C before Na_2SO_3 (6.9 g, 53.3 mol) was added. Stirring was continued for another 30 min, then the mixture was washed with EtOAc and the organic extracts were discarded. The aqueous solution was covered with EtOAc (100 mL) and acidified to pH 2 with 5% $KHSO_4$, the layers were separated and the aqueous layer was further extracted with EtOAc (3×100 mL). The

combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated to give the title compound (1.49 g, 91%) as a clear oil. $[\alpha]_D^{20}$ −5.4 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.14 (d, J= 7.0 Hz, 3H), 1.33–1.44 (m, 5H), 1.56–1.70 (m, 3H), 2.37–2.46 (m, 1H), 3.42–3.45 (m, 2H), 4.47 (s, 2H), 7.21–7.31 (m, 5H), 10.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 16.8, 26.0, 26.9, 29.4, 33.4, 39.2, 70.2, 72.7, 127.4, 127.6, 128.3, 138.4, 183.0; HR-ESIMS calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found 251.1647.

4.3.9. (2*R*)-7-Benzyloxy-2-methyl-heptanoic acid methyl ester 19. (2*R*)-7-benzyloxy-2-methyl-heptanoic acid (1.49 g, 5.9 mmol) in ether (20 mL) was treated with freshly prepared diazomethane (large excess) and the reaction was monitored by TLC. When all of the acid had been consumed, a flow of nitrogen was used to bubble the excess CH_2N_2 into a solution of acetic acid. When this was complete, the residue was diluted with ethyl acetate (120 mL), washed with dilute acetic acid, water and brine, dried and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, to provide the title compound (1.56 g, 99%) as a clear oil. $[\alpha]_D^{20}$ −9.3 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.15 (d, J= 7.0 Hz, 3H), 1.28–1.45 (m, 5H), 1.59–1.68 (m, 3H), 2.42–2.47 (m, 1H), 3.46 (t, J=6.6 Hz, 2H), 3.66 (s, 3H), 4.50 (s, 2H), 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.0, 26.0, 27.0, 29.5, 33.7, 39.3, 51.4, 70.2, 72.8, 127.4, 127.5, 128.3, 138.5, 177.2; HR-ESIMS calcd for $C_{16}H_{24}O_3Na$ $[M+Na]^+$ 287.1623, found 287.1595.

4.3.10. (2*R*)-7-Hydroxy-2-methyl-heptanoic acid methyl ester. Compound **19** (1.56 g, 5.92 mmol) was dissolved in methanol (50 mL), a catalytic amount of (10%) Pd/C was added, and the reaction mixture was stirred vigorously under a hydrogen atmosphere for 4 h. The reaction mixture was filtered through a plug of celite and concentrated to give the title compound (1.03 g, 99%) as a clear oil. $[\alpha]_D^{20}$ −15.2 (*c* 0.8, $CHCl_3$);^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.15 (d, J=7.0 Hz, 3H), 1.26–1.47 (m, 5H), 1.52–1.59 (m, 2H), 1.62–1.71 (m, 1H), 2.42–2.48 (m, 1H), 2.79 (s, 1H), 3.60 (t, J=6.6 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 16.4, 25.1, 26.4, 31.8, 33.1, 38.7, 50.8, 61.4, 176.7; HR-ESIMS calcd for $C_9H_{19}O_3$ $[M+H]^+$ 175.1334, found 175.1349.

4.3.11. (2*R*)-2-Methyl-7-oxo-heptanoic acid methyl ester 20. To a solution of $(COCl)_2$ (0.9 mL, 10.5 mmol) in dichloromethane (20 mL) at −78 °C was added DMSO (1.49 mL, 21.0 mmol) in dichloromethane (5 mL). After 10 min, a pre-cooled solution of (2*R*)-7-hydroxy-2-methyl-heptanoic acid methyl ester (0.91 g, 5.3 mmol) in dichloromethane (5 mL) was added dropwise. The reaction was kept at −78 °C for 1 h before Et_3N (5.9 mL, 42.1 mmol) was added. The reaction mixture was warmed up to −60 °C during 1 h, then quenched by slow addition of a saturated aqueous solution of NH_4Cl. The volatiles were removed under vacuum and the remaining solution was extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, to give the title compound (0.76 g, 84%) as a yellow oil. $[\alpha]_D^{20}$ −24.9 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.13 (d, J= 7.0 Hz, 3H), 1.28–1.33 (m, 2H), 1.34–1.45 (m, 1H), 1.57–1.69 (m, 3H), 2.40–2.46 (m, 3H), 3.65 (s, 3H), 9.74 (t, J= 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.0, 212.8, 26.7, 33.4, 39.2, 43.6, 51.5, 177.0, 202.4; HR-ESIMS calcd for $C_9H_{16}O_3Na$ $[M+Na]^+$ 195.0997, found 195.1028.

4.3.12. (2*R*)-2-Methyl-oct-7-ynoic acid methyl ester 21. To a solution of diethyl 1-diazo-2-oxopropylphosphonate (4.3 g, 19.7 mmol) in methanol (50 mL) at 0 °C was added K_2CO_3. After stirring for 30 min at this temperature, a solution of **20** (0.67 g, 3.9 mmol) in methanol (40 mL) was added slowly and stirring was continued at 0 °C for 1 h then room temperature overnight. The reaction was quenched by adding brine (20 mL), the mixture was concentrated and extracted with dichloromethane (3×100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1:10) as eluent, to give the title compound (0.51 g, 78%) as a yellow oil. $[\alpha]_D^{20}$ −13.3 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.15 (d, J=7.0 Hz, 3H), 1.37–1.49 (m, 3H), 1.51–1.56 (m, 2H), 1.63–1.70 (m, 1H), 1.94 (t, J=2.6 Hz, 1H), 2.16–2.21 (m, 2H), 2.42–2.47 (m, 1H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.0, 18.1, 26.2, 28.2, 33.1, 39.2, 51.4, 68.3, 84.2, 177.1; HR-ESIMS calcd for $C_{10}H_{17}O_2$ $[M+H]^+$ 169.1229, found 169.1234.

4.3.13. (2*R*)-2-Methyl-oct-7-ynoic acid 3. To a solution of **21** (0.11 g, 0.64 mmol) in THF–water (2 mL/0.5 mL) at 0 °C was added $LiOH\cdot H_2O$ (0.08 g, 1.92 mmol). The reaction mixture was stirred at room temperature for 12 h and then extracted with EtOAc (30 mL). The organic layer was discarded. The aqueous solution was covered with EtOAc (20 mL) and acidified to pH 2 with 5%$KHSO_4$, the layers were separated and the aqueous phase was further extracted with EtOAc (2×20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated to give the title compound (91 mg, 92%) as a clear oil. $[\alpha]_D^{20}$ −12.9 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.18 (d, J=7.0 Hz, 3H), 1.40–1.57 (m, 5H), 1.66–1.73 (m, 1H), 1.93 (t, J=2.6 Hz, 1H), 2.17–2.21 (m, 2H), 2.42–2.50 (m, 1H), 10.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 16.7, 18.2, 26.2, 28.2, 32.8, 39.2, 68.3, 84.2, 183.3; HR-ESIMS calcd for $C_9H_{15}O_2$ $[M+H]^+$ 155.1072, found 155.1091.

4.4. Completion of the total synthesis of 1

4.4.1. (*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu. To a solution of **13** (1.28 g, 1.68 mmol) in DMF (13 mL) at 0 °C was added solid $LiOH\cdot H_2O$ (0.73 g, 16.8 mmol) followed by mercaptoacetic acid (239 μL, 3.36 mol). The reaction mixture was stirred at room temperature for 2 h, quenched by pouring it into saturated NH_4Cl (8 mL) then extracted with benzene–ethyl acetate (1/3, v/v) (3×10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2×20 mL), brine (2× 20 mL), dried (Na_2SO_4) and concentrated to give the title compound as a yellow oil, which was used in next step without further purification.

4.4.2. (2*R*)-2-Methyl-oct-7-ynoyl-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu 23. Acid moiety **3** (0.25 g, 1.63 mmol) and (*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu (0.92 g, 1.6 mmol) were dissolved in dichloromethane (20 mL). After the solution was cooled to 0 °C, BOPCl (0.84 g, 3.20 mmol) was added with stirring. After 5 min, DIPEA (1.06 mL, 6.4 mmol) was introduced via a syringe. The reaction was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and the solution was successively washed with saturated NH_4Cl (2×20 mL), saturated $NaHCO_3$ (2×20 mL), brine (2×20 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/2) as eluent, to provide the desired compound (0.41 g, 36%) as a yellow oil. $[\alpha]_D^{20}$ −294.8 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.66 (d, J=6.8 Hz, 3H), 0.71 (d, J=6.7 Hz, 3H), 0.74 (d, J=6.4 Hz, 3H), 0.83 (d, J=4.0 Hz, 3H), 0.84 (d, J=3.6 Hz, 3H), 0.90 (d, J=6.3 Hz, 3H), 1.07 (d, J=6.8 Hz, 3H), 1.36–1.42 (m, 3H), 1.46 (s, 9H), 1.49–1.54 (m, 2H), 1.72–1.76 (m, 1H), 1.92 (t, J=2.6 Hz, 1H), 2.16–2.20 (m, 2H), 2.23–2.34 (m, 3H), 2.47 (s, 3H), 2.70–2.71 (m, 1H), 2.86 (s, 3H), 2.91 (dd, J=11.8, 14.8 Hz, 1H), 2.98 (s, 3H), 3.00 (s, 3H), 3.36 (dd, J=4.6, 14.8 Hz, 1H), 4.98 (d, J=10.7 Hz, 1H), 5.04 (d, J=10.6 Hz, 1H), 5.20 (d, J=10.8 Hz, 1H), 5.46 (dd, J=11.8, 4.6 Hz, 1H), 7.13–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm:17.3, 17.5, 17.9, 18.2, 18.3, 19.3, 19.6, 19.7, 26.7, 26.9, 27.0, 27.0, 28.0, 28.4, 29.6, 30.1, 30.2, 31.7, 33.3, 34.2, 36.2, 57.9, 58.1 (3C), 68.3, 81.8, 84.3, 126.7, 128.4, 128.7, 137.1, 169.6, 169.6, 169.8, 170.9, 176.8; HR-ESIMS calcd for $C_{41}H_{67}N_4O_6$ $[M+H]^+$ 711.5061, found 711.5027.

4.4.3. (2*R*)-2-Methyl-oct-7-ynoyl-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-NH_2 1. Compound **23** (135 mg, 0.19 mmol) in dichloromethane (16 mL) was treated with TFA (7 mL) at 0 °C and the reaction was monitored by TLC. After all the starting material was consumed the reaction mixture was concentrated to leave a dark red oil, which was subsequently dissolved in THF (15 mL) and cooled to 0 °C. PyBOP (198 mg, 0.38 mmol) was added under a protective flow of nitrogen and after 5 min DIPEA (94.2 μL, 0.57 mmol) was introduced via syringe. The reaction mixture was then stirred for 20 min at 0 °C and 30 min at room temperature. After cooling to 0 °C again, it was exposed to NH_3 for 25 min and then aqueous ammonia (29 μL, 0.38 mmol) was added. Stirring was continued for 20 min at room temperature, and the reaction was quenched with brine (10 mL). All volatiles were removed under reduced pressure and the residue was extracted with EtOAc (3×20 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was subjected to chromatographic purification, using ethyl acetate–hexane (2/1) as eluent, to give compound 1 (39 mg, 32%, over two steps) as a white solid. $[\alpha]_D^{20}$ −639.6 (*c* 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.66 (d, J=6.8 Hz, 3H), 0.71 (d, J=6.6 Hz, 3H), 0.73 (d, J=6.6 Hz, 3H), 0.83 (d, J=6.7 Hz, 3H), 0.84 (d, J=6.5 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 1.07 (d, J=6.8 Hz, 3H), 1.32–1.40 (m, 3H), 1.49–1.55 (m, 2H), 1.74–1.76 (m, 1H), 1.92 (t, J=2.6 Hz, 1H), 2.16–2.19 (m, 2H), 2.23–2.34 (m, 3H), 2.44 (s, 3H), 2.69–2.72 (m, 1H), 2.94 (s, 3H), 2.96 (s, 3H), 2.99 (s, 3H), 3.02–3.08 (m, 1H), 3.26 (dd, J=5.4, 15.1 Hz, 1H), 4.94 (d, J=10.7 Hz, 1H), 5.09 (d, J=10.6 Hz, 1H), 5.19 (d, J=10.7 Hz, 1H), 5.54 (s, 1H), 5.58 (dd, J=11.2, 5.4 Hz, 1H), 6.02 (s, 1H), 7.15–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.3, 17.5, 17.9 (2C), 18.2, 19.4, 19.6, 20.0, 26.7, 26.8, 26.9, 27.0, 28.4, 29.6, 30.2, 30.2, 30.6, 30.9, 33.3, 36.2, 56.3, 57.9, 58.0, 58.4, 68.3, 84.3, 126.9, 128.6, 128.7, 136.6, 169.7, 170.9, 171.2, 171.9, 176.8; HR-ESIMS calcd for $C_{37}H_{60}N_5O_5$ $[M+H]^+$ 654.4594, found 654.4580.

4.4.4. (2*S*)-2-Methyl-oct-7-ynoyl-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu. $[\alpha]_D^{20}$ −282.6 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.66 (d, J=6.8 Hz, 3H), 0.72–0.75 (m, 6H), 0.81 (d, J=7.0 Hz, 3H), 0.83 (d, J=6.9 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 1.12 (d, J=6.7 Hz, 3H), 1.30–1.34 (m, 3H), 1.46 (s, 9H), 1.49–1.55 (m, 2H), 1.62–1.78 (m, 1H), 1.94 (t, J=2.7 Hz, 1H), 2.14–2.16 (m, 2H), 2.18–2.35 (m, 3H), 2.46 (s, 3H), 2.69–2.74 (m, 1H), 2.86 (s, 3H), 2.91 (dd, J=11.8, 14.8 Hz, 1H), 2.97 (s, 3H), 2.98 (s, 3H), 3.36 (dd, J=4.6, 14.8 Hz, 1H), 4.99 (d, J=10.7 Hz, 1H), 5.04 (d, J=10.6 Hz, 1H), 5.20 (d, J=10.8 Hz, 1H), 5.46 (dd, J=11.8, 4.6 Hz, 1H), 7.13–7.31 (m, 5H)

4.4.5. (2*S*)-2-Methyl-oct-7-ynoyl-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-NH_2. $[\alpha]_D^{20}$ −237.2 (*c* 2.4, $CHCl_3$); lit.[6] $[\alpha]_D$ −260.8 (*c* 2.6, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.63 (d, J=6.7 Hz, 3H), 0.67 (d, J=6.5 Hz, 3H), 0.68 (d, J=6.8 Hz, 3H), 0.76 (d, J=6.7 Hz, 3H), 0.79 (d, J=6.4 Hz, 3H), 0.85 (d, J=6.4 Hz, 3H), 1.08 (d, J=6.7 Hz, 3H), 1.25–1.33 (m, 3H), 1.42–1.51 (m, 2H), 1.56–1.78 (m, 1H), 1.89 (t, J=2.5 Hz, 1H), 2.10–2.14 (m, 2H), 2.16–2.32 (m, 3H), 2.40 (s, 3H), 2.63–2.70 (m, 1H), 2.90 (s, 3H), 2.92 (s, 3H), 2.94 (s, 3H), 2.95–2.98 (m, 1H), 3.22 (dd, J=5.3, 15.1 Hz, 1H), 4.91 (d, J=10.7 Hz, 1H), 5.05 (d, J=10.5 Hz, 1H), 5.15 (d, J=10.8 Hz, 1H), 5.32 (s, 1H) 5.54 (dd, J=11.0, 5.3 Hz, 1H), 5.97 (s, 1H), 7.11–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.3, 17.6, 17.9 (2C), 18.2, 19.4, 19.6, 20.0, 26.7, 26.9, 27.0, 27.0, 28.3, 29.6, 30.1, 30.3, 30.6, 33.1, 33.5, 36.1, 56.2, 57.8 (2C), 58.4, 68.3, 84.1, 126.9, 128.5, 128.6, 136.5, 169.6, 170.7, 171.2, 171.7, 176.7

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