Total Synthesis of (–)-Muscoride A: A Novel Bis-Oxazole Based Alkaloid from the Cyanobacterium *Nostoc muscorum*

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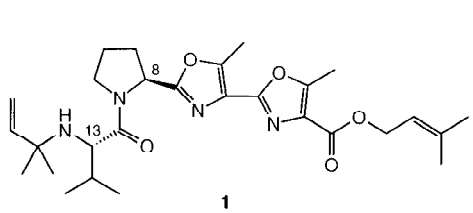
Abstract: A convergent total synthesis of the substituted bis-oxazole (–)-muscoride A (**1**), isolated from a cyanobacterium, is described based on coupling of the *N*-functionalised "reverse prenyl" dipeptide acid **8a** to the threonine-based oxazole **9a**, followed by elaboration of the tetrapeptide **7**, via the oxazoline-oxazole **16** and the bis-oxazole ester **6**.

Key words: muscoride A, bis-oxazole

Muscoride A (**1**) is a novel bis-oxazole based peptidic alkaloid found in the terrestrial cyanobacterium *Nostoc muscorum*.[1] It displays weak antibacterial activity, and the compound is related structurally to the other bis-oxazole containing natural products hennoxazole A (**2**)[2] and diazonamide A (**3**).[3] Indeed, structures based on the presence of three contiguous oxazoles, e.g. ulapualide A (**4**)[4] and thiazolines, e.g. thiangazole (**5**)[5] are also well-known, and they exhibit a wide range of interesting biological properties, i.e. anti-HIV, anti-tumoral. Muscoride A is unique at this time since it is the only known bis-oxazole natural product whose ring system originates, presumably, from a cyclodehydration-oxidation sequence involving two threonine units. Our wide-ranging interests in polyoxazole/oxazoline/thiazoline based natural products,[6] their biogenetic interrelationships, and their metal-chelating and transport properties,[7] drew us to muscoride A as a challenging synthetic target. At the outset of our work the absolute stereochemistry of the natural product had not been established, but we reasoned that the stereochemistries at C-8 and C-13 were most likely derived from L-proline and L-valine. Indeed, a timely publication by Wipf and Venkatraman,[8] describing their contemporaneous synthetic studies with muscoride A confirmed this supposition. We now present details of our own total synthesis of (–)-muscoride A.

Our convergent synthesis of (–)-muscoride A **(1)** was based on elaboration of the proline-valine dipeptide unit **8a** containing the *N*-functionalised reverse prenyl function and the threonine-based oxazole **9a**, followed by coupling of these two units to the tetrapeptide **7**, cyclisation of **7** to the bis-oxazole **6**, and finally transesterification of **6** to the dimethylallyl ester **1**.



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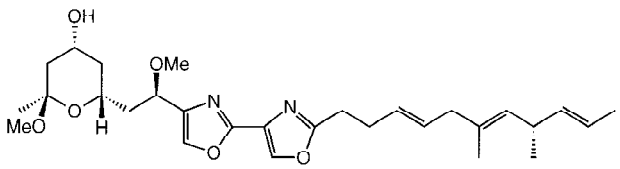

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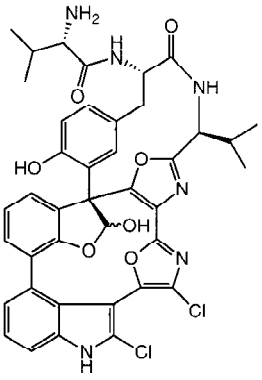

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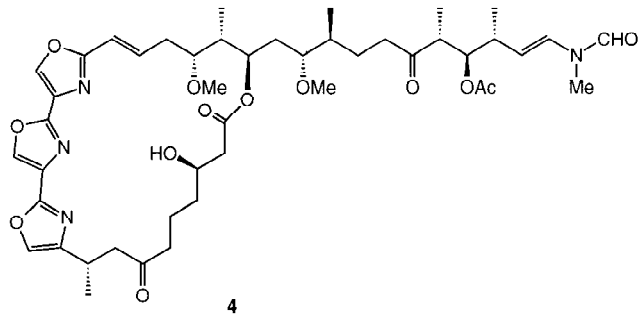

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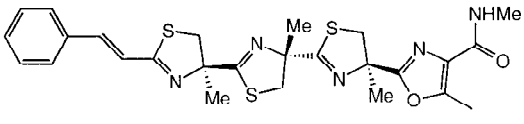

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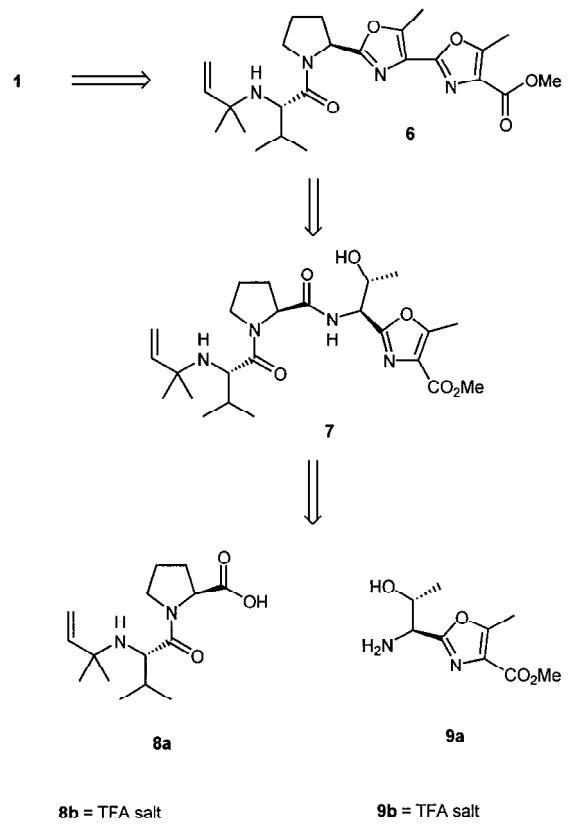
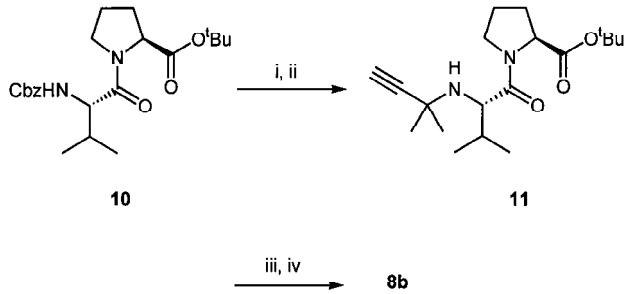


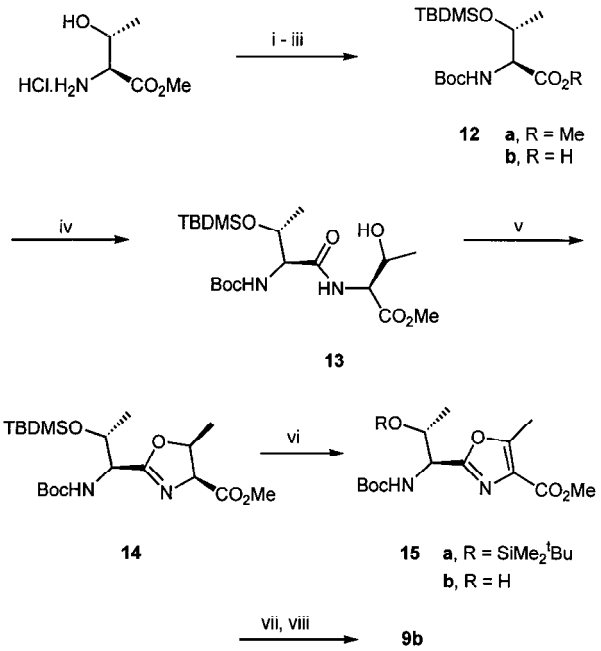
Thus, the known dipeptide **10**[9] derived from L-proline and L-valine was first converted into the *N*-propargyl derivative **11**, following removal of the benzyloxycarbonyl protection and treatment of the resulting free amine with 3-acetoxy-3-methylbut-1-yne in the presence of copper(I) chloride.[10] Hydrogenation of the triple bond in **11**, using 10% palladium on carbon in the presence of quinoline, and ester hydrolysis then provided the reverse prenyl functionalised proline-valine dipeptide **8b** (Scheme 1).



i) H_2/Pd-C, ~98%; ii) HC≡CCMe$_2$OAc/CuCl/Et$_3$N, 60%; iii) H_2/Pd-C/quinoline, 99%; iv) CF_3CO_2H/CH_2Cl_2

Scheme 1

The threonine-based oxazole **9b** was prepared starting from the *O-tert*-butyldimethylsilyl ether of *N*-BOC threonine methyl ester **12a** as shown in Scheme 2. Thus, saponification of **12a** followed by coupling of the resulting carboxylic acid **12b** with L-threonine methyl ester using pyBOP/Et$_3$N first led to the amide **13** in 91% yield. Cyclodehydration of **13** in the presence of Burgess' reagent (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt)[11] next gave the corresponding oxazoline **14** which was smoothly converted into the oxazole **15** using the conditions of Jung et al,[12] i.e. DBU and CCl_4 in pyridine and MeCN. Removal of the silyl and BOC protection from **15**, then gave the substituted threonine **9b** in readiness for coupling to **8b**.

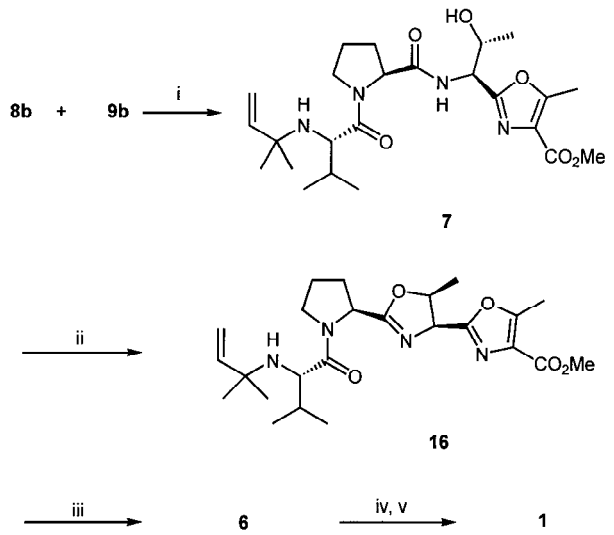


i) Boc$_2$O/Et$_3$N, ~100%; ii) TBDMS-Cl/imidazole, 95%; iii) NaOH/THF/MeOH, r.t., 6 h, then 1N HCl; iv) L-thr-OMe/pyBOP/Et$_3$N, 91%; v) Burgess' reagent/THF, 73%; vi) DBU/CCl_4/Py/MeCN, 85%; vii) TBAF, 73%; viii) CF_3CO_2H/CH_2Cl_2

Scheme 2

The coupling between **8b** and **9b** was smoothly accomplished in the presence of benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (pyBOP)/Et$_3$N[13] giving the amide **7** in 86% yield (Scheme 3). The cyclodehydration of **7** to the oxazoline oxazole **16** was most conveniently effected using diethylaminosulphur trifluoride (DAST)[14] which gave **16** in a reproducible 45–50% yield; the use of Burgess' reagent in this particular instance led to non-reproducible yields, sometimes 10%, at other times 65%. The dehydrogenation of **16**, leading to the bis-oxazole **6**, proceeded efficiently using the conditions described by Jung et al,[12] and saponification of the ester then led to the corresponding carboxylic acid which was obtained as a colourless gum. The synthesis of (–)-muscoride (**1**) was then completed by esterification of the carboxylic acid using dimethylallyl alcohol in the presence of pyBOP/Et$_3$N. This procedure afforded **1** as a viscous oil, $[\alpha]_D$ –76 (*c* = 0.09, MeOH) [Lit.[1] $[\alpha]_D$ –89 (*c* = 0.70, MeOH)], which exhibited nmr spectroscopic data which were identical to those recorded for the natural product.[1]

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a JASCO DIPA-370 polarimeter at 21 °C. UV spectra were recorded on a Philips PU 8700 specrophotometer as solutions in specroscopic grade



i) pyBOP/(*i*-Pr)$_2$EtN, 86%; ii) DAST/CH_2Cl_2, –78 °C, 45–55%; iii) DBU/CCl_4/Py/MeCN, 68%; iv) NaOH/THF/MeOH, r.t., 2 h, then 1 N HCl; v) $Me_2C{=}CHCH_2OH$/pyBOP/Et_3N, 55% (over 2 steps)

Scheme 3

EtOH. IR spectra were obtained using a Perkin-Elmer 1600 series FT-IR instument as either liquid films or dilute solutions in spectroscopic grade $CHCl_3$. ^{1}H NMR spectra were recorded on either a Bruker DPX 360 (360 MHz), a Bruker AM 400 (400 MHz) or a Bruker DRX 500 (500 MHz) spectrometer. The chemical shifts are recorded relative to TMS internal standard or relative to $CHCl_3$ and the multiplicity of a signal is designated by one of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad and m, multiplet. All coupling constants, *J*, are reported in Hertz. ^{13}C NMR spectra were recorded on either a Bruker DPX 360 (90.6 MHz), a Bruker AM 400 (100.4 MHz), a Bruker DRX 500 (125.8 MHz) or a Jeol EX-270 (67.8 MHz) spectrometer. The spectra were recorded as dilute solutions in deuteriosolvents with chemical shifts quoted relative to TMS or $CHCl_3$ standard on a broad band decoupled mode and the multiplicities obtained using a DEPT sequence. The following symbolisms are used for the multiplicities in ^{13}C NMR spectra: q, primary methyl; t, secondary methylene; d, tertiary methine and s, quaternary. Mass spectra were recorded on an AE1 MS-902, MM-701CF or VG Micromass 70E spectrometer using electron ionisation (EI), fast atom bombardment (FAB) or chemical ionisation (CI) techniques. Microanalytical data were obtained on a Perkin-Elmer 240B element analyser. Flash chromatography was performed using Merck silica gel 60 as the stationary phase. All reactions were monitored by TLC using Merck silica gel F_{254} precoated aluminium plates which were visualised with ultraviolet light and then developed with either vanillin solution, basic $KMnO_4$ or $(NH_4)_2Ce(NO_3)_6$ solution. Organic solvents were dried by distillation as follows: THF (sodium benzophenone ketyl), CH_2Cl_2 and MeCN (CaH_2). Other organic solvents and reagents were purified by the accepted literature procedures. Where necessary, reactions requiring anhydrous conditions were performed in flame or oven dried apparatus under a N_2 or Ar atmosphere. Light petroleum used had bp 40–60 °C, and all organic extracts were dried over $MgSO_4$ before evaporation in vacuo.

***N*-[*N*-(1,1-Dimethylpropagyl)-L-valyl]-L-proline *tert*-Butyl Ester (11):**

The protected dipeptide **10**[9] (5.32g, 13.15 mmol) was added in one portion to a stirred suspension of 5% Pd/C (1.06g) in MeOH (50 mL). The mixture was cooled to 0 °C and shaken in an atmosphere of H_2 for 45 min, and then filtered through a pad of Celite. The solvents were removed in vacuo to leave *N*-[L-valyl]-L-proline *tert*-butyl ester (3.4g, 100%) as a colourless oil which was used in the next step without further purification.

3-Acetoxy-3-methylbut-1-yne (1.65 g, 13.15 mmol) was added in one portion to a stirred mixture of the above amine (3.37 g, 13.15 mmol), CuCl (65 mg, 0.66 mmol) and diisopropylethylamine (4.58 mL, 26.30 mmol) in THF (50 mL).[10] The mixture was heated under reflux in an atmosphere of N_2 for 4 h and the solvents were then removed in vacuo to leave a blue coloured residue. The residue was purified by column chromotography on silica gel using 15% EtOAc/light petroleum as eluant to give the propagylic amide **11** (2.7g, 60% over two steps) as a white solid. Recrystallisation from cyclohexane/*iso*-hexane (1:3) gave white crystals; mp 92–93 °C; $[\alpha]_D$ –37.5 (*c* = 1.11, $CHCl_3$).

IR ($CHCl_3$): ν = 3363, 1731, 1638 cm^{-1}.

^{1}H NMR (360 MHz; $CDCl_3$): δ = 4.31 [1 H, dd, *J* = 8.2, 5.2 Hz, C*H*($CO_2C(CH_3)_3$)], 3.66 (1 H, m, NC*H*H), 3.55 (1 H, m, NCH*H*), 3.18 (1 H, d, *J* = 5.1 Hz, C*H*NH), 2.35 (1 H, br, NH), 2.13–1.94 (1 H, m, CH_2CH), 2.04 (1 H, s, HCCC), 1.87 (1 H, m, $CH_2CH_2CH_2$), 1.75 [1 H, m, C*H*(CH_3)$_2$], 1.39 [9 H, s, $CO_2C(CH_3)_3$], 1.28 [3 H, s, C(C*H*$_3$)CH_3], 1.24 [3 H, s, C(CH_3)C*H*$_3$], 0.96 [3 H, d, *J* = 6.7 Hz, CH(C*H*$_3$)CH_3], 0.85 [3 H, d, *J* = 6.7 Hz, CH(CH_3)C*H*$_3$].

^{13}C NMR (67.8 MHz; $CDCl_3$): δ = 174.4 (s), 171.4 (s), 89.2 (s), 80.8 (s), 68.9 (d), 59.9 (d), 48.8 (s), 46.8 (t), 31.6 (d), 30.6 (q), 29.6 (q), 29.0 (t), 27.8 (q), 24.9 (t), 19.6 (q), 17.5 (q).

LRMS (EI): *m/z* (%) = 336 (M^+, 1), 263 (8), 237 (16), 171 (6), 138 (100).

HRMS (EI): *m/z* found M^+, 336.2405; $C_{19}H_{32}O_3N_2$ requires 336.2413.

Anal. calcd. for $C_{19}H_{32}O_3N_2$ (336.5): C, 67.8; H, 9.6; N, 8.3; found: C, 67.8; H, 9.9; N, 8.3.

***N*-[*N*-(1,1-Dimethylallyl)-L-valyl]-L-proline Trifluoroacetate (8b):**

The propagylic amine **11** (0.51 g, 1.51 mmol) was added in one portion to a stirred mixture of 10% Pd/C (50 mg) and quinoline (2.5 mL) in MeOH (15 mL). The mixture was cooled to 0 °C and shaken in an atmosphere of H_2 for 20 min, and then filtered through a pad of Celite. The solvents were removed in vacuo and the residual quinoline was removed by distillation under reduced pressure to leave a pale yellow residue. The residue was purified by column chromotography on silica gel using 10% EtOAc/light petroleum as eluant to give the corresponding allylic amide (0.5g, 99%) as a white oily solid; $[\alpha]_D$ –93.3 (*c* = 1.39, $CHCl_3$).

IR (film): ν = 2973, 1739, 1640, 1416, 1154 cm^{-1}.

^{1}H NMR (360 MHz; $CDCl_3$): δ = 5.74 (1 H, dd, *J* = 17.6, 10.7 Hz, C*H*=CH_2), 4.93 (1 H, dd, *J* = 17.6, 1.4 Hz, CH=CH*H*), 4.87 (1 H, dd, *J* = 10.7, 1.4 Hz, CH=C*H*H), 4.34 [1 H, dd, *J* = 8.4, 4.9 Hz, C*H*$CO_2C(CH_3)_3$], 3.52 (1 H, m, NCH_2), 2.91 (1 H, d, *J* = 5.1 Hz, C*H*NH), 2.09 (1 H, m, CH_2CH), 2.08 (1 H, br, NH), 1.90 (1 H, m, $CH_2CH_2CH_2$), 1.74 [1 H, m, C*H*(CH_3)$_2$], 1.44 [9 H, s, $CO_2C(CH_3)_3$], 1.10 [3 H, s, C(C*H*$_3$)CH_3], 1.07 [3 H, s, C(CH_3)C*H*$_3$], 0.98 [3 H, d, *J* = 6.8 Hz, CH(C*H*$_3$)CH_3], 0.90 [3 H, d, *J* = 6.8 Hz, CH(CH_3)C*H*$_3$].

^{13}C NMR (67.8 MHz; $CDCl_3$): δ = 175.4 (s), 171.5 (s), 147.7 (d), 110.8 (t), 80.9 (s), 59.7 (d), 58.7 (d), 54.1 (s), 46.7 (t), 31.7 (d), 29.0 (t), 27.9 (q), 27.8 (q), 26.2 (q), 24.9 (t), 19.7 (q), 17.6 (q).

LRMS (FAB): *m/z* (%) = 339 (MH^+, 100), 215 (22), 140 (54), 116 (10).

HRMS (FAB): *m/z* found MH^+, 339.2645; $C_{19}H_{35}O_3N_2$ requires 339.2648.

A solution of the above allyl amide (0.73 g, 2.16 mmol) in CH_2Cl_2 (7 mL) was added dropwise to a solution of CF_3CO_2H (33 mL) and CH_2Cl_2 (7 mL) at 0 °C and under an atmosphere of N_2. The solution was allowed to warm to r.t. and stirred for 2 h. The mixture was poured into toluene (200 mL) and evaporated in vacuo to give the acid **8** as a pale yellow viscous oil which was used without further purification.

***N*-(*tert*-Butoxycarbonyl)-*O*-(*tert*-butyldimethylsilyl)-L-threonine (12b):**

Et_3N (12.33 mL, 88.44 mmol) was added dropwise over 10 min to a suspension of L-threonine methyl ester hydrochloride (10.00 g,

58.96 mmol) in MeCN (100 mL) at 0 °C and under an atmosphere of N_2. Di-*tert*-butyl dicarbonate (15.44 g, 70.75 mmol) in MeCN (150 mL) was added dropwise and the resulting mixture stirred at r.t. overnight. The solvents were removed in vacuo and the residue was taken up in EtOAc (1000 mL) and washed with $NaHCO_3$, water and brine, dried and evaporated in vacuo to leave a colourless residue. The residue was purified by column chromatography on silica gel using 30–50% EtOAc/light petroleum as eluant to give N-(*tert*-butoxycarbonyl)-L-threonine methyl ester (13.7 g, 100%) as a colourless viscous oil; $[\alpha]_D$ –6.7 (*c* = 6.9, $CHCl_3$).
IR (film): ν = 3435, 2978, 1742, 1720, 1511, 1368, 1166 cm^{-1}.
^1H NMR (360 MHz; $CDCl_3$): δ = 5.45 (1 H, d, *J* = 9.0 Hz, NH), 4.27 [1 H, m, C*H*(OH)CH_3], 4.22 [1 H, d, *J* = 9.0 Hz, C*H*(CO_2Me)], 3.74 (3 H, S, CO_2CH_3), 2.83 (1 H, d, *J* = 4.9 Hz, OH), 1.42 [9 H, S, $CO_2C(CH_3)_3$], 1.21 [3 H, d, *J* = 6.3 Hz, CH(OH)C*H*$_3$].
^{13}C NMR (67.8 MHz; $CDCl_3$): δ = 171.90 (s), 156.10 (s), 79.82 (s), 67.69 (d), 58.73 (d), 52.24 (q), 28.09 (q), 19.68 (q).
tert-Butyldimethylsilyl chloride (6.80 g, 45.08 mmol) was added in three portions to a solution of the above alcohol (9.56 g, 40.98 mmol) and imidazole (5.58 g, 81.97 mmol) in CH_2Cl_2 (100 mL) at 0 °C and under an atmosphere of N_2. The resulting mixture was allowed to warm to r.t. and stirred overnight. The solvents were removed in vacuo to leave a residue which was partitioned between Et_2O (400 mL) and H_2O (200 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were dried and evaporated in vacuo to leave a cloudy oil. The oil was purified by column chromatography on silica gel using 15 % Et_2O/light petroleum as eluant to give the corresponding silyl ether **12a** (13.5 g, 95%) as a colourless oil; $[\alpha]_D$ –1.1 (*c* = 2.4, $CHCl_3$).
IR (film): ν = 1756, 1721, 1500, 1254, 1168 cm^{-1}.
^1H NMR (360 MHz; $CDCl_3$): δ = 5.17 (1 H, d, *J* = 9.9 Hz, NH), 4.41 [1 H, dq, *J* = 6.3, 1.8 Hz, C*H*(OSi)CH_3], 4.20 [1 H, dd, *J* = 9.9, 1.8 Hz, C*H*(CO_2CH_3)], 3.71 (3 H, s, CO_2CH_3), 1.46 [9 H, s, $CO_2C(CH_3)_3$], 1.19 [3 H, d, *J* = 6.3 Hz, CH(OSi)C*H*$_3$], 0.84 [9 H, s, $(CH_3)_3$CSi], 0.03 (3 H, s, C*H*$_3$SiCH$_3$), –0.02 (3 H, s, CH$_3$SiC*H*$_3$).
^{13}C NMR (67.8 MHz; $CDCl_3$): δ = 171.46 (s), 156.10 (s), 79.66 (s), 68.73 (d), 59.30 (d), 51.93 (q), 28.16 (q), 25.48 (q), 20.56 (q), 17.68 (s), –4.56 (q), –5.50 (q).
1 N NaOH solution (374 mL, 374 mmol) was added dropwise over 10 min to a solution of **12a** (52 g, 150 mmol) in THF/MeOH (3:1, 800 mL) and stirred at r.t. for 6 h. The volatile solvents were removed in vacuo and the aqueous phase was poured into EtOAc (1000 mL) and acidified to pH 3 using 1 N HCl solution. The aqueous phase was extracted with EtOAc (3 x 200 mL) and the combined organic extracts were washed with H_2O and dried. The solvents were removed in vacuo to give the acid **12b** (46.4 g, 93%) as a colourless solid. Recrystallisation from petroleum ether (40–60 °C) gave white crystals; mp 128–130 °C; $[\alpha]_D$ 10.7 (*c* = 3.9, $CHCl_3$).
IR (film): ν = 3272, 2930, 1721, 1666, 1504, 1395, 1367, 1254, 1168, 1071 cm^{-1}.
^1H NMR (360 MHz; $CDCl_3$): δ = 10.18 (1 H, br, CO_2H), 5.24 (1 H, d, *J* = 8.6 Hz, NH), 4.45 [1 H, m, C*H*(OSi)CH_3], 4.27 (1 H, dd, *J* = 8.6, 2.0 Hz, C*H*CO_2H), 1.47 [9 H, s, $CO_2C(CH_3)_3$], 1.21 [3 H, d, *J* = 6.1 Hz, CH(OSi)C*H*$_3$], 0.87 [9 H, s, $(CH_3)_3$CSi], 0.09 (3 H, s, C*H*$_3$SiCH$_3$), 0.06 (3 H, s, CH$_3$SiC*H*$_3$).
^{13}C NMR (67.8 MHz; $CDCl_3$): δ = 176.12 (s), 156.14 (s), 80.00 (s), 68.75 (d), 59.12 (d), 28.23 (q), 25.61 (q), 20.38 (q), 17.79 (s), –4.60 (q), –5.28 (q).
LRMS (FAB): *m/z*(%) = 334 (MH^+, 50), 278 (100), 234 (46), 220 (18).
HRMS (FAB): *m/z* found MH^+, 334.2074; $C_{15}H_{32}O_5NSi$ requires 334.2050.

N-[N-(*tert*-Butoxycarbonyl)-O-(*tert*-butyldimethylsilyl)-L-threonyl]-L-threonine Methyl Ester (13):
Et_3N (44.4 mL, 318.6 mmol) was added dropwise over 30 min to a mixture of **12b** (42.5 g, 127.4 mmol), benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate[13] (73.0 g, 140.2 mmol) and L-threonine methyl ester hydrochloride (23.8 g, 140.2 mmol) in CH_2Cl_2 (600 mL) at 0 °C and under an atmosphere of N_2. The resulting solution was stirred at r.t. for 24 h and the solvents were removed in vacuo to leave a pale yellow viscous oil. The oil was purified by column chromatography on silica gel using 30–50% EtOAc/light petroleum as eluant to give the amide **13** (52.0 g, 91%) as a white solid. Recrystallisation from CH_2Cl_2/light petroleum gave white crystals; mp 120–122 °C; $[\alpha]_D$ 11.3 (*c* = 1.52, $CHCl_3$).
IR ($CHCl_3$): ν = 3416, 1711, 1674, 1367, 1097 cm^{-1}.
^1H NMR (400 MHz; $CDCl_3$): δ = 7.51 (1 H, d, *J* = 7.5 Hz, NH), 5.51 (1 H, d, *J* = 6.8 Hz, NH), 4.58 [1 H, m, C*H*(OSi)CH_3], 4.36 [1 H, dq, *J* = 6.4, 2.5 Hz, C*H*(OH)CH_3], 4.31 (1 H, m, C*H*CO_2CH_3), 4.22 [1 H, m, C*H*NHCO_2C$(CH_3)_3$], 3.77 (3 H, s, CO_2CH_3), 2.14 (1 H, br, OH), 1.46 [9 H, s, $CO_2C(CH_3)_3$], 1.21 [3 H, d, *J* = 6.4 Hz, CH(OSi)C*H*$_3$], 1.16 [3 H, d, *J* = 6.4 Hz, CH(OH)C*H*$_3$], 0.91 [9 H, s, $(CH_3)_3$CSi], 0.16 (3 H, s, C*H*$_3$SiCH$_3$), 0.14 (3 H, s, CH$_3$SiC*H*$_3$).
^{13}C NMR (67.8 MHz; $CDCl_3$): δ = 171.00 (s), 170.55 (s), 155.58 (s), 79.66 (s), 68.48 (d), 67.40 (d), 58.89 (d), 57.36 (d), 52.22 (q), 28.16 (q), 25.59 (q), 19.75 (q), 18.01 (q), 17.72 (s), –4.83 (q), –5.12 (q).
LRMS (FAB): *m/z*(%) = 449 (MH^+, 54), 393 (58), 349 (100), 335 (21), 188 (41), 159 (31), 134 (26), 116 (22).
HRMS (FAB): *m/z* found MH^+, 449.2697; $C_{20}H_{41}O_7N_2Si$ requires 449.2683.
Anal. calcd for $C_{20}H_{40}O_7N_2Si$ (448.6): C, 53.5; H, 9.0; N, 6.3; found: C, 53.8; H, 9.3; N, 6.4.

Methyl 2-[(1'*S*)-[(*tert*-Butoxycarbonyl)amino]-(2'*R*)-[(*tert*-butyldimethylsilyl)oxy]propyl]-(5*S*)-methyl-Δ^2-oxazoline-(4*S*)-carboxylate (14):
Burgess' reagent[11] (3.88 g, 16.30 mmol) was added in one portion to a solution of the amide **13** (6.65 g, 14.82 mmol) in THF (300 mL) and the resulting solution heated under reflux for 6 h under an atmosphere of N_2. The solvents were removed in vacuo to leave an oily residue which was partitioned between Et_2O (500 mL) and brine (100 mL). The separated aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were then dried and evaporated in vacuo to leave an oil. The oil was purified by column chromatography on silica gel using 25–35% EtOAc/light petroleum as eluant to give the oxazoline **14** (4.7g, 73%) as a colourless oil; $[\alpha]_D$ –7.5 (*c* = 1.87, $CHCl_3$).
IR (film): ν = 2930, 1756, 1720, 1664, 1502, 1366, 1255, 1172, 1046 cm^{-1}.
^1H NMR (360 MHz; $CDCl_3$): δ = 5.20 (1 H, d, *J* = 9.3 Hz, NH), 4.93 (1 H, m, OC*H*CH_3), 4.81 (1 H, d, *J* = 10.5 Hz, C*H*CO_2CH_3), 4.37 [1 H, m, C*H*NHCO_2C$(CH_3)_3$], 4.32 [1 H, m, C*H*(OSi)CH_3], 3.74 (3 H, s, CO_2CH_3), 1.45 [9 H, s, $CO_2C(CH_3)_3$], 1.26 [3 H, d, *J* = 6.4 Hz, CH(OSi)C*H*$_3$], 1.21 (3 H, d, *J* = 6.1 Hz, OCHC*H*$_3$), 0.87 [9 H, s, $(CH_3)_3$CSi], 0.06 (3 H, s, C*H*$_3$SiCH$_3$), 0.03 (3 H, s, CH$_3$SiC*H*$_3$).
^{13}C NMR (67.8 MHz; $CDCl_3$): δ = 170.01 (s), 169.06 (s), 155.76 (s), 79.57 (s), 77.47 (d), 71.29 (d), 69.31 (d), 54.84 (d), 51.93 (q), 28.20 (q), 25.61 (q), 20.45 (q), 17.79 (s), 16.19 (q), –4.49 (q), –5.10 (q).
LRMS (FAB): *m/z* (%) = 431 (MH^+, 17), 375 (15), 281 (11), 243 (12), 221 (16), 207 (13), 147 (35).
HRMS (FAB): *m/z* found MH^+, 431.2610; $C_{20}H_{39}O_6N_2Si$ requires 431.2577.

Methyl 2-[(1'*S*)-[(*tert*-Butoxycarbonyl)amino]-(2'*R*)-[(*tert*-butyldimethylsilyl)oxy]propyl]-5-methyloxazole-4-carboxylate (15a):
DBU (1.8 mL, 11.61 mmol) was added dropwise to a solution of the oxazoline **14** (1.2 g, 2.79 mmol) in CCl_4 (6 mL), MeCN (9 mL) and pyridine (9 mL) and under an atmosphere of N_2.[12] The resulting solution was stirred for 12 h and the solvents were removed in vacuo to leave a brown coloured residue. The residue was purified by column chromatography on silica gel using 20% EtOAc/light petroleum as eluant to give the oxazole **15a** (1.0 g, 85%) as a colourless viscous oil; $[\alpha]_D$ –20.8 (*c* = 2.48, $CHCl_3$).

IR (film): ν = 2930, 1721, 1502, 1351, 1255, 1169, 1099 cm^{-1}.
^1H NMR (360 MHz; $CDCl_3$): δ = 5.41 (1 H, d, J = 9.5 Hz, NH), 4.82 [1 H, m, CH(oxazole)], 4.36 [1 H, m, C*H*(OSi)CH_3], 3.90 (3 H, s, CO_2CH_3), 2.59 (3 H, s, CH_3), 1.47 [9 H, s, $CO_2C(CH_3)_3$], 1.22 [3 H, d, J = 6.3 Hz, CH(OSi)C*H*$_3$], 0.79 [9 H, s, $(CH_3)_3CSi$], –0.02 (3 H, s, C*H*$_3$SiCH_3), –0.20 (3 H, s, CH_3SiC*H*$_3$).
^{13}C NMR (100.6 MHz; $CDCl_3$): δ = 162.46 (s), 161.13 (s), 156.01 (s), 155.58 (s), 127.29 (s), 79.80 (s), 69.82 (d), 54.75 (d), 51.69 (q), 28.12 (q), 25.37 (q), 20.07 (q), 17.58 (s), 11.68 (q), –4.87 (q), –5.64 (q).
LRMS (FAB): *m/z*(%) = 429 (MH^+, 24), 373 (100), 329 (17), 159 (19), 147 (15), 109 (15), 95 (26).
HRMS (FAB): *m/z* found MH^+, 429.2425; $C_{20}H_{37}O_6N_2Si$ requires 429.2421.

Methyl 2-[(1'*S*)-Amino-(2'*R*)-hydroxypropyl]-5-methyloxazole-4-carboxylate Trifluoroacetate (9b):
The oxazole **15a** (6.0 g, 14.00 mmol) in THF (50 mL) was added dropwise over 10 min to a 1.0 M solution of TBAF in THF (15.40 mL, 15.40 mmol) at 0 °C and under an atmosphere of N_2. The resulting solution was allowed to warm to r.t. and stirred for 2 h. H_2O (50 mL) was added and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried and evaporated in vacuo to leave a pale yellow oil which was purified by column chromatography on silica gel using 50–100% Et_2O/light petroleum as eluant to give the alcohol **15b** (3.4 g, 78%) as a white solid. Recrystallisation from Et_2O/light petroleum gave white crystals; mp 177–177.5 °C; $[\alpha]_D$ –53.8 (c = 1.17, $CHCl_3$).
IR ($CHCl_3$): ν = 3434, 1714, 1622, 1368, 1353, 1102 cm^{-1}.
^1H NMR (360 MHz; $CDCl_3$): δ = 5.50 (1 H, d, J = 9.2 Hz, NH), 4.80 [1 H, m, CH(oxazole)], 4.38 [1 H, m, C*H*(OH)CH_3], 3.90 (3 H, s, CO_2CH_3), 2.94 (1 H, br, OH), 2.61 (3 H, s, CH_3), 1.46 [9 H, s, $CO_2C(CH_3)_3$], 1.27 [3 H, d, J = 6.4 Hz, CH(OH)C*H*$_3$].
^{13}C NMR (90.6 MHz; $CDCl_3$): δ = 162.22 (s), 161.35 (s), 156.28 (s), 155.81 (s), 126.83 (s), 79.80 (s), 67.81 (d), 53.72 (d), 51.73 (q), 28.05 (q), 19.07 (q), 11.81 (q).
LRMS (FAB): *m/z*(%) = 315 (MH^+, 13), 259 (53), 154 (22), 136 (22), 109 (21), 95 (35).
HRMS (FAB): *m/z* found MH^+, 315.1569; $C_{14}H_{23}O_6N_2$ requires 315.1556.
UV (EtOH): λ_{max} (ε) = 217 nm (11680).
Anal. calcd. for $C_{14}H_{22}O_6N_2$ (314.3): C, 53.5; H, 7.05; N, 8.9; found: C, 53.6; H, 7.0; N, 8.9.
A solution of the BOC protected amine **15b** (0.65 g, 2.08 mmol) in CH_2Cl_2 (6 mL) was added dropwise to a solution of CF_3CO_2H (18 mL) and CH_2Cl_2 (12 mL) at 0 °C and under an atmosphere of N_2. The solution was allowed to warm to r.t. and stirred for 2 h. The mixture was poured into toluene (200 mL) and evaporated in vacuo to give **9b** as a pale brown viscous oil which was used without further purification.

Methyl 2-[(1'*S*)-[[*N*-[*N*-(1,1-Dimethylallyl)-L-valyl]-L-prolyl]amino]-(2'*R*)-hydroxypropyl]-5-methyloxazole-4-carboxylate (7):
Diisopropylethylamine (1.31 mL, 7.55 mmol) was added dropwise over 10 min to a solution of the acid **8b** (0.86 g, 2.16 mmol), the oxazole **9b** (0.66 g, 2.01 mmol) and pyBOP[13] (1.23 g, 2.37 mmol) in CH_2Cl_2 (15 mL) at 0 °C and under an atmosphere of N_2. The solution was allowed to warm to r.t. and stirred for 24 h. The mixture was poured into satd $NaHCO_3$ solution and extracted with EtOAc (4 × 100 mL). The combined organic extracts were washed with H_2O and brine, dried and evaporated in vacuo to leave a pale yellow residue. The residue was purified by column chromatography on silica gel using ethyl acetate as eluant to give the amide **7** (1.0 g, 86%) as a white oily solid: $[\alpha]_D$ –92.3 (c = 1.00, $CHCl_3$).
IR ($CHCl_3$): ν = 3315, 2972, 1726, 1681, 1621, 1519, 1444, 1375, 1196, 1101 cm^{-1}.
^1H NMR (500 MHz; $CDCl_3$): δ = 7.68 (1 H, br, NH), 5.68 (1 H, dd, J = 17.5, 10.6 Hz, C*H*=CH_2), 5.02 [1 H, d, J = 6.0 Hz, C*H*(oxazole)], 4.93 (1 H, d, J = 17.5 Hz, CH=CH*H*), 4.87 (1 H, d, J = 10.6 Hz, CH=C*H*H), 4.55 [1 H, br, C*H*(OH)CH_3], 4.26 (1 H, br, NC*H*CH_2), 3.82 (3 H, s, CO_2CH_3), 3.50 (1 H, m, NCH_2), 2.93 [1 H, d, J = 4.5 Hz, C*H*NHCH$(CH_3)_2$], 2.53 (3 H, s, CH_3), 2.16 (1 H, br, NCHC*H*H), 2.08 (1 H, m, NCHCH*H*), 1.90 (1 H, m, $CH_2CH_2CH_2$), 1.66 [1 H, m, C*H*$(CH_3)_2$], 1.15 [3 H, d, J = 5.9 Hz, CH(OH)C*H*$_3$], 1.08 [3 H, s, C(C*H*$_3$)CH_3], 1.04 [3 H, s, C(CH_3)C*H*$_3$], 0.90 [3 H, d, J 6.6 Hz, CH(C*H*$_3$)CH_3], 0.85 [3 H, d, J = 6.6 Hz, CH(CH_3)C*H*$_3$].
^{13}C NMR (67.8 MHz; $CDCl_3$): δ = 176.96 (s), 172.00 (s), 162.41 (s), 160.79 (s), 156.42 (s), 147.44 (d), 126.95 (s), 111.25 (t), 68.27 (d), 60.13 (d), 58.94 (d), 54.29 (s), 52.74 (d), 51.88 (q), 47.32 (t), 32.02 (d), 27.96 (t), 27.84 (q), 26.11 (q), 25.07 (t), 19.64 (q), 19.39 (q), 17.70 (q), 11.92 (q).
LRMS (EI): *m/z*(%) = 478 (M^+, 2), 350 (4), 140 (100).
HRMS (EI): *m/z* found M^+, 478.2776; $C_{24}H_{38}O_6N_4$ requires 478.2791.

Methyl 2-[(4'S)-2'-[*N*-[*N*-(1,1-Dimethylallyl)-L-valyl]-L-prolyl]-(5'S)-methyl-Δ^2-oxazoline]-5-methyloxazole-4-carboxylate (16):
DAST[14] (111 µl, 0.84 mmol) was added dropwise over 30 min to a stirred solution of the amide **7** (100 mg, 0.21 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C and under an atmosphere of N_2. The mixture was stirred at –78 °C for 3 h and then an aq sat. solution of $NaHCO_3$ (2 mL) was added cautiously. The mixture was allowed to warm to r.t. and then extracted with EtOAc (4 × 10mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to leave a pale yellow oil. The oil was purified by column chromatography on silica gel using EtOAc to 5% MeOH/EtOAc as eluant to give the oxazoline **16** (53.1 mg, 55%) as a colourless viscous oil; $[\alpha]_D$ –16.1 (c = 0.66, $CHCl_3$).
IR (film): ν = 2923, 1725, 1662, 1642, 1631, 1443, 1185, 1103 cm^{-1}.
^1H NMR (500 MHz; $CDCl_3$): δ = 5.73 (1 H, dd, J = 17.6, 10.7 Hz, C*H*=CH_2), 5.33 [1 H, d, J = 9.9 Hz, CH(oxazole)], 4.96 (1 H, m, OCH), 4.95 (1 H, dd, J = 17.6, 1.0 Hz, CH=CH*H*), 4.89 (1 H, dd, J = 10.7, 1.0 Hz, CH=C*H*H), 4.77 (1 H, dd, J = 7.9, 4.9 Hz, NC*H*CH_2), 3.86 (3 H, s, CO_2CH_3), 3.55 (1 H, m, NC*H*$_2$), 2.91 (1 H, d, J = 5.4 Hz, C*H*NH), 2.60 (3 H, s, CH_3), 2.40–2.20 (1 H, br, NH), 2.17 (1 H, m, NCHC*H*$_2$), 2.07 (1 H, m, CH_2CHHCH_2), 1.96 (1 H, m, CH_2CHHCH_2), 1.65 [1 H, m, C*H*$(CH_3)_2$], 1.10 [3 H, s, C(C*H*$_3$)CH_3], 1.08 [3 H, s, C(CH_3)C*H*$_3$], 1.04 (3 H, d, J = 6.5 Hz, OCHC*H*$_3$), 0.90 [3 H, d, J = 6.7 Hz, CH(C*H*$_3$)CH_3], 0.84 [3 H, d, J = 6.7 Hz, CH(CH_3)C*H*$_3$].
^{13}C NMR (125.8 MHz; $CDCl_3$): δ = 175.90 (s), 170.61 (s), 162.55 (s), 159.63 (s), 156.89 (s), 147.57 (d), 127. 20 (s), 111.20 (t), 79.07 (d), 66.39 (d), 59.05 (d), 54.68 (d), 54.36 (s), 52.06 (q), 46.91 (t), 31.93 (d), 29.63 (t), 27.72 (q), 26.17 (q), 24.91 (t), 19.55 (q), 17.75 (q), 16.09 (q), 12.01 (q).
LRMS (FAB): *m/z*(5) = 461 (MH^+, 36), 393 (8), 154 (39), 137 (31), 123 (16), 109 (27).
HRMS (FAB): *m/z* found MH^+, 461.2796; $C_{24}H_{37}O_5N_4$ requires 461.2764.

Methyl 2-[4'-2'-[*N*-[*N*-(1,1-Dimethylallyl)-L-valyl]-L-prolyl]-5'-methyloxazole]-5-methyloxazole-4-carboxylate (6):
DBU (63 µL, 0.42 mmol) was added dropwise to a solution of the oxazoline **16** (31 mg, 0.067 mmol) in CCl_4 (212 µL), MeCN (316 µL) and pyridine (316 µL) under an atmosphere of N_2.[12] The resulting mixture was stirred for 24 h and evaporated in vacuo to leave a brown coloured oily residue. The residue was purified by column chromatography on silica gel using 50% EtOAc/light petroleum as eluant to give **6** (21.0 mg, 68%) as a colourless oily solid; $[\alpha]_D$ –64.0 (c = 0.13, $CHCl_3$).
IR (film): ν = 2923, 1729, 1650, 1445, 1393, 1181, 1107, 1059 cm^{-1}.
^1H NMR (500 MHz; $CDCl_3$): δ = 5.75 (1 H, dd, J = 17.6, 10.7 Hz, C*H*=CH_2), 5.19 [1 H, dd, J = 7.4, 5.2 Hz, CH(oxazole)], 4.97 (1 H,

dd, J = 17.6, 1.0 Hz, CH=CH*H*), 4.91 (1 H, dd, J = 10.7, 1.0 Hz, CH=C*H*H), 3.91 (3 H, s, CO_2CH_3), 3.66 (1 H, m, NC*H*H), 3.61 (1 H, m, NCH*H*), 2.95 (1 H, d, J = 5.1 Hz, C*H*NH), 2.67 (3H, s, CH_3), 2.63 (3 H, s, CH_3), 2.22 (1 H, m, NCHCH_2), 2.17 (1 H, m, CH_2CHHCH_2), 2.01 (1 H, m, CH_2CHHCH_2), 1.90 (1 H, br, NH), 1.75 [1 H, m, C*H*$(CH_3)_2$], 1.12 [3 H, s, C(CH_3)CH_3], 1.10 [3 H, s, C(CH_3)CH_3], 0.97 [3 H, d, J = 6.8 Hz, CH(CH_3)CH_3], 0.85 [3 H, d, J = 6.8 Hz, CH(CH_3)CH_3].

^{13}C NMR (125.8 MHz; $CDCl_3$): δ = 175.95 (s), 163.13 (s), 162.79 (s), 155.81 (s), 154.14 (s), 150.05 (s), 147.88 (d), 128. 20 (s), 124.59 (s), 111.00 (t), 59.13 (d), 54.49 (d), 54.17 (s), 51.88 (q), 46.68 (t), 31.95 (d), 30.59 (t), 28.04 (q), 26.19 (q), 24.96 (t), 19.70 (q), 17.55 (q), 12.04 (q), 11.75 (q).

LRMS (CI, methane): *m/z*(%) = 459 (MH^+, 83), 391 (100), 348 (12), 292 (5), 167 (4), 140 (60), 113 (6).

HRMS (CI, methane): *m/z* found MH^+, 459.2584; $C_{24}H_{35}O_5N_4$ requires 459.2607.

UV (EtOH): λ_{max} (ε) = 204 nm (13199), 254 (13222).

Muscoride A (1):

1N NaOH solution (65 µL, 0.07 mmol) was added dropwise to a solution of the methyl ester **6** (12 mg, 0.03 mmol) in THF/MeOH (3:1, 135 µL) and the mixture was stirred for 2 h. The solvents were removed in vacuo to leave a residue which was diluted with H_2O (0.5 mL) and neutralised using 1N HCl solution. The mixture was extracted with EtOAc (5 × 5 mL) and the combined extracts were dried and evaporated in vacuo to give 2-[4'-2'-[*N*-[*N*-(1,1-dimethylallyl)-L-valyl]-L-prolyl]-5'-methyloxazole]-5-methyloxazole-4-carboxylic acid as a colourless gum which was used without further purification; $[\alpha]_D$ –41.3 (c = 0.18, $CHCl_3$).

IR (film): ν = 3354, 2922, 1718, 1650, 1416, 1058 cm^{-1}.

^{1}H NMR (500 MHz; $CDCl_3$): δ = 5.87 (1 H, dd, J = 17.5, 10.9 Hz, C*H*=CH_2), 5.22 [1 H, m, CH(oxazole)], 5.10 (1 H, d, J = 17.5 Hz, CH=CH*H*), 5.06 (1 H, d, J = 10.9 Hz, CH=C*H*H), 3.70 (1 H, m, NC*H*H), 3.62 (1 H, m, NCH*H*), 3.22 (1 H, br, C*H*NH), 2.68 (3 H, s, CH_3), 2.62 (3 H, s, CH_3), 2.28 (1 H, m, NCHC*H*H), 2.20 (1 H, m, NCHCH*H*), 2.20 (1 H, m, $CH_2CH_2CH_2$), 2.03 [1 H, m, N*H*, C*H*$(CH_3)_2$], 1.32 [3 H, s, C(CH_3)CH_3], 1.26 [3 H, s, C(CH_3)CH_3], 1.03 [3 H, d, J = 6.6 Hz, CH(CH_3)CH_3], 0.96 [3 H, d, J = 6.6 Hz, CH(CH_3)CH_3].

^{13}C NMR (125.8 MHz; $CDCl_3$): δ = 175.99 (s), 164.16 (s), 162.65 (s), 155.90 (s), 153.68 (s), 150.30 (s), 145.15 (d), 128. 40 (s), 124.54 (s), 113.33 (t), 59.53 (d), 54.84 (d), 54.84 (s), 47.00 (t), 31.50 (d), 30.60 (t), 29.68 (q), 27.14 (q), 24.98 (t), 19.19 (q), 17.71 (q), 12.03 (q), 11.75 (q).

LRMS (CI, methane): *m/z*(%) = 445 (MH^+, 84), 405 (21), 391 (8), 377 (100), 140 (61).

HRMS (CI, methane): *m/z* found MH^+, 445.2446; $C_{23}H_{33}O_5N_4$ requires 445.2450.

pyBOP[13] (7.72 mg, 0.015 mmol) was added in one portion to a solution of the above prepared bis-oxazole acid (6.0 mg, 0.013 mmol), 3-methylbut-2-en-1-ol (34 µL, 0.337 mmol) and Et_3N (5.6 µL, 0.040 mmol) in CH_2Cl_2 (0.1 mL) at 0 °C and under an atmosphere of N_2. The mixture was allowed to warm to r.t. and stirred for 24 h. The solvents were removed by passing a stream of N_2 over the surface to leave a pale yellow residue. The residue was purified by column chromatography on silica gel using 40% EtOAc/light petroleum as eluant to give muscoride A **(1)** (3.8 mg, 55%) as a colourless viscous oil; $[\alpha]_D$ –76.0 (c = 0.09, MeOH).

IR (film): ν = 3323, 2963, 1713, 1644, 1400, 1200, 1169, 1104, 1057 cm^{-1}.

^{1}H NMR (500 MHz; $CDCl_3$): δ = 5.76 (1 H, dd, J = 17.6, 10.7 Hz, C*H*=CH_2), 5.47 [1 H, m, C*H*=C$(CH_3)_2$], 5.19 [1 H, dd, J = 7.3, 5.3 Hz, CH(oxazole)], 4.97 (1 H, dd, J = 17.6, 1.2 Hz, CH=CH*H*), 4.91 (1 H, dd, J = 10.7, 1.2 Hz, CH=C*H*H), 4.83 (1 H, d, J = 7.3 Hz, OCH_2), 3.66 (1 H, m, NC*H*H), 3.61 (1 H, m, NCH*H*), 2.95 (1 H, d, J = 5.1 Hz, C*H*NH), 2.66 (3 H, s, CH_3), 2.63 (3 H, s, CH_3), 2.22 (1 H, m, NCHCH_2), 2.16 (1 H, m, CH_2CHHCH_2), 2.00 (1 H, m, CH_2CHHCH_2), 1.78 [3 H, s, CH=C(CH_3)CH_3], 1.77 [3 H, s, CH=C(CH_3)CH_3], 1.74 [1 H, m, C*H*$(CH_3)_2$], 1.58 (1 H, br, NH), 1.12 [3 H, s, C(CH_3)CH_3], 1.10 [3 H, s, C(CH_3)CH_3], 0.97 [3 H, d, J = 6.7 Hz, CH(CH_3)CH_3], 0.85 [3 H, d, J = 6.7 Hz, CH(CH_3)CH_3].

^{13}C NMR (125.8 MHz; $CDCl_3$): δ = 175.96 (s), 163.10 (s), 162.42 (s), 155.54 (s), 154.09 (s), 150.05 (s), 147.92 (d), 139.10 (s), 128.52 (s), 124.66 (s), 118.57 (d), 111.01 (t), 61.81 (t), 59.12 (d), 54.51 (d), 54.16 (s), 46.69 (t), 31.98 (d), 30.60 (t), 28.05 (q), 26.21 (q), 25.80 (q), 24.98 (t), 19.72 (q), 18.13 (q), 17.55 (q), 12.16 (q), 11.77 (q).

LRMS (FAB): *m/z*(%) = 513 (MH^+, 27), 445 (13), 391 (9), 307 (8), 154 (58), 136 (42).

HRMS (FAB): *m/z* found MH^+, 513.3067; $C_{28}H_{41}O_5N_4$ requires 513.3077.

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