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# α-Alkylation versus retro-*O*-Michael/γ-alkylation of bicyclic *N*,*O*-acetals: an entry to α-methylthreonine

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ABSTRACT

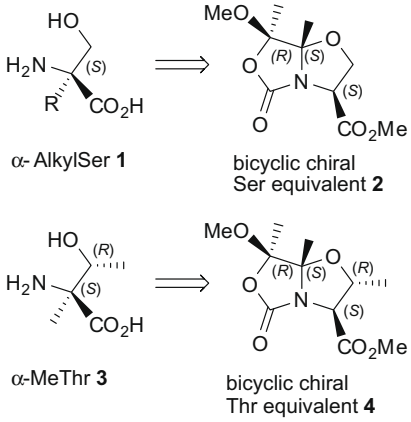
The synthesis of a new threonine equivalent based on a bicyclic *N*,*O*-acetal substructure incorporating four stereogenic centres is developed from Boc-L-threonine methyl ester in one step. Its use as an excellent chiral building block was demonstrated in a new diastereoselective synthesis of α-methylthreonine by an α-alkylation reaction and in the synthesis of chiral α,β-dehydroamino acid derivatives, using the tandem retro-*O*-Michael/γ-alkylation reactions as key steps.



## 1. Introduction

Peptides based on proteinogenic amino acids find limited application as drugs due to rapid metabolism by proteolysis.[1] The study and design of modified peptides that incorporate non-natural amino acids have therefore found increased application as surrogates in different biological processes. Several non-natural amino acids are already important industrial targets as drugs.[2] Moreover, non-natural amino acids are versatile building blocks in the synthesis of chiral compounds and are useful as templates in asymmetric synthesis. In this context, the current interest in α,α-dialkyl-α-amino acids[3] relates to the important effects they have on the biological activity of peptides that incorporate these quaternary amino acids, because they induce alterations in the conformations of the backbone and lateral chain. Among these compounds, chiral α-alkyl-β-hydroxyamino acids have been extensively studied owing to their important roles in synthetic and biological chemistry, particularly in glycobiology, since their hydroxyl group is crucial for the formation of *O*-glycosidic linkages with carbohydrates.[4]

In this sense, we have contributed to this field by developing synthetic routes for α,α-disubstituted α-amino acids based on the use of five-membered cyclic *N*,*O*-acetals[5] (Garner's aldehyde derivatives). More recently, in the context of the synthesis of α-alkylserines, we have published a new methodology involving the use of a serine equivalent as an excellent chiral building block.[6] Starting with the novel bicyclic *N*,*O*-acetal **2**, diastereoselective enolate alkylation reaction and subsequent acid hydrolysis gave the required α-alkyl-β-hydroxy-α-amino acids with one stereogenic centre (α-alkylserine derivatives **1**) (Scheme 1).




**Scheme 1.** Retrosynthesis of α-alkyl-β-hydroxyamino acids from bicyclic *N*,*O*-acetals.

## 2. Results and discussion

With the aim of synthesizing quaternary amino acids with two stereogenic centres, we envisioned the design of other more complex chiral five-membered cyclic *N*,*O*-acetal derived from threonine by incorporating a new stereogenic centre in its structure **4**. Consequently, we herein report the synthesis of a new threonine equivalent **4** and its reactivity as an excellent precursor of an

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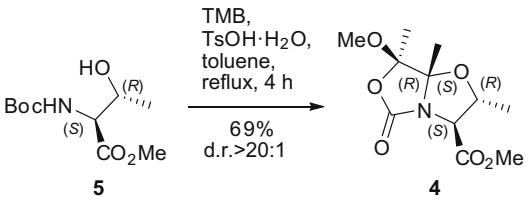
α-alkyl-β-hydroxy-α-amino acid with two chiral stereogenic centres; α-methylthreonine **3**, abbreviated as α-MeThr (Scheme 1).

This new chiral building block **4** derived from threonine was obtained following a similar protocol already published for its analogue of serine.[6a] Indeed, 2,2,3,3-tetramethoxybutane (TMB) was treated with commercially available Boc-L-threonine methyl ester **5** in the presence of *p*-toluenesulfonic acid ($TsOH{\cdot}H_2O$) in refluxing toluene for 4 h, allowing the synthesis of bicyclic compound **4** in good yield on a multigram scale (Scheme 2).




**Scheme 2.** Synthesis of threonine-derived chiral building block 4 from Boc-L-Thr-OMe **5**.

This process proceeded with a high diastereoselectivity (dr >20:1, as demonstrated by $^1$H NMR), and the absolute configuration of this new compound **4**, which contains four chiral carbons, was unambiguously determined by X-ray diffraction analysis[7] of single crystals obtained by slow evaporation of hexane/ethyl acetate (Fig. 1). The bridgehead carbamate N atom is strongly pyramidalized in these compounds, and both five-membered rings are folded, in accordance with similar structures previously published.[6]

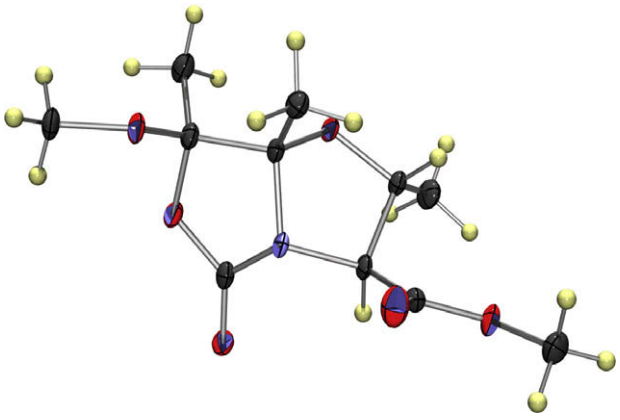
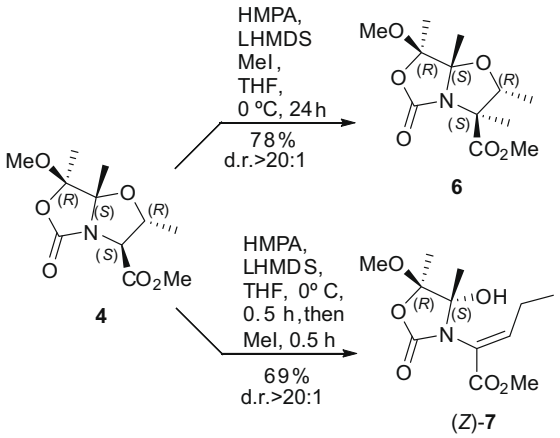
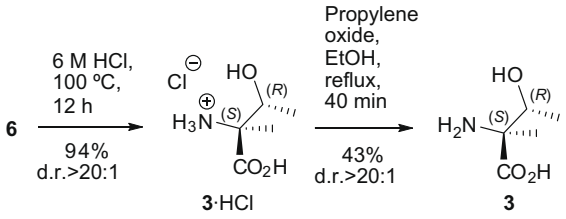


**Figure 1.** ORTEP3 diagram for chiral building block **4**.

Given the easy access to chiral threonine-derived building block **4**, and with the aim of assessing its use as a precursor for the asymmetric synthesis of quaternary α-amino acids, we attempted the alkylation of this compound under standard conditions. Nevertheless, at low temperature (−78 °C) and using methyl triflate as an electrophile the reaction did not progress, probably due to the steric impediment of the β-methyl group arising from threonine. This feature forced us to increase the temperature (0 °C) of the alkylation reaction, which made necessary the change of electrophile, due to polymerization problems encountered with methyl triflate in THF at this temperature.[8] Thus, treatment of bicycle **4** with methyl iodide (MeI) at 0 °C and 4 equiv of hexamethylphosphoramide (HMPA) in THF as a solvent, followed by the addition of lithium hexamethyldisilazide (LHMDS), produced in 24 h the methylated derivative **6** as a single diastereoisomer (dr >20:1) (Scheme 3). Fortunately and contrary to what had happened with the bicycle **2** derived from serine, in this case, we did not detect the formation of a secondary product (acrylate derivative) generated by the well-known retro-*O*-Michael reaction involving the lithium enolate.[4]




**Scheme 3.** α-Alkylation versus retro-*O*-Michael/γ-alkylation of bicyclic *N*,*O*-acetal **4**.




**Scheme 5.** Synthetic pathway used to obtain the quaternary amino acid α-MeThr **3**.

The stereochemistry of this new compound **6** was unambiguously determined by its transformation into a compound of known absolute configuration (see Scheme 5). Alternatively, the stereochemistry of **6** was confirmed by 2D NOESY experiments.[9] 2D NOESY experiments were made using phase-sensitive ge-2D NOESY in $CDCl_3$ and show positive cross-peaks between the OMe

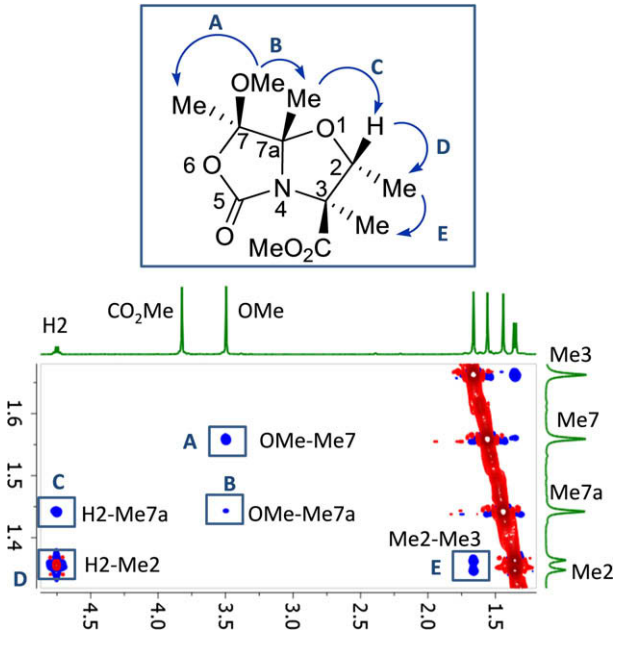


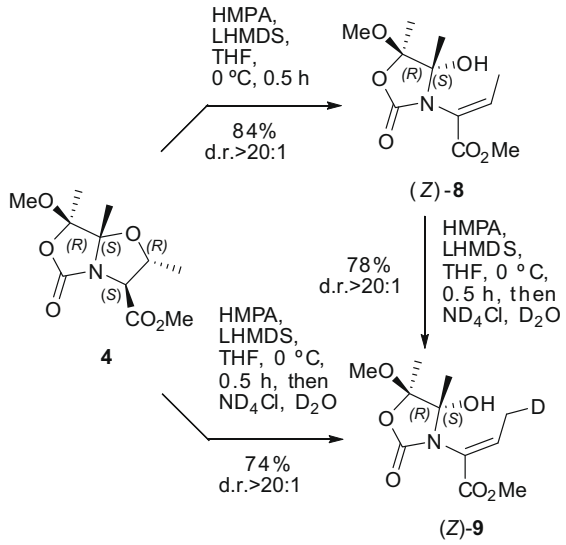

**Figure 2.** 2D NOESY experiments for alkylation product **6**.

and Me groups attached at 7a carbon (B, Fig. 2). This Me group shows a positive cross-peak with the H2 proton (C, Fig. 2), indicating that all these groups are located in the same face. The H2 proton displays NOE and COSY effects with the Me group attached at the same carbon (D, Fig. 2). Finally, this Me group shows an NOE effect with the new Me group arising from the alkylation step (E, Fig. 2). Indeed, we could be assured that the new stereogenic quaternary centre created in the alkylation reaction of bicycle **6** retained the initial configuration showed in starting bicycle **4**. Therefore, a similar mechanism to that calculated for the alkylation of the analogue serine equivalent **2** can be proposed. In this theoretical study, we found that the formation of a highly pyramidalized ester enolate was the true source of the high diastereoselectivity. In fact, the inversion barrier of this enolate was calculated to be greater than any other process occurring under the reaction conditions.[6a]

Curiously, when the same alkylation reaction of bicycle **4** was carried out by adding the electrophile (MeI) as the last reagent (30 min after stirring the reaction mixture at 0 °C), only the new product (*Z*)-**7**, which did not correspond to an α-alkylation product, was cleanly isolated in good yield after another additional 30 min of reaction. The structure of this compound corresponded to a γ-methylation of the acrylate derivative generated in the retro-*O*-Michael reaction of bicycle **4** (Scheme 3). Similar γ-alkylation reactions of acrylate derivatives have been well-documented.[10]

To gain some insights of the proposed mechanism, we carried out the reaction of bicycle **4** under the same conditions but in the absence of electrophile (MeI), obtaining in this case the corresponding non-γ-methylated acrylate derivative (*Z*)-**8**. Moreover, this compound (*Z*)-**8** was treated in the same way but in the presence of deuterated ammonium chloride ($ND_4Cl$), giving compound (*Z*)-**9**, which incorporated a deuterium atom in the γ-position. This compound (*Z*)-**9** could be also directly obtained from bicycle **4** in one single step, using the same conditions that those described for compound (*Z*)-**7**, but changing the electrophile from MeI to $ND_4Cl$ (Scheme 4).

The stereochemistry of these new α,β-unsaturated amino acid derivatives was assessed by NMR. As an example, we show in Figure 3 the selective NOE experiments[11] performed on (*Z*)-**8**. The selective ge-1D NOESY experiments were carried out using the




**Scheme 4.** Synthesis of α,β-dehydroamino acid derivatives from chiral building block **4**.

1D DPFGE NOE pulse sequence.[11] These experiments show an NOE effect between the vinyl proton (H3, blue colour in Fig. 3) and the methyl ester group. This fact along with the NOE effect observed in Me4' and OMe groups when Me4 group (red colour in Fig. 3) is irradiated confirms the *Z* configuration of this alkene.

This last methodology opens the way for the synthesis of interesting chiral α,β-dehydroamino acid derivatives, which are considered important targets as building blocks to carry out asymmetric reactions to prepare α-amino acids, oxalamic acid derivatives or α-keto acids.[12] Moreover α,β-dehydroamino acids[13] also show exciting biological activities and have been used to modify the conformational properties of peptides.[14]

On the other hand, and to show the synthetic applicability of the highly diastereoselective α-alkylation of the new chiral building block **4**, derived from threonine, and with the aim of expanding this methodology to the preparation of α-alkyl-β-hydroxy-α-amino acids with two chiral stereogenic centres, we carried out the

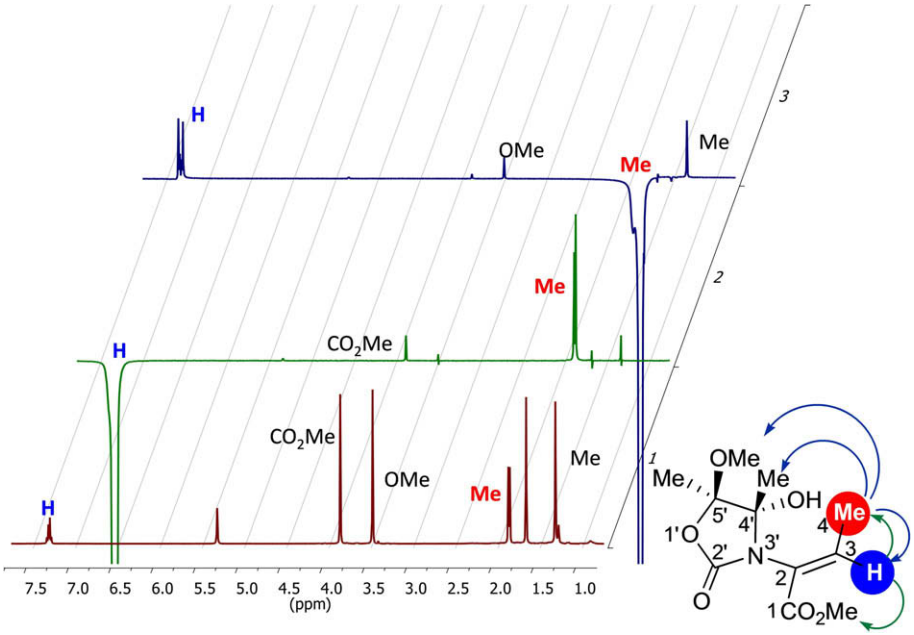



**Figure 3.** Selective 1D NOESY experiments on compound (*Z*)-**8**.

synthesis of (2*S*,3*R*)-α-methylthreonine **3** from the precursor **6**. Hydrolysis of the substrate **6** in an acidic medium gave the required amino acid **3** as an hydrochloride derivative in a 94% yield (Scheme 5). An aliquot of this compound was treated with propylene oxide to obtain the free amino acid **3** in a 43% yield. The structural and optical properties of this compound were almost identical to those reported in the literature ($[\alpha]_D^{25} = -13.6$).[5f] It is important to note that although several synthetic methods have been reported for α-methylserines, to the best of our knowledge, there are only four methodologies (six reports) on the asymmetric synthesis of enantiomerically pure α-methylthreonine.[5f,15] The interest in α-methylthreonines has been recently illustrated by our group in glycopeptide chemistry[16] since it has been shown that the replacement of the natural amino acid threonine with the non-natural α-methylthreonine in O-glycosylated derivatives markedly influences the conformational properties of glycopeptides.[17]

## 3. Conclusions

Starting from a commercially available protected threonine derivative, we have synthesized a new chiral bicyclic threonine equivalent as an excellent precursor of non-natural amino acids. The chemoselectivity of the reaction between this new chiral building block **4** and methyl iodide promoted by a base in the presence of HMPA could be modulated by the order of addition of reagents. Thus, the α-alkylation reaction of bicycle **4** allowed us to obtain a quaternary amino acid that incorporates two stereogenic centres (α-MeThr), while the tandem reaction (retro-*O*-Michael/γ-alkylation) opened the way to obtain interesting α,β-unsaturated amino acid derivatives.

## 4. Experimental

### 4.1. General procedures

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Silica Gel 60 (230–400 mesh). $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in $D_2O$ with TMS as the external standard using a coaxial microtube (chemical shifts are reported in ppm on the $\delta$ scale, coupling constants in hertz). The assignment of all separate signals in the $^1$H NMR spectra was made on the basis of coupling constants, selective proton–proton homonuclear decoupling experiments and COSY and HSQC experiments. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter in 1.0 dm cells of 1.0 and 0.3 mL capacity, respectively. Electrospray mass spectra were recorded on a Bruker Microtof-Q spectrometer; accurate mass measurements were achieved using sodium formate as an external reference.

### 4.2. Methyl (2*R*,3*S*,7*R*,7a*S*)-7-methoxy-2,7,7a-trimethyl-5-oxotetrahydro-2*H*-oxazolo[4,3-b]oxazole-3-carboxylate 4

#### 4.2.1. Synthesis of compound 4

Boc-L-threonine methyl ester **5** (6.90 g, 29.6 mmol), 2,2,3,3-tetramethoxybutane (15.82 g, 88.7 mmol) and *p*-toluenesulfonic acid (560 mg, 2.96 mmol) were dissolved in toluene (200 mL). The mixture was stirred and heated at reflux for 4 h. The mixture was allowed to cool at room temperature, and was then diluted with diethyl ether (60 mL) and washed with saturated $NaHCO_3$. The aqueous layer was extracted with more diethyl ether (2 × 50 mL) and the organic layers were combined, washed with brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the crude product was purified by a silica gel column chromatography eluting with hexane/ethyl acetate (7:3) to give 5.30 g of product **4** (69%) as brown crystals. $[\alpha]_D^{25} = -122.3$ (*c* 0.95, $CHCl_3$); mp = 52.8 °C; $^1$H NMR ($CDCl_3$): $\delta$ 4.46 (m, 1H, C*H*CH$_3$), 4.26 (d, 1H, *J* = 5.78 Hz, C*H*CO$_2$CH$_3$), 3.81 (s, 3H, CO$_2$CH$_3$), 3.46 (s, 3H, OCH$_3$), 1.59 (s, 3H, CC*H*$_3$OCH$_3$), 1.44 (d, 3H, *J* = 6.06 Hz, CHC*H*$_3$), 1.39 (s, 3H, CNCH$_3$); $^{13}$C NMR ($CDCl_3$): $\delta$ 170.0 (*C*O$_2$CH$_3$), 160.6 (*C*NO$_2$), 106.7 (*C*CH$_3$OCH$_3$), 101.4 (*C*NCH$_3$OCH), 76.0 (*C*HCH$_3$), 66.6 (*C*HCO$_2$CH$_3$), 52.4 (CHCO$_2$*C*H$_3$), 50.7 (OCH$_3$), 20.3 (CH*C*H$_3$), 16.2 (CN*C*H$_3$), 15.3 (CCH$_3$OCH$_3$); HRMS (ESI) *m*/*z* = 282.0951 [M + Na]$^+$; calcd for $C_{11}H_{17}NNaO_6$ = 282.0954.

#### 4.2.2. Crystal data of compound 4

Molecular formula $C_{11}H_{17}NO_6$, $M_w$ = 259.26, colourless prism of 0.7 × 0.2 × 0.2 mm, *T* = 100 K, monoclinic, space group *P*2$_1$, *Z* = 2, *a* = 6.9030(3) Å, *b* = 12.0450(6) Å, *c* = 7.7740(3) Å, β = 96.828(2)°, *V* = 641.80(5) Å$^3$, $d_{calc}$ = 1.342 g cm$^{-3}$, *F*(000) = 276, λ = 0.71073 Å (Mo, Kα), $\mu$ = 0.110 mm$^{-1}$, Nonius kappa CCD diffractometer, $\theta$ range 3.42–27.49°, 4786 collected reflections, 2723 unique, full-matrix least-squares (SHELXL97),[18] $R_1$ = 0.0635, $wR_2$ = 0.0706, ($R_1$ = 0.1536, $wR_2$ = 0.1613 all data), goodness of fit = 1.092, residual electron density between 0.426 and −0.486 e Å$^{-3}$. Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions). Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number CCDC 702053.[7]

### 4.3. Methyl (2*R*,3*S*,7*R*,7a*S*)-7-methoxy-2,3,7,7a-tetramethyl-5-oxotetrahydro-2*H*-oxazolo[4,3-*b*]oxazole-3-carboxylate 6

Compound **4** (924 mg, 3.56 mmol) was dissolved in dry THF (90 mL) under an argon atmosphere, and HMPA (2.48 mL, 14.26 mmol) was added by syringe. The solution was stirred at 0 °C, and methyl iodide (1.33 mL, 21.36 mmol) and 1 M solution of LHMDS in THF (14.26 mL, 14.26 mmol) were added dropwise by syringe. After being stirred for 24 h at 0 °C, the reaction was quenched with saturated $NH_4Cl$ solution (90 mL). The mixture was diluted with diethyl ether and the aqueous layer was separated and extracted with more diethyl ether. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the crude product was purified by a silica gel column chromatography eluting with chloroform/ethyl acetate (20:1) to give 760 mg of product **6** (78%) as a colourless oil. $[\alpha]_D^{25} = -118.3$ (*c* 1.08, $CHCl_3$); $^1$H NMR ($CDCl_3$): $\delta$ 4.72 (q, 1H, *J* = 6.33 Hz, C*H*CH$_3$), 3.79 (s, 3H, CO$_2$CH$_3$), 3.46 (s, 3H, OCH$_3$), 1.63 (s, 3H, CC*H*$_3$CO$_2$CH$_3$), 1.53 (s, 3H, CC*H*$_3$OCH$_3$), 1.41 (s, 3H, CNCH$_3$), 1.33 (d, 3H, *J* = 6.33 Hz, CHC*H*$_3$); $^{13}$C NMR ($CDCl_3$): $\delta$ 173.4 (*C*O$_2$CH$_3$), 154.5 (*C*NO$_2$), 107.4 (*C*CH$_3$OCH$_3$), 99.9 (*C*NCH$_3$OCH), 80.4 (*C*HCH$_3$), 67.1 (*C*CO$_2$CH$_3$), 53.0 (CCO$_2$CH$_3$), 51.6 (OCH$_3$), 18.0 (CNCH$_3$), 16.7 (CCH$_3$OCH$_3$), 16.1 (CC*H*$_3$CO$_2$CH$_3$), 15.7 (CHCH$_3$); HRMS (ESI) *m*/*z* = 296.1107 [M+Na]$^+$; calcd for $C_{12}H_{19}NNaO_6$ = 296.1110.

### 4.4. (*Z*)-Methyl 2-((4′*S*,5′*R*)-4′-hydroxy-5′-methoxy-4′,5′-dimethyl-2′-oxooxazolidin-3′-yl)pent-2-enoate (*Z*)-7

Compound **4** (104 mg, 0.40 mmol) was dissolved in dry THF (10 mL) under an argon atmosphere, and HMPA (0.27 mL, 1.60 mmol) was added by syringe. The solution was stirred at 0 °C, and 1 M solution of LHMDS in THF (0.79 mL, 0.79 mmol) was added by syringe. After being stirred for 30 min at 0 °C, methyl iodide (0.07 mL, 1.20 mmol) was added by syringe. The reaction

was stirred for another 30 min and then quenched with $NH_4Cl$ solution (10 mL). The mixture was diluted with diethyl ether and the aqueous layer was separated and extracted with more diethyl ether. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the crude product was purified by a silica gel column chromatography eluting with hexane/ethyl acetate (1:1) to give 76 mg of product (*Z*)-**7** (69%) as a colourless oil. $[\alpha]_D^{25} = -122.3$ (*c* 1.15, $CHCl_3$); $^1H$ NMR ($CDCl_3$): $\delta$ 7.15 (t, 1H, *J* = 7.44 Hz, C=C*H*$CH_2CH_3$), 5.28 (s, 1H, OH), 3.83 (s, 3H, $CO_2CH_3$), 3.45 (s, 3H, $OCH_3$), 2.32–2.19 (m, 1H, C=CHC*H*$_2$$CH_3$), 2.23–2.11 (m, 1H, C=CHC*H*$_2$$CH_3$), 1.63 (s, 3H, CC*H*$_3$$OCH_3$), 1.28 (s, 3H, CC*H*$_3$OH), 1.08 (t, 3H, *J* = 7.54 Hz, $CH_2CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 167.1 (*C*$O_2CH_3$), 154.5 ($NCO_2$), 151.0 (C=CH$CH_2CH_3$), 123.6 (*C*=CH$CH_2CH_3$), 108.7 (*C*$CH_3OCH_3$), 90.5 (*C*N$CH_3$OH), 53.1 ($CO_2CH_3$), 50.6 ($OCH_3$), 21.8 (C=CH*C*H$_2$$CH_3$), 19.6 (*C*$CH_3$OH), 14.2 (*C*$CH_3OCH_3$), 12.3 (C=CHCH$_2$*C*H$_3$); HRMS (ESI) *m/z* = 296.1109 $[M+Na]^+$; calcd for $C_{12}H_{19}NNaO_6$ = 296.1110.

### 4.5. (*Z*)-Methyl 2-(4′*S*,5′*R*)-4′-hydroxy-5′-methoxy-4′,5′-dimethyl-2′-oxooxazolidin-3′-yl)but-2-enoate (*Z*)-8

Compound **4** (86 mg, 0.33 mmol) was dissolved in dry THF (10 mL) under an argon atmosphere, and HMPA (0.22 mL, 1.32 mmol) was added by syringe. The solution was stirred at 0 °C, and 1 M solution of LHMDS in THF (0.66 mL, 0.66 mmol) was added by syringe. After being stirred for 30 min at 0 °C, the reaction was quenched with saturated $NH_4Cl$ solution (10 mL). The mixture was diluted with diethyl ether and aqueous layer was separated and extracted with more diethyl ether. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the crude product was purified by a silica gel column chromatography eluting with hexane/ethyl acetate (1:1) to give 73 mg of product (*Z*)-**8** (84%) as a colourless oil. $[\alpha]_D^{25} = -116.5$ (*c* 1.02, $CHCl_3$); $^1H$ NMR ($CDCl_3$): $\delta$ 7.27 (q, 1H, *J* = 7.09 Hz, C=C*H*$CH_3$), 5.28 (s, 1H, OH), 3.82 (s, 3H, $CO_2CH_3$), 3.44 (s, 3H, $OCH_3$), 1.82 (d, 3H, *J* = 7.09 Hz, C=CHC*H*$_3$), 1.62 (s, 3H, CC*H*$_3$$OCH_3$), 1.28 (s, 3H, CC*H*$_3$OH); $^{13}C$ NMR ($CDCl_3$): $\delta$ 166.9 (*C*$O_2CH_3$), 154.2 ($NCO_2$), 144.6 (C=*C*H$CH_3$), 125.4 (*C*=CH$CH_3$), 108.7 (*C*$CH_3OCH_3$), 90.5 (*C*N$CH_3$OH), 53.1 ($CO_2CH_3$), 50.5 ($OCH_3$), 19.5 (*C*$CH_3$OH), 14.1 (C=CH*C*H$_3$), 14.0 (*C*$CH_3OCH_3$); HRMS (ESI) *m/z* = 282.0949 $[M + Na]^+$; calcd for $C_{11}H_{17}NNaO_6$ = 282.0954.

### 4.6. (*Z*)-Methyl 2-((4′*S*,5′*R*)-4′-hydroxy-5′-methoxy-4′,5′-dimethyl-2′-oxooxazolidin-3′-yl) -4-deuteriumbut-2-enoate (*Z*)-9

*Method A (one pot method)*: Compound **4** (50 mg, 0.19 mmol) was dissolved in dry THF (5 mL) under an argon atmosphere, and HMPA (0.12 mL, 0.76 mmol) was added by syringe. The solution was stirred at 0 °C, and 1 M solution of LHMDS in THF (0.38 mL, 0.38 mmol) was added by syringe. After being stirred for 30 min at 0 °C, the reaction was quenched with $ND_4Cl$ solution (2.5 mL). The mixture was diluted with diethyl ether and the aqueous layer was separated and extracted with more diethyl ether. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the crude product was purified by a silica gel column chromatography eluting with hexane/ethyl acetate (1:1) to give 37 mg of product (*Z*)-**9** (74%). $[\alpha]_D^{25} = -96.8$ (*c* 0.97, $CHCl_3$); $^1H$ NMR ($CDCl_3$): $\delta$ 7.28 (t, 1H, *J* = 6.80 Hz, C=C*H*$CH_2D$), 5.30 (s, 1H, OH), 3.84 (s, 3H, $CO_2CH_3$), 3.45 (s, 3H, $OCH_3$), 1.86–1.81 (m, 2H, C=CHC*H*$_2$D), 1.64 (s, 3H, CC*H*$_3$$OCH_3$), 1.29 (s, 3H, CC*H*$_3$OH); $^{13}C$ NMR ($CDCl_3$): $\delta$ 167.0 (*C*$O_2CH_3$), 154.3 ($NCO_2$), 144.7 (C=CH$CH_2D$), 125.4 (*C*=CH$CH_2D$), 108.8 (*C*$CH_3OCH_3$), 90.6 (*C*N$CH_3$OH), 53.1 ($CO_2CH_3$), 50.6 ($OCH_3$), 19.6 (*C*$CH_3$OH), 14.1 (C=CH*C*H$_2$D), 14.1 (*C*$CH_3OCH_3$); HRMS (ESI) *m/z* = 283.1019 $[M+Na]^+$; calcd for $C_{11}H_{16}DNNaO_6$ = 283.1016. *Method B:* Compound (*Z*)-**8** (49 mg, 0.19 mmol) was dissolved in dry THF (5 mL) under an argon atmosphere, and HMPA (0.12 mL, 0.76 mmol) was added by syringe. The solution was stirred at 0 °C, and 1 M solution of LHMDS in THF (0.38 mL, 0.38 mmol) was added by syringe. After being stirred for 30 min at 0 °C, the reaction was quenched with $ND_4Cl$ solution (2.5 mL). The mixture was diluted with diethyl ether and the aqueous layer was separated and extracted with more diethyl ether. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the crude product was purified by a silica gel chromatography eluting with hexane/ethyl acetate (1:1) to give 39 mg of product (*Z*)-**9** (78%).

### 4.7. (2*S*,3*R*)-2-Amino-3-hydroxy-2-methylbutanoic acid 3

A round bottomed flask was charged with compound **6** (93 mg, 0.34 mmol) and an aqueous 6 M HCl solution. The mixture was stirred overnight at reflux. The solvent was removed in vacuo, and the residue partitioned between water and ethyl acetate. The aqueous phase was evaporated to give the hydrochloride derivative of compound **3** (54 mg, 94%). An aliquot of this material was treated with ethanol/propylene oxide (2:1, 3 mL) at reflux for 40 min to give the corresponding amino acid **3,** abbreviated as α-MeThr (19.3 mg, 0.14 mmol), as a white solid; yield 43%. $[\alpha]_D^{25} = -15.6$ (*c* 0.97, $H_2O$). The spectroscopic data were identical to those reported on the literature.[3f] HRMS (ESI) *m/z* = 134.0810 $[M + H]^+$; calcd for $C_5H_{12}NO_3$ = 134.0817.

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## References

1. For a review see: Marshall, S. A.; Lazar, G. A.; Chirino, A. J.; Desjarlais, J. R. *Drug Discovery Today* **2003**, *8*, 212–221.
2. (a) Ripka, A.; Rich, D. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441–452; (b) Vagner, J.; Qu, H.; Hruby, V. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 292–296.
3. (a) Williams, R. M. Synthesis of Optically Active α-Amino Acids. In *Organic Chemistry Series*, Baldwin, J. E., Ed.; Pergamon Press: New York. 1989; p 410.; (b) Williams, R. M.; Sinclair, P. J.; DeMong, D. E.; Chen, D.; Zhai, D. *Org. Synth.* **2003**, *80*, 18–30; (c) Williams, R. M.; Sinclair, P. J.; DeMong, D. E.; Chen, D.; Zhai, D. *Org. Synth.* **2003**, *80*, 31–37; (d) Williams, R. M. Asymmetric Synthesis of α-Amino Acids. In *Advances in Asymmetric Synthesis*, Hassner, A., Ed.; JAI Press, 1995; Vol. 1, pp 45–94.; (e) Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276–9286; (f) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11–25; (g) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650; (h) Wirth, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 225–227; (i) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; (j) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732; (k) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342–351; (l) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430; (m) Hruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389–397; (n) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623.
4. (a) Van den Steen, P.; Rudd, P. M.; Dwek, R. A.; Opdenakker, G. *Crit. Rev. Biochem. Mol. Biol.* **1998**, *33*, 151–208; (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720; (c) Angata, T.; Varki, A. *Chem. Rev.* **2002**, *102*, 439–470; (d) Taylor, C. M. *Tetrahedron* **1998**, *54*, 11317–11362; (e) Helzner, H.; Reipen, T.; Schultz, M.; Kunz, H. *Chem. Rev.* **2000**, *100*, 4495–4537; (f) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624; (g) Pratt, M. R.; Bertozzi, C. R. *Chem. Soc. Rev.* **2005**, *34*, 58–68; (h) Varki, A. *Glycobiology* **1993**, *3*, 97–130; (i) Corzana, F.; Busto, J. H.; Jiménez-Osés, G.; Asensio, J. L.; Jiménez-Barbero, J.; Peregrina, J. M.; Avenoza, A. *J. Am. Chem. Soc.* **2006**, *128*, 14640–14648; (j) Corzana, F.; Busto, J. H.; Jiménez-Osés, G.; García de Luis, M.; Asensio, J. L.; Jiménez-Barbero, J.; Peregrina, J. M.; Avenoza, A. *J. Am. Chem. Soc.* **2007**, *129*, 9458–9467.
5. (a) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220–8225; (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4653–4661; (c) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195–2204; (d) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron:*

*Asymmetry* **2001**, *12*, 949–957; (e) Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 399–405; (f) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2004**, *15*, 719–724; (g) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Synthesis* **2005**, 575–578.

6. (a) Aydillo, C.; Jiménez-Osés, G.; Busto, J. H.; Peregrina, J. M.; Zurbano, M. M.; Avenoza, A. *Chem.-Eur. J.* **2007**, *13*, 4840–4848; (b) Jiménez-Osés, G.; Aydillo, C.; Busto, J. H.; Zurbano, M. M.; Peregrina, J. M.; Avenoza, A. *J. Org. Chem.* **2007**, *72*, 5399–5402; (c) Jiménez-Osés, G.; Aydillo, C.; Busto, J. H.; Zurbano, M. M.; Peregrina, J. M.; Avenoza, A. *J. Org. Chem.* **2007**, *72*, 7070.
7. CCDC 702053 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
8. (a) Yoshida, E.; Sugita, A. *Macromolecules* **1996**, *29*, 6422–6426; (b) Howells, R. D.; Mc Cown, J. D. *Chem. Rev.* **1977**, *77*, 69–92.
9. Wagner, R.; Berger, S. *J. Magn. Reson. A* **1996**, *123*, 119–121.
10. (a) Savu, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1981**, *46*, 239–250; (b) Aurell, M. J.; Gil, S.; Mestres, R.; Parra, M.; Parra, L. *Tetrahedron* **1998**, *54*, 4357–4366; (c) Gil, S.; Parra, M.; Rodríguez, P. *Tetrahedron Lett.* **2007**, *48*, 3451–3453.
11. Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302–324.
12. (a) Zhang, W.; Zhang, X. *J. Org. Chem.* **2007**, *72*, 1020–1023; (b) Hu, X.-P.; Huang, J.-D.; Zeng, Q.-H.; Zheng, Z. *Chem. Commun.* **2006**, 293–295; (c) Hoen, R.; Van den Berg, M.; Bernsmann, H.; Minnaard, A. J.; De Vries, J. G.; Feringa, B. L. *Org. Lett.* **2004**, *6*, 1433–1436; (d) Cerić, H.; Kovačević, M.; Šindler-Kulyk, M. *Tetrahedron* **2000**, *56*, 3985–3993; (e) Hou, D.; Mas, J. L.; Chan, T. M.; Wong, Y. S.; Steinman, M.; McPhail, A. T. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2171–2176; (f) Farina, V.; Hauck, S. I.; Walker, D. G. *Synlett* **1992**, 761–763; (g) Ashry, El; Ramadan, E. S. H.; Abdel, E. S.; Hamid, H.; Hagar, M. *Lett. Org. Chem.* **2005**, *2*, 415–418; (h) Cvetovich, R. J.; Pipik, B.; Hartner, F. W.; Grabowski, E. J. J. *Tetrahedron Lett.* **2003**, *44*, 5867–5870; (i) Nagasaki, A.; Adachi, Y.; Yonezawa, Y.; Shin, C.-G. *Heterocycles* **2003**, *60*, 321–335; (j) Arnold, Z. *Synthesis* **1990**, 39–40; (k) Breslow, R.; Canary, J. W.; Varney, M.; Waddell, S. T.; Yang, D. *J. Am. Chem. Soc.* **1990**, *112*, 5212–5219; (l) Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690–7696; (m) Palacios, F.; Vicario, J. *Synthesis* **2007**, 3923–3925; (n) Palacios, F.; Vicario, J. *Org. Lett.* **2006**, *8*, 5405–5408; (o) Bonauer, C.; Walenzyk, T.; König, B. *Synthesis* **2006**, 1–20.
13. (a) Ager, D. J. *Curr. Opin. Drug Discov. Dev.* **2002**, *5*, 892–905; (b) Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans 1* **2000**, 4197–4212; (c) Soloshonok, V. A. *Curr. Org. Chem.* **2002**, *6*, 341–364; (d) RajanBabu, T. V.; Yan, Y. Y.; Shin, S. *Curr. Org. Chem.* **2003**, *7*, 1759–1770; (e) Drexler, H. J.; You, J.; Zhang, S.; Fisher, C.; Bauman, W.; Spannenberg, A.; Heller, D. T. *Org. Process Res. Dev.* **2003**, *7*, 355–361; (f) Brunner, H. *Curr. Org. Chem.* **2002**, *6*, 441–451; (g) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159–171.
14. (a) Broda, M. A.; Siodłak, D.; Rzeszotarska, B. *J. Pept. Sci.* **2005**, *11*, 546–555; (b) Mathur, P.; Ramakumar, S.; Chauhan, V. S. *Biopolymers (Pept. Sci.)* **2004**, *76*, 150–161; (c) Vijayaraghavan, R.; Kumar, P.; Dey, S.; Singh, T. P. *J. Pept. Res.* **2003**, *62*, 63–69.
15. (a) Weber, T.; Aeschimann, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365–1377; (b) Goodman, M.; Shao, H. *Pure Appl. Chem.* **1996**, *68*, 1303–1308; (c) Moon, S.-H.; Ohfune, Y. *J. Am. Chem. Soc* **1994**, *116*, 1405–1406; (d) Moon, S.-H.; Ohfune, Y.; Horikawa, M. *Pure Appl. Chem.* **1996**, *68*, 645–648; (e) Shao, H.; Rueter, J. K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 5240–5244.
16. Fernández-Tejada, A.; Corzana, F.; Busto, J. H.; Jiménez-Osés, G.; Peregrina, J. M.; Avenoza, A. *Chem.-Eur. J.* **2008**, *14*, 7042–7058.
17. Corzana, F.; Busto, J. H.; Engelsen, S. B.; Asensio, J. L.; Jiménez-Barbero, J.; Peregrina, J. M.; Avenoza, A. *Chem.-Eur. J.* **2006**, *12*, 7864–7871.
18. Sheldrick, G. M. SHELXL97. *Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.