Tetrahedron: *Asymmetry* 20 (2009) 1824–1827

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# New isosteres of (*R*)-2-methylhomoserine and (*R*)-2-methylaspartic acid by alkylation of a chiral imine leading stereoselectively to a quaternary stereogenic center

Emanuela Crucianelli, Gianluca Martelli *, Mario Orena, Samuele Rinaldi, Federica Sgolastra

*Dipartimento I.S.A.C., Università Politecnica delle Marche, Via Brecce Bianche, I-60131 Ancona, Italy*

ARTICLE INFO

*Article history:*
Received 10 June 2009
Accepted 1 July 2009
Available online 5 August 2009

ABSTRACT

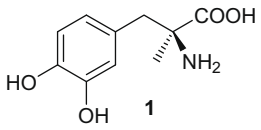
Imines obtained from either chiral 3-amino-4-silyloxymethylpyrrolidin-2-one **5a** or **5b** underwent alkylation to give, in good yield and total stereoselection, the corresponding 3,3,4-trisubstituted pyrrolidin-2-ones **8a**–**d** where both the amino and the silyloxymethyl groups lie *cis* to each other, as shown by $^1$H NMR spectroscopic data and NOE experiments. By removal of both the imino group and the chiral inducer from **8b**, the pyrrolidin-2-one **12**, an isostere of (*R*)-2-methylhomoserine **2** and the pyrrolidin-2-one **14**, an isostere of (*R*)-2-methylaspartic acid **4** were obtained straightforwardly.



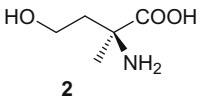
## 1. Introduction

Structural modifications are often required in order to overcome problems arising from current drug-delivery strategies of biologically active peptides, which have a large potential for therapeutical applications. In fact, the properties desired but often not present in the native ligand include: receptor/acceptor selectivity; high potency; stability against proteolytic breakdown; and appropriate biodistribution and bioavailability, so that analogues are often employed in order to circumvent these drawbacks.[1] Owing to their biological properties, both as free amino acids and as components of peptides, and to their conformational properties, α-methyl amino acids have assumed an important role in bioorganic chemistry in recent years. For example, (*S*)-α-methyl-DOPA (Aldomet) **1**, an inhibitor of DOPA decarboxylase, is an important commercial antihypertensive.[2] Substitution of (5′)-α-methyltyrosine for tyrosine-4 in angiotensin II results in a peptide that is resistant to chymotrypsin degradation, but retains 93% of the pressor activity of the parent peptide.[3] In an analogue of the locust CRF-like diuretic peptide, methionines at the 1-, 3-, and 13-positions were replaced by isosteric methyl-homoserine residues **2**. This analogue has been tested for biological activity on Malpighian tubules in vitro, and feeding behavior in vivo. It is highly active in the stimulation of fluid secretion and accumulation of cAMP in tubules, and on increasing the latency to feed and reduce meal duration.[4]

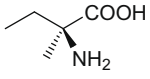
For the de novo design of peptides and proteins, several chiral α-methyl amino acids are useful building blocks for engineering helical secondary structures. For instance, (*S*)-isovaline (α-methylbutyrine) **3** has been used to construct peptides with a $3_{10}$ helical structure.[5] On the other hand, (*R*)-α-methylaspartate **4** is an especially effective building block for engineering α-helical structures.[6]



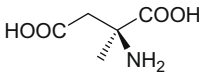

1




2




3




4

Eventually, incorporation of amino acids isosteres into proteins that carry conformational restrictions due to rigidity elements such as double bonds, carbocyclic, or heterocyclic rings is a versatile technique for affecting or enhancing their biological activity.[7] Therefore, the development of methods for the stereoselective synthesis of 3,3,4-trisubstituted pyrrolidin-2-ones is of growing interest directed toward the preparation of strongly conformationally restricted analogues of naturally occurring amino acids.

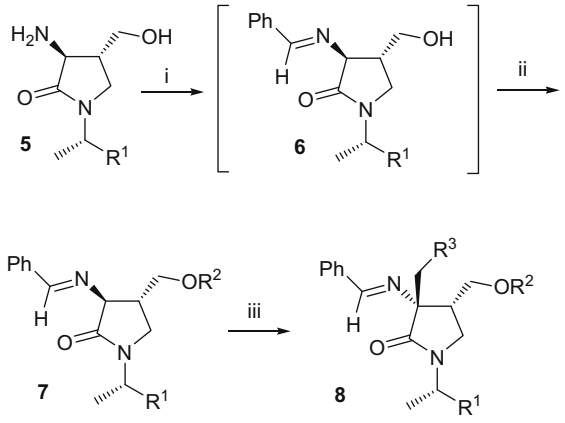
## 2. Results and discussion

We have already reported the stereoselective synthesis of conformationally restricted analogues of proteinogenic amino acids where the rigidity arises from a γ-lactam ring.[8] Herein we report

* Corresponding author. Tel.: +39 071 2204720; fax: +39 071 2204714.
*E-mail address:* gmartell@univpm.it (G. Martelli).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.07.005

work directed to cyclic homoserine and aspartic acid analogues with an α quaternary carbon. In fact an additional alkyl substituent was introduced via the stereoselective alkylation of the chiral imine **7**, easily prepared from the enantiomerically pure 3,4-*trans*-disubstituted pyrrolidin-2-one **5**, already synthesized in our laboratory (Scheme 1). At first, the pyrrolidin-2-one **5** was treated with benzaldehyde in dry THF, in the presence of 4 Å molecular sieves, to afford the corresponding imine **6** in high purity, which was not separated, but directly underwent reaction with TBDMS-Cl to give in quantitative yield the corresponding TBDMS ether **7**, which was subsequently used without any further purification. The alkylation of the imine **7** was carried out with LiHMDS, and proceeded in very high yield and total stereoselection, to give 3,3,4-disubstituted pyrrolidin-2-ones **8** as the sole isomers, as evidenced by $^1$H NMR data (Scheme 1).

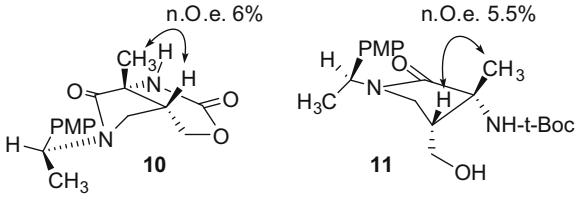


**Scheme 1.** Reagents and conditions. (i) PhCHO, MS 4 Å, dry THF, (a) $R^1 = C_6H_5$, (b) $R^1 = 4\text{-}CH_3OC_6H_4$; (ii) TBDMSCl, imidazole, THF, (a) $R^1 = C_6H_5$, $R^2$ = TBDMS, 92%, (b) $R^1 = 4\text{-}CH_3OC_6H_4$, $R^2$ = TBDMS, 92%; (iii) LiHMDS, THF, 0 °C, then $R^3CH_2X$, (a) $R^1 = C_6H_5$, $R^2$ = TBDMS, $R^3$ = H, 78%, (b) $R^1 = 4\text{-}CH_3OC_6H_4$, $R^2$ = TBDMS, $R^3$ = H, 78%, (c) $R^1 = C_6H_5$, $R^2$ = TBDMS, $R^3 = C_6H_5$, 76%, (d) $R^1 = C_6H_5$, $R^2$ = TBDMS, $R^3 = CH{=}CH_2$, 67%.

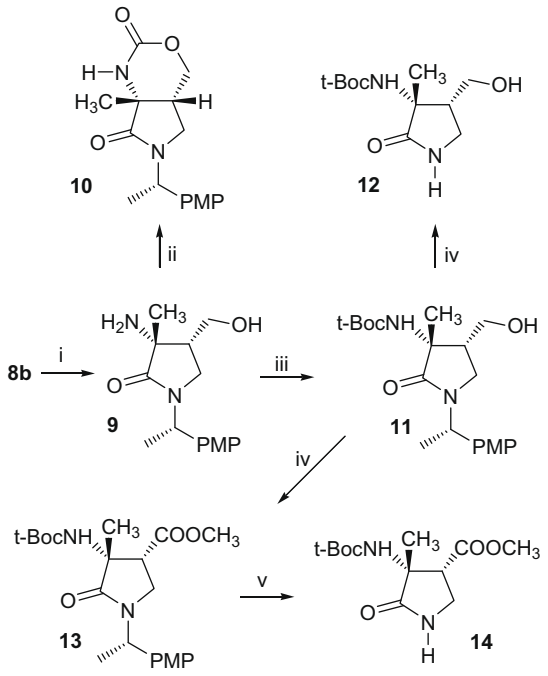
The configuration of compounds **8** was first assigned on the basis of chemical shifts and the stereochemical outcome of the reaction, leading to trisubstituted compounds **8**, exclusively, where H-4 and the alkyl substituent at C-3 are *cis*- to each other, could be ascribed to the effect of the substituent at C-4 (Scheme 2). In fact, by steric hindrance, the alkylating reagent is biased to an attack of the planar enolate anion of **7** from only the opposite side with respect to the trialkylsilyloxymethyl group at C-4.[9] In order to confirm the structural assignment, compound **8b** was first converted into **9**, which by treatment with phosgene afforded the corresponding 1,3-oxazin-2-one **10**. Next, NOE experiments were carried out on **10** in order to establish a *cis*-relationship between the methyl group and H-4 of the parent **9** (Scheme 2).

The configuration was definitively confirmed when the amino alcohol **9** was converted into the *t*-Boc derivative **11**, where a *cis*-relationship between the methyl group and H-4 was evidenced by further NOE experiments (Scheme 2). The synthetic usefulness of the chiral 3,3,4-trisubstituted pyrrolidin-2-one **11** was proven by the preparation of conformationally restricted analogues of the bioactive non-proteinogenic amino acids **2** and **4** (Scheme 3). Thus, the chiral inducer 4-methoxyphenylethyl group was removed from **11** by using CAN in MeCN–$H_2O$,[10] to give the corresponding pyrrolidin-2-one **12** analogue of α-methylhomoserine **2**.

On the other hand, the oxidation of **12**, performed by using Jones' reagent, gave **14** in very low yield. Thus, in order to circumvent this result, compound **11** was first treated with the Jones' reagent at low temperature, to give the carboxylic acid, which was converted without isolation into the methyl ester **13** by using $CH_2N_2$. Eventually, removal of the chiral inducer 4-methoxyphenylethyl group by using CAN in MeCN–$H_2O$[9] allowed us to obtain **14**, a conformationally restricted analogue of α-methylaspartic acid **4**.



**Scheme 2.** Significant NOE effects for compounds **10** and **11**.



**Scheme 3.** Reagents and conditions. (i) 6 M HCl, MeOH, rt, 76%; (ii) $COCl_2$, DCM, $NaHCO_3$, 0 °C, 83%; (iii) $Boc_2O$, $Na_2CO_3$,THF, 0 °C, 61%; (iv) CAN, MeCN–$H_2O$, rt, 82%; (v) Jones' reagent, rt, then $CH_2N_2$, 73%.

## 3. Experimental

$^1$H and $^{13}$C NMR spectra were determined on a Varian Gemini 200 spectrometer at 200 and 50.3 MHz for $^1$H and $^{13}$C, respectively, in $CDCl_3$ unless otherwise reported. Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in hertz. Diastereomeric purity was determined by g.l.c. analysis by using a Chrompack 9001 gas-chromatograph equipped with a capillary column Chrompack 7720 (50 m × 0.25 mm i.d.; stationary phase CP-Sil-5 CB). Optical rotations, $[\alpha]_D$, were recorded at room temperature on a Perkin–Elmer Model 241 polarimeter at the sodium D line (concentration in g/100 mL). MS spectral analyses were obtained on a Hewlett–Packard spectrometer model 5890, series II. Column chromatography was performed using Kieselgel 60 Merck (230–400 mesh ASTM). Tetrahydrofuran was distilled from sodium/benzophenone under an argon atmosphere. Compounds **5a** and **5b** were obtained according to Ref. 8b.

### 3.1. General procedure for the preparation of the imines 7

In a flask under an argon atmosphere, pyrrolidin-2-ones **5** (3.0 mmol), benzaldehyde (3.0 mmol), and dried molecular sieves

4 Å (0.8 g) were added to dry THF (12 mL) and the mixture was stirred for 4 h at rt. The mixture was then filtered off on Celite, and the filtrate was washed with ethyl ether (3 × 20 mL). Volatiles were evaporated under reduced pressure and the imines **6** were recovered as colorless oils which were immediately dissolved in dry THF (10 mL). Then imidazole (3.1 mmol) and *t*-butyldimethylchlorosilane (3.1 mmol) were added and the mixture was stirred at rt for 12 h. The solution was poured in $H_2O$ (20 mL) and extracted with ethyl acetate (2 × 50 mL). After drying over $Na_2SO_4$ the solvent was removed under reduced pressure to give analytically pure compounds **7**.

#### 3.1.1. (3*S*,4*R*,1′*S*)-3-Benzylideneamino-4-*t*-butyldi-methylsilyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 7a

Starting from **5a** and benzaldehyde, compound **7a** (1.2 g; 92% yield) was obtained as a colorless oil. $^1$H NMR: 0.03 (s, 2 × 3H), 0.87 (s, 9H), 1.56 (d, 3H, *J* = 7.0), 2.56–2.73 (m, 1H), 3.14 (dd, 1H, *J* = 9.2, *J* = 9.5), 3.24 (dd, 1H, *J* = 9.2, *J* = 9.5), 3.65 (dd, 1H, *J* = 1.2, *J* = 10.3), 3.67 (dd, 1H, *J* = 1.2, *J* = 10.3), 4.06 (d, 1H, *J* = 7.8), 5.51 (q, 1H, *J* = 7.0), 7.22–7.44 (m, 8 ArH), 7.71–7.82 (m, 2 ArH), 8.41 (s, 1H); $^{13}$C NMR: −5.6, 16.0, 18.0. 25.6, 42.0, 42.1, 49.4, 61.3, 71.6, 126.9, 127.3, 128.2, 128.3, 128.8, 129.5, 130.8, 135.6, 139.5, 164.6, 171.4; $[\alpha]_D$ = −218.4 (*c* 1.19, $CHCl_3$). MS (ESI): *m/z* 436.2 [$M^+$], 459.2 [M+Na]$^+$. Anal. Calcd for $C_{26}H_{36}N_2O_2Si$: C, 71.52; H, 8.31; N, 6.42. Found: C, 71.42; H, 8.37; N, 6.51.

#### 3.1.2. (3*S*,4*R*,1′*S*)-3-Benzylideneamino-4-*t*-butyldi-methylsilyloxymethyl-1-[1′-(4-methoxyphenyl)ethyl] pyrrolidin-2-one 7b

Starting from **5b** and benzaldehyde, compound **7b** (1.29 g; 92% yield) was obtained as a colorless oil. $^1$H NMR: 0.03 (s, 2 × 3H), 0.88 (s, 9H), 1.53 (d, 3H, *J* = 7.0), 2.54–2.75 (m, 1H), 3.13 (dd, 1H, *J* = 9.2, *J* = 9.5), 3.22 (dd, 1H, *J* = 9.2, *J* = 9.5), 3.64 (dd, 1H, *J* = 1.2, *J* = 10.3), 3.68 (dd, 1H, *J* = 1.2, *J* = 10.3), 3.81 (s, 3H, $OCH_3$), 4.05 (d, 1H, *J* = 7.7), 5.47 (q, 1H, *J* = 7.0), 6.88 (d, *J* = 8.8, 2 ArH), 7.28 (d, *J* = 8.8, 2 ArH), 7.35–7.72 (m, 5 ArH), 8.40 (s, 1H); $^{13}$C NMR: −5.6, 16.2, 18.0. 25.6, 42.0, 42.2, 49.0, 55.1, 61.5, 71.7, 113.7, 128.1, 128.2, 128.3, 128.4, 128.9, 129.6, 130.8, 131.7, 134.3, 135.8, 158.8, 164.6, 171.3; $[\alpha]_D$ = −230.7 (*c* 1.04, $CHCl_3$). MS (ESI): *m/z* 466.3 [$M^+$], 489.3 [M+Na]$^+$. Anal. Calcd for $C_{27}H_{38}N_2O_3Si$: C, 69.49; H, 8.21; N, 6.00. Found: C, 69.42; H, 8.13; N, 6.06.

### 3.2. General procedure for the alkylation of imines 7a,b

To a solution of imine **7a** or **7b** (1.0 mmol) in dry THF (8 mL), LiHMDS (1.0 M solution in hexanes; 1.1 mL; 1.1 mmol) was added dropwise at 0 °C. After stirring for 1 h, a solution of the appropriate halide (1.1 mmol) dissolved in dry THF (3 mL) was added at 0 °C and the mixture was stirred for a further 2 h. Then the reaction mixture was poured in $H_2O$ (100 mL) and extracted with ethyl acetate (3 × 100 mL). The organic layer was dried ($Na_2SO_4$) and evaporated to give the pure pyrrolidin-2-ones **8a**–**d**.

#### 3.2.1. (3*R*,4*R*,1′*S*)-3-Benzylideneamino-4-*t*-butyldimethylsilyloxymethyl-3-methyl-1-(1′-phenylethyl)pyrrolidin-2-one 8a

Starting from **7a** and methyl iodide, compound **8a** (0.35 g; 78% yield) was obtained as a colorless oil. $^1$H NMR: −0.01 (s, 3H), 0.00 (s, 3H), 0.84 (s, 9H), 1.50 (s, 3H), 1.52 (d, 3H, *J* = 7.0), 2.27–2.42 (m, 1H), 3.04 (dd, 1H, *J* = 7.4, *J* = 9.3), 3.14 (dd, 1H, *J* = 8.6, *J* = 9.3), 3.69 (dd, 1H, *J* = 8.3, *J* = 10.4), 4.01 (dd, 1H, *J* = 6.2, *J* = 10.4), 5.49 (q, 1H, *J* = 7.0), 7.18–7.43 (m, 8 ArH) 7.66–7.78 (m, 2 ArH), 8.46 (s, 1H); $^{13}$C NMR: −5.4, 16.2, 18.0, 21.7, 25.7, 42.8, 47.5, 49.2, 61.5, 68.1, 126.7, 127.3, 128.0, 128.3, 128.4, 128.8, 129.5, 130.6, 136.4, 140.0, 159.7, 173.9; $[\alpha]_D$ = −6.7 (*c* 0.74, $CHCl_3$); MS (ESI): *m/z* 450.3 [$M^+$], 473.3 [M+Na]$^+$. Anal. Calcd for $C_{27}H_{38}N_2O_2Si$: C, 71.95; H, 8.50; N, 6.22. Found: C, 71.85; H, 8.44; N, 6.29.

#### 3.2.2. (3*R*,4*R*,1′*S*)-3-Benzylideneamino-4-*t*-butyldi-methylsilyloxymethyl-1-[1′-(4-methoxyphenyl)ethyl]-3-methylpyrrolidin-2-one 8b

Starting from **7b** and methyl iodide, compound **8b** (0.37 g; 78% yield) was obtained as a colorless oil. $^1$H NMR: −0.01 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 1.49 (d, 3H, *J* = 7.0), 1.50 (s, 3H), 2.22–2.41 (m, 1H), 3.02 (dd, 1H, *J* = 7.8, *J* = 9.4), 3.14 (dd, 1H, *J* = 8.6, *J* = 9.4), 3.69 (dd, 1H, *J* = 7.9, *J* = 11.3), 3.82 (s, 3H), 4.01 (dd, 1H, *J* = 6.2, *J* = 11.3), 5.45 (q, 1H, *J* = 7.0), 6.88 (d, 2 ArH, *J* = 8.6), 7.24 (d, 2 ArH, *J* = 8.6), 7.31–7.45 (m, 3 ArH) 7.71–7.77 (m, 2 ArH), 8.46 (s, 1H); $^{13}$C NMR: −5.8, 16.0, 17.7, 21.4, 25.4, 42.3, 47.2, 48.5, 54.7, 61.2, 67.9, 113.4, 127.6, 127.8, 128.0, 128.5, 129.2, 130.3, 131.7, 136.2, 158.4, 159.4, 173.5; $[\alpha]_D$ = −17.5 (*c* 1.14, $CHCl_3$); MS (ESI): *m/z* 480.3 [$M^+$], 503.3 [M+Na]$^+$. Anal. Calcd for $C_{28}H_{40}N_2O_3Si$: C, 69.96; H, 8.39; N, 5.83. Found: C, 81.11; H, 7.28; N, 3.47.

#### 3.2.3. (3*R*,4*R*,1′*S*)-3-Benzyl-3-benzylideneamino-4-*t*-butyldi-methylsilyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 8c

Starting from **7a** and benzyl bromide, **8c** (0.32 g; 76% yield) was obtained as a colorless oil. $^1$H NMR: −0.01 (s, 3H), 0.01 (s, 3H), 0.86 (s, 9H), 1.47 (d, 3H, *J* = 7.0), 2.39–2.59 (m, 1H), 2.76 (dd, 1H, *J* = 7.9, *J* = 9.4), 2.94 (dd, 1H, *J* = 9.0, *J* = 9.4), 3.06 (d, 1H, *J* = 12.9), 3.39 (d, 1H, *J* = 12.9), 3.66 (dd, 1H, *J* = 7.8, *J* = 10.1), 4.01 (dd, 1H, *J* = 6.8, *J* = 10.1), 5.48 (q, 1H, *J* = 7.0), 6.95–7.06 (m, 2 ArH), 7.14–7.49 (m, 11 ArH) 7.73–7.82 (m, 2 ArH), 8.63 (s, 1H); $^{13}$C NMR: −5.5, 16.3, 18.2, 25.8, 41.0, 42.7, 48.9, 53.1, 61.7, 72.2, 126.3, 126.4, 126.8, 127.0, 128.0, 128.2, 128.4, 128.6, 128.8, 128.9, 129.2, 129.5, 130.7, 131.0, 136.5, 136.9, 139.7, 159.9, 172.6; $[\alpha]_D$ = −22.7 (*c* 1.25, $CHCl_3$); MS (ESI): *m/z* 526.3 [$M^+$], 549.3 [M+Na]$^+$. Anal. Calcd for $C_{33}H_{42}N_2O_2Si$: C, 75.24, H, 8.04; N, 5.32. Found: C, 75.30; H, 7.98; N, 5.27.

#### 3.2.4. (3*R*,4*R*,1′*S*)-3-Allyl-3-benzylideneamino-4-*t*-butyldimethylsilyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 8d

Starting from **7a** and allyl bromide, **8d** (0.32 g; 67% yield) was obtained as a colorless oil. $^1$H NMR: 0.00 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 1.51 (d, 3H, *J* = 7.0), 2.51–2.68 (m, 3H), 2.62 (dd, 1H, *J* = 8.2, *J* = 8.5), 3.05 (dd, 1H, *J* = 4.1, *J* = 8.5), 3.69 (dd, 1H, *J* = 8.3, *J* = 10.1), 4.05 (dd, 1H, *J* = 6.0, *J* = 10.1), 5.11–5.22 (m, 2H), 5.52 (q, 1H, *J* = 7.0), 5.68–5.92 (m, 1H), 7.21–7.44 (m, 8 ArH), 7.68–7.75 (m, 2 ArH), 8.54 (s, 1H); $^{13}$C NMR: −5.6, 16.2, 18.1, 25.7, 40.1, 42.4, 42.9, 49.1, 61.8, 70.8, 119.0, 126.7, 126.8, 127.0, 127.2, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 130.6, 133.4, 136.4, 139.9, 160.0, 172.7; $[\alpha]_D$ = −31.7 (*c* 1.5, $CHCl_3$); MS (ESI): *m/z* 476.3 [$M^+$], 499.3 [M+Na]$^+$. Anal. Calcd for $C_{29}H_{40}N_2O_2Si$: C, 73.06; H, 8.46; N, 5.88. Found: C, 73.00; H, 8.38; N, 5.82.

### 3.3. (3*R*,4*R*,1′*S*)-3-Amino-4-hydroxymethyl-1-[1′-(4-methoxyphenyl)ethyl]-3-methylpyrrolidin-2-one 9

To a solution containing pyrrolidin-2-one **8b** (0.48 g; 1.0 mmol) in methanol (3.0 mL), 6 M HCl (1.0 mL) was added and the mixture was stirred for 12 h at rt. The volatiles were removed under reduced pressure, after which ethyl acetate (25 mL) and 3 M NaOH (10 mL) were added to the residue and the aqueous layer was further extracted with ethyl acetate (2 × 25 mL). After drying over $Na_2SO_4$, removal of the solvent gave compound **9** (0.21 g; 76% yield) as a clear oil. $^1$H NMR: 1.28 (s, 3H), 1.52 (d, 3H, *J* = 7.1), 2.05–2.17 (m, 1H), 2.87–3.04 (m, 2H), 3.06 (br s, $NH_2$+OH), 3.67 (d, 2H, *J* = 6.1), 3.78 (s, 3H), 5.39 (q, 1H, *J* = 7.1), 6.87 (d, 2 ArH, *J* = 8.7), 7.20 (d, 2 ArH, *J* = 8.7); $^{13}$C NMR: 15.6, 26.2, 41.6, 43.1, 48.6, 54.9, 58.9, 62.0, 118.6, 127.8, 131.3, 158.6, 176.0; $[\alpha]_D$ = −110.0 (*c* 0.54, $CHCl_3$); MS (ESI): *m/z* 278.2 [$M^+$], 301.2 [M+Na]$^+$. Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.67; H, 8.04; N, 9.98.

### 3.4. (4a*R*,7a*R*,1'*S*)-6-[-1-(4-Methoxyphenyl)ethyl]-7a-methyl-hexahydropyrrolo[3,4-d][1,3]oxazine-2,7-dione 10

To a mixture of DCM (5 mL) containing compound **9** (0.3 g; 1.1 mmol) and saturated $NaHCO_3$, (5 mL) phosgene (1.9 M in toluene, 0.85 mL; 1.62 mmol) was added at 0 °C. After 15 min the mixture was extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over $Na_2SO_4$ and after removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 6:4) to give **10** (0.27 g; 83% yield) as a colorless oil. $^1$H NMR: 1.37 (s, 3H), 1.48 (d, 3H, *J* = 6.8), 2.35–2.43 (m, 1H), 3.06 (dd, 1 H, *J* = 10.0, *J* = 14.0), 3.11 (dd, 1H, *J* = 6.4, *J* = 14.0), 3.76 (s, 3H), 4.02 (dd, 1H, *J* = 9.2, *J* = 15.6), 4.27 (dd, 1H, *J* = 5.6, *J* = 15.6), 5.38 (q, 1H, *J* = 6.8), 5.74 (s, 1H, NH), 6.84 (d, 2 ArH, *J* = 8.8), 7.16 (d, 2 ArH, *J* = 8.8); $^{13}$C NMR: 15.8, 23.7, 29.6, 35.1, 40.4, 49.0, 55.2, 59.4, 64.9, 113.8, 128.0, 130.8, 152.9, 158.9, 171.9; $[\alpha]_D = -108.2$ (*c* 1.04, $CHCl_3$); MS (ESI): *m/z* 304.1 [$M^+$], 327.1 [M+Na]$^+$. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.20; H, 6.69; N, 9.16.

### 3.5. (3*R*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-4-hydroxy-methyl-1-[1′-(4-methoxyphenyl)ethyl]-3-methylpyrrolidin-2-one 11

To a solution of **9** (0.1 g; 0.36 mmol) in THF (5 mL) at 0 °C, a saturated solution of $Na_2CO_3$ (2.2 mL) was added, followed by di-*t*-butyl dicarbonate (0.24 g; 1.08 mmol). After 12 h, the volatiles were removed under reduced pressure, after which $H_2O$ (10 mL) was added and the mixture was extracted with ethyl acetate (2 × 50 mL). After drying over $Na_2SO_4$ and removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 1:1) to give **11** (0.08 g; 61% yield) as a colorless oil. $^1$H NMR: 1.35 (s, 3H), 1.42 (s, 9H), 1.52 (d, 3H, *J* = 7.1), 1.55 (br s, 1H, OH), 2.33–2.49 (m, 1H), 2.87 (dd, 1H, *J* = 6.6, *J* = 10.3), 3.30 (dd, 1H, *J* = 1.2, *J* = 10.3), 3.44 (dd, 1H, *J* = 7.2, *J* = 11.3), 3.67 (dd, 1H, *J* = 5.0, *J* = 11.3), 3.78 (s, 3H), 5.28 (br s, 1H, NH), 5.37 (q, 1H, *J* = 7.1), 6.85 (d, 2 ArH, *J* = 8.7), 7.17 (d, 2 ArH, *J* = 8.7); $^{13}$C NMR: 15.6, 21.9, 28.2, 42.1, 44.2, 48.9, 55.1, 59.4, 61.2, 79.7, 119.8, 128.0, 131.4, 155.3, 158.9, 173.4; $[\alpha]_D = -125.0$ (*c* 1.16, $CHCl_3$); MS (ESI): *m/z* 378.2 [$M^+$], 401.2 [M+Na]$^+$. Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.55; H, 7.92; N, 7.46.

### 3.6. (3*R*,4*R*)-3-*t*-Butoxycarbonylamino-3-methyl-4-hydroxy methylpyrrolidin-2-one 12

To a solution of **11** (0.38 g; 1 mmol) in $CH_3CN$ (3 mL) and $H_2O$ (3 mL), CAN (1.1 g; 2 mmol) was added and the mixture was stirred for 15 min at rt. Then, a saturated $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 15 mL). After drying over $Na_2SO_4$ and removal of volatiles under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 3:7) to give product **12** (0.2 g; 82% yield) as a colorless oil. $^1$H NMR: 1.42 (s, 9H), 1.47 (s, 3H), 2.53–2.63 (m, 1H), 3.00 (br s, 1H, OH), 3.42 (d, 2H, *J* = 4.8), 3.52 (dd, 1H, *J* = 6.7, *J* = 11.1), 3.68 (dd, 1H, *J* = 4.9, *J* = 11.1), 5.27 (br s, 1H, NH), 6.70 (br s, 1H, NH); $^{13}$C NMR: 22.5, 28.2, 42.1, 46.6, 58.2, 61.2, 79.9, 155.4, 177.8; $[\alpha]_D = -50.0$ (*c* 0.6, $CHCl_3$); MS (ESI): *m/z* 244.14 [$M^+$], 267.14 [M+Na]$^+$. Anal. Calcd for $C_{11}H_{20}N_2O_4$: C, 54.08; H, 8.25; N, 11.47. Found: C, 54.98; H, 8.19; N, 11.55.

### 3.7. (3*R*,4*R*,1′*S*)-Methyl 4-*t*-butoxycarbonylamino-1-[1′-(4-methoxyphenyl)ethyl]-4-methyl-5-oxopyrrolidine-3-carboxylate 13

To a solution containing compound **11** (0.23 g; 0.6 mmol) in acetone (7 mL), the Jones' reagent (0.92 mL) was added at −15 °C and the mixture was stirred for 5 min. Then ethyl acetate (20 mL) and then saturated aqueous $Na_2CO_3$ solution (15 mL) were added at 0 °C. After extraction of the aqueous phase with ethyl acetate (50 mL), the organics were discarded and the pH of the aqueous layer raised to pH 2 by the slow addition of 1 M HCl under stirring. Then, extraction with ethyl acetate (2 × 50 mL) followed by drying over $Na_2SO_4$ and removal of the solvent under reduced pressure gave a residue which was dissolved in methanol (5 mL). This solution was treated with an ethereal solution of $CH_2N_2$ until nitrogen evolution ceased and the solvent was evaporated under reduced pressure to give a residue which was purified by silica gel chromatography (cyclohexane/acetate 70:30) affording the ester **13** (0.9 g; 73% yield) as a colorless oil. $^1$H NMR: 1.41 (s, 9H), 1.49 (s, 3H), 1.56 (d, 3H, *J* = 7.2), 2.95 (dd, 1H, *J* = 7.0, *J* = 10.2), 3.24 (dd, 1H, *J* = 2.3, *J* = 7.2), 3.45–3.53 (m, 1H), 3.66 (s, 3H), 3.79 (s, 3H), 5.18 (s, 1H, NH), 5.42 (q, 1H, *J* = 7.2), 6.86 (d, 2 ArH, *J* = 8.4), 7.19 (d, 2 ArH, J = 8.4); $^{13}$C NMR: 15.3, 22.7, 28.2, 42.3, 48.1, 49.2, 51.9, 55.2, 59.8, 79.6, 114.0, 128.2, 131.4, 154.3, 159.0, 171.4, 172.1; $[\alpha]_D = -104.5$ (*c* 1.32, $CHCl_3$); MS (EI): *m/z* 406.21 [$M^+$], 429.22 [M+Na]$^+$. Anal. Calcd for $C_{21}H_{30}N_2O_6$: C, 62.05; H, 7.44; N 6.89. Found: C, 61.93; H, 7.36; N, 6.94.

### 3.8. (3*R*,4*R*)-Methyl 4-*t*-butoxycarbonylamino-4-methyl-5-oxopyrrolidine-3-carboxylate 14

To a solution of **13** (0.13 g; 0.32 mmol) in $CH_3CN$ (3 mL) and $H_2O$ (3 mL), CAN (0.36 g; 0.65 mmol) was added and the mixture was stirred for 15 min at rt. Then, a saturated $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 15 mL). After drying ($Na_2SO_4$) and removal of volatiles under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 3:7) to give product **14** (0.12 g; 82% yield) as a colorless oil. $^1$H NMR: 1.39 (s, 9H), 1.55 (s, 3H), 3.31–3.54 (m, 2H), 3.68 (s, 3H), 3.70–3.79 (m, 1H), 5.11 (s, 1H, NH), 6.72 (s, 1H, NH); $^{13}$C NMR: 23.6, 28.1, 41.8, 50.0, 52.0, 58.2, 79.7, 154.3, 170.9, 176.2; $[\alpha]_D = -43.8$ (*c* 0.57, $CHCl_3$); MS (ESI): *m/z* 272.14 [$M^+$], 295.15 [M+Na]$^+$. Anal. Calcd for $C_{12}H_{20}N_2O_5$: C, 52.93; H, 7.40; N, 10.29. Found: C, 53.98; H, 7.29; N, 10.25.

## Acknowledgments

We thank Nanodream s.r.l. [Iesi (Ancona), Italy] for financial support whereas Dr. Antonella Monsignori and Dr. Stefania Tiburtini are acknowledged for valuable technical support.

## References

1. Adessi, C.; Soto, C. *Curr. Med. Chem.* **2002**, *9*, 963–978.
2. (a) Markovitz, D. C.; Fernstrom, J. D. *Science* **1977**, *197*, 1014–1015; (b) Berkowitz, D. B.; Smith, M. K. *J. Org. Chem.* **1995**, *60*, 1233–1238.
3. Khosla, A.; Stachowiak, K.; Smeby, R. R.; Bumpus, F. M.; Piriou, F.; Lintner, K.; Fermandjian, S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 757–760.
4. Goldsworthy, G. J.; Chung, J. S.; Simmonds, M. S. J.; Tatari, M.; Varouni, S.; Poulos, C. P. *Peptides* **2003**, *24*, 1607–1613.
5. Valle, G.; Crisma, M.; Toniolo, C.; Beisswenger, R.; Rieker, A.; Jung, G. *J. Am. Chem. Soc.* **1989**, *111*, 6828–6833.
6. Altmann, K.-H.; Altmann, E.; Mutter, M. *Helv. Chim. Acta* **1992**, *75*, 1198–1210.
7. Perdih, A.; Kikelj, D. *Curr. Med. Chem* **2006**, *13*, 1525–1556.
8. See, for examples: (a) Galeazzi, R.; Martelli, G.; Orena, M.; Rinaldi, S.; Sabatino, P. *Tetrahedron* **2005**, *61*, 5465–5473; (b) Galeazzi, R.; Martelli, G.; Natali, D.; Orena, M.; Rinaldi, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1779–1787; (c) Galeazzi, R.; Marcucci, E.; Martelli, G.; Mobbili, G.; Natali, D.; Orena, M.; Rinaldi, S. *Eur. J. Org. Chem.* **2007**, 4402–4407.
9. Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Panagiotaki, M. *Heterocycles* **2003**, *60*, 2485–2498.
10. For reviews on CAN catalyzed reactions: (a) Nair, V.; Panicker, S. B.; Nair, L. G. *Synlett* **2003**, 156–165; (b) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21–30.