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ORIGINAL ARTICLE

Synthesis of a cyclic isostere of α-methyl homoserine by a stereoselective acylation–alkylation sequence of a chiral γ-lactam

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Abstract Starting from a chiral 4-hydroxymethyl pyrrolidin-2-one, an isostere of α-methyl homoserine tethered on a γ-lactam ring was prepared exploiting a stereoselective acylation–methylation sequence, followed by Curtius rearrangement, and structural assignment was confirmed by n.O.e. experiments. By reverting the sequence, the 3-carboxy-3-methyl derivative having the opposite configuration at C-3 was obtained with total stereoselection, but Curtius rearrangement invariably afforded only inseparable mixtures of decomposition products.

Keywords Conformational constriction · Amino acids · Lactams · Alkylation · Stereoselection

Introduction

Biologically active peptides are molecules endowed with high therapeutic potential. However, they are scarcely used as drugs owing to their conformational flexibility that contributes to their promiscuous selectivity, high proteolytic susceptibility, limited cellular permeability, low bioavailability, and fast clearance (Hanessian and Auzzas 2008). Structural rigidification through lactam ring (Freidinger 2003; Perdih and Kikelj 2006; Dolbeare et al. 2003; Galaud and Lubell 2005; Broadrup et al. 2005; Seufert et al. 2006; Otvos et al. 2007; Jamieson et al. 2009; Lesma et al. 2009; Virlouvet and Podlech 2010; St-Cyr et al. 2010; Boy et al. 2011) or quaternary carbon introduction (Benedetti 1996; Toniolo et al. 2001; Sagan et al. 2004; Crisma et al. 2006; Feng et al. 2007; Storcken et al. 2007; Calaza and Cativiela 2008; Cativiela and Ordoñez 2009; Balducci et al. 2010; Nguyen et al. 2010; Iosub et al. 2010; Lu and Lin 2011; Ilies et al. 2011; Weber et al. 2012; Hugelshofer et al. 2013) represents one of the promising strategies to preferentially stabilize an ensemble of closely related bioactive conformations. Such modifications may lead to enhanced potency, better selectivity, and improvement on many of the above-mentioned shortcomings and, therefore, are largely employed within development of peptide-based therapeutics.

Within this topic, we already reported about the stereoselective synthesis of isosteres of proteinogenic amino acids, and the chiral pyrrolidin-2-one **1** was the key intermediate for preparation of **2**, a cyclic isostere of β-homoserine (Galeazzi et al. 2005). Moreover, alkylation of pyrrolidin-2-one **1** allowed to obtain in good yield and total stereoselection compounds **3** and **4,** the isosteres of (*R*)-2-methyl-β-homoserine (Martelli et al. 2010) and (*R*)-2-methylaspartic acid (Crucianelli et al. 2010), respectively (Scheme 1).

Results and discussion

We disclose here a novel approach to *ent*-**3**, already prepared in our laboratory (Galeazzi et al. 2003), exploiting a stereoselective acylation–alkylation sequence starting from the hydroxymethyl derivative **5** (Scheme 2).

Thus, the TIPS-derivative **6** was treated with LiTMP, followed by methyl chloroformate, to give in good yield and nearly total stereoselection the acylated product **7**. We were delighted to observe that the TIPS group was essential for *trans* stereoselection, since when less sterically demanding groups such as Bn or TBDMS were employed,

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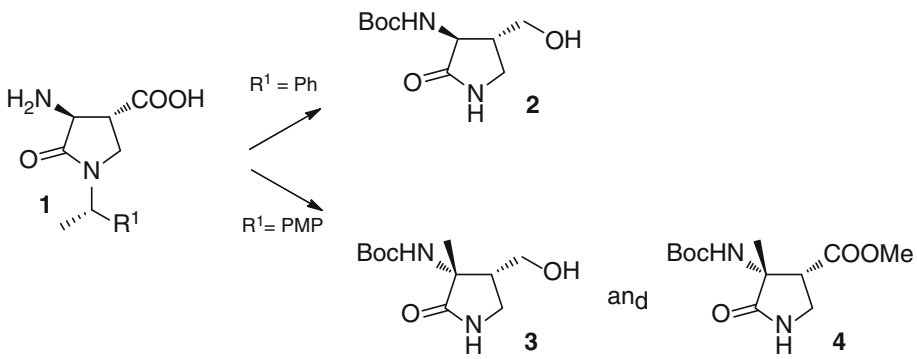
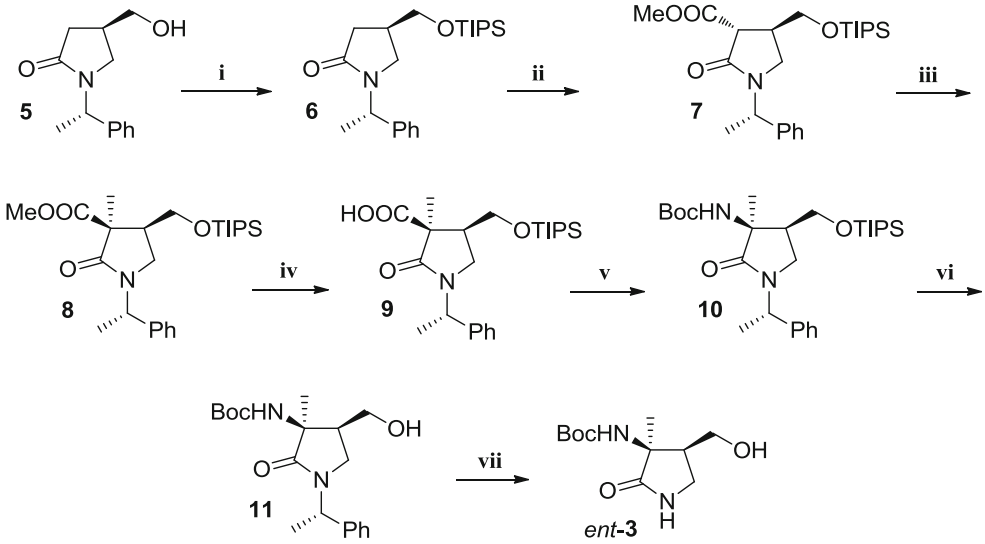
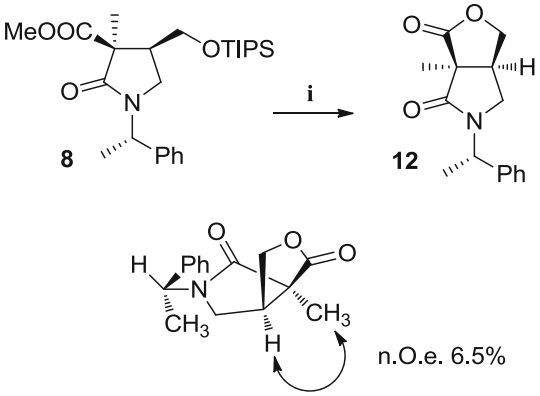
Scheme 1 Isosteres prepared from lactam **1**



Scheme 2 Reagents and conditions: **i** TIPSCl, imidazole, DCM, 72 %; **ii** LiTMP, THF, 0 °C, then MeOOCCl, THF, 0 °C, 86 %; **iii** *n*-BuLi, THF, 0 °C, then MeI, 72 %; **iv** 2 M NaOH, MeOH, 50 °C, then 0.2 M HCl, 95 %; **v** DPPA, *t*-BuOH, Et_3N, 70 °C, 46 %; **vi** 3 M HCl, MeOH, 50 °C, then 2 M NaOH, quantitative yield; **vii** Li, NH_3, −78 °C, 82 %



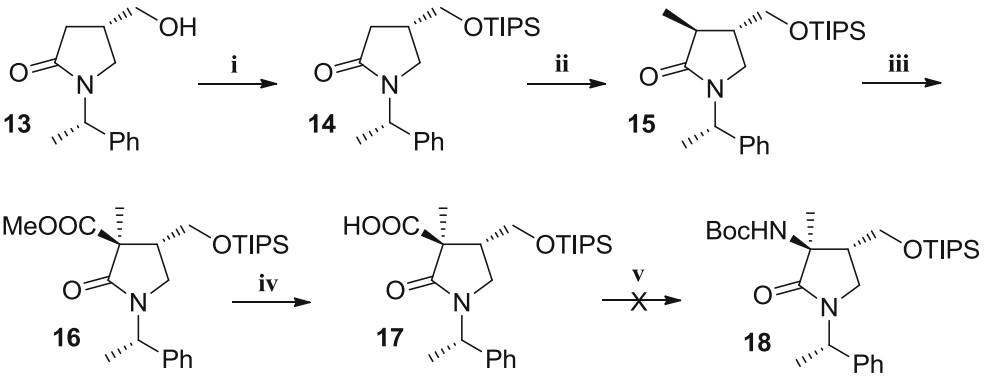


Scheme 3 Reagents and conditions: **i** $LiOH{\cdot}H_2O$ at reflux, MeOH, then 0.1 M HCl, 64 %

the acylation reaction afforded mixtures in 60:40 and 90:10 *trans:cis* dr, respectively (Orena unpublished observations). Then, metalation of **7** with *n*-BuLi, followed by addition of methyl iodide, allowed to introduce the methyl group at C-3 in moderate yield but with total stereoselection. In fact, compound **8** was isolated as the sole isomer, and its configuration was unambiguously ascertained after conversion into the corresponding lactone **12**, where the *cis*-relationship between the hydrogen at C-4 and the methyl group at C-3, expected from mechanistic considerations, was confirmed on the basis of n.O.e. experiments (Scheme 3).

Having compound **8** in hands, hydrolysis under basic conditions gave the carboxylic acid **9** that by reaction with DPPA in t-BuOH was converted into the carbamate **10** in moderate yield. Since prolonged treatment of **10** with fluoride anion was not effective for removal of the silyl ether, cleavage was carried out under acidic conditions, to give compound **11** where *N*-Boc group remained unaffected, probably owing to steric congestion at the quaternary center. Eventually, by treatment with Li in NH_3, the chiral inducer phenylethyl group was easily removed, and the isostere *ent*-**3** was recovered in good yield.

With the aim of preparing also the 3,4-*trans*-3,3,4-trisubstituted compound **18**, again displaying (3*S*) configuration, we envisaged a synthetic strategy starting from hydroxymethyl derivative **13** (Galeazzi et al. 2003), exploiting reversal of the above-reported acylation–methylation sequence (Scheme 4).



Scheme 4 Reagents and conditions: **i** TIPSCl, imidazole, DCM, 85 %; **ii** *n*-BuLi, THF, −15 °C, then MeI, THF, −15 °C, 71 %; **iii** *n*-BuLi, THF, −15 °C, then MeOOCCl, THF, −15 °C, 46 %; **iv** 2 M NaOH, MeOH, 50 °C, then 0.2 M HCl, 98 %; **v** DPPA, *t*-BuOH, Et_3N, 70 °C, complex inseparable mixture, product **18** was missing

In fact, the silyl derivative **14**, after conversion into its lithium enolate was treated with methyl iodide to afford product **15** in good yield and with total *trans* stereoselection. Metalation at C-3 followed by addition of methyl chloroformate afforded the ester **16** in low yield, albeit with total *trans* stereoselection. After basic hydrolysis, the acid **17** was isolated in excellent yield but, in spite of many attempts carried out under different reaction conditions, and in contrast to the favorable results obtained starting from **9**, all rearrangement reactions mediated by DPPA led to complex mixtures of products, from which no identifiable material could be isolated. Thus, since both the starting acid **17** and the acylazide intermediate, initially generated by the reaction with DPPA, were missing, extended decomposition was reasonably attributed to side reactions of either the acylnitrene or the subsequent isocyanate intermediate.

Conclusions

In summary, the 2-methylhomoserine constrained isostere *ent*-**3** was prepared exploiting a totally stereoselective acylation–alkylation sequence. Although we planned to synthesize also lactam **18**, key intermediate to a diastereomer of **3**, we were not able to achieve this goal owing to the unexpected behavior of compound **17** that decomposed under the reaction conditions. Thus, to make available all four stereoisomers of **3** a totally different approach was envisaged, and synthetic procedures currently underway will be reported in due course.

Experimental

^1H and ^{13}C NMR spectra were determined on a Varian Gemini 200 spectrometer at 200 and 50 MHz for ^1H 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. 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). LC electrospray ionization mass spectra were obtained with an Agilent Technologies MSD1100 single-quadrupole mass spectrometer, eluting samples in MeOH. Elemental analyses were performed with a Carlo Erba CHN Elemental Analyzer. Column chromatography was performed using Kieselgel 60 Merck (230–400 mesh ASTM). Tetrahydrofuran and dichloromethane were distilled from sodium-benzophenone and CaH_2, respectively, under an argon atmosphere. Compounds **5** and **13** were obtained according to Galeazzi et al. (2003).

Synthesis of silyl ethers **6** and **14**: general procedure

To a solution of 4-hydroxymethyl pyrrolidin-2-ones **5** or **13** (1.25 g, 5.73 mmol) dissolved in dry DCM (6 mL) at rt under inert atmosphere, imidazole (430 mg, 6.3 mmol) and TIPSCl (1.3 mL, 6.3 mmol) were added. After 8 h, the reaction mixture was poured into H_2O-ice and extracted with ethyl acetate (3 × 50 mL). The organic layer was dried (Na_2SO_4) and volatiles removed under reduced pressure. The residue was then purified on silica gel (cyclohexane:ethyl acetate 80:20) to give the corresponding silyl ethers **6** and **14** as colorless oils.

(*R*)-1-((*S*)-1-Phenylethyl)-4-(((triisopropylsilyl)oxy) methyl)pyrrolidin-2-one, **6**

Compound **6** (1.55 g, 72 % yield): ^1H NMR (200 MHz, $CDCl_3$): δ 0.96 (m, 21H), 1.52 (d, $J = 7.4$, 3H), 2.18–2.33 (m, 1H), 2.44–2.59 (m, 2H), 2.89 (dd, $J = 4.8$, $J = 10.0$, 1H), 3.36 (dd, $J = 7.6$, $J = 10.0$, 1H), 3.40–3.57 (m, 2H), 5.50 (q, $J = 7.4$, 1H), 7.18–7.27 (m, 5 ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.7, 16.0, 17.8, 33.5, 34.0, 44.4, 48.8, 64.5, 127.0, 127.3, 128.4, 140.0, 173.6. $[\alpha]_D$ 81.8 (c 1.1, $CHCl_3$). MS (ESI): *m/z* 375.4 $[M]^+$, 398.4 $[M + Na]^+$. Anal. calcd for $C_{22}H_{37}NO_2Si$: C 70.35; H 9.93; N 3.73. Found: C, 70.25; H, 9.84; N, 3.69.

(3*R*,4*R*)-Methyl 2-oxo-1-((*S*)-1-phenylethyl)-4-(((triisopropylsilyl)oxy)methyl)pyrrolidine-3-carboxylate, **7**

Compound **6** (1.02 g, 2.7 mmol) was dissolved in dry THF (10 mL) under inert atmosphere at 0 °C and tetramethylpiperidine (0.5 mL, 2.9 mmol) and *n*-BuLi (5.2 mmol, 5.2 mL of a 1 M solution in hexane) were sequentially added. After 15 min methyl chloroformate (0.22 mL, 2.9 mmol) was slowly added and the mixture was stirred for 15 min at 0 °C. After quick sequential addition of H_2O (100 mL) and ethyl acetate (100 mL), the organic phase was separated, and then the aqueous phase was extracted with additional ethyl acetate (2 × 100 mL). The organic layers were dried (Na_2SO_4) and volatiles were removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 90:10) to give compound **7** in 86 % yield (1.01 g, 2.3 mmol) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (m, 21H), 1.54 (d, $J = 7.4$, 3H), 2.78–2.92 (m, 2H), 3.38–3.46 (m, 2H), 3.50–3.61 (m, 2H), 3.79 (s, 3H), 5.49 (q, $J = 7.4$, 1H), 7.24–7.30 (m, 5ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.7, 15.9, 17.8, 38.1, 42.8, 49.5, 51.2, 52.5, 63.0, 127.0, 127.3, 127.5, 128.5, 139.5, 168.7, 170.3. $[\alpha]_D$ −25.0 (c 1, $CHCl_3$). MS (ESI): *m/z* 433.3 $[M]^+$, 456.3 $[M + Na]^+$. Anal. calcd for $C_{24}H_{39}NO_4Si$: C, 66.47; H, 9.06; N, 3.23. Found: C, 66.38; H, 9.00; N, 3.18.

(3*S*,4*R*)-Methyl 3-methyl-2-oxo-1-((*S*)-1-phenylethyl)-4-(((triisopropylsilyl)oxy)methyl)pyrrolidine-3-carboxylate, **8**

To a solution of compound **7** (1.01 g, 2.3 mmol) in dry THF (10 mL) under inert atmosphere at 0 °C, *n*-BuLi (2.5 mmol, 2.5 mL of a 1 M solution in hexane) was added and the mixture was stirred for 15 min at 0 °C. Then, methyl iodide (156 μL, 2.5 mmol) was added and the mixture was stirred for a further 10 min at 0 °C. After quick sequential addition of H_2O (100 mL) and ethyl acetate (100 mL), the organic phase was separated, and then the aqueous phase was extracted with additional ethyl acetate (2 × 100 mL). The organic layers were dried (Na_2SO_4) and volatiles were removed under reduced pressure. The residue was eventually purified by silica gel chromatography (cyclohexane:ethyl acetate 80:20) to give the title product **8** (745 mg; 72 % yield) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98 (m, 21H), 1.49 (s, 3H), 1.57 (d, $J = 7.2$, 3H), 2.35–2.47 (m, 1H), 2.77 (dd, $J = 9.0$, $J = 9.6$, 1H), 3.29 (dd, $J = 8.0$, $J = 9.6$, 1H), 3.46 (dd, $J = 8.0$, $J = 10.0$, 1H), 3.55 (s, 3H), 3.73 (dd, $J = 6.6$, $J = 10.0$, 1H), 5.55 (q, $J = 7.2$, 1H), 7.29–7.36 (m, 5 ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.6, 15.7, 17.5, 17.7, 20.5, 43.5, 45.7, 49.6, 53.1, 55.3, 61.8, 126.4, 126.7, 127.3, 128.0, 128.5, 138.7, 173.2, 173.9. $[\alpha]_D$ −70.8 (c 1, $CHCl_3$). MS (ESI): *m/z* 447.3 $[M]^+$, 470.4 $[M + Na]^+$. Anal. calcd for $C_{25}H_{41}NO_4Si$: C, 67.07; H, 9.23; N, 3.13. Found: C, 66.98; H, 9.10; N, 3.19.

(3*S*,4*R*)-3-Methyl-2-oxo-1-((*S*)-1-phenylethyl)-4-(((triisopropylsilyl)oxy)methyl)pyrrolidine-3-carboxylic acid, **9**

To a solution containing the ester **8** (675 mg, 1.5 mmol) in MeOH (8 mL) 2 M NaOH (8 mL) was added at rt. The mixture was heated at 50 °C for 3 h and then, after cooling to rt, 0.2 M HCl (85 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 50 mL) and the organic layer was dried (Na_2SO_4). Solvents were removed under reduced pressure and the title product **9** was recovered (620 mg; 95 % yield) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (m, 21H), 1.53 (s, 3H), 1.56 (d, $J = 7.2$, 3H), 2.34–2.36 (m, 1H), 3.05 (dd, $J = 4.8$, $J = 10.2$, 1 H), 3.39 (dd, $J = 7.4$, $J = 10.2$, 1H), 3.52 (dd, $J = 8.2$, $J = 9.8$, 1H), 3.79 (dd, $J = 5.0$, $J = 9.8$, 1H), 5.44 (q, $J = 7.2$, 1H), 7.26–7.34 (m, 5 ArH), 9.17 (bs, 1H, COOH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.4, 15.9, 17.3, 17.5, 20.6, 43.5, 45.7, 49.6, 53.1, 61.9, 126.6, 126.9, 127.2, 128.1, 128.3, 138.5, 173.4, 173.8. $[\alpha]_D$ −40.1 (c 1, $CHCl_3$). MS (ESI): *m/z* 433.4 $[M]^+$, 456.4 $[M + Na]^+$. Anal. calcd for $C_{24}H_{39}NO_4Si$: C, 66.47; H, 9.06; N, 3.23. Found: C, 66.43; H, 9.11; N, 3.17.

tert-Butyl ((3*S*,4*S*)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)-4-(((triisopropylsilyl)oxy)methyl)pyrrolidin-3-yl)carbamate, **10**

To a solution containing compound **9** (319 mg, 1.05 mmol) in *t*-BuOH (3 mL), DPPA (363 μL, 1.68 mmol) and Et_3N (234 μL, 1.68 mmol) were added and the mixture was heated at 70 °C for 8 h. After cooling, water (15 mL) was added, and then the mixture was extracted with ethyl acetate (2 × 30 mL). The organic layer was dried (Na_2SO_4), solvents were removed under reduced pressure, and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 70:30) to give compound **10** (245 mg, 46 % yield) as colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (m, 21H), 1.51 (s, 3H), 1.53 (d, $J = 7.4$, 3H), 2.51–2.70 (m, 1H), 3.10 (dd, $J = 9.5$, $J = 9.8$, 1H), 3.21–3.50 (m, 2H), 3.58 (dd, $J = 4.6$, $J = 9.8$, 1H), 5.39 (q, $J = 7.4$, 1H), 5.72 (s, 1H, NH), 7.19–7.35 (m, 5 ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.8, 16.1, 17.8, 20.2, 43.6, 46.7, 49.5, 51.8, 54.1, 62.4, 127.3, 127.4, 128.2, 128.5, 139.3, 171.1, 173.0. $[\alpha]_D$ 48.4 (c 0.6, $CHCl_3$). MS (ESI): *m/z* 504.3 $[M]^+$, 527.3 $[M + Na]^+$. Anal. calcd for $C_{28}H_{48}N_2O_4Si$: C, 66.62; H, 9.58; N, 5.55. Found: C, 66.53; H, 9.51; N, 5.47.

t-Butyl ((3*S*,4*S*)-4-(hydroxymethyl)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)carbamate, **11**

To a solution containing compound **10** (218 mg, 0.43 mmol) in MeOH (1.0 mL), 3 M HCl (1.0 mL) was added and the mixture was stirred at 50 °C for 1.5 h and then at rt for 12 h. After addition of 2 M NaOH (2 mL), the mixture was extracted with ethyl acetate (2 × 20 mL), the organic layer was dried (Na_2SO_4), and removal of volatiles under reduced pressure gave a residue that after silica gel chromatography (cyclohexane:ethyl acetate 50:50) afforded product **11** (140 mg, 95 %yield) as a viscous colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.47 (s, 3H), 1.55 (d, $J = 7.4$, 3H), 2.42–2.54 (m, 1H), 2.70 (dd, $J = 3.2$, $J = 10.6$, 1 H), 3.44 (dd, $J = 7.2$, $J = 10.6$, 1H), 3.74 (dd, $J = 8.6$, $J = 11.8$, 1H), 4.09 (dd, $J = 4.8$, $J = 11.8$, 1H), 5.45 (q, $J = 7.4$, 1H), 5.48 (br s, 1H, NH), 7.18–7.39 (m, 5 ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.1, 15.5, 17.5, 23.6, 34.9, 40.2, 49.2, 59.3, 64.7, 126.7, 127.8, 128.2, 128.3, 138.5, 153.0, 172.4. $[\alpha]_D$ −86.7 (c 1.5, $CHCl_3$). MS (ESI): *m/z* 348.2 $[M]^+$, 371.2 $[M + Na]^+$. Anal. calcd for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.43; H, 8.01; N, 8.13.

t-Butyl ((3*S*,4*S*)-4-(hydroxymethyl)-3-methyl-2-oxopyrrolidin-3-yl)carbamate, ent-**3**

Ammonia (about 4 mL) was condensed in a three-necked flask at −78 °C, Li shots (14 mg, 2.0 mmol) were added, and the blue solution was stirred at this temperature for 20 min. Then compound **11** (105 mg, 0.3 mmol) was dissolved in a mixture of dry THF (0.9 mL) and t-BuOH (0.1 mL), and the solution added in one portion. After 3 min, the reaction mixture was quenched by addition of solid NH_4Cl (200 mg) and warmed to room temperature. Then ammonia was removed, ethyl acetate (10 mL) and water (3 mL) added, the mixture extracted with ethyl acetate (2 × 20 mL) and the combined organic layers dried over Na_2SO_4. After the solvent was removed in vacuo, the crude product was purified by silica gel chromatography (cyclohexane:ethyl acetate 40:60 as eluent) to give *ent*-**3** (60 mg, 82 % yield) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.47 (s, 3H), 2.53–2.63 (m, 1H), 3.00 (br s, 1H, OH), 3.42 (d, $J = 4.8$, 2H), 3.52 (dd, $J = 6.7$, $J = 11.1$, 1H), 3.68 (dd, $J = 4.9$, $J = 11.1$, 1H), 5.27 (br s, 1H, NH), 6.70 (br s, 1H, NH).^{13}C NMR (50 MHz, $CDCl_3$): δ 22.5, 28.2, 42.1, 46.6, 58.2, 61.2, 79.9, 155.4, 177.8. $[\alpha]_D$ 49.6 (c 0.6, $CHCl_3$) [Lit. −50.0 (c 0.6, $CHCl_3$) (Martelli et al. 2010)]. MS (ESI): *m/z* 244.3 $[M]^+$, 267.3 $[M + Na]^+$. 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.

(3a*R*,6a*S*)-6a-Methyl-5-((*S*)-1-phenylethyl)tetrahydro-1H-furo[3,4-c]pyrrole-1,6(6aH)-dione, **12**

The pyrrolidin-2-one **8** (100 mg, 0.22 mmol) was dissolved in MeOH (1 mL) containing $LiOH{\cdot}H_2O$ (0.28 mmol, 12 mg) and the mixture was refluxed for 5 h. After removal of the solvent under reduced pressure, 0.1 M HCl (2.8 mL) was added, and the mixture was extracted with ethyl acetate (3 × 5 mL). After drying (Na_2SO_4) and removal of the solvent, compound **12** (37 mg, 64 % yield) was obtained as a yellow oil. ^{1}H NMR (200 MHz,$CDCl_3$): δ 1.53 (s, 3H), 1.56 (d, $J = 7.2$ Hz, 3H), 2.76 (dd, $J = 2.1$ Hz, $J = 10.8$ Hz, 1H), 2.92 (m, 1H), 3.53 (dd, $J = 6.6$ Hz, $J = 10.8$ Hz, 1H), 3.60 (dd, $J = 6.9$ Hz, $J = 9.6$ Hz, 1H), 4.38 (dd, $J = 8.4$ Hz, $J = 9.6$ Hz, 1H), 5.50 (q, $J = 7.2$ Hz, 1H), 7.26–7.37 (m, 5H, Ar). $[\alpha]_D$ −16.3 (c 1.0, $CHCl_3$). MS (ESI): *m/z*: 259.1 $[M]^+$, 282.1 $[M + Na]^+$. Anal. calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.38; H, 6.55; N, 5.33.

(*S*)-1-((*S*)-1-Phenylethyl)-4-(((triisopropylsilyl)oxy)methyl)pyrrolidin-2-one, **14**

Compound **14** (1.83 g, 85 % yield) was obtained according to the general procedure above reported. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (m, 21H), 1.46 (d, $J = 7.2$, 3H), 2.22–2.57 (m, 3H), 3.02 (dd, $J = 8.5$, $J = 9.0$, 1H), 3.22 (dd, $J = 5.5$, $J = 9.0$, 1H), 3.55–3.66 (m, 2H), 5.53 (q, $J = 7.2$, 1H), 7.22–7.78 (m, 5 ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.0, 16.2, 18.1, 27.0, 30.3, 33.6, 34.3, 44.6, 48.9, 64.9, 127.2, 127.5, 128.6, 140.3, 173.8. $[\alpha]_D$ −60.0 (c 1.0, $CHCl_3$). MS (ESI): *m/z* 375.4 $[M]^+$, 398.4 $[M + Na]^+$. Anal. calcd for $C_{22}H_{37}NO_2Si$: C 70.35; H 9.93; N 3.73. Found: C, 70.27; H, 9.87; N, 3.66.

(3*S*,4*S*,1′*S*)-1-(1′-Phenylethyl)-3-methyl-4-triisopropylsilyloxymethylpyrrolidin-2-one, **15**

To a solution of pyrrolidin-2-one **14** (1.02 g, 2.71 mmol) in dry THF (10 mL) under inert atmosphere at −15 °C, *n*-BuLi (3 mmol, 1.87 mL of a 1.6-M solution in hexane) was added and the mixture was stirred for 15 min at −15 °C. Then, methyl iodide (181 µL, 2.9 mmol) was added and the mixture was stirred for a further 10 min at −15 °C. After addition of H_2O (100 mL) and ethyl acetate (100 mL), the organic phase was separated, and the aqueous phase was extracted with additional ethyl acetate (2 × 100 mL). The organic layers were dried (Na_2SO_4) and volatiles were removed under reduced pressure, and then the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 90:10) to give compound **15** (750 mg, 71 % yield) as colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (m, 21H), 1.22 (d, $J = 7.2$, 3H), 1.51 (d,

$J = 7.4$, 3H), 1.92–2.03 (m, 1H), 2.43 (dq, $J = 7.2$, $J = 7.4$, 1H), 2.97 (dd, $J = 8.2$, $J = 9.4$, 1H), 3.14 (dd, $J = 7.8$, $J = 9.4$, 1H), 3.64–3.78 (m, 2H), 5.55 (q, $J = 7.4$, 1H), 7.19–7.41 (m, 5 ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.8, 15.4, 15.9, 17.9, 39.2, 42.7, 42.8, 48.7, 63.4, 126.8, 126.9, 127.2, 128.3, 140.3, 176.2. $[\alpha]_D$ −94.4 (c 1, $CHCl_3$). MS (ESI): *m/z* 389.3 $[M]^+$, 412.3 $[M + Na]^+$. Anal. calcd for $C_{23}H_{39}NO_2Si$: C, 70.90; H, 10.09; N, 3.59. Found: C, 70.76; H, 9.97; N, 3.51.

(3*S*,4*S*,1′*S*)-1-(1′-Phenylethyl)-3-methyl-3-methoxycarbonyl-4-triisopropylsilyloxymethylpyrrolidin-2-one, **16**

To a solution containing pyrrolidin-2-one **15** (700 mg, 1.79 mmol) in dry THF (7 mL) at −15 °C under argon, n-BuLi (3.94 mmol, 2.46 mL of a 1.6-M solution in hexane) was added, the mixture was stirred for 15 min, and then methyl chloroformate (152 μL, 1.97 mmol) was slowly dropped at −15 °C. After 10 min, H_2O (50 mL) and ethyl acetate (100 mL) were quickly added, the organic phase was separated, then the aqueous phase was extracted with additional ethyl acetate (2 × 100 mL). The organic layers were dried (Na_2SO_4) and volatiles were removed under reduced pressure: then the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 90:10) to give compound **16** (370 mg, 46 % yield) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98 (m, 21H), 1.49 (s, 3H), 1.55 (d, $J = 7.4$, 3H), 2.21–2.42 (m, 1H), 3.00 (dd, $J = 8.3$, $J = 8.9$, 1H), 3.19 (dd, $J = 8.6$, $J = 8.9$, 1H), 3.58 (dd, $J = 8.0$, $J = 10.2$, 1H), 3.71 (s, 3H), 3.79 (dd, $J = 7.0$, $J = 10.2$, 1H), 5.49 (q, $J = 7.4$, 1H), 7.18–7.41 (m, 5 ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.2, 16.4, 18.0, 21.0, 27.4, 41.0, 44.5, 48.2, 52.5, 55.7, 64.8, 127.3, 127.6, 127.7, 128.7, 140.3, 171.1, 172.1. $[\alpha]_D$ 19.8 (c 1, $CHCl_3$). MS (ESI): *m/z* 447.3 $[M]^+$, 470.3 $[M + Na]^+$. Anal. calcd for $C_{25}H_{41}NO_4Si$: C 67.07; H 9.23; N 3.13. Found: C 67.16; H 9.27; N 3.01.

(3*S*,4*S*)-3-Methyl-2-oxo-1-((*S*)-1-phenylethyl)-4-(((triisopropylsilyl)oxy)methyl)pyrrolidine-3-carboxylic acid, **17**

To a solution containing the ester **16** (360 mg, 0.8 mmol) in MeOH (3 mL) 2 M NaOH (3 mL) was added at rt. The mixture was heated at 50 °C for 3 h and then, after cooling, 0.2 M HCl (31 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 30 mL) and the organic layer was dried (Na_2SO_4). Solvents were removed under reduced pressure and the title product **17** was recovered (340 mg, 98 % yield) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (m, 21H), 1.42 (s, 3H), 1.54 (d, $J = 7.2$, 3H), 2.21–2.31 (m, 1H), 3.08 (dd, $J = 7.2$, $J = 10.5$, 1H), 3.31 (dd, $J = 2.4$, $J = 10.5$, 1H), 3.68 (dd, $J = 2.7$, $J = 9.9$, 1H), 3.99 (dd, $J = 5.1$, $J = 9.9$, 1H), 5.51 (q, $J = 7.2$, 1H), 7.20–7.43 (m, 5ArH), 7.60–8.20 (br, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.1, 16.2, 18.0, 21.3, 27.1, 40.6, 44.1, 48.4, 55.1, 65.0, 127.2, 127.6, 128.6, 128.7, 140.2, 170.9, 174.0. $[\alpha]_D$ 25.1 (c 1, $CHCl_3$). MS (ESI): *m/z* 433.3 $[M]^+$, 456.3 $[M + Na]^+$. Anal. calcd for $C_{24}H_{39}NO_4Si$: C, 66.47; H, 9.06; N, 3.23. Found: C, 66.55; H, 9.18; N, 3.11.

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