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Synthesis of spiroazabicycloalkane amino acid scaffolds as reverse-turn inducer dipeptide mimics

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Abstract—A practical approach to the synthesis of a conformationally constrained spiroazabicycloalkane aminoacid scaffold as a reverse-turn inducer dipeptide mimic is described.

Peptidomimetics have gained enormous popularity and relevance in recent years because they can mimic a natural peptide without changing its biological effect, but at the same time improve its metabolic stability.[1]

Our efforts in this area are directed towards the development of general methods for the synthesis of conformationally restricted molecules that mimic Ala-Pro dipeptide units, or more generally, molecules able to replace the central ($i+1$ and $i+2$) residues of β-turns.

In the course of our studies we have shown that the azaoxobicyclo[X.3.0]alkane skeleton can induce a reverse-turn when inserted in a peptide chain.[2] The possibility of functionalizing these molecules with hydrophobic appendages is very attractive because they could improve peptide-receptor affinity by interacting with hydrophobic pockets. With this aim we have designed the synthesis of the spiro-bicyclic lactams **14**–**17** (Fig. 1).

The synthesis was so designed that all four possible stereoisomers would be accessible in a facile manner from the same starting material.

Starting from the known compound **1**,[3] hydrogenolysis (Pd–C, MeOH) followed by LiOH hydrolysis afforded an acid which was treated with *t*-BuOAc in the presence of $HClO_4$ to yield the *tert*-butyl ester **2** (65% over the 3 steps). The ester **2** was then protected at the nitrogen atom as a carbobenzyloxy derivative **3** (CbzCl, NaH, THF, 94%); the carbonyl group in position 5 of the pyrrolidine moiety was reduced ($LiEt_3BH$), the hydroxy group acetylated and the acetoxy derivatives were treated with allyltributyl tin and $BF_3{\cdot}Et_2O$ to afford the 5-allyl-pyrrolidine **4** via a *N*-acyl immonium ion in 70% yield over three steps[4] (Scheme 1).

Dihydroxylation of **4** with $OsCl_3$, Me_3NO in 8:1 acetone/water, followed by $NaIO_4$ cleavage and reductive work-up ($NaBH_4$) gave the alcohols **5a** and **5b** (1.5:1), which were easily separated by flash chromatography. The configuration of the two diastereoisomeric alcohols was secured by single crystal diffraction analysis[5,6] performed on **5b** (Fig. 2).

The alcohol **5b** (Scheme 2) was oxidised using the Swern procedure affording **8** (80% yield) which was submitted to Horner–Emmons olefination with the potassium enolate of (±)-*Z*-α-phosphonoglycine[7] trimethyl ester, thus setting up the necessary carbon chain in 82% yield. Reaction of the

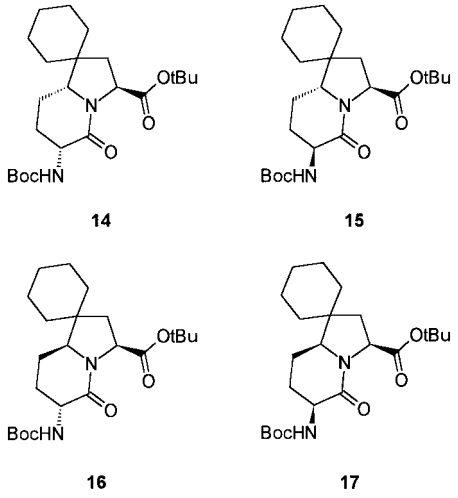

Figure 1. Spiroazabicyclo[4.3.0]nonane aminoacids **14**–**17**.

Keywords: spiroazabicycloalkane; dipeptide; reverse-turn inducer.
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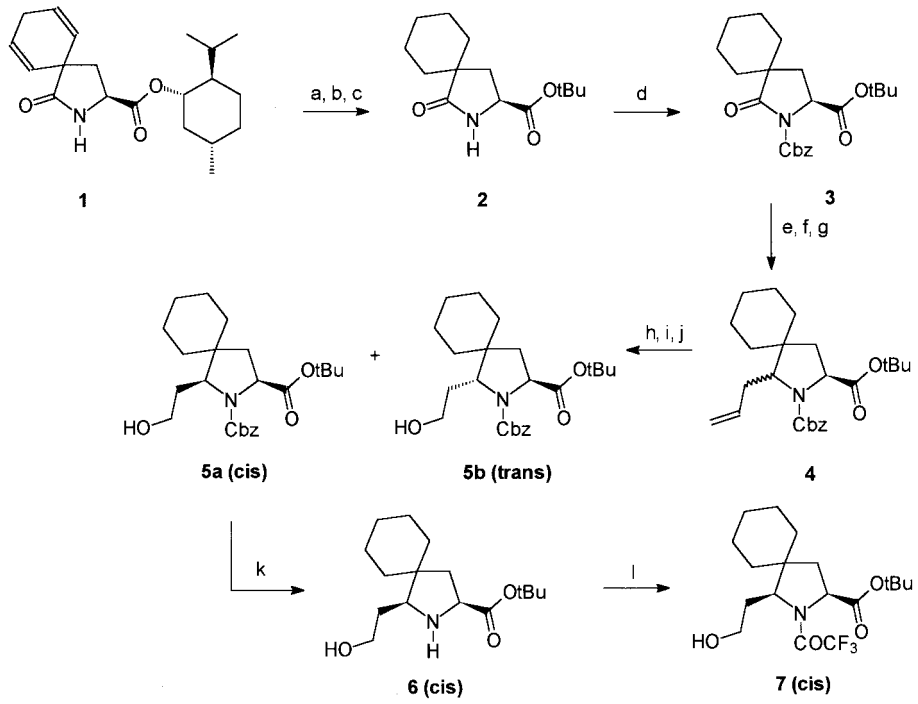


Scheme 1. Synthesis of the intermediate alcohols **5a**–**b** and **7**. (a) H_2, Pd–C, MeOH, 95%; (b) LiOH, MeOH, 86%; (c) *t*-BuOAc, $HClO_4$, 80%; (d) CbzCl, NaH, THF, 94%; (e) $LiEt_3BH$, THF, −78°C; (f) Ac_2O, pyridine, 0°C; (g) Allyltributyl tin, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 70% over 3 steps; (h) $OsCl_3$, $Me_3NO{\cdot}2H_2O$, acetone/H_2O; (i) $NaIO_4$; (j) $NaBH_4$, MeOH, 87% over 3 steps; (k) H_2, Pd–C, MeOH; (l) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 88% over two steps.

dehydroaminoester **10** (pure *Z* isomer) with $(Boc)_2O$ gave **12**, which was hydrogenated (Pd–C) and refluxed in xylene to give a mixture of easily separated **14** and **15** (1:2.5) in 69% yield over the two steps.

To further explore the potential of this strategy we have also performed the synthesis of compounds **16** and **17** using a trifluoroacetamide as the nitrogen protecting group. For this purpose, the alcohol **5a** was hydrogenated (Pd–C, MeOH) and the crude material was treated with $(CF_3CO)_2O$ and Et_3N affording the suitably protected compound **7**. Compound **7** was submitted to the same synthetic sequence described above (Scheme 3) to afford in comparable yields the *N*-Boc-acrylester **13**. Hydrogenation of **13** (Pd–C, MeOH), treatment with $NaBH_4$ in MeOH and thermal cyclization afforded a separable mixture of **16** and **17** (1:2.5) in 37% yield over three steps.

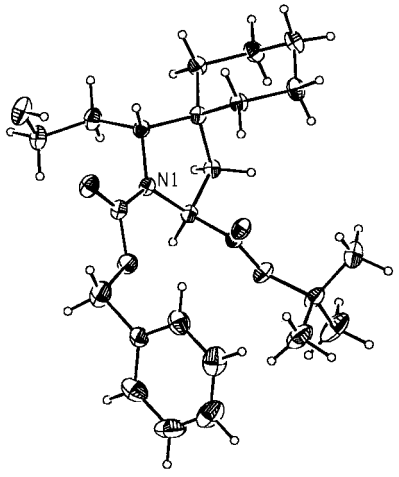


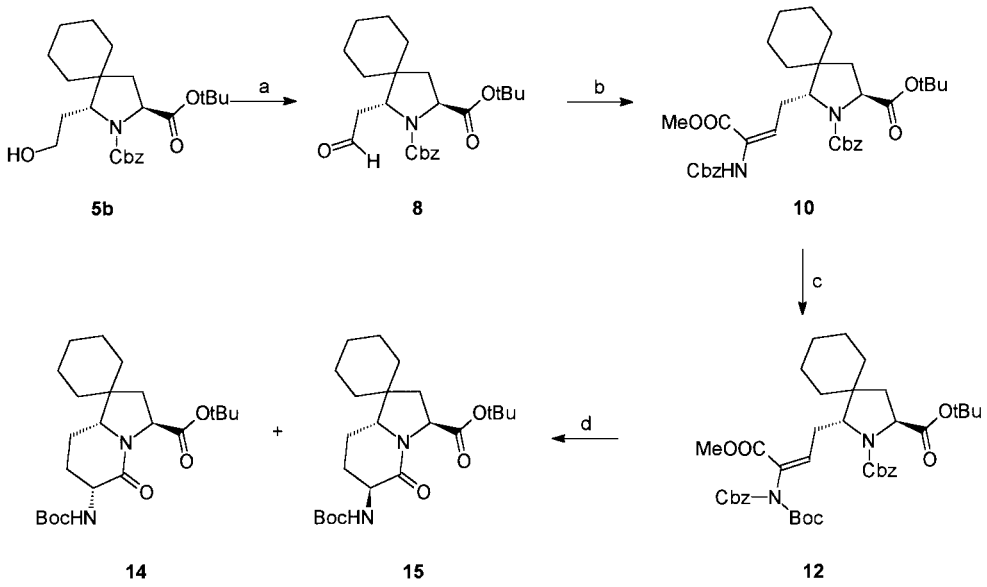
Figure 2. X-Ray structure of alcohol **5b**.

In conclusion, we have shown that our methodology for the synthesis of fused bicyclic[2c] lactams can be extended to the preparation of more complex molecules that could find applications as conformationally constrained peptidomimetics, and we have prepared a small library of four 6,5-fused spiro-substituted bicyclic lactams.

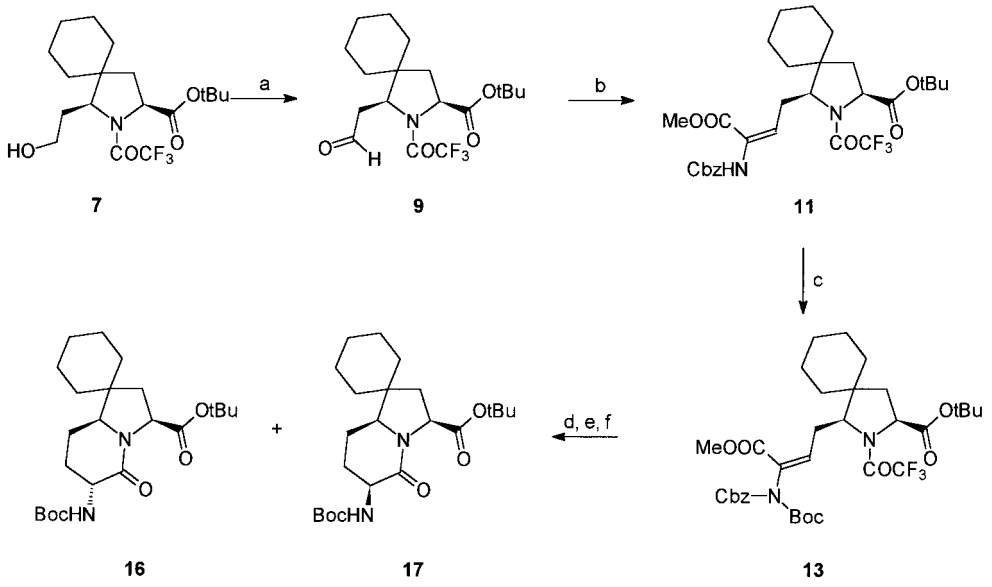
1. Experimental

1.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as indicated, at 200 and 50.3 MHz, respectively (the usual abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet). The positive chemical shift values are given in ppm and the coupling constants in Hz. Elemental analyses were performed with a Perkin–Elmer 240 instrument. Mass spectra were obtained with a VG 7070 EQ spectrometer. Optical rotations were measured in 1 dm pathlength cells of 1 mL capacity by using a Perkin–Elmer 241 polarimeter. Thin-layer chromatography (TLC) was carried out using Merck precoated silica gel F-254 plates. Flash chromatography was carried out with Macherey–Nagel Silica Gel 60, 230–400 mesh. Solvents were dried using standard procedures and reactions requiring anhydrous conditions were performed under a positive nitrogen atmosphere. Final product solutions were dried over Na_2SO_4, filtered and evaporated under reduced pressure on a rotary evaporator.



Scheme 2. Synthesis of **14** and **15** from **5b**. (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60°C, 80%; (b) (±)-*Z*-α-phosphonoglycine trimethyl ester, *t*-BuOK, CH_2Cl_2, −78°C, 82%; (c) $(Boc)_2O$, 4-DMAP, THF, 98%; (d) H_2, Pd–C, MeOH; xylene, reflux, 70% over two steps.



Scheme 3. Synthesis of **16** and **17** from **7**. (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60°C, 78%; (b) (±)-*Z*-α-phosphonoglycine trimethyl ester, *t*-BuOK, CH_2Cl_2, −78°C, 78%; (c) $(Boc)_2O$, 4-DMAP, THF, 89%; (d) H_2, Pd–C, MeOH; (e) $NaBH_4$, MeOH; (f) MeOH, reflux, 37% over three steps.

1.1.1. *tert*-Butyl ester (2). A solution of **1** (4.2 g, 12.7 mmol) and a catalytic quantity of Pd–C 10% in MeOH (130 mL) was stirred under hydrogen for 12 h, the catalyst was then filtered through celite and the filtration pad was washed with MeOH. The solvent was evaporated under reduced pressure yielding 4.1 g (95%) of menthyl ester as a white solid.

1.1.2. Menthyl ester. Mp 162–163°C; ^{1}H NMR ($CDCl_3$): 0.78 (d, 3H, *J*=6.5 Hz, C*H*$_3$CH), 0.93 (m, 6H, C*H*$_3$CHC*H*$_3$), 1.0–2.05 (m, 19H, C*H*$_2$), 2.10–2.22 (dd, 1H, *J*=14, 6 Hz, HC*H*–CHCOO–Menthyl), 2.35–2.50 (dd, 1H, *J*=14, 9 Hz, *H*CH–CHCOO–Menthyl), 4.16 (dd, 1H, *J*=9, 6 Hz, C*H*COO–Menthyl), 4.76 (ddd, 1H, J_1=J_2=11, 6.6 Hz, C*H*OCO), 5.90 (bs, 1H, N*H*); ^{13}C NMR ($CDCl_3$): 15.8, 20.7, 21.8, 22.0, 22.1, 23.0, 25.2, 26.1, 31.2, 32.6, 32.9, 34.0, 35.6, 40.5, 44.0, 46.8, 52.7, 75.5, 171.9, 181.9; Elemental analysis for $C_{20}H_{33}NO_3$: Calculated: C, 55.77; H, 15.44; N, 6.50; Found: C, 55.44; H, 15.41; N, 6.46; MS (FAB$^+$): M^+ 335.

To a crude solution of the menthyl ester (3.95 g, 11.8 mmol) in MeOH (100 mL) a 2N solution of LiOH (5 equiv.) was added and the solution was stirred for 2 h. The solvent was evaporated and the residue was diluted with water (25 mL) and extracted with Et_2O. The aqueous solution was acidified with 2N HCl to pH 4 and extracted with EtOAc. The collected organic phases were dried over Na_2SO_4, filtered and evaporated yielding 2 g (86%) of acid as white solid.

1.1.3. Acid. ^{1}H NMR (D_2O): 1.0–1.60 (m, 10H, CH_2), 1.90–2.04 (dd, 1H, *J*=14, 6 Hz, HC*H*–CHCOOH), 2.35–2.48 (dd, 1H, *J*=14, 9 Hz, *H*CH–CHCOOH), 4.18 (dd, 1H, *J*=9, 6 Hz, C*H*COOH).

To a solution of crude acid (2 g) in *tert*-butyl acetate (50 mL) was added $HClO_4$ 70% (0.3 mL) and stirred for 24 h then was neutralised with a saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic layers were dried over Na_2SO_4, filtered and evaporated yielding 2 g (80%) of **2** as white solid.

1.1.4. Ester 2. Mp 148–150°C; ^{1}H NMR ($CDCl_3$): 1.20–1.84 (m, 10H, CH_2), 1.48 (s, 9H, COO*t*-Bu), 2.03–2.15 (dd, 1H, *J*= 14, 6.5 Hz, HC*H*–COO*t*-Bu), 2.33–2.48 (dd, 1H, *J*=14, 9 Hz, *H*CH–COO*t*-Bu), 4.08 (dd, 1H, *J*=9, 6.5 Hz, C*H*COO*t*-Bu), 6.40 (sb, 1H, N*H*); ^{13}C NMR ($CDCl_3$): 22.0, 22.2, 25.2, 27.9, 32.3, 33.0, 35.7, 53.0, 82.2, 171.3, 181.7; Elemental analysis for $C_{14}H_{23}NO_3$: Calculated: C, 66.37; H, 9.15; N, 5.53; Found: C, 66.2; H, 9.05; N, 5.38; MS (FAB$^+$): M^+ 253.

1.1.5. *N*-Cbz-*tert*-Butyl ester (3). To a suspension of NaH (0.360 g, 9 mmol, 60% dispersion in oil) in THF (20 mL) was added a solution of **2** (2 g, 7,9 mmol) in THF (80 mL), and after 15 min benzyl chloroformate (1.24 mL, 8.69 mmol) was added and the solution was stirred overnight. Then a NH_4Cl saturated solution was added, the aqueous phase extracted with EtOAc and the organic phase dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash chromatography (Hexane/EtOAc 6:4) yielding 2.8 g (94%) of **3** as white solid.

1.1.6. Ester 3. Mp 79°C; ^{1}H NMR ($CDCl_3$): 1.25–1.87 (m, 10H, CH_2), 1.40 (s, 9H, COO*t*-Bu), 1.97–2.10 (dd, 1H, *J*=14, 5 Hz, HC*H*–COO*t*-Bu), 2.15–2.30 (dd, 1H, *J*=14, 9 Hz, *H*CH–COO*t*-Bu), 4.48 (dd, 1H, *J*=9, 5 Hz, C*H*COO*t*-Bu), 5.30 (s, 2H, PhCH_2OCO), 7.30–7.50 (m, 5H, *Ph*CH_2OCO); ^{13}C NMR ($CDCl_3$): 21.6, 21.7, 25.0, 27.6, 32.6, 32.7, 33.8, 45.9, 56.5, 68.1, 82.2, 128.0, 128.2, 128.4, 128.5, 135.0, 151.2, 170.4, 177.7; Elemental analysis for $C_{22}H_{29}NO_5$: Calculated: C, 66.37; H, 9.15; N, 5.53; Found: C, 66.56; H, 9.16; N, 5.54; MS (FAB$^+$): M^+ 387.

1.1.7. Allyl pyrrolidine (4). To a solution of **3** (2.8 g, 7.23 mmol) in dry THF (50 mL), $LiEt_3BH$ 1 M (9 mL, 9 mmol) was added at −78°C and the solution was stirred for 3 h then warmed to room temperature. A saturated $NaHCO_3$ solution (20 mL) and H_2O_2 (5 mL) were added and the mixture was stirred for 30 min then extracted with EtOAc. The organic layers were dried over Na_2SO_4, filtered and evaporated. The crude, as a yellowish oil, was submitted to the next reaction without further purification.

1.1.8. 5-Hydroxy-pyrrolidine (*cis*/*trans* mixture). ^{1}H NMR ($CDCl_3$): 0.75–2.45 (m, 24H, CH_2), 1.37 (s, 9H, COO*t*-Bu), 1.45 (s, 9H, COO*t*-Bu), 3.0 (db, 2H, O*H*), 4.0–4.31 (m, 2H, C*H*COO*t*-Bu), 5.10–5.33 (m, 6H, C*H*OH, PhCH_2OCO), 7.30–7.50 (m, 10H, *Ph*CH_2OCO).

To a solution of the crude mixture (2.65 g, 6.81 mmol) in pyridine (50 mL) was added acetic anhydride (3.5 mL) at 0°C. The solution was stirred at room temperature for 20 h then the solvent was evaporated and AcOEt was added to the residue. The organic phases were washed with phosphate buffer (25 mL) then dried with Na_2SO_4, filtered and evaporated. The crude material, as a yellowish oil, was submitted to the next reaction without further purification.

1.1.9. 5-Acetoxy-pyrrolidine (*cis*/*trans* mixture). ^{1}H NMR ($CDCl_3$): 1.20–2.45 (m, 24H, CH_2), 1.40 (s, 9H, COO*t*-Bu), 1.45 (s, 9H, COO*t*-Bu), 2.0 (s, 3H, CH_3COO), 2,1 (s, 3H, CH_3COO), 4.05 (dd, 1H, *J*=9, 5 Hz, C*H*COO*t*-Bu), 4.22 (dd, 1H, *J*=9, 5 Hz, C*H*COO*t*-Bu), 5.05–5.38 (m, 4H, PhCH_2OCO), 6.40 (bs, 1H, C*H*OAc), 7.30–7.50 (m, 10H, *Ph*CH_2OCO).

To a solution of $BF_3{\cdot}Et_2O$ (1.4 mL, 10.5 mmol) in dry CH_2Cl_2 (25 mL) at −78°C and under nitrogen, a solution of the crude 5-acetoxy-pyrrolidine (2.6 g, 6 mmol) and allyltributyltin (2.8 mL, 9 mmol) in dry CH_2Cl_2 (35 mL) was added. The solution was stirred at this temperature for 3 h, then warmed to room temperature. After 3 h, a buffer solution (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 The collected organic phases were dried over Na_2SO_4, filtered and evaporated The crude material was purified by flash chromatography (hexane/EtOAc 9:1) affording 1.7 g (70%) of **4** as a colourless oil in a 1.5:1 *cis*:*trans* diastereoisomeric mixture.

1.1.10. 5-Allyl-pyrrolidine (*cis*/*trans* mixture) 4. ^{1}H NMR ($CDCl_3$): 1.35, 1.45 (2 s, 18H, COO*t*-Bu), 1.35–2.77 (m, 28H, CH_2), 3.70–3.95 (m, 2H, CH_2C*H*N), 4.10–4.30 (m, 2H, C*H*COO*t*-Bu), 4.85–5.20 (m, 8H, CH_2=CH, PhCH_2OCO), 5.65–6.18 (m, 2H, CH_2=C*H*), 7.30–7.50 (m, 10H, *Ph*CH_2OCO); ^{13}C NMR ($CDCl_3$): 14.1, 22.0, 22.4, 23.3, 23.4, 25.9, 27.7, 27.8, 29.6, 32.4, 33.0, 33.2, 33.5, 34.7, 35.1, 35.7, 36.1, 37.6, 38.8, 43.8, 44.5, 44.8, 45.2, 58.4, 58.5, 58.7, 60.2, 65.3, 65.6, 66.2, 66.7, 66.8, 80.9, 115.9, 117.3, 117.4, 127.5, 127.7, 129.2, 129.7, 134.9, 135.2, 136.4, 136.6, 154.4, 154.8, 155.1, 155.5, 171.0, 171.6, 171.9, 172.1; Elemental analysis for $C_{25}H_{34}NO_4$: Calculated: C, 72.79; H, 8.31; N, 3.40; Found: C, 72.59; H, 8.23; N, 3.30; MS (FAB$^+$): M^+ 412.

1.1.11. Alcohols (5a), (5b). To a solution of **4** (1.6 g, 3.87 mmol) in 8:1 acetone/water (35 mL) were added $OsCl_3$ (0.114 g, 0,387 mmol) and $Me_3NO{\cdot}2H_2O$ (0.860 g, 7.74 mmol), and the solution was stirred for 2 h. Then $NaIO_4$ (1.8 g) was added and after 30 min the solution was evaporated. The crude material was dissolved in MeOH, and $NaBH_4$ (0.250 g, 6.7 mmol) was added. When the reaction was completed, it was diluted with water (5 mL) and the aqueous layers were extracted with EtOAc, the collected organic phases were dried over Na_2SO_4, filtered and evaporated. The crude was purified by flash chromatography (hexane/EtOAc 8:2) affording 1.21 g (87%) of **5a** and **5b** in 1.5:1 diastereoisomeric ratio.

1.1.12. Alcohol 5a (*cis*). White solid mp 109–110°C; ^{1}H NMR ($CDCl_3$): 1.30 (s, 9H, COO*t*-Bu), 1.32–1.55 (m, 10H, CH_2), 1.55–1.67 (dd, 1H, *J*=14, 11 Hz, HC*H*–COO*t*-Bu), 1.72–1.90 (m, 2H, CH_2CH_2OH), 2.10–2.26 (dd, 1H, *J*=14, 8 Hz, *H*CH–COO*t*-Bu), 3.60–3.90 (m, 2H, CH_2CH_2OH), 4.0–4.10 (dd, 1H, *J*=13.3, 4.4 Hz, CH_2C*H*N),

4.15–4.29 (dd, 1H, J=11, 8 Hz, C*H*COO*t*-Bu), 4.28 (bs, 1H, O*H*), 4.98–5.28 (AB system, 2H, J=13.3 Hz, PhCH_2OCO), 7.25–7.40 (m, 5H, *Ph*CH$_2$OCO); ^{13}C NMR ($CDCl_3$): 22.5, 23.1, 25.9, 27.7, 32.3, 32.6, 35.0, 38.9, 44.4, 58.4, 61.6, 67.5, 81.3, 127.6, 127.9, 128.3, 136.0, 156.6, 171.9; Elemental analysis for $C_{24}H_{35}NO_5$: Calculated: C, 69.04; H, 8.45; N, 3.35; Found: C, 68.9; H, 8.40; N, 3.28; MS (FAB$^+$): M$^+$ 417.

1.1.13. Alcohol 5b (*trans*). White solid mp 111–113°C; ^{1}H NMR ($CDCl_3$): 1.35 (s, 9H, COO*t*-Bu), 1.33–1.70 (m, 10H, CH_2), 1.75–2.15 (m, 4H, CH_2CH$_2$OH, CH_2CH–COO*t*-Bu), 3.40–3.70 (m, 2H, CH$_2$CH_2OH), 4.0–4.19 (m, 2H, CH$_2$C*H*N, C*H*COO*t*-Bu), 4.95–5.28 (AB system, 2H, J=13.3 Hz, PhCH_2OCO), 7.25–7.40 (m, 5H, *Ph*CH$_2$OCO); ^{13}C NMR ($CDCl_3$): 22.4, 23.3, 25.8, 27.7, 33.2, 33.4, 35.3, 38.7, 43.5, 57.6, 58.4, 61.8, 67.4, 81.2, 127.9, 128.3, 136.0, 156.4, 171.0; Elemental analysis for $C_{24}H_{35}NO_5$: Calculated: C, 69.04; H, 8.45; N, 3.35; Found: C, 69.2; H, 8.35; N, 3.40; MS (FAB$^+$): M$^+$ 417.

1.1.14. Alcohol (6). A solution of **5a** (*cis*) (0.420 g, 1.007 mmol) and a catalytic quantity of Pd–C 10% in MeOH (10 mL) was stirred under hydrogen for 12 h. The catalyst was then filtered through celite and the filtration pad was washed with MeOH. The solvent was evaporated under reduced pressure yielding alcohol **6** (0.275 g) as a yellowish oil which was used without further purification.

1.1.15. Alcohol 6. ^{1}H NMR ($CDCl_3$): 1.50 (s, 9H, COO*t*-Bu), 1.20–1.80 (m, 12H, CH_2), 1.89–2.10 (m, 2H, CH_2CHCOO*t*-Bu), 2.92–3.05 (dd, 1H, J=11.1, 4.4 Hz, CH$_2$C*H*N), 3.18 (sb, 2H, O*H*, N*H*), 3.80–3.96 (m, 3H, CH$_2$CH_2OH, C*H*COO*t*-Bu).

1.1.16. Alcohol (7). To a solution of **6** (0.270 g, 0.954 mmol) in dry CH_2Cl_2 (10 mL) $(CF_3CO)_2O$ (0.15 mL, 1.05 mmol) and Et_3N (0.15 mL, 1.05 mmol) was added at room temperature. After 5 h the reaction was quenched with a saturated $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude material was purified by flash chromatography (hexane/EtOAc 8:2) affording 0.318 g (88%) of **7** as a colourless oil.

1.1.17. Alcohol 7. ^{1}H NMR ($CDCl_3$): 1.3 (s, 9H, COO*t*-Bu), 1.3–2.0 (m, 13H, CH_2), 2.35–2.5 (m, 1H, HC*H*–COO*t*-Bu), 3.60–3.80 (m, 3H, O*H*, CH$_2$CH_2OH), 4.3–4.4 (dd, 1H, J=13.0, 4.0 Hz, CH$_2$C*H*N), 4.45–4.6 (m, 1H, C*H*COO*t*-Bu); ^{13}C NMR ($CDCl_3$): 22.3, 22.9, 25.6, 27.6, 27.7, 29.5, 31.6, 32.1, 34.8, 39.4, 43.2, 58.2, 58.3, 64.0, 82.6, 113.5, 119.0, 170.5; Elemental analysis for $C_{18}H_{28}NO_4F_3$ Calculated: C, 56.98; H, 7.44; N, 3.68; Found: C, 56.84; H, 7.48; N, 3.70; MS (FAB$^+$): M$^+$ 379.

1.1.18. Aldehyde (8). To a stirred solution of oxalyl chloride (0.0838 mL, 0.961 mmol) in 3 mL of CH_2Cl_2, cooled at −60°C, were added in sequence DMSO (0.0932 mL, 1.312 mmol), the alcohol **5b** (0.134 g, 0.320 mmol) dissolved in 2 mL of CH_2Cl_2 and Et_3N (0.365 mL, 2.624 mmol). The reaction was warmed to room temperature. After one hour the reaction was washed with 5 mL of water and the aqueous phase was extracted with CH_2Cl_2. The collected organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude material purified by flash chromatography (hexane/EtOAc 8:2), yielding 0.106 g (80%) of aldehyde **8** as a colourless oil.

1.1.19. Aldehyde 8. ^{1}H NMR ($CDCl_3$): 1.36 (s, 9H, COO*t*-Bu), 1.8–2.8 (m, 14H, CH_2), 4.1 (m, 2H, CH$_2$C*H*N, C*H*COO*t*-Bu), 5.1 (s, 2H, PhCH_2OCO), 7.3 (s, 5H, PhCH_2OCO), 9.85 (s, 1H, C*H*O); Elemental analysis for $C_{24}H_{32}NO_5$: Calculated: C, 69.54; H, 7.78; N, 3.38; Found: C, 69.34; H, 7.52; N, 3.10; MS (FAB$^+$): M$^+$ 414.

1.1.20. Aldehyde 9. Prepared according to the method described for **8**, starting from **7**, in 78% yield as a colourless oil. $[\alpha]_D^{22}$=−44.5 (c=1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.45 (s, 9H, COO*t*-Bu), 2.3–3.0 (m, 14H, CH_2), 4.3–4.6 (m, 2H, CH$_2$C*H*N, C*H*COO*t*-Bu), 9.80 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$): 22.8, 23.0, 27.6, 31.9, 34.0, 34.2, 34.7, 43.9, 46.4, 58.3, 58.4, 59.3; Elemental analysis for $C_{18}H_{26}NO_4F_3$: Calculated: C, 57.29; H, 6.94; N, 3.71; Found: C, 57.03; H, 6.90; N, 3.78; MS (FAB$^+$): M$^+$ 377.

1.1.21. Acrylester (10). To a stirred solution of *t*-BuOK (0.0285 g, 0.254 mmol) in 2 mL of dry CH_2Cl_2 under nitrogen atmosphere, at −78°C, was added a solution of *Z*-(α)-phosphonoglycine trimethyl ester (0.0842 g, 0.254 mmol) in 1 mL of dry CH_2Cl_2. The solution was stirred for 30 min at this temperature and then a solution of aldehyde **8** (0.088 g, 0.212 mmol) in dry CH_2Cl_2 (1 mL) was added. After 5 h the solution was neutralised with a phosphate buffer. The aqueous phase was extracted with CH_2Cl_2, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude material was purified by flash chromatography (hexane/EtOAc 7:3), affording 0.101 g (82%) of acrylester **10** (only *Z*-isomer) as a sticky solid.

1.1.22. Acrylester 10 (*Z*). ^{1}H NMR ($CDCl_3$): 1.36, (s, 9H, COO*t*-Bu), 1.8–2.8 (m, 14H, CH_2), 3.7 (s, 3H, COOCH_3), 3.8 (m, 1H, CH$_2$C*H*N), 4.2 (m, 1H, C*H*COO*t*-Bu), 5.15 (m, 4H, PhCH_2OCO), 6.5 (dd, 1H, J_1=J_2=13 Hz, CH$_2$C*H*=), 7.0 (bs, 1H, N*H*), 7.2–7.5 (m, 10H, *Ph*CH$_2$OCO); Elemental analysis for $C_{35}H_{44}N_2O_8$: Calculated: C, 67.72; H, 7.14; N, 4.51; Found: C, 67.50; H, 6.89; N, 4.30; MS (FAB$^+$): M$^+$ 620.

1.1.23. Acrylester 11 (*Z*/*E* mixture, mainly *Z* isomer). Prepared according to the method used for **10**, starting from **9**, in 78% yield, as a colourless oil. ^{1}H NMR ($CDCl_3$): 1.40, (s, 18H, COO*t*-Bu), 1.6–1.8 (m, 12H, CH_2), 2.2–2.6 (m, 16H, CH_2), 3.75 (s, 6H, COOCH_3), 4.3–4.5 (m, 4H, CH$_2$C*H*N, C*H*COO*t*-Bu), 5.15 (m, 4H, PhCH_2OCO), 6.5–6.7 (m, 2H, CH$_2$C*H*=), 7.1 (bs, 2H, N*H*), 7.2–7.4 (m, 10H, *Ph*CH$_2$OCO); ^{13}C NMR ($CDCl_3$): 22.1, 22.3, 23.7, 25.6, 27.6, 27.7, 29.2, 29.5, 30.0, 31.6, 32.1, 32.2, 34.4, 34.7, 35.5, 39.3, 43.4, 46.2, 52.2, 52.3, 58.2, 59.8, 65.6, 66.3, 66.9, 67.1, 82.6, 83.6, 113.0, 127.5, 127.8, 127.9, 128.0, 128.2, 128.3, 131.5, 132.1, 135.9, 135.2, 154.2, 154.5, 164.7, 164.8, 170.4, 171.6; Elemental analysis for $C_{29}H_{37}N_2O_7F_3$: Calculated: C, 59.79; H, 6.40; N, 4.81; Found: C, 59.89; H, 6.29; N, 4.66; MS (FAB$^+$): M$^+$ 582.

1.1.24. *N*-Boc-acrylester (12). A solution of acrylester **10** (0.098 g, 0.168 mmol), $(Boc)_2O$ (0.0733 g, 0.336 mmol) and a catalytic quantity of DMAP in 1 mL of dry THF, was stirred for 30 min under nitrogen. The solution was then quenched with water (1 mL) and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude material was purified by flash chromatography (hexane/EtOAc 7:3), yielding 0.111 g (98%) of **12** as a colourless oil.

1.1.25. *N*-Boc-acrylester 12. ^{1}H NMR ($CDCl_3$): 1.36, 1.41 (2 s, 18H, COO*t*-Bu), 1.8–2.8 (m, 14H, CH_2), 3.7 (s, 3H, COOCH_3), 3.9 (m, 1H, CH_2CHN), 4.2 (m, 1H, CHCOO*t*-Bu), 5.0–5.3 (m, 4H, PhCH_2OCO), 6.8 (m, 1H, CH_2CH=), 7.1–7.5 (m, 10H, *Ph*CH_2OCO); ^{13}C NMR ($CDCl_3$): 20.9, 22.2, 25.7, 27.3, 32.7, 35.6, 51.7, 52.2, 58.3, 66.9, 68.3, 127.8, 127.9, 128.1, 128.2, 128.4; Elemental analysis for $C_{40}H_{52}N_2O_{10}$: Calculated: C, 66.65; H, 7.27; N, 3.89; Found: C, 66.43; H, 7.38; N, 3.88; MS (FAB$^+$): M^+ 720.

1.1.26. *N*-Boc-acrylester 13 (*Z*/*E* mixture, mainly *Z* isomer). Prepared according to the method used for **12**, starting from **11**, in 89% yield, as a colourless oil. ^{1}H NMR ($CDCl_3$): 1.4 (s, 36H, COO*t*-Bu), 2.0–2.6 (m, 28H, CH_2), 3.7 (s, 6H, COOCH_3), 3.9–4.5 (m, 4H, CH_2CHN, CHCOO*t*-Bu), 5.1–5.2 (m, 4H, PhCH_2OCO), 6.8–7.1 (m, 2H, CH_2CH=), 7.3–7.4 (m, 10H, *Ph*CH_2OCO); Elemental analysis for $C_{34}H_{45}N_2O_9F_3$: Calculated: C, 59.82; H, 6.64; N, 4.10; Found: C, 59.59; H, 6.58; N, 4.03; MS (FAB$^+$): M^+ 682.

1.1.27. 6,5-Fused bicyclic lactam (14), (15). A solution of **12** (0.380 g, 0.56 mmol) and a catalytic quantity of Pd–C 10% in 5 mL of MeOH was stirred under H_2 for one night. The catalyst was then filtered through celite and the filtration bed was washed with MeOH. The solvent was evaporated under reduced pressure, the residue was dissolved in xylene and refluxed for 48 h. The solvent was removed and the two diastereoisomers formed were separated by flash cromatography (hexane/EtOAc 7:3), yielding 0.032 g of **14** and 0.08 g of **15** (70%) (1:2.5 diastereoisomeric ratio) as white foams.

1.1.28. 6,5-Fused bicyclic lactam 14. Mp 75–78°C; $[\alpha]_D^{22}=-54.8$ (c=0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.45, 1.49 (2 s, 18H, COO*t*-Bu), 1.0–2.0 (m, 14H, CH_2), 2.3 (m, 1H, HC*H*), 2.5 (m, 1H, *H*CH), 3.4 (dd, 1H, J=6.3 Hz, CH_2CHN), 4.1 (m, 1H, CHNHBoc), 4.3 (dd, 1H, J=8.1 Hz, CHCOO*t*-Bu), 5.5 (bs, 1H, N*H*); ^{13}C NMR ($CDCl_3$): 20.1, 22.0, 23.9, 27.2, 27.9, 28.1, 28.3, 35.4, 36.9, 52.6, 58.6, 69.6; Elemental analysis for $C_{23}H_{38}N_2O_5$: Calculated: C, 65.38; H, 9.06; N, 6.63; Found: C, 65.01; H, 8.98; N, 6.58; MS (FAB$^+$): M^+ 422.

1.1.29. 6,5-Fused bicyclic lactam 15. Mp 74–75°C; $[\alpha]_D^{22}=-33.8$ (c=1.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.41, 1.43 (2 s, 18H, COO*t*-Bu), 1.1–1.9 (m, 14H, CH_2), 2.4–2.7 (m, 2H, CH_2), 3.4 (m, 1H, CH_2CHN), 4.0 (m, 1H, CHNHBoc), 4.2 (dd, 1H, J=7.8 Hz, CHCOO*t*-Bu), 5.3 (bs, 1H, N*H*); ^{13}C NMR ($CDCl_3$): 21.1, 21.9, 23.1, 26.0, 27.9, 28.1, 28.2, 34.6, 37.0, 52.2, 57.0, 68.6; Elemental analysis for $C_{23}H_{38}N_2O_5$: Calculated: C, 65.38; H, 9.06; N, 6.63; Found: C, 65.20; H, 8.95; N, 6.50; MS (FAB$^+$): M^+ 422.

1.1.30. 6,5-Fused bicyclic lactam (16), (17). A solution of **13** (0.150 g, 0.220 mmol) and a catalytic quantity of Pd–C 10% in 2.5 mL of MeOH was stirred under hydrogen for one night. The catalyst was filtered through celite and the filtration pad was washed with MeOH. The solvent was evaporated under reduced pressure, the crude was dissolved in MeOH (2.5 mL) and $NaBH_4$ (0.033 g, 0.880 mmol) was added. After 2 h the reaction was washed with 4 mL of water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure and the crude material was dissolved in MeOH and refluxed for 2 days. The solvent was removed and the two diastereoisomers formed were separated by flash chromatography (hexane/EtOAc 7:3) yielding 0.01 g of **16** and 0.024 g of **17** (37%) (1:2.5 diastereoisomeric ratio) as white foams.

1.1.31. 6,5-Fused bicyclic lactam 16. Mp 74–77°C; $[\alpha]_D^{22}=-22.6$ (c=0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.41, 1.43 (2 s, 18H, COO*t*-Bu), 1.0–2.0 (m, 14H, CH_2), 2.3 (m, 1H, HC*H*), 2.6 (m, 1H, *H*CH), 3.22 (m, 1H, CH_2CHN), 3.94 (m, 1H, CHNHBoc), 4.3 (m, 1H, CHCOO*t*-Bu), 5.4 (bs, 1H, N*H*); ^{13}C NMR ($CDCl_3$): 19.9, 20.9, 22.9, 25.9, 26.9, 28.5, 28.6, 35.2, 36.8, 52.6, 58.3, 70.6; Elemental analysis for $C_{23}H_{38}N_2O_5$: Calculated: C, 65.38; H, 9.06; N, 6.63; Found: C, 65.20; H, 8.93; N, 6.60; MS (FAB$^+$): M^+ 422.

1.1.32. 6,5-Fused bicyclic lactam 17. Mp 76–79°C; $[\alpha]_D^{22}=-11.3$ (c=0.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.41, 1.43 (2 s, 18H, COO*t*-Bu), 1.0–2.0 (m, 14H, CH_2), 2.15 (m, 1H, HC*H*), 2.4 (m, 1H, *H*CH), 3.35 (dd, 1H, J=6.12 Hz, CH_2CHN), 4.15 (m, 1H, CHNHBoc), 4.3 (dd, 1H, J=4.5, 9.0 Hz, CHCOO*t*-Bu), 5.5 (bs, 1H, N*H*); ^{13}C NMR ($CDCl_3$): 21.2, 21.9, 23.3, 26.9, 27.9, 28.2, 28.4, 36.6, 38.0, 56.2, 58.2, 71.6; Elemental analysis for $C_{23}H_{38}N_2O_5$: Calculated: C, 65.38; H, 9.06; N, 6.63; Found: C, 65.30; H, 8.98; N, 6.60; MS (FAB$^+$): M^+ 422.

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5. Crystal dimensions: 0.65×0.5×0.2 mm^3; crystal system: monoclinic, space group: $P2_1$, Z=2; cell dimensions: a=6.0472(4) Å, b=17.6124(14) Å, c=11.1750(9) Å, β=97.208(6)°, V= 1180.6(2) $Å^3$; D_{calc}=1.177 g cm^{-3}, linear absorption coeff. μ= 0.081 mm^{-1}, radiation MoK_α, $(\sin\theta/\lambda)^{Max}_{Mo} = 0.59$ $Å^{-1}$; number of reflections collected: 4442, number of independent reflections: 2150, number of observed reflections ($I>2\sigma$): 1917, number of variables: 279, number of restraints: 54, final R indices (observed data): $R(F)$=0.0434, $wr(F^2)$=0.1164, GoF=1.056.
6. All X-ray crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-149629.
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