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Synthesis of a 3-aminopiperidin-2,5-dione as a conformationally constrained surrogate of the Ala-Gly dipeptide

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Abstract—The preparation of the Boc-{Ala-Gly}-OBn pseudopeptide **4** is reported. The key intermediate, aminoester **5b**, was obtained by a cross-coupling reaction of alaninezinc iodide **6** and the thioester of glycine **9**.

Compounds that possess a 3-amino-2-piperidone nucleus often show important biological activities. For instance, compound **1** (Fig. 1) has been reported as a serine protease inhibitor,[1] and compound **2** is an angiotensin converting enzyme (ACE) inhibitor.[2] Compound **1** consists of the thiazolopiperidone bicyclic system known to be a β-turn mimetic,[3] and cyclo-arginine. Compound **3**, a thrombin inhibitor,[4] is a combination of compound **2** and cyclo-arginine. We present here the preparation of 3-aminopiperidin-2,5-dione **4**. Compound **4** is a new conformationally constrained Ala-Gly surrogate, functionalised at C5, in which the conformational restriction is caused by the cyclisation between the Cα of alanine and the nitrogen atom of glycine. We also intend to use diketopiperidine **4** for the preparation of other pseudodipeptides by using the reactivity of the C5 carbonyl group.

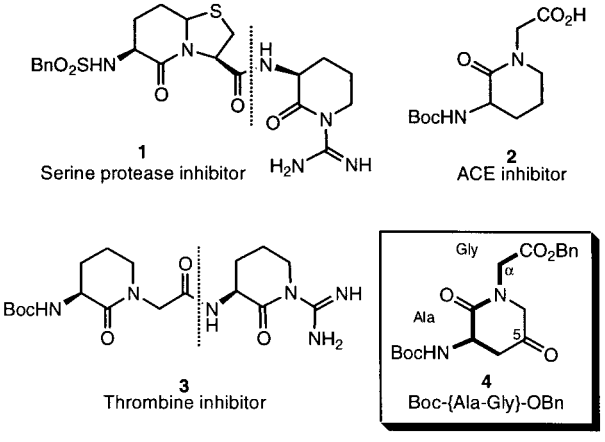

Figure 1.

We considered that 2,5-dioxopiperidine **4** could be prepared by lactamisation of an appropriate aminoester, such as **5** (Fig. 2). In turn, compound **5** could be obtained from simple aminoacid precursors, by acylation of an alanine β-anion equivalent.

Such acylations are usually best achieved by palladium-catalysed coupling of the organozinc derivative **6a** with acid chlorides in benzene/dimethylacetamide as solvent.[5] Although we have successfully coupled the Fmoc-protected glycine acid chloride with the iodoalanine-derived zinc reagent **6a**, to give ketone **5a** (Scheme 1), the yield was very poor (26%).[6]

Therefore, we decided to apply the recently reported palladium-catalysed acylation of simple organozinc iodides with thioesters,[7] which proceeds well in THF, in contrast with acylation using acid chlorides which is generally inefficient in this solvent. In order to assess the reactivity towards thioesters of zinc reagent **6b**, obtained from protected iodoalanine **7** by zinc insertion,[8] we first treated compound **6b** with ethyl acetylthiolate.[9] The coupling,

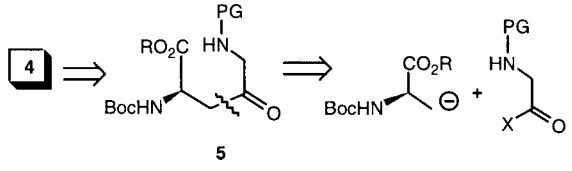

Figure 2.

Keywords: aminolactam; diketopiperidine; dioxopiperidine; peptide mimetic; β-turn mimetic.
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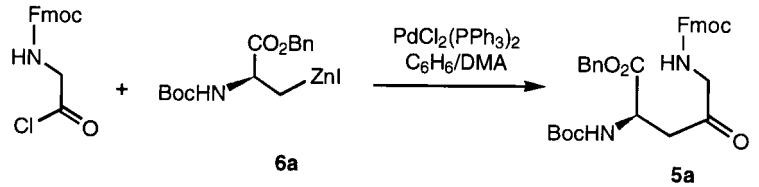
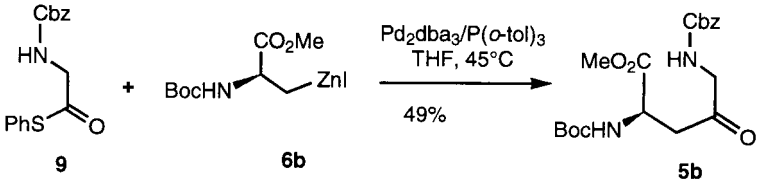


Scheme 1.



Scheme 2.

using $PdCl_2(PPh_3)_2$ as the catalyst, gave the expected ketoester **8** in 39% yield. The modest yield partly reflects the use of the less reactive ethyl thioester.

Once the reactivity of **6b** towards thioesters had been established, we studied its coupling to the thioester derived from Cbz-glycine **9**.[9] The reaction gave the expected ketoester **5b** in 39% yield, together with the protonated by-product Boc-Ala-OMe (51%). In order to improve this result, we explored various reaction conditions, and identified a catalyst prepared in situ from $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$, as optimal (Scheme 2).[10]

Once the preparation of compound **5b** had been optimised, its lactamisation to obtain compound **11** was first attempted by hydrogenolysis of the Cbz group. The only compound isolated from the reaction was identified as pyrazine **10**, and resulted from the dimerisation and aromatisation of the deprotected aminoketone (Scheme 3).

Since all attempts to prepare ethylene acetal **12** were unsuccessful[11] (Scheme 4), we treated compound **5** with L-Selectride, which yielded lactone *trans*-**13**.[6,12] The most characteristic ^{1}H NMR signals of lactone *trans*-**13** were a broad doublet at δ 4.22 and a broad singlet at δ 4.73, corresponding to H-3 and H-5, respectively. The *trans* stereochemistry was assigned on the basis of the small chemical shift difference between the protons at C-4 ($\Delta\delta \approx 0.16$).[6] Hydrogenolysis of the Cbz group of lactone **13** gave the desired 5-hydroxylactam **14** in 15% yield, which was identified by comparison of its spectral data to that reported.[13]

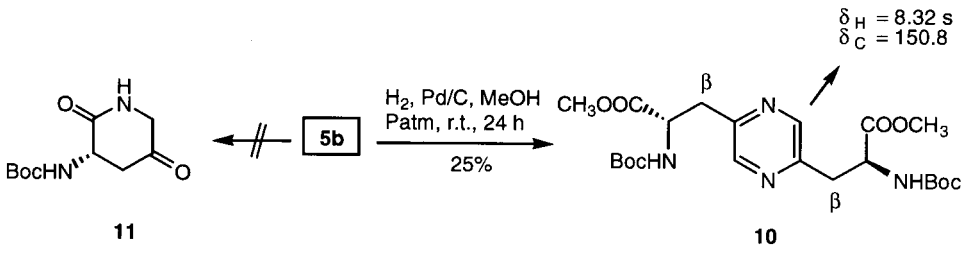
As an alternative to promote lactamisation over dimerisation, we activated the methyl ester **5b** by transforming it into a pentafluorophenyl ester, via acid **15** (Scheme 5). To our satisfaction, hydrogenolysis of the Cbz group of the pentafluorophenyl derivative **16** gave 3-amino-2,5-dioxopiperidine **11** in 79% yield. The most relevant ^{13}C NMR data of lactam **11** were the C3 methine carbon at δ 47.8, and two methylene signals at δ 42.3 and 51.5, corresponding to C4 and C6, in addition to the new lactam carbonyl signal at δ 170.9. Finally, alkylation of lactam **11** with benzyl bromoacetate using LHMDS as the base yielded the target piperidin-2,5-dione **4**, albeit in poor yield. In the ^{1}H NMR spectrum, compound **4** showed a characteristic AB system at δ 3.78 and 4.25 (J=17 Hz), corresponding to the exocyclic NCH_2 protons (α-H), and two singlets at δ 4.25 and 5.12 corresponding to the 6-H and benzyl protons, respectively. In the ^{13}C NMR spectrum C6 and Cα were coincident at δ 48.4.

With the synthesis of compound **4**, we have demonstrated the usefulness of organozinc chemistry for the preparation of 3-amino-2,5-dioxopiperidines. In future work, we intend to study some applications of compound **4**, both as a constrained surrogate of the Ala-Gly dipeptide and as a precursor of other pseudopeptides.

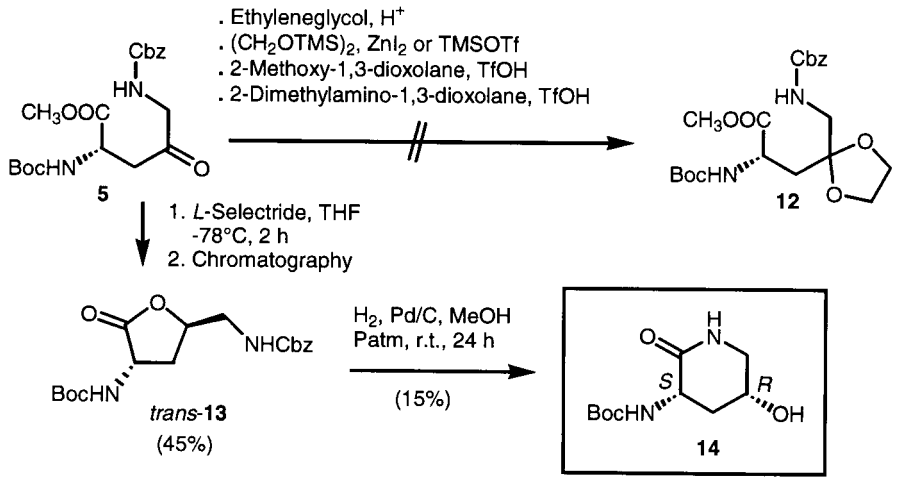
1. Experimental

1.1. General

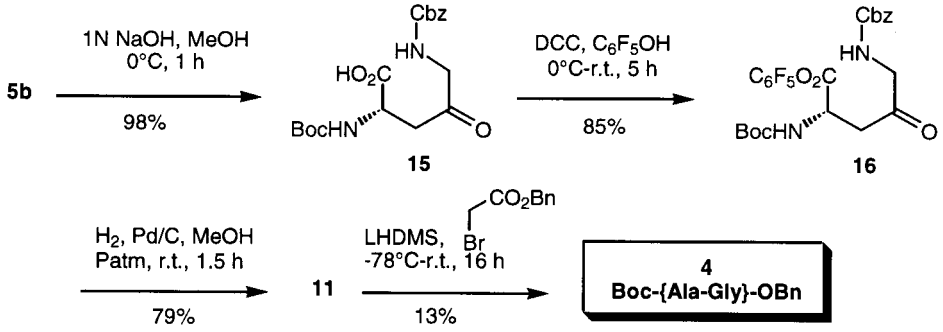
Melting points were determined in a capillary tube on a



Scheme 3.



Scheme 4.



Scheme 5.

Büchi apparatus. Optical rotations were measured with a Perkin–Elmer 241 polarimeter, at 23°C. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, on a Varian Gemini-300 instrument. Chemical shifts are expressed in parts per million (δ) relative to Me_4Si. Mass spectra were determined on a Hewlett–Packard 5988A mass spectrometer by electronic impact (EIMS). TLC was performed on SiO_2 (silica gel 60 F254, Macherey–Nagel) and developed with the eluent described for column chromatography. The spots were located with ninhydrin, potassium hexachloroplatinate, anisaldehyde, or $KMnO_4$. Purification of reagents and solvents was performed according to standard methods. Microanalyses were performed on a Carlo Erba 1106 analyzer at the Serveis Científico-Tècnics (Universitat de Barcelona). Protected iodoalanine **7** was prepared by the literature method.[8]

1.1.1. Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-4-oxopentanoate (8). To a suspension of Zn (1.17 g, 18 mmol) in dry THF (2 ml) 1,2-dibromoethane (77 μl, 0,9 mmol) was added and the mixture was stirred at 45°C under N_2 atmosphere for 20 min. The mixture was cooled, TMSCl (22 μl, 0.18 mmol) was added, and the suspension was stirred for 20 min at rt. A solution of protected iodoalanine **7** (987 mg, 3 mmol) in dry THF (2 ml) was added via syringe. The mixture was stirred at 45°C until complete consumption of the substrate (tlc control, 1.45 h). *S*-Ethylsulfanylacetic acid (470 μl, 4.5 mmol) and $PdCl_2(PPh_3)_2$ (111 mg, 0.15 mmol) were sequentially added to the organozinc derivative thus obtained. After stirring at 45°C for 4.5 h, the reaction was quenched by addition of AcOEt and 1 M NH_4Cl. The mixture was filtered through Celite® to remove the excess of Zn, the solution was diluted with AcOEt, and washed with brine. The organic extracts were dried and evaporated to give a yellow oil which was chromatographed (hexane: AcOEt, 7:3) to obtain the desired ketoester **8** (lower R_f, 279 mg, 39%) and a small proportion of Boc-Ala-OMe (higher R_f, 43 mg, 7%). Ketoester **8**: $[\alpha]_D^{22}=+32.7$ (*c* 1, $CHCl_3$). IR (NaCl) 1718 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.48 (s, 9H, $C(CH_3)_3$), 2.17 (s, 3H, H-5), 2.96 (dd, J=18, 4 Hz, 1H, H_A-3), 3.18 (dd, J=18, 4 Hz, 1H, H_B-3), 3.73 (s, 3H, CO_2CH_3), 4.49 (t, J=4 Hz, 1H, H-2), 5.51 (d, J=8 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$) 28.3 ($C(CH_3)_3$), 29.9 (C-5), 45.4 (C-3), 49.4 (C-2), 52.6 (CO_2CH_3), 80.0 ($C(CH_3)_3$), 155.5 (NH–CO-Boc), 171.8 (CO_2CH_3), 206.6 (C-4). EIMS *m/z* (%) 245 (M^+, 0.1), 130 (12), 86 (28), 57 (100). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.40; H, 7.93; N, 5.76.

1.1.2. *S*-Phenyl *N*-benzyloxycarbonylaminoethanothioate (9). To a solution of *Z*-Gly (20 g, 95.6 mmol) in dry THF (500 ml) cooled at −10°C and under N_2 atmosphere, DMAP (2.92 g, 23.9 mmol) was added. After 10 min, DCC (49.2 g, 239 mmol) was added, and the formation of a white precipitate was observed. After 30 min at −10°C, recently

distilled C_6H_5SH (54 ml, 382 mmol) was added, and the mixture was stirred for 2 h at −10°C and 1 h at rt. The reaction mixture was filtered, the solvent was evaporated, and the residue was dissolved in AcOEt and was washed with 1 M HCl. The organic extracts were dried and evaporated to give a yellow oil which was flash chromatographed (hexane:AcOEt, 7:3) to yield thioester **9** as a white solid (21 g, 73%). Mp 72–74°C (hexane–AcOEt). IR (KBr) 1687 and 1656 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 4.30 (d, J=6 Hz, 2H, H-α), 5.16 (s, 2H, $CH_2C_6H_5$), 5.40–5.55 (m, 1H, NH), 7.35 (s, 5H, $CH_2C_6H_5$), 7.40 (s, 5H, SC_6H_5); ^{13}C NMR ($CDCl_3$) 50.6 (C-α), 67.4 ($CH_2C_6H_5$), 126.4 ($CH_2C_6H_5$-*ipso*), 128.2, 128.3, 128.6, 129.4, 129.7, 134.7 (C_6H_5), 136.1 (SC_6H_5-*ipso*), 156.2 (NH–CO-Cbz), 196.0 ($COSC_6H_5$). EIMS *m/z* (%) 301 (M^+, 0.1), 200 (30), 109 (39), 91 (100).

1.1.3. Methyl (*S*)-5-(benzyloxycarbonylamino)-2-(*tert*-butoxycarbonylamino)-4-oxopentanoate (5b). Operating as for the preparation of **8**, from Zn (588.5 mg, 9 mmol) activated with 1,2-dibromoethane (38 μl, 0.45 mmol) and TMSCl (11 μl, 0.09 mmol), iodoalanine **7** (493 mg, 1.5 mmol), dry THF (2 ml), thioester **9** (677 mg, 2.25 mmol), $Pd_2(dba)_3$ (34 mg, 0.03 mmol), and P(*o*-tol)$_3$ (45.65 mg, 0.15 mmol), a yellow oil was obtained, which was chromatographed (hexane:AcOEt, 8:2 and 2:8) to obtain the desired aminoester **5b** (288 mg, 49%), Boc-Ala-OMe (92 mg, 30%), and the unaltered excess thioester **9** (305 mg). **Aminoester 5b**: $[\alpha]_D^{22}$=+22.4 (*c* 1, $CHCl_3$). Mp 80–81°C (AcOEt). IR (NaCl) 1760, 1750 and 1725 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.43 (s, 9H, $C(CH_3)_3$), 2.95 (dd, J=17, 4 Hz, 1H, H_A-3), 3.09 (br d, J=17 Hz, 1H, H_B-3), 3.72 (s, 3H, CO_2CH_3), 4.11 (d, J=5 Hz, 2H, H-5), 4.56 (br s, 1H, H-2), 5.24 (s, 2H, $CH_2C_6H_5$), 5.48 (d, J=6 Hz, 2H, NH), 7.27 (s, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$) 28.3 ($C(CH_3)_3$), 41.9 (C-3), 49.4 (C-2), 50.6 (C-5), 52.8 (CO_2CH_3), 67.1 ($CH_2C_6H_5$), 80.3 ($C(CH_3)_3$), 128.1 (C_6H_5-*o and -p*), 128.4 (C_6H_5-*m*), 136.2 (C_6H_5-*ipso*), 155.4 (NH–CO-Boc), 156.1 (NH–CO-Cbz), 171.5 (CO_2CH_3), 203.6 (C-4). EIMS *m/z* (%) 395 (M^++1, 0.1), 294 (3), 174 (14), 146 (14), 91 (100), 57 (63). Anal. Calcd for $C_{19}H_{26}N_2O_7$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.70; H, 6.60; N, 6.76.

1.1.4. (*S,S*)-2,5-Bis(2-*tert*-butoxycarbonylamino-2-methoxycarbonylethyl)pyrazine (10). To a solution of ketoester **5b** (100 mg, 0.25 mmol) in CH_3OH (1.3 ml) a catalytic amount of 10% Pd/C was added and the dispersion was hydrogenated in a shaker at rt for 24 h. The reaction mixture was filtered through Celite®, the solvent was evaporated, and the residue was chromatographed (hexane:AcOEt, 3:7) to obtain pyrazine **10** (75 mg, 25%) as a yellow oil. $[\alpha]_D^{22}$=+27.3 (*c* 1, $CHCl_3$). IR (NaCl) 1748, 1716 and 1680 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.42 (s, 9H, $C(CH_3)_3$), 3.29 (d, J=5 Hz, 2H, H-3′), 3.71 (s, 3H, CO_2CH_3), 4.68–4.74 (m, 1H, H-2′), 5.55 (d, J=8 Hz, 1H, NH), 8.32 (s, 1H, H-3, and H-6 Ar); ^{13}C NMR ($CDCl_3$) 28.2 ($C(CH_3)_3$), 36.5 (C-1′), 52.4 (CO_2CH_3), 52.6 (C-2′), 80.0 ($C(CH_3)_3$), 143.9 (C-3 and C-6), 150.8 (C-2 and C-5), 155.2 (NH–CO-Cbz), 171.9 (CO_2CH_3). EIMS *m/z* (%) 482 (M^+, 0.1), 426 (3), 353 (7), 57 (100).

1.1.5. (3*S*,5*R*)-5(*N*-Benzyloxycarbonylaminomethyl)-3-(*tert*-butoxycarbonylamino)-δ-butyrolactone (13). To a solution of ketoester **5** (125 mg, 0.31 mmol) in dry THF (1.6 ml) cooled at −78°C and under N_2 atmosphere, L-Selectride (0.37 ml, 0.37 mmol) was slowly added. After stirring for 2 h at −78°C, the reaction was quenched by addition of 1 M NH_4Cl. The THF was evaporated, the residue was dissolved in AcOEt and was washed with 1 M NH_4Cl and with brine. The organic extracts dried and evaporated yielded an oil which was chromatographed (hexane:AcOEt, 2:1) to obtain lactone *trans*-**13** (40 mg, 45%). $[\alpha]_D^{22}$=−22.4 (*c* 0.5, $CHCl_3$). Mp 143–145°C (AcOEt). IR (NaCl) 3400 (NH), 1706 and 1802 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.43 (s, 9H, $C(CH_3)_3$), 2.27–2.37 (m, 1H, H-4a), 2.48 (br t, J=9 Hz, 1H, H-4b), 3.34 (dt, J=15, 6 Hz, 1H, H-1′a), 3.53 (ddd, J=15, 6 and 4 Hz, 1H, H-1′b), 4.22 (br d, J=7.5 Hz, 1H, H-3), 4.73 (br s, 1H, H-5), 5.10 (s, 3H, NH-Boc, $CH_2C_6H_5$), 5.20 (t, J=6 Hz, 1H, NH-Cbz), 7.35 (s, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$) 28.2 ($C(CH_3)_3$), 31.5 (C-4), 44.7 (C-1′), 49.5 (C-3), 67.1 ($CH_2C_6H_5$), 77.1 (C-5), 80.8 ($CO_2(CH_3)_3$), 128.1 (C_6H_5-*o*), 128.2 (C_6H_5-*p*), 128.5 (C_6H_5-*m*), 136.0 (C_6H_5-*ipso*), 155.1 (NH–CO-Boc), 156.5 (NH–CO-Cbz), 174.8 (C-2). EIMS *m/z*(%) 308 ($M^+-CO_2(CH_3)_3$, 2), 201 (3), 91 (72), 57 (100). Anal. Calcd for a $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.28; H, 6.76; N, 7.48.

1.1.6. (3*S*,5*R*)-3-*tert*-Butoxycarbonylamino-5-hydroxy-2-piperidone (14). To a solution of lactone **13** (80 mg, 0.21 mmol) in CH_3OH (1 ml) a catalytic amount 10% of Pd/C was added, and the dispersion was hydrogenated at P_{atm} and room temperature for 2 h. The mixture was filtered through Celite®, the solvent was evaporated, and the resulting oil was chromatographed (AcOEt:CH_3OH, 94:6) to obtain 5-hydroxylactam **14**[13] (10 mg, 19%). ^1H NMR ($CDCl_3$) 1.46 (s, 9H, $C(CH_3)_3$), 1.65–1.85 (m, 1H, H-4a), 2.85 (br s, 1H, H-4b), 3.24–3.52 (m, 2H, H-6), 4.05 (br s, 1H, H-3), 4.20 (br s, 1H, H-5), 5.59 (d, J=4 Hz, NH–Boc), 6.62 (br s, NH-lactam); ^{13}C NMR ($CDCl_3$) 28.4 ($C(CH_3)_3$), 37.0 (C-4), 49.8 (C-6), 51.6 (C-3), 63.6 (C-5), 80.4 ($C(CH_3)_3$), 155.2 (NH-Boc), 170.9 (C-2). EIMS *m/z* (%) 175 ($M^+-C(CH_3)_3$, 11), 157 (12), 57 (100).

1.1.7. (*S*)-5-(Benzyloxycarbonylamino)-2-(*tert*-butoxycarbonylamino)-4-oxopentanoic acid (15). To a solution of ketoester **5** (150 mg, 0.38 mmol) in CH_3OH (0.95 ml) cooled at 0°C, 1 M NaOH (0.38 ml) was slowly added. After 1 h the reaction mixture was acidified by addition of AcOH at 0°C, and the solvent was removed under reduced pressure. The residue was dissolved in AcOEt and was washed with H_2O and brine to give acid **15** as a red foam (144 mg, 98%). IR (NaCl) 3600 (CO_2H), 1790 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.44 (s, 9H, $C(CH_3)_3$), 2.96 (dd, J=18, 6 Hz, 1H, H_A-3), 3.12 (br d, J=18 Hz, 1H, H_B-3), 4.07–4.17 (m, 2H, H-5), 4.58 (br s, 1H, H-2), 5.11 (s, 2H, $CH_2C_6H_5$), 5.48 (br s, 1H, NH), 5.56 (d, J=4 Hz, 1H, NH), 7.35 (s, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$) 28.3 ($C(CH_3)_3$), 41.6 (C-3), 49.3 (C-2), 50.4 (C-5), 67.2 ($CH_2C_6H_5$), 80.5 ($C(CH_3)_3$), 128.1 (C_6H_5-*o* and *m*), 128.4 (C_6H_5-*p*), 136.0 (C_6H_5-*ipso*), 155.6 (NH–CO-Boc), 156.4 (NH–CO-Cbz), 174.4 (CO_2H), 204.5 (C-4). EIMS *m/z* (%) 381 (M^++1, 0.1), 91 (100), 57 (47).

1.1.8. Pentafluorophenyl (*S*)-5-benzyloxycarbonylamino-2-*tert*-butoxycarbonylamino-4-oxopentan-oate (16). To a solution of acid **15** (650 mg, 1.71 mmol) in dry THF

(8.55 ml) cooled at 0°C and under N_2 atmosphere, DCC (352 mg, 1.71 mmol) was added. After 10 min pentafluorophenol (346 g, 1.88 mmol) was added, and the temperature was left to rise to rt. After stirring for 5 h, the reaction mixture was filtered and the solvent was evaporated under reduced pressure. The resulting yellow oil was chromatographed (hexane:AcOEt, 7:3) to yield the activated ester **16** (766 mg, 85%). IR (NaCl) 1713 (CO), 1520 (CF) cm^{-1}; ^1H NMR ($CDCl_3$) 1.45 (s, 9H, $C(CH_3)_3$), 3.14 (dd, J=18, 4 Hz, 1H, H_A-3), 3.31 (dd, J=18, 4 Hz, 1H, H_B-3), 4.13 (t, J=5 Hz, 2H, H-5), 4.94 (t, J=5 Hz, 1H, H-2), 5.12 (s, 2H, $CH_2C_6H_5$), 5.41 (br s, 1H, NH), 5.55 (d, J=8 Hz, 1H, NH), 7.35 (s, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$) 28.2 ($C(CH_3)_3$), 41.9 (C-3), 49.0 (C-2), 50.4 (C-5), 67.3 ($CH_2C_6H_5$), 81.0 ($C(CH_3)_3$), 128.2 (C_6H_5-*o* and -*m*), 128.5 (C_6H_5-*p*), 135.9 (C_6H_5-*ipso*), 139–143 (C_6F_5), 155.1 (NH–CO-Boc), 156.2 (NH–CO-Cbz), 167.5 ($CO_2C_6F_5$), 203.2 (C-4). MS *m/z* (%) 527 (M+−F, 0.1), 184 (13), 136 (16), 91 (96), 57 (100).

1.1.9. (*S*)-3-*tert*-Butoxycarbonylaminopiperidin-2,5-dione (11). To a solution of pentafluorophenyl ester **16** (650 mg, 1.19 mmol) in CH_3OH (119 ml) a catalytic amount of 10% Pd/C was added, and the mixture was hydrogenated for 1.5 h under atmospheric pressure. The reaction mixture was filtered through Celite®, the solvent was evaporated, and the oily residue was chromatographed (hexane:AcOEt, 1:9) to obtain 5-oxolactam **11** (215 mg, 79%). IR (NaCl) 3300 (NH), 1682 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.46 (s, 9H, $C(CH_3)_3$), 2.53 (dd, J=17, 13 Hz, 1H, H-6a), 3.25 (dd, J=17, 4.5 Hz, 1H, H-6b), 3.85 (dd, J=19, 5 Hz, 1H, H-4a), 4.00 (d, J=19 Hz, 1H, H-4b), 4.50 (br t, J=6 Hz, 1H, H-3), 5.59 (d, J=4.5 Hz, NH–Boc), 6.62 (br s, NH-lactam); ^{13}C NMR ($CDCl_3$) 28.3 ($C(CH_3)_3$), 42.3 (C-4), 47.8 (C-3), 51.5 (C-6), 80.4 ($C(CH_3)_3$), 155.2 (NH–CO-Boc), 170.9 (CO lactam), 202.3 (C-5). EIMS *m/z* (%) 155 (M^+−$OC(CH_3)_3$, 13), 111 (38), 57 (100). Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.63; H, 7.01; N, 12.28. Found: C, 53.03; H, 6.98; N, 12.30.

1.1.10. (*S*)-*N*-Benzyloxycarbonylethyl-3-(*N*-*tert*-butoxycarbonylamino)piperidin-2,5-dione (4). To a solution of lactam **11** (60 mg, 0.26 mmol) in dry THF (1 ml) cooled at −78°C and under N_2 atmosphere, LHMDS (0.26 ml, 0.26 mmol) was added. After stirring for 30 min, benzyl bromoacetate (0.06 ml, 0.39 mmol) was added, and the temperature was left to raise to rt. After 5 h, the reaction was quenched by addition of saturated aqueous NH_4Cl and was partitioned with AcOEt/H_2O. The organic extracts, dried and evaporated gave a yellow oil which was chromatographed (hexane: AcOEt, 7:3) to obtain the target lactam **4** (13 mg, 13%). IR (NaCl) 3500 (NH), 1741, 1728 and 1676 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.46 (s, 9H, $C(CH_3)_3$), 2.58 (dd, J=16, 13 Hz, 1H, H-4a), 3.25 (dd, J=16, 4.5 Hz, 1H, H-4b), 3.78(d, J=17 Hz, 1H, NCH_A), 4.25 (d, J=17 Hz, 1H, NCH_B), 4.25 (s, 2H, H-6), 4.45-4.56 (m, 1H, H-3), 5.12 (s, 2H, CH_2Ph), 5.59 (d, J=4 Hz, NH-Boc); ^{13}C NMR ($CDCl_3$) 28.3 ($C(CH_3)_3$), 42.3 (C-4), 48.4 (C-3 and C-α), 58.0 (C-6), 67.6 (CH_2Ph), 81.3 ($C(CH_3)_3$), 128.4 (Ph-*m*and Ph-*p*), 156.1 (NH-Boc), 170.1 (C-2), 201.3 (C-5). EIMS *m/z* (%) 375 (M^+−1, 0.1), 303 (1), 259 (28), 91 (95), 57 (100). Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.52; H, 6.57; N, 7.21.

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