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Cyclic Endiamino Peptides: A New Synthesis of Imidazopyrazines

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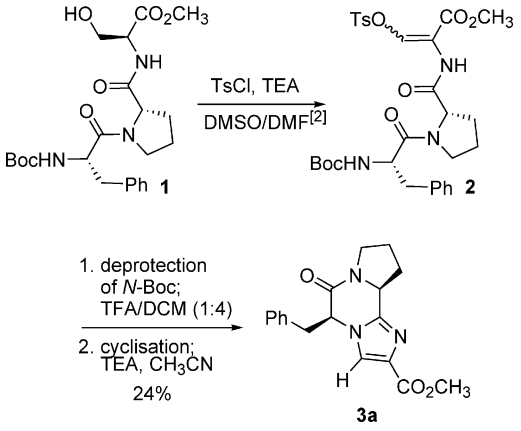
By applying the cyclic endiamino cyclisation methodology to linear tripeptides embodying a β-turn-directing amino acid, the imidazopyrazine ring system was afforded. A mechanism involving the originally desired nine-membered cyclic endiamine is suggested.

Introduction

Following the discovery of callynormine A, a natural endiamino peptide, in which the lactone group of depsipeptides is replaced by an endiamino functionality,[1] we synthesized several cyclic endiamino peptides. Herewith we present the investigation of the scope of cyclisation of small oligopeptides to endiamino peptides.[2] As could be expected,[3] oligotri- and oligotetrapeptides gave upon cyclisation, between the N-terminal and an enol-tosylate[2] group on the C-terminus, mainly dimeric compounds.[3] The hexapeptide was the first compound not to dimerize but rather to afford the monomeric cyclic hexapeptide.[4] To favour monomeric over dimeric cyclisations of the latter small peptides, β-turn-directing acids were inserted into the oligopeptide. Namely, proline and *N*-methylleucine, both possessing high β-turn values,[5]were inserted into a tripeptide.

Results and Discussion

The first cyclisation, starting from tripeptide **1**, which was oxidised to enol-tosylate **2**, afforded major compound **3a** (24% yield, the serine residue was oxidised to formyl glycine, FGly); however, this was not the expected product (Scheme 1).[6] The MS showed, instead of the anticipated monomer peak, one that fits [M – H_2O].[7] Also unexpected in the NMR spectra were two, instead of three, amide CO group resonances (162.9 and 163.0 ppm) and the appearance of a nonanticipated singlet at 143.6 ppm.[8] Comprehensive analysis of the 1D and 2D data (Figure 1) suggested a substituted imidazopyrrolopyrazine structure for compound **3a**.



Scheme 1. Cyclisation of BocPheProSerOMe enol-tosylate **2**.

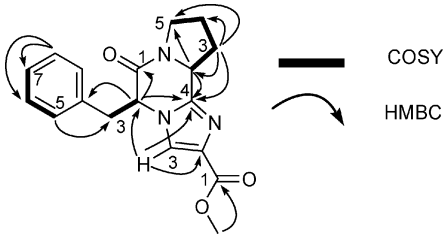


Figure 1. Selected COSY and ^{13}CH-HMBC correlations for compound **3a**.

A suggested mechanism for obtaining the imidazopyrrolopyrazine ring system is depicted in Scheme 2. It is suggested that cyclisation of the tripeptide to afford the expected cyclic endiamino peptide does indeed take place initially (**a**–**c**, Scheme 2). However, the high ring-strain of the nine-membered cyclic peptide triggers a *trans* annular nucleophilic attack; that is, the endiamino amine group, the best nucleophile in the nine-membered ring, attacks the proline amide carbonyl group to afford azacyclol **d**, which

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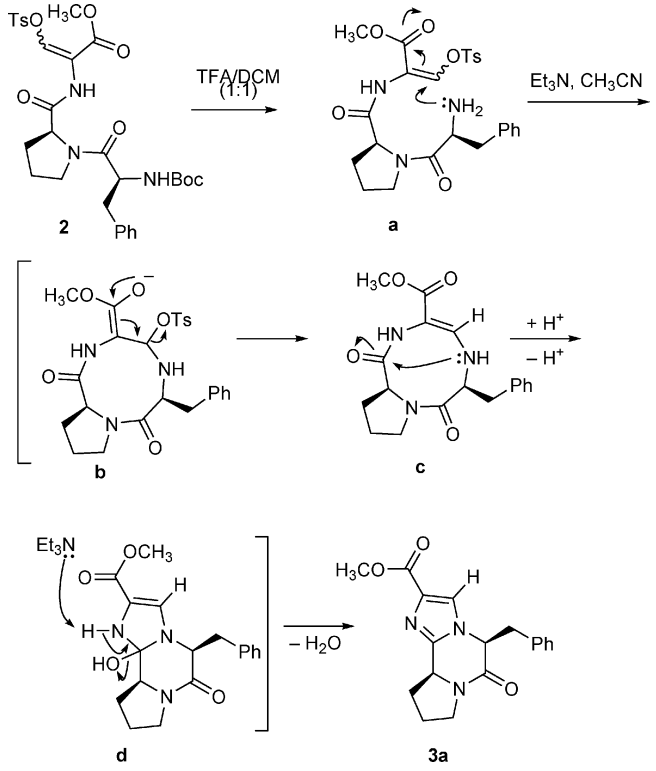
after dehydration affords imidazopyrrolopyrazine **3a**.[9,10] In addition, it was found that compound **3a** isomerises slowly in MeOH (50 °C) to a 2:1 mixture of compounds **3a/3b**.



Scheme 2. Proposed mechanism for the formation of imidazopyrrolopyrazine via enol-tosylate.

In order to clarify the isomerisation spot, we next cyclised diastereoisomer tripeptide **4** containing a D-Pro instead of the L-Pro residue in **3a** (Scheme 3). The product was found to be identical to **3b**, thus establishing the epimerisation site. In addition, dimer **5** was obtained in the latter reaction.

The ^{15}NH-HMBC experiment showed four informative correlations for three nitrogen atoms of compound **3b** (Figure 2).

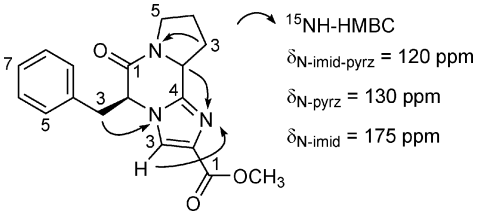
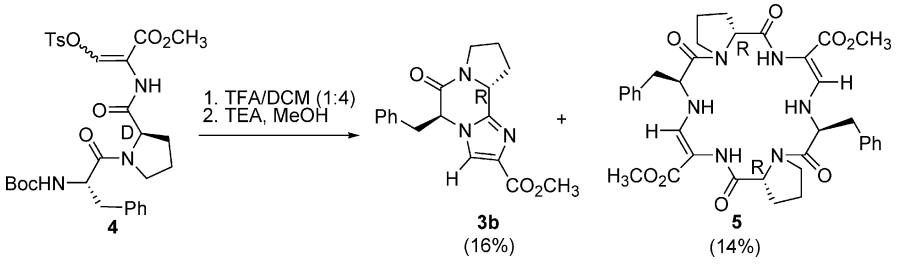


Figure 2. Selected HN correlations for compound **3b**.

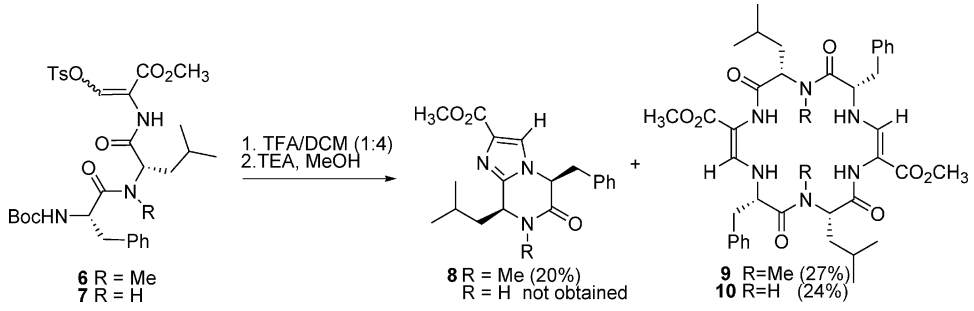
The third examined cyclisation was that of BocPheN-Me-LeuSerOMe enol-tosylate **6**,[12] embodying the β-turn inducing N–Me–Leu. Indeed, desired imidazopyrazine **8** accompanied by dimeric endiamine **9**[13] were obtained. Cyclisation of the non-methylated counterpart tripeptide, BocPheLeuSerOMe enol-tosylate **7**, in contrast, led as expected to dimeric product **10** (Scheme 4).

Conclusions

In summary, the linear enol-tosylate tripeptide embodying a β-turn-inducing amino acid cyclised to afford a cyclic nine-membered endiamino peptide, which collapses to the imidazopyrazine.



Scheme 3. Cyclisation of BocPhe-D-ProSerOMe enol-tosylate **4**.[11]



Scheme 4. Cyclisation of enol-tosylates **6** and **7**.

Experimental Section

General Experimental Procedures: Optical rotations were obtained with a Jasco P-1010 polarimeter. IR spectra were obtained with a Bruker FTIR Vector 22 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Avance-500 and Avance-400 spectrometers.^{1}H, ^{13}C, COSY, HSQC, NOESY and HMBC were recorded by using standard Bruker pulse sequences. MS (FAB) measurements were recorded with a Fisons, Autospec Q instrument. MALDI (HRMS) measurements were recorded with an Applied Biosystem Voyager DE-STR MALDI TOF instrument.

General Procedure for the Oxidation of the "Serine Peptide": A solution of the "serine peptide" (1 mmol) in DMF (5 mL) was added to a mixture of *p*-toluenesulfonyl chloride (5 mmol) in DMSO/DMF (1:1, 5 mL) at –5 °C under an argon atmosphere. After stirring for 5 min at the same temperature, TEA (15 mmol) was added, and the mixture was warmed up to room temperature over 1 h. The reaction was quenched by the addition of ice-cold water (50 mL), and the aqueous solution was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (50 mL), dried with Na_2SO_4, and filtered, and the solvents were evaporated in vacuo. The residue was purified by VLC to afford the enol-tosylate of the FGly (formyl glycine) peptide.

General Procedure for the Preparation of "Imidazopyrazines": The "enol-tosylate FGly tripeptide" (0.1 mmol) was dissolved in an ice-cold mixture of TFA/DCM (1:10, 4 mL) and stirred at room temperature for 3 h. The solvent was then evaporated, and the residue was dissolved in CH_3CN (50 mL), basified with TEA (0.3 mmol) and stirred at room temperature. After 18 h, CH_3COOH (10%, 0.3 mL) was added, and the solvents were evaporated. The residue was purified by sephadex LH20 chromatography and HPLC (Hiber prepacked column 250–25 lichrospher 60 RP –select B 5 μm).

3a: Yellow oil. Yield: 8 mg (14%). $[\alpha]_D^{26}$ = –44 (*c* = 0.5,MeOH). IR (KBr): $\tilde{\nu}$ = 2948, 1734, 1681, 1495, 1212 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ = 8.10 (s, 1 H), 7.16 (m, 3 H), 6.83 (m, 2 H), 5.23 (dd, *J* = 4.2 Hz, 1 H), 4.45 (m, 1 H), 3.75 (s, 3 H), 3.55 (m, 2 H), 3.50 (m, 2 H), 2.18 (dquint., *J* = 2.6 Hz, 1 H), 1.80 (m, 1 H), 1.72 (m, 1 H), 0.74 (m, 1 H) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 163.0 (s), 162.9 (s), 143.6 (s), 135.6 (s), 132.5 (s), 129.1 (d), 128.4 (d), 127.1 (d), 124.1 (d), 58.8 (d), 54.7 (d), 51.4 (q), 44.7 (t), 37.5 (t), 30.6 (t), 21.7 (t) ppm. HRMS (MALDI-TOF): calcd. for $C_{18}H_{19}N_3NaO_3$ [M + Na$^+$] 348.1318; found 348.1288.

3b: Yellow oil. Yield: 8 mg (24%). $[\alpha]_D^{26}$ = +107 (*c* = 0.5,MeOH). IR (KBr): $\tilde{\nu}$ = 2952, 1723, 1683, 1495, 1292, 1210 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ = 7.81 (s, 1 H), 7.13–7.29 (m, 3 H), 6.81 (dd, *J* = 2.6 Hz, 2 H), 5.16 (t, *J* = 5 Hz, 1 H), 3.74 (s, 3 H), 3.42 (dt, *J* = 8.12 Hz, 1 H), 3.33 (m, 1 H), 3.28 (m, 1 H), 3.25 (m, 2 H), 2.28 (quint., *J* = 6 Hz, 1 H), 1.92 (m, 1 H), 1.66 (m, 2 H) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 163.7 (s), 162.9 (s), 144.9 (s), 135.1 (s), 132.6 (s), 129.6 (d), 128.8 (d), 127.8 (d), 124.8 (d), 60.7 (d), 53.9 (s), 51.5 (q), 45.0 (t), 39.3 (t), 30.5 (t), 22.2 (t) ppm. HRMS (MALDI-TOF): calcd. for $C_{18}H_{20}N_3O_3$ [M + H$^+$] 326.1426; found 326.1498.

5: Yellow oil. Yield: 9 mg (16%). $[\alpha]_D^{26}$ = –184 (*c* = 0.5,MeOH). IR (KBr): $\tilde{\nu}$ = 2957, 3227, 1669, 1559, 1496 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ = 8.57 (br. s, 1 H), 7.40 (d, *J* = 14 Hz, 1 H), 7.27–7.35 (m, 5 H), 6.42 (dd, *J* = 12.8 Hz, 1 H), 4.58 (q, *J* = 8 Hz, 1 H), 4.08 (dd, *J* = 12.4 Hz, 1 H), 3.52 (s, 3 H), 3.46 (m, 1 H), 2.94 (br. d, *J* = 8 Hz, 2 H), 2.77 (m, 1 H), 1.86 (m, 1 H), 1.83 (m, 1 H), 1.70 (quint., *J* = 8 Hz, 1 H), 1.37 (m, 1 H) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 170.8 (s), 169.1 (s), 166.5 (s), 145.2 (s), 136.6 (s), 130.0 (d), 128.6 (d), 127.2 (d), 96.1 (s), 60.1 (d), 60.0 (d), 50.7 (q), 47.2 (t), 43.0 (t), 28.8 (t), 25.0 (t) ppm. HRMS (MALDI-TOF): calcd. for $C_{36}H_{42}N_6NaO_8$ [M + Na$^+$] 709.2943; found 709.2956.

8: Yellow oil. Yield: 3 mg (4%). $[\alpha]_D^{26}$ = +55 (*c* = 0.5, MeOH). IR (KBr): $\tilde{\nu}$ = 2926, 1734, 1684, 1653, 1647, 1207 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ = 7.29 (s, 1 H), 7.22–7.24 (m, 3 H), 6.92 (m, 2 H), 4.95 (t, *J* = 5 Hz, 1 H), 4.38 (dd, *J* = 8.4 Hz, 1 H), 3.87 (s, 3 H), 3.37 (qd, *J* = 14.6 Hz, 2 H), 3.02 (s, 3 H), 1.81 (m, 1 H), 1.08 (m, 1 H), 0.88 (d, *J* = 7 Hz, 3 H), 0.72 (d, *J* = 7 Hz, 3 H), 0.43 (m, 1 H) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 164.4 (s), 164.4 (s), 143.6 (s), 134.5 (s), 133.9 (s), 129.6 (d), 128.9 (d), 127.8 (d), 122.8 (d), 60.1 (d), 56.3 (d), 51.7 (q), 44.2 (t), 40.5 (t), 34.1 (q), 23.8 (q), 22.9 (q), 21.7 (q) ppm. MS (FAB): *m*/*z* (%) = 378 (40) [M + Na$^+$].

9: Yellow oil. Yield: 6 mg (4%). $[\alpha]_D^{26}$ = –193 (*c* = 0.5, MeOH). IR (KBr): $\tilde{\nu}$ = 3279, 2952, 1652, 1559, 1383 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ = 7.22–7.24 (m, 3 H), 7.20 (d, *J* = 14 Hz, 1 H), 6.92 (m, 2 H), 6.66 (br. s, 1 H), 6.37 (dd, *J* = 9.14 Hz, 1 H), 4.31 (dt, *J* = 9.6 Hz, 1 H), 3.62 (s, 3 H), 3.50 (dd, *J* = 5.9 Hz, 1 H), 3.27 (dd, *J* = 13.6 Hz, 1 H), 3.07 (dd, *J* = 13.6 Hz, 1 H), 2.96 (s, 3 H), 1.91 (m, 1 H), 1.28 (m, 2 H), 0.87 (d, *J* = 4 Hz, 3 H), 0.86 (d, *J* = 4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 172.3 (s), 168.4 (s), 167.6 (s), 144.4 (d), 136.8 (s), 130.3 (d), 129.5 (d), 127.9 (d), 96.8 (s), 65.0 (d), 61.4 (d), 51.8 (q), 42.1 (t), 39.7 (q), 38.2 (t), 25.6 (d), 24.1 (q), 22.6 (q) ppm. MS (FAB): *m*/*z* (%) = 747 (55) [M + H$^+$].

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[6] All tripeptides were synthesized by the well-established methodology for oligopeptides. The serine alcohol was oxidized and trapped to the appropriate enol-tosylate by Nakazawa oxidation.[2] Cyclisation conditions: serine peptide (1.6 mM), CH_3CN (50 mL), TEA (3 equiv.).
[7] Compound **3** (**a** or **b**): HRMS (MALDI-TOF): calcd. for $C_{18}H_{19}N_3NaO_3$ [M + Na$^+$] 348.1318; found 348.1288.
[8] Data recorded in $CDCl_3$ with Bruker Avance 500 and 400 MHz instruments (100 MHz for ^{13}C).
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[11] The structure of compound **5** was established by 1D and 2D NMR spectroscopic data. HRMS (MALDI-TOF): calcd. for $C_{36}H_{42}N_6NaO_8$ [M + Na$^+$] 709.2943; found 709.2956.
[12] The structure of compound **6** was established by 1D and 2D NMR spectroscopic data. HRMS (MALDI-TOF): calcd. for $C_{25}H_{39}N_3O_7$ [M$^+$] 494.2860; found 494.2873.
[13] Compound **8**: MS (FAB): *m*/*z* = 355.2 [M$^+$] for $C_{20}H_{25}N_3O_3$. Compound **9**: MS (FAB): *m*/*z* = 747.2 [M + H$^+$] for $C_{40}H_{55}N_6O_8$.

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