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A novel approach for the asymmetric synthesis of (3*S*,4*R*)-3-amino-4-alkyl-2-piperidinones: conformationally constrained dipeptides

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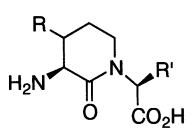
Abstract—A straightforward method is developed for the synthesis of enantiopure (3*S*,4*R*)-3-amino-4-alkyl-2-piperidinone derivatives, six-membered lactam-bridged dipeptides, via highly diastereofacial selective 1,4-addition of organocuprate to the chiral oxazolidine α,β-unsaturated ester **1** as the key step.

Lactams have been considered to be a useful type of conformational constraint in peptide backbones. Incorporation of such lactams into pharmacologically important peptides may provide useful information regarding the bioactive conformation, enhance biological potency and/or increase metabolic stability relative to unmodified original peptides. This concept has led numerous groups to develop lactam-bridged dipeptides as conformationally constrained mimics of peptide derivatives.[1] However, in order for the use of these mimetics in peptide synthesis to be practical, certain criteria are to be met. For instance, (i) synthetic route provides enantiomerically pure lactams, (ii) a substituent that represents the side chain of the former amino acid residue is attached at the specific position of a lactam ring, (iii) the nitrogen atom of a lactam is the part of an amino acid so that the extension of the peptide chain can be continued. For the five-membered lactam-bridged dipeptides, two groups have developed general synthetic methodologies that satisfy the above criteria.[2] On the other hand, surprisingly, only a few laborious syntheses have been reported to obtain the six-membered analogs to the best of our knowledge[3] (Fig. 1).

In this report, we describe the preliminary result of our straightforward approach for the synthesis of enantiomerically pure (3*S*,4*R*)-3-amino-4-alkyl-2-piperidinone derivatives, δ-lactam-bridged dipeptides.

Thus, the α,β-unsaturated ester **1** with *E* configuration was obtained according to the methods known in the literature.[4] The 1,4-addition of dimethylcuprate to the chiral oxazolidine α,β-unsaturated ester **1** in the presence of trimethylsilyl chloride provided the single diastereoisomer, *syn*-**2**, in 94% yield with excellent diastereofacial selectivity.[5,6] Reduction of **2** with $LiAlH_4$ followed by Swern oxidation gave the aldehyde **3** in 94% yield (two steps). The aldehyde **3** was then treated with L-phenylalanine methyl ester in the presence of $NaBH(OAc)_3$ to provide the amine **4**[7] in 90% yield. It is worthy to note that in this reductive amination, the use of THF instead of dichloroethane as solvent and the free amine in lieu of the hydrochloric salt of the methyl ester of L-phenylalanine afforded the optimal yield. The protection of the amine with Cbz group followed by treatment with Jones' reagent gave the acid **6** in 76% yield (two steps). Transformation of the acid **6** into the pentafluorophenol ester and subsequent catalytic hydrogenolysis led to the lactam **7**[8] in 58% yield (two steps) (Scheme 1).



R = alkyl, aryl, carboxylic, alkylamine groups

R' = side chain groups of α-amino acids

Figure 1.

Keywords: peptidomimetics; 3-amino-4-alkyl-2-piperidinone; δ-lactam-bridged dipeptide.

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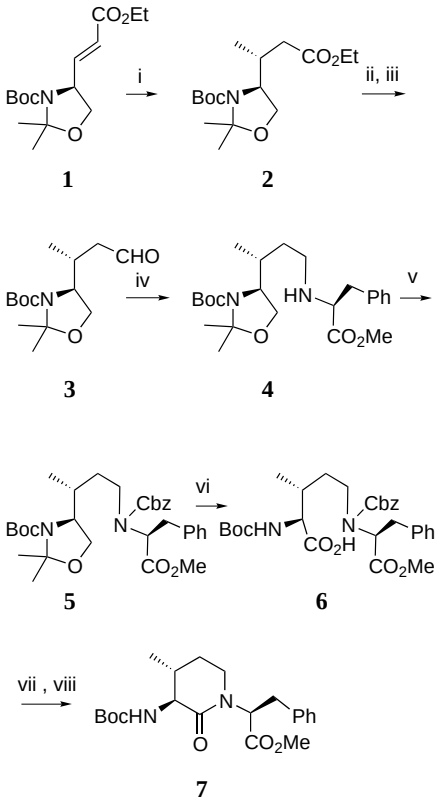

Scheme 1. *Reagents and conditions*: (i) Me_2CuLi, Me_3SiCl, THF, −78°C to rt, 94%; (ii) $LiAlH_4$, THF, rt, 2 h, 98%; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, Et_3N, 96%; (iv) L-phenylalanine methylester, $NaBH(OAc)_3$, THF, rt, 15 h, 90%; (v) CbzCl, Na_2CO_3, THF/H_2O: 3/1, rt, 1 h, 85%; (vi) Jones' reagent, acetone, 0°C to rt, 1 h, 89%; (vii) C_6F_5OH, EDC, CH_2Cl_2, 0°C to rt, 1 h, 74%; (viii) H_2, 10% Pd/C, MeOH, 3 h, 79%.

In conclusion, we have developed a concise method for the synthesis of enantiomerically pure six-membered lactam-bridged dipeptides that can be incorporated into biologically important peptides. Further work is in progress in order to obtain analogs of the lactam **7** with various substituents at the C-4 position of the piperidinone moiety.

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6. Spectral data for **2** (two rotamers): $[\alpha]_D=+18$ (*c* 2, $CHCl_3$), lit. $[\alpha]_D=+19.8$ (*c* 2.18, $CHCl_3$) (Ref. 5a); ^1H NMR ($CDCl_3$, 250 MHz): δ 0.95 (d, 3H, $J=6.7$ Hz), 1.26 (t, 3H, $J=7.2$ Hz), 1.45–1.63 (m, 15H), 1.96–2.20 (m, 1H), 2.46–2.56 (m, 2H), 3.77–3.96 (m, 3H), 4.14 (q, 2H, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 14.3, 16.5, 16.7, 22.7, 24.0, 26.3, 26.9, 28.4, 32.6, 33.0, 36.5, 37.1, 60.3, 61.2, 64.2, 80.0, 94.0, 94.3, 152.5, 173.2; MS (ESI) *m/z* 316 $[M+H]^+$, 338 $[M+Na]^+$, 653 $[2M+Na]^+$. Anal. calcd for $C_{24}H_{38}N_2O_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.84; H, 9.51; N, 4.31.
7. Spectral data for **4** (two rotamers): $[\alpha]_D=+29$ (*c* 3.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.83 (d, 3H, $J=7.2$ Hz), 1.17–1.25 (m, 1H), 1.47 (s, 12H), 1.55–1.68 (m, 4H), 1.80–2.05 (m, 1H), 2.35–2.49 (m, 1H), 2.68 (dt, 1H, $J=5.1$, 10.8 Hz), 2.94 (d, 2H, $J=7.2$ Hz), 3.51 (t, 1H, $J=7.2$ Hz), 3.63 (s, 3H), 3.76–3.89 (m, 3H), 7.15–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 22.8, 24.3, 26.3, 26.9, 28.4, 32.0, 33.3, 33.7, 39.7, 46.4, 51.5, 61.9, 63.1, 64.5, 65.0, 79.5, 79.8, 93.6, 94.0, 126.6, 128.3, 129.1, 137.3, 152.5, 152.9, 175.0; MS (ESI) *m/z* 435 $[M+H]^+$, 457 $[M+Na]^+$, 473 $[M+K]^+$. Anal. calcd for $C_{24}H_{38}N_2O_5$: C, 66.33; H, 8.81; N, 6.45. Found: C, 66.09; H, 8.84; N, 6.47.
8. Spectral data for **7**: $[\alpha]_D=-59$ (*c* 2.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.00 (d, 3H, $J=5.1$ Hz), 1.20–1.44 (m, 10H), 1.65–1.86 (m, 2H), 2.98–3.27 (m, 3H), 3.31–3.42 (dd, 1H, $J=5.6$, 14.4 Hz), 3.65–3.72 (m, 4H), 4.98–5.11 (m, 2H), 7.21–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.8, 28.2, 29.3, 34.0, 34.2, 43.8, 52.2, 57.2, 58.9, 79.3, 126.7, 128.5, 128.7, 136.8, 156.4, 170.3, 170.8; MS (CI) *m/z* 391 $[M+H]^+$; HRMS calcd for $C_{21}H_{31}N_2O_5$ (M+1): 391.2232. Found: 391.2243.