Pergamon

Tetrahedron Letters 43 (2002) 4899–4902

TETRAHEDRON LETTERS

Synthesis of chiral 1,6,8-trioxoperhydropyrazino[1,2-*c*]pyrimidines as novel highly functionalized scaffolds for peptidomimetics

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Received 22 April 2002; revised 17 May 2002; accepted 22 May 2002

Abstract—The synthesis of novel chiral 4,7-disubstituted- and 2,4,7-trisubstituted-1,6,8-trioxoperhydropyrazino[1,2-*c*]pyrimidines from suitably protected TrpΨ[CH(CN)NH]Asp pseudodipeptides is described. This synthesis involves the cyclization of the Ψ[CH(CN)NH] pseudodipeptides, via catalytic hydrogenation and in situ lactamization, to give 3,5-disubstituted-2-oxopiperazine derivatives, which upon reaction with isocyanates, followed by base-catalyzed cyclization lead to the target 4,7-disubstituted-1,6,8-trioxoperhydropyrazino[1,2-*c*]-pyrimidines. The alkylation of these bicyclic heterocycles gives their corresponding 2,4,7-trisubstituted derivatives.

To circumvent the known drawbacks of peptides as potential drugs, the search of small nonpeptide molecules, referred to as peptidomimetics, that are able to bind to peptide receptors, has been a growing area of research in recent years.[1] In this sense, the design of scaffold based di- and tripeptidomimetics aimed to replace the peptide backbone with a cyclic structure onto which the pharmacophoric amino acid side chains are attached in an appropriate orientation, has proven to be a useful strategy.[1] To this aim, nitrogen bridged lactams and cyclic urea based heterocycles are found to be scaffolds of particular interest.[1b,2] Thus, in the course of our efforts to find novel cholecystokinin (CCK) mimetics, we have recently reported on a new series of highly potent and selective CCK_1 receptor antagonists that are based on the 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine scaffold such as compounds **1**[3] (Fig. 1). This fact and our current interest in versatile methodology for constructing peptidomimetics directed our attention to the related 1,6,8-trioxoperhydropyrazino[1,2-*c*]pyrimidine analogues **2**, where the fused piperidine of compounds **1** has been replaced with a 2-oxopiperazine ring, also a pharmacologically privileged skeleton.[4] Although several related heterocyclic systems have recently been reported as peptidomimetics,[5] to the best of our knowledge, no synthesis of this 6,6-bicyclic heterocycle with pendant substituents on the ring carbons has been reported to date.

Taking into account the versatility of the cyano group of Ψ[CH(CN)NH] pseudopeptides for cyclization reactions,[6–9] we thought that the use of suitably protected XaaΨ[CH(CN)NH]Asp pseudodipeptides could give access to 5-substituted-2-oxopiperazine-3-acetate derivatives, via catalytic hydrogenation followed by δ-lactamization, which upon reaction with isocyanates would lead to the target 4,7-disubstituted nitrogen bridged compounds bearing the Xaa amino acid residue at 4 position (Scheme 1). As shown in the scheme, additional side chains can be appended at the ring N-2, via alkylation, in order to mimic tripeptides. Besides a diversity of pendant substituents, this approach allows

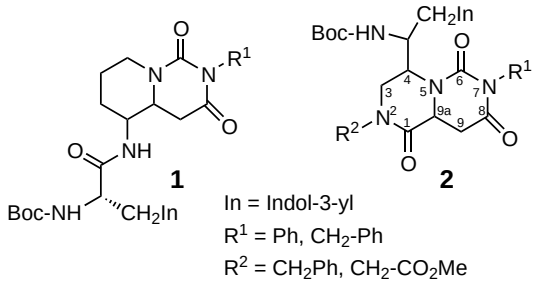

Figure 1.

Keywords:1,6,8-trioxoperhydropyrazino[1,2-*c*]pyrimidines;Ψ[CH(CN)-NH] pseudodipeptides; 3,5-disubstituted-2-oxopiperazines; nitrogen bridged bicyclic heterocycles; peptidomimetics; lactams; urea derivatives.

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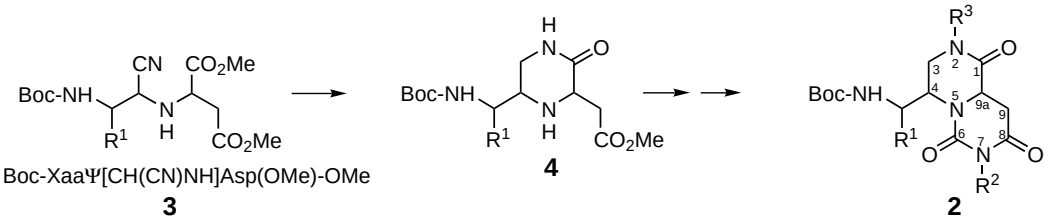
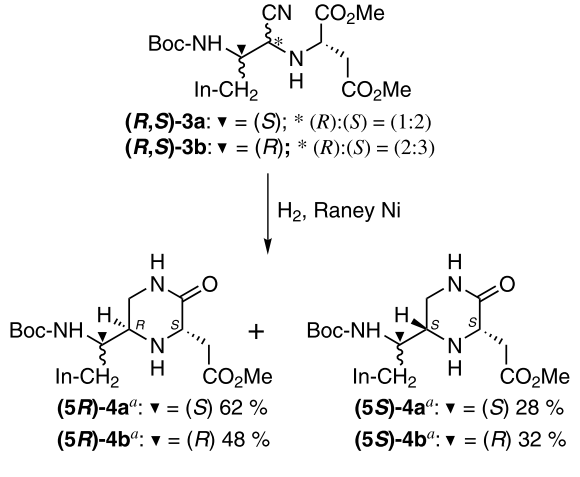
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00964-4



Scheme 1. General approach for the synthesis of 1,6,8-trioxoperhydropyrazino[1,2-*c*]pyrimidines.

the construction of enantiopure 4,7-disubstituted- and 2,4,7-trisubstituted-1,6,8-trioxoperhydropyrazino[1,2-*c*] pyrimidines with stereocontrol at C_4 and at the ring-fusion C_{9a} centers. Because of the importance of the stereochemistry in tryptophan- and indolyl-based CCK receptor ligands,[3a,10] we have used pseudodipeptides (*R*,*S*)-**3a** and (*R*,*S*)-**3b**, containing L- and D-Trp, respectively, as starting materials for the work herein reported. These pseudodipeptides were obtained, as (1:2) and (2:3) (*R*,*S*)-epimeric mixtures at the peptide bond surrogate, from the reaction of Boc-L-Trp-H and Boc-D-Trp-H, respectively, with H-Asp(OMe)-OMe and trimethylsilyl cyanide (TMSCN).[11] The catalytic hydrogenation of the epimeric mixtures (*R*,*S*)-**3a** and (*R*,*S*)-**3b** at room temperature and 1 atm of H_2 pressure, in the presence of Raney nickel, led to the corresponding 2-oxopiperazine derivatives (5*R*,*S*)-**4a** and (5*R*,*S*)-**4b**, which were chromatographically resolved into both (5*R*)- and (5*S*)-epimers (Scheme 2).

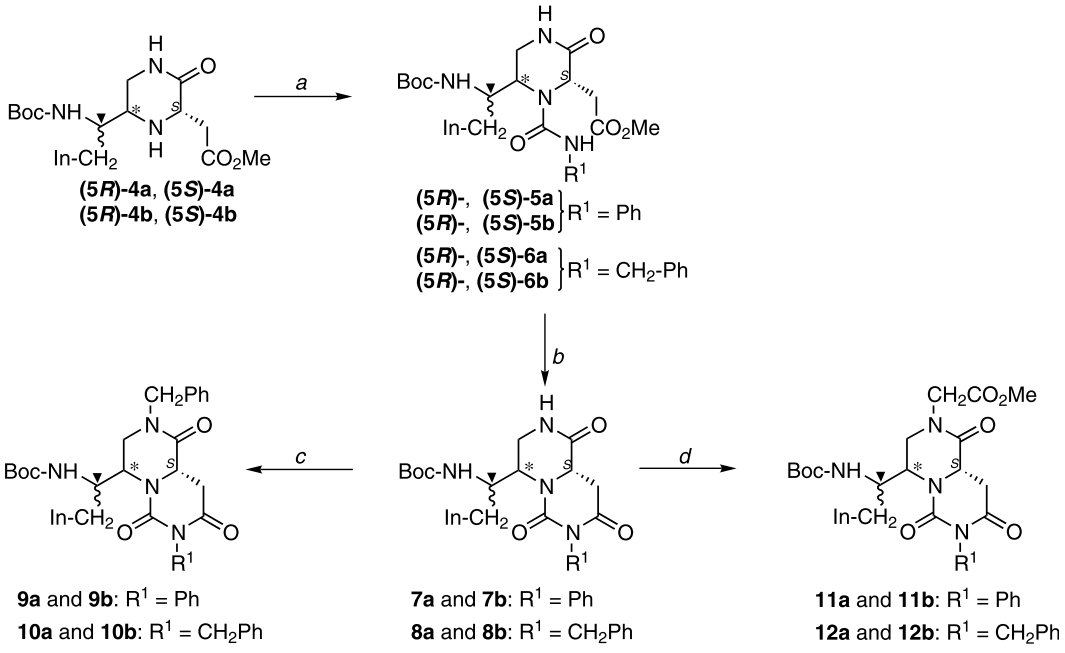
The $J_{5,6}$ coupling constant values (2–4 and 9–12 Hz) in the ^{1}H NMR spectra of all these 2-oxopiperazine derivatives indicated that 5-H adopts an axial disposition. Furthermore, a weak NOE effect (0.5–1%) was observed between 3-H and 5-H in the 3,5-*cis* isomers (5*S*)-**4a** and -**4b**, indicative of a 3,5-*cis*-diaxial disposition.



Scheme 2. Synthesis of 5-substituted-2-oxopiperazine-3-acetates. [a]According to the CIP system, the ligand preference for the stereogenic center denoted with * changes after the CN reduction. Thus, the (*R*)-**3** epimers would be denoted (5*S*)-**4** after the hydrogenation.

As shown in Scheme 3, reaction of the resolved 2-oxopiperazine derivatives (5*R*)-, (5*S*)-**4a** and (5*R*)-, (5*S*)-**4b** with phenyl or benzyl isocyanate in dry THF, at room temperature for 24 h, led to the corresponding urea derivatives **5a**, **5b**, and **6a**, **6b** in 85–95% yield. In the case of the compounds derived from Boc-D-tryptophan **4b**, traces of the 1,4-diacylated compounds were also obtained. In contrast to the 1,4-unsubstituted 2-oxopiperazines **4**, the low $J_{5,6}$ values for the urea derivatives **5** and **6** (3–4 and 3–5 Hz) indicated that 5-H adopts an equatorial disposition in these compounds, independently of the stereochemistry at this position. The treatment of the L-tryptophan urea derivatives (5*R*)-, (5*S*)-**5a** and (5*R*)-, (5*S*)-**6a** with an equimolar amount of DBU, at room temperature in dry THF, produced the desired intramolecular condensation to give the 1,6,8-trioxoperhydropyrazino[1,2-*c*]pyrimidine derivatives **7a** and **8a** in good yields (>90%). However, in the case of the D-tryptophan derivatives **5b** and **6b**, it was necessary to heat at refluxing temperature to achieve their cyclization to **7b** and **8b**. Finally, the alkylation of all these bicyclic compounds, by reaction with benzyl bromide or methyl bromoacetate, yielded the desired 2,4,7-trisubstituted-1,6,8-trioxoperhydropyrazino[1,2-*c*]-pyrimidines **9a**,**b**–**12a**,**b**. Traces of compounds dialkylated, at position 2 and at the indol NH, were detected in this reaction. To minimize the additional alkylation at the indolic NH, molar excesses of alkylating agent and base (Cs_2CO_3) higher than 50% were not used, although some of the starting material was recovered unchanged (30–50%). Epimerization at any of the three stereogenic centers of the starting pseudodipeptides **3a** and **3b** was not observed in any of the synthetic steps. In the NMR spectra of compounds (4*S*)-**9a**, (4*S*)-**11a**, (4*R*)-**11b**, and (4*R*)-**12b** some signals appeared duplicated in an (~1:1) ratio, indicating the presence of two rotamers, probably due to restricted rotation at the N_2–C or C_4–C bonds. In the ^{1}H NMR spectra in DMSO these duplicated signals did not completely collapse at the highest spectrometer work temperature (90°C).

Independently of the stereochemistry, the ^{1}H NMR spectra of the 1,6,8-trioxoperhydropyrazino[1,2-*c*]pyrimidine derivatives **7**–**12** showed $J_{9,9a}$ values (4–5 and 9–11 Hz) indicative of an axial disposition for 9a-H proton, while the low values for $J_{3,4}$ (1–4 and 3–5 Hz) showed that the proton at position 4 adopts an equatorial orientation, and, therefore, the voluminous substituent at this position, 1-(*tert*-butyloxycarbonyl-



Scheme 3. Synthesis of 4,7-disubstituted- and 2,4,7-trisubstituted-1,6,8-trioxoperhydropyrazino[1,2-*c*]pyrimidine. *Reagents and conditions*: (a) R^1NCO, THF, 85–95%; (b) DBU, THF, >90%; (c) $BrCH_2Ph$, Cs_2CO_3, acetone, 50°C, 50–65%; (d) $BrCH_2CO_2Me$, Cs_2CO_3, acetone, 50°C, 50–65%.

amino)-2-(indol-3-yl)ethyl, would be situated in an axial disposition.

All the new compounds herein described were evaluated as CCK_1 and CCK_2 receptor ligands, by measuring the inhibition of the specific [^{3}H]propionyl-CCK-8 binding to rat pancreas and cerebral cortex homogenates,[12] respectively. Unfortunately, none of them showed significant affinity for any of the CCK receptors at concentrations below 10^{-6} M. The lack of affinity in the novel 1,6,8-trioxoperhydropyrazino[1,2-*c*]pyrimidine derivatives **7**–**12**, with respect to our 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine-based CCK_1 receptor antagonist **1**, gives further support to our recently reported findings on the crucial importance of the topography defined by the 1,3-dioxoperhydropyrido[1,2-*c*]-pyrimidine skeleton of this antagonist family for the binding at CCK_1 receptors.[13]

In conclusion, we report an efficient synthesis for a novel type of highly functionalized bicyclic scaffold with controlled chirality at three stereogenic centers. Additionally, this synthetic methodology gives a new example of the versatility of cyanomethyleneamino pseudopeptides for the multigeneration of privileged heterocyclic structures with high diversity. It also suggests that other related nitrogen bridged bicyclic systems could be constructed from this type of pseudopeptides via 3,5-disubstituted-2-oxopiperazines.

Supplementary material

Experimental procedures and characterization data for the 2-oxopiperazines **4a**,**b**–**6a**,**b** and for the 1,6,8-trioxoperhydropyrazino[1,2-*c*]pyrimidine derivatives **7**–**12** are included as supplementary material.

Acknowledgements

This work has been supported by CICYT (SAF2000-0147).

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