Tetrahedron Letters 51 (2010) 2820–2823

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Expedient synthesis of novel bicyclic peptidomimetic scaffolds

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ARTICLE INFO

Article history:
Received 7 January 2010
Revised 15 March 2010
Accepted 16 March 2010
Available online 20 March 2010

ABSTRACT

In the past, bicyclic structures mimicking dipeptides have been designed and successfully used to prepare enzyme inhibitors. We report herein our preliminary results in the design and expedient synthesis of a novel series of diastereomeric *N*-amino-hexahydro-1*H*-isoindolone scaffolds built from three commercially available building blocks in only two steps, with high yields, a single protecting group and a single purification step.

1. Introduction

When developing drugs, two major strategies have traditionally been envisioned. On the one hand, large screening of drug-like molecules can provide hits that could eventually be optimized to afford candidate drugs. On the other hand, rational design of peptides, pseudopeptides, and/or peptidomimetics designed from the natural peptidic substrate of an enzyme or from the natural ligand of a given receptor will provide potential enzyme inhibitors or receptor agonists/antagonists.

As a hybrid strategy, designed focused libraries can also be screened. In many cases these libraries are designed to fit a combinatorial chemistry scheme. For instance, one can use a judiciously selected chiral scaffold with two or three diversity points. These diversity points are then used to spatially deploy pharmacophoric groups. As an example, we have used carbohydrates to deploy side chain mimics in the development of integrin antagonists.[1]

Following the rational design strategy, a number of peptidic and pseudopeptidic lead structures have been developed based on the growing number of identified biologically active peptides. However, despite their promising biological activity, peptides possess a number of unfavorable pharmacological properties that prevent them from being widely used in the drug industry. These peptides may be substrates or ligands for more than one protein, hence resulting in selectivity problems. They are also rarely bioavailable due to poor metabolitic stability and cannot be administered orally. These various issues prompted the design and development of pseudopeptides and peptidomimetics.

In order to mimic biologically active conformations and ensure suitable selectivity and stability toward proteolysis, the conformational constraint or simple modification of peptides is an important strategy.[2] In addition, the replacement of peptide bonds by other functionalities prevents the hydrolysis of these structures, further increasing their inherent stability. Based on these premises, medicinal chemists have developed a number of constrained peptide mimetics that retain the structural features of lead peptide structures while introducing favorable pharmacokinetic properties to the structure and amine and carboxylic acid diversity points (Fig. 1).[3] These scaffolds were later used successfully to prepare enzyme inhibitors including a number of Smac mimetics,[4] prolyl oligopeptidase inhibitors,[5] and thrombin inhibitors.[6]

Following our successful work on the computer aided design and synthesis of bicyclic scaffold-based POP inhibitors,[5] we have endeavored to design and synthesize novel bicyclic rigid scaffolds for the design of enzyme inhibitors. Though many such dipeptide mimetics have been developed,[3] the presence of many chiral centers makes their synthesis often long and laborious. In addition, as illustrated in Figure 1, many of the reported bicyclic scaffolds mimic proline-containing dipeptides.

Increasing the number of synthetically accessible scaffolds to the medicinal chemist toolkit remains an active area of research. In this work, we planned to design novel scaffolds mimicking a larger series of dipeptides (Fig. 2) that can be used in the preparation

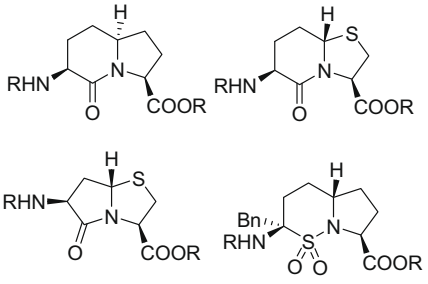

Figure 1. Selected dipeptide mimetics.[7–10]

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doi:10.1016/j.tetlet.2010.03.066

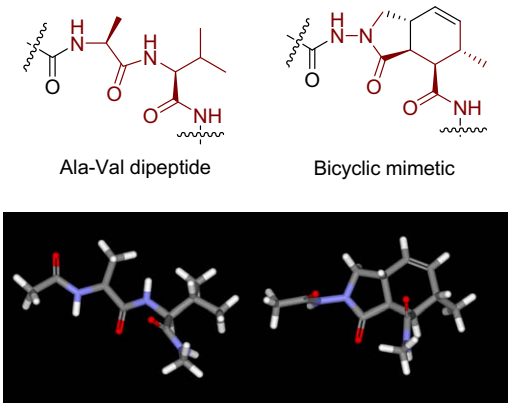


Figure 2. Designed dipeptide mimetic and modeled conformations using ACE 1.0.

of focused combinatorial libraries. Herein, we report our preliminary results in the design and expedient synthesis of a dipeptide (e.g., alanine valine, Fig. 2) mimetic which incorporates an intramolecular Diels Alder reaction (IMDA) in order to form the mimetic scaffold. To our knowledge, this is the most expedient synthesis of such a bicyclic scaffold.

2. Design and synthetic strategy

Our design started with the structure of a dipeptide (Ala-Val in Fig. 2). A number of bicyclic cores were selected and assessed computationally to mimic the general shape of this dipeptide. We chose to incorporate hydrazide motifs to reduce the peptidic nature of the core hence potentially improving the resistance to proteases. Computational studies using our program ACE[11] predicted a preferred orthogonal arrangement for the N–N bond as previously described.[12]

Although tridimensional shape and placement of diversity points are the primary criterion, we also kept in mind synthetic feasibility as we believe that a useful scaffold should fulfill several requirements such as being readily available from commercially available (and inexpensive) building blocks, it should be made with good stereocontrol and should be prepared in high yields and in few synthetic steps without lengthy purifications or isolations. An environmentally friendly synthesis also requires a reduction in the amount of solvent (solventless reaction would be preferred), the number of protecting groups and purification steps. Based on these many criteria, a first scaffold shown in Figure 2 was designed. In order to develop a synthetic strategy, we did not opt for an asymmetric synthesis but rather prepared the racemic mixtures. Our main focus was therefore on the above-mentioned criteria rather than the stereocontrol of the key reaction, although a large systematic investigation to improve the diastereoselectivity has been carried out. Asymmetric versions are currently under investigation and may resolve the issue of racemic mixtures.

Using an IMDA reaction strategy should allow for the formation of the 6,5-bicyclic scaffold and in the process set the stereochemistry of all four stereocenters in a single step (Fig. 3). With this key cycloaddition reaction, the scaffold can be synthesized in few synthetic steps and in high yields.

3. Synthesis

The synthesis started from commercially available *tert*-butyl carbazate (**4**) (Scheme 1). A *solventless* condensation of this protected hydrazine with commercially available *trans*,*trans*-2,4-hexadienal affords the α,β,γ,δ-unsaturated hydrazone in high yields.

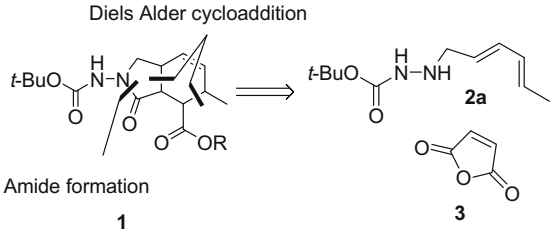
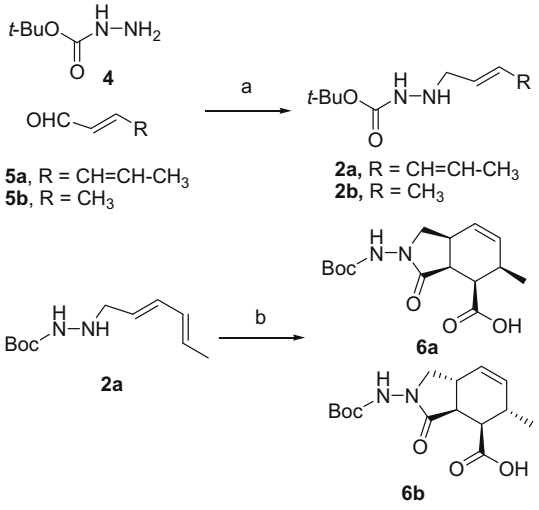


Figure 3. Synthetic strategy.

With no need for a work-up or purification step this product was obtained in high yield and purity. Initial attempts at reduction of the conjugated imine with sodium cyano borohydride proved fruitless, therefore a reagent that would perform the 1,2-reduction selectively was sought. Using dimethylamine-borane/*p*-toluene sulfonic acid as the reducing agent,[13] the desired diene (**2**) was isolated as the sole product in high yields. Once more, the product was obtained with good yields and purity with no need for further purifications.

The tandem amide formation/IMDA reaction with commercially available maleic anhydride (**3**) was performed in a mixture of toluene and THF at reflux overnight. With the prior knowledge that 2,4-pentadien-1-ols when reacted with maleic anhydrides forms fused lactone acids,[14] we thought we could form the analogous fused *N*-amino lactam acid following the same strategy. Gratifyingly, the amide formation / IMDA reaction did run smoothly under thermal conditions in a toluene/THF mixture. However, a 2.3:1 mixture of inseparable diastereomers was formed.

As predicted by our program ACE (Fig. 4), the major diastereomeric adduct, **6b**, was the trans fused ring, being the *exo* Diels–Alder adduct as confirmed by extensive 2D NMR on these diastereomers and some derivatives (Fig. 5). As initially hypothesized, the tandem reaction takes place with the initial amide transformation and then the sequential IMDA reaction. This was confirmed by the isolation of the intermediate triene when the reaction was run at −30 °C. At this stage, an exhaustive optimization of the reaction conditions was carried out in order to probe the solvent effect on the diastereoselectivity.[15] A large screening of solvents and solvent mixtures was successful in increasing *exo*/*endo* selectivity as we found that this ratio rises to as high as 3.3:1 in chloroform while highly solvophobic solvents or solvent mixtures



Scheme 1. Reagents and conditions: (a) neat then $Me_2NH{\cdot}BH_3$, PTSA, MeOH 85%; (b) maleic anhydride (**3**), $CHCl_3$, rt, 71%.

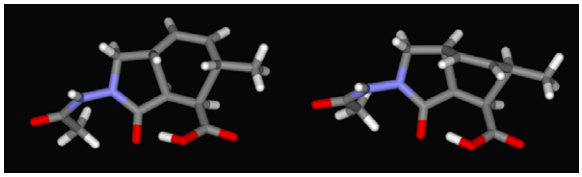


Figure 4. Transition states leading to **6b** (left) and **6a** (right) predicted using Ace 1.0.[11]

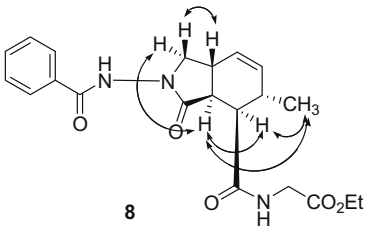
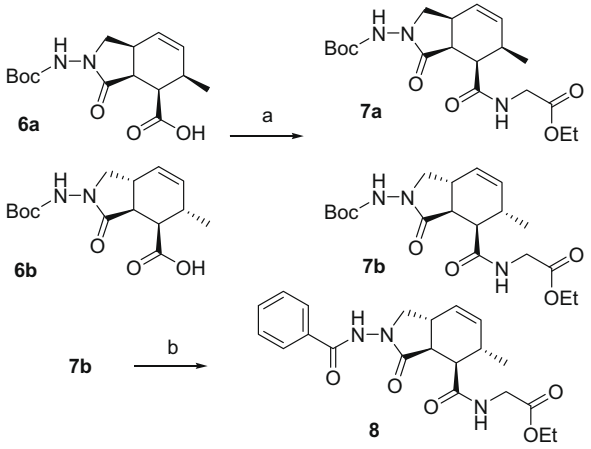


Figure 5. Selected NOE signals enabling the structural assignment.



Scheme 2. Reagents and conditions: (a) Gly-OMe, EDC, HOBT, DIEA DCM, 89%; (b) TFA then BzlCl, pyridine, 71%.

led to poor selectivities (as low as 1.1:1 with a 30% mixture v/v of methanol in water).

In order to establish the applicability of these scaffolds in the preparation of focused libraries and/or peptide mimics, we used them to build tetrapeptide mimics (Scheme 2). Thus, coupling of glycine ethyl ester to the scaffolds **6a** and **6b** under standard conditions provided the amino acid coupled, mono protected scaffolds **7a** and **7b** in good yields and allowed for the clean separation of diastereomers. Deprotection of the hydrazide functional group followed by the N terminal coupling to benzoyl chloride furnished the scaffold incorporated into a peptidomimetic structure **8**.[16]

4. Conclusions

Overall, this synthetic strategy proved very successful as it enabled the high-yielding synthesis of the monoprotected scaffolds **6a** and **6b** as a 3.3:1 mixture of diastereoisomers in only two steps from commercially available starting material. In addition, a solventless step, and a single purification made this expedient synthesis greener than the reported synthesis of other similar scaffolds. It is worth mentioning that as an additional advantage, the presence of a single protecting group enables the first functionalization of this scaffold with no need for a deprotection step while the second derivatization was achieved with a one-pot deprotection/coupling reaction.

Acknowledgments

We thank CIHR, Virochem Pharma, CFI (New Opportunities Fund), NSERC, and FQRNT for financial support. M.H. was supported by a scholarship from CIHR (Strategic Training Initiative in Chemical Biology).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.066.

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16. *tert-Butyl 2-((1E,3E)-penta-1,3-dienyl)hydrazine carboxylate* (**2a**). To melted Boc-hydrazide (1.19 g, 9.0 mmol) at 70 °C was added *trans,trans*-2,4-hexadienal (1.0 mL, 9.0 mmol) dropwise. The mixture was stirred for 15 min and cooled down to rt. The resulting solid was dissolved in MeOH (50 mL) and $Me_2NH{\cdot}BH_3$ (848 mg 14.4 mmol) was added slowly at 0 °C followed by a solution of PTSA (10.3 g, 54.0 mmol) in MeOH (50 mL). After stirring for another 2 h, a solution of $Na_2CO_{3(aq)}$ (120 mL, 10% w/v) was added and the mixture was refluxed for 2 h then concentrated in vacuo, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo to afford **2a** (yellow oil 1.620 g, 85% yield). IR (film) ν_{max}: 3308, 2978, 2933, 1704 cm^{-1}; ^1H NMR, 500 MHz, $CDCl_3$, (ppm): δ 6.73 (s, 1H), 6.02 (dd, J = 10.5, 15.1, 1H), 5.80–5.95 (m, 1H), 5.52 (td, J = 6.6, 13.5, 1H), 5.45–5.37 (m, 1H), 3.99 (s, 1H), 3.32 (d, J = 6.7, 2H), 1.60 (d, J = 6.8, 3H), 1.32 (s, 9H); ^{13}C NMR, 125 MHz, $CDCl_3$, (ppm): δ 156.6, 133.7, 130.9, 129.0, 126.1, 80.0, 28.2, 17.8; HRMS (ESI+) calcd for $C_{11}H_{20}N_2O_2Na$ 235.14170, found 235.14169.
2-(tert-Butoxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (**6**). Compound **2a** (54 mg, 0.25 mmol) was dissolved in

$CHCl_3$ (1 mL). To the solution was added maleic anhydride (25 mg, 0.25 mmol). After stirring for 15 h, the solution was concentrated in vacuo and the residue was purified by flash chromatography (EtOAc/hexanes, 3:1) to afford **6** (brown oil, 56 mg, 71%). The following data have been collected on a 2.3:1 mixture. IR (film) ν_{max}: 3267, 2979, 2934, 2879, 2623, 1772, 1713, 1633. ^{1}H NMR, 500 MHz, $CDCl_3$, (ppm): δ 9.87–8.58 (br s, 1H), 5.84 (s, 0.3H), 5.77 (d, J = 9.9, 0.7H), 5.59 (d, J = 9.9, 0.7H), 5.54 (d, J = 10.1, 0.3H), 3.90 (s, 0.3H), 3.56 (t, J = 7.4, 0.7H), 3.45 (s, 0.7H), 3.33 (d, J = 8.8, 0.3H), 3.22 (s, 0.3H), 3.15 (t, J = 5.2, 0.3H), 3.05 (s, 0.3H), 2.98 (d, J = 3.6, 0.7H), 2.93 (s, 1.4H), 2.70 (s, 0.3H), 2.39 (s, 0.3H), 1.45 (s, 9H), 1.15 (d, J = 7.3, 2.1H), 1.11 (d, J = 7.4, 0.9H). ^{13}C NMR, 125 MHz, $CDCl_3$, (ppm): δ 175.8, 174.8, 174.4, 174.3, 154.7, 154.7, 134.1, 125.5, 124.5, 82.6, 82.1, 54.1, 52.5, 45.0, 43.0, 42.6, 38.7, 38.7, 33.4, 32.9, 30.9, 28.3, 28.3, 21.9, 18.0. HRMS (ESI+) calcd for $C_{15}H_{21}N_2O_5$ 309.14560, found 309.14504.