Short and Efficient Synthesis of Diazabicycloalkane Dipeptide Mimics

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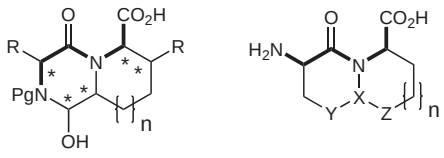
Abstract: A new synthetic route to enantiomerically pure diazabicycloalkanes is reported. Key step of this synthesis is an oxidative cleavage of azabicycloalkene precursors that are synthesized in enantiomerically pure form via aza-Diels–Alder reaction. A range of diazabicycloalkanes with different amino acid side chains have been synthesized and their structure has been elucidated by NMR analysis.

Key words: Diels–Alder reactions, heterocycles, peptides, dihydroxylations, peptide mimics

Interactions of peptides with receptors and enzymes are important for a great number of physiological processes. In consequence, many peptides serve as lead structures for the development of new pharmaceuticals. However, peptides are not ideal drug candidates due to their low metabolic stability, poor oral availability and rapid excretion.[1] In addition, many small peptides lack selectivity to a certain receptor due to their high conformational flexibility. A common strategy to overcome these problems is the synthesis of conformationally constrained peptide analogues mimicking the bioactive conformation of native peptides at the receptor level.[2] These rigid peptidomimetics should then bind with high affinity and specificity to the receptor and have improved pharmacological profiles. In this context, fused bicyclic systems play an important role in the field of drug discovery. Especially azabicycloalkanes of type **II** in Figure 1 have been used as tools for rigidifying peptide structures in order to probe conformation-activity relationships.[3] A number of structurally related bicyclic peptide mimics with different ring sizes and heteroatoms have been prepared and incorporated into peptides for example as turn mimics.[3,4]



I **II**

Pg = protecting group; n = 0, 1
X, Y, Z = N, O or S

Figure 1 Proposed (**I**) and known (**II**) bicyclic dipeptide mimics.

In contrast to azabicycloalkanes like **II**, synthesis and structural properties of diazabicycloalkanes similar to **I** have rarely been reported so far.[5] In the course of a project directed to the development of rigid bioactive peptidomimetics, that should serve as modular ligands for cancer specific receptors,[6] we became interested in highly functionalized diazabicycloalkane derivatives of the general structure **I** (Figure 1) in enantiomerically pure form.

Although a multistep protocol to a proline derivative similar to structure **I** is known,[5] a more general synthetic scheme for the synthesis of new bicyclic compounds **V** (Scheme 1) with various side chains R^1 and R^2 is needed. Such a general route to diazabicycloalkanes **V** would be especially desirable if both residues R^1 and R^2 were easily converted into a range of different groups mimicking the side chains of α-amino acids and thus offering a route to constrained dipeptide mimics. Since it is important for us to conjugate these dipeptides to fluorescence[7] or radiopharmaceutical markers,[8] we wanted to establish a synthetic route that yields polyfunctional diazabicycloalkanes like **V**. Within these structures, the aminal OH should be easily converted into a suitable anchor group by standard *N*-acyliminium chemistry.[9]

We have recently demonstrated that azabicycloalkenes **III** are ideal precursors for substituted derivatives of proline and pipecolic acid like **VI**.[10] Since these substituted analogues of cyclic amino acids are key components for the synthesis of the target compounds **V**, bicyclic alkenes **III** may thus also serve as intermediates for diazabicycloalkanes **V** as depicted in Scheme 1. A possible route to peptidomimetics like **V** would thus require synthesis of suitable cyclic amino acids **VI**, peptide coupling to their N-terminus and subsequent intramolecular ring closure. However, peptide couplings to sterically hindered 5-substituted prolines **VI** (n = 0) and especially 6-substituted pipecolic acids **VI** (n = 1) are problematic in general. Couplings to azabicycloalkanes (like **IV** in Scheme 1) in contrast, are known to proceed in good yields under standard peptide coupling conditions.[11] Compounds **IV** were therefore key intermediates of our synthetic plan for the preparation of dipeptide analogues **V** depicted in Scheme 1. Peptide coupling to these azabicycloalkanes should be easy to perform and a periodate cleavage of the diol function should lead to a bisaldehyde, that in turn should spontaneously form bicyclic structures **V** by intramolecular cyclization with the previously coupled amino acid.

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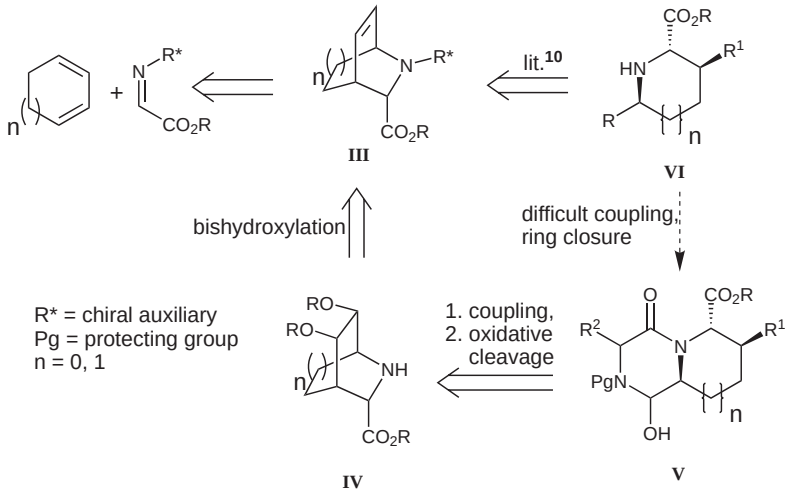
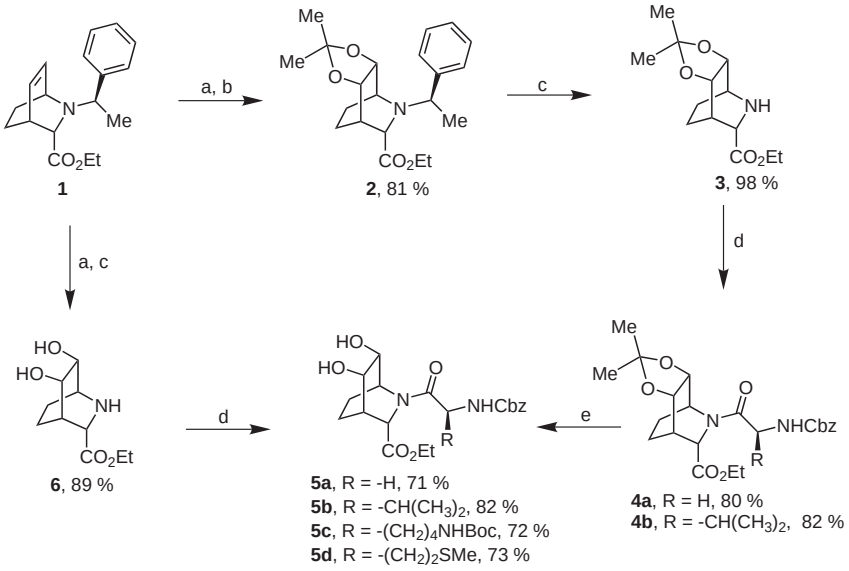


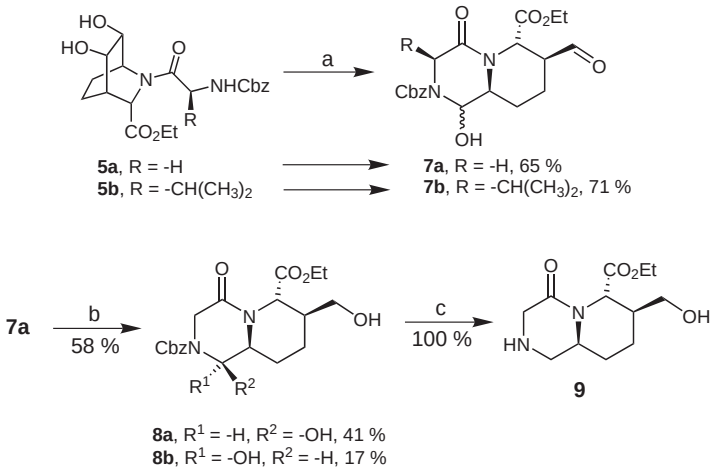
Scheme 1 Retrosynthetic analysis of dipeptide mimics **V**.

The bicyclic alkene **1** is conveniently prepared via stereoselective aza-Diels–Alder reaction of a cyclic diene and a chiral imine derived from enantiomerically pure (*R*)-phenylethylamine following a known protocol.[12] Acetonide **2** was prepared by bishydroxylation of alkene **1** with a catalytic amount of $K_2OsO_2(OH_4)$ and $K_3Fe(CN)_6$ and subsequent protection of the intermediate diol with dimethoxypropane in a good yield over two steps. The *N*-benzyl group in **2** was removed with palladium on activated charcoal to give secondary amine **3** in excellent yield. Cbz-protected glycine and valine, respectively, were subsequently coupled to the N-terminus of **3** under standard conditions (DCC/HOBt) to give **4a** and **4b** in good yields. Finally, hydrolysis of the acetonide yielded diols **5a** and **5b** in good yields.

Hydrolysis of the acetonides in **4a** and **4b** required strongly acidic conditions that are not compatible with acid labile protecting groups like Boc or *t*-butyl of side chain functionalized amino acids. Therefore, we tried a direct coupling of Boc/Cbz-protected lysine and Cbz-protected methionine to the unprotected amino alcohol **6**, which was obtained in good yield over two steps from alkene **1** (Scheme 2). The desired dipeptides **5c** and **5d**, respectively, were obtained in good yields following the standard coupling procedure (DCC/HOBt), indicating that protection of the intermediate diol prior to peptide coupling is not essential. With diols **5a** and **5b** in hand, we synthesized bicyclic dipeptide mimics **7a** and **7b** by cleavage of the diol group and subsequent intramolecular cyclization of the intermediate bisaldehyde. The resulting aminals **7a**



Scheme 2 Conversion of azabicyclooctene **1** to dipeptides **5**. *Reagents and conditions*: a) Cat. $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, *tert*-BuOH/H_2O, 12 h, r.t.; b) PTSA, 2,2-dimethoxypropane, MeOH, 3 h, r.t.; c) H_2 (1 atm), 5% Pd/C, EtOH, r.t., 24 h; d) Cbz-protected amino acid, DCC, HOBt, DMF, 12 h, r.t.; e) 2 N HCl, THF, 45 min, 60 °C.



Scheme 3 Synthesis of dipeptide mimics **7**, **8** and **9**. *Reagents and conditions*: a) $NaIO_4$, acetone/H_2O, –25 °C, 30 min; b) $NaBH_4$, MeOH, 0 °C, 1 h; c) H_2 (1 atm), 5% Pd/C, EtOH, r.t., 24 h.

and **7b** were obtained as 1:1 mixtures of stereoisomers at the aminal position, which can be separated by column chromatography on silica gel if needed. Oxidative cleavage of diols **5a** and **5b** was achieved by treatment with sodium periodate at 0 °C for 45 minutes affording bicyclic aminals **7a** and **7b** in reasonable yields. It should be noted that reaction conditions of this periodate cleavage have to be controlled carefully, as prolonged reaction times and higher temperatures lead to decomposition of the product resulting in complex product mixtures. Azabicycloalkanes **7a** and **7b** with suitable functional groups right in place for further manipulation were thus synthesized in only 4 steps and good overall yield from readily available azabicycloalkene **1**. Treatment of compound **7a** with $NaBH_4$ (Scheme 3) reduced selectively the free aldehyde function to give the corresponding primary alcohol as a mixture of diastereoisomers **8a** and **8b**. The structure of both diastereoisomers was determined by 2D-NOESY-NMR. The combined diastereoisomers **8a** and **8b** were subsequently Cbz-deprotected and reduced with hydrogen and Pd/C to give quantitatively the bicyclic compound **9**.

As illustrated by the synthesis of Gly-Hse mimic **9**[13] (Scheme 3) from **7a**, aminals of the general structure **7** and **8** may serve as versatile educts for the preparation of a range of different dipeptide analogues as the aldehyde may be converted into different side chain functionalities. Furthermore, the aminal OH might be easily modified to a conjugation site by standard *N*-acyliminium chemistry.[9] The stereochemistry of compound **9** was determined unambiguously by 2D-NOESY-NMR and is in accordance with a recently published X-ray structure of a pipecolic acid derivative, which was also synthesized from azabicyclooctene **1**.[10]

In summary, we presented an efficient synthesis of polyfunctional diazabicycloalkanes **7** in enantiomerically pure form. These versatile precursors for dipeptide mimics were synthesized in only 4 steps starting from azabicycloalkene **1** that in turn can be prepared via stereoselective aza-Diels–Alder reaction on a large scale. We have demonstrated the synthetic potential of bicyclic compounds **7** by the synthesis of Gly-Hse mimic **9** and evaluated its structure by NMR. To the best of our knowledge our route is the shortest and most versatile synthetic protocol for enantiomerically pure diazabicycloalkanes **V** known so far. It should be noted that it could be easily expanded to the synthesis of further diazabicycloalkanes with different ring sizes and stereochemistry by varying the azabicycloalkene input. The resulting different dipeptide mimics **V** (Scheme 1) can therefore be used to systematically screen certain dihedral angles in bioactive dipeptides. We are currently probing these compounds for their potential as modular ligands for cancer cell specific enzymes.

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(13) **Typical Procedure for the Synthesis of Peptidomimetics like 9:** 8.86 g (31.0 mmol) of alkene **1** were dissolved in 90 mL *tert*-BuOH and 90 mL water. 30.4 g (93 mmol) $K_3Fe(CN)_6$, 12.7 g (93 mmol) K_2CO_3, together with a catalytic amount (100 mg) $K_2OsO_2(OH)_4$ were added. The resulting yellowish slurry was stirred for 12 h at r.t. Addition of 100 mL water, extraction with ethyl acetate, drying of the combined organics over Na_2SO_4 and removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate 1:1, R_f = 0.33) to give 7.53 g (23.6 mmol) of the diol as a yellow oil. This diol was dissolved in abs. EtOH and 500 mg 5% Pd on activated charcoal was added. The suspension was stirred for 24 h under a hydrogen atmosphere and subsequently filtered through a plug of celite. The solvent was removed under reduced pressure to give **6** as a yellow oil in 5.96 g (89% over two steps) yield. ^{1}H NMR (MeOH-d_4, 500 MHz): δ = 4.33–4.21 (m, 2 H), 4.10 (ddd, 1 H, *J* = 8.5 Hz, 2.8 Hz, 1.4 Hz), 4.06 (ddd, 1 H, *J* = 8.5 Hz, 3.8 Hz, 1.4 Hz), 3.66–3.63 (m, 1 H), 2.96–2.94 (m, 1 H), 2.18–2.16 (m, 1 H), 1.96–1.90 (m, 1 H), 1.89–1.82 (m, 1 H), 1.60–1.51 (m, 1 H), 1.31 (t, 3 H, *J* = 7.3 Hz), 1.27–1.24 (m, 1 H) ppm. HRMS (FAB) calcd for $C_{10}H_{17}NO_4$ (MH+): 216.1236. Found: 216.1239.

1.00 g (4.65 mmol) of amine **6** and 1.94 g (9.29 mmol) Cbz-Gly-OH were dissolved in 20 mL abs. DMF. 0.63 g (4.65 mmol) HOBt dissolved in 20 mL abs. DMF as well as 1.15 g (5.58 mmol) DCC, dissolved in 10 mL abs. DMF, was added. The resulting suspension was stirred for 12 h at r.t. under nitrogen. DCU was filtered off and DMF was removed in vacuo. The crude product was purified by column chromatography on silica gel (dichloromethane/MeOH 95:5, R_f = 0.21) to give 1.34 g (71%) of dipeptide **5a** as a colourless sticky solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.37–7.33 (m, 5 H), 5.83 (br, 1 H), 4.33 (s, 1 H), 4.26 (q, 2 H, *J* = 7.1 Hz), 4.13 (dd, 1 H, *J* = 17.0 Hz, 5.0 Hz), 4.06 (dd, 1 H, *J* = 17.0 Hz, 3.5 Hz), 3.98–3.93 (m, 2 H), 3.81 (m, 1 H), 3.73–3.71 (br, 1 H), 3.62–3.60 (br, 1 H), 2.36 (m, 1 H), 2.12–2.10 (m, 1 H), 1.93–1.89 (m, 1 H), 1.77–1.72 (m, 1 H), 1.37–1.33 (m, 1 H), 1.30 (t, 1 H, *J* = 7.1 Hz) ppm. HRMS (FAB) calcd for $C_{20}H_{27}N_2O_7$ (MH^+): 407.1818. Found: 407.1840.
450 mg (1.11 mmol) of diol **5a** were dissolved in 20 mL acetone/8 mL water and cooled to –25 °C. 400 mg (1.87 mmol) $NaIO_4$ were added and the solution was stirred for 30 min at –25 °C. 50 mL brine were added and the resulting aqueous solution was extracted with ethyl acetate. The organics were dried over Na_2SO_4, filtered and the solvent was removed in vacuo to give 290 mg (65%) **7a** as a colourless oil. The product contained some minor impurities but was used without further purification in the next step.
290 mg (0.72 mmol) of aminal **7a** were dissolved in 25 mL abs. MeOH and 65 mg (1.43 mmol) $NaBH_4$ were added at 0 °C. The solution was stirred for 1 h at 0 °C. After addition of 25 mL water the solution was stirred for additional 15 min at r.t. The solution was subsequently saturated with NaCl and extracted with ethyl acetate. Drying of the combined organics over Na_2SO_4 and removal of the solvent in vacuo gave the crude product as a 7:3 mixture of diastereoisomers, which was purified by column chromatography on silica gel (hexane/ethyl acetate 1:9, R_f = 0.28, 0.35) to give 119 mg (41%) of **8a** as a first fraction and 51 mg (17%) of **8b** as a second fraction as colourless oils. ^{1}H NMR for the major diastereoisomer **8a** ($CDCl_3$, 500 MHz): δ = 7.41–7.34 (m, 5 H), 5.59 (m, 1 H), 5.50 (m, 1 H), 5.19 (s, 2 H), 4.45 (d, 1 H, *J* = 17.7 Hz), 4.30–4.21 (m, 2 H), 4.05 (d, 1 H, *J* = 17.7 Hz), 3.82–3.79 (m, 2 H), 3.55–3.50 (m, 2 H), 2.54–2.53 (m, 1 H), 1.85–1.61 (m, 3 H), 1.50–1.42 (m, 1 H), 1.30 (t, 3 H, *J* = 7.1 Hz) ppm. HRMS (FAB) calcd for $C_{20}H_{26}N_2O_7$ (MH+): 407.1818. Found: 407.1815.
The combined diastereoisomers **8a** and **8b** (170 mg, 0.42 mmol) were dissolved in abs. EtOH and 100 mg 5% Pd on activated charcoal was added. The suspension was stirred for 24 h under a hydrogen atmosphere and subsequently filtered through a plug of celite. The solvent was removed under reduced pressure to give **9** as a colourless oil in 107 mg (100%) yield. R_f = 0.54 (dichloromethane/methanol 8:2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.45 (s, 1 H), 4.15 (q, 1 H, *J* = 7.1 Hz), 3.62–3.57 (m, 3 H), 3.53–3.48 (m, 2 H), 3.18–3.17 (m, 1 H), 2.69–2.65 (m, 1 H), 2.52–2.50 (m, 1 H), 1.68–1.65 (m, 1 H), 1.60–1.52 (m, 1 H), 1.42–1.31 (m, 2 H), 1.31 (t, 3 H, *J* = 7.1 Hz) ppm. HRMS (FAB) calcd for $C_{12}H_{21}N_2O_4$ (MH^+): 257.1501. Found: 257.1532.