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Azabicycloalkenes as Synthetic Intermediates: Application to the Preparation of Diazabicycloalkane Scaffolds

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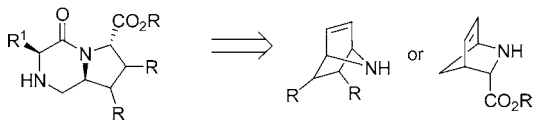
ABSTRACT



A general method to synthesize bicyclic dipeptide mimetics is reported. Key intermediates are azabicycloalkenes 9 and 17, which are prepared via Diels–Alder reactions and subsequent mild deprotection. These unsaturated bicyclic heterocycles are versatile intermediates for different dipeptide mimetics of the aza- and diazabicycloalkane type, which is demonstrated by the synthesis of diazabicycloalkanes 11 and 19 in only 3–6 steps and good overall yield.

Fused bicyclic systems such as aza[*x*.*y*.0]bicycloalkanes **2**[1,2] and diazabicyclo[*x*.*y*.0]alkanes **1** in Figure 1 play an important role in the field of drug discovery and natural product synthesis.[3] They have been used as turn mimetics[4] or scaffolds for combinatorial chemistry[5] and form the core structures of numerous alkaloids.[6]

Although a number of efficient synthetic protocols to certain dipeptide mimetics of type **2** are known,[7] less attention has been paid to diazabicyclo[*x*.*y*.0]alkane derivatives such as **1**.[8] However, general protocols for the synthesis of **1** and **2** were still missing.

Demands for a suitable synthetic route to compounds of type **1** and **2** are high. Such a route has to be (a) short and high yielding, (b) compatible with various side-chain functionalities R^1 and R^2, (c) stereoselective with respect to several stereocenters, and (d) variable concerning stereochemistry.

An obvious starting point for a retrosynthetic analysis of peptide mimetics **1** and **2** is the disconnection of the bicyclic ring system along the tertiary amide. A substituted proline derivative would thus be a suitable synthetic intermediate. However, this approach resulted in somewhat lengthy syntheses so far since the required substituted prolines are difficult to prepare in enantiomerically pure form.[9] Furthermore, introduction of side chains R^2 (if feasible at all) is

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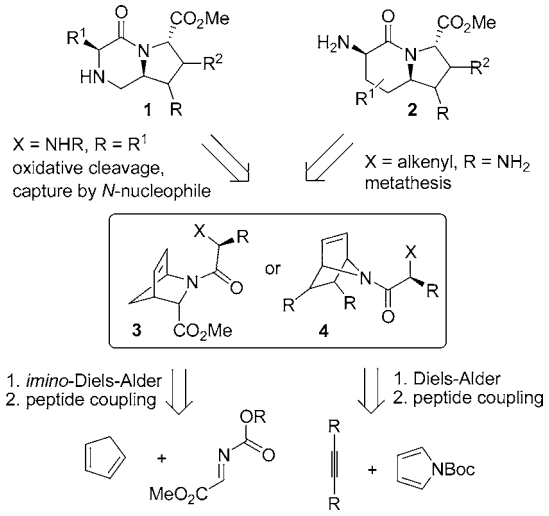

Figure 1. Retrosynthetic analysis of diaza[4.3.0]- and aza[4.3.0]-bicycloalkanes **1** and **2**.

performed at an early stage of the syntheses, limiting structural diversity in this position.

We propose azabicycloalkenes **3** and **4** as synthetic intermediates for dipeptide mimetics **1** and **2**. Compounds **3** and **4** are masked substitutes of substituted prolines: If submitted to the right cleavage conditions, their alkene moiety permits the formation of the second ring system in **1** or **2** and generates at the same time a suitable functional group for the introduction of side chains. This strategy finds precedent in the work of Steglich, who has used diastereoselective *imino*-Diels−Alder reactions for the introduction of the azanorbornene scaffold into peptides and its subsequent conversion into disubstituted proline derivatives.[10]

The practicability of our strategy is demonstrated by the synthesis of diazabicyclo[4.3.0]alkanes **1** in this paper. A complete retrosynthetic analysis is shown in Figure 1. Following this scheme, diazabicycloalkanes **1** would be synthesized by an oxidative cleavage of alkenes **3** or **4**. The azabicycloalkene core of **3** and **4** would be synthesized by a stereoselective *imino*-Diels−Alder reaction[11] of carbamate protected imines (**3**) or a known Diels−Alder reaction of pyrrol (**4**).

We have been particularly interested in diazabicycloalkanes of type **1** and have recently introduced a diastereoselective synthesis[12] of these heterocycles. Scaffolds **1** are functionalized dipeptide analogues that are useful as modular ligands with micromolar affinities for the prostate specific membrane antigene (PSMA), a well-known tumor marker.[13] In addition, they form the core structure of a number of fungal metabolites with antimitotic properties such as the spirotryprostatines, which we are currently synthesizing in our lab. Although we have prepared a number of different peptide mimetics **1** using our diastereoselective synthesis,[14] it remains somewhat ineffective due to unproductive steps for introduction and removal of a chiral auxiliary. For large scale synthesis of scaffolds **1** for the combinatorial search of cancer specific ligands and natural product syntheses we were therefore in need of more efficient approaches.

Bicyclic allylamines such as **3** have been shown to be excellent precursors for numerous attractive target structures such as amino alcohols for catalysis,[15] unnatural amino acids,[16] and other natural products[17] and it was therefore surprising to us, that preparation of enantiomerically pure **9** (Scheme 2) had not been achieved so far.[18] The stereoselective synthesis of *N*-terminally deprotected azabicycloalkene **9** is not a trivial task since the bicyclic ring system is unstable with respect to a range of different deprotection conditions.[19] We were therefore focusing on *imino*-Diels−Alder reactions of carbamate protected imines[20,21] particularly the copper-catalyzed protocol of Jørgensen,[22] since some carbamate protecting groups can be removed under mild

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(20) There is little precedent for this reaction in the literature: (a) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435−2448. (b) Bunch, L.; Liljefors, T.; Greenwood, J. R.; Frydenvang, K.; Bräuner-Osborne, H.; Krogsgaard-Larsen, P.; Madsen, U. *J. Org. Chem.* **2003**, *68*, 1489−1495.

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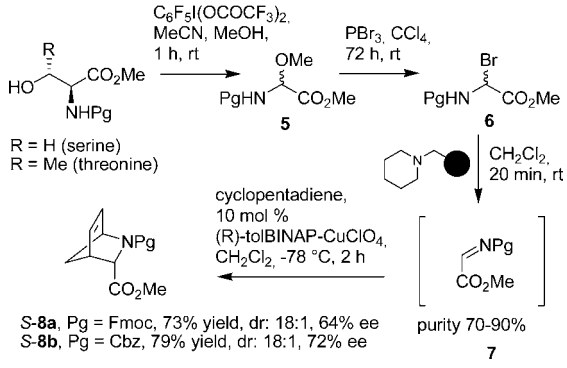
alkaline conditions that should be compatible with the bicyclic allylamine in **3**.

We have found the preparation of carbamate protected imines **7** (Scheme 1) to be a critical step in our sequence.

Scheme 1. Preparation of Imines and Subsequent *imino*-Diels−Alder Reaction to Azabicyclo[2.2.1]alkenes **8**



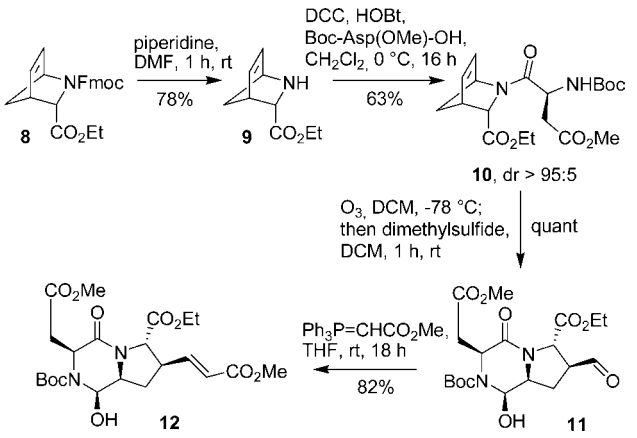
Different methods for the synthesis of these versatile synthetic intermediates are known, but in our hands all of these procedures were either low yielding or gave side products that were not compatible with our Lewis acid-catalyzed Diels−Alder protocol.

A suitable strategy is depicted in Scheme 1. We started from commercially available serine or threonine derivatives, which were converted quantitatively to aminals **5** by using a very recent oxidation protocol of Kita.[23] Alternative methods for the preparation of aminals **5** starting from glyoxylates[24] and serine or threonine derivatives[25b] have been reported. However, we found the Kita protocol to be the shortest and most convenient approach. Crude aminals **5** were then transferred to bromo glycinates **6** again in nearly quantitative yield. Dehydrohalogenation of α-bromo glycinates to *N*-acylated imines has been used successfully in the past.[25] However, these dehydrohalogenations have been performed with an excess of base, which we found not to be compatible with our Lewis acid catalyzed *imino*-Diels−Alder protocol. A suitable workaround is the use of solid supported bases[26] as outlined in Scheme 1. Bromo glycinates **6** were thus converted in high yields to imines **7**, which were transferred with a syringe to a reaction vessel containing a chiral Cu(I) complex.[27] After addition of cyclopentadiene, enantiomerically enriched azabicycloalkenes (3*S*)-**8a** and (3*S*)-**8b** were obtained in high yields and decent enantioselectivities. It should be noted that the yields for azabicycloalkenes **8** are given for the overall process starting from serine or threonine derivatives. Fmoc-protected compounds **6** and **7**, to the best of our knowledge, have not been reported so far. However, they were of special interest to us, since the resulting Diels−Alder adduct (3*S*)-**8a** can be deprotected under mild alkaline conditions which are compatible with the labile azanorbornene scaffold. Absolute stereochemistry for compound (3*S*)-**8b** was verified by hydrogenation to the known ethyl ester of azabicyclo[2.2.1]heptane carboxylic acid[28] and comparison of optical rotations.

With enantiomerically enriched compounds **8** in hand we tried to establish a synthesis of dipeptide mimetics. Starting from Fmoc-protected azabicycloalkene **8**, deprotection of the Fmoc group was performed under standard conditions in DMF with piperidine to give the free amine **9**.

Having in mind that a carbamate function provides a suitable *N*-nucleophile for the desired ring closure to diazabicycloalkanes,[29] amine **9** was coupled to a Boc-protected aspartate derivative with use of DCC/HOBt to give dipeptide **10** in good yield. The minor diastereoisomer of **10** was readily separated on this stage by column chromatography giving pure **10** (dr > 95:5). Oxidative double bond cleavage of dipeptide **10** was performed with ozone according to Scheme 2. Dipeptide **10** is thus converted to a bisaldehyde

Scheme 2. Mild Deprotection of Azabicycloalkene **8** and Subsequent Conversion of Unsaturated Dipeptide **10** to Diazabicycloalkanes **11** and **12**



intermediate that immediately cyclizes to give bicyclic aminal **11** in almost quantitative yield.

This intermediate can be used for further derivatization of the aldehyde function without purification. Wittig reaction of **11**, for example, gives diazabicycloalkane **12** in good yield for this two- step sequence. Relative stereochemistry of **12** was established by 2D-NOESY NMR. The reaction in Scheme 2 is illustrating the general applicability of our

(23) Harayama, Y.; Yoshida, M.; Kamimura, D.; Kita, Y. *Chem. Commun.* **2005**, 1764−1766.

(24) (a) Williams, R. M.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1990**, *55*, 4657−4663. (b) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863−866.

(25) For example: (a) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10−19 and references therein. (b) Apitz, G.; Jäger, M.; Jaroch, S.; Kratzel, M.; Schäffeler, L.; Steglich, W. *Tetrahedron* **1993**, *49*, 8223−8232. (c) Bretschneider, T.; Miltz, W.; Muenster, P.; Steglich, W. *Tetrahedron* **1988**, *44*, 5403−5414. (d) Malassa, I.; Matthies, D. *Liebigs Ann. Chem.* **1986**, 1133−1139.

(26) This method has been used in a different context before: see ref 21c.

(27) No loss of the Fmoc-protecting group was detected upon dehydrohalogenation of bromoglycinate **6** with immobilized piperidine.

(28) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530−2535.

(29) Grohs, D. C.; Maison, W. *Tetrahedron Lett.* **2005**, *46*, 4373−4376.

method since we had shown previously that aldehydes such as **11** are extremely versatile precursors for a number of different diazabicycloalkane peptide mimetics.[30]

In contrast to the sequence depicted in Scheme 2, syntheses of diazabicycloalkanes **1** from alkenes **4** (Figure 1) start from symmetrical azabicycloalkenes such as **13**, **14**, and **15** (Figure 2). A variety of these compounds is easily available by

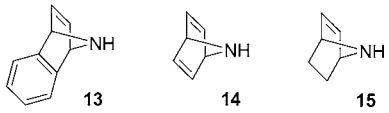
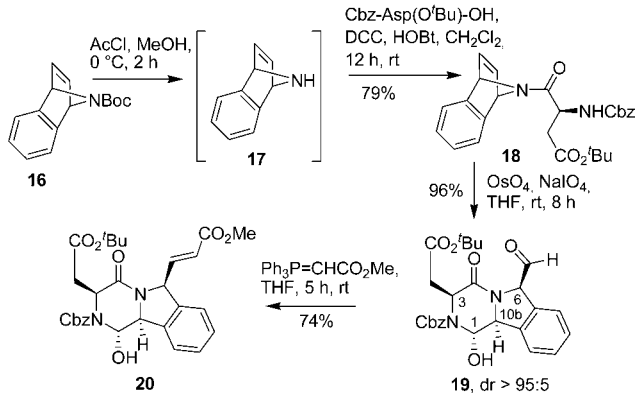


Figure 2. Symmetrical azabicycloalkene scaffolds.

known Diels−Alder reactions of alkynes or benzynes with pyrrole.[31] Azabicycloalkene **13**, for example, can be synthesized from anthranilic acid (which is in situ converted to benzyne) and *N*-Boc-pyrrole in good yield. We were hoping for a stereoselective desymmetration of these heterocycles at a later stage of the synthesis as depicted in Scheme 3.

Scheme 3. Formation and Oxidative Cleavage of Dipeptide **18**, Spontaneous Intramolecular Ring Formation, and Subsequent Wittig Olefination of Aldehyde **19**



Azabicycloalkene **16** was converted to amide **18** by deprotection with HCl in methanol and coupling of the resulting free amine **17** to an aspartate derivative with standard coupling conditions. The azabicycloalkene was cleaved oxidatively and the resulting bisaldehyde cyclized in excellent yield to diazabicycloalkane **19**.

It is interesting to note that amide **18** exists as a 1:1 mixture of isomers (observable by ^{1}H and ^{13}C NMR) most likely due to hindered rotation around the partial CN-double bond between the aspartate and the azabicycloalkene core. The cyclization to **19** proceeds, however, with excellent diastereoselectivity with respect to stereocenters at C3, C6, and C10b. The aminal at C1 is initially formed as an epimeric mixture, which is converted to the 1,3-trans-isomer during purification on silica gel. Aldehyde **19** is an excellent intermediate for dipeptide mimetics imitating a phenylglycine moiety in their *C*-terminal part and can be modified according to our reported procedures.[30] An example is the Wittig olefination of **19** to give alkene **20** in good yield.

In summary, we have reported an efficient synthesis of diazabicycloalkane dipeptide mimetics such as **12** and **20** in four steps from enantiomerically enriched azabicycloalkenes **8** or achiral derivatives **16**. The key step in these sequences is a domino reaction of oxidative cleavage and intramolecular nucleophilic capture of the resulting bisaldehydes by a nitrogen nucleophile. Azabicycloalkenes **8** are synthesized via a catalytic enantioselective *imino*-Diels−Alder reaction. Major advantages of our route are the low number of steps required for the synthesis of dipeptide mimetics such as **11** and **19** and its variability with respect to stereochemistry and the introduction of different side chains.

Enantiomerically enriched azabicycloalkenes **8** and achiral analogues **16** are highly versatile synthetic intermediates. They are useful for the synthesis of diazabicycloalkane dipeptide mimetics and are also valuable intermediates for natural product synthesis. We are currently elaborating a suitable route to a number of antimitotic fungal metabolites based on a 1,4-diazabicycloalkane scaffold along these lines.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) **13**: Lautens, M.; Fagnou, K.; Zunic, V. *Org Lett* **2002,** 4, (20), 3465−3468. **14**: Hodgson, D. M.; Bebbington, M. W. P.; Willis, P. *Org. Biomol. Chem.* **2003**, *1*, 3787−3798. **15**: Otten, A.; Namyslo, J. C.; Stoermer, M.; Kaufmann, D. E. *Eur. J. Org. Chem.* **1998**, 1997−2001.