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An improved cyclization protocol for the synthesis of diazabicyclo[4.3.0]alkanes

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Abstract—We have recently described the synthesis of diazabicyclo[4.*X*.0]alkanes and their use as ligands for the prostate specific membrane antigene (PSMA). The key step of our synthetic route toward these diazabicycloalkanes is an oxidative cleavage of a bicyclic diol moiety followed by the attack of a nitrogen nucleophile to the resulting intermediate bisaldehyde. We herein describe the mechanism of this ring closure and its stereochemical consequences. In addition, we report a convenient method for trapping intermediate bisaldehydes by Wittig reagents. This trapping allows the synthesis of 3,5-disubstituted proline derivatives, which are shown to be versatile precursors for functionalized diazabicycloalkane dipeptide mimetics.

Conformationally constrained peptide mimetics are useful entities for medicinal chemistry as their preorganized conformations allow improved recognition by certain receptors, by reducing the entropy penalty for the receptor-binding event.[1] Furthermore, such peptidomimetics show fairly good pharmacological profiles. In particular, fused bicyclic systems of the aza- and diazabicycloalkane type (structures **1**–**3** in Fig. 1), as well as heteroanalogs thereof have therefore found numerous applications in medicinal chemistry in order to probe conformation–activity relationships or as turn mimetics.[2]

In consequence, a number of different methods for the synthesis of these scaffolds have been developed.[3] Most of these approaches target azabicycloalkane structures of type **1** and **2**[4] mimicking turn structures or *cis*-prolyl fragments and less effort has been devoted to the synthesis of diazabicycloalkanes **3**[5] which are complementary scaffolds to **1** and **2** mimicking more extended peptide conformations. Key aspects of these sequences are stereoselectivity as well as variability with respect to ring sizes and stereochemistry. The backbone dihedral angles ψ, ω, and ϕ as well as at least the first side chain torsional angle χ of the imitated dipeptide unit in **1**–**3** (backbone indicated with bold lines in Fig. 1) might be tuned by variation of stereochemistry and ring sizes (*n* and *m*) within the bicyclic ring system.

We have recently reported an efficient method for the preparation of bicyclic dipeptide mimetics of general type **3** and accomplished the synthesis of various diazabicycloalkanes **3** mimicking polar dipeptides.[6] Key intermediates of our route are dipeptides **4**, that upon

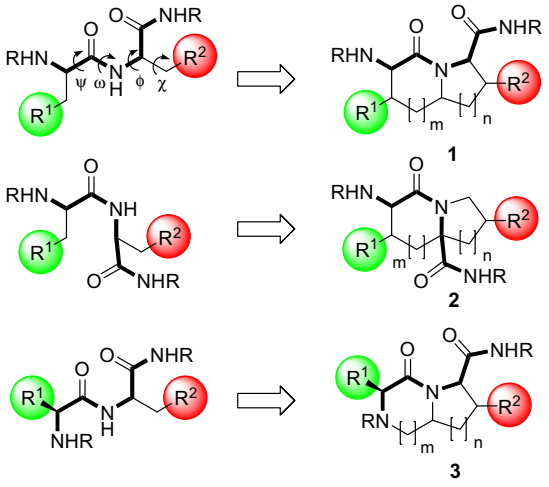

Figure 1. Aza- and diazabicycloalkane dipeptide mimetics **1**–**3**. R^1, R^2: amino acid side chains (N-terminal in green, C-terminal in red); the peptide backbone is indicated with bold lines.

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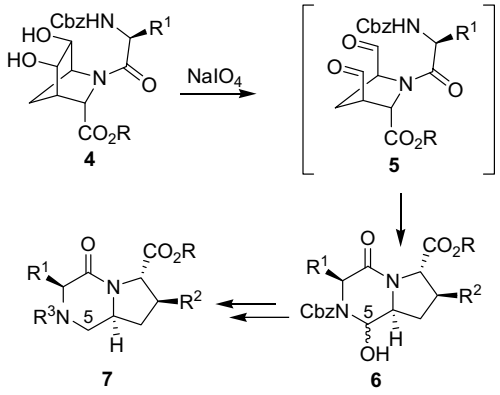


Scheme 1. Intramolecular cyclization to **6** and conversion to diazabicycloalkane dipeptide mimetics **7**.

oxidative cleavage give intermediate bisaldehydes **5** (Scheme 1), that were cyclized to aminals **6**.

Varying the amino acid side chain R^1 as well as the ester moiety R, we have recently found that the efficiency of the cyclization to **6** is dependent on the steric demand of residues R^1 and R in **4**. The cyclization was furthermore found to be sensitive to reaction conditions, with fastest conversion to **6** being observed under slightly acidic conditions. In addition, we observed variable stereochemistry at C5 in different solvents. All these observations prompted us to investigate this piperazinone formation in more detail.

We started a detailed study with model compound **8a** featuring a N-terminal glutamate and *tert*-butyl esters for protection of carboxylates. Immediately after addition of periodate, two products were detected by NMR-spectroscopy: a small portion of the desired aminal **11** and a larger portion of dihydrate **10** which is stable in THF and DMSO but not in chloroform. Ring closure of **10** to **11** is apparently a slow process in acetone/water or other non acidic reaction media. However, it is accelerated dramatically under slightly acidic conditions. To drive cyclization to completion, a solution of **10** and **11** in chloroform was thus prepared leading to quantitative formation of **11** after 14 h at room temperature. Treatment of aminal **11** with a Wittig reagent gave diazabicycloalkane **12**[7] in 83% yield from dipeptide **8a**. We were thus able to improve the yield for dipeptide mimetic **12** significantly in comparison to our previously reported protocol (21% from **8a**).[6]

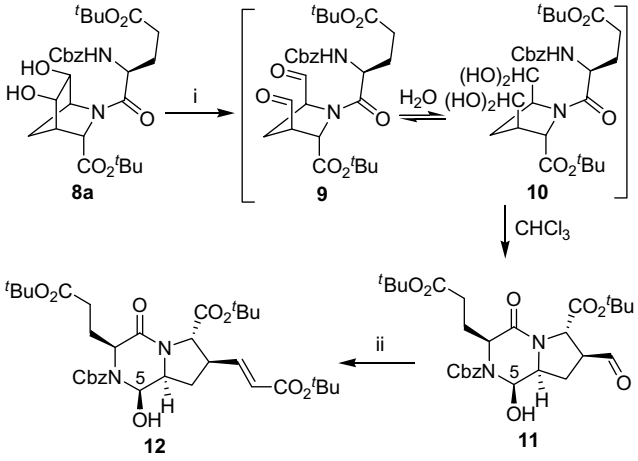
With this finding, we were able to use **8a**–**d** as suitable precursors for both, the preparation of diazabicycloalkanes such as **11** by intramolecular aminal formation and 3,5-disubstituted proline derivatives by trapping both aldehyde functions in **9**. The latter reaction was achieved by the addition of a Wittig reagent and sodium periodate to a solution of dipeptides **8a**–**d** in diethylether to give prolines **13a**–**d** in up to 55% yield.

Bisolefines **13a**–**d** are interesting dipeptides incorporating an unnatural cyclic amino acid and are good synthetic precursors for a number of different 3,5-disubstituted proline derivatives, a class of compounds with interesting structural properties.[8] In addition, **13a**–**d** are excellent intermediates for 5-substituted diazabicycloalkanes like **14a**–**d**. Cyclization of bisolefines **13** to diazabicycloalkanes **14** was achieved with potassium *tert*-butoxide in a diastereoselective Michael type addition of the carbamate NH-group to the vinylogous ester in 5-position of the proline scaffold. The remaining olefin in **14d** was then cleaved by ozonolysis to give dipeptide mimetic **15**[9] with an aldehyde function in 8-position. Since the aldehyde function is easily converted to a number of different amino acid side chains, compounds like **15** are extremely versatile precursors for various mimetics of dipeptides Glu-X_{AA}.

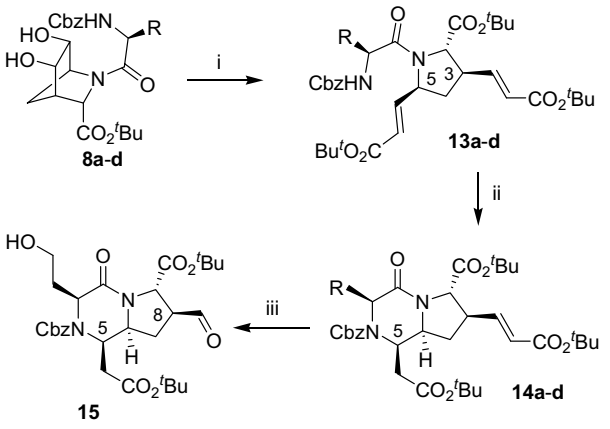
The route depicted in Scheme 3 addresses one of the major drawbacks of our previously published protocol, because it allows the introduction of orthogonally protected side chains in 5-position of the diazabicycloalkane core. These side chains can be used to conjugate dipeptide mimetics like **15** to other functional molecules such as reporter groups for imaging[10] or a solid phase for applications in combinatorial chemistry.[11]

A 3,5-*cis* configuration was assigned to all diazabicycloalkanes **11**, **12**, **14**, and **15** by 2D-NOESY analysis. The NOESY spectra indicated strong crosspeaks for 3-H, 5-H, and 8-H in accordance with relative configurations depicted in Schemes 2 and 3.

In contrast, direct NMR spectroscopic analysis[12] of the crude mixture derived from periodate cleavage of **8a** in acetone/water revealed that the 3,5-*trans* configured aminal **11** (structure not shown in Scheme 2) is the kinetically favored product. However, *trans*-**11** is not stable and rearranges slowly on standing at room temperature or, more rapidly, under acid catalysis to give the thermodynamically stable diastereoisomer *cis*-**11**. Stability of *cis*-**11** is most likely a consequence of pseudo allylic 1,3-strain[13] of residues in 3- and in 5-position with the



Scheme 2. Tandem sequence of oxidative cleavage of **8** and cyclization of bisaldehyde **9** to diazabicycloalkane **11** and its subsequent conversion to olefin **12**. Reagents and conditions: (i) $NaIO_4$, acetone/H_2O, 0 °C to rt, 30 min, then $CHCl_3$, rt, 14 h, 100%; (ii) $Ph_3P{=}CHCO_2C(CH_3)_3$, THF, rt, 12 h, 83%.

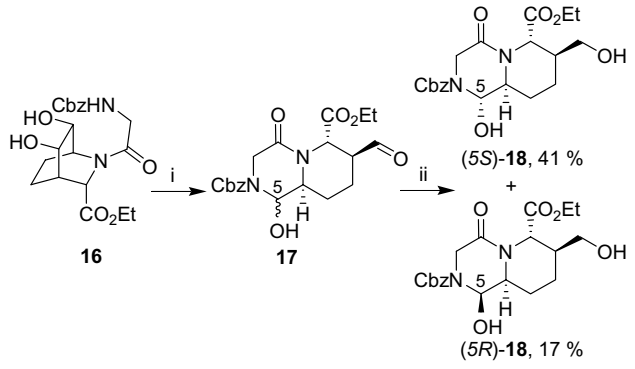


Scheme 3. Synthesis of 3,5-disubstituted prolines **13a–d** and the two-step conversion to 5-substituted diazabicycloalkane **15**. Residue R: $(CH_2)_2CO_2{}^tBu$ (**a**); CH_2CO_2Me (**b**); $(CH_2)_2CO_2{}^tBu$ (**c**); $(CH_2)_2O$-TBDMS (**d**); Reagents and conditions: (i) $NaIO_4$, $Ph_3P{=}CHCO_2R^2$, Et_2O/H_2O, rt, 12 h (13–55%); (ii) KO^tBu, THF/H_2O, reflux, 6 h, rt, 15 h (37–54%); (iii) O_3, DCM, −78 °C (50%).

carbamate, making the 3,5-*trans* substitution a less favorable configuration. This hypothesis is in accordance with findings from a periodate cleavage of dipeptide **16** with glycine as a C-terminal amino acid (Scheme 4).[5a,14]

In this case, the oxidative cleavage gives aminal **17** as a mixture of C5-epimers. After reduction of the aldehyde function in **17**, both diastereoisomers (5*S*)-**18** and (5*R*)-**18** were fairly stable and separated by column chromatography on silica gel.

In summary, we have presented a short and efficient synthetic route to 3,5-disubstituted proline derivatives and their conversion to 5-substituted diazabicycloalkanes via a base mediated intramolecular Michael type addition. Key step is an oxidative cleavage of dipeptide **8** to give bisaldehyde **9**. Depending on steric demand and solvent effects, these intermediate bisaldehydes can be trapped by Wittig reagents to give 3,5-disubstituted proline derivatives like **13** or cyclized to bicyclic aminals like **11**. Yields of this cyclization can be significantly improved in slightly acidic solvents like chloroform.



Scheme 4. Periodate cleavage of glycine containing dipeptide **16**. Reagents and conditions: (i) $NaIO_4$, acetone/H_2O, −25 °C, 30 min; (ii) $NaBH_4$, MeOH, 0 °C, 1 h.

In addition, 3,5-disubstituted prolines have been shown to be versatile precursors for 5-substituted diazabicycloalkanes like **15**. These compounds are of special value to us because they permit the conjugation of diazabicycloalkanes to other functional molecules, such as reporter groups or a solid phase. In consequence, diazabicycloalkanes **15** are modular dipeptide mimetics[15] and might be useful scaffolds for tumor imaging and applications in combinatorial chemistry.

Acknowledgements

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9. Typical experimental procedure is as follows: Synthesis of peptide mimetic: **15**: Preparation of **13d** was carried out in analogy to the method previously described.[6] Compound **14d**: 0.41 g (0.53 mmol) **13d** (1.0 equiv) were dissolved in 10 mL THF and 0.24 g (2.12 mmol) KO^{t}Bu (4.0 equiv) was added. After addition of 1 mL water the resulting solution was refluxed for 6 h and then stirred for 12 h at rt The reaction was quenched with 10 mL citric acid (10% in water) and stirred for another hour at rt. An aqueous solution of NaOH (2 M) was added to adjust to pH 10–12 before the mixture was extracted with ethyl acetate. The organic phase was dried with Na_2SO_4, filtered, and the solvent was removed in vacuo. This crude product was purified by column chromatography (EA/PE, gradient) to give **14d** as colorless sticky solid in 150 mg (0.19 mmol, 37%) yield. ^{1}H NMR (500 MHz, $CDCl_3$, 7:3 mixture of rotamers): δ = 7.27–7.31 (m, 5H), 6.61–6.70 (m, 1H), 5.71–5.83 (m, 1H), 5.13–5.19 (m, 0.5H), 4.99–5.12 (m, 2.5H), 4.42–4.59 (m, 1H), 4.04–4.17 (m, 0.3H), 3.86–4.04 (m, 1.7H), 3.74–3.84 (m, 0.3H), 3.64–3.73 (m, 1H), 3.55–3.64 (m, 0.7H), 2.80–2.86 (m, 0.3H), 2.70–2.80 (m, 0.7H), 2.28–2.49 (m, 1.4H), 2.00–2.26 (m, 1.6H), 1.67–1.81 (m, 1H), 1.28–1.39 (m, 27H), 0.71–0.77 (m, 9H), −0.17 to −0.05 (m, 6H). HRMS (FAB) calcd for $C_{41}H_{65}N_2O_{10}Si$ $(M+H)^+$: 773.4409, found: 773.4412. Compound **15**: 50.0 mg (64.7 μmol) **14d** were dissolved in 25 mL dry dichloromethane and cooled to −78 °C. Ozone was bubbled through the solution for 5 min until a blue color persisted. The solution was purged with nitrogen for 2 min and then treated with dimethyl sulfide (0.84 g, 13.5 mmol) in 5 mL dry dichloromethane. The solution was allowed to reach rt and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (EA/PE, gradient) to give the TBDMS-deprotected compound **15** in 18.2 mg (32.3 μmol, 50%) yield. Compound **15**: ^{1}H NMR (500 MHz, $CDCl_3$, 1:1 mixture of rotamers): δ = 9.74 (s, 1H), 7.29–7.43 (m, 5H), 5.07–5.29 (m, 3H), 4.76 (dd, 0.5H, J = 6.5, 7.5 Hz), 4.68 (d, 1H, J = 7.9 Hz), 4.61 (dd, 0.5H, J = 3.2, 8.5 Hz), 4.08–4.20 (m, 1H), 3.59–3.74 (m, 2H), 2.99–3.07 (m, 1H), 2.45–2.56 (m, 1H), 2.35–2.44 (m, 0.5H), 2.14–2.33 (m, 2.5H), 1.68–1.83 (m, 2H), 1.47 (s, 9H), 1.41 (s, 9H). HRMS (FAB) calcd for $C_{29}H_{41}N_2O_9(M+H)^+$: 561.2812, found: 561.2780.
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