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A short stereoselective synthesis of disubstituted cyclic amino acids

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Abstract—A new synthetic route to enantiomerically pure disubstituted derivatives of cyclic amino acids 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 different disubstituted pipecolic acid derivatives has been synthesized and their structure has been evaluated by X-ray analysis.

α-Amino acids with a rigid backbone structure are synthetically interesting targets because they can be used as building blocks for the preparation of peptides or peptidomimetic structures with biological activity.[1] In particular, incorporation of cyclic amino acids based on proline or pipecolic acid with well-defined structural properties into peptides leads to useful model compounds for studying peptide conformation and protein folding.[2] In addition, these substitutions often go along with improved pharmacological profiles in pharmacologically relevant peptides.[3] Derivatives of proline and pipecolic acid have been used as constrained analogues of proteinogenic amino acids[4] and as rigid modules to constrain peptide conformation.[5] In particular, 5-substituted prolines[6] as well as 3,6-substituted pipecolic acids[7] have been demonstrated to serve as rigid analogues of the *cis*- and *trans*-prolyl amide portion in natural peptides and have been used as educts for the synthesis of constrained dipeptide analogues.[8] In addition, these compounds serve as valuable intermediates in the synthesis of a range of different pyrollidine and piperidine alkaloids for example of the indolizidine and quinolizidine type.[9]

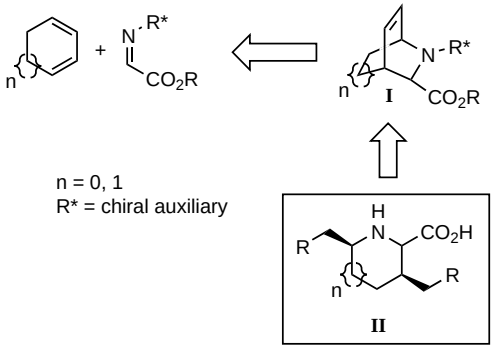

Figure 1. Retrosynthetic analysis of cyclic amino acids **II**.

All these facts have contributed to the growing interest in finding short and efficient stereoselective synthetic routes to substituted cyclic amino acids. Efforts in this direction have met with some success in the past and a number of stereoselective routes to substituted prolines[10] and pipecolic acids[11] have been developed. However, most routes are multistep procedures and general synthetic schemes suitable for 3,5-substituted prolines and 3,6-substituted pipecolic acids are still missing.

In the course of a project directed to the development of rigid bioactive peptidomimetics, that should serve as modular ligands for cancer specific receptors, we became interested in highly functionalized derivatives of proline and pipecolic acid of the general structure **II** (Fig. 1) in enantiomerically pure form. Although some multistep protocols to proline derivatives **II** ($n=0$) are known,[12] routes to the corresponding pipecolic acids **II** ($n=1$) are extremely rare.[11b]

A general route to cyclic amino acids of type **II** would be especially valuable if both residues R were easy to

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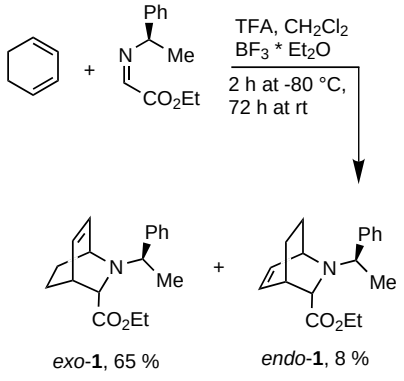
convert into a range of different natural amino acid side chains or other functionalities, thus offering a route to constrained amino acid analogues and versatile intermediates for natural product synthesis.

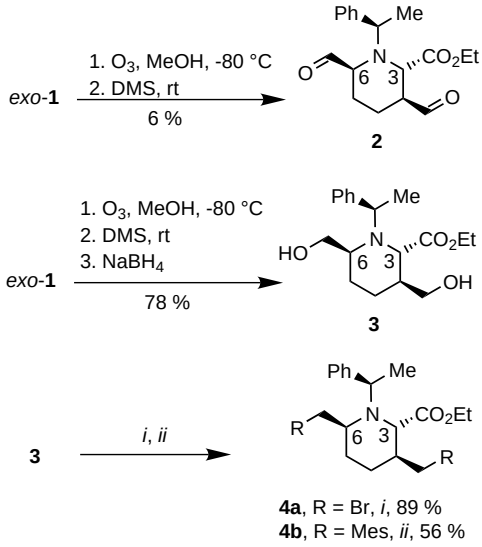
We envisioned azabicycloalkenes **I** as ideal precursors for cyclic amino acids of type **II**. As depicted in Fig. 1 these bicyclic precursors **I** in turn should be easily accessible via stereoselective aza-Diels–Alder reaction of a cyclic dien and a chiral imine. This kind of stereoselective aza-Diels–Alder reaction has been studied extensively in the past and was shown to yield various nitrogen heterocycles in a highly stereoselective way if chiral amines are used as the stereochemical source of information.[13] Oxidative cleavage of the double bond in resulting azabicycloalkenes **I** should then give the desired disubstituted amino acid derivatives **II** with suitable functionalities right in place for further manipulation.

Adopting a known protocol,[14] we started with a one-pot synthesis of azabicyclooctenes **1** according to Scheme 1 from 1,3-cyclohexadiene and a chiral imine, which was derived from (*R*)-phenylethylamine and ethylglyoxylate. A mixture of *exo*-**1** and *endo*-**1** strongly favoring the *exo* product was obtained in reasonable yield. It should be noted that the reaction may be performed on a large scale, thus offering a convenient access to precursors of the general type **I** in Fig. 1. Both isomers *exo*-**1** and *endo*-**1** are easily separated by column chromatography on silica gel.

With azabicyclooctenes **1** in hand, we tried an ozonolytic cleavage of the double bond under standard conditions to the bisaldehyde **2** according to Scheme 2. Unfortunately we were not able to isolate bisaldehyde **2** using a standard flash chromatographic workup procedure although TLC and NMR of the crude reaction mixture indicated that **2** was formed. However, a rapid workup yielded **2** in disappointingly low yield of 18% after flash filtration over a silica gel plug. Suspecting that the chemical instability of amino aldehyde **2** under workup conditions did not allow its isolation in better yields, we tried the ozonolysis of *exo*-**1** with subsequent reduction of the intermediate bisaldehyde **2** in one pot with sodium borohydride next. As anticipated, this



Scheme 1. Aza-Diels–Alder protocol to azabicyclooctenes *exo*-**1** and *endo*-**1**.



Scheme 2. Synthesis of disubstituted pipecolic acid derivatives. (i) Br_2, PPh_3, CH_2Cl_2, pyridine, 0°C; (ii) MesCl, DIPEA, CH_2Cl_2, 0°C (compound **4b** was isolated as its hydrochloride salt).

procedure yielded pipecolic acid derivative **3** in good yield after chromatographic workup. The relative stereochemistry of substituents attached to the piperidine ring was established by NOESY NMR and was found to be not altered by the oxidation reaction. Finally, the absolute stereochemistry was determined by X-ray crystal structure analysis[15] of dibromide **4a** (Fig. 2) which was prepared according to Scheme 2 from diol **3** with triphenylphosphine bromide in good yield.

Diol **3**, dibromide **4a** and mesylate **4b** may serve as versatile precursors for a number of different 3,6-symmetrically substituted pipecolic acid derivatives by standard functional group transformations. The intrinsic

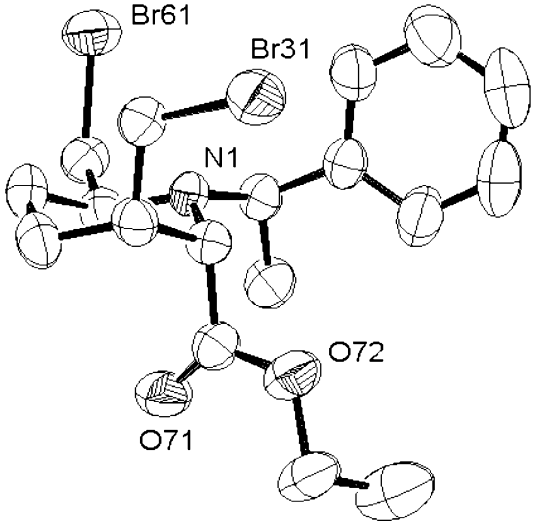


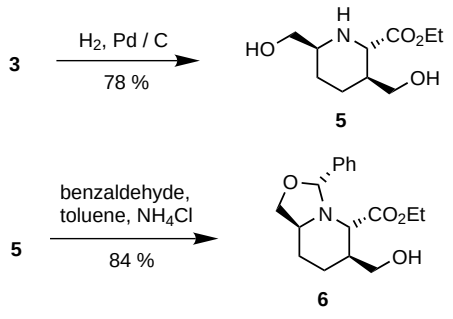
Figure 2. ORTEP plot of dibromide **4a** (heteroatoms are marked with element symbols and hydrogen atoms are omitted for clarity).

basicity of compound **4b**, due to the internal tertiary amine, caused initial problems with its work up because of elimination of mesylate. However, these problems were solved by isolating **4b** as its hydrochloride salt.

Taking advantage of the vicinal aminoalcohol moiety in diol **3**, it can furthermore be derivatized selectively at substituents in 3- or 6-position enlarging its synthetic potential. Compound **3** was therefore debenzylated with hydrogen (balloon) and 5% palladium on activated charcoal in ethanol for 24 h according to Scheme 3 to give N-terminally deprotected pipecolic acid **5** in quantitative yield. When treated with benzaldehyde in toluene (Dean–Stark conditions for 12 h), selective protection of the 1,2-aminoalcohol moiety as a benzylidene aminal in **6**[16] was achieved in good yield.

Protected pipecolic acid **6** was obtained in diastereomerically pure form and the stereochemistry at the aminal C assigned to be (*R*)-configuration based on NOESY NMR experiments. Compound **6** may serve as a precursor for selective functionalization at C3 and C6 of the piperidine ring, giving thus access to a number of enantiomerically pure constrained amino acid derivatives.

In summary, we have developed an efficient protocol for the stereoselective synthesis of polyfunctionalized derivatives of pipecolic acid. Key steps of this synthesis are an aza-Diels–Alder reaction of a chiral imine and subsequent oxidative cleavage of the resulting azabicycloalkene. It should be noted that this protocol may easily be expanded to the synthesis of proline derivatives by using cyclopentadien instead of cyclohexadien in the aza-Diels–Alder reaction. Furthermore, both enantiomers of the chiral educt, (*R*)- and (*S*)-phenylethylamine, are commercially available at low cost thus giving access to both enantiomers of cyclic amino acid derivatives like **3** in only two steps. We are currently using these highly functionalized amino acids as building blocks for the synthesis of conformationally constrained dipeptide mimics (results of this work will be reported elsewhere), but they may also serve as intermediates for natural product synthesis.



Scheme 3. Synthesis of pipecolic acid **6**.

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16. Selected analytical data: **2** ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 9.50 (d, 1H, $J=1.3$ Hz), 8.97 (d, 1H, $J=4.7$ Hz), 7.33 (m, 5H), 4.19–4.27 (m, 2H), 4.14 (d, 2H, $J=2.6$ Hz), 4.06–4.11 (m, 2H), 2.62 (m, 1H), 2.21 (m, 1H), 1.72 (m, 1H), 1.5 (m, 2H), 1.37 (d, 3H, $J=6.9$ Hz), 1.32 (t, 3H, $J=7.3$ Hz); HRMS (FAB) calcd for $C_{18}H_{23}NO_4$ (MH^+) 318.1705, found 318.1702. **3** ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm 7.41 (d, 2H, $J=7.3$ Hz), 7.36 (m, 2H), 7.26 (t, 1H, $J=7.2$ Hz), 4.50 (q, 1H, $J=7.0$ Hz), 4.17 (m, 2H), 3.88 (dd, 1H, $J=3.4$ Hz, 11.0 Hz), 3.84 (m, 1H), 3.76 (dd, 1H, $J=3.8$ Hz, 10.7 Hz), 3.54 (dd, 1H, $J=5.3$ Hz, 10.7 Hz), 3.53 (m, 1H), 3.52 (d, 1H, $J=2.6$ Hz), 1.92 (m, 1H), 1.82 (m, 1H), 1.76 (m, 1H), 1.57 (m, 1H), 1.50 (m, 1H), 1.33 (d, 3H, $J=7.0$ Hz), 1.29 (t, 3H, $J=7.3$ Hz); HRMS (FAB) calcd for $C_{18}H_{27}NO_4$ (MH^+) 322.2018, found 322.2014. **4a** ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm 7.47 (m, 2H), 7.34 (m, 2H), 7.26 (m, 1H), 4.48 (q, 1H, $J=6.9$ Hz), 4.08–4.15 (m, 3H), 3.78 (dd, 1H, $J=3.6$ Hz, 11.4 Hz), 3.55 (d, 1H, $J=9.5$ Hz), 3.50 (d, 1H, $J=11.4$ Hz), 3.36 (dd, 1H, $J=6.9$ Hz, 9.5 Hz), 3.30 (s, 1H), 2.03 (m, 1H), 1.78–1.88 (m, 3H), 1.49 (m, 1H), 1.30 (d, 3H, $J=6.9$ Hz), 1.29 (t, 3H, $J=6.9$ Hz); HRMS (FAB) calcd for $C_{18}H_{25}Br_2NO_2$ (MH^+) 446.0330, found 446.0332. **4b** ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm 7.36 (m, 4H), 7.25 (m, 1H), 4.40 (q, 1H, $J=7.0$ Hz), 4.32 (dd, 1H, $J=4.0$ Hz, 10.4 Hz), 4.12–4.24 (m, 6H), 3.37 (s, 1H), 2.98 (s, 3H), 2.82 (s, 3H), 2.20 (m, 1H), 1.83 (m, 1H), 1.66 (m, 3H), 1.33 (d, 3H, $J=7.0$ Hz), 1.30 (t, 3H, $J=7.1$ Hz); HRMS (FAB) calcd for $C_{20}H_{31}NO_8S_2$ (MH^+) 478.1569, found 478.1571. **5** ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm 4.22 (m, 2H), 3.87 (dd, 1H, $J=8.2$ Hz, 10.7 Hz), 3.84 (d, 1H, $J=2.5$ Hz), 3.70 (dd, 1H, $J=5.4$ Hz, 10.7 Hz), 3.64 (br, 3H), 3.57 (dd, 1H, $J=3.4$ Hz, 11.1 Hz), 3.42 (dd, 1H, $J=7.9$ Hz, 11.1 Hz), 2.99 (m, 1H), 2.35 (m, 1H), 1.62 (m, 2H), 1.37 (m, 2H), 1.29 (t, 3H, $J=7.3$ Hz); HRMS (FAB) calcd for $C_{10}H_{19}NO_4$ (MH^+) 218.1392, found 218.1391. **6** ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm 7.35–7.39 (m, 5H), 5.38 (s, 1H), 4.12–4.20 (m, 3H), 3.80 (m, 1H), 3.68 (m, 2H), 3.61 (dd, 1H, $J=6.4$ Hz, 6.6 Hz), 3.39 (d, 1H, $J=1.3$ Hz), 2.19 (m, 1H), 1.93 (m, 1H), 1.77 (m, 3H), 1.28 (t, 3H, $J=7.3$ Hz); HRMS (FAB) calcd for $C_{17}H_{23}NO_4$ (MH^+) 306.1705, found 306.1708.