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Stereoselective synthesis of novel conformationally restricted β- and γ-amino acids

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Dedicated to Professor Armin de Meijere on the occasion of his 65th birthday

Abstract—Novel conformationally restricted β- and γ-amino acids containing a cyclopropane ring could be stereoselectively synthesized from readily available 5-methoxyindole and pyridine by copper(I)-catalyzed cyclopropanation with methyl diazoacetate followed by subsequent oxidative cleavage of the resulting adducts.

The introduction of conformationally restricted amino acids into peptides is an important tool in the elucidation of the biologically active conformation of proteins.[1] Proline, α-aminoisobutyric acid (AIB)[2] and α-aminocyclopropane carboxylic acid[3] (α-ACC) are three prominent examples for such amino acids, which have been used extensively in the design of peptidomimetics directed towards the development of new drugs (Fig. 1).

Recently, β-aminocyclopropanecarboxylic acids[4] (β-ACCs), especially the *cis*-β-ACC **3b**,[5] have been recognized as uniquely constrained building blocks in the synthesis of peptidic ligands, for example, with high affinity towards the neuropeptide Y receptors[6] and in the synthesis of helical α,β-foldamers.[7] Both, *cis*- and *trans*-β-ACCs **3** can be conveniently synthesized[5a] from *N*-Boc-pyrrole **1** via cyclopropanation with methyl diazoacetate followed by ozonolysis of the bicyclic adduct **2** (Fig. 2) and subsequently incorporated into peptides using an in situ Boc[5b] or Alloc[8] coupling approach.

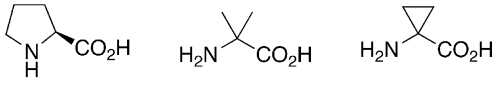

Figure 1. Conformationally restricted α-amino acids.

In extension of this strategy we report here the cyclopropanation of indoles and dihydropyridines that leads to novel β- and γ-amino acids, being conformationally restricted by the incorporation of a cyclopropane moiety into the backbone.

Following the pioneering work of Welstead et al.[9] and of Wenkert et al.,[10] cyclopropanation of *N*-Boc protected indoles **4** with methyl diazoacetate catalyzed by copper(I)triflate, being generated in situ from copper(II)triflate and phenylhydrazine, led to the expected [2+1] cycloadducts of the double bond in the five-membered ring (Scheme 1).

Both indoles **4** gave the cyclopropanated adducts in a clean reaction. Initially only 1.4 equiv of methyl diazoacetate were used, which resulted in an incomplete conversion of **4a**, but nevertheless, high yield of **5a**/**6a** after recovery of the starting material (90%). When a

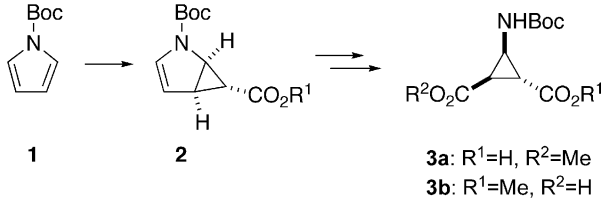

Figure 2. Synthesis of β-ACCs **3**.

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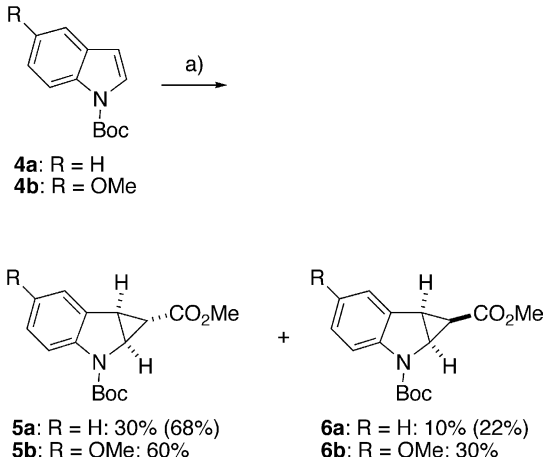
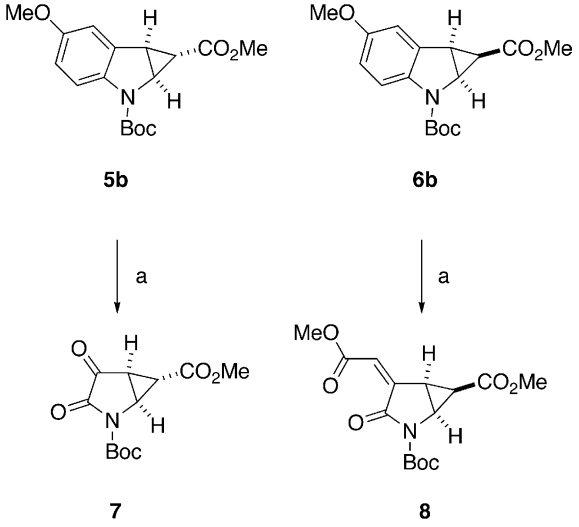


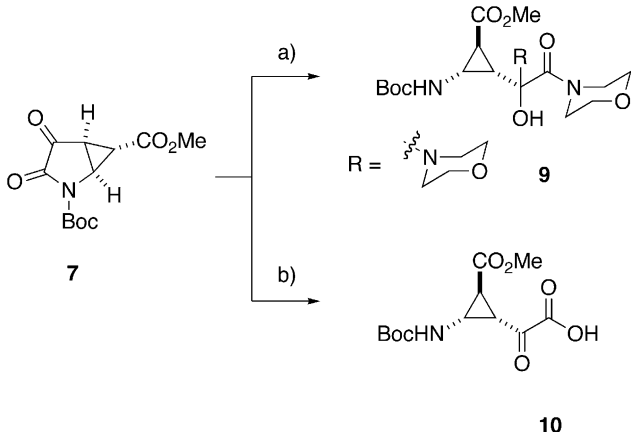
Scheme 1. Cyclopropanation of indoles **4**. (a) N_2CHCO_2Me (**4a**: 1.4 equiv, **4b**: 7.3 equiv), $Cu(OTf)_2$ (0.02 equiv), $PhNHNH_2$, (0.02 equiv), CH_2Cl_2.

large excess (7.3 equiv) of methyl diazoacetate was employed in the cyclopropanation of **4b**, a nearly quantitative yield of **5b/6b** was obtained. However, in contrast to the cyclopropanation of **1**, for which only the *exo*-adduct **2** was observed, with **4** both, the *exo*-adducts **5** as well as the *endo*-adducts **6** were obtained (2–3:1). In both cases, the diastereomers could be readily separated by chromatography on silica and individually investigated further.

Oxidative degradation of either **5a** or **6a** was not successful under various conditions tested. However, the more electron rich aromatic moiety in the derivatives **5b** and **6b** could be both cleaved by ozone, however, with a very different outcome depending on the stereochemistry of the adducts (Scheme 2). The *exo*-stereoisomer **5b** was converted to the expected pyrrolidone **7**, in which complete oxidative cleavage of the arene moiety has been taken place. In contrast, the *endo*-stereoisomer **6b**



Scheme 2. Ozonolysis of cyclopropanated indoles **5b** and **6b**. (a) (i) O_3, MeOH, −78 °C; (ii) Me_2S, −78 °C → room temp, **5b** → **7**: 56%, **6b** → **8**: 54%.



Scheme 3. Ring opening of **7**. (a) Morpholine (1 or 2 equiv), CH_2Cl_2, 0 °C → room temp, 35%; (b) MeOH (aq), NH_4Cl, 45 °C, 3 h, 63%.

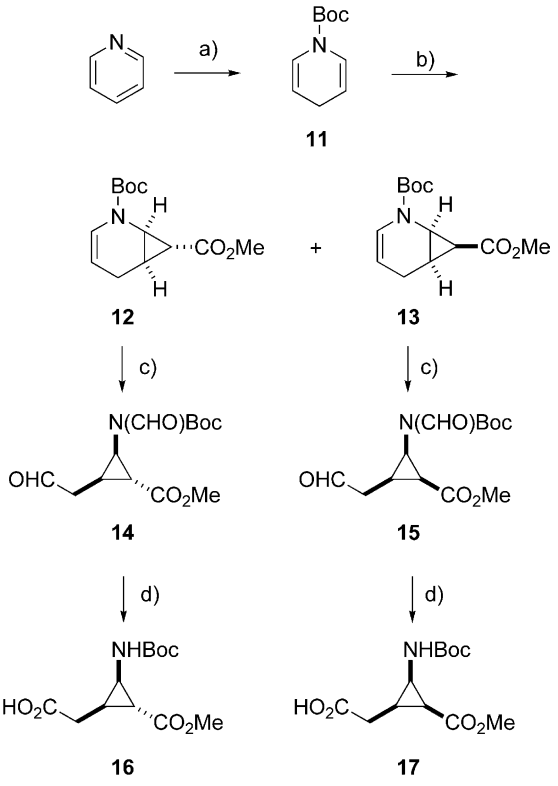
gave in reasonable yield the partial oxidized alkene **8** as the sole product.

Following the precedent set for isatins,[11] ring opening of **7** could be effected either with a secondary amine or with hydroxide (Scheme 3). With morpholine, two-fold addition giving rise to **9** occurred, which was surprisingly stable in spite of its hemi aminal functionality. Alternatively, the ketoacid **10**[12] was cleanly formed with ammonium chloride in methanol, representing a novel γ-amino acid that should prove to be interesting as a complimentary building block to the *trans*-β-ACC **3a**.

Starting from dihydropyridine **11**, which can be conveniently synthesized directly from pyridine following the protocol reported in the literature,[13] novel β- and γ-amino acids containing a cyclopropane ring can also be readily obtained (Scheme 4). Cyclopropanation[14] of **11** with methyl diazoacetate as described before for indoles **4** gave rise to both, *exo*- and *endo* (ratio 8:3) monocyclopropanated adducts **12** and **13** (55% overall yield), respectively, which were separated by chromatography on silica. Ozonolysis of the individual isomers followed by reductive work up cleanly gave rise to the aldehydes **14** and **15**, respectively, which should prove to be valuable, trifunctional building blocks not only in light of the synthesis of unnatural amino acids described here. Nevertheless, oxidation using sodium chlorite/hydrogen peroxide according to the Dalcanale protocol[15] proceeded in an almost quantitative way to the new *cis*-γ-amino acids **16** and **17**, complementing the *cis*-β-ACC **3b**.

Alternatively, the *trans*-β-ACC **19** can be obtained by saponification of **12** followed by ozonolysis and reductive work up (Scheme 5). It should be noted that the direct saponification of **14** with base towards **19** results only in decomposition of the starting material.

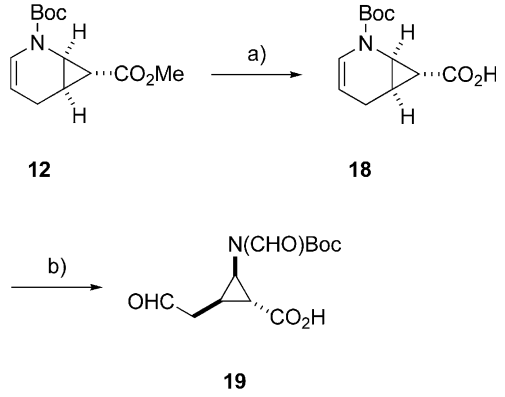
The aldehyde group in **14** can be functionalized by standard transformations, which can be applied to the synthesis of β-ACCs with α-amino acid side chain functionality.[16] Reductive amination with concomitant deprotection of the *N*-formyl group leads to the deriv-



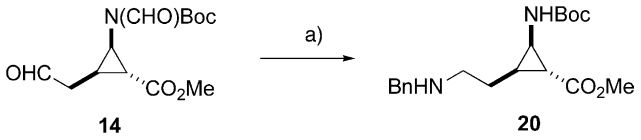
Scheme 4. Synthesis of γ-amino acids containing a cyclopropane ring from pyridine. (a) Ref. 8; (b) N_2CHCO_2R (1.4 equiv), $Cu(OTf)_2$ (0.05 equiv), $PhNHNH_2$, CH_2Cl_2, room temp, **12** (40%), **13** (15%); (c) O_3, DMS (5 equiv), CH_2Cl_2, −78 °C → room temp, **14** (91%), **15** (91%); (d) (i) $NaClO_2$, H_2O_2 (1.1 equiv), CH_3CN, 0 °C → room temp; (ii) 2-diethylaminoethylamine (DEAEA, 2.2 equiv), CH_3CN, room temp, 10–12 h, yield (two steps): **16** (84%), **17** (72%).

ative **20**, representing a *trans*-β-ACC derivative with a lysine side chain (Scheme 6).

In conclusion, we have demonstrated that pyridine and 5-methoxyindole can be readily transformed into a variety of new β- and γ-amino acids containing a cyclopropane moiety, which further extends the scope of this class of conformationally restricted amino acids as building blocks for peptidomimetics.



Scheme 5. Synthesis of trifunctional *trans*-β-ACC **19**. (a) NaOH (1.25 equiv), MeOH/H_2O, room temp, 89%; (b) O_3, DMS (5 equiv), CH_2Cl_2, −78 °C → room temp, 93%.



Scheme 6. Synthesis of the β-ACC derivative **20** with lysine side chain functionality. (a) benzylamine (2.2 equiv), $NaBH(OAc)_3$ (2.5 equiv), molecular sieves (4 Å), THF, 0 °C → room temp 12 h, 47%.

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12. All new compounds were characterized by IR, NMR and MS and gave sufficient elemental analyses or high resolution mass spectra. Selected ^{1}H NMR data. Compound **10**: ^{1}H NMR ($CDCl_3$, signal doubling due to rotamers) δ 1.54 (9H, s, $-CO_2C(CH_3)_3$), 1.86–1.94 (m, 1H, cyclopropyl-H), 2.30–2.42 (m, 1H, cyclopropyl-H), 3.71 and 3.72 (s, 3H, $-CO_2CH_3$), 3.95–4.02 (m, 1H, cyclopropyl-H). Compound **16**: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H, $-CO_2C(CH_3)_3$), 1.57–1.61 (m, 1H, cyclopropyl-H), 1.77–1.83 (m, 1H, cyclopropyl-H), 2.39–2.56 (m, 2H, CH_2), 3.02–3.07 (m, 1H, cyclopropyl-H), 3.68 (s, 3H, OCH_3). Compound **17**: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H, $-CO_2C(CH_3)_3$), 1.77–1.85 (m, 1H, cyclopropyl-H), 1.98–2.05 (m, 1H, cyclopropyl-H), 2.71 (d, J 7.6 Hz, 2H, CH_2), 3.13 (dd, J 7.4, 7.5 Hz, 1H, cycopropyl-H), 3.63 (s, 3H, OCH_3). Compound **19**: ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 9H, $-CO_2C(CH_3)_3$), 1.76 (dd, J 4.3, 5.5 Hz, 1H, cyclopropyl-H_1), 1.89–2.19 (m, 2H, CH_2), 2.95–3.04 (m, 1H, cyclopropyl-H), 3.43 (dd, J 4.1, 7.3 Hz, 1H, cyclopropyl-H), 9.12 (s, 1H, N–CHO), 9.69 (s, 1H, CHO). Compound **20**: ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H, $-CO_2C(CH_3)_3$), 1.62–1.79 (m, 3H, CH_2 and cyclopropyl-H), 1.87.–1.98 (m, 2H, CH_2) 2.78–2.86 (m, 1H, cyclopropyl-H), 3.31–3.39 (m, 1H, cyclopropyl-H), 3.63 (s, 1H, OCH_3), 3.89 (br s, 2H, CH_2Ph), 7.1–7.32 (m, 5H, phenyl-H).
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