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Synthesis of Cyclic Peptidomimetics from Aldol Building Blocks

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Abstract: Aldol products (3-hydroxy acids) with an allyl-protected hydroxy group were converted to amino alcohols by Curtius rearrangement. Combination of the carboxylic acid with the amino alcohols gave the amides **10**. Ring-closing metathesis led to the 12-membered lactams **12** as mixtures of *E*/*Z*-isomers. The scheme was also transferred to the solid-phase. In this case the macrolactams are formed via cyclorelease. For a pair of *E*/*Z*-isomers the solution conformation was determined by ROESY spectroscopy.

With the appearance of new targets for the treatment of diseases, the need for selective small molecules has increased. One strategy to cope with these challenges is diversity oriented synthesis of large libraries of compounds.[1] In designing such libraries it seems advantageous to follow the so-called "rule of five".[2] The more classical strategy relies on a structure-based approach which utilizes biologically active natural products as a starting point for modifications. Combined with solid-phase techniques this can lead to small libraries in a short period of time.[3,4] With this approach the likelihood of finding active molecules is rather high.[5] However, it might be difficult to discover a more active molecule or to find a new mode of action. Therefore, it might be better to combine the above-mentioned strategies. Thus, using rough guiding principles that result from inspecting natural products might increase the probability for hits. Some common features of biologically active compounds are cyclic, polycyclic, or macrocyclic ring systems, the presence of H-bond donors and acceptors, and hydrophobic regions. Some obvious lead compounds in this regard are cyclic peptides,[6−8] depsipeptides,[9] or macrolactones.[10] If targeting peptidelike molecules, a departure from typical α-amino acids is tantamount to a sometimes substantial synthetic effort. Thus, there is a need for adapting powerful organic reactions to the synthesis of building blocks that can replace amino acids in cyclic peptides. In this paper we show that aldol building blocks can be fashioned into macrocyclic peptidomimetics.[11]

The asymmetric aldol reaction is one of the most important reactions in natural product synthesis because a new carbon−carbon bond is formed with the simultaneous creation of two stereocenters.[12] A well-known and reliable reaction in this context is the Evans aldol reaction.[13] Because this reaction combines an aldehyde with a carboxylic acid it is predestinated for generating variability due to the large number of available aldehydes and acids. In addition, the aldol products can be transformed to other difunctionalized derivatives. We planned to convert aldol products via Curtius rearrangement to the corresponding amino alcohols[14] and then to combine them with the typical aldol product, a 3-hydroxy acid. If the two secondary hydroxy groups are connected to functional groups that can be used for a cyclization reaction, macrocyclic compounds with a constrained conformation should result (Figure 1). In this paper we show that with allyl ethers a short synthesis of macrolactams is possible via ring-closing metathesis.

Using standard conditions (1.2 equiv of Bu_2BOTf, 1.3 equiv of $EtNiPr_2$, CH_2Cl_2, −78 to 0 °C) the aldol products **5** were prepared (Scheme 1). Subsequently, the secondary

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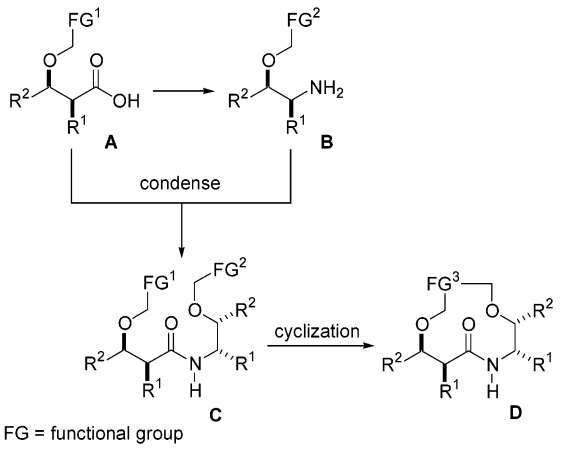
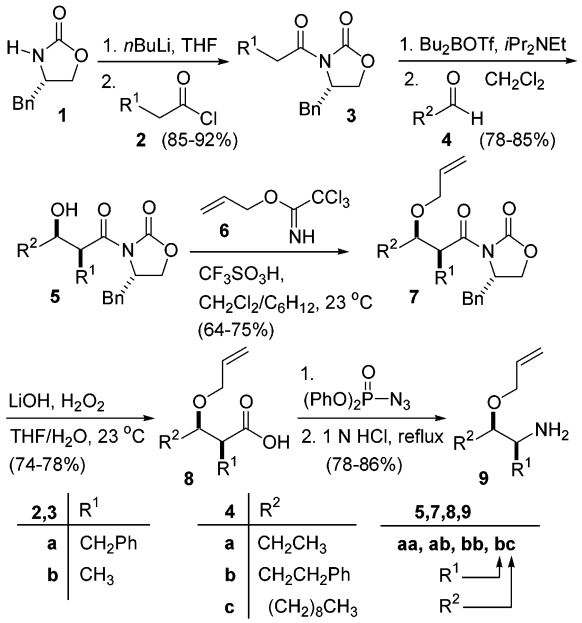


FIGURE 1. Peptidomimetics from 3-hydroxy acids and 1,2-amino alcohols followed by macrocyclization.

SCHEME 1. Synthesis of the Allylated Hydroxy Acids 7 and the Amino Alcohols 9



hydroxyl function was protected as allyl ether **7** with the trichloroacetimidate **6** under acidic conditions.[15] Thereafter the chiral auxiliary was removed under basic conditions yielding the carboxylic acids **8**. To prepare the amino alcohols **9**, the carboxylic acids were subjected to a Curtius rearrangement with the Shiori reagent,[16] diphenylphosphoryl azide. The intermediate isocyanates were not isolated but rather hydrolyzed to the amines **9** with aqueous HCl. The amino alcohol derivatives were obtained in yields ranging form 78 to 86%.

Coupling of the carboxylic acids **8** with the amines **9** was performed with benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) in acetonitrile providing the amides **10** (Scheme 2). This was followed by macrocyclization with the Grubbs catalyst **11** in dichloromethane at room temperature.[17] This led to the 12-membered macrolactams **12** in good yields. These compounds were obtained as *E*/*Z*-isomers with a roughly 3:1 ratio. By careful chromatography the double bond isomers could be separated to a purity of >95%.

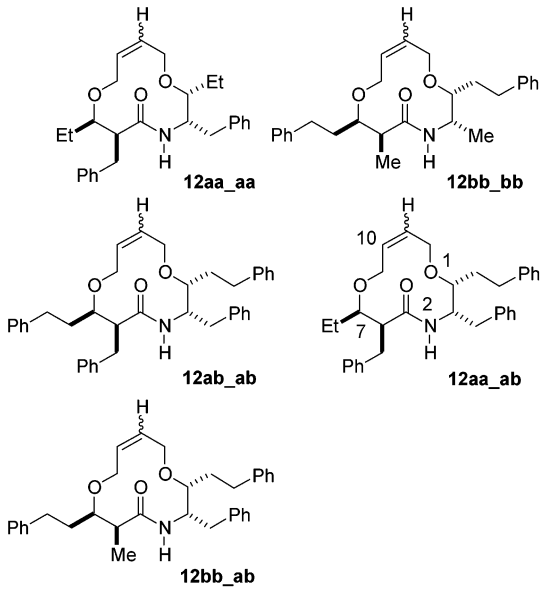
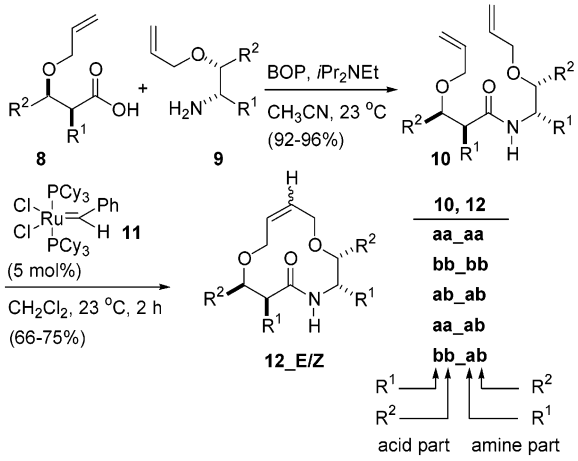


FIGURE 2. Structures of the macrolactams **12**.

SCHEME 2. Condensation to the Amides 10 and Ring Closing Metathesis to 12



The structures of the synthesized macrolactams **12** are depicted in Figure 2.

The solution phase assembly of the amide and the macrocyclization provides the macrocycles **12** with reasonable efficiency. However, if large numbers of the macrolactams would be needed, a solid-phase assembly might be advantageous. With a view toward the synthesis of cyclic ethers by rcm-mediated cyclization with the

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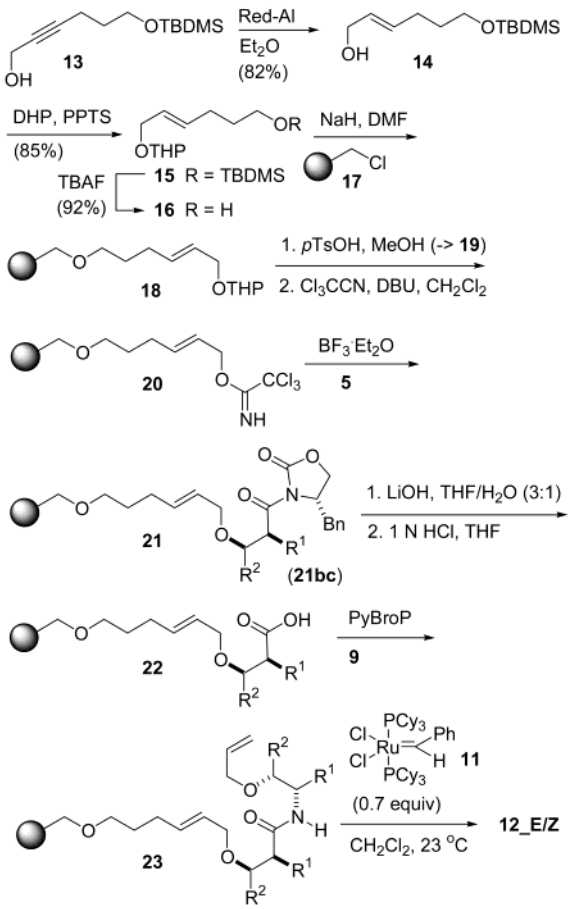
SCHEME 3. Synthesis of the Macrolactams 12 via Solid-phase Assembly and Cyclorelease Reaction



simultaneous release of the products, we prepared the immobilized allylic imidiate **20** (Scheme 3). This would also allow to address the regiochemical issue (S_N2 versus S_N2') in the substitution reactions with **5**.[18] The synthesis of **20** required the monoprotected alcohol **16** which was prepared by straightforward alkyne chemistry as shown in Scheme 3. Treatment of the known propargylic alcohol **13** with Red-Al in diethyl ether gave the *trans*-allyl alcohol **14**.[19] By a protection/deprotection sequence the alcohol **16** was obtained. This was attached to the Merrifield resin **17** under basic conditions.[20] After removal of the THP protecting group, the immobilized allylic imidate **20** was prepared by reaction of **19** with trichloroacetonitrile in the presence of DBU.[15] The formation of **20** could be followed by ATR−FT-IR spectroscopy directly on the beads. Thus, new characteristic peaks appeared at 1663 (C═N) and 3337 (N−H) cm^{-1}. For the attachment of the aldol products, a suspension of the resin **20** in dichloromethane/cyclohexane, containing an excess of the 3-hydroxycarbonyl compound **5** was treated with BF_3-Et_2O. Again, the completion of the reaction was evident from the IR-spectrum which showed new characteristic C═O peaks at 1699 and 1779 cm^{-1}. At this stage, however, it was not possible to ascertain the ratio

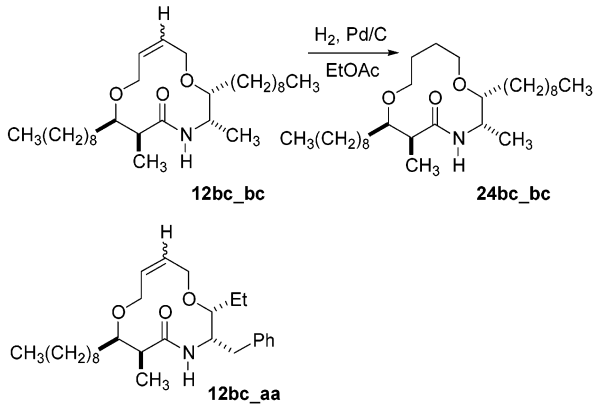


FIGURE 3. Structures of the peptidomimetics obtained via solid-phase synthesis.

of the regioisomers. Subsequently, the chiral auxiliary was removed under basic conditions[21] to give the acid **22**. In the next step, the amide bond was created by reacting **22** with the amine **9** in the presence of bromo-tris-pyrrolidino-phosphonium hexafluorophosphate[22] (PyBroP) and Hünig's base. Finally, a suspension of the amide **23** in dichloromethane containing the Grubbs catalyst **11** led to the appearance of the macrolactams **12bc_bc** and **12bc_aa**, respectively. The reaction required relatively large amounts of the Grubbs catalyst. On the basis of the yields obtained, it can be assumed that the etherification occurs mostly at the primary carbon atom. In the case of the macrolactam **12bc_aa** the *E*- and *Z*-isomer could be separated. Since this was not possible with lactam **12bc_bc**, the mixture of double bond isomers was hydrogenated to the saturated compound **24**.

Using the solid-phase strategy, the macrocycles **12bc_bc**, **12bc_aa**, and **24bc_bc** were prepared (Figure 3).

Conformational Studies. To gain insight in the conformation of these constrained peptide derivatives, the solution conformation for one set (**12aa_ab**) of double bond isomers was determined by NMR spectroscopy on the basis of homo- and heteronuclear chemical shifts, *J*-couplings and NOE (ROE) data in DMSO-d_6.[23] Long-range ^4J-couplings prohibited the unequivocal analysis of the allyl spin systems, and therefore the double bond isomers were distinguished from their ^{13}C chemical shifts. All peak assignments and coupling constants are included in the Supporting Information.

The 12-membered ring of **12aa_ab_E** consists of two sets of five single bonds separated by two trans-configured double bonds, regarding the amide bond as partial double bond. Similar rotamer distributions were observed for the benzylic side chains. $^3J_{H,H}$ couplings identify the rotamer with an antiperiplanar orientation of the backbone proton (H-3 and H-6, respectively) and the benzylic H^{proS} as the dominating rotamer. The NOE correlations were quantified from compensated rotating-

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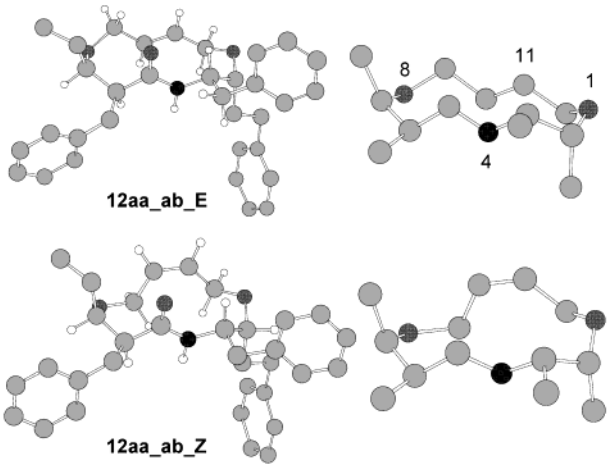

FIGURE 4. Energy-minimized average conformations of the *E*- and *Z*-isomer of **12aa_ab**. The right column shows the ring atoms plus the first atom of the side chains.

frame NOESY spectra.[24] Several sequential NOEs were detected along the backbone. The amide proton for example shows strong NOEs with H-15^{proS} and H-6. These NOE correlations served as distance constraints for a 100 ps molecular dynamics simulation. Averaging of 10 snapshots was followed by energy minimization without distance constraints. The energy-minimized conformation of **12aa_ab_E** is shown in Figure 4. The twelve ring atoms assume a C_2-symmetric conformation with the *trans*-configured double bonds on opposite ring sides. The two benzyl groups flanking the amide bond populate equatorial orientations while the substituents in positions 2 and 7 are found in *pseudo*-axial orientations.

The same NMR strategy and modeling procedure was applied to the *Z*-isomer **12aa_ab_Z**. The higher internal mobility of this rings structure is reflected by transannular NOEs between one of the protons H-9 and the amide proton as well as H-6. The conformation is depicted in Figure 4.

In conclusion, we could illustrate the use of aldol building blocks for the preparation of peptidelike structures by converting aldol products to amino alcohols via Curtius rearrangement. The hydroxyl groups enable the attachment of functional handles that can be used to form a macrocyclic ring, thereby constraining the conformation. Thus, we demonstrated the great potential of the aldol reaction for generating structural diversity.

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Supporting Information Available: Experimental procedures for the sequence aldol reaction, Curtius rearrangement, condensation, and ring-closing metathesis reaction. Details for the solid-phase route. In addition, copies for NMR spectra for important compounds, and the peak assignments and the ROESY spectra of compounds **12aa_ab_E** and **12aa_ab_Z**. This material is free of charge via the Internet at http://pubs.acs.org.

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