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Pyrrolidines bearing a quaternary α-stereogenic center. Part 2: Access to proline chimeras, stereoselective approach and mechanistic aspects

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Abstract

The present work describes the access to various proline chimeras bearing a quaternary α-stereogenic center, via the Duhamel ring contraction of heterocyclic enamines. Attempts to induce diastereoselectivity are reported. The 'chiral enamine' strategy afforded the required aminoaldehydes with diastereomeric ratios as high as 85:15.

Keywords: amino aldehydes; diastereoselection; enamines; pyridinium salts; pyrrolidines.

Conformational constraint is a usual way to modify the properties of bioactive peptides. In some cases such modification improves their activity as well as their affinity for their biological target.[1] Proline analogs play a pivotal role in such studies, thus encouraging the development of new methodologies allowing access to so-called 'proline chimeras',[2] in which the heterocycle of the amino acid is substituted in such a way that the chimera combines the conformational constraint of proline with the side chain of another amino acid. Our ongoing research on pyrrolidines bearing a quaternary α-stereogenic center[3] gave us the methodology allowing easy access to new proline chimeras, which could be functionalized in the α-position.[4] Such compounds could be used for structural modifications of peptides, or as starting materials for the synthesis of bioactive molecules such as kaitocephalin,[5] cephalotaxin,[6] anti HIV agents,[7] and peptidomimetics.[1,2]

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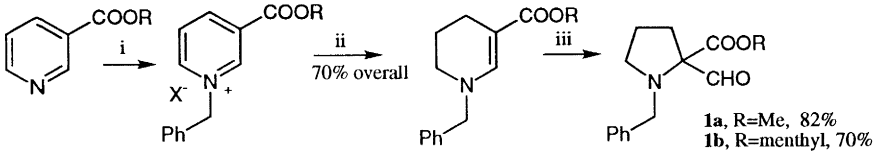
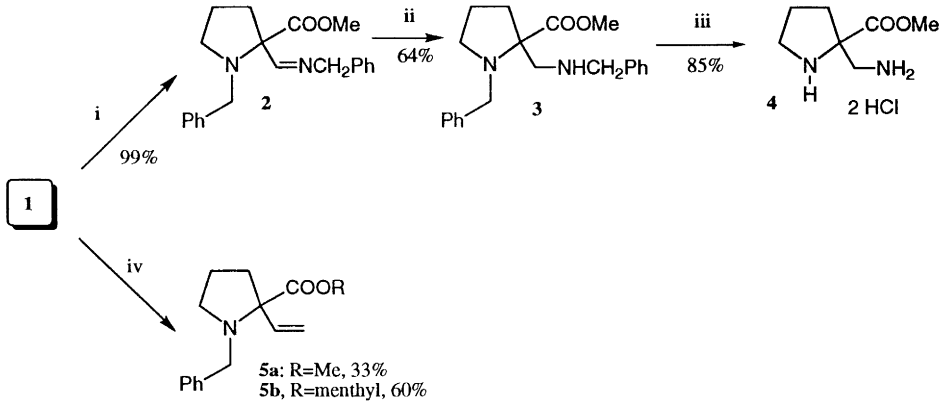
1. Access to new proline chimeras

Our strategy for constructing the proline chimeras relies on a similar reaction scheme as published previously for quaternary analogs of alkaloids (Scheme 1).[3,8]



Scheme 1. Reagents and conditions: (i) $PhCH_2X$ (X=Br or Cl); (ii) AgCl, MeOH, reflux (if X=Br) then H_2/Pd/C (10%), MeOH; (iii) Br_2 (3 equiv.)/Et_2O, −60°C then H_2O/Et_3N

Benzylation of the starting nicotinates by benzyl halide gave the corresponding pyridinium salts in excellent yield. The hydrogenation was performed at atmospheric pressure according to Wenkert et al.[9] The counteranion exchange by means of AgCl was necessary in the case of bromide since this anion could poison the catalyst. Finally, the Duhamel ring contraction was realized under previously reported conditions,[3,8] thus giving the required aminoaldehydes **1a**–**b** (glycinal-PRO chimeras) efficiently which were purified by flash chromatography. One can observe that in the menthyl series, the diastereomeric ratio of **1b** was rather low (55:45). Discussion about diastereoselectivity of the ring contraction process appears in the following part. Functional modifications of compounds **1** gave access to other proline chimeras (β-alanine-PRO and vinylglycine-PRO), either protected or free (Scheme 2).



Scheme 2. Reagents and conditions: (i) $PhCH_2NH_2$, 3 ÅMS; (ii) $NaBH_4$, EtOH; (iii) $Pd(OH)_2/H_2$; (iv) $Ph_3P^+Me\ I^-$, *n*-Buli, THF, −60°C

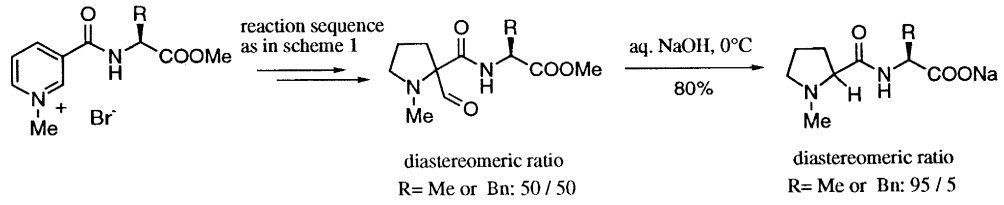
Thus the present methodology permits the construction of some new proline chimeras which can be functionalized in the α-position. The compounds were readily obtained from **1** using standard procedures and were purified by flash chromatography. Interestingly, the carbonyl group of **1** was stable enough under most reaction conditions, thus leading to the desired quaternary products, bearing various functional groups, such as imine (**2**), secondary amine (**3**), primary amine (**4**), and vinyl (**5a**,**5b**) substituents. In the latter case, one can observe that the yield was significantly improved when starting from compound **1b** bearing a bulky ester moiety.

The lower yield obtained in the case of **1a** (R=Me) resulted mainly from decarbonylation of the starting material, as previously described in the literature.[8b] The rather high yields which were obtained highlight the synthetic interest of the Duhamel ring contraction in this context.

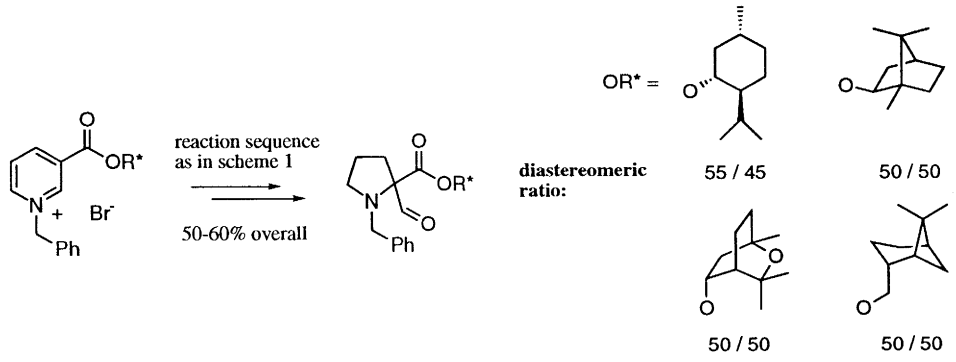
2. Study of the diastereoselectivity of the ring-contraction process: first attempts (chiral side chain)

Having in hand the possibility of preparing various proline chimeras, we turned our studies to the asymmetric access to these compounds. Since the generally reported mechanism of the contraction process relies on intramolecular substitution giving an aziridinium ion intermediate,[8] we expected that the diastereoselective control of the bromination step would be the key step for the asymmetric construction of the chiral aldehydes **1**. Nevertheless, one can also consider the possibility of a competitive mechanism involving an intermediate carbocation, as previously postulated in the literature.[10] In this latter case, one cannot exclude a loss of stereoselectivity even if the bromination step was stereoselective.

First, we prepared starting materials bearing either chiral amide or ester residues on the side chain, and submitted them to the contraction process (see Schemes 3 and 4).



Scheme 3.



Scheme 4.

In this first series, results were disappointing, while giving the expected peptide in satisfactory yields (30–40% overall yield). Nevertheless, no asymmetric induction was obtained, as checked by NMR analysis (^{1}H and ^{13}C). Interestingly, alkaline decarbonylation of the peptidic aldehyde occurred with high diastereoselectivity. Obviously, this reaction proceeded through a prochiral anionic intermediate which was stereoselectively protonated under the influence of the chiral side chain.

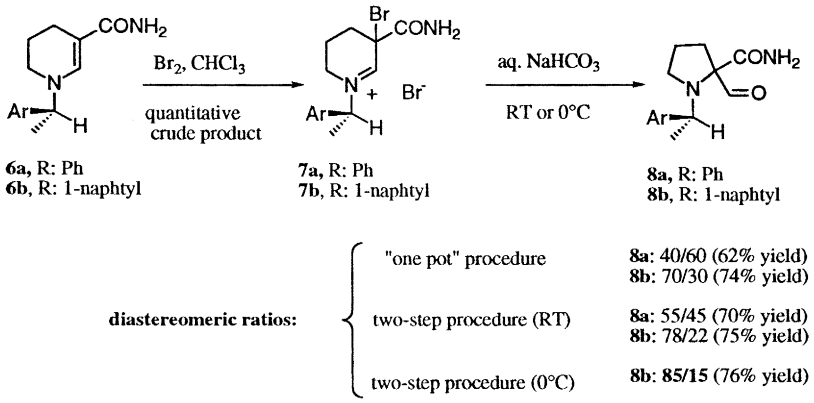
As in the previous case, no significant diastereoselectivity was observed in the chiral terpenic esters series, as checked by NMR (^{1}H and ^{13}C) and GC/MS analyses. We then turned to another series of chiral precursors in which the chiral moiety was directly linked to the nitrogen atom of the heterocyclic system (chiral enamine strategy, vide infra).

3. Diastereoselectivity in the ring-contraction process via chiral enamine strategy

Chiral enamines **6** were prepared by hydrogenation of the corresponding pyridinium salts, which were obtained by Zincke reaction starting from nicotinamide, according to recent developments.[11] We

expected that a chiral moiety directly linked to the nitrogen of the heterocyclic system could be more efficient for asymmetric bromination compared with the chiral side chains approach (vide supra). Another interesting point was the possibility to isolate the intermediate iminium salts **7**,[10] and thus to have the possibility to examine a two-steps versus 'one-pot' ring-contraction process. Accordingly, the ring contraction of enamines **6a**,**b** led to major new information (see Scheme 5):

– poor but significant diastereoselection in the case of Ar=Ph (**8a**), with inversion of stereoselectivity in the two-steps procedure (contraction starting from isolated iminium salt) with respect to the'one-pot' procedure (bromination and alkaline treatment without isolation of the intermediate iminium salt), clearly indicating the competition of two mechanisms. This inversion was not observed when starting from **6b**.
– improvement of diastereomeric excess when crowding the chiral enamine (Ar=1-naphtyl, **8b**), up to 78:22 (two-steps procedure).
– improvement of diastereoselection when cooling at 0°C the aqueous treatment of the iminium bromide **7b**, giving a diastereomeric ratio as high as 85:15 (**8b**).



Scheme 5.

Diastereomeric ratios were determined by means of NMR analyses (^{1}H and ^{13}C), respectively by integration of CHO and C=O signals. The mixture of diastereoisomers showed two distinct spots on TLC, allowing the separation by chromatography.

4. Conclusion

The present study describes handy access to proline chimeras by means of Duhamel ring contraction and demonstrates the possibility to control with rather high *de* the newly created stereogenic center. The 'chiral enamine' strategy appears much more successful than the 'chiral side chain' approach. To the best of our knowledge, these results constitute the first asymmetric Duhamel ring contraction by means of a removable chiral auxiliary. Some experimental results suggest the possibility of two concurrent mechanisms, depending on the starting material and experimental conditions. Current studies are focusing on the improvement of asymmetric synthesis of the key aminoaldehydes **1**.

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