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Efficient stereoselective syntheses of piperidine, pyrrolidine, and indolizidine alkaloids*

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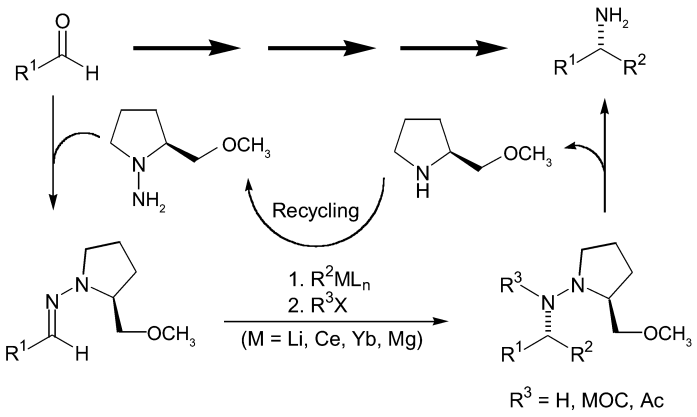
Abstract: Recent advances in the diastereo- and enantioselective synthesis of piperidine, pyrrolidine, and indolizidine alkaloids, based on the highly stereoselective 1,2-addition to the CN double bond of chiral aldehyde-SAMP/RAMP hydrazones, are described. The enantioselective syntheses of the pyrrolidine alkaloids bgugaine and (2*S*,12′*R*)-2-(12′-aminotridecyl)-pyrrolidine, a defense alkaloid of the Mexican bean beetle are reported. Furthermore, the SAMP/RAMP-hydrazone method was applied to the syntheses of two 5,8-disubstituted indolizidine alkaloids that have been extracted from neotropical poison-dart frogs. The α-alkylation of aldehyde-SAMP/RAMP hydrazones has been used in the enantioselective synthesis of two epimers of stenusine, a 3-substituted piperidine alkaloid and spreading reagent of the beetle *Stenus comma*.

ENANTIOSELECTIVE SYNTHESIS OF AMINES BY DIASTEREOSELECTIVE 1,2-ADDITION TO THE CN DOUBLE BOND OF ALDEHYDE-SAMP/RAMP-HYDRAZONES

Amines of high enantiomeric purity are important chiral building blocks for the synthesis of naturally occurring and biologically active substances and for the synthesis of chiral auxiliaries, ligands, etc. For that reason, the asymmetric synthesis of amines has been receiving much interest, and a lot of work is still being carried out toward the development of new methods that can provide these important compounds. The approach to the asymmetric synthesis of α-branched amines pursued by our group involves



Scheme 1 Asymmetric synthesis of amines by 1,2-addition to the CN double bond of aldehyde-SAMP hydrazones.

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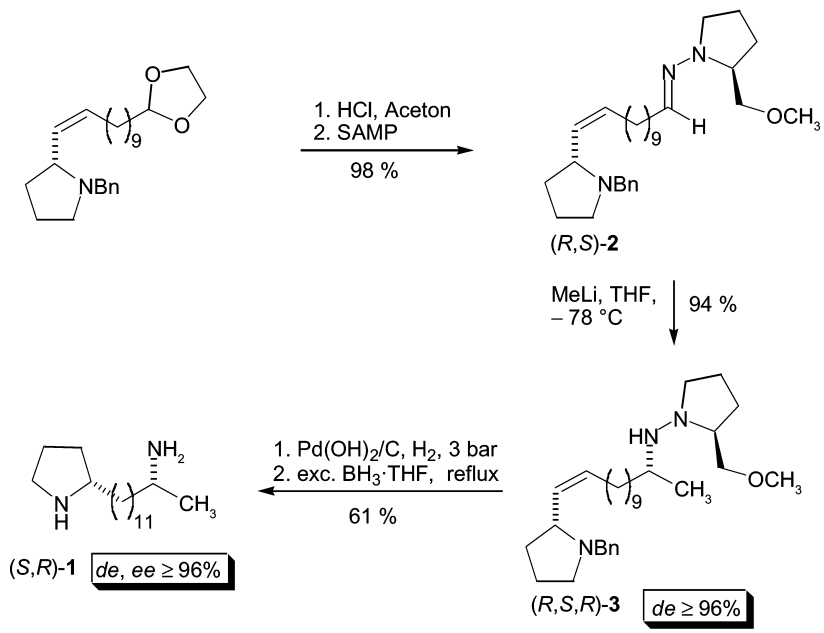
the 1,2-addition of organometallic nucleophiles to the CN double bond of chiral hydrazones and furnishes the desired substances in excellent enantiomeric purities (Scheme 1) [1].

STEREOSELECTIVE SYNTHESIS OF PIPERIDINE, PYRROLIDINE, AND INDOLIZIDINE ALKALOIDS

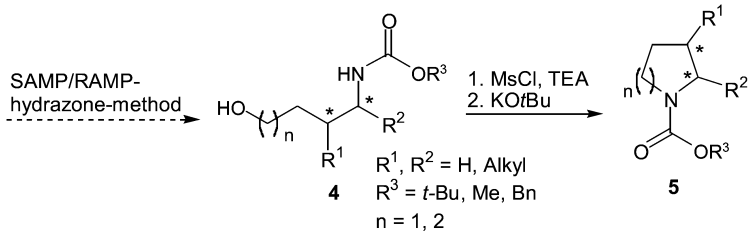
Based on this method, we were able to accomplish the stereoselective syntheses of alkaloids belonging to various structural classes. The stereogenic center in the side chain of (2*S*,12′*R*)-2-(12′-aminotridecyl)-pyrrolidine (**1**), a defense alkaloid of the Mexican bean beetle, *Epilachna varivestis* for example, could be generated very effectively by the addition of methyllithium to the CN double bond of hydrazone **2** (Scheme 2). Hydrazine **3** was obtained as a single diastereomer in very high yield and could be transformed to the target molecule by concurrent removal of the benzyl protecting group and hydrogenation of the double bond, followed by reductive cleavage of the NN bond. The last transformation could be accomplished by reaction of the trisubstituted hydrazine obtained after hydrogenation by treatment with excess borane-tetrahydrofuran-complex, leading to **1** in excellent diastereomeric and enantiomeric purity (de, ee ≥ 96%) and in good yield (35%) over nine steps starting from (*R*)-proline [2].



Scheme 2 Stereoselective synthesis of (2*S*,12′*R*)-2-(12′-aminotridecyl)-pyrrolidine, a defense alkaloid of the Mexican bean beetle, *Epilachna varivestis*.

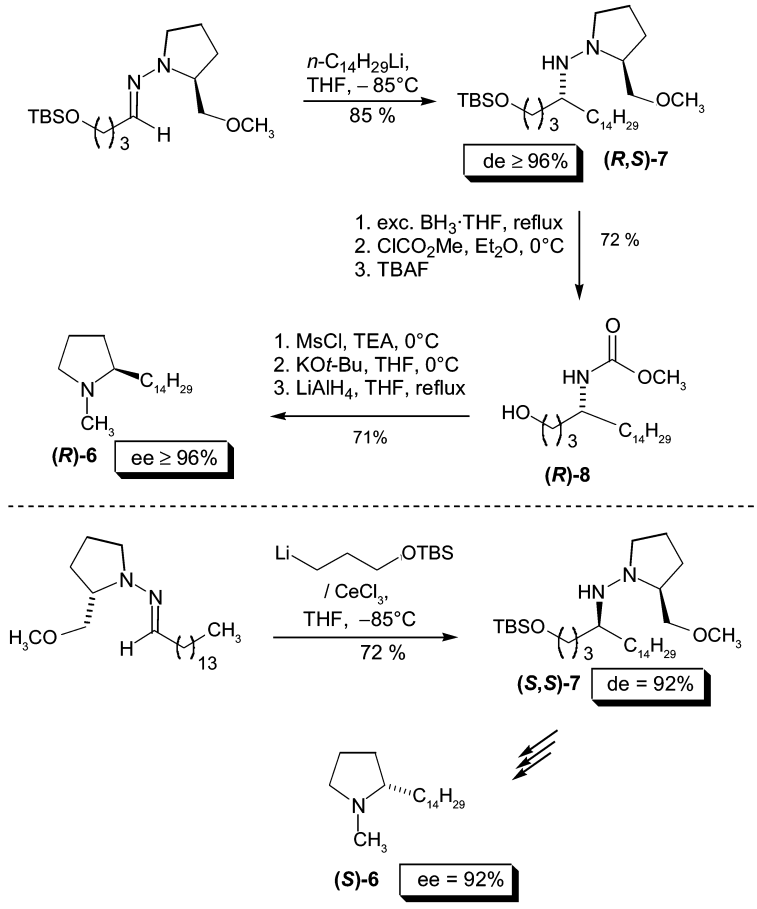
To extend this method to the asymmetric synthesis of piperidines, pyrrolidines, and indolizidines, structures that are frequently encountered in alkaloids that play an important role in the chemical ecology of plants, arthropods, and amphibians, we envisioned that a cyclization of carbamate-protected amino alcohols **4** to the corresponding protected saturated nitrogen heterocycles **5** would be a promising approach (Scheme 3). The suitable amino alcohols **4** themselves are easily available employing our SAMP/RAMP-hydrazone method.

Using this strategy, we synthesized both enantiomers of bgugaine (**6**), a 2-substituted pyrrolidine alkaloid that has been extracted from the tubers of *Arisarum vulgare*, a toxic aracea species that is found on the Mediterranean coasts of Morocco and Spain (Scheme 4). By choosing the proper building blocks



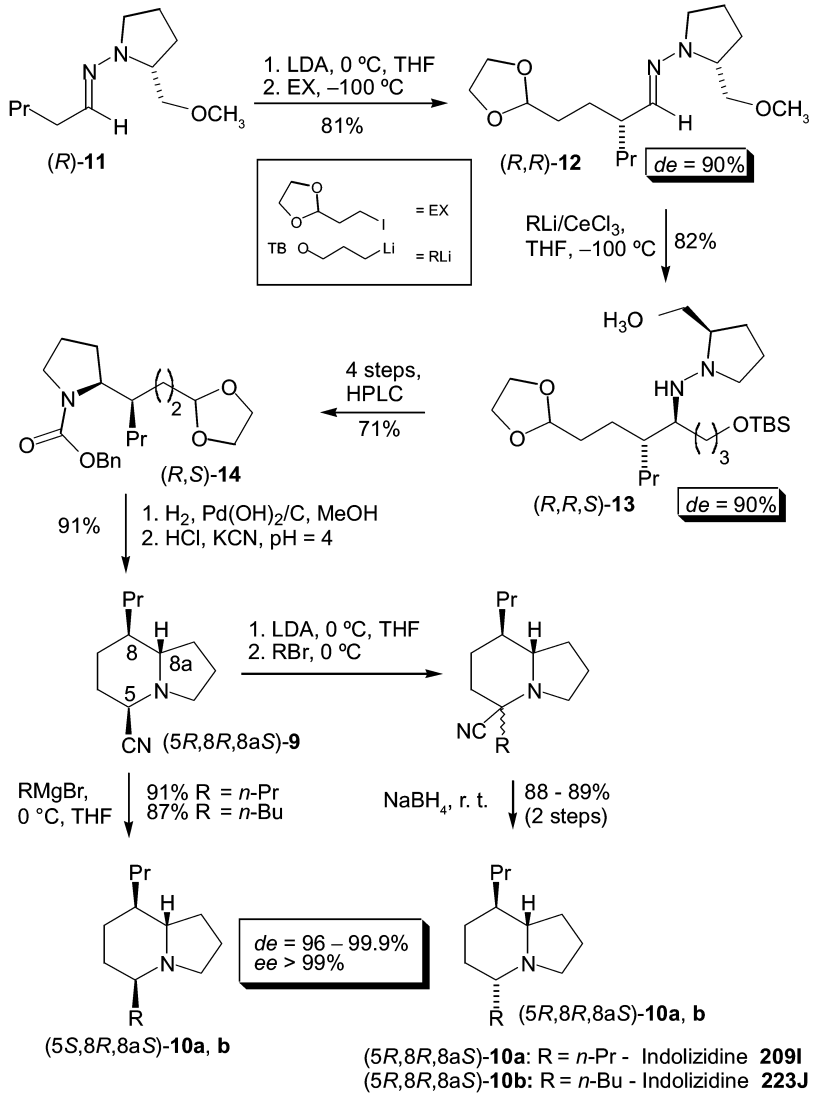
Scheme 3 Synthesis of pyrroldines and piperidines by cyclization of amino alcohols.

of hydrazone and nucleophile, we were able to obtain both epimers of the SAMP-hydrazine **7** (synthon control of stereoselectivity). As nucleophiles we used tetradecyl lithium and an organocerium reagent prepared from 3-*tert*-butyldimethylsiloxypropyllithium and cerium trichloride, respectively. Reductive NN bond cleavage, amine protection, and removal of the silyl protecting group furnished amino alcohols **8**, which could be transformed to both enantiomers of bgugaine with good to excellent enantiomeric excesses (≥96% and 92%, respectively) [3].



Scheme 4 Enantioselective synthesis of both enantiomers of bgugaine.

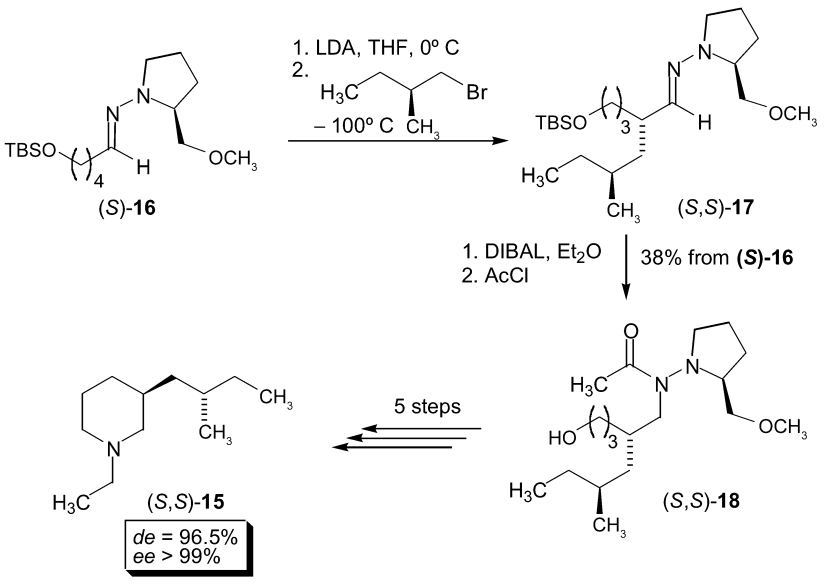
We then extended this method to the synthesis of amino nitrile **9** (Scheme 5), which was then used in the first enantioselective syntheses of the 5,8-disubstituted indolizidine alkaloids (–)-209I and (–)-223J [(5*R*,8*R*,8a*S*)-**10a, b**], which have been discovered in the skins of dendrobatid and mantelline frogs [4]. Starting from pentanal-RAMP-hydrazone **11** we could obtain hydrazone **12** by α-alkylation. We found that the organocerium reagent previously used in the synthesis of bgugaine added to the CN bond of **12** with complete asymmetric induction, furnishing hydrazine **13** in good yield and diastereomeric purity. After cleavage of the NN-bond and protection group manipulations pyrrolidine **14** was obtained by using the standard cyclization sequence. Purification by HPLC furnished **14** as a single diastereomer. The enantiomeric purity was not determined at this point, but should be very high, since the complete induction in the addition step discriminates the formation of the other enantiomer. After removal of the amino protecting group and acidic hydrolysis in the presence of potassium cyanide according to Husson's protocol, we could obtain amino nitrile **9**, which was then used for the synthesis



Scheme 5 First enantioselective synthesis of the dendrobatid alkaloids indolizidine **209I** and **223J**.

of indolizidines (–)-**209I** and (–)-**223J** [(5*R*,8*R*,8a*S*)-**10a, b**] and their C-5-epimers. This strategy had previously been used by Polniaszek and Belmont in the synthesis of 5- and 5,8-substituted indolizidine alkaloids [5,6]. Alkylation of **9** with *n*-propyl bromide and *n*-butyl bromide respectively and subsequent stereoselective reduction with sodium borohydride yielded (5*R*,8*R*,8a*S*)-**10a, b** in high diastereomeric and enantiomeric excesses (de = 96–99%, ee > 99%). Alternatively, the C-5 epimers (5*S*,8*R*,8a*S*)-**10a, b** were prepared by Bruylants reaction of **9** with propyl magnesium bromide and butyl magnesium bromide, respectively, with excellent diastereomeric and enantiomeric purity (de = 96–99.9%, ee > 99%) [7].

The 3-substituted piperidine alkaloid stenusine **15,** the spreading agent of the beetle *Stenus comma*, was synthesized with excellent stereoselectivity starting from readily available (*S*)-2-bromobutane which was used in the diastereoselective alkylation of SAMP-hydrazone (*S*)-**16** to yield hydrazone (*S*,*S*)-**17** (Scheme 6) [8]. Reaction of **17** with DIBAL resulted in 1,2-addition of hydride to the CN double bond. N-Acylation and removal of the silyl protecting group furnished hydrazine (*S*,*S*)-**18**. Stenusine **(*S*,*S*)-15** could be prepared from (*S*,*S*)-**19** by standard procedures (de = 96.5%, ee > 99%). The (*R*,*S*)-epimer of stenusine was prepared accordingly by employing RAMP as chiral auxiliary directing the stereochemical outcome of the alkylation reaction. With two of the four possible stereoisomers and a racemic sample of **15** in hand, the relative and absolute configurations of natural stenusine were investigated. Interestingly, all four stereoisomers are produced by the beetle in different quantities [9].



Scheme 6 Diastereo- and enantioselective synthesis of (*S*,*S*)-stenusine.

CONCLUSION

The highly diastereoselective 1,2-addition of organometallic reagents to aldehyde-SAMP/RAMP hydrazones followed by NN-bond cleavage opens an efficient route to the synthesis of amines with high diastereomeric and enantiomeric excesses. Combination of this method with the well-established α-alkylation of aldehyde-SAMP/RAMP hydrazones and application of the concept of synthon control of stereoselectivity greatly enhances the flexibility and provides an entry into amines and amino alcohols with different substitution patterns. Amino alcohols **4** have been used as suitable building blocks of a variety of piperidine and pyrrolidine alkaloids, while choice of proper substituents allows extension of

this method to the synthesis of indolizidines. The concept described here should be easily applied to the asymmetric synthesis of azepines, pyrrolizidines, and quinolizidines with different substitution patterns.

ACKNOWLEDGMENTS

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