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Asymmetric Synthesis of (+)-Coniine, (-)-Coniceine, (+)- β -Conhydrine, (+)-Sedamine and (+)-Allosedamine by a Strategic Combination of RCM with Nucleophilic 1,2-Addition on SAMP-Hydrazones

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Abstract: A tactically new approach to the asymmetric synthesis of the piperidine alkaloids (+)-coniine, (-)-coniceine, (+)- β -conhydrine, (+)-sedamine and (+)-allosedamine has been developed. The key step is the elaboration of the piperidine template equipped with suitably functionalized appendages at the stereodefined C-2 position. Subsequent manipulation of the appropriate functionalities gave rise to the targeted compounds in high yields and high level of enantioselectivity.

Introduction

The piperidine ring is a ubiquitous structural feature of numerous naturally occurring alkaloids and can be frequently recognized in the structure of drug candidates [1]. The interest in piperidine alkaloids is well displayed by the wealth of published material detailing their sources and biological activities and their structural diversity makes them interesting proving grounds for organic chemists. As a consequence numerous methods have been developed for the synthesis of substituted piperidines in a stereo- and enantioselective manner [2] and interest in their chemistry continues unabated.

Piperidine alkaloids incorporating a stereogenic center at C-2, as exemplified by (+)-coniine (1), (-)-coniceine (2), (+)- β -conhydrine (3), (+)-sedamine (4) and (+)-allosedamine (5) (Figure 1), fall into this category and consequently have attracted considerable attention from the synthetic community.

Objectives and Synthetic Strategy

We were then interested in developing a feasible and highly stereoselective route giving rise to the specific embodiment of these piperidine alkaloids presented in Figure 1. The salient features of the synthetic strategy are (i) the early creation of the C-2 stereogenic center of the piperidine unit on reliance with the highly diastereoselective 1,2-addition on chiral SAMP-hydrazone [3] and (ii) the creation of the piperidine template by ring closing metathesis which ranks highly in the hierarchy of synthetic tactics for the elaboration of nitrogen containing ring systems [4].

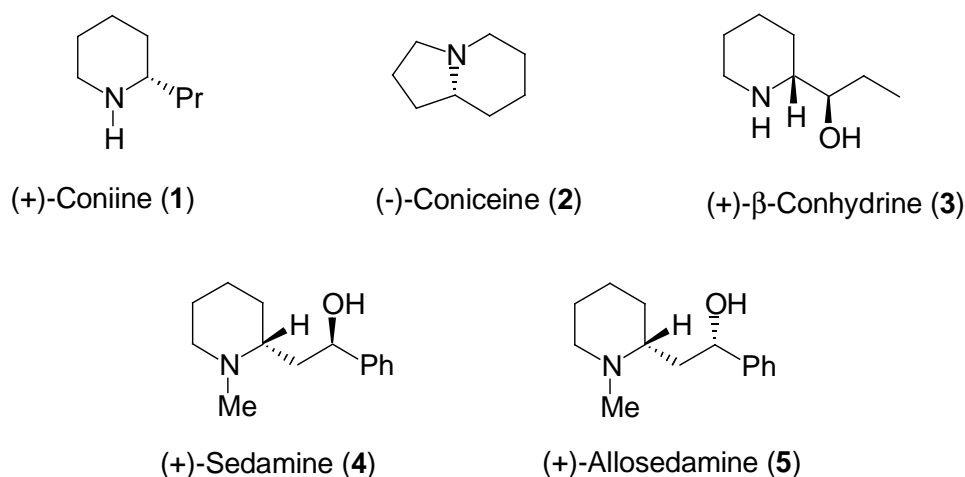


Figure 1.

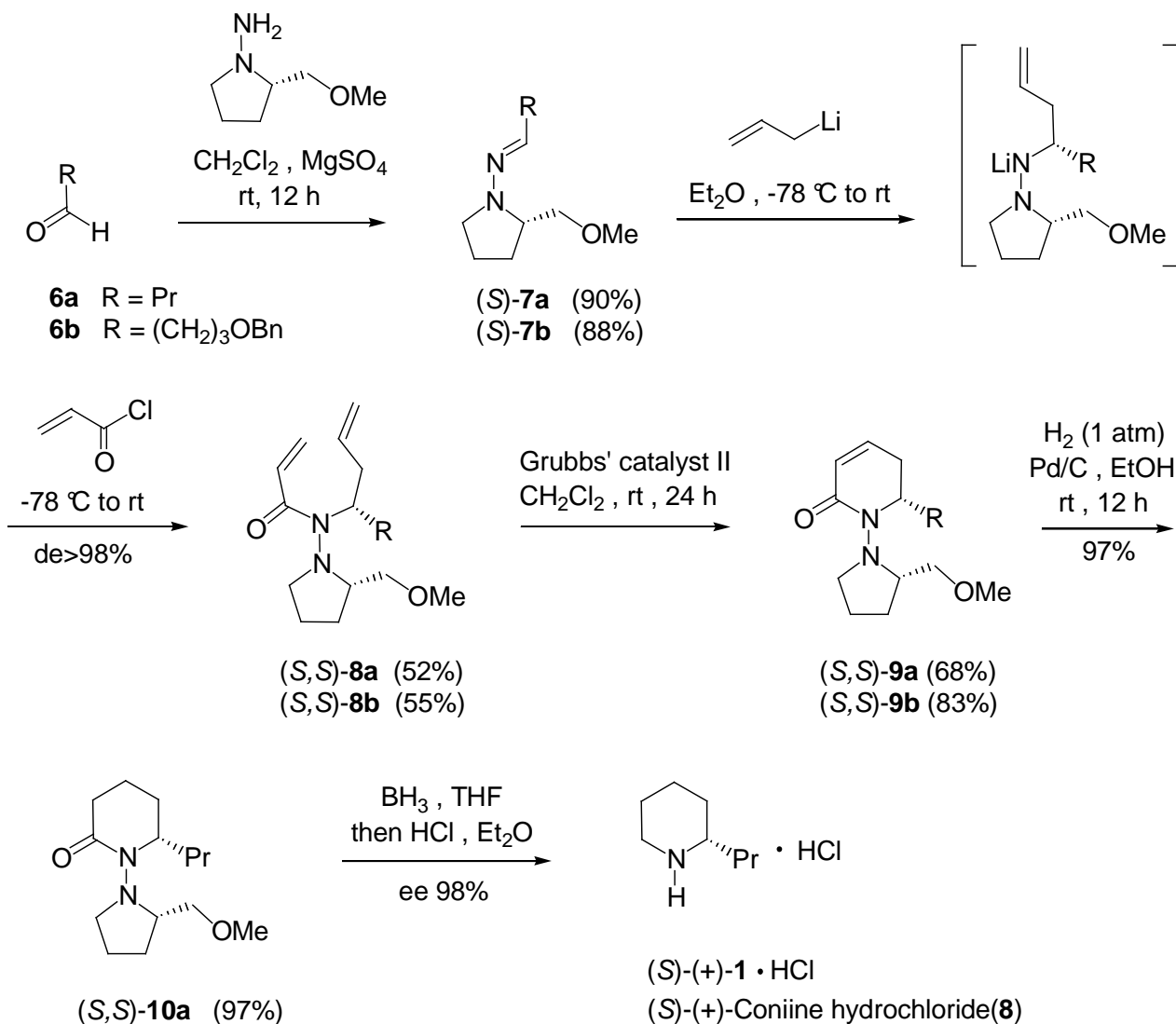
Enantioselective Synthesis of (S)-(+)-Coniine (1). Extension to the Synthesis of (-)-Coniceine (2).

To test the viability of our conceptually new synthetic approach the synthesis of the structurally simple piperidine alkaloid (+)-coniine (1) was envisaged since it was anticipated that its elaboration could serve as a testing ground and provide foundation for extension to more complex and functionalized systems.

1. (S)-(+)-Coniine (1)

The first facet of the synthesis was the assembling of the requisite dienehydrazone **8a**, which was readily obtained by the three-step sequence depicted in Scheme 1. This olefinic precursor was obtained essentially as single diastereoisomer detectable by NMR making evident the high selectivity of the initial diastereofacial 1,2-addition process allowing introduction of the absolute stereochemistry early in the sequence.

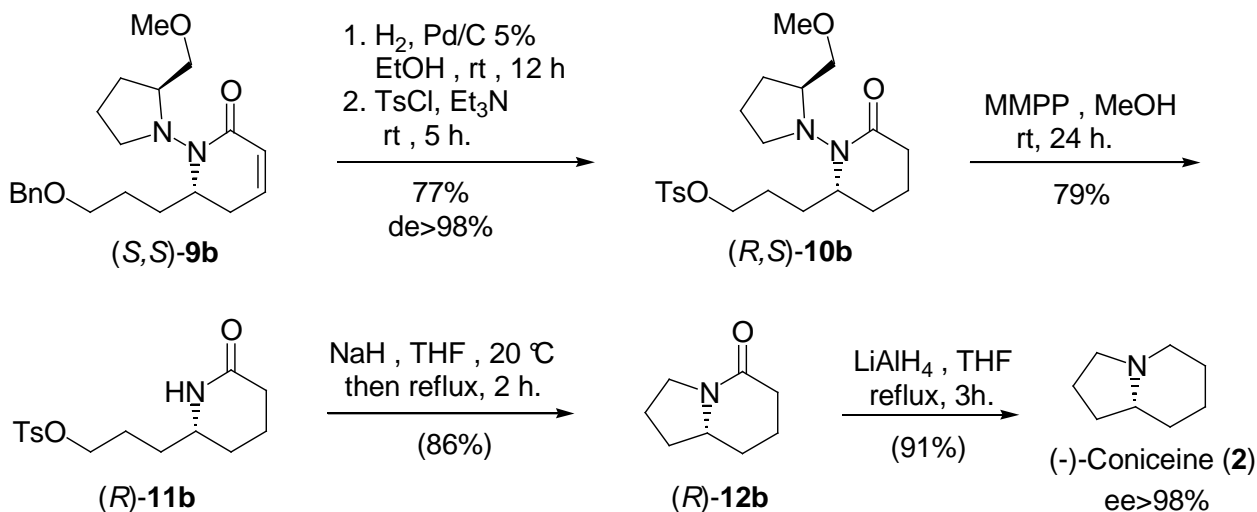
RCM reaction with Grubb's second generation ruthenium catalyst proceeded uneventfully to afford diastereopure enehydrazone (S,S)-**9a**. Catalytic hydrogenation afforded hydrazone (S,S)-**10a** and subsequent treatment of (S,S)-**4a** with $\text{BH}_3 \cdot \text{THF}$ triggered off the formation of the NH free model with the concomitant release of the chiral appendage, thereby providing high yield of the targeted alkaloid **1** with excellent enantioselectivity.



Scheme 1.

2. (-)-Coniceine (2)

This bicyclic alkaloid is a representative member of the biologically active indolizidine alkaloids that have been isolated from the skin secretions of neotropical amphibians [5].



Scheme 2.

Its elaboration was readily achieved as depicted in Scheme 2 starting from the diastereopure (*S,S*)-**9b**. This diastereochemically enriched enehydrazide equipped with a protected hydroxypropyl appendage was accessed via the synthetic route depicted in Scheme 1 starting from the appropriate aliphatic aldehyde **6b**.

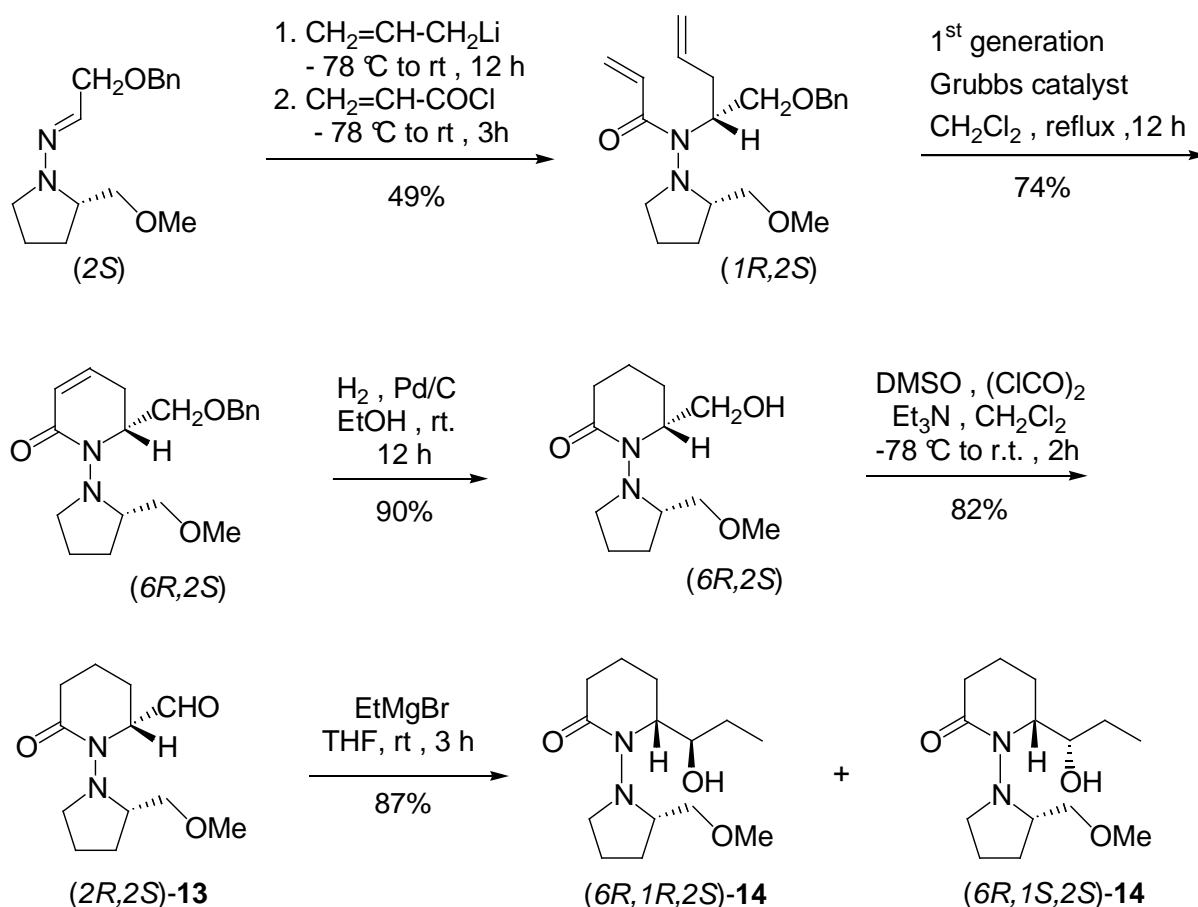
Treatment of (*R,S*)-**10b** with magnesium monoperoxyphthalate afforded the virtually enantiopure NH free piperidone (*R*)-**11b**.

The subsequent deprotonation/annulation/lactam reduction sequence delivered the piperidine alkaloid (–)-Coniceine (**2**) in high yield and excellent enantioselectivity.

Enantioselective Synthesis of (+)-β-Conhydrine (3).

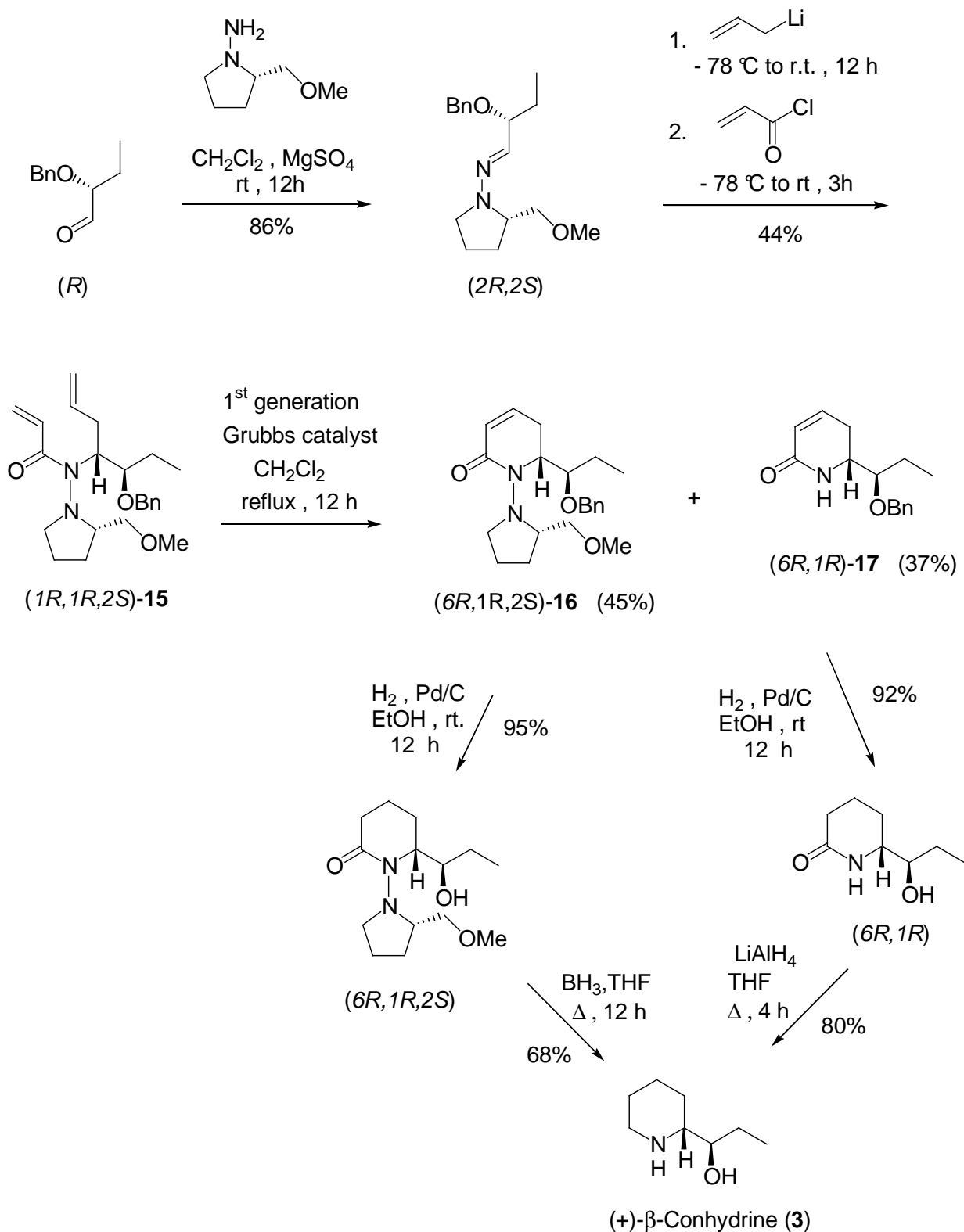
This piperidine alkaloid is representative of the hemlock alkaloids isolated from the seeds and leaves of the poisonous plant *Conium maculatum* L. whose extracts were used in the ancient Greece to get rid of criminals and undesirable intellectuals, for example Socrates [6].

Initially we planned to synthesize the carboxaldehyde derivative **13** and we surmised that treatment of diastereopure **13** with EtMgBr would provide the potential for a direct access to the piperidine template tailed with the required hydroxypropyl appendage. The highly functionalized compound (*R,S*)-**13** was obtained in high yield and high enantioselectivity as outlined in Scheme 3. Disappointingly, when diastereopure (*R,S*)-**13** was allowed to react with EtMgBr a 2:3 mixture of (*R,R,S*)-**14** and (*R,S,S*)-**14** diastereoisomers was obtained.



Scheme 3.

We then set out to achieve the alternative strategy depicted in Scheme 4 which secured the stereochemistry of the hydroxyalkyl appendage on the piperidine template at an early stage of the synthesis. Interestingly, when bis-olefin **15**, readily assembled as portrayed in Scheme 4, was subjected to RCM a 55:45 mixture of diastereomerically pure **16** along with the NH free piperidine **17** was obtained. This unprecedented phenomenon had no impact on the outcome of the process since the targeted (+)- β -conhydrine (**3**) could be readily accessed from **16** and **17** as well.

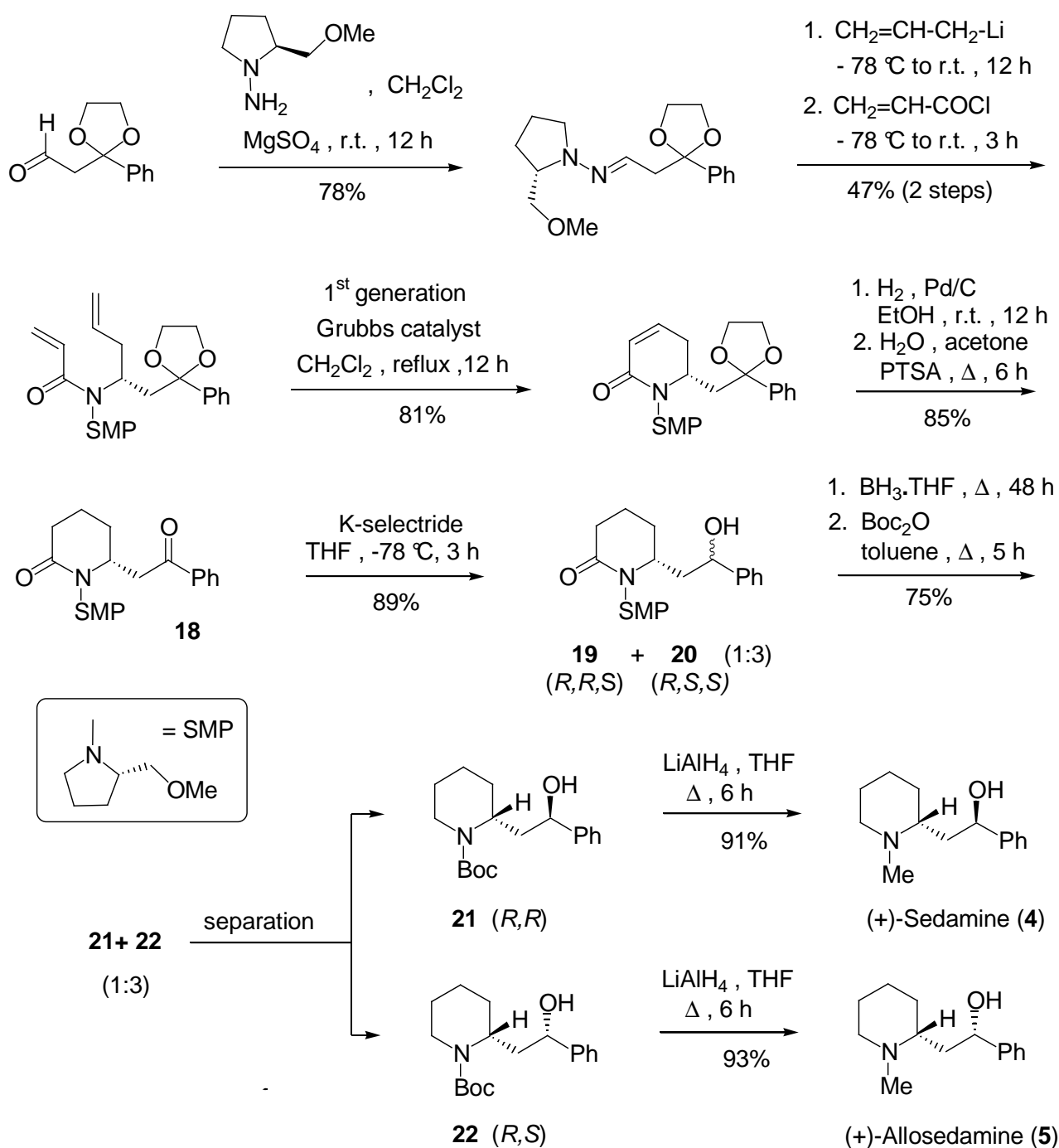


Scheme 4.

Enantioselective Synthesis of (+)-Sedamine (4) and (+)-Allosedamine (5).

The 1,3-aminoalcohol moiety is found in many synthetic and natural products possessing physiological activities and is the integral part of a variety of potent drugs [7]. It is also the most distinguishing structural feature of 2-(2-hydroxyalkylsubstituted)piperidine based alkaloids such as sedamine and allosedamine. This type of alkaloid has been shown to display memory enhancing properties and may be effective for the treatment of cognitive disorders [8].

A new synthetic approach to these compounds has been developed and is outlined in Scheme 5.



Scheme 5.

Noteworthy, for the reduction of the carbonyl functionality of diastereopure **18** a variety of reducing agents were screened. By making use of K-selectride a 1:3 mixture of the diastereoisomeric forms **19** and **20** was obtained.

Conclusion

In summary we have devised a new, general and flexible method for the highly enantioselective synthesis of chiral piperidines. The method tolerates the presence of diverse functionalized appendages at C-2, namely 1- and 2-hydroxyalkylated moieties. The main advantages of this synthetic method lie in the readily availability of the aliphatic and aromatic aldehyde SAMP-hydrazone precursors. In addition, with the present synthetic approach, optically active antipodes of the titled compounds should be readily accessed by simple choice of the RAMP chiral auxiliary.

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