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Asymmetric Synthesis of 6-Alkyl- and 6-Arylpiperidin-2-ones. Enantioselective Synthesis of (*S*)-(+)-Coniine

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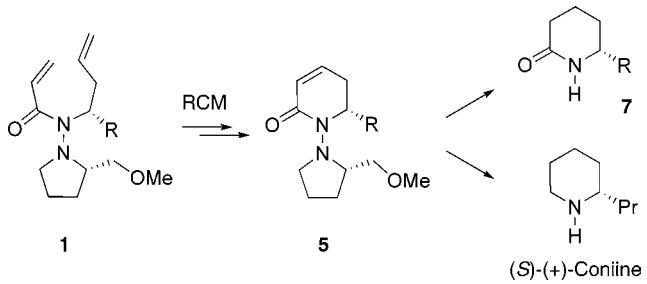
ABSTRACT



A variety of diolefinic hydrazides (1) have been assembled in a highly diastereoselective manner by addition of allyllithium to chiral SAMP hydrazones followed by *N*-acylation with acryloyl chloride. Substrates 1 undergo ring-closing metathesis to give the cyclic enehydrazides (5) which can be easily converted into virtually enantiopure 6-alkyl- or 6-arylpiperidin-2-ones (7). The versatility of this hydrazone addition–RCM protocol has been further exemplified by the conversion of the unsaturated heterocycle 5b into the piperidine alkaloid (*S*)-(+)-coniine.

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.[3] Piperidinones are somewhat less prominent but very often they serve a role as advanced intermediates prior to their conversion to piperidines.[2c,4] In this context the corresponding saturated or unsaturated δ-lactams have emerged as powerful tools as they possess the requisite structure and functional group locations for further elaboration to synthetic targets,

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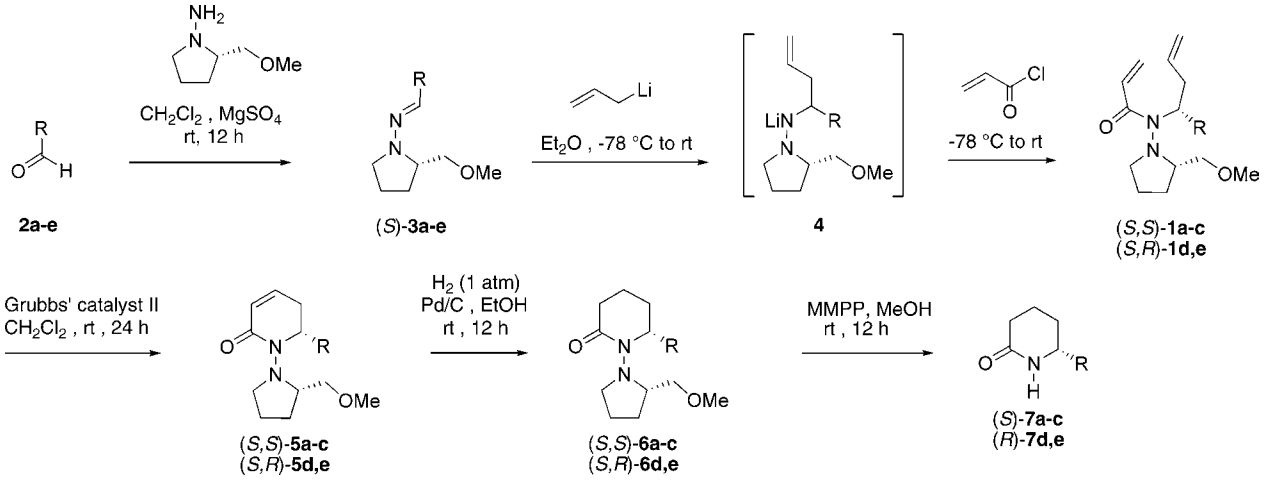
Scheme 1. Asymmetric Synthesis of 6-Alkyl- and 6-Arylpiperidin-2-ones **7a−e**



particularly piperidine alkaloids. The subsequent introduction of substituents on the carbon atoms of the piperidine ring may indeed be achieved by α-amidoalkylation, enolate or homoenolate alkylations, manipulation of the amide carbonyl group, and functionalization of the olefinic moiety including but not limited to epoxydation or dihydroxylation.[5] The substituted piperidin-2-ones are also substructural units of barbiturates and glutarimides[6] and are key intermediates for the synthesis of aminopentanoic acids.[7] Thus the development of chiral nonracemic piperidinone building blocks with the final aim of synthesizing enantiopure piperidine derivatives still constitutes an area of current interest and alternative methods are currently the object of intensive synthetic endeavors.

Herein we wish to report the use of chiral cyclic enehydrazides as substrates for catalytic hydrogenation, which provides a new efficient and general route to optically active 6-alkyl- and 6-arylpiperidin-2-ones. The utility of this method has been emphasized by the synthesis of the poisonous hemlock alkaloid (*S*)-(+)-coniine.[8] Organic chemists have at their disposal a variety of synthetic strategies for the asymmetric synthesis of 6-substituted piperidin-2-ones[9−17] but varying degrees of success have been claimed with regard to their enantioselectivities. Except for some catalyst based synthesis of these lactams[10] most convenient strategies involve the intramolecular cyclization of enantioenriched *β*-keto,[11] saturated,[9,12] or unsaturated[13] *δ*-aminoesters and some of the corresponding azido derivatives.[14] These highly functionalized precursors are usually equipped with chiral auxiliaries derived from the natural chiral pool or with tailor-made stereocontrolling agents. They also have been obtained by reductive opening of diastereochemically pure oxazolopiperidones[15] or via an asymmetric amidoalkylation involving interception of variously generated chiral iminium salts with silyl derivatives[16] or cyanocuprates.[5c,17] On the other hand, studies on the corresponding α,*β*- or *γ*,*δ*-unsaturated *δ*-lactams are scarce and most of the chiral 6-substituted models have been assembled from the corresponding saturated lactams[18] by a multistep sequence involving metalation/electrophilic capture with phenylselenyl bromide/oxidation reactions followed by an ultimate elimination reaction.

We now report combinations of a highly diastereoselective nucleophilic 1,2-addition on chiral aliphatic and aromatic

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Table 1. Compounds **3**, **1**, **5**, **6**, and **7** Prepared[a]

R	yield, %									
	hydrazone		dienehydrazide		enehydrazide		hydrazide		δ-lactam	
Et	(*S*)-**3a**	85	(*S*,*S*)-**1a**	50	(*S*,*S*)-**5a**	73	(*S*,*S*)-**6a**	95	(*S*)-**7a**	80
Pr	(*S*)-**3b**	90	(*S*,*S*)-**1b**	52	(*S*,*S*)-**5b**	68	(*S*,*S*)-**6b**	97	(*S*)-**7b**	78
Bu	(*S*)-**3c**	87	(*S*,*S*)-**1c**	45	(*S*,*S*)-**5c**	65	(*S*,*S*)-**6c**	95	(*S*)-**7c**	83
Ph	(*S*)-**3d**	80	(*S*,*R*)-**1d**	49	(*S*,*R*)-**5d**	70	(*S*,*R*)-**6d**	93	(*R*)-**7d**	85
p-$MeOC_6H_4$	(*S*)-**3e**	83	(*S*,*R*)-**1e**	54	(*S*,*R*)-**5e**	75	(*S*,*R*)-**6e**	98	(*R*)-**7e**	80

[a] The diastereomeric excess de ≥98% was determined by ^1H NMR and ^{13}C NMR spectroscopy after flash chromatography. For all compounds the de values were about the same before and after purification by chromatography.

SAMP hydrazones and subsequent acylation with acryloyl chloride with a ring-closing metathesis (RCM) for the synthesis of diastereochemically pure cyclic enehydrazides, suitable candidates for the asymmetric synthesis of 6-alkyl- or 6-arylpiperidin-2-ones.

The first facet of the synthesis was the elaboration of the diolefinic hydrazides **1a**−**e**. These highly conjugated precursors were easily obtained by the three-step sequence depicted in Scheme 1. Initially the appropriate aliphatic and aromatic carboxaldehydes **2a**−**e** were converted into the corresponding chiral hydrazones (*S*)-**3a**−**e** by simply mixing the enantiomerically pure hydrazine (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) with the commercially available aldehydes **2a**−**e**. Owing to the sensitivity of hydrazones to nucleophilic attacks and to the high degree of stereoselectivity observed upon reaction of SAMP hydrazones with organometallic reagents, a property aptly exploited by Enders,[19] the subsequent installation of the mandatory olefinic entities was performed as a single one-pot reaction. Chiral hydrazones (*S*)-**3a**−**e** were allowed to react with allyllithium and the transient lithium hydrazide salt **4** was intercepted with acryloyl chloride in the sequel. Gratifyingly, conducting this operation under this procedure afforded excellent yields of the requisite opened dienehydrazides (*S*,*S*)-**1a**−**c** and (*S*,*R*)-**1d**,**e** (Table 1). These olefinic precursors were obtained essentially as single diastereomers detectable by NMR (de ≥98% after chromatographic treatment) making evident the high selectivity of the initial diastereofacial 1,2-addition process[19] allowing introduction of the absolute stereochemistry early in the sequence. With the properly substituted dienehydrazides **1** in hand we next examined ring-closing metathesis conditions to achieve the chiral α,β-unsaturated piperidones **5**. The olefin metathesis reaction has been widely used in the recent past as a result of the development of highly stable and active ruthenium alkylidene catalysts.[2d,20] To ensure the optimal formation of the annulated compounds, RCM reactions were carried out with variable amounts of commercially available Grubb's ruthenium catalysts, which is the less expensive first generation benzylidenebis(tricyclohexylphosphine)dichloro-ruthenium I and the recent second generation benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)-ruthenium II in CH_2Cl_2 at rt or at reflux. The diolefinic hydrazide **1a** was chosen as the starting material for our study. In all cases ring closure proceeded smoothly with yields ranging from 32% to 75% but Grubb's catalyst II performed significantly better than its analogue I. The best results were obtained by employing 5% of catalyst II at rt in CH_2Cl_2 for 24 h and these optimal conditions were then used to perform the annulation reactions of diolefinic substrates **1b**−**e**. Results are presented in Table 1 where it can be seen that this simple procedure afforded very satisfactory yields of the virtually diastereochemically pure cyclic enehydrazides (*S*,*S*)-**5a**−**c** and (*S*,*R*)-**5d**,**e**. At this stage it should be a priori possible to effect both the RCM reaction and the subsequent reduction of the double bond as a single operation by using the same ruthenium catalyst.[21] However, this possibility was not investigated since the double bond of **5**, still equipped with the chiral auxiliary, provides a useful chemical handle for alternative functionalization chemistries. Catalytic hydrogenation proceeded uneventfully to provide excellent yields of the corresponding hydrazides (*S*,*S*)-**6a**−**c** and (*S*,*R*)-**6d**,**e**. The subsequent removal of the chiral auxiliary was readily achieved by cleavage of the N−N bond upon treatment of **6a**−**e** with magnesium monoperoxyphthalate (MMPP) in MeOH and this operation delivered the virtually enantiopure (*S*)-6-alkyl- and (*R*)-6-arylpiperidin-2-one, (*S*)-**7a-c** and (*R*)-**7d**,**e**, respectively, with excellent yields (Table 1). The absolute configuration as well as the enantiopurity of these δ-lactams were determined by comparing the optical rotation values with that of authentic samples assembled by conceptually different synthetic routes, thus confirming the stereochemistry of the original addition reaction, e.g., **7b** {$[\alpha]^{20}_D$ +17.9 (*c* 0.5, $CHCl_3$); lit.[13c] $[\alpha]^{22}_D$ +18.1 (*c* 0.6, $CHCl_3$)} and **7d** {$[\alpha]^{20}_D$ +58.5 (*c* 1.0, $CHCl_3$); lit.[13c] $[\alpha]^{25}_D$ +58.2 (*c* 1.0, $CHCl_3$)}.

To illustrate further the utility of this methodology in natural product synthesis the procedure was applied to the asymmetric synthesis of the naturally occurring (*S*)-2-propylpiperidine alkaloid (*S*)-(+)-coniine (**8**), a popular target

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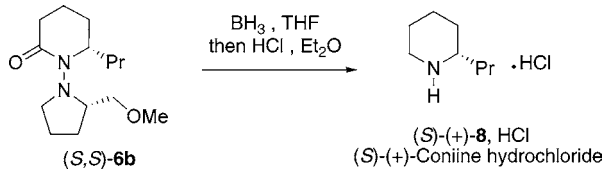
for the demonstration of chiral methodology in the piperidine field.[22,23] (*S*)-Coniine is a poisonous hemlock alkaloid extracted from the plant *Conium maculatum* and from many tropical subspecies.[8] The choice of the 2-C substituted pyrrolidine as the chiral auxiliary was rewarded here. Treatment with the borane−THF complex of (*S*,*S*)-**6b** followed by aqueous alkaline workup effected reductive N−N bond cleavage with the concomitant reduction of the lactam carbonyl group and final treatment with HCl in Et_2O afforded the target natural product **8** as its hydrochloride salt (Scheme 2). The absolute configuration of the stereogenic

Scheme 2. Asymmetric Synthesis of (*S*)-(+)-Coniine



center was confirmed to be (*S*) from the sign of the specific rotation of the hydrochloride and the enantiopurity of our synthetic (*S*)-(+)-coniine [(*S*)-**8**] was clearly established from the optical rotation and spectroscopic data that matched those reported for the natural product {(*S*)-**8**, HCl: mp 215−216 °C, $[\alpha]^{20}_D$ +7.8 (*c* 0.5, EtOH); (*S*)-(+)−coniine, HCl: lit.[3c] mp 216−217 °C, lit.[22g] $[\alpha]^{25}_D$ +8.1 (*c* 0.6, EtOH)}.

In conclusion we have devised a new, convenient, general, and flexible method for the highly diastereo- and enantioselective synthesis of N-substituted and free NH 6-substituted piperidin-2-ones. The key steps are the highly diastereoselective nucleophilic 1,2-addition to SAMP hydrazones and the unprecedented ring-closing metathesis of diastereopure diolefinic hydrazides. The utility of the chiral building blocks was illustrated by a five-step asymmetric synthesis of piperidine alkaloid (*S*)-(+)-coniine. The main advantages of this synthesis method lie in the small number of synthetic steps and the ready availability of the aliphatic and aromatic aldehyde SAMP hydrazone precursors. We believe that this work provides a strong incentive for the elaboration of larger or structurally modified alkaloids as well as their biogenetically related congeners.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org..

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