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Synthesis of *trans*-(3*S*)-Amino-(4*R*)-alkyl- and -(4*S*)-Aryl-piperidines via Ring-Closing Metathesis Reaction

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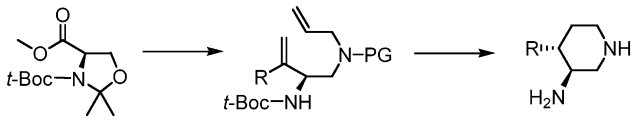
ABSTRACT



***trans*-(3*S*)-Amino piperidines bearing various alkyl and aryl substituents at the C-4 position were synthesized via a ring-closing metathesis reaction. The absolute stereochemistry was controlled using a protected D-serine as a starting material. Stereoselective hydrogenation of allylamines provided *trans*-(3*S*)-amino-(4*R*)-alkyl- and -(4*S*)-aryl-piperidines. This procedure presents the first method for the asymmetric synthesis of 4-substituted 3-amino piperidines.**

Piperidine and substituted piperidines have been broadly studied subjects of synthetic chemistry investigations for a long time. This work has included development of numerous methods for the synthesis of these compounds and wide applications of these unique heterocycles as synthetic building blocks useful for other syntheses.[1,2] Piperidines have become a particularly interesting topic due to their important position as bioactive components in pharmaceutical research in recent years.[3] However, our literature search revealed that no general synthetic methods were readily available for the preparation of 4-substituted 3-amino-piperidines as a relatively simple but potentially important subclass of piperidines. The only related report found in the literature described piperidine ring closure via an intramolecular Michael addition resulting in formation of *trans*-3-amino-4-(propanon-2′-yl)-piperidine.[4] However, this method provides a nonasymmetric synthesis of these piperidines and is limited to only those based upon having a Michael acceptor component in the precursor. Very recently, we communicated our results of a carbanionic nucleophilic addition to an aziridinopiperidine[5] and a heteronucleophilic addition under Lewis acid conditions.[6] In both cases, high regio- and stereoselectivities were achieved. Despite the fact that these interesting methods developed in our lab were very robust in generating analogues quickly for our drug screening purposes, we wished to explore an asymmetric synthetic method for *trans*-3-amino 4-substituted piperidines.

It was of interest to us in quinolone antibacterial research to seek new substituents for introduction at the quinolone C-7 position. The most commonly occurring substituents in the literature are piperazines and pyrrolidines,[7] whereas piperidines are a much less explored group. The only report found in the literature pertained to 7-(3-aminopiperidin-1-yl)quinolones,[8] which exhibited limited improvement of antibacterial activity. We sought to investigate substituted piperidinyl quinolones to improve antibacterial potency,

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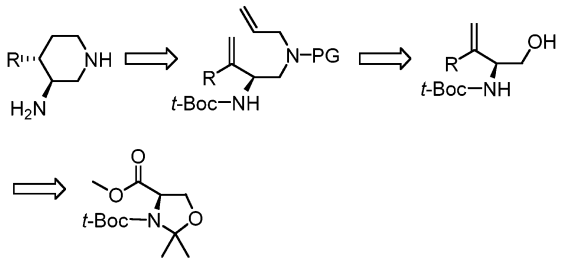


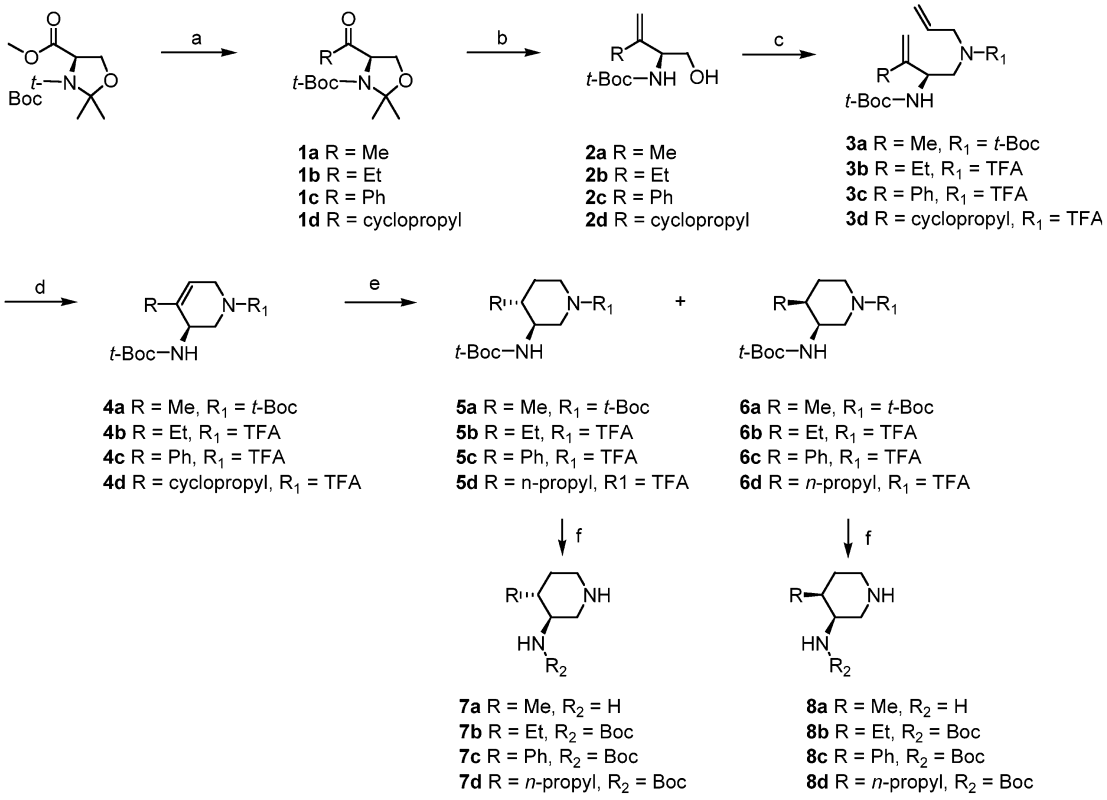
Figure 1.

broad spectrum of activity, and activity against resistant pathogens.[9] To synthesize these 3-amino 4-substituted piperidines, there were two issues that we identified that needed to be addressed in our strategy: the first was how we could establish the absolute stereochemistry, and the second was how we could achieve trans relative stereochemistry at the C-3 and C-4 positions. Herein, we report our recent results on the synthesis of (3*S*)-amino-(4*R*)-alkyl- and -(4*S*)-aryl-piperidines.

As shown in Figure 1 in our retrosynthetic analysis, we chose to employ a ring-closing metathesis method to form the piperidine ring followed by stereoselective reduction. The diene intermediate could be generated from substituted allylamines, which could be derived from a readily available protected amino acid.

Our asymmetric synthesis of (3*S*)-amino 4-substituted piperidines was based on the introduction of the chiral amino group from a fully protected D-serine amino acid. As shown in Scheme 1, the methyl ester was reduced by DIBAL to produce Garner's aldehyde,[10] which underwent addition with methyl, ethyl, cyclopropyl, and phenyl Grignard reagents[11] followed by Swern oxidation to afford the corresponding ketone intermediates **1a**−**d**. Olefination of the ketones with Ph_3PCH_3Br/KOBu-*t* and then selective deprotection by *p*-TsOH (10 mol %) resulted in homoallylic alcohols **2a**−**d**. In the case of styrene **2c**, 0.5 equiv of $(t\text{-Boc})_2O$ and Et_3N was added to the reaction mixture at the end of the deprotection reaction to retrieve the product from an over-deprotection. The hydroxyl compounds were converted to dienes **3a**−**d**, precursors for ring-closing reactions, via a three-step sequence: activation of the hydroxyl groups with

Scheme 1[a]

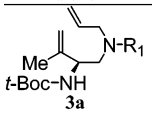
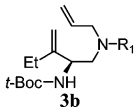
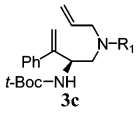
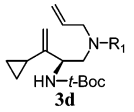


[a] Reagents and conditions: (a) (i) DIBAL, toluene, < −60 °C, 30 min, then 0 °C, 2 h, yield 95%; (ii) MeMgBr, EtMgBr, *c*-PrMgBr or PhMgBr, THF, from −65 to 0 °C, 1.5 h, yield 87−95%; (iii) $(COCl)_2$, DMS, < −65 °C, 30 min, then Et_3N, −78 °C, 5 min, warmed to 0 °C over 30 min, yield 92−100%. (b) (i) CH_3PPh_3Br, KOBu-*t*, THF, rt, 10 min, yield 84−95%; (ii) *p*-TsOH (0.1 equiv), MeOH, 55 °C, 18 h, then 0.5 equiv $(t\text{-Boc})_2O$, 0.5 equiv Et_3N, rt, 2 h, yield 65−91%. (c) (i) *p*-TsCl, Et_3N, CH_2Cl_2, reflux, 6 h; (ii) allylamine, neat, reflux, 2 h; (iii) then $(t\text{-Boc})_2O$, yield 40% for three steps, or TFAA/Et_3N, rt, 1 h, yield 33−47% for three steps. (d) $Cl_2Ru(=CHPh)(Pcy_3)_2$ (10 mol %), see Table 1. (e) H_2, 10% Pd/C, MeOH, rt, flash chromatography separation of two diastereomers. (f) Concentrated HCl, rt, 15 min, 100%, or K_2CO_3, MeOH, reflux, 10 min, yield 85−100%.

p-TsCl, displacement of the tosylates in neat allylamine, followed by protection of the secondary amines either with a *t*-Boc or with a trifluoroacetate (TFA) group.

The conventional ring-closing reaction conditions[12] were applied using $Cl_2Ru(=CHPh)(Pcy_3)_2$ catalyst (10 mol %) in a solvent upon heating, and the results are summarized in Table 1 below. We noticed that the protecting groups at the secondary amine played a significant role in effecting the reaction rate of the ring-closing metathesis. In the case of the methyl diene (**3a**), the cyclization proceeded smoothly in refluxing CH_2Cl_2 in 4 h to give 4-methyl-tetrahydropiperidine **4a** in 87% yield after purification, whereas under the same conditions the cyclization of the ethyl diene (**3b**) in 45 h resulted in 4-ethyl product **4b** in an unacceptable low yield (23%) and with the starting diene recovered. Even worse was the cyclization of the phenyl diene (**3c**), in which only 5% cyclized product was isolated. In both cases, unidentified byproducts were observed as major components when more catalyst was used in an extended reaction time in refluxing benzene or toluene. However, another commonly used amino protecting group, trifluoroacetyl (TFA),[13] appeared to us to be another alternative for our RCM reaction, possibly because of less steric effect on cyclization by altering either the diene precursor conformation or the product conformation.[14] TFA-protected **3b**−**d** were prepared and subjected to the RCM reaction conditions. Much improved reaction results were obtained this time: ethyl diene (**3b**) in 88% yield in 21 h and the phenyl diene (**3c**) in 81% in 24 h. However, slow reaction occurred in the cyclization of the diene (**3d**). Higher temperatures and longer times were needed to convert the diene to the product in order to get a reasonable yield (60% of the product and 25% of the recovered starting diene).

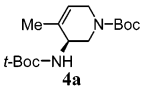
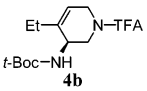
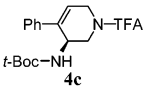
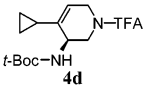
Table 1. Protecting Group Influence on Ring-Closing Metathesis Reaction

diene	R_1	solvent	temp. (°C)	time (h)	yield (%)[a]
 **3a**	*t*-Boc	CH_2Cl_2	Reflux	4	87
 **3b**	*t*-Boc	CH_2Cl_2	Reflux	45	23
	TFA	CH_2Cl_2	Reflux	21	88
 **3c**	*t*-Boc	CH_2Cl_2	Reflux	48	5
	TFA	CH_2Cl_2	Reflux	24	81
 **3d**	TFA	Toluene	60	96	85[b]

[a] After flash chromatography. [b] Recovered yield.

With the (3*S*)-*t*-Boc-amino 4-substituted 1,2,3,6-tetrahydropyridines (**4a**−**d**) synthesized, our next step was to examine stereocontrolled reduction of the carbon−carbon double bond under hydrogenation conditions. We anticipated that the stereochemistry outcome in reduction of the allylamines would be influenced by neighboring group participation, in which the 3-*t*-Boc amino group might interact with the catalyst surface and the hydrogen may be delivered from the same side of the amino group.[15] Therefore, the trans isomers would be obtained as the predominant products. The double-bond reduction of **4a** was initially carried out under hydrogenation conditions (5% Pd/C in EtOH at 1 atm of H_2 pressure) to afford two isomers, **5a** and **6a**, which were separated by flash chromatography (see Table 2). We found that the catalyst loading impacted the diastereomer distribution in reduction: loading of 0.1 equiv of the catalyst by weight gave an isomer ratio of 3.5:1 in 24 h, whereas loading of 0.5 and 1.0 equiv of the catalyst gave diastereomer ratios of 2:1 in 12 h and 1:1 in 1 hour, respectively. The stereochemistry of the trans and cis isomers was unambiguously assigned by NOE NMR analysis on the basis of deprotected piperidines **7a** and **8a** (Figure 2), indicating that the major stereoisomer was trans piperidine **7a**. In addition, a large coupling constant (J_{trans} = 11.6 MHz) between C(3)H

Table 2. Reduction of Carbon−Carbon Double Bond under Hydrogenation Conditions

diene	amount of Pd/C (by Weight)	time (h)	ratio (**5**/**6**)[a]	yield (**5**+**6**)
 **4a**	100%	1.0	1:1	98%
	50%	12	2:1	91%
	10%	24	3.5:1	95%
 **4b**	10%	24	3:1	93%
 **4c**	15%	24	15:1	82%
 **4d**	50%	4	1:1	95%

[a] Based on flash chromatography separation. [b] Combined yield.

(9) Unpublished results.
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(12) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677.
(13) Phillip, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75 and references cited therein.
(14) The effect of the TFA protecting group on the ring-closing metathesis reaction is not completely understood, and one may argue that a possible electronic effect could play a role in this reaction.
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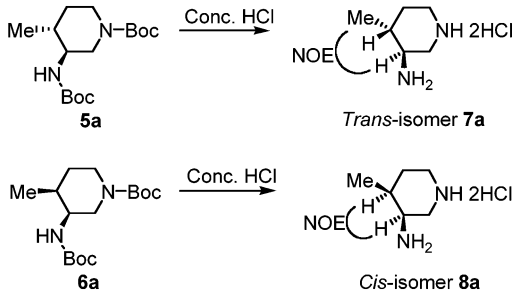

Figure 2.

and C(4)H in the trans isomer vs the coupling constant (J_{trans} = 4.6 MHz) in the cis isomer also supports the stereochemistry assignments. This was further verified by an independent nonasymmetric synthesis of *trans*-3-amino-4-methyl piperidine.[5] A similar diastereomer ratio distribution was observed in the ethyl piperidine case. Interestingly, significantly enhanced diastereoselectivity was seen in a phenyl-substituted tetrahydropyridine reduction in up to a 15:1 ratio in favor of the trans isomer formation. However, the reduction of the cyclopropyl analogue (**4d**) resulted in a complete loss of the selectivity. We also noticed that the cyclopropyl ring opening occurred in the reduction of **4d** to give *n*-propyl piperidine products **5d** and **6d**. Both the *t*-Boc and TFA protecting groups of products **5a**−**d** and **6a**−**d** were removed under mild conditions to give *trans*-(3*S*)-amino-(4*R*)-alkyl- and -(4*S*)-phenyl-piperidines **7a**−**d** and their cis counterparts **8a**−**d** in good to excellent yields.

In conclusion, a general method for the synthesis of *trans*-(3*S*)-amino-4-alkyl- and -4-aryl-piperidines has been developed. D-Serine was used to control the absolute stereochemistry, and the piperidine ring was constructed using ring-closing metathesis reaction. In addition, the trans relative stereochemistry between the 3-amino group and the 4-substituents was controlled via a selective hydrogenation method. This has become the first asymmetric synthesis of *trans*-4-alkyl- and -4-aryl-substituted (3*S*)-amino-piperidines. The application of these substituted piperidines to the synthesis of piperidinyl quinolones will be reported elsewhere.

Acknowledgment. We acknowledge Mrs. Anne Russell and Mrs. Karen Strader for two-dimensional and NOE NMR analyses for the assignment of relative stereochemistry of piperidine compounds. We also thank Professor Paul Helquist for a helpful discussion during the preparation of this manuscript.

Supporting Information Available: Full experimental procedures and spectroscopic data for **1**(**a**−**d**)−**7**(**a**−**d**) and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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