

Tandem Overman Rearrangement and Intramolecular Amidomercuration Reactions. Stereocontrolled Synthesis of *cis*- and *trans*-2,6-Dialkylpiperidines

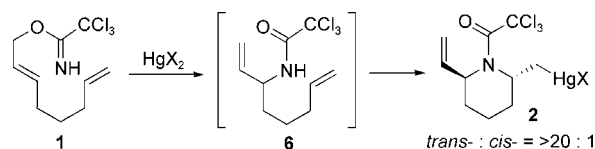
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ABSTRACT



Hg(II)-mediated tandem Overman rearrangement and intramolecular amidomercuration reactions were proven to provide a convenient tool for the stereoselective synthesis of *cis*- and *trans*-2,6-disubstituted piperidines. Thus, upon treatment with $\text{Hg}(\text{OTFA})_2$ in THF, the trichloroacetimidate **1** directly transformed into the 2,6-dialkyl piperidine **2** with almost exclusive *trans* selectivity. The amidomercuration reaction of the carbamate **7** by $\text{Hg}(\text{OTFA})_2$ in nitromethane showed an excellent *cis* selectivity. Also reported is the stereoselective synthesis of solenopsin A and isosolenopsin A.

Substituted piperidine ring compounds are abundant in nature, and their therapeutic potential has been a subject of intensive research.^{1,2} Particularly, 2,6-disubstituted piperidines have attracted much attention in both academia and the pharmaceutical industry because they are one of the most common piperidine skeletons and are found in many pharmaceutically interesting compounds. They appear in various ring forms (Figure 1) and exhibit a broad range of biological activities. For examples, solenopsin A and isosolenopsin A, which are active ingredients in the venom of fire ants, showed cytotoxic, haemolytic, necrotic, insecticidal, antibacterial, antifungal, and anti-HIV properties, as well as activities as neuronal nitric oxide synthase inhibitors.³ Clavepictines have cytotoxic activities against various cancer cell lines,⁴ and precoccinelline is one of defense alkaloids in ladybird beetles.⁵ As a consequence, numerous synthetic

methods have been developed for the stereoselective synthesis of 2,6-disubstituted piperidines.² However, most of them were directed toward the synthesis of either *trans*-2,6-dialkylpiperidines⁷ or *cis*-2,6-dialkylpiperidines.⁸ Methodologies for the stereoselective synthesis of both *cis*- and *trans*-

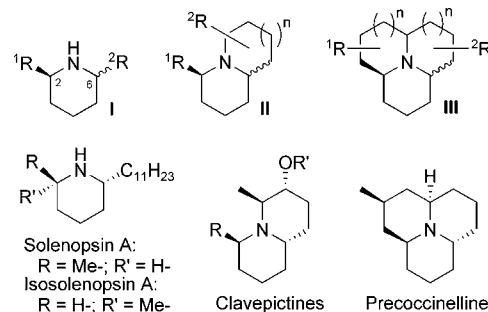


Figure 1. Three widely found structures containing a 2,6-disubstituted piperidine framework.

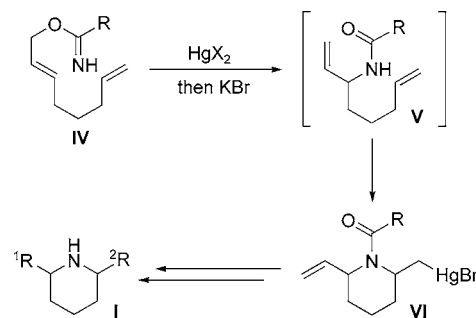
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2,6-dialkylpiperidines from a common intermediate have been sporadic in the literature.⁹ Therefore, there is still considerable interest in developing methodologies that not only allow the stereoselective synthesis of 2,6-dialkylpiperidines but also are efficient and amenable to synthetic manipulation.

During the course of our recent studies on developing new methodologies for the asymmetric synthesis of bioactive five- and six-membered nitrogen heterocycles, especially polyhydroxylated pyrrolidines and piperidines,¹⁰ it was noticed that Hg(II) could mediate the Overman rearrangement reaction¹¹ of allylic imidates to allylic amine derivatives, as well as the intramolecular amidomercuration reaction¹² of ϵ -alkenylcarbamate/amides to form piperidine rings. Also known is that the stereochemistry of the intramolecular amino-/amido-mercuration reactions is often dependent upon the structure of substrates and reaction conditions used.¹² As shown in Scheme 1, these findings strongly suggest that 2,6-disubstituted piperidine rings can be stereoselectively synthesized from an allylic imidate such as **IV** by the Hg(II)-mediated tandem Overman rearrangement and intramolecular amidomercuration reactions. Furthermore, considering that allylic alcohols required for the synthesis of the requisite allylic imidates are readily available, the Hg(II)-mediated

Scheme 1. Tandem Overman Rearrangement and Amidomercuration Strategy for Construction of 2,6-Disubstituted Piperidine Rings



tandem Overman rearrangement and intramolecular amidomercuration reactions can provide an efficient and general solution for the stereoselective synthesis of 2,6-disubstituted piperidine rings from the relatively simple allylic alcohols. Despite such possibility, as well as the efficiency and versatility of the reactions, the Hg(II)-mediated tandem Overman rearrangement and intramolecular amidomercuration reactions have never been realized so far. Herein, we report that the above strategy indeed enables the stereoselective synthesis of *cis*- and *trans*-2,6-disubstituted piperidines from commercially available 2,7-octadienol. Application of the developed methodology to the stereoselective synthesis of solenopsin A and isosolenopsin A is also described.

The tandem Overman rearrangement and intramolecular amidomercuration reactions were accessed with the allylic imidate **1** (see Supporting Information for the synthesis of **1**) by screening various Hg(II) salts at room temperature, and the results are summarized in Table 1. Only the reactive Hg(II) salts (entries 1–3) enabled the tandem reactions to generate the desired piperidine **2**. Interestingly, mercuric acetate (entry 4) gave the oxazoline product **3** as a sole identifiable product, which formed probably through the Hg(II)-mediated 5-exo cyclization of **1**.^{11c,d} The reactions did not take place with mercuric bromide and mercuric chloride (entries 5 and 6).

To establish relative stereochemistry of the 2,6-substituents of the piperidine **2**, conversion to the known 2,6-disubstituted

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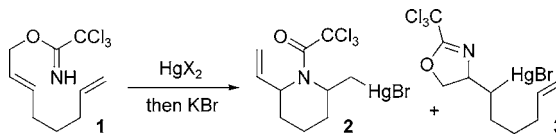
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Table 1. Effects of Hg(II) Reagents on the Overman Rearrangement and Amidomercuration Reactions of Trichloroacetimidate **1**^a

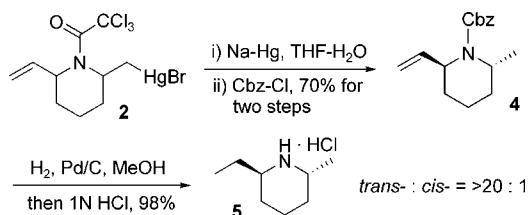


entry	HgX ₂	products (yield)
1	Hg(ClO ₄) ₂	2 (90)
2	Hg(OCOCF ₃) ₂	2 (90)
3	Hg(NO ₃) ₂	2 (90)
4	Hg(OAc) ₂	3 (75)
5	HgCl ₂	no reaction
6	HgBr ₂	no reaction

^a All reactions were carried out with **1** (1.0 mmol) and HgX₂ (1.2 mmol) in THF (10 mL) at room temperature. After **1** disappeared on TLC, the reaction mixture was quenched with aqueous KBr solution.

piperidines was accomplished (Scheme 2). The organomercurial **2** was reductively demercurated with sodium amalgam¹³ in aqueous THF, and deprotection of the *N*-trichloroacetyl group also took place under the reaction conditions.

Scheme 2. Conversion of Organomercurial **2** to Known 2-Methyl-6-ethylpiperidine



Thus, the demercurated product was isolated in the Cbz-protected form **4** by adding benzyl chloroformate to the reaction mixture. It is worthwhile to mention that reductive demercuration of **2** by the more popular NaBH₄ in DMF produced the desired demercurated product without deprotection of the trichloroacetyl group but in a low reaction yield (20–25%). This may be attributed to the fact that such reductive demercuration reactions are believed to proceed through radical intermediates,¹⁴ and the trichloroacetyl groups are susceptible to react under radical conditions.¹⁵ Hydrogenation of **4** under atmospheric pressure of H₂ over Pd–C followed by treatment with 1 N HCl furnished 2-ethyl-6-methylpiperidine hydrochloride (**5**), the stereochemistry of which was determined to be *trans* by comparing its ¹H and ¹³C NMR data with those reported in the literature.¹⁶

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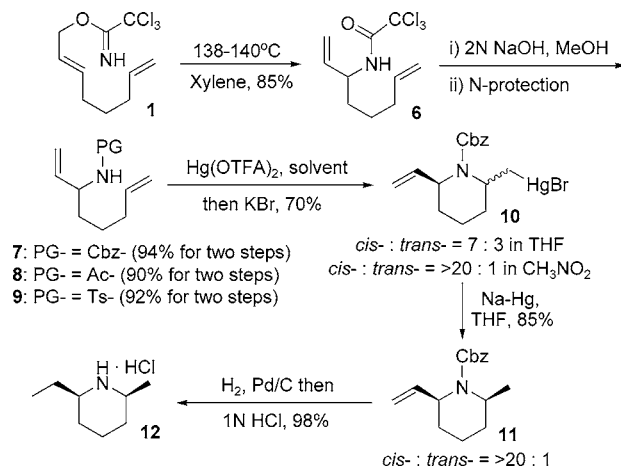
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To study effects of different *N*-protection groups on the stereochemistry of the intramolecular amidomercuration reactions, the compounds **7–9** were synthesized from **6**, which was prepared by the thermal Overman rearrangement reaction of **1** (Scheme 3). Basic hydrolysis of **6** followed by

Scheme 3. Stereoselective Synthesis of *cis*-2-Ethyl-6-methylpiperidine



protection of the resulting amine with benzyl chloroformate, acetic anhydride, and tosyl chloride produced the differently *N*-protected amidomercuration substrates **7**, **8**, and **9** respectively. As expected, the amidomercuration reaction of **6** with Hg(OTFA)₂ in THF at room temperature led to the formation of *trans*-**2** (>20:1). Interestingly, the amidomercuration reaction of **7** under similar conditions gave an inseparable mixture of the *cis* and *trans* mercuric bromides **10**, favoring the *cis* isomer in a ratio of 7:3. Varying temperature and reaction time had little effects on the stereochemical outcome of the amidomercuration reaction of **6** and **7**. No reaction was observed with **8** and **9** under the similar amidomercuration conditions (this remains to be explained).

Although the origin of the contrasting stereochemical outcomes in the amidomercuration reaction of **6** and **7** is not clear yet, they can be rationalized by considering the equilibrium between two chair conformers **VII** and **VIII** where the vinyl group at C3 and the *N*-protection group occupy equatorial positions (Figure 2). According to the Dreiding models of **VII** and **VIII**, the trichloroacetyl group (R = CCl₃) favors **VII** and thus formation of the *trans* isomer, whereas the Cbz-group prefers **VIII** and thus formation of the *cis* isomer. With the trichloroacetyl group (R = CCl₃), the severe steric repulsion between the CCl₃ group and the terminal CH₂ group (C8) in **VIII** can shift the equilibrium far toward **VII**. On the other hand, with the Cbz group (R = OBn), the quasi 1,3-diaxial interactions between the two axial C–H bonds (at C3 and C5) and the terminal CH₂ group in **VII** could become more unfavorable relative to steric hindrance between the OBn group and the terminal CH₂ group in **VIII**, making **VIII** the predominant conformer in the equilibrium.

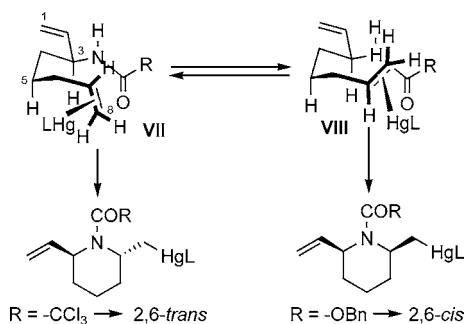
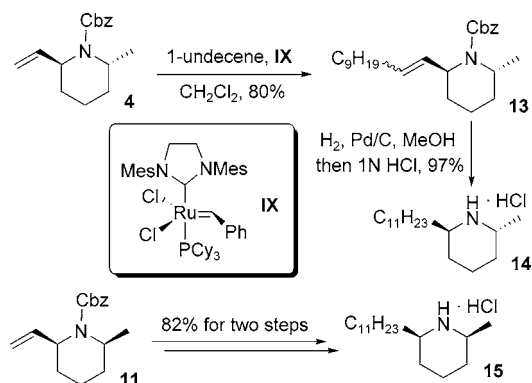


Figure 2. A plausible explanation for the contrasting stereochemical outcomes in the amidomercuration reaction of **6** and **7**.

Compound **7** was also subjected to the equilibrating amidomercuration conditions [$\text{Hg}(\text{OTFA})_2$ in CH_3NO_2 at room temperature], under which the thermodynamically more stable *cis* isomer of **10** was expected to form predominantly.^{12m} Gratifyingly, under these conditions, the amidomercuration reaction of **7** indeed proceeded with an excellent *cis* selectivity (>20:1). Such an exceptional *cis* selectivity of the reaction is a result of the equilibrium between the *cis* and *trans* isomers of **10** and thermodynamic control. The equilibrium is catalyzed by trifluoroacetic acid produced during the reaction. Neutralization of trifluoroacetic acid by K_2CO_3 reduced the stereoselectivity of the amidomercuration reaction significantly to *cis:trans* = 7:3. As with **5**, **10** was converted to *cis*-2-ethyl-6-methylpiperidine hydrochloride (**12**) by a reaction sequence of reductive demercuration and hydrogenation (Scheme 3).

With the efficient routes for the stereoselective formation of *cis*- and *trans*-2,6-disubstituted piperidines established, the stereoselective synthesis of solenopsin A (**14**) and isosolenopsin A (**15**) was pursued (Scheme 4). Cross metathesis reaction of the olefin **4** with 1-undecene using the 2nd generation Grubbs' catalyst **IX** in refluxing CH_2Cl_2 afforded **13** as a mixture of *E* and *Z* isomers. Hydrogenation

Scheme 4. Synthesis of Solenopsin A and Isosolenopsin A



of **13** gave solenopsin A, which was isolated and characterized as its HCl salt by treating the hydrogenation product with 1 N HCl.^{9d} Similarly, isosolenopsin A was prepared from **11**.^{9d}

In summary, it has been shown that the Hg(II)-mediated tandem Overman rearrangement and intramolecular amidomercuration reactions can provide an efficient and general route for the stereoselective synthesis of *trans*- and *cis*-2,6-dialkylpiperidines from the readily available starting allylic imidate **1**. The catalytic asymmetric version of the present strategy using neutral chiral Pd(II) catalysts^{11f} is currently under investigation.

Acknowledgment. Financial support from National Institute of Health (GM 08194) and The Welch Foundation (AX-1534) is gratefully acknowledged.

Supporting Information Available: Complete experimental procedures for all new compounds and copies of ^1H and ^{13}C NMR spectra of the compounds **1**, **3**–**7**, and **10**–**15**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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