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Asymmetric synthesis of (+)-*iso*-6-cassine via stereoselective intramolecular amidomercuration

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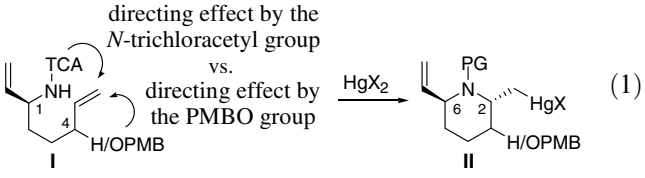
Abstract—The first asymmetric synthesis of (+)-*iso*-6-cassine is described. Lipase-catalyzed resolution, enantioselective Overman rearrangement, and diastereoselective intramolecular amidomercuration were used for the installation of the three stereocenters in (+)-*iso*-6-cassine, and cross-metathesis was employed for the attachment of the side-chain.

Substituted piperidine ring systems constitute the core structures of many chemically and biologically important compounds,[1] and thus have been a focus of many synthetic studies.[2] Particularly, electrophile-induced stereoselective heterocyclization reactions have provided a convenient tool for the construction of such ring systems from the corresponding linear precursors.[3] In this context, we recently reported that Hg(II)-mediated tandem Overman rearrangement and intramolecular amidomercuration reactions could be a very efficient method for the stereoselective formation of *cis*- and *trans*-2,6-dialkyl piperidine ring systems.[4] The highlight of the report is dominant trans stereoselection by *N*-trichloroacetyl (TCA) protection group in the Hg(II)-mediated intramolecular amidomercuration reactions of 5-alkenyl amides (H at the C4 in Eq. 1).



(1)

A literature survey revealed that allylic alkoxy/hydroxy groups could also exhibit stereodirecting effects in the Hg(II)-mediated intramolecular amidomercuration reactions.[5] These prompted us to investigate 'matching' and 'mismatching' effects (double stereodifferentiation) by allylic *p*-methoxybenzyloxy (PMBO) group and *N*-trichloroacetyl group in the Hg(II)-mediated intramolecular amidomercuration reactions of 4-alkoxy-5-alkenyl amides **I** (PMBO at the C4 in Eq. 1).[6] Furthermore, the amidomercuration products of **I** contain 2,6-disubstituted 3-piperidinol structures **II**, which have been found in many bioactive alkaloids such as julifloridine,[7] cassine,[8] Bao Gong Teng A,[9] juliprosine,[10] clavepictines,[11] and lepadines[12] (Fig. 1). Therefore, the development of the highly diastereoselective amidomercuration reactions of **I** would be of particular use for the stereoselective/asymmetric synthesis of such alkaloids.[13]

The requisite optically pure 4-PMBO-5-alkenyl amides **I** for double stereodifferentiation studies could be accessed from the optically pure allylic alcohols **3** and

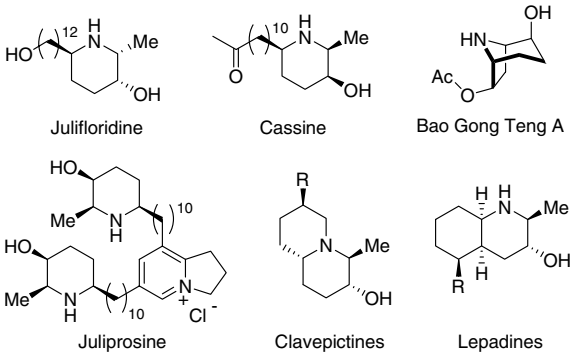


Figure 1. Various 2,6-disubstituted 3-piperidinol alkaloids.

Keywords: Intramolecular amidomercuration; 2,6-Dialkylpiperidines; 2,6-Disubstituted 3-piperidinols; Double stereodifferentiation; (+)-*iso*-6-Cassine.
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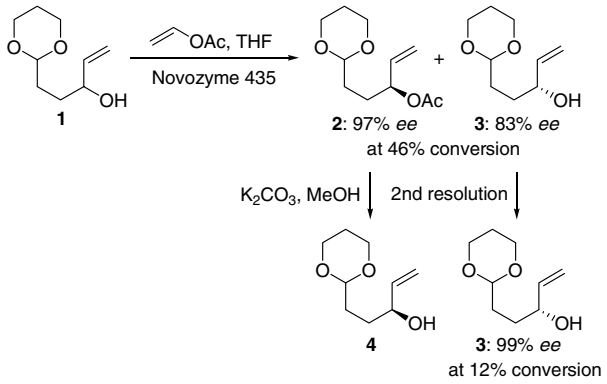
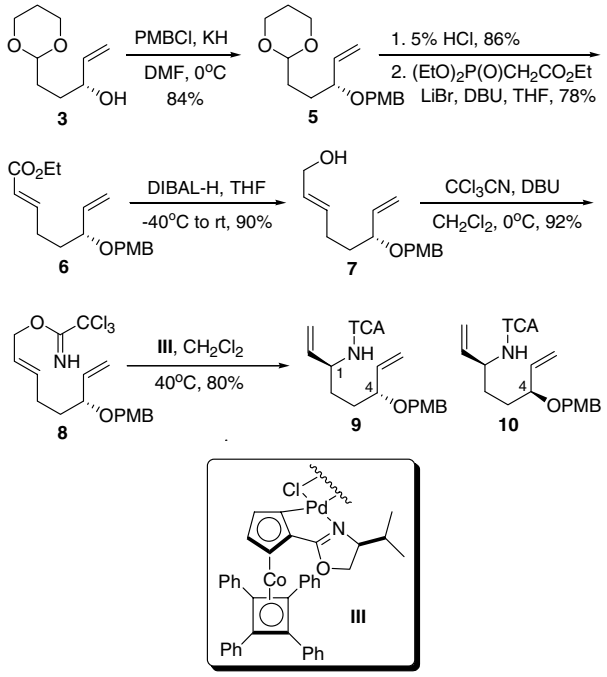


Scheme 1. Synthesis of optically pure allylic alcohols.

4. As shown in Scheme 1, **3** and **4** were obtained via the lipase-catalyzed kinetic resolution of the readily available racemic allylic alcohol **1**[14] with vinyl acetate as an acyl donor in THF.[15] At 46% conversion, the ee's of the acetate **2** and the remaining alcohol **3** were 97% and 83%, respectively. The optical purity of **3** was further improved to 99% (at 12% conversion) by subjecting **3** to the second round of the resolution. The transesterification reaction of **2** with MeOH in the presence of K_2CO_3 provided the optically pure allylic alcohol **4**.

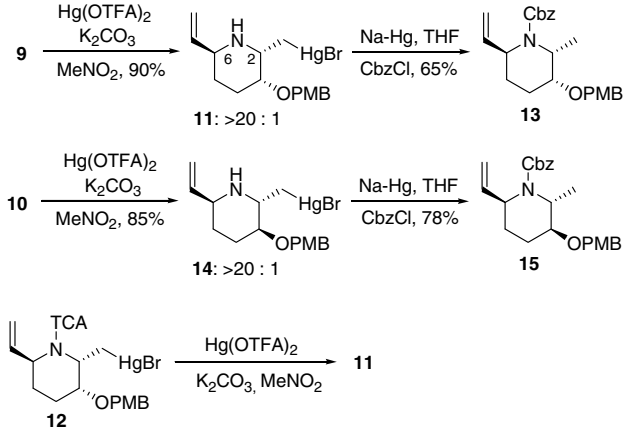
Scheme 2 depicts how the optically pure allylic alcohols **3** and **4** were converted to the optically pure **I** (= the compounds **9** and **10**). The hydroxy group of **3** was protected by PMBCl and KH in DMF to give the PMB ether **5**. Acidic hydrolysis of **5** followed by the modified Horner–Wadsworth–Emmons olefination of the resulting aldehyde generated the α,β-unsaturated ester **6**.[16] DIBAL reduction of **6** furnished the allylic alcohol **7**, which upon treatment with CCl_3CN and DBU in CH_2Cl_2 at 4 °C transformed into the trichloroacetimidate **8**.[17] Enantioselective Overman rearrangement reaction of the imidate **8** by a chiral cobalt oxazoline palladacycle **III** [(*S*)-(+)-COP-Cl] in CH_2Cl_2 gave rise to the *N*-trichloroacetyl derivative **9** of the optically pure **I**.[18] The *N*-trichloroacetyl derivative **10** of the optically pure **I**, where the stereochemistry of the PMBO group at C4 is opposite to that in **9**, was obtained by applying Scheme 2 to compound **4**.



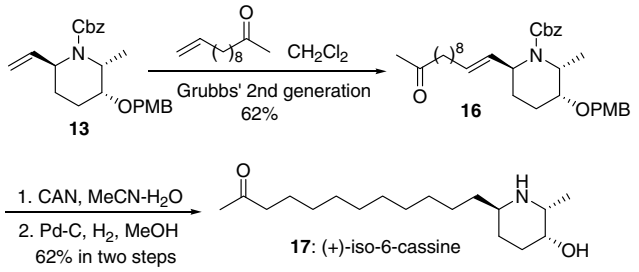
Scheme 2. Synthesis of substrates for the amidomercuration.

Double stereodifferentiation studies were conducted with **9** and **10**, and the results are given in Scheme 3. Compound **9** represented a matched case, since the 2,6-trans-directing effect of the *N*-trichloroacetyl group and the 2,3-cis-directing effect of the PMBO group were expected to reinforce each other to give the diastereomer **11** in a high diastereoselectivity.[4,5] Indeed, the amidomercuration reaction of **9** with $Hg(TFAO)_2$ in the presence of K_2CO_3 (to prevent the deprotection of the PMB group as well as the establishment of the equilibrating amidomercuration conditions by trifluoroacetic acid generated during the amidomercuration reaction) in nitromethane produced the 2,6-trans diastereomer **11** in >20:1 diastereoselectivity, and the trichloroacetyl group was deprotected under the conditions. When **9** was subjected to K_2CO_3 in nitromethane, the trichloroacetyl group was not deprotected even after a prolonged reaction time. Furthermore, the amidomercuration product of **9** (compound **12**) was independently prepared by treating **11** with trichloroacetyl chloride and Et_3N in CH_2Cl_2. Upon exposure to the amidomercuration conditions, **12** was converted to **11** in almost quantitative reaction yield. These results indicated that the amidomercuration reaction took place on **9**, not on the amine resulting from the trichloroacetyl deprotection of **9**, and the deprotection of the trichloroacetyl group occurred after the amidomercuration to give **11**.

Surprisingly, the amidomercuration reaction of the mismatched diastereomer **10** also proceeded with >20:1 diastereoselectivity in favor of the 2,6-trans diastereomer **14**, despite the expectation that the *N*-trichloroacetyl group and the allylic PMBO group should



Scheme 3. Double stereodifferentiation in the amidomercuration.



Scheme 4. Asymmetric synthesis of (+)-*iso*-6-cassine.

oppose each other. These results indicate that the stereochemical outcome of the amidomercuration reactions is completely governed by the *N*-trichloroacetyl group, and the allylic PMBO group has little effect. In both cases, diastereoselectivities of the amidomercuration reactions were determined by measuring the relative integration of the diastereomeric methyl groups at C-2 after the reductive demercuration of the mercurial compounds **11** and **14** followed by the Cbz protection of the resulting amines to **13** and **15**, respectively.

For the confirmation of the stereochemistry of **13** and a synthetic utility of the developed reactions, compound **13** was elaborated to (+)-*iso*-6-cassine (Scheme 4). Cross metathesis reaction of the olefin **13** with dodec-11-en-2-one using the 2nd generation Grubbs' catalyst[19] in refluxing CH_2Cl_2 afforded **16** as a mixture of *E* and *Z* isomers. Deprotection of the PMB group by CAN[20] followed by hydrogenation gave rise to (+)-*iso*-6-cassine (**17**), ^1H and ^{13}C NMR spectra of which matched those in the literature.[21]

In summary, it has been shown that stereoselection in the Hg(II)-mediated intramolecular amidomercuration reactions of 5-alkenyl amides with a pendant allylic PMBO group is completely governed by *N*-TCA group, and the stereochemistry of the allylic PMBO group has little effect on the cyclization stereochemistry. The developed intramolecular amidomercuration reactions were used for the first asymmetric synthesis of (+)-*iso*-6-cassine. The origin and generality of the dominant 2,6-trans directing effect by the *N*-trichloroacetyl group in the intramolecular amidomercuration reactions are currently under investigation, and the results will be reported in due course.

Acknowledgments

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