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ASYMMETRIC SYNTHESIS OF TETRAHYDROQUINOLINE DERIVATIVE, A BUILDING BLOCK OF MARTINELLINES, *VIA* INTRAMOLECULAR ALLYLIC AMINATION USING 9-PBN †

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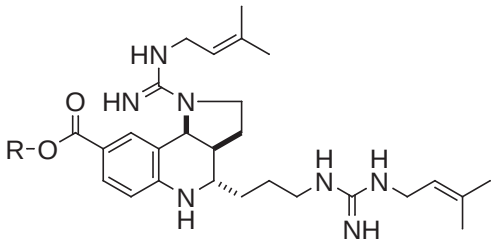
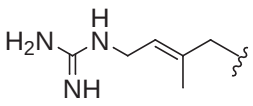
Abstract – A tetrahydroquinoline derivative, a core structure of martinellines, was prepared through intramolecular allylic amination of the racemic precursor with a stereogenic center using 9-PBN and palladium. The reaction proceeded in a reagent-controlled manner based on the chiral phosphine to give two diastereomeric products with moderate enantioselectivities.

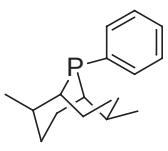
Heterocycles bearing a nitrogen atom, quinolines and piperidines, constitute the core structure of a number of biologically interesting alkaloids. Among them, pyrroloquinolines have a unique structure of fused tetrahydroquinoline and pyrrolidine rings, and certain derivatives have attracted attention for their interesting pharmacological activities.[1] Recently, martinelline (**1**) and martinellic acid (**2**) bearing the pyrroloquinoline nucleus and two prenylguanidines were isolated as the first example of pyrroloquinolines of natural origin from the roots of the tropical plant, *Martinella iquitosensis*.[2] These alkaloids also are the first naturally occurring nonpeptide bradykinin receptor antagonists. Their intriguing structures as well as biological activities have prompted several groups to investigate the synthesis of the pyrroloquinoline nucleus.[3] Recently, our efforts have demonstrated that the new monodentate chiral phosphines, (1*R*, 2*S*, 5*R*, 6*S*)-2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane and its enantiomer, ((*R*)-(-)- and (*S*)-(+)-9-PBNs), are valuable ligands for transition-metal catalyzed asymmetric synthesis, and these phosphines in combination with palladium are efficient catalysts for formation of carbon-carbon, carbon-nitrogen, and carbon-oxygen bonds through asymmetric allylic substitution reaction.[4]



Martinelline (**1**) R = H

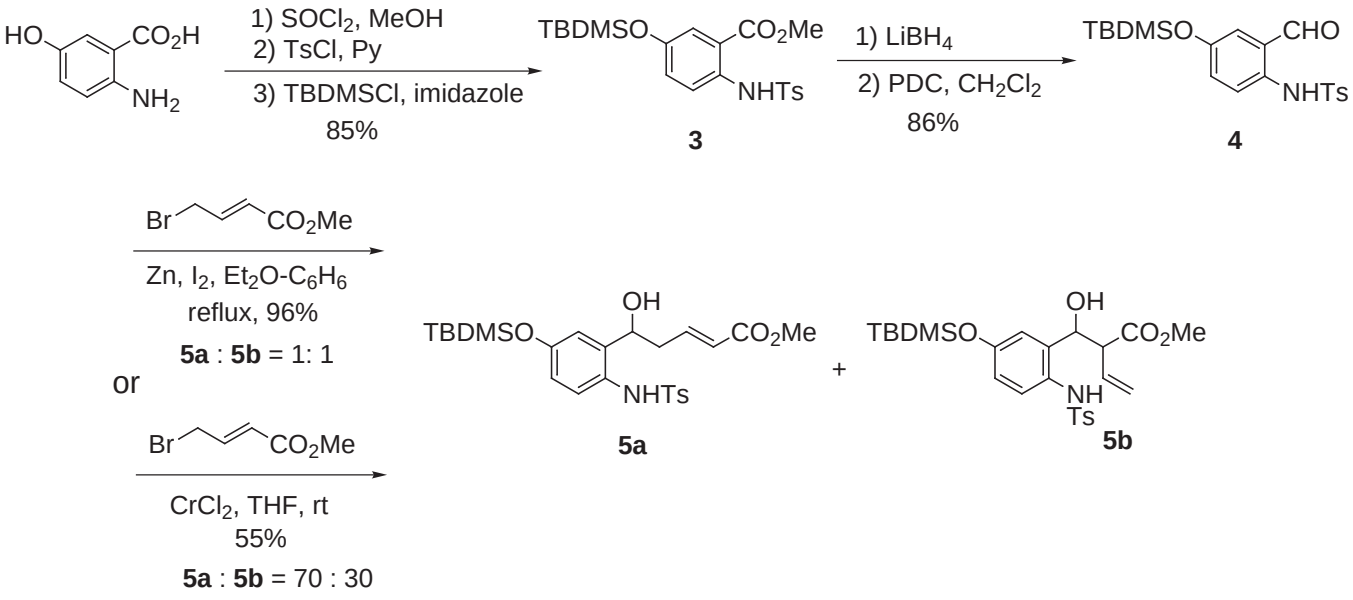
Martinellic acid (**2**) R =





(-)-9-PBN

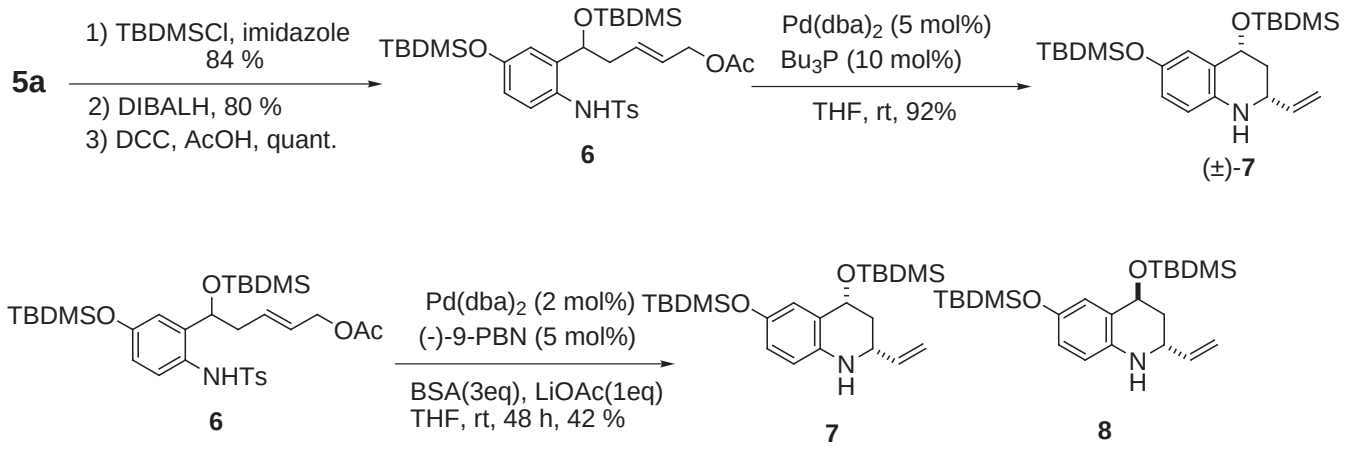
† Dedicated to Professor James P. Kutney on the occasion of his 70th birthday.



Scheme 1

As an expansion of our investigation along this line, we focused on an intramolecular version of the asymmetric allylic substitution reaction for construction of heterocylces.[5] We describe here the synthetic studies towards total synthesis of martinelline (**1**) and martinellic acid (**2**) using our developed phosphine, 9-PBN.

The synthesis of the substrate for the asymmetric allylic substitution reaction was carried out in a straightforward manner from a commercially available 5-hydroxyanthranilic acid (Scheme 1). First, 5-hydroxyanthranilic acid was converted into fully protected derivative (**3**) in three steps with 85 % yield: (1) esterification using thionyl chloride in methanol, (2) N-tosylation, and (3) silyl protection of the phenolic function. For the chain elongation, ester (**3**) was reduced with lithium borohydride and the resulting alcohol was oxidized with pyridinium dichromate (PDC) to produce aldehyde (**4**) in 86 % yield. Vinylogous Reformatsky reaction of aldehyde (**4**) using methyl 4-bromocrotonate in the presence of zinc and iodine in ether-benzene smoothly proceeded under refluxing conditions, but gave, unsurprisingly, a mixture of regioisomers (**5a**) and (**5b**) with the ratio of 1:1 in 96 % yield.[6] In the case of employing chromous chloride instead of zinc,[7] the ratio was moderately improved to 70:30, but a significant decrease in yield was observed. Fortunately, the desired regioisomer (**5a**) was separable by column chromatography. After purification and protection of the hydroxy group with *t*-butylchlorodimethylsilane, the conversion of the allylic alcohol into the substrate for the key allylic substitution reaction was performed in two steps. Reduction of **5a** with diisobutylaluminum hydride (DIBALH) afforded the allylic alcohol in 80 % yield. Acetylation of the alcohol under the standard conditions, acetic anhydride and pyridine, was surprisingly difficult for the concomitant acetylated product at the sulfonamide function. Finally, reaction of **5a** with acetic acid and dicyclohexylcarbodiimide (DCC) in the presence of dimethylaminopyridine (DMAP) in methylene

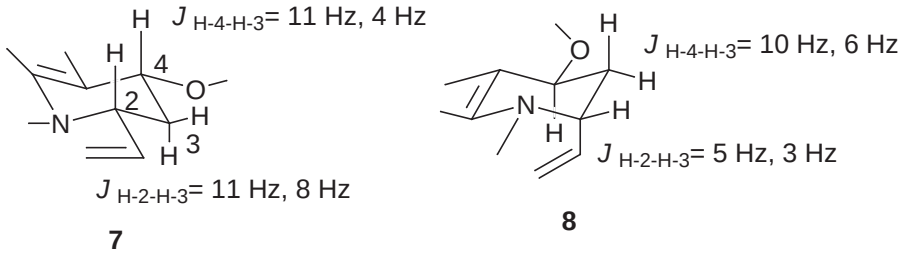


Scheme 2

chloride at –20°C was found to furnish allyl ester (**6**) in quantitative yield.

Preliminary cyclization of **6** using allylic substitution reaction was examined by use of 10 mol% of tributylphosphine and 5 mol% of bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) in tetrahydrofuran (THF) at room temperature. The reaction stereoselectively took place in a substrate-controlled manner to afford exclusively the *cis*-substituted tetrahydroquinoline (**7**) as the sole product in 92 % yield. With this satisfactory result in hand, the key cyclization of **6** using (-)-9-PBN in place of tributylphosphine was carried out in the presence of lithium acetate and bistrimethylsilylacetamide (BSA). The reaction was somewhat sluggish but provided two cyclic products (**7**) and (**8**) with 60 %ee each in the ratio of 68:32.[8] Both stereostructures were confirmed by their ^{1}H NMR spectra. The values of the coupling constants of **7** and **8** at the C-4 hydrogen are 11 Hz and 4 Hz, and 10 Hz and 6 Hz, respectively. These values show that both C-4 hydrogens are placed on the pseudo-axial position. While the values of the coupling constants of **7** at the C-2 hydrogen are 11 Hz and 8 Hz, the values of **8** at the C-2 hydrogen are 5 Hz and 3 Hz. These results show that C-2 hydrogen of **7** and **8** is placed on the axial and equatorial positions, respectively.

In summary, we have described that the intramolecular asymmetric allylic amination of the racemic substrate (**6**) with a stereogenic center using our developed phosphine, 9-PBN, and $Pd(dba)_2$ proceeds in a reagent-controlled manner based on the chiral phosphine to produce two tetrahydroquinolines in moderate enantioselectivities. During this work, we have observed that cyclization of the same substrate (**6**) using achiral phosphine takes place in substrate-controlled manner to afford the *cis*-



Figure

substituted tetrahydroquinoline as the sole product. Further investigations towards total synthesis of martinellines are in progress in our labaratories.

ACKNOWLEDGEMENT

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8 Optical purity was determined by HPLC analysis using Daicel Chiralpak AD.