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ENANTIOSELECTIVE SYNTHESIS OF (*S*)-2,3,9,10,11-PENTA-METHOXYHOMOPROTOBERBERINE AND (*S*)-*O*-METHYL-KREYSIGINE USING AN ASYMMETRIC ADDITION TO AN ISOQUINOLINE RING

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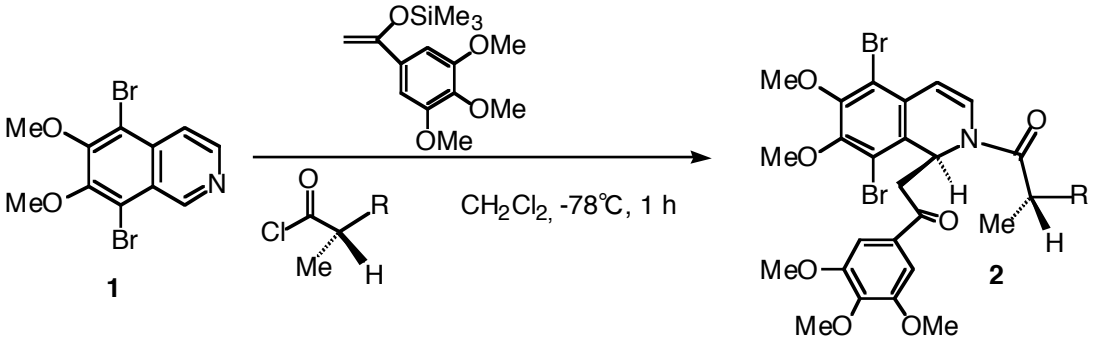
Abstract – Total synthesis of (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine (**7**) was carried out using an asymmetric nucleophilic addition of a silyl enol ether to 5,8-dibromo-6,7-dimethoxyisoquinoline (**1**) in the presence of an acid chloride derived from alanine. The addition proceeded in high diastereoselectivity to give a 1-substituted 1,2-dihydroisoquinoline (**2**), which was converted to the target alkaloid in short steps. One of the intermediates was readily transformed to a product (**8**) which was known as a precursor for synthesis of *O*-methylkreysigine (**9**).

Recently we have found that nucleophilic additions of silyl enol ethers[1] and allyltin[2] reagents to *N*-acylated azaaromatics generated *in situ* were effective methods for introduction of a substituent to azaaromatics. It was also demonstrated that asymmetric additions to isoquinolines[3] and β–carboline[4] at C1 position proceeded in good yields with high diastereoselectivities using *N*-protected amino acid chlorides as an acylating reagent. It was therefore presumed that optically active 1-substituted tetrahydroisoquinoline derivatives would be synthesized straightforwardly by this method. Since 1-substituted tetrahydroisoquinoline alkaloids have important physiological and pharmacological activities,[5] there have been many synthetic methods[6] for them. Only one example, however, was reported in which isoquinoline ring was used as a starting material.[7] In the paper, Comins *et al.* reported the synthesis of (+)-carnegine *via* simple procedures, but the stereoselectivity of the product was low (62% ee).

We would like to report here a new and direct route to the titled compounds using an isoquinoline derivative as a starting material. The latest synthesis of (*S*)-2,3,9,10,11-pentamethoxy-homoprotoberberine was reported by Czarnocki *et al.*[8] In their procedure, (*R*)-2-ethoxycarbonyl-1-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, which was obtained through several steps from D-(-)-tartaric acid, was converted to the alkaloid in 4 steps. However, it was reported that the starting material was proved to racemize easily, thus the product obtained from this process showed only moderate stereoselectivity.

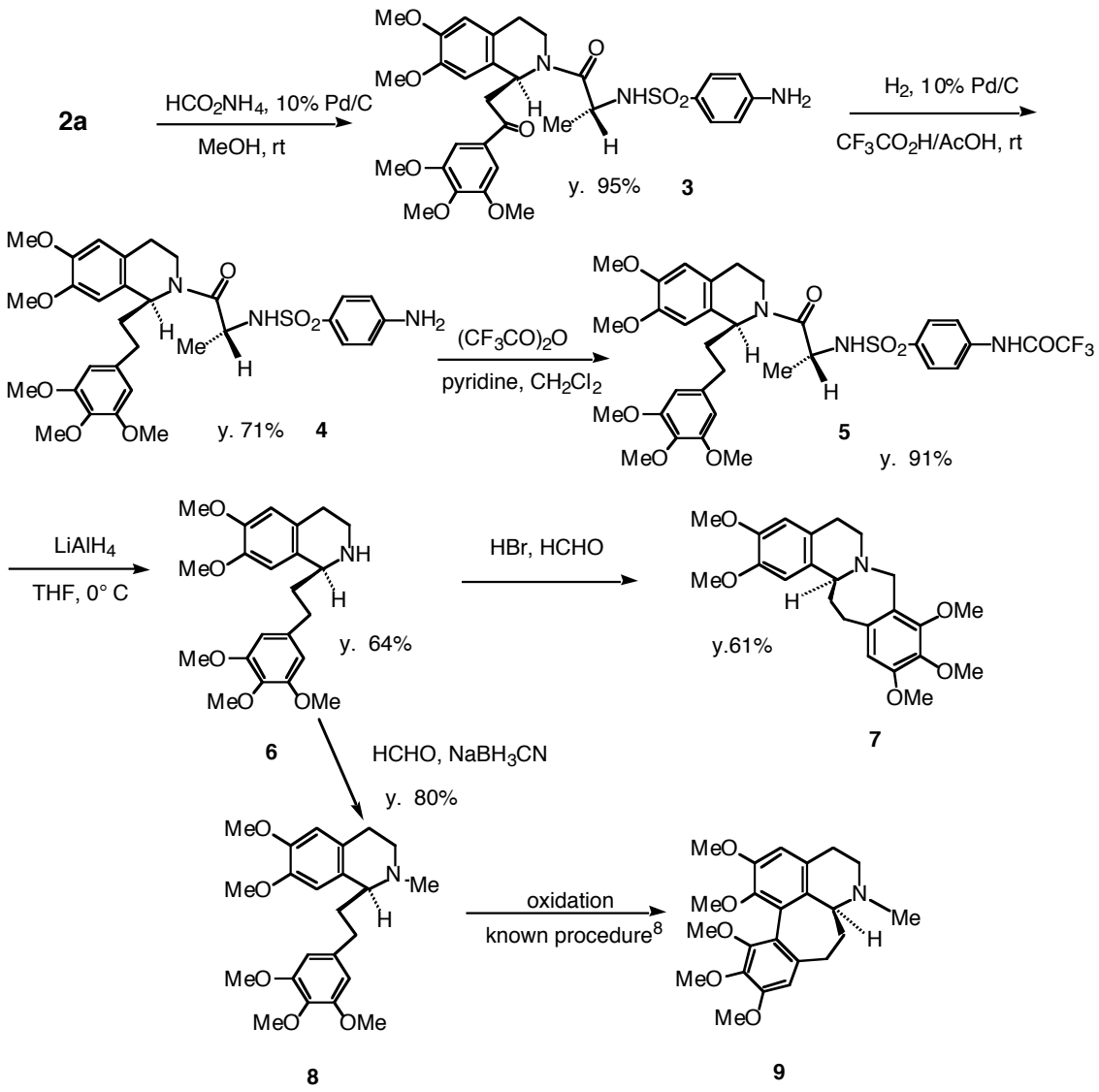
The synthesis of the titled compound was commenced using 5,8-dibromo-6,7-dimethoxyisoquinoline as a starting material, because it has been found that the compound affords corresponding 1-substituted dihydroisoquinolines in high yields with high diastereoselectivity in the reaction with silyl enol ethers in the presence of *N*-protected L-alanyl chloride.[3] This asymmetric addition reaction with 1-(3,4,5-trimethoxyphenyl)-1-trimethylsilyloxyethylene in the presence of *N*-protected D-alanyl chloride was applied to construct a required carbon skeleton and absolute configuration at C-1. Our previous study showed that *p*-nitrophenylsulfonyl and phthaloyl groups acted as good *N*-protecting groups, thus they were also adopted in this procedure. As a result, 1-substituted 1,2-dihydroisoquinolines (**2a**) and (**2b**) were obtained in high diastereoselectivities (Scheme 1). Each of the adducts (**2a**) and (**2b**) was purified to be a single diastereomer by recrystallization.



2a	R= *p*-nitrophenylsulfonylamino	y. 98%, 92% de
2b	R= phthalimido	y. 85%, 82% de

Scheme 1

Reduction of **2a** with HCO_2NH_4 in the presence of 10% Pd/C[9] gave a debrominated 1,2,3,4-tetrahydroisoquinoline (**3**) in 95% yield. The reduction of **2b**, however, did not give a desired 1,2,3,4-tetrahydro product,[10] and thus subsequent conversions were carried out by using tetrahydroisoquinoline (**3**) (Scheme 2). The keto group in **3** was transformed to methylene by a catalytic hydrogenation of **3** under acidic conditions. At the next step, all of our attempts failed to remove the chiral auxiliary from the compound (**4**) under mild conditions, for example by treatment with KOH and/or NaOH in $MeOH/H_2O$ at 70°C, with LiOH- H_2O_2 in THF, and with $LiAlH_4$ in THF. Only under harsh conditions with KOH in $HOCH_2CH_2OH$ at 170°C was obtained the desired compound (**6**), but the yield was low (37%) and partial racemization was observed. Therefore, 1,2,3,4-tetrahydroisoquinoline (**4**) was subjected to trifluoroacetylation at aromatic amino group in order to increase electron deficiency of **4**. Then trifluoroacetylated compound (**5**) was allowed to react with $LiAlH_4$ at 0°C to give **6** ($[\alpha]_D^{25}$ = -14.1° (c 0.34, $CHCl_3$)) in 64% yield. Finally, **6** was treated with 48% HBr solution in H_2O and formaldehyde at 100° C under reported conditions,[8b] to give (*S*)-2,3,9,10,11-pentamethoxy-homoprotoberberine (**7**) in 61% yield. It was converted to a hydrochloride salt to compare the optical rotation with that of reported one.[11] Its specific rotation showed $[\alpha]_D^{25}$ = -111.3° (c 0.13, MeOH) (literature value $[\alpha]_D^{25}$ = -112.5° (MeOH)). In addition, *N*-methylation of **6** using formaldehyde in $NaBH_3CN$ gave a precursor (**8**) of (*S*)-*O*-methylkreysigine (**9**) in 80% yield ($[\alpha]_D^{25}$ = +6.1° (c 0.92,



Scheme 2

MeOH)) (literature[12] value $[\alpha]_D^{25}$ = +4.8° (MeOH)).

In conclusion, optically active (*S*)-2,3,9,10,11- pentamethoxyhomoprotoberberine was synthesized concisely with 99% ee using an asymmetric nucleophilic addition of a silyl enol ether to 5,8-dibromo-4,7-dimethoxyisoquinoline as a key step, and subsequent treatment resulted in short steps preparation of the target molecule. The overall yield from 5,8-dibromo-4,7-dimethoxyisoquinoline was 23%. In addition, a precursor of (*S*)-*O*-methylkreysigine (**9**) was also synthesized from an intermediary compound. Application of the asymmetric addition to synthesis of other alkaloids is now under investigation.

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