Synthetic Study of Serotobenine

Yasuaki Koizumi
Department of Medical Sciences, Graduate School of Pharmaceutical Sciences

Serotobenine was isolated from the seeds of safflower by Sato and co-workers in 1985 and the structurally-related compound decursivine was isolated by Fong *et al*. in 2002. Both of these compounds are characterized by the fused polycyclic ring systems including indole, dihydrobenzofuran and 8-membered lactam rings. Although biosynthesis of both compounds would be similar, serotobenine existed as a racemic form and decursivine existed as an optically active form. The difference of stereochemistry also prompted us to investigate the synthetic study of these compounds. Herein, we report the total synthesis of optically active serotobenine.

Recently we found that an intramolecular C-H insertion reaction by the combination of Davies' Rh catalyst and the chiral auxiliary provided an optically active *trans*-2,3-dihydro-3-benzofuran derivatives efficiently. We envisioned that this method would be applicable for the synthesis of the optically active dihydrobenzofuran ring of serotobenine.

5-Allyloxyindole derivative, readily synthesized by Leimgruber-Batcho's protocol was converted to 4-allylindole derivative by regioselective Claisen rearrangement. Conversion to the diazoester from 4-allylindole derivative was achieved by diazotransfer reaction. Upon treatment of diazoester with achiral rhodium catalyst $Rh_2(OAc)_4$, the C-H insertion reaction was proceeded smoothly to afford dihydrobenzofuran in high diastereoselectivity. After the transformation to the activated ester, construction of 8-membered lactam ring was accomplished by after reduction of azide group. Finally, deprotection of Ts and Bn group was carried out in stepwise manner and total synthesis of (-)-serotobenine has been accomplished. We are currently investigating the stereochemical behavior of serotobenine, according to our racemization hypothesis.