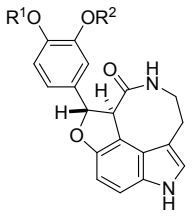
Total synthesis of serotobenine

Yasuaki Koizumi

Department of Medicinal Sciences, Graduate School of Pharmaceutical Sciences



(±)-Serotobenine (**1**) : R^1 = H, R^2 = Me
(+)-Decursivine (**2**) : R^1, R^2 = -CH_2-

Serotobenine (**1**) was isolated from the seed of safflower by Sato and co-workers in 1985. Safflower is one of the most famous health food, therefore serotobenine (**1**) and its related compounds attracted attention from pharmaceutical companies as key bioactive components in safflower. The structurally-related compound decursivine (**2**) 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, **1** existed as a racemic form and **2** 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 (**1**).

5-Allyoxyindole derivative (**3**), readily synthesized by Leimgruber-Batcho's protocol was converted to 4-allylindole derivative by regioselective Claisen rearrangement. Conversion to the diazoester (**4**) from 4-allylindole derivative was achieved by diazotransfer reaction. Upon treatment of **4** with $Rh_2(OAc)_4$, the C-H insertion reaction was proceeded smoothly to afford dihydrobenzofuran in high diastereoselectivity. After the transformation to the activated ester (**5**), 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 (-)-serotobenien (**1**) has been accomplished. We are currently investigating the stereochemical behavior of **1**, according to our racemization hypothesis.