Serotobenine (1), which is a pentacyclic indole alkaloid, was initially isolated from safflower seeds (Carthamus tinctorius L.) by Sato and co-workers in 1985.1 The unique heterocyclic structure of 1, which includes an indole, dihydrobenzofuran, and eight-membered lactam and should be a significant structure in medicinal chemistry, has prompted us to investigate its total synthesis. Furthermore, natural 1 has been isolated as the racemic form, although structurally related decursivine (2) has been isolated in the optically active form from Rhaphidophora decursiva. Because the biosynthesis of both 1 and 2 appear to be similar, a special mechanism for racemization of 1 might exist during biosynthesis. Hence, to clarify the possibility of racemization of 1, we started to synthesize serotobenine (1) in an optically active form. Recently, we developed a novel methodology to construct optically active dihydrobenzofuran rings by rhodium carbenoid mediated intramolecular C–H insertion reaction.3 We envisioned that applying this strategy for 3 would provide an optically active dihydrobenzofuran ring of 1 as shown in Figure 1. Herein we report a total synthesis of (−)-serotobenine (1) as well as corroborative evidence for the racemization of 1.

As shown in Scheme 1, the indole skeleton of 1 was synthesized by the Leimgruber–Batcho procedure.4 O-Allylation of 3-methyl-4-nitrophenol (4), an enamine formation in the presence of pyrrolidine, and subsequent reduction of the nitro group provided 5-allyloxy-1H-indole (5). After protecting 5 with a Ts group, a regioselective Claisen rearrangement5 proceeded under thermal conditions to give 6. In this reaction, rearrangement at the C6-position was not observed even at the sterically more hindered site. Incorporating benzyl halide derivative 7 to resultant phenol 6 was carried out under basic conditions to give 8. Oxidative cleavage of the olefin was performed in a stepwise manner, including dihydroxylation, treatment with Pb(OAc)₄, and oxidation of the resulting aldehyde by NaClO₂5 to furnish carboxylic acid 9.

Recently, we clarified that the C–H insertion reaction of diazostereoisomers possessing piperidinyl mandelate as a chiral auxiliary proceeded efficiently to give a bicyclo[3.3.0]octane skeleton.7 Thus, chiral alcohol 10 was incorporated into carboxylic acid 9, and the subsequent diazotransfer reaction was conducted by treating with p-acetamidobenzensulfonyl azide (p-ABSA) and DBU to provide C–H insertion precursor 11. Upon treating 11 with 0.3 mol% of Davies catalyst,8 the C–H insertion reaction proceeded smoothly to afford exclusively trans-dihydrobenzofuran 12 in 92% yield in a completely stereoselective manner.9 In this C–H insertion reaction, combining the mandelate chiral auxiliary10 and Rh₂(S-DOSP)₄ provided an excellent result; asymmetric induction strongly depended on the chiral auxiliary rather than the catalyst.

With desired optically active dihydrobenzofuran 12 in hand, we then focused on constructing the eight-membered macro lactam ring. Due to instability of 12 under both acidic and basic conditions, a cross coupling reaction should be suitable for the alkylation at the 3-position of indole. Thus, incorporating a bromine atom into the 3-position of 12 was achieved by treating with NBS. After numerous efforts using Pd mediated reactions, a Stille type reaction1 of 13 was found to be suitable. Upon treating 13 with allyltributyltin and 30 mol% of Pd(dppf)Cl₂·CH₂Cl₂, the cross coupling reaction proceeded smoothly to provide desired 14. The allyl group was converted to ethyl azide 15 via a five-step sequence involving dihydroxylation, oxidative cleavage with Pb(OAc)₄, reduction of the aldehyde, mesylation of the alcohol, and displacement of the mesylate with NaI. Removing the chiral auxiliary of 15 by hydrolysis and subsequent condensation of the resultant carboxylic acid with pentfluorophenol gave ester 16.

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Figure 1. Structures of (−)-Serotobenine (1) and (−)-Decursivine (2).

Scheme 1. Preparation of trans-Dihydrobenzofuran 12a

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Upon treating azide 16 with PPh₃ in the presence of H₂O, reduction to the amine and simultaneous macrolactam formation proceeded to provide eight-membered lactam 17 in excellent yield. Removing the Ts group¹² and cleaving the benzyl ether under hydrogenolysis condition yielded (−)-serotobenine (1), the spectral data of which (¹H, ¹³C NMR, IR, and HRMS) fully agreed with those of the natural product.¹³ Because natural serotobenine (1) was reported as a racemic form, we examined the stability of optically active 1 under several conditions. Neither racemization nor epimerization occurred upon treating 1 under acidic and/or basic conditions.¹⁴ On the other hand, treating N-Ts derivative 21 with Cs₂CO₃ decreased the enantiomeric excess to 15%.²⁰

Scheme 3. Our Hypothesis for Racemization of 20

4 Reagents and conditions: (a) NBS, CH₂Cl₂, 96%; (b) allyltributyltin, Pd(dppf)Cl₂·CH₂Cl₂, K₂CO₃, benzene, 90 °C, 95%; (c) Cs₂CO₃, NMO, acetone/H₂O; (d) NaBH₄, MeOH, 0 °C, 62% (3 steps); (f) MsCl, Et₃N, CH₂Cl₂, 82% (2 steps); (j) PPh₃, MeCN/H₂O, 50 °C, 95%; (k) Cs₂CO₃, THF/MeOH, 64 °C, 96%; for 17, 82%; for 17, 79%; for 20: (l) 10% Pd/C, H₂, THF/MeOH, 97%; (m) Ac₂O, pyridine, 0 °C, 97%.

References
(5) The selectivity was depended on a stability of the intermediate. The similar reaction was reported; see: Moody, C. J. J. Chem. Soc., Perkin Trans. 1 1984, 1333.
(9) The detailed selectivity by employment with other catalysts was described in supporting information.
(10) In the total synthesis of ephedradine-A, a similar dihydrobenzofuran ring was constructed via a lactamide auxiliary; see ref 3b. As expected, changing the corresponding methyl group to a bulky phenyl derivative increased the selectivity.
(13) Detailed data are described in the Supporting Information.
(15) During the course of isolating decursivine (4), Professor Fong detected serotobenine (1) from the same natural source; see ref 2a. Although they did not verify the optical purity of 1, biosynthesis of 2 would be derived from 1.