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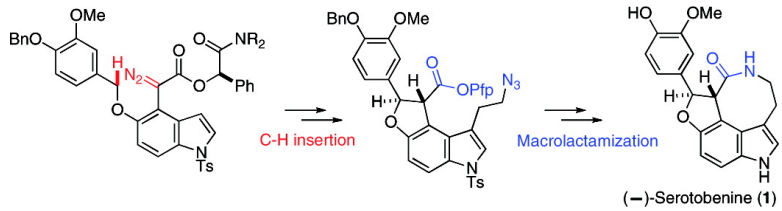


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# Total Synthesis of (−)-Serotobenine

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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**)[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

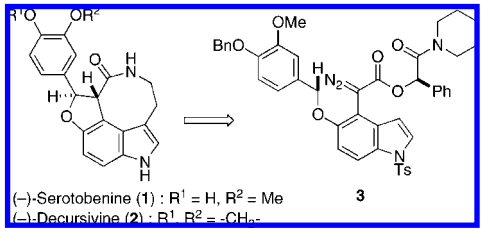


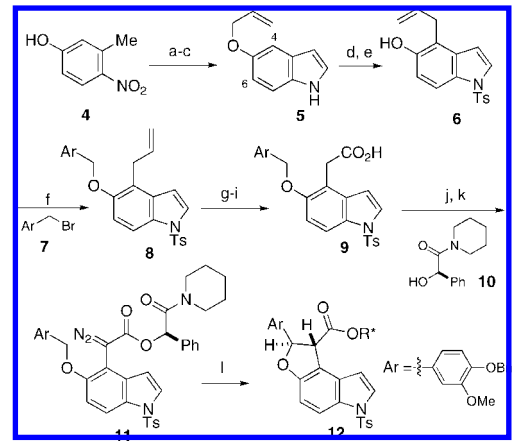

***Figure 1.*** Structures of (−)-Serotobenine (**1**) and (−)-Decursivine (**2**).

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-1*H*-indole (**5**). After protecting **5** with a Ts group, a regioselective Claisen rearrangement[5] proceeded under thermal conditions to give **6**. In this reaction, rearrangement at the C6-position was not observed even at the sterically less 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 $NaClO_2$[6] to furnish carboxylic acid **9**.

Recently, we clarified that the C−H insertion reaction of diazoesters possessing piperidinyl mandelate as a chiral auxiliary proceeded

***Scheme 1.*** Preparation of *trans*-Dihydrobenzofuran **12**[a]




[a] Reagents and conditions: (a) allyl bromide, $K_2CO_3$, DMF; (b) $Me_2NCH(OMe)_2$, pyrrolidine, DMF, 100 °C; (c) Zn, AcOH, $CH_2Cl_2$, 0 °C; (d) TsCl, NaOH, $CH_2Cl_2$, 75% (4 steps); (e) $Et_2NPh$, 160 °C; (f) **7**, $K_2CO_3$, acetone, reflux, 74% (2 steps); (g) $OsO_4$, NMO, acetone/$H_2O$; (h) $Pb(OAc)_4$, $K_2CO_3$, benzene, 80% (2 steps); (i) $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, THF/*t*-BuOH/$H_2O$, 92%; (j) **10**, EDCI, DMAP, $CH_2Cl_2$, 95%; (k) *p*-ABSA, DBU, MeCN, 80%; (l) $Rh_2$(*S*-DOSP)$_4$ (0.3 mol%), $CH_2Cl_2$ (92%, 93% de).

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*-acetamidobenzenesulfonyl 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 auxiliary[10] and $Rh_2$(*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 macrolactam 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 reaction[11] of **13** was found to be suitable. Upon treating **13** with allyltributyltin and 30 mol% of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, 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 $NaN_3$. Removing the chiral auxiliary of **15** by hydrolysis and subsequent condensation of the resultant carboxylic acid with pentafluorophenol gave ester **16**.

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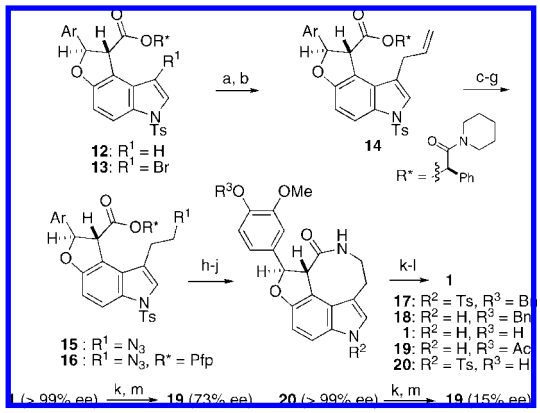
***Scheme 2.*** Completion of Synthesis of (−)-Serotobenine (**1**) [a]

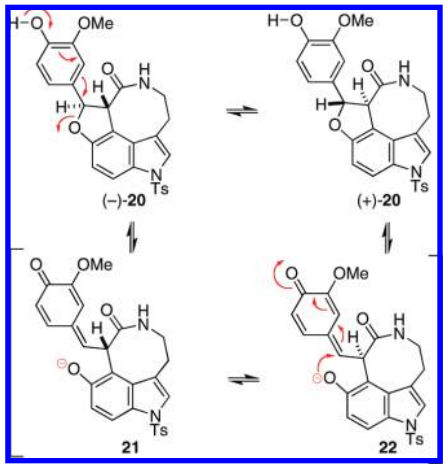



[a] Reagents and conditions: (a) NBS, $CH_2Cl_2$, 96%; (b) allyltributyltin, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, toluene, 90 °C, 95%; (c) $OsO_4$, NMO, acetone/$H_2O$; (d) $Pb(OAc)_4$, $K_2CO_3$, benzene; (e) $NaBH_4$, MeOH, 0 °C, 62% (3 steps); (f) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C; (g) $NaN_3$, DMF, 50 °C, 70% (2 steps); (h) $LiOH \cdot H_2O$, THF/MeOH/$H_2O$; (i) Pfp-OH, EDCI, DMAP, $CH_2Cl_2$, 82% (2 steps); (j) $PPh_3$, MeCN/$H_2O$, 50 °C, 95%; (k) $Cs_2CO_3$, THF/MeOH, 64 °C, 96%: for **17**, 82%: for **1**, 79%: for **20**; (l) 10% Pd/C, $H_2$, THF/MeOH, 97%; (m) $Ac_2O$, pyridine, 0 °C, 97%.

Upon treating azide **16** with $PPh_3$ in the presence of $H_2O$, reduction to the amine and simultaneous macrolactam formation proceeded to provide eight-membered lactam **17** in excellent yield. Removing the Ts group[12] and cleaving the benzyl ether under hydrogenolysis condition yielded (−)-serotobenine (**1**), the spectral data of which ($^1H$, $^{13}C$ NMR, IR, and HRMS) fully agreed with those of the natural product,[1,2] except for the optical rotation. Enantiomeric excess was confirmed by comparing the behavior on a chiral HPLC of its acetate **19** derived from **1**.[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.[13] On the other hand, treating *N*-Ts derivative **20** with $Cs_2CO_3$ decreased the enantiomeric excess to 15% ee[13] because incorporating the Ts group promoted the leaving ability of 5-hydroxy indole. Thus, the ring opening reaction of the dihydrobenzofuran ring proceeded to afford *p*-quinonemethide intermediate **21** as shown in Scheme 3. Furthermore, the acidic α-proton of the amide of **21** should enable **21** and **22** to equilibrate. On the other hand, the methylenedioxy bridge likely prevents conversion from **2** to the *p*-quinonemethide intermediate,[14] which may be the reason **2** is optically active, whereas natural **1** exists as a racemic mixture.[15] Further investigation into the discrepancy of the optical activity of **1** and **2** is currently underway in our laboratory.

***Scheme 3.*** Our Hypothesis for Racemization of **20**




In conclusion, an efficient total synthesis of (−)-serotobenine (**1**) was accomplished by a Rh-catalyzed C−H insertion reaction developed by our group. The C−H insertion precursor, 4,5-disubstituted indole, was efficiently synthesized by the Leimgruber−Batcho protocol and a regioselective Claisen rearrangement. The racemization of **1** is suggested by the *p*-quinonemethide intermediate of **21**.

**Acknowledgment.** We thank Professor Hiroshi Sato (Hokkaido Agricultural Laboratory for Business Development) for providing **19** derived from natural product **1**. This work was financially supported by Takeda Science Foundation, Naito Foundation, Nagase Science and Technology Foundation, and a Grant-in-Aid for Scientific Research on Priority Areas 12045232 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

**Supporting Information Available:** Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) During the course of isolating decursivine (**2**), 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**.

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