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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

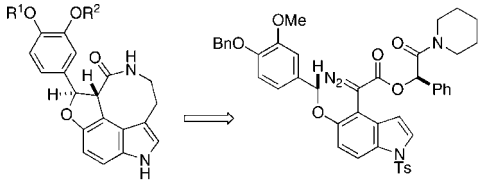


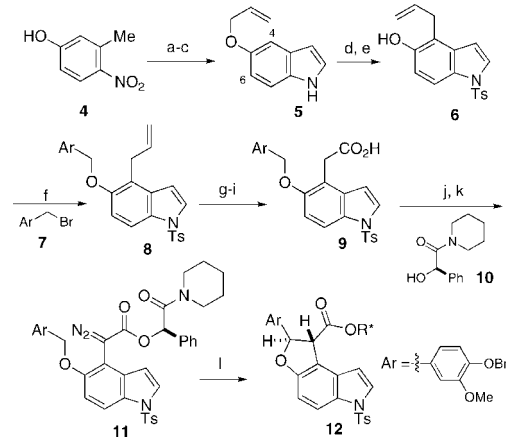
Figure 1. Structures of (−)-Serotobenine (**1**) and (−)-Decursivine (**2**).

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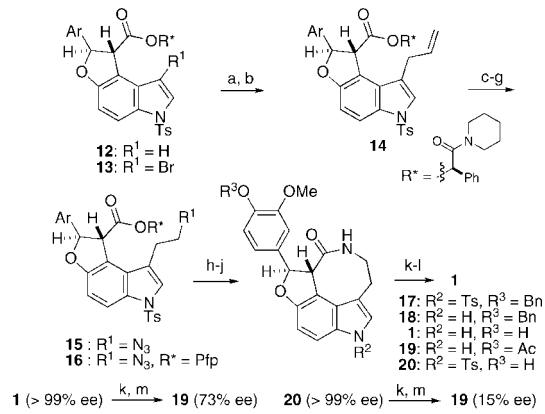
Scheme 2. Completion of Synthesis of (−)-Serotobenine (**1**) [a]

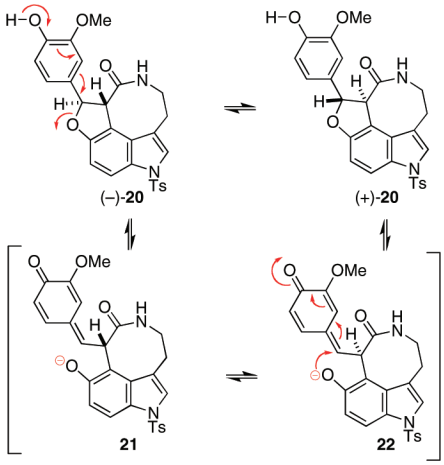


[a] Reagents and conditions: (a) NBS, CH_2Cl_2, 96%; (b) allyltributyltin, Pd(dppf)Cl_2·CH_2Cl_2, toluene, 90 °C, 95%; (c) OsO_4, NMO, acetone/H_2O; (d) $Pb(OAc)_4$, K_2CO_3, benzene; (e) $NaBH_4$, MeOH, 0 °C, 62% (3 steps); (f) MsCl, Et_3N, CH_2Cl_2, 0 °C; (g) NaN_3, DMF, 50 °C, 70% (2 steps); (h) LiOH·H_2O, 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 (^{1}H, ^{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**.

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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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