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Total synthesis of (+)-kopsihainanine A†

Masaya Mizutani, Shigeo Yasuda and Chisato Mukai*

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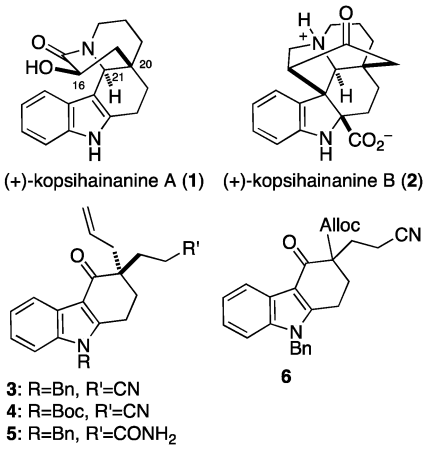
Total synthesis of (+)-kopsihainanine A was accomplished on the basis of (i) Stoltz's enantioselective decarboxylative asymmetric allylation and (ii) the proposed biogenetic pathway from the related alkaloid, kopsihainanine B. In addition, HPLC analysis of the synthetic (+)-kopsihainanine A confirmed its ee to be 99% with $[\alpha]_D^{30}$ = 25.35.

In 2011, Gao and co-workers[1] isolated the novel monoterpenoid indole alkaloid, (+)-kopsihainanine A (**1**), together with the biogenetically related (+)-kopsihainanine B (**2**) from the leaves and stems of *Kopsia hainanesis*, which is a native species historically used in folk medicine for the treatment of rheumatoid arthritis, pharyngitis, tonsillitis, and dropsy in the Hainan Province, China. The unprecedented strained pentacyclic skeleton of **1** as well as its relative stereochemistry were elucidated by spectral analysis, specifically by careful ^{1}H NMR considerations. The absolute configuration of **1** was deduced to be 16*R*, 20*R*, 21*S* based on a comparison of the actual electronic circular dichroism trace of (+)-**1** to those predicted for four candidates using AMI calculations and the ZINDO method. The first total synthesis of kopsihainanine A (**1**) was achieved from the tricyclic tetrahydrocarbazol-4-one derivative **3** in a racemic form by Xie, She and co-workers[2] in 2012. Shao and co-workers[3] very recently succeeded in the preparation of the optically active (−)-**3** by taking advantage of the palladium-catalyzed asymmetric decarboxylative allylation of **6** in the presence of the PHOX ligand and completed the total synthesis of (+)-**1** according to Xie and She's procedure.[2] This total synthesis unambiguously confirmed the absolute structure of (+)-**1** as depicted in Scheme 1. A similar palladium-catalyzed asymmetric decarboxylative allylation[4] produced the optically active **4**, which was converted into the carbamoyl derivative **5**, but further transformation into the target natural product has not yet been achieved, although the racemic **5** has already been converted into (±)-**1** by Xie, She and co-workers.[2]



Scheme 1 Structures of kopsihainanines A (**1**) and B (**2**) and 3,3,-disubstituted-tetrahydrocarbazol-4-ones (**3–6**).

Gao and co-workers[1] proposed a possible biogenetic pathway for the production of (+)-kopsihainanine A (**1**) from (+)-kopsihainanine B (**2**). Namely, the initial decarboxylative carbon–carbon bond cleavage of **2** would lead to the tetracyclic compound **I** with the C_4-carbon tether at the ring juncture, which would be susceptible to the selective oxidative fission of the terminal double bond giving rise to the formation of the α-ketoaldehyde derivative **II**. The following condensation between the secondary amine and aldehyde moieties would produce the hemiacetal **III**, which would spontaneously collapse to (+)-**1** *via* the keto–enol tautomerized intermediate **IV**.

During our investigation of the syntheses of indole alkaloids and derivatives,[5] the strained and unprecedented pentacyclic framework of (+)-**1** as well as its biological background strongly intrigued us and (+)-**1** immediately became our next target molecule. We noted Gao's proposal[1] for the biogenetic pathway from (+)-**2** to (+)-**1**. If the plausible biogenetic intermediate **II** or its equivalent could be obtained in an optically active form, the biomimetic-type transformation of them into (+)-**1** would be achieved. The retrosynthetic analysis of (+)-**1** afforded the reasonable tactics outlined in Scheme 3. The alkylation of the δ-lactam **d** with the indole derivative **e** would

Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan.
E-mail: mukai@p.kanazawa-u.ac.jp; Fax: +81-76-234-4410; Tel: +81-76-234-4411

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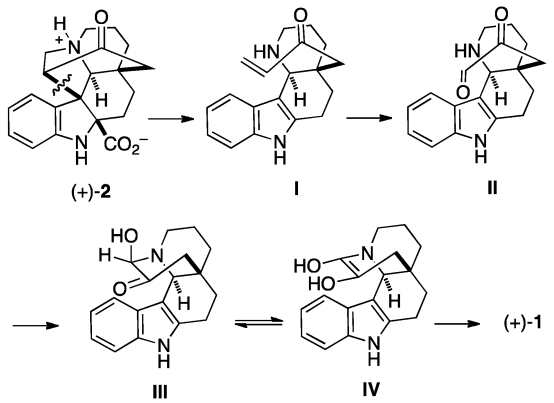
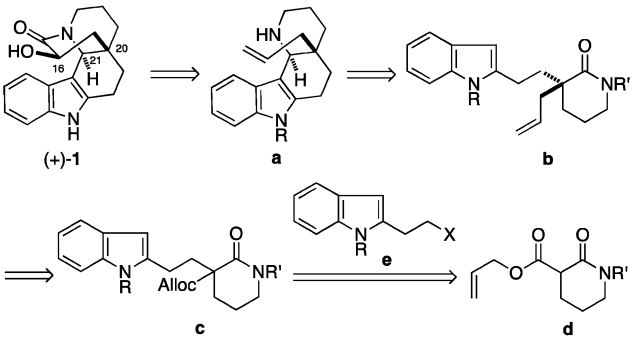
produce the condensation product **c**. The decarboxylative allylation of **c** under suitable chiral circumstances[6] would furnish the optically active δ-lactam **b** with all the carbon units required for (+)-**1**. The Bischler–Napieralski reaction[7] at the C_3-position of the indole nucleus of **b** followed by stereoselective reduction would result in the production of the precursor **a**, an equivalent of the plausible biogenetic intermediate **II**. Consecutive oxidation and condensation of **a** would finally deliver the target natural product (+)-**1**.

Treatment of the known α-allyloxycarbonyl-*N*-benzoyl-δ-lactam (**7**)[8a] with 1-(*tert*-butoxycarbonyl)-2-(2-iodoethyl)indole (**8**), easily derived from indole over 4 steps in 67% yield,[9] in the presence of potassium carbonate provided the condensation product **9** in 75% yield. The decarboxylative allylation of **9** to the optically active **10** in the presence of a suitable asymmetric catalyst must be the most crucial step in this synthesis. However, we initially determined and optimized the synthetic route using racemic **10**. Thus, compound **9** was exposed to the achiral conditions ($Pd(PPh_3)_4$ in THF) at room temperature to afford the racemic decarboxylated product **10** in 80% yield; the two protecting groups on the nitrogen atoms of which were subsequently removed by potassium hydroxide to produce **11** in 84% yield. The Bischler–Napieralski reaction of **11** with phosphorus chloride[7a] in refluxing toluene smoothly occurred to form the iminium salt. The stereoselective attack of the hydride species of $NaBH_4$ on the iminium salt occurred from the opposite side of the allyl moiety resulting in the exclusive formation of the tetracyclic compound **12** in 82% overall yield from **11**. Thus, we could easily prepare the precursor for the plausible biogenetic intermediate **II** (see Scheme 2). Our next endeavor focused on adjustment of the allyl group of **12** to the suitably oxidized form for completion of the total synthesis. Prior to the oxidative chemical modification of the allyl moiety, both secondary nitrogen atoms of the indole nucleus and the piperidine of **12** were successively protected with *tert*-butoxycarbonyl (**13**, 83%) and benzyloxycarbonyl groups, respectively, to furnish **14**.[10] Upon exposure to RuO_4-mediated oxidation conditions ($RuCl_3/CeCl_3/NaIO_4$),[11] compound **14** underwent dihydroxylation to give **15**.[10] Conversion of the dihydroxy moiety of **15** to the α-ketoaldehyde functionality was examined under several oxidation conditions, but the α-ketoaldehyde derivative could not be obtained. We tentatively assumed that the labile α-ketoaldehyde functionality might immediately decompose after its production even if the oxidation proceeded as expected.



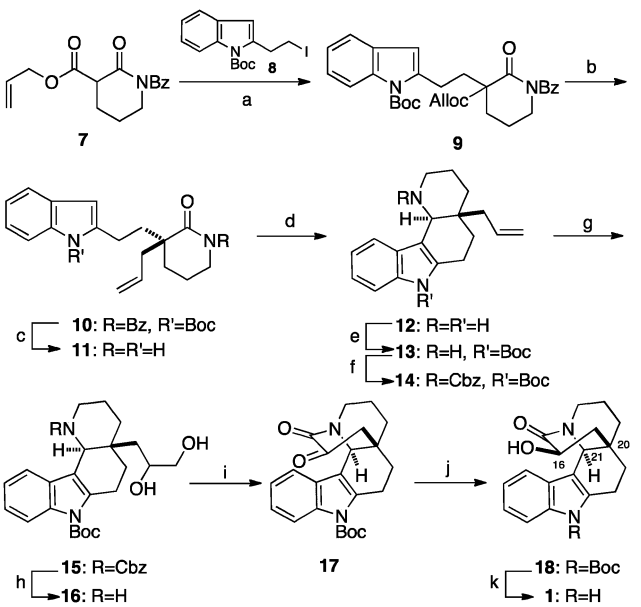
Scheme 2 Proposed biogenetic pathway for production of (+)-**1** from (+)-**2**.



Scheme 3 Retrosynthesis of (+)-**1**.

In order to intramolecularly capture the labile α-ketoaldehyde by the amine moiety, the benzyloxycarbonyl group of **15** was removed under hydrogenation conditions to provide **16**,[10] which was then treated with IBX to give the over-oxidized pentacyclic diketone derivative **17** (in 19% overall yield from **13**) instead of the expected N-protected **III** and/or **1** (see Schemes 1 and 2). The direct conversion of **16** into **1** was again examined under several oxidation conditions, but a favorable result could not be realized. Thus, the over-oxidized product **17** was reduced with $NaBH_4$ in *t*-BuOH/THF at 0 °C to room temperature to produce the N-protected kopsihainanine A **18** in 31% yield. The total synthesis of (±)-**1** was finally accomplished by removal of the *tert*-butoxycarbonyl group in 80% yield (Scheme 4).

We could develop the synthetic route towards the target molecule in a racemic form. Our next effort, therefore, was directed toward the preparation of the optically active **10** with a high enantiomeric excess (ee), which is mandatory for the total synthesis of (+)-**1**. Stoltz and

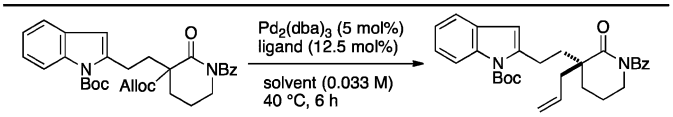


Scheme 4 Total synthesis of (±)-kopsihainanine A. (a) **8**, K_2CO_3, DMF, 50 °C, 75%. (b) $Pd(PPh_3)_4$ (8 mol%), THF, rt, 80%. (c) KOH, MeOH, reflux, 84%. (d) $POCl_3$, toluene, reflux, then $NaBH_4$, MeOH, 0 °C to rt, 82%. (e) $(Boc)_2O$, Et_3N, DMAP, DCM, rt, 83%. (f) CbzCl, Na_2CO_3, DCM, rt. (g) $RuCl_3{\cdot}nH_2O$, $CeCl_3{\cdot}7H_2O$, AcOEt/CH_3CN/H_2O (3/3/1), 0 °C. (h) H_2 (1 atm), $Pd(OH)_2$, EtOH, rt. (i) IBX, DMSO, rt, 19% from **13**. (j) $NaBH_4$, *t*-BuOH/THF (1/1), 0 °C to rt, 31%, (k) KOH, MeOH, reflux, 80%.

co-workers[8a] recently developed the palladium-catalyzed highly enantioselective decarboxylative allylation of 1-acyl-3-alkyl-3-(allyloxycarbonyl)lactams to 3-alkyl-3-allylpyrrolidinone, piperidinone, and caprolactams. Thus, application of Stoltz's procedure using (*S*)-*t*-BuPHOX (**19**) to **9** was examined. A solution of racemic **9** in toluene was heated at 40 °C in the presence of $Pd_2(dba)_3$ (5 mol%) and (*S*)-*t*-BuPHOX (**19**) (12.5 mol%) for 6 h to obtain (+)-**10** in 66% yield with 71% ee (Table 1, entry 1). According to the literature,[8a] several solvents were screened to get the best results. Neither toluene/hexane or tetrahydrofuran afforded results better than that of toluene alone (entries 2 and 3). Methyl *tert*-butyl ether (MTBE) was found to produce a better chemical yield as well as a better ee (entry 4). A slight improvement in the ee was attained when a combination of MTBE with hexane or cyclohexane was employed (entries 5 and 6). A similar result was observed upon treatment with a half amount of the palladium catalyst and the ligand **19** (entry 7). Finally, a more electron-poor catalyst, (*S*)-$(CF_3)_3$-*t*-BuPHOX (**20**),[8,12] became the most powerful catalyst for our purpose. Indeed, treatment of **9** with $Pd_2(dba)_3$ (5 mol%) and **20** (12.5 mol%) in MTBE effected the highly enantioselective asymmetric allylation to produce (+)-**10** in 80% yield with 98% ee (entry 8). These tendencies regarding the solvent and ligand are in complete agreement with those reported by Stoltz.[8a] Furthermore, the enantioselective allylation could be scaled up to the 1 mmol scale (entry 9).

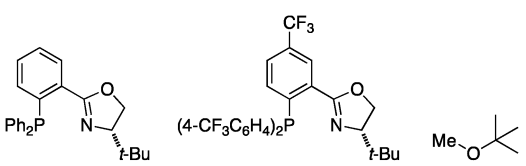
The total synthesis of (+)-kopsihainanine A (**1**) was accomplished from (+)-**10** (98% ee) according to the procedure described in a racemic series. Compound (+)-**10** was subsequently converted into (−)-**11** (77%), (+)-**12** (92%), and (+)-**13** (83%). The *N*-benzyloxycarbonylation of (+)-**13** was followed by dihydroxylation, debenzyloxycarbonylation, and oxidation to produce (+)-**17** in 33% overall yield from (+)-**13**. Reduction of (+)-**17** afforded (−)-**18** in 45% yield,

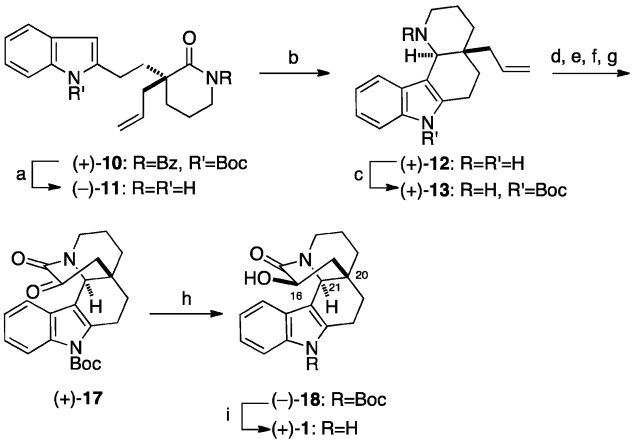
Table 1 Asymmetric decarboxylative allylation of δ-lactam **9**[a]



Entry	Ligand	Solvent	Yield (%)	ee[b] (%)
1	**19**	Toluene	66	71
2	**19**	Hexane–toluene (2 : 1)	65	27
3	**19**	THF	65	39
4	**19**	MTBE	76	81
5	**19**	Hexane–MTBE (2 : 1)	77	84
6	**19**	Cyclohexane–MTBE (2 : 1)	75	85
7[c]	**19**	Cyclohexane–MTBE (2 : 1)	75	86
8	**20**	MTBE	80	98
9[d,e]	**20**	MTBE	82	98

[a] The reactions were performed on the 0.12 mmol scale. [b] ee was determined by HPLC analysis (Diacel CHIRALCEL OD-H). [c] 2.5 mol% of $Pd_2(dba)_2$ and 6.3 mol% of **19** were used. [d] The reaction was performed on the 1.0 mmol scale. [e] Reaction time was 15 h.





Scheme 5 Total synthesis of (+)-kopsihainanine A (**1**). (a) KOH, MeOH, reflux, 77%. (b) $POCl_3$, toluene, reflux, then $NaBH_4$, MeOH, 0 °C to rt, 92%. (c) $(Boc)_2O$, Et_3N, DMAP, DCM, rt, 83%. (d) CbzCl, Na_2CO_3, DCM, rt. (e) $RuCl_3{\cdot}nH_2O$, $CeCl_3{\cdot}7H_2O$, AcOEt/CH_3CN/H_2O (5/3/1), 0 °C. (f) H_2 (1 atm), $Pd(OH)_2$, EtOH, rt. (g) IBX, DMSO, rt, 33% from **13**. (h) $NaBH_4$, *t*-BuOH/THF (1/1). 0 °C to rt, 45%. (i) KOH, MeOH, reflux, 85%.

which was then transformed into (+)-kopsihainanine A (**1**) in 85% yield under basic conditions (Scheme 5). The spectral data for the synthetic (+)-**1** was in accordance with those of the natural one.[1] However, the synthetic (+)-**1** showed its specific rotation as $[\alpha]_D^{30}$ = 25.35 (*c* = 0.33, $CHCl_3$), while that of the natural product was $[\alpha]_D^{25}$ = 60 (*c* = 0.10, $CHCl_3$).[1] Furthermore, Shao reported the specific rotation of the synthetic (+)-**1** as $[\alpha]_D^{25}$ = 55.0 (*c* = 0.5, $CHCl_3$)[3] which is very similar to that of the natural (+)-**1**. We measured the specific rotation of the synthetic (+)-**1** by changing the solvent, but similar low values were again observed [$[\alpha]_D^{16}$ = 39.44 (*c* = 0.10, MeOH) and $[\alpha]_D^{19}$ = 10.00 (*c* = 0.10, AcOEt)]. The simplest interpretation about these results is the assumption that racemization must have occurred during the conversion of (+)-**10** into the final product. Therefore, the HPLC analysis of (+)-**1** was carried out. It was not an easy task to determine the suitable conditions for the HPLC analysis of **1** due to its poor solubility. After screening various conditions using the racemic **1**, we finally found the optimal conditions (CHIRALPAK IE, hexane/MeOH/CH_2Cl_2/ethylenediamine = 70/6/24/0.06, 280 nm) showing two diagnostic peaks due to (+)- and (−)-**1** in the ratio of 50 to 50. Thus, the HPLC analysis of (+)-**1** by applying the optimal conditions unambiguously demonstrated that a high ee (99%)[13] is still maintained. Currently we do not have any clues to explain the difference between the specific rotation of our compound and those of the natural and Shao's ones.

Stoltz's enantioselective decarboxylative asymmetric allylation of α-allyloxycarbonyl-*N*-benzoyl-α-(2-indolyl-2-ethyl)-δ-lactam produced the corresponding optically active δ-lactam derivative with 98% ee, which was exposed to the Bischler–Napieralski conditions and $NaBH_4$ to afford the indoloperhydroquinoline framework. According to the proposed biogenetic pathway from kopsihainanine B (**2**) to A, several chemical manipulations were executed resulting in the completion of total synthesis of (+)-kopsihainanine A. HPLC analysis of the synthetic (+)-kopsihainanine A confirmed its ee to be 99% with $[\alpha]_D^{30}$ = 25.35 (*c* = 0.33, $CHCl_3$). We have completed the total synthesis of (+)-kopsihainanine A (**1**) from indole through 15 steps in 3.0%

overall yield (previous synthesis reported by Shao: from *N*-benzylcarbazolone through 10 steps in 3.6% overall yield[3]).

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13 HPLC analysis of both compounds (+)-**12**, derived from the Bischler–Napieralski reaction, and the precursor (−)-**18** for the final product was also carried out just for confirmation. As predicted, no racemization was observed at these stages: (+)-**12** shows 98% ee, while (−)-**18**, 99% ee.