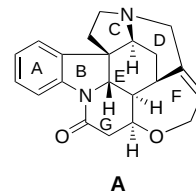


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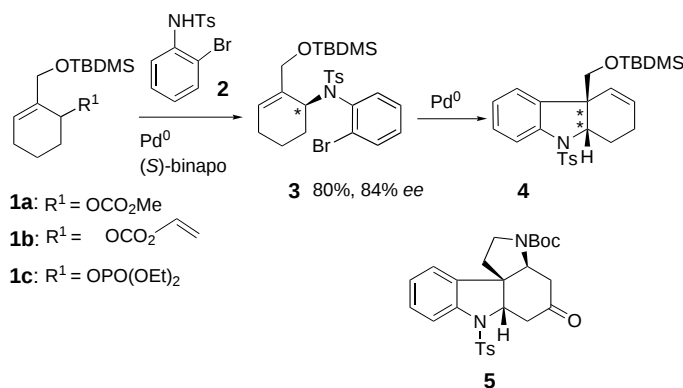
Total Synthesis of (–)-Strychnine

Masato Nakanishi and Miwako Mori*

(–)-Strychnine (**A**),^[1] the most famous of the *Strychnos* alkaloids, has seven rings and six stereogenic centers in the molecule and is one of the most complex natural products of its size. Although Woodward et al. succeeded in the total synthesis of (–)-strychnine in 1954,^[2] there were no reports of its total synthesis for 40 years. In 1992, Magnus et al. reported the total synthesis of strychnine,^[3] and then Overman and co-workers succeeded in the first asymmetric total synthesis of (–)- and (+)-strychnine in 1993.^[4] Since then, several groups have reported the total synthesis of (–)- or (±)-strychnine.^[5,6] Very recently, Vollhardt and co-workers completed the total synthesis of (±)-strychnine by using an ingenious cobalt-catalyzed [2+2+2] cycloaddition as a key step.^[7]



We recently reported a novel method for synthesizing indole derivative **4** by means of palladium-catalyzed cyclization of 2-bromoaniline **3**. The aniline derivative **3** was obtained from cyclohexenol **1** and aniline **2** by using palladium-catalyzed asymmetric allylic substitution (Scheme 1).^[8] (–)-Dehydrotubifolin and (–)-tubifolin were synthesized from tetracyclic ketone **5**, which was formed from **10** (Scheme 3; cf. **4**).

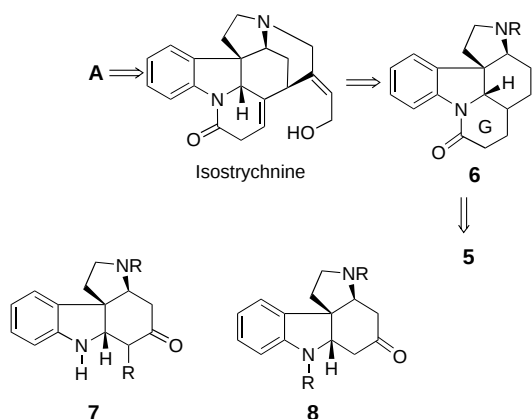


Scheme 1. Palladium-catalyzed asymmetric allylic substitution. Ts = toluene-4-sulfonyl, TBDMS = *tert*-butyldimethylsilyl, binapo = (*S*)-2,2'-bis-(diphenylphosphanoxy)-1,1'-binaphthyl, Boc = *tert*-butoxycarbonyl.

These results prompted us to synthesize (–)-strychnine, as tetracyclic ketone **5** is considered to be a very important intermediate in the syntheses of *Strychnos* indole alkaloids. Our retrosynthetic analysis of (–)-strychnine is shown in Scheme 2. The method for the construction of the G ring is

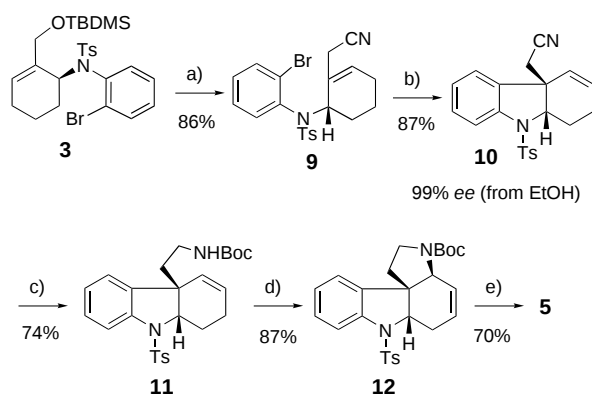
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Scheme 2. Retrosynthetic analysis of (–)-strychnine (**A**).

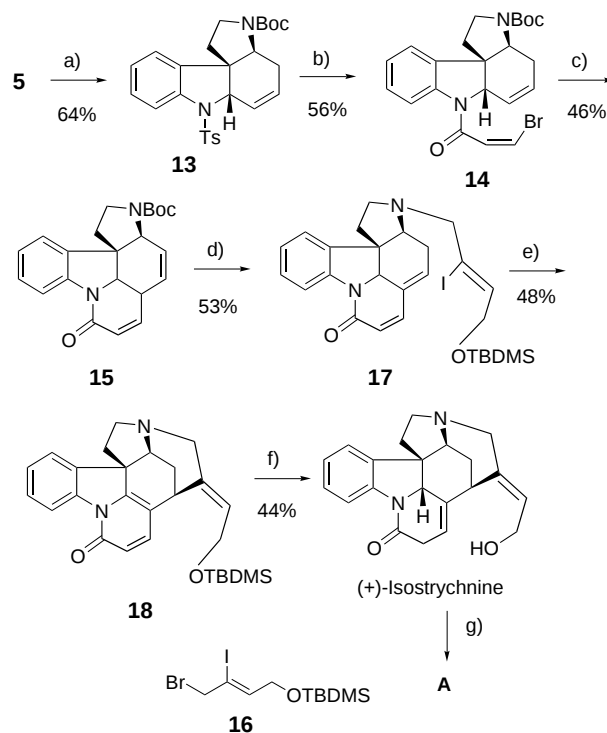
important for the synthesis of (–)-strychnine from **5**. Two pathways should be considered: 1) introduction of an alkyl group at the α position of the carbonyl group to give **7** followed by C–N bond formation to construct the G ring; 2) introduction of an acyl group at the nitrogen atom to form **8** followed by construction of the G ring.

The synthesis of **5** is summarized in Scheme 3. Indoline **10** (84 % *ee*) was recrystallized from EtOH to give the enantiomerically pure form (99 % *ee*, 73 % recovery, $[\alpha]_D^{20} = -46.7$ (*c* 2.16, CHCl_3)).^[9] The optically pure tetracyclic ketone **5** could then be prepared from **10**.



Scheme 3. Synthesis of **5**. a) 1) HCl; 2) PBr_3 ; 3) NaCN; b) $\text{Pd}(\text{OAc})_2$ (2 mol %), PPhMe_2 , Ag_2CO_3 , DMSO, 90 °C, 17 h; c) 1) LiAlH_4 ; 2) $(\text{Boc})_2\text{O}$; d) $\text{Pd}(\text{OAc})_2$, benzoquinone, MnO_2 , AcOH, 50 °C; e) 1) 9-BBN, then H_2O_2 , NaOH; 2) DMSO, $(\text{COCl})_2$, then NEt_3 . DMSO = dimethyl sulfoxide, Boc = *tert*-butoxycarbonyl, 9-BBN = 9-borabicyclo[3.3.1]nonane.

At first we chose the reaction pathway in which an acyl group is introduced at the α position of the carbonyl group in **5**. However, several attempts were unsuccessful as a result of the steric hindrance of the large Ts protecting group on the nitrogen atom. Instead, we tried to introduce an acyl group at the nitrogen atom to form a C–C bond by a Heck-type reaction. Conversion of **5** into **13** was carried out by a known method (Scheme 4). Detosylation followed by treatment with (*Z*)-3-bromoacryloyl chloride gave **14**, which was treated with $\text{Pd}(\text{OAc})_2$ (10 mol %) and PPh_3 (20 mol %) in the presence of $i\text{Pr}_2\text{NEt}$ in DMSO at 80 °C for 1.5 h. We were pleased to find



Scheme 4. Synthesis of (–)-strychnine. a) 1. PhNTf_2 , $\text{KN}(\text{TMS})_2$, 2. $\text{Pd}(\text{OAc})_2$, PPh_3 , HCO_2H , $i\text{Pr}_2\text{NEt}$; b) 1. $\text{NaC}_{10}\text{H}_8$, 2. (*Z*)-3-bromoacryloyl chloride, K_2CO_3 ; c) $\text{Pd}(\text{OAc})_2$ (10 mol %), PPh_3 (20 mol %), $i\text{Pr}_2\text{NEt}$, DMSO, 80 °C, 1.5 h; d) 1. NaOiPr , 2. $\text{CF}_3\text{CO}_2\text{H}$, 3. **16**, Li_2CO_3 , DMF, 40 °C; e) $\text{Pd}(\text{OAc})_2$, Bu_4NCl , K_2CO_3 , DMF, 70 °C, 0.5 h; f) 1. LiAlH_4 , 2. HCl; g) KOH, EtOH. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, DMF = *N,N*-dimethylformamide.

that pentacyclic compound **15** was obtained in 46 % yield after the usual work-up procedure. Isomerization of the double bond of **15** by treatment with NaOiPr in 2-propanol followed by removal of the Boc group and then alkylation with **16** afforded compound **17**, which is an intermediate in the synthesis of (±)-strychnine by Vollhardt and co-workers. By following their procedure, **17** was converted into pentacyclic compound **18** by treatment with $\text{Pd}(\text{OAc})_2$, Bu_4NCl , and K_2CO_3 (Scheme 4).

Treatment of **18** with LiAlH_4 followed by cleavage of the silyl group gave (+)-isostrychnine, whose spectral data and $[\alpha]_D^{20}$ value (+23.7 (*c* 0.59, EtOH)) agreed with those of (+)-isostrychnine reported by Woodward and co-workers.^[2] (+)-Isostrychnine was converted into our final target (–)-strychnine (**A**) by treatment with KOH in EtOH according to a known method.^[10]

In summary, palladium catalysis played an important role in our total synthesis of (–)-strychnine: 1) rings A, B, and E were constructed by using by palladium-catalyzed asymmetric allylic substitution of a cyclohexenol derivative followed by palladium-catalyzed cyclization; 2) ring C was formed by means of a palladium-catalyzed allylic oxidation; 3) the synthesis of ring G and then ring F required $\text{Pd}(\text{OAc})_2$. The extensive use of Pd^0 or Pd^{II} highlights the importance of palladium catalysts in modern synthetic organic chemistry.

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