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TOTAL SYNTHESIS OF OPTICALLY ACTIVE CHANOCLAVINE-I[1].

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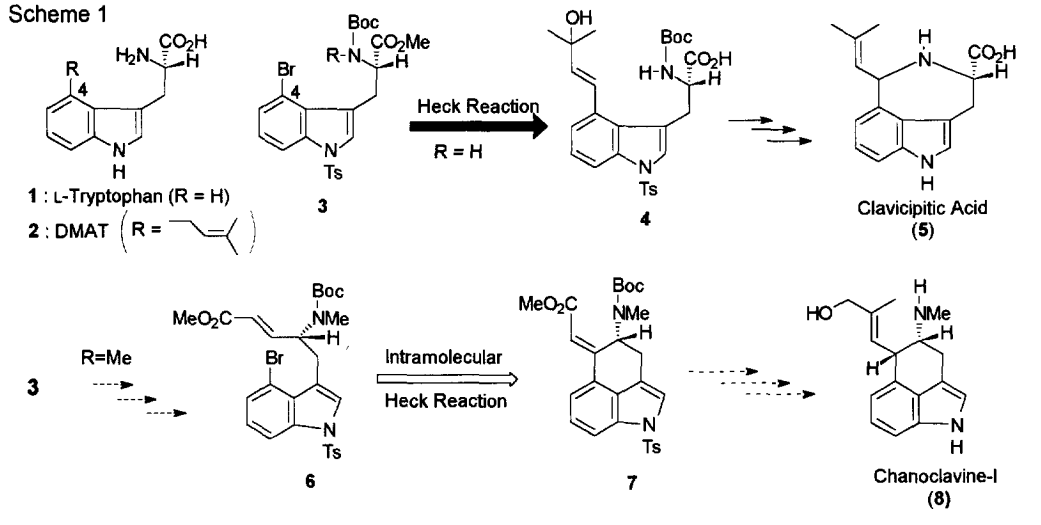
Abstract : The total synthesis of optically active chanoclavine-I, an ergot alkaloid, was accomplished using palladium-catalyzed intramolecular cyclization (Heck reaction) as a key step. The conjugate ester (**6**) was obtained in 2 steps from optically active 4-bromotryptophan (**10**), and the cyclization of **6** proceeded smoothly without racemization to give the key intermediate, tricyclic tetrahydrobenz[*c,d*]indole derivative (**7**), in high yield. Copyright © 1996 Elsevier Science Ltd

The ergot alkaloids are biosynthesized[2] from L-tryptophan (**1**) via dimethylallyltryptophan (**2**, DMAT). Therefore, commercially available **1** might be a good starting material for the synthesis of those alkaloids as an optically active form, but only limited successful achievement has been reported[3]. The main reason is that the regioselective introduction of the carbon side chain at the C_4-position of indole nucleus without racemization has been difficult. In the course of our investigation for the selective activation of the aromatic carbon-hydrogen bond of the aromatic bromides with Pd (II)[4], we have developed[5] a convenient 2-step synthesis of optically active 4-bromotryptophan (**3**) from 4-bromo-



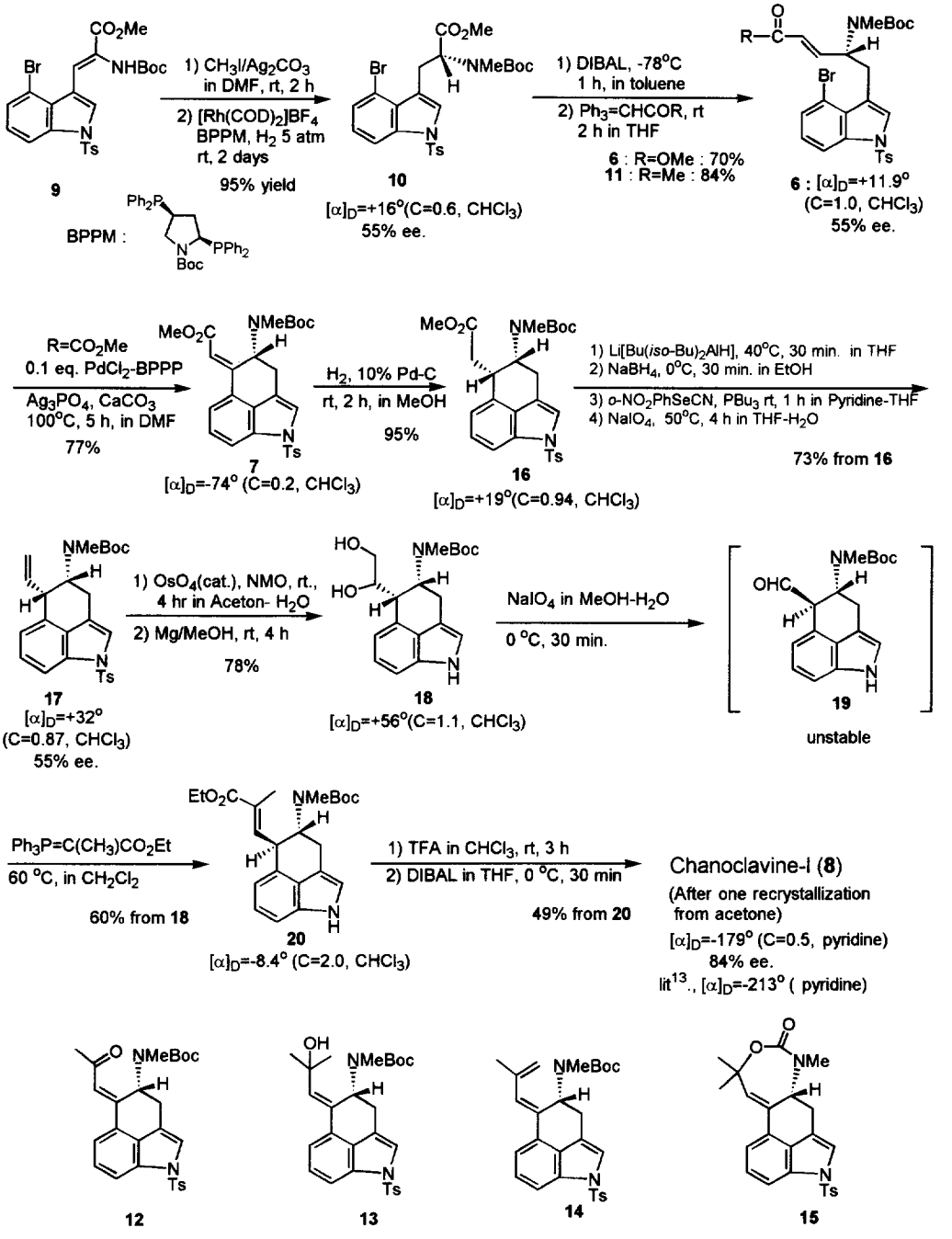
1-tosylindole by utilizing this method. The compound (**3**) should be a useful intermediate for the synthesis of ergot alkaloids, because various carbon side chains can be introduced at the C_4-position by the transition metal catalyzed coupling reaction. Total synthesis of optically active clavicipitic acid (**5**) was first accomplished[5] through 4-(3-hydroxy-3-methyl-1-butenyl)tryptophan (**4**) by applying this strategy. We report here the total synthesis of optically active chanoclavine-I (**8**)[6] using palladium catalyzed intramolecular cyclization of conjugate ester (**6**) as a key step. Compound (**6**) would be easily prepared from **3** as an optically active form[7].

Scheme 2 shows the synthetic route of chanoclavine-I (**8**). To prepare 4-bromo-N-methyltryptophan (**10**), methylation of 4-bromotryptophan (**3** ; R=H) was attempted. Unfortunately, the reaction caused racemization (*t*-BuOK /CH_3I) or did not proceed (Ag_2CO_3/CH_3I). Therefore, dehydrotryptophan (**9**) was methylated at first, and then the asymmetric reduction was carried out using BPPM as a chiral phosphine ligand. The obtained optically active N-methyl-4-bromo-tryptophan (**10**)[8] was converted to the conjugate ester (**6**) by DIBAL reduction followed by Wittig reaction. The palladium catalyzed cyclization of **6** successfully proceeded in the presence of 1,3-bisdiphenylphosphinopropane (BPPP) and Ag_3PO_4-$CaCO_3$ to give the expected tricyclic ester (**7**)[9] in good yield. Radical cyclization of **6** by heating with *n*-Bu_3SnH and AIBN led to disappointing results. The same cyclization of the conjugate ketone (**11**) did not give the desired cyclic ketone **12**. Although the reaction of **7** with NH_2OCH_3 (the first step of Weinreb' s ketone synthesis[10]) or with $Cp_2Ti(CH_3)_2$[11] was attempted to synthesize the cyclic ketone (**12**), the reactivity of the ester carbonyl was so weak due to the steric hindrance that the reaction did not proceed. Then we attempted to prepare the diene (**14**) by the acid catalyzed dehydration of dimethylallyl alcohol (**13**) which was easily obtained by methylation of ester (**7**) with 2 equivalents of CH_3Li (0 °C, 30 min., 77%), but the cyclic lactone (**15**) was formed unexpectedly in high yield by the attack of a lone pair of Boc group to tertiary cation derived from allyl alcohol. This abnormal reactivity might be caused by the short distance between the ester group and tertiary alcohol group.

As the catalytic reduction of tricyclic compound (**7**) gave only the product (**16**) having undesired *cis* configuration, we planned to convert **16** to aldehyde (**19**) which might spontaneously isomerize to a more stable *trans* isomer. Conversion of ester (**16**) to olefin (**17**)[12] was smoothly accomplished by a straightforward 4-step sequence (one-pot reduction, selenenylation, and *syn*-elimination). Oxidation of olefin (**17**) with OsO_4/NMO followed by deprotection of tosyl group with Mg/MeOH[13] and cleavage of diol with $NaIO_4$ gave unstable aldehyde (**19**) which was immediately converted to the ester (**20**) by the Wittig reaction. As a result of spontaneous isomerization of aldehyde (**19**), the *trans*-ester (**20**) was obtained as a sole product. The olefin geometry and stereochemistry of the side chain of C ring were confirmed by the comparison of NMR spectra reported[6d] by Oppolzer in the synthesis of *racemic*-chanoclavine-I (**8**). Conversion of **20** to chanoclavine-I (**8**) was accomplished by the treatment of CF_3COOH followed by DIBAL reduction[6d]. The synthetic optically active chanoclavine-I (**8**) has the same absolute configuration with the natural product[14]. After one recrystalization from acetone, the optical purity rose to 84% ee.

Although several attempts of intramolecular cyclization at the C_4-position of the tryptophan analogue have been reported[3, 15], this work is the first successful example of the construction of optically

Scheme 2 : Total Synthesis of Chanoclavine-I



active secoergoline skeleton by using such cyclization. The tricyclic ester (**7**) is considered to be a useful intermediate for other ergot alkaloids such as lysergic acid, and further studies are underway.

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7. The ***R*** configuration of **3**, the opposite configuration to natural tryptophan, has to be used to obtain the same stereoisomer as natural product.
8. The absolute configuration of **10** was unambiguously confirmed as ***R*** by the comparison of optical rotation with **10** which was prepared from **3** (R=H) having known absolute configuration[5], and the optical purity was determined as 55% ee. by HPLC using a chiral column (Daicel Chiralcel OD, Hexane : EtOH = 50 : 1).
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12. The optical purities of **6** and **17** were both 55% determined by HPLC (Daicel Chiralcel OD, Hexane : EtOH = 70 :1 for **6**; Hexane : EtOH : *i*-Pro_2NH = 200 : 1 : 0.3 for **17**). This means that the conversion step (**10** → **6**) and cyclization step (**6** → **7**) did not cause racemization.
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