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# A novel enantioselective synthesis of the key intermediate of (−)-huperzine A employing asymmetric palladium-catalyzed bicycloannulation

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***Abstract:*** The key intermediate (+)-**5** of (−)-huperzine A **1** was prepared in an enantiomerically pure form *via* the asymmetric palladium-catalyzed bicycloannulation of the β-keto ester **2** with 2-methylene-1,3-propanediol diacetate **3**. The chiral ferrocenylphosphine ligand **7d** gave the highest enantioselectivity of 64% ee in the asymmetric bicycloannulation. © 1997 Elsevier Science Ltd. All rights reserved.

(−)-Huperzine A **1** isolated from the clubmoss *huperzia serrata* (Thunb.) Trev., has been shown to be a potent reversible acetylcholinesterase inhibitor.[1] This natural product is anticipated to be a promising agent for the treatment of Alzheimer's disease, and is now being investigated in clinical trials.[1] Due to the difficulty in obtaining a large quantity of (−)-**1** from plants together with the fact that only the natural enantiomer (−)-**1** exhibits significant pharmacological activity, considerable attention has been focused on the enantioselective synthesis of (−)-**1**.[2,3] In connection with our studies on the synthesis of **1** and its analogues with the aim of exploring the structure–activity relationships,[4] we have recently developed an enantioselective synthetic route to (−)-**1** *via* the *Cinchona* alkaloids-promoted asymmetric Michael reaction.[5] Herein we wish to report a novel method for the synthesis of the key intermediate (+)-**5** for (−)-**1** *via* asymmetric palladium-catalyzed bicycloannulation which is more efficient and practical than that previously reported by us.[5]

In 1993, Kozikowski reported the synthetic route to racemic **1** *via* palladium-catalyzed bicycloannulation as outlined in Scheme 1.[3d,e] Enantioselective constructions of the optically active bridged-tricyclic compound **4** by the palladium-catalyzed bicycloannulation have not, to our knowledge, been reported to date. Therefore, we became interested in investigating the possibility of an asymmetric variant of this transformation employing chiral phosphine ligands. Recently, Hayashi developed the chiral ferrocenyl phosphine ligand (*R*)-(*S*)-**6** possessing a hydroxyl group at the end of the pendant chain and used it in the asymmetric palladium-catalyzed allylation of β-diketones with allyl acetate, giving high levels of enantiomeric excess (up to 82% ee).[6,7]

On the basis of this information, we initially examined the palladium-catalyzed bicycloannulation of the β-keto ester **2**[3d,e] with 2-methylene-1,3-propanediol diacetate **3**[3d,e] employing (*R*)-(*S*)-**6** as a chiral ligand under various conditions (Scheme 2).[8] The results are summarized in Table 1. In all cases the reaction smoothly took place to provide (+)-**4** with a moderate ee in a good to excellent yield. The ee was determined by HPLC analysis using a chiral column.[9] The absolute configuration of the preferentially formed enantiomer (+)-**4** was assigned as shown by converting it to the known compound (+)-**5**[5] (*vide infra*, see, Scheme 3). In terms of ee, chemical yield as well as reaction time, the best conditions were found to be using 1,1,3,3-tetramethylguanidine (TMG) as a base and 1,4-dioxane or 1,2-dimethoxyethane (DME) as a solvent (entries 3 and 6). In $Et_2O$ the enantioselectivity was not largely affected, while the rate of reaction decreased (entry 4). Although the highest ee was

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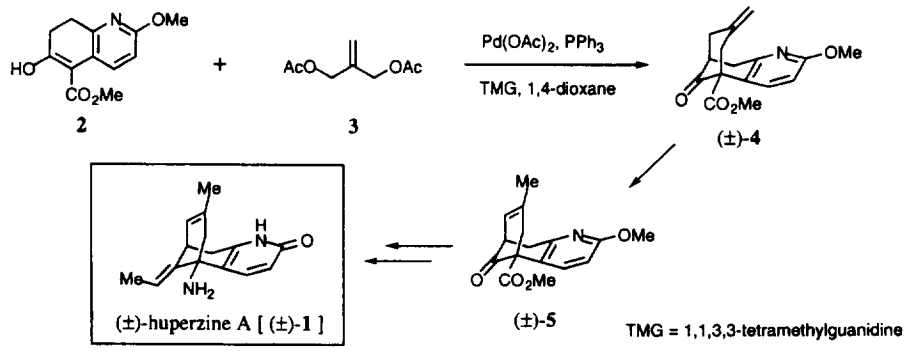
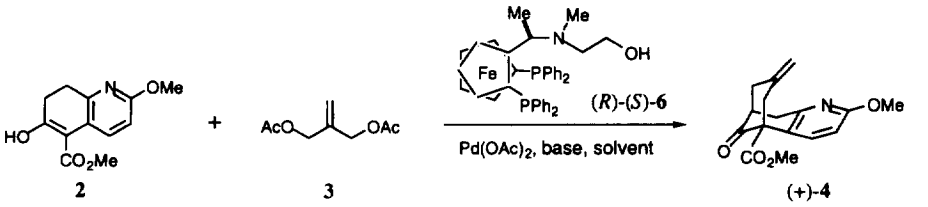



**Scheme 1.** Kozikowski's palladium-catalyzed route to racemic huperzine A [(±)-**1**].

observed in THF, the yield was not satisfactory (entry 5). Use of other standard bases gave similar levels of ee to those found using TMG, however yields of (+)-**4** were reduced in these cases (entries 7–10).



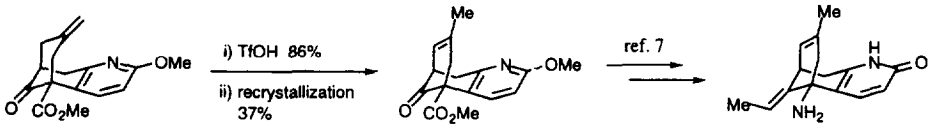

**Scheme 2.** Asymmetric palladium-catalyzed bicycloannulation of β-keto ester **2** with diacetate **3** employing ferrocenylphosphine ligand (*R*)-(*S*)-**6**.

In order to obtain higher enantioselectivity, we next pursued the asymmetric bicycloannulation using various ferrocenylphosphine ligands (*R*)-(*S*)-**7a–e** bearing appropriate linker chains, because the length of linker chain between the hydroxyl group and the ferrocene moiety is thought to play a key role in respect of the enantioselectivity.[7b] The ligand (*R*)-(*S*)-**7a** is commercially available and the ligand (*R*)-(*S*)-**7b** is known in the literature.[7a,b] The new ligands (*R*)-(*S*)-**7c–e** were readily prepared according to

**Table 1.** Asymmetric palladium-catalyzed bicycloannulation of β-keto ester **2** with diacetate **3**[a]

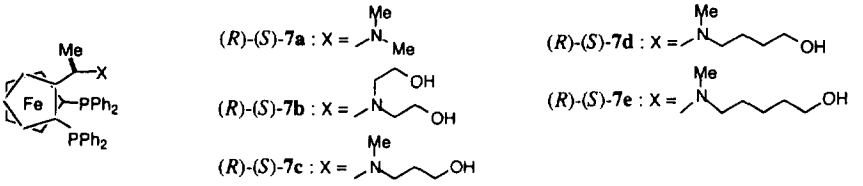
| entry | solvent | base | reaction time (h) | yield (%)[b] | ee (%)[c,d] |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | TMG | 13 | 90 | 29 |
| 2 | DMF | TMG | 10 | 75 | 30 |
| 3 | DME | TMG | 13 | 90 | 38 |
| 4 | $Et_2O$ | TMG | 72 | 93 | 41 |
| 5 | THF | TMG | 24 | 39 | 47 |
| 6 | 1,4-dioxane | TMG | 12 | 85 | 39 |
| 7 | 1,4-dioxane | DBU | 13 | 76 | 41 |
| 8 | 1,4-dioxane | 2,6-di-*tert*-Bu-Py[e] | 12 | 70 | 39 |
| 9 | 1,4-dioxane | KF | 48 | 64 | 40 |
| 10 | 1,4-dioxane | KHMDS | 10 | 58 | 37 |

a) Reactions were performed with 0.1 mmol of **2** and 0.1 mmol of **3** in the presence of 0.02 mmol of $Pd(OAc)_2$ and 0.04 m mol of (*R*)-(*S*)-**6** in 2.5 ml of solvent at ambient temperature under argon.
b) Isolated yield by chromatography on silica gel.
c) The preferentially formed enantiomer was (+)-**4** when (*R*)-(*S*)-**6** was used as a ligand.
d) The enantiomeric excess of (+)-**4** was determined by HPLC analysis using a chiral column.[11]
e) 2,6-di-*tert*-butylpyridine.




**Scheme 3**. Preparation of the key intermediate (+)-**5** from the compound (+)-**4**.

**Table 2**. Asymmetric palladium-catalyzed bicycloannulation of β-keto ester **2** with diacetate **3** and employing various ferrocenylphosphine ligands **7a–e**[a]




| entry | ligand | temperature | reaction time (h) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | (*R*)-(*S*)-**7a** | rt | 8 | 84 | 24 |
| 2 | (*R*)-(*S*)-**7b** | rt | 13 | 73 | 33 |
| 3 | (*R*)-(*S*)-**6** | rt | 12 | 85 | 39 |
| 4[d] | (*R*)-(*S*)-**6** | -30 °C → 15 °C | 5 | 75 | 48 |
| 5 | (*R*)-(*S*)-**7c** | rt | 8 | 91 | 43 |
| 6[d] | (*R*)-(*S*)-**7c** | -30 °C → 15 °C | 6 | 81 | 54 |
| 7 | (*R*)-(*S*)-**7d** | rt | 7 | 98 | 47 |
| 8[d] | (*R*)-(*S*)-**7d** | -30 °C → 15 °C | 6 | 92 | 64 |
| 9 | (*R*)-(*S*)-**7e** | rt | 7 | 63 | 35 |

a) Reactions were carried out with 0.1 mmol of **2** and 0.1 mmol of **3** in the presence of 0.02 mmol of $Pd(OAc)_2$, 0.04 mmol of ligand, and 0.22 mmol of TMG in 2.5 ml of 1,4-dioxane ( except for entries 4, 6, and 8 ) at a given temperature under argon.
b) Isolated yields by chromatography on silica gel.
c) The enantiomeric excess of (+)-**4** was determined by HPLC analysis using a chiral column.[11]
d) In this reaction at low temperature, 1,2-dimethoxyethane (DME) was used as a solvent instead of 1,4-dioxane.

the reported procedures.[7a,b,10] The reactions were performed under the conditions optimized above. The results shown in Table 2 disclosed that the most effective ligand is (*R*)-(*S*)-**7d** (entries 7 and 8) and that lowering temperature improved the ee of (+)-**4** (entries 4, 6 and 8). The best result was obtained when the reaction was carried out by employing (*R*)-(*S*)-**7d** at −30°C followed by warming to 15°C in DME, affording the enantioselectivity of 64% ee in 92% yield (entry 8). It is worthy to note that the observed ee is the best result reported so far for the asymmetric palladium-catalyzed allylation of β-keto esters.[6,11]

As shown in Scheme 3, the compound (+)-**4** (64% ee) was converted to the key intermediate (+)-**5** (>99% ee[9]), mp 139–140°C [lit.,[5] mp 140–141°C ], $[\alpha]_D^{20}$ +67.8 (c 0.52, $CHCl_3$) [lit.,[5] $[\alpha]_D^{20}$ +69.9 (c 1.37, $CHCl_3$) ], by isomerization of the exomethylene moiety with triflic acid[3d,e] followed by recrystallization from hexane. Transformation of (+)-**5** to natural (−)-huperzine A **1** was carried out according to our previously reported method.[6] Unnatural (+)-huperzine A was also synthesized in the same manner as described above *via* the asymmetric palladium-catalyzed bicycloannulation employing the enantiomeric ligand (*S*)-(*R*)-**7d** instead of (*R*)-(*S*)-**7d**.

In conclusion, we have succeeded in developing an improved synthetic pathway to natural (−)-huperzine A **1** wherein the key intermediate (+)-**5** was prepared in an enantiomerically pure form by employing asymmetric palladium-catalyzed bicycloannulation followed by recrystallization. The

explored synthetic scheme may have potential as one of the most reliable synthetic methods for producing a large quantity of (−)-**1** and its analogues.

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7. The high enantioselectivity observed in this asymmetric allylation using the ligand (*R*)-(*S*)-**6** was explained by a concept of *secondary ligand-substrate interaction* involving hydrogen bonding between the hydroxyl group in the ligand and the attaking enolate anion, see, a) T. Hayashi, T. Mise, M. Fukushima, M. Kagotani, N. Nagashima, Y. Hamada, A. Matsumoto, S. Kawakami, M. Konishi, K. Yamamoto, M. Kumada, *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 1138; b) T. Hayashi, K. Kanehira, T. Hagihara, M. Kumada, *J. Org. Chem.*, **1988**, *53*, 113. c) M. Sawamura, H. Nagata, H. Sakamoto, Y. Ito, *J. Am. Chem. Soc.*, **1992**, *114*, 2586. e) M. Sawamura, Y. Ito, *Chem. Rev.*, **1992**, *92*, 857.
8. Using other chiral phosphine ligands, the representative ees observed for the reactions in the presence of 1,1,3,3-tetramethylguanidine (TMG) in 1,4-dioxane at room temperature were as follows: (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (12% ee), (*2S,4S*)-1-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl pyrrolidine (24% ee), (*R,R*)-1,2-ethanediylbis[(2-methoxyphenyl)phenyl-phosphine] (12% ee).
9. CHIRALCEL OD-H (DAICEL CHEMICAL INDUSTRIES, LTD) was used. Eluent (hexane:2-propanol=20:1) was flown by 0.5 ml/min and the products were detected by UV (254 nm).
10. The new ligands **7c–e** were prepared by reactions of commercially available (*R*)-1-[(*S*)-1′,2-bis(diphenyl-phosphino)ferrocenyl]ethyl acetate with the corresponding aminoalcohols.[7a,b]
11. To the best of our knowledge, the highest enantioselectivity of 22% ee has been reported for the asymmetric palladium-catalyzed allylation of β-keto esters.[7b]


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