AN ENANTIOSELECTIVE SYNTHESIS OF NATURAL (–)-HUPERZINE A *VIA CINCHONA* ALKALOIDS-PROMOTED ASYMMETRIC MICHAEL REACTION‡

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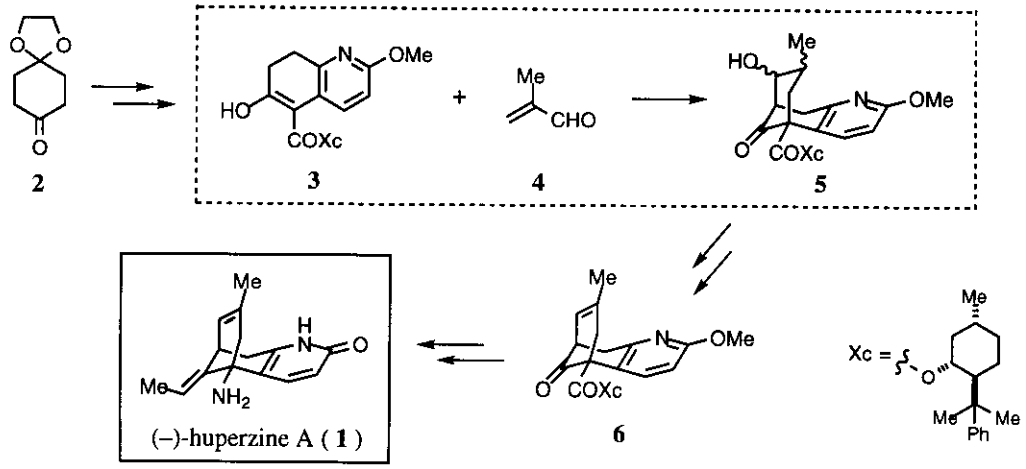
Abstract - An enantioselective synthesis of natural (–)-huperzine A (**1**) was achieved by a method featuring the *Cinchona* alkaloids-promoted asymmetric Michael reaction. Employing (–)-cinchonidine as a chiral catalyst, the asymmetric Michael reaction gave 64% ee of the product. The optically pure (+)-**9** (>99% ee) obtained by recrystallization was converted to (–)-**1**.

(–)-Huperzine A (**1**) isolated from *Huperzia serrata* (Thunb.) Trev., a Chinese folk medicine, exhibits a reversible potent inhibitory activity against acetylcholinesterase (AChE).[3] Since the use of **1** can increase the level of the neurotransmitter acetylcholine in the central nervous system, this natural product holds considerable promise in the treatments of Alzheimer's disease, and is currently under clinical trials.[3] Total syntheses of racemic **1** were achieved by Qian[4] and Kozikowski,[5] independently. Kozikowski also accomplished the enantioselective synthesis of (–)-**1** and disclosed that natural (–)-**1** displays 33-fold more potent inhibitory activity against AChE than unnatural (+)-**1**.[6]

Scheme 1. Kozikowski's enantioselective route to (–)-huperzine A (**1**)



‡ This paper is dedicated to the memory of the late Professor Emeritus Shun-ichi Yamada.

In the course of our ongoing synthetic studies of **1** and its analogues with the aim of exploring the structure-activity relationships,[7] we have taken much interest in the Kozikowski's route[6] outlined in **Scheme 1** because it appeared to have potential for synthesizing the therapeutically useful analogues of **1**. However, a stoichiometric amount of expensive (–)-8-phenylmenthol is employed as a chiral auxiliary as well as introduction of the chiral auxiliary and its subsequent removal requires a multi-step operation. Furthermore, the undesired diastereomer produced in a minor product must be separated by silica gel chromatography.[6] In order to produce a large quantity of optically pure (–)-huperzine A (**1**), a novel enantioselective synthetic method was sought which is more efficient and practical than that reported by Kozikowski.[6] We have now found that some chiral amines exemplified by *Cinchona* alkaloids effectively catalyze the asymmetric Michael reaction of the dihydroquinoline (**7**) with methacrolein (**4**) in a good enantioselectivity (**Scheme 2**). It was also found that simple recrystallization of the partially optically active compound (**9**) derived from **8** readily affords optically pure (+)-**9** (>99% ee), the key intermediate for the synthesis of (–)-**1**. In this paper, we wish to report a novel enantioselective synthesis of (–)-**1** by employing the *Cinchona* alkaloids-promoted asymmetric Michael reaction as the key steps.

A catalytic asymmetric Michael reaction remains as a field to be explored even though there have been reported several examples which are successful to some extent.[8] Since it was known that *Cinchona* alkaloids effectively promote an asymmetric Michael reaction when a β-keto ester is used as a Michael donor,[9] we applied these conditions to our reaction system employing **7** as shown in **Scheme 2**. The substrate (**7**) was prepared from commercially available 1,4-cyclohexanedione monoethylene ketal (**2**) according to the reported method.[5] The asymmetric Michael reaction of **7** with **4** and subsequent intramolecular aldol reaction smoothly took place in the presence of *Cinchona* alkaloids, leading to the formation of the bridged-tricyclic compound (**8**).[10] This was a mixture of diastereomers with respect to the methyl and/or hydroxy group(s), therefore, **8** was transformed to the endo-olefin (**9**) *via* a two-step sequence of reactions involving mesylation and elimination. Since compound (**9**) consists of a pair of

Scheme 2. Preparation of the optically active **8** by the asymmetric Michael reaction

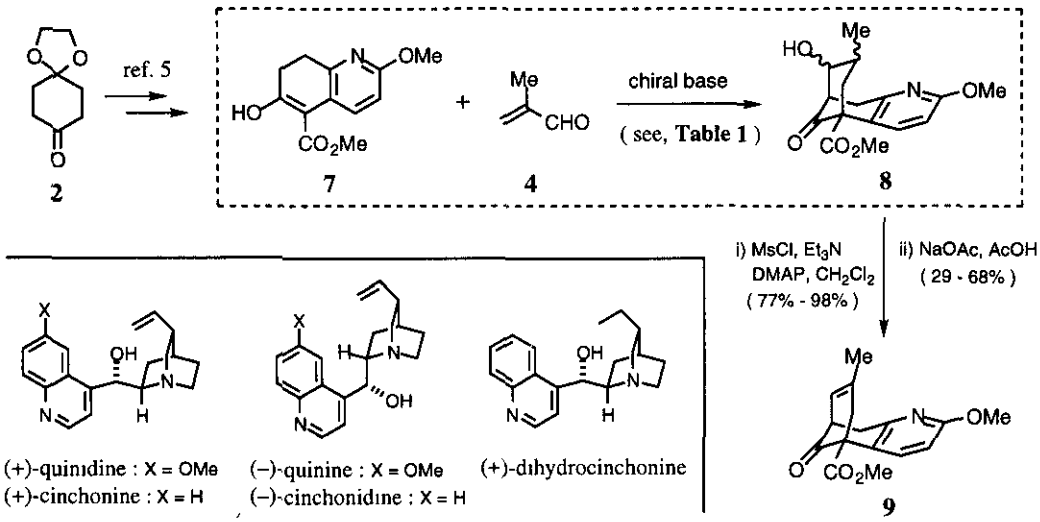


Table 1. Asymmetric Michael reaction of **7** with **4** promoted by *Cinchona* alkaloids

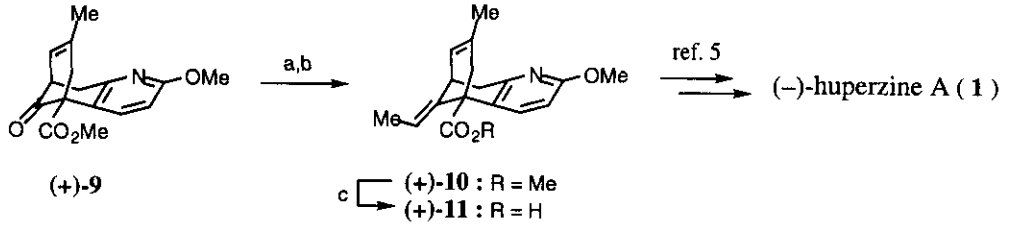
entry	chiral base [a]	temperature	time (h)	yield of **8** (%) [b]	major enantiomer [c]	ee (%) [d]
1	(+)-quinidine	20 °C	43	100	(–)-**9**	31
2	(–)-quinine	20 °C	36	98	(+)-**9**	37
3	(+)-dihydrocinchonine	20 °C	88	62	(–)-**9**	55
4	(+)-cinchonine	20 °C	115	89	(–)-**9**	55
5	(+)-cinchonine	-16 °C	384	45	(–)-**9**	61
6	(–)-cinchonidine	20 °C	86	76	(+)-**9**	59
7 [e]	(–)-cinchonidine	-10 °C	253	43	(+)-**9**	64

a) The reaction was performed with *Cinchona* alkaloid (1 equiv) and methacrolein (**4**) (10 equiv) in dichloromethane.
b) Isolation yield of **8** obtained as a mixture of diastereomers after the tandem Michael/aldol reaction.
c) The preferentially formed enantiomer derived from the product of the tandem Michael/aldol reaction by sequential mesylation and elimination.
d) The enantiomeric excess of (–)- or (+)-**9** was determined by HPLC analysis using a chiral column.[11]
e) This reaction was performed in dichloromethane-toluene (1 : 1).

enantiomers, its enantiomeric excess was determined at this stage by HPLC analysis using a chiral column.[11]

The results summarized in **Table 1** deserve some comment. In the presence of (+)-quinidine or (–)-quinine, the asymmetric Michael reaction proceeded in an excellent chemical yield (100% or 98%) with moderate enantioselectivity (31% or 37% ee) (entries 1 and 2). Employing (+)-dihydrocinchonine or (+)-cinchonine as a chiral base, the reaction gave **8** in a good chemical yield (62% or 89%) with 55% ee (for both the reactions) (entries 3 and 4). The enantiomer of (+)-cinchonine is not commercially available, however, the use of (–)-cinchonidine provided **8** in 76% yield with 59% ee (entry 6). To improve the enantioselectivity, we further examined some conditions.[12] Finally, enhancement of the enantioselectivity was observed when the reaction was carried out at lower temperature, providing the highest enantiomeric excess (64% ee) of (+)-**9** at -10°C[13,14] although the chemical yield is not optimized yet (entry 7). Enantiomeric (–)-**9** was similary prepared in 61% ee by employing (+)-cinchonine (entry 5). The *Cinchona* alkaloids used as chiral catalysts can be recovered by concentration and subsequent filtration. It is worthy to note that enantiomerically pure (+)-**9** (>99% ee), mp 140-141°C and $[\alpha]_D^{20}$ +69.9° (c 1.37, $CHCl_3$), was readily obtained by recrystallization of the partially optically active (+)-**9** from hexane.

Scheme 3. Synthesis of natural (–)-huperzine A (**1**) from the key intermediate ((+)-**9**)



Reagents and conditions: a) $Ph_3P^+EtBr^-$, *n*-BuLi, THF, 0 °C, 93% b) PhSH, AIBN, toluene, 85 °C, 95% c) aq NaOH. THF-MeOH (2:1), reflux, 64%

The absolute configuration of (+)-**9** was determined by its conversion to natural (–)-huperzine A (**1**) as shown in **Scheme 3**.[5] Since racemic version of **9** is an intermediate in Kozikowski's synthesis of (±)-**1**, the conversion was carried out according to his protocol.[5] Thus, Wittig reaction of (+)-**9** (>99% ee) with ethylidenetriphenylphosphorane and subsequent isomerization of the ethylidene moiety furnished the desired (*E*)-ester ((+)-**10**), mp 146-147 °C and $[\alpha]_D^{20}$ +45.0° (c 0.80, $CHCl_3$), in 88% yield for the two steps. Hydrolysis of (+)-**10** gave the corresponding carboxylic acid ((+)-**11**), $[\alpha]_D^{20}$ +42.8° (c 1.01, $CHCl_3$) [lit.,[6] $[\alpha]_D^{25}$ +40.9° ($CHCl_3$)] in 64% yield, whose spectral properties (IR, ^{1}H-NMR, MS) were identical with those reported in the literature.[5] Finally, Curtius rearrangement of (+)-**11** followed by deprotection provided natural (–)-**1**, mp 229-230 °C [lit.,[6] mp 230 °C] and $[\alpha]_D^{20}$ -149° (c 1.78, $CHCl_3$) [lit.,[6] $[\alpha]_D^{20}$ -150° ($CHCl_3$)]. Further studies to explore more efficient asymmetric synthesis of the key tricyclic intermediate ((+)-**9**) are now in progress in our laboratories.

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1. Visiting scientist from Exploratory Chemistry Research Laboratory, Sankyo Co., Ltd.
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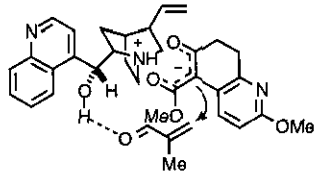
10. The representative enantiomeric excesses observed for the reactions employing other chiral amines in dichloromethane at 20 °C were as follows: *N*-methylephedrine (12% ee), (*S*)-(+)-1-(2-pyrrolidinyl-methyl)pyrrolidine (14% ee), (*R*)-(+)-2-methoxymethylpyrrolidine (17% ee), (*R*)-α-phenylethylamine (43% ee).
11. 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).
12. Neither sonification nor decrease of the amount of catalyst (20 mol%) affects the enantiomeric excess.
13. The asymmetric Michael reaction did not proceed below -20°C.
14. It is presently quite obscure what kind of roles the catalyst plays in the reaction. However, taking into account the ion-pairing mechanism reported for the similar asymmetric reactions,[15] the transition state model shown below may be postulated based on the observed enantiomeric excess and absolute configuration of the products.



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