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Synthetic Studies of Huperzine A and Its Fluorinated Analogues. 1. Novel Asymmetric Syntheses of an Enantiomeric Pair of Huperzine A[1]

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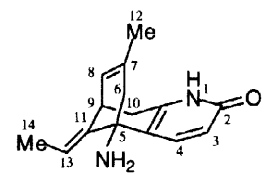
Abstract: *Syntheses of an enantiomeric pair of huperzine A were accomplished by employing two types of methods which feature the tandem Cinchona alkaloids-promoted asymmetric Michael addition / aldol reaction of the β-keto ester 3 with methacrolein (4) (max. 64% ee, 3+4→5, **Scheme 2**) and the asymmetric bicycloannulation of 3 with 2-methylene-1,3-propanediol diacetate (7) catalyzed by palladium catalysts carrying chiral ferrocenylphosphine ligands (max. 64% ee, 3+7→8, **Scheme 3**) as the key steps. Recrystallization of the partially optically active tricycles (+)- and (–)-6 derived from the products of the asymmetric reactions, readily provided the corresponding optically pure samples (both >99% ee). According to the reported method, the total synthesis of an enantiomeric pair of 1 [(–)- and (+)-1] was completed starting with optically pure (+)- and (–)-6 (**Scheme 4**).*

Introduction

(–)-Huperzine A [(–)-**1**] isolated from *Huperzia Serrata* (Thunb.) Trev.=*Lycopodium serratum* Thunb., Chinese folk medicine, has been shown to be a potent reversible acetylcholinesterase (AChE) inhibitor.[4,5] Since the use of (–)-**1** can increase the level of the neurotransmitter acetylcholine in the central nervous system, this natural product is anticipated to hold promise in the treatments of Alzheimer's disease,[4,5] and is currently under clinical trials.[5,6]

Figure 1. Structure of (–)-huperzine A



(–)-huperzine A [(–)-**1**]

Due to some difficulties associated with obtaining a large quantity of (–)-**1** from plants,[4] considerable attention has hitherto been focused on its total synthesis.[7] As shown in **Scheme 1**, Kozikowski *et al.* accomplished the first total synthesis of racemic **1** by the method employing the tandem Michael addition / aldol reaction of the β-keto ester **3** with methacrolein (**4**) as the key step to construct the 5,9-methanocycloocta[*b*]-pyridine system characterizing the tricyclic structure of (–)-**1** (*route a*).[8] Independently, Qian *et al.*[9] explored the synthetic pathway to racemic **1** which is almost the same as that reported by Kozikowski *et al.*[8] (*route a*). In 1993, it was disclosed by Kozikowski *et al.* that the characteristic 5,9-methanocycloocta[*b*]pyridine system can be constructed more effectively by employing the palladium-catalyzed bicycloannulation of **3** with 2-methylene-1,3-propanediol diacetate (**7**) (*route b*).[10] Furthermore, the enantioselective synthesis of (–)-**1** was also achieved by Kozikowski *et al.* by performing the *route a* by the use of the β-keto ester carrying a chiral

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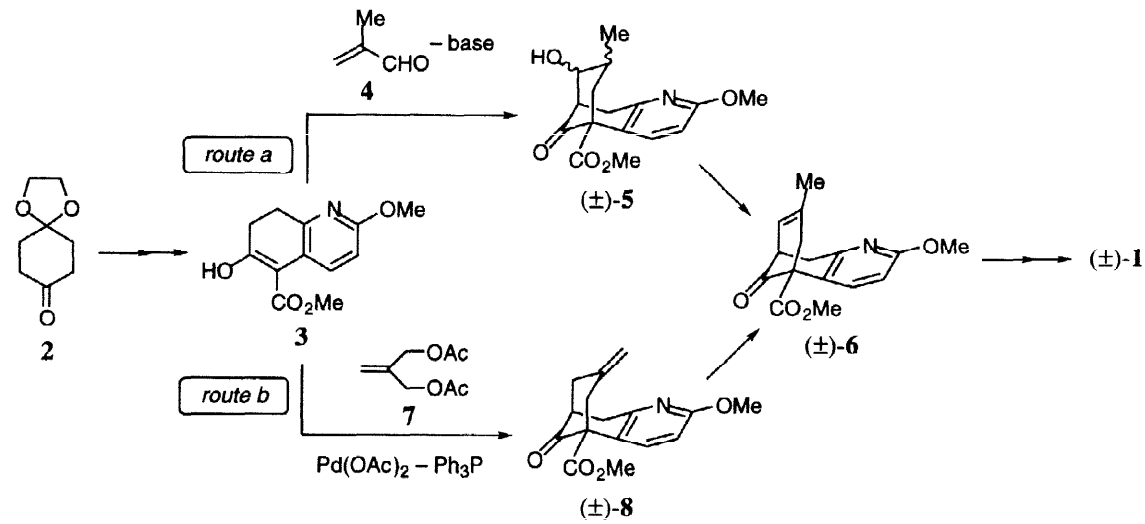
Scheme 1. Synthetic routes to racemic huperzine A [(±)-**1**] reported by Kozikowski *et al.* (*route a* and *route b*) and Qian *et al.* (*route a*)



8-phenylmenthyl group in place of achiral **3**.[11] These studies definitely uncovered that natural (–)-**1** exhibits 33-fold more potent inhibitory activity against AChE than unnatural (+)-**1**.[11] However, this enantioselective synthesis of (–)-**1** seems to lack practicality due to the facts that a stoichiometric amount of expensive (–)-8-phenylmenthol is necessary as a chiral auxiliary and that introduction of the chiral source and its subsequent removal require a multi-step operation.[11]

In order to obtain a large quantity of optically pure (–)-**1** and its therapeutically useful analogues,[5,8,10,12,13] a novel enantioselective synthetic method was sought which is more efficient and practical than that reported by Kozikowski *et al.*[11] We have now found that some chiral amines exemplified by *Cinchona* alkaloids promote the tandem asymmetric Michael addition / aldol reaction of **3** with **4** in a good enantioselectivity (max. 64% ee)[1a] and that the palladium catalysts bearing chiral ferrocenylphosphine ligands effectively undergo the asymmetric bicycloannulation of **3** with **7** (max. 64% ee).[1b] Recrystallization of the partially optically active tricycles (+)- and (–)-**6** derived from the products of the asymmetric syntheses [**5** and *ent*-**5**, and (+)- and (–)-**8**], readily provided the corresponding optically pure samples (both >99% ee) which are usable for preparing optically pure (–)- and (+)-**1** as well as their analogues.

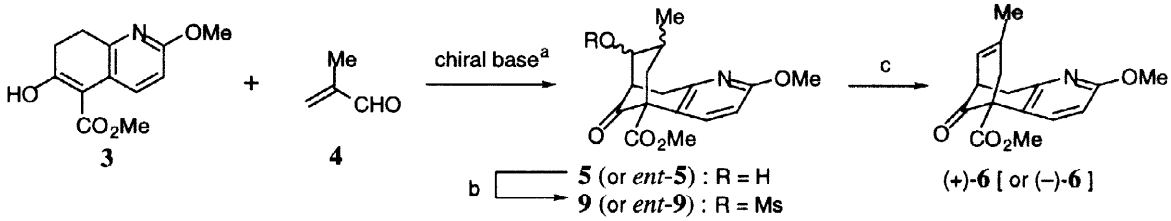
This paper details our two types of novel asymmetric syntheses of both enantiomers of huperzine A [(–)- and (+)-**1**]. The syntheses were accomplished by applying chiral amines and chiral palladium catalysts to the synthetic pathways to racemic **1** (*routes a* and *b*) previously explored.[1,14,15]

Results and Discussion

1. Synthesis of the optically pure tricycles (+)- and (–)-6 by the tandem asymmetric Michael addition / aldol reaction

A catalytic asymmetric Michael addition reaction remains as a field to be explored even though there have been reported several examples which meet with success to some extents.[16] 1,1,3,3-Tetramethylguanidine (TMG) was used as a base catalyst to promote the tandem Michael addition / aldol reaction of **3** with **4** in the first synthesis of racemic **1**,[11] therefore, the same reaction was examined by employing various types of the chiral bases (*R*)-**10**~**22** summarized in **Figure 2** in place of TMG (**Scheme 2**). Since the product **5** was found to usually consist of a mixture of the diastereomers with respect to the methyl and/or hydroxyl group(s), it

Scheme 2. Preparation of the optically active tricycles (+)- or (–)-**6** *via* the tandem asymmetric Michael addition / aldol reaction of the β-keto ester **3** with methacrolein (**4**)



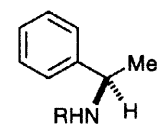
[a] For the chiral bases, see **Figure 2** and **3**. The reaction was carried out using **3** (1 equiv) and **4** (10 equiv) in the presence of a chiral base (1 equiv) shown in **Figure 2** in dichloromethane (20 ml for 1.1 mmol of **3**). The reaction was continued until **3** disappeared (13~233 h). The reactions utilizing *Cinchona* alkaloids shown in **Figure 3** were carried out under the conditions described in footnote a) in**Table 1**.

[b] MsCl (5 equiv)–Et_3N (10 equiv)–DMAP(1 equiv) in dichloromethane, rt, 2h, 62-100%. For the detailed conditions, see the experimentat part. In the cases where *Cinchona* alkaloids shown in **Figure 2** were used, the chemical yields of **9** and *ent*-**9** were summarized in **Table 1**.

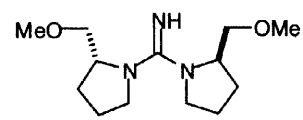
[c] AcONa (1.3 equiv) in AcOH, 120°C, 24 h, 18-54%. For the detailed conditions, see the experimental part. In the cases where *Cinchona* alkaloids shown in **Figure 2** were used, the chemical yields of (+)- and (–)-**6** were summarized in **Table 1**. The enantiomeric excesses (ee's) of (+)- and (–)-**6** were estimated by HPLC analysis using a chiral column as described in the experimental part.

was directly converted to (+)- or (–)-**6** by mesylation followed by elimination according to the reported method.[8] The enantiomeric excess (ee) of the preferentially formed **6** was determined by HPLC analysis using a chiral column (see the experimental part) and the absolute configuration of **6** was confirmed by the successful synthesis of natural (–)-**1** from (+)-**6** (*vide infra*). The chemical yields of **5**, **9**, and (+)- or (–)-**6** were found to be highly erratic and ranged in 19-100%, 62-100%, and 18-54%, respectively. As shown in **Figure 2**, the ee's of (+)- or (–)-**6** were usually less than 20% except for the case using (*R*)-**10** (43% ee). However, it appeared

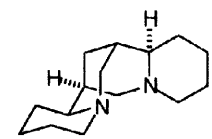
Figure 2. Structures of chiral amines used for the tandem asymmetric Michael addition / aldol reaction[a,b]



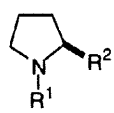
(*R*)-**10**: R = H (43% ee, 19%)
(*R*)-**11**: R = Me (0.3% ee, 98%)



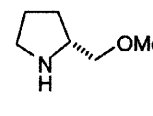
(*R*)-**12**[17]: (8% ee, 90%)



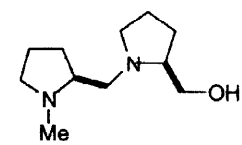
13 : sparteine (3% ee, 89%)



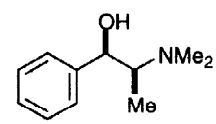
(*S*)-**14** : R^1 = H, R^2 = CO_2H (no reaction)
(*S*)-**15** : R^1 = H, R^2 = CO_2Me (complex mixture)
(*S*)-**16** : R^1 = H, R^2 = CH_2OH (3% ee, 61%)
(*S*)-**17** : R^1 = Me, R^2 = CH_2OH (2% ee, 100%)
(*S*)-**18** : R^1 = H, R^2 = CH_2N (14% ee, 75%)
(*S*)-**19** : R^1 = H, R^2 = $CH_2OTBDMS$ (5% ee, 51%)



(*S*)-**20** [17% ee, 88%]



(*S, S*)-**21** [14% ee, 75%]

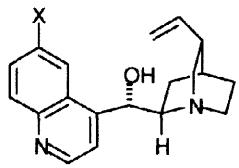


22 : *N*-methylephedrine [12% ee, 69%]

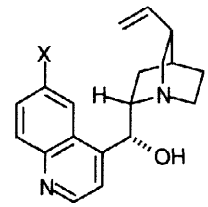
[a] The numbers in parentheses show enantiomeric excess (% ee) estimated at the stage of the bridged tricycle (+)- or (–)-**6** and chemical yield (%) of **5**.

[b] The bridged tricycle (–)-**6** was obtained from *ent*-**5** when **13** or (*S*)-**20** was used as a chiral base. (+)-**6** was produced by way of **9** as a major enantiomer in other cases.

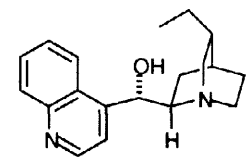
Figure 3. Structures of *Cinchona* alkaloids used for the tandem asymmetric Michael addition / aldol reaction.



23 : X = OMe [(+)-quinidine]
26 : X = H [(+)-cinchonine]



24 : X = OMe [(–)-quinine]
27 : X = H [(–)-cinchonidine]



25 : (+)-dihydrocinchonine

Table 1. Tandem asymmetric Michael addition / aldol reaction promoted by *Cinchona* alkaloids[a]

Entry	Chiral base	Temp (°C)	Time (h)	Yield of **5**[b] (%)	Yield of **9**[c] (%)	Yield of **6**[d] (%)	Major enant.[e]	ee (%)[f]
1	**23**	20	43	100	86	48	(–)-**6**	31
2	**24**	20	36	98	92	56	(+)-**6**	37
3	**25**	20	88	62	79	67	(–)-**6**	55
4	**26**	20	115	89	93	19	(–)-**6**	55
5	**26**	-16	384	43	97	29	(–)-**6**	61
6	**27**	20	86	76	96	68	(+)-**6**	59
7[g]	**27**	-10	253	45	77	60	(+)-**6**	64

[a] The reaction was performed with **3** (1 equiv), **4** (10 equiv), and *Cinchona* alkaloid (1equiv) in dichloromethane (20 ml for 1 mmol of **3**).
[b] Isolation yield of **5** obtained as a mixture of the diastereomers after the tandem Michael addition / aldol reaction.
[c] Isolation yield of **9** obtained as a mixture of the diastereomers. For the detailed reaction conditions, see the footnote b) in **Scheme 2** and the experimental part.
[d] Isolation yield of (+)- or (–)-**6**. For the detailed reaction conditions, see the footnote c) in **Scheme 2** and the experimental part.
[e] The perferentially formed enantiomer.
[f] The enantiomeric excess of (–)- or (+)-**6** was determined by HPLC analysis using a chiral column.
[g] The reaction was carried out in dichloromethane-toluene (1:1).

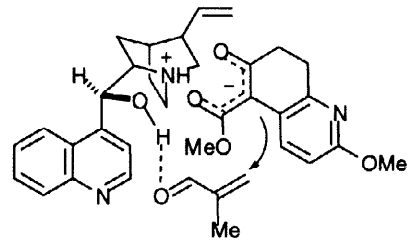
that (*R*)-**10** gives the low chemical yields for **5** (19%) and **9** (18%).

With these numerous unsuccessful results in hand, we next examined the tandem asymmetric Michael addition / aldol reaction in the presence of commercially available *Cinchona* alkaloids, (+)-quinidine (**23**), (–)-quinine (**24**), (+)-dihydrocinchonine (**25**), (+)-cinchonine (**26**), and (–)-cinchonidine (**27**), as depicted in **Figure 3**. This is because these *Cinchona* alkaloids were reported to effectively induce an asymmetric Michael addition reaction when a β-keto ester is used as a Michael acceptor.[18] Thus, as shown in **Scheme 2** and **Table 1**, the tandem reaction was found to smoothly take place in the presence of **23**-**27**, giving rise to **5**. Since **5** was a mixture of the diastereomers (*vide supra*), it was transformed to (+)- or (–)-**6** by way of **9** or *ent*-**9** similarly to the cases shown in **Figure 2**. The enantiomeric excess was also determined at this stage.

The results summarized in **Table 1** deserve some comments. In the presence of **23** or **24**, the tandem reaction occurred in an excellent chemical yield (100% or 98%) with moderate enantioselectivity (31% or 37% ee) (entries 1 and 2). Employing **25** or **26** as a chiral base, the reaction provided *ent*-**5** in a good chemical yield (62% or 89%) with 55% ee (for both the reactions) (entries 3 and 4). The use of **27** afforded **5** in 76% yield with 59% ee (entry 6). In order to improve the enantioselectivity, some modifications were further attempted on

the reaction conditions. Finally, increase of the enantioselectivity was observed when the reaction was performed at lower temperature (-10 °C) in the presence of **27**, providing the highest ee (64% ee) of **5** in 45% yield (entry 7). Enantiomeric **5** (*ent*-**5**) (61% ee) was similarly prepared in 43% yield by employing **26** as a chiral catalyst (entry 5). The chemical yields of **5** or *ent*-**5** and (+)- or (–)-**6** were found to range in 43-100% and in 19-68%, respectively, similarly to the cases shown in **Figure 2**. The reason why these chemical yields are so erratic, is quite obscure, but probably depends upon the formation ratio of four possible diastereomers. It is also quite ambiguous what kind of roles the catalyst plays in the reaction. However, taking into account of the *ion-pairing mechanism* reported for the similar asymmetric reactions,[19] the transition state model shown in **Figure 4** may be postulated for the reaction promoted by **27** based on the observed ee and the absolute configuration of (+)-**6**.

Figure 4. A plausible transition state model of the asymmetric Michael addition reaction promoted by (–)-cinchonidine (**27**)



Recrystallization of partially optically active (+)- and (–)-**6** from hexane readily gave the corresponding optically pure samples (both >99% ee), from which both enantiomers of huperzine A [(–)- and (+)-**1**] were prepared according to the procedure reported by Kozikowski *et al.* for the synthesis of racemic **1** (*vide infra*).[8] These results definitely established the absolute configurations of (+)- and (–)-**6**.

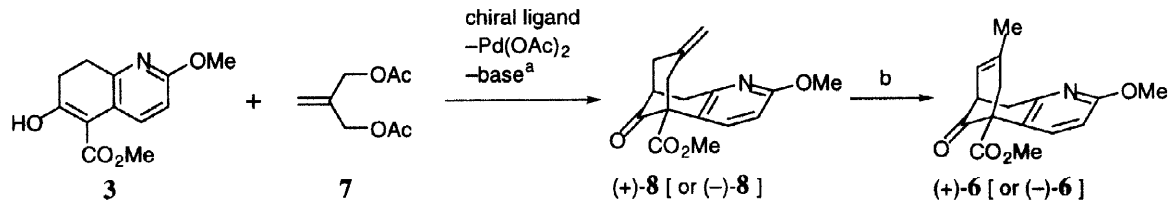
As mentioned above, we have succeeded in exploring the asymmetric Michael addition of the β-keto ester **3** with methacrolein (**4**) promoted by *Cinchona* alkaloids. Although we obtained the good ee's (max. 64% ee), the total chemical yield from **3** to the tricycle (+)-**6** [or (–)-**6**] by way of the alcohol **5** (or *ent*-**5**) and the mesylate **9** (or *ent*-**9**) was uncovered to be fairly low. Accordingly, our next attention was focused on the asymmetric bicycloannulation of **3** with 2-methylene-1,3-propanediol diacetate (**7**) in the presence of a palladium catalyst carrying a chiral ligand. This is the subject of the next section.

2. Synthesis of the optically active tricycles (+)- and (–)-6 by the asymmetric palladium-catalyzed bicycloannulation

Having the results delineated in section **1**, we next attempted the bicycloannulation of the β-keto ester **3** with 2-methylene-1,3-propanediol diacetate (**7**) in the presence of a palladium catalyst carrying a chiral ligand shown in **Scheme 3**.[10] To the best of our knowledge, enantioselective construction of (+)- or (–)-**6** by the palladium-catalyzed bicycloannulation have not been reported to date.[15,20]

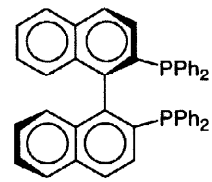
At first, we examined the bicycloannulation by using various types of the bisphosphines, (*R*)-BINAP (**28**), (*S*,*S*)-BPPM (**29**), (*R*,*R*)-DIPAMP (**30**), **31**,[20] and **32**,[20] as chiral ligands for palladium. All the reactions were carried out in 1,4-dioxane in the presence of TMG. As shown in **Figure 5**, **28**-**30** were found to give the methylene tricycle (+)- or (–)-**8** with 12-24% ee in 53-68% yield. However, no bicycloannulation occurred with **31** and **32**.[21] The enantiomeric excess (ee) and the absolute configuration of the preferentially formed **8** were determined by HPLC using a chiral column and by successful respective conversion of (+)- and (–)-**8** to (+)- and (–)-**6** (*vide infra*).

Scheme 3. Preparation of the optically active tricycle (+)- or (–)-**6** *via* the asymmetric palladium-catalyzed bicycloannulation of the β-keto ester **3** with the diacetate **7**

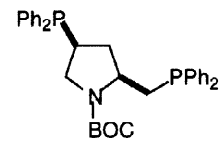


[a] For the chiral ligands, see **Figure 5** and **6**. The reaction was carried out using **3** (1 equiv), **7** (1 equiv), and chiral ligand (0.8 equiv), $Pd(OAc)_2$ (0.4 equiv), and base (1 equiv) in a solvent (20 ml for 1.1 mmol of **3**). The reaction was continued until **3** disappeared. The reactions utilizing the ferrocenylphosphine ligands shown in **Figure 6** were carried out under the conditions described in footnote a) in **Table 2** and **3**. The enantiomeric excess (ee) of (+)-**8** [or (–)-**8**] was estimated by HPLC analysis using a chiral column as described in the experimental part.
[b] TfOH (1.4 equiv) in 1,4-dioxane, 95°C, 6 h. For the detailed conditions, see the experimental part.

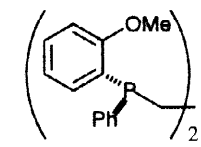
Figure 5. Structure of the chiral ligands used for the asymmetric palladium-catalyzed bicycloannulation[a]



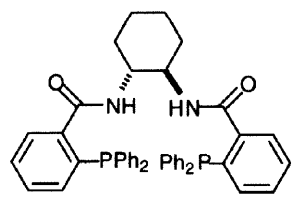
28 [(*R*)-BINAP]
[(+)-**8** : 12% ee, 53%]



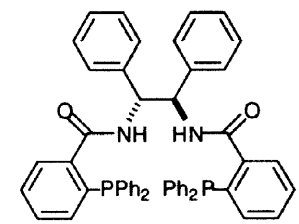
29 [(*S*,*S*)-BPPM]
[(–)-**8** : 24% ee, 68%]



30 [(*R*,*R*)-DIPAMP]
[(+)-**8** : 12% ee, 64%]



31 (no reaction)

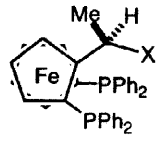


32 (no reaction)

[a] The numbers in parentheses show enantiomeric excess (% ee) and chemical yield (%) of the methylene tricycle (+)- or (–)-**8**.

Recently, Hayashi *et al.* developed the chiral ferrocenylphosphine (*R*)-(*S*)-**33** possessing a hydroxyl group at the end of the pendant chain (see, **Figure 6**).[22] This ligand [(*R*)-(*S*)-**33**] was found to give high levels of ee (max. 82% ee) in the asymmetric palladium-catalyzed allylation where a new chiral center is created in the nucleophile side and not in the allylic substrate side.[22,23] Based on this information, we next investigated the asymmetric palladium-catalyzed bicycloannulation of **3** with **7** in 1,4-dioxane in the presence of TMG by employing (*R*)-(*S*)-**33**[20a] as a chiral ligand. As shown in **Scheme 3** and **Table 2**, (+)-**8** with 39% ee was found to be produced in 85% yield (entry 1). In order to improve the ee of (+)-**8**, effects of bases and solvents were studied. These results were also summarized in **Table 2**. In terms of ee, chemical yield, and reaction time, the best conditions were disclosed to be using TMG as a base and 1,4-dioxane, 1,2-dimethyoxyethane (DME), or toluene as a solvent (entries 1, 2 and 4). In diethyl ether (Et_2O), the enantioselectivity was not largely affected, while the rate of reaction decreased (entry 3). Although the highest ee was observed in tetrahydrofuran (THF), the yield was not satisfactory (entry 5). Uses of other standard bases gave similar levels of ee to those obtained with TMG, however, the yields of (+)-**8** were obviously reduced in these cases (entries 11-14).

Figure 6. Structures of the chiral ferrocenylphosphine ligands used for the asymmetric palladium-catalyzed bicycloannulation



(R)-(S)-**33** : X = $NMe(CH_2)_2OH$ *(R)-(S)*-**36** : X = $NMe(CH_2)_3OH$
(R)-(S)-**34** : X = NMe_2 *(R)-(S)*-**37** : X = $NMe(CH_2)_4OH$
(R)-(S)-**35** : X = $N(CH_2CH_2OH)_2$ *(R)-(S)*-**38** : X = $NMe(CH_2)_5OH$

Table 2. Asymmetric palladium-catalyzed bicycloannulation carried out using the chiral ferrocenylphosphine ligand *(R)*-*(S)*-**33**[a]

Entry	Solvent	Base	Time (h)[b]	Yield (%) of (+)-**8**[c]	ee (%) of (+)-**8**[d]
1	1,4-dioxane	TMG[e]	12	85	39
2	DME	TMG	13	90	38
3	Et_2O	TMG	72	93	41
4	toluene	TMG	12	83	42
5	THF	TMG	24	39	47
6	DMSO	TMG	14	81	22
7	$MeNO_2$	TMG	14	32	27
8	CH_2Cl_2	TMG	13	90	29
9	DMF	TMG	10	75	30
10	MeCN	TMG	9	58	31
11	1,4-dioxane	DBU[f]	13	76	41
12	1,4-dioxane	2,6-di-^{t}Bu-Py[g]	12	70	39
13	1,4-dioxane	KF	48	64	40
14	1,4-dioxane	$KN(TMS)_2$	10	58	37

[a] The reaction was performed with **3** (1 equiv) and **7** (1 equiv) in the presence of $Pd(OAc)_2$ (0.2 equiv) and *(R)*-*(S)*-**33** (0.4 equiv) in a solvent (25 ml for 1.0 mmol of **3**) at room temperature under argon.
[b] The reaction was continued until **3** disappeared.
[c] Isolation yield after separation by column chromatography on silica gel.
[d] The enantiomeric excess of (+)-**8** was determined by HPLC analysis using a chiral column. See the experimental part.
[e] 1,1,3,3-Tetramethylguanidine.
[f] 1,8-Diazabicyclo[5,3,0]undec-7-ene.
[g] 2,6-Di-*tert*-butylpyridine.

In order to obtain even higher enantioselectivity, we next pursued the asymmetric palladium-catalyzed bicycloannulation using various ferrocenylphosphine ligands *(R)*-*(S)*-**34**~*(R)*-*(S)*-**38** carrying appropriate linker chains pictured in **Figure 6**. This is because the length of linker chain between the hydroxyl group and the ferrocenyl moiety is thought to play an important role in respect of the enantioselectivity. The ligand *(R)*-*(S)*-**34** is commercially available and *(R)*-*(S)*-**35** is reported in the literature.[22a,b] The new ligands *(R)*-*(S)*-**36**~*(R)*-*(S)*-**38** were readily prepared according to the reported procedure.[22a,b] All the reactions were carried out under the conditions optimized with *(R)*-*(S)*-**33**. The results summarized in **Table 3** disclosed that the most effective ligand is *(R)*-*(S)*-**37** (entries 7 and 8), and that lowering temperature improved the ee of (+)-**8** (entries 1, 2, 5, 6, 7, and 8). The best result was obtained when the reaction was performed at -30 °C followed by gradual warming to 15 °C in DME, affording the enantioselectivity of 64% ee in 92% yield (entry 8). When the enantiomeric ligand *(S)*-*(R)*-**37** was used, (–)-**8** with 63% ee could be also produced in 91% yield (entry 10). It

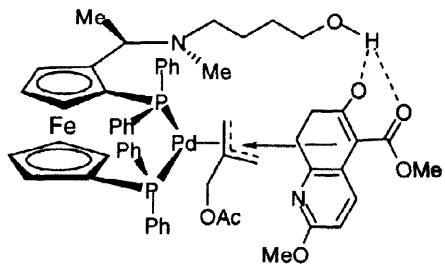
Table 3. Asymmetric palladium-catalyzed bicycloannulation carried out using various types of chiral ferrocenylphosphine ligands (*R*)-(*S*)-**33**~(*R*)-(*S*)-**38** and (*S*)-(*R*)-**37**[a]

Entry	Ligand	Temp (°C)	Reac.Time (h)	Yield (%) of (+)-**8**[b]	Ee (%) of (+)-**8**[c]
1	(*R*)-(*S*)-**33**	rt	12	85	39
2[d]	(*R*)-(*S*)-**33**	-30 °C → 15 °C	5	75	48
3	(*R*)-(*S*)-**34**	rt	8	84	24
4	(*R*)-(*S*)-**35**	rt	13	73	33
5	(*R*)-(*S*)-**36**	rt	8	91	43
6[d]	(*R*)-(*S*)-**36**	-30 °C → 15 °C	6	81	54
7	(*R*)-(*S*)-**37**	rt	7	98	47
8[d]	(*R*)-(*S*)-**37**	-30 °C → 15 °C	6	92	64
9	(*R*)-(*S*)-**38**	rt	7	63	35
10[d]	(*S*)-(*R*)-**37**	-30 °C → 15 °C	6	91[e]	63[e]

[a] The reaction was carried out with **3** (1 equiv) and **7** (1 equiv) in the presence of $Pd(OAc)_2$ (0.2 equiv), a chiral ligand (0.4 equiv), and 1,1,3,3-tetramethylguanidine (TMG) (2.2 equiv) in 1,4-dioxane (25 ml for 1 mmol of **3**) (except for entries 2, 6, 8, and 10) at a given temperature under argon.
[b] Isolated yield after separation by column chromatography on silica gel.
[c] The enantiomeric excess of (+)-**8** was determined by HPLC analysis using a chiral column.
[d] See the experimental section.
[d] 1,2-Dimethoxyethane (DME) was used as a solvent instead of 1,4-dioxane.
[e] The preferentially formed enantiomer was (–)-**8**.

is noteworthy that the observed ee is one of the best results reported so far for the asymmetric palladium-catalyzed allylation of β-keto esters.[22,23] It is of interest, among the ligands having methylene groups in the pendant chains, (*R*)-(*S*)-**37** carrying a four methylene group gives the best ee. The enantioselectivity observed for this asymmetric bicycloannulation may be explained by a concept of *secondary ligand-substrate interaction* involving hydrogen bonding between the terminal hydroxyl group of the pendant chain and the attacking nucleophile as postulated in **Figure 7**.[22] This explanation might agree well with the observation that (*R*)-(*S*)-**37** affords the best result.

Figure 7. A plausible transition state of the asymmetric palladium-catalyzed allylic alkylation using (*R*)-(*S*)-**37** as a chiral ligand

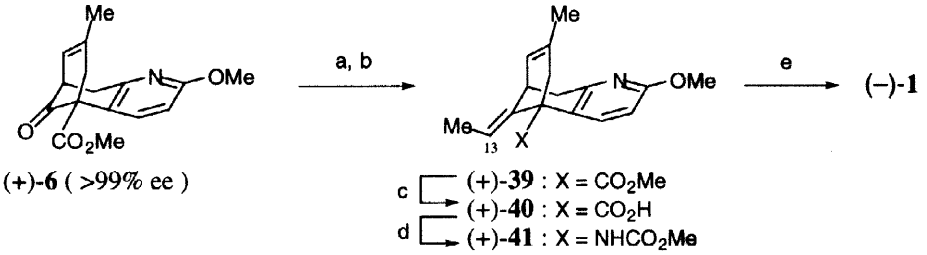


Compounds (+)- and (–)-**8** (64% and 63% ee) were converted to the tricycles (+)- and (–)-**6** by acid-catalyzed isomerization of the exo-methylene moiety with trifluoromethane sulfonic acid according to the reported procedure.[10] Similarly to the cases described in section **1**, recrystallization of partially optically active (+)- and (–)-**6** from hexane gave rise to optically pure samples of (+)- and (–)-**6** (both >99% ee), respectively. These results also unambiguously established the absolute configurations of (+)- and (–)-**8**.

3. Synthesis of natural (–)- and unnatural (+)-huperzine A [(–)- and (+)-1] from the tricycles (+)- and (–)-6

With optically pure (+)- and (–)-**6** in hand, our next efforts were devoted to completion of the synthesis of both enantiomers of huperzine A [(–)- and (+)-**1**]. Since racemic version of **6** is an intermediate in Kozikowski's synthesis of (±)-**1**, the conversion was carried out according to his protocol. Thus, as shown in **Scheme 4**, Wittig reaction of (+)-**6** (>99% ee) with ethylidenetriphenylphosphorane and subsequent isomerization of the ethylidene moiety provided the desired (*E*)-ester (+)-**39** in 88% yield for the two steps. Alkaline hydrolysis of (+)-**39** afforded a 64% of the corresponding carboxylic acid (+)-**40**. Finally, modified Curtius rearrangement of (+)-**40** following the protocol reported by Shioiri *et al.*[24] (66%) and subsequent deprotection (81%) furnished natural (–)-**1**. Unnatural (+)-**1** was similarly prepared from (–)-**6**.

Scheme 4. Synthesis of natural (–)-huperzine A [(–)-**1**] from the bridged tricycle [(+)-**6**]



a) $Ph_3P^+EtBr^-$, BuLi, THF, 0 °C, 93% b) PhSH, AIBN, toluene, 85 °C, 95% c) aq NaOH, THF-MeOH (2:1), reflux, 64% d) $(PhO)_2P(O)N_3$, Et_3N, toluene, 85 °C ; MeOH, reflux, 66% e) TMSI, $CHCl_3$, reflux ; MeOH, reflux, 81%

Conclusion

We have succeeded in developing two types of novel asymmetric syntheses of an enantiomeric pair of huperzine A [(–)- and (+)-**1**]. The methods for the syntheses feature the tandem *Cinchona* alkaloids-promoted asymmetric Michael addition / aldol reaction of the β-keto ester **3** with methacrolein (**4**) and the asymmetric bicycloannulation of **3** with 2-methylene-1,3-propanediol diacetate (**7**) catalyzed by palladium catalysts with chiral ferrocenylphosphine ligands. Taking into account of chemical yield as well as operational simplicity, the latter method utilizing chiral palladium catalysts seems to be more efficient and practical. According to the protocol reported by Kozikowski *et al.*,[8] natural (–)- and unnatural (+)-**1** were synthesized from optically pure tricycles (+)- and (–)-**6** obtainable by the asymmetric syntheses followed by chemical manipulations and recrystallization. Since various types of huperzine A congeners are accessible not only from (+)- and (–)-**6** but also from (–)- and (+)-**1** themselves, our successful results are anticipated to pave the way to future drugs which hold promise for the treatments of Alzheimer's disease.

Experimental

General: All melting points were determined with a Yanaco MP-3 micro melting point apparatus and are uncorrected. Measurements of ^{1}H-NMR spectra were carried out using a Brucker AM-400 (400 MHz) and a Brucker AM-200 (200 MHz) spectrometer. The chemical shifts were expressed in ppm using tetramethylsilane (δ=0) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), broad (br). Infrared (IR) spectra were measured with a JASCO FT/IR-5300 Fourier transform spectrometer. Low resolution mass (EIMS) spectra were taken with a Hitachi RMU-6MG spectrometer, and high resolution mass (HREIMS) spectra were obtained on a Hitachi M-80A spectrometer. Routine monitoring of reactions was carried out using glass-supported Merck Silica gel 60 F254 TLC plates. Flash column chromatography was performed on Merck Silica gel 60 F254 (230-400 mesh) with an indicated solvent. Solvents and commercial reagents were dried and purified before use. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon. All the combined organic extracts were dried over anhyd. Na2SO4

and filtered before concentration *in vacuo* with a rotary evaporator. Following abbreviations are used for reagent and solvents: AcOH (acetic acid), AIBN [α,α-azobis(isobutyronitril)], $CHCl_3$ (chloroform), CH_2Cl_2 (dichloromethane), Et_2O (diethyl ether), DME (1,2-dimethoxyethane), DMAP (4-dimethylaminopyridine), EtOAc (ethyl acetate), C_6H_{14}(hexane), MeOH (methanol), NaOAc (sodium acetate), THF (tetrahydrofuran), TMG (1,1,3,3-tetramethylguanidine), C_6H_5Me (toluene), Et_3N (triethylamine), H_2O (water).

Methyl 7,8,9,10-tetrahydro-8-hydroxy-2-methoxy-7-methyl-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (5) (Table 1, entry 7)

Methacrolein (**4**) (88 μL, 1.0 mmol) and (–)-cinchonidine (**27**) (31.0 mg, 0.10 mmol) were added to a solution of the β-keto ester **3**[8] (25.0 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) and C_6H_{14} (1.0 mL) at -10 °C under argon, and the mixture was stirred at the same temperature for 253 h. After concentration *in vacuo*, the residue was purified by preparative thin layer chromatography (C_6H_{14}/EtOAc, 3:2) to give **5** as a colorless oil (14.6 mg, 45%). Since three sorts of proton signals were observed in the ^{1}H-NMR spectrum, **5** was found to at least consist of a mixture of three diastereomers in a ratio of 10:7:1. The ^{1}H-NMR spectrum of the major isomer is as follows: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.06 (1H, d, J=7.0 Hz, C4-H), 6.62 (1H, d, J=7.0 Hz, C3-H), 3.91 (3H, s, OCH_3), 3.81 (3H, s, CO_2CH_3), 3.90-3.60 (1H, m, C8-H), 3.47 (1H, dd, J=12.6, 6.7 Hz, C10-H), 3.16 (1H, d, J=12.6 Hz, C10-H), 2.95 (1H, dd, J=6.7, 2.6 Hz, C9-H), 2.20-1.60 (4H, m, OH, C6-H x 2, C7-H), 1.02 (3H, d, J=5.3 Hz, CH_3). The following signals in the ^{1}H-NMR spectrum were used for estimating the ratio of three diastereomers. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.02, 7.06, 7.10 (intensity ratio 1:10:7, all d, C4-H). This mixture was directly subjected to the next step.

Methyl 7,8,9,10-tetrahydro-8-mesyloxy-2-methoxy-7-methyl-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate (9) (Table 1, entry 7)

Triethylamine (70 μL, 0.50 mmol) and DMAP (5.0 mg, 41 μmol) and methanesulfonyl chloride (15 μL, 0.19 mmol) were added to a solution of **5** (14.6 mg, 48 μmol) in CH_2Cl_2 (1.5 mL) at 0 °C under argon. The mixture was stirred at room temperature for 2 h, poured into sat. NH_4Cl, then extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by preparative thin layer chromatography (C_6H_{14}/EtOAc, 3:2) to give **9** as a colorless oil (14.1 mg, 77%). The ^{1}H-NMR spectrum of the major isomer of **9** is as follows: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.08 (1H, d, J=7.0 Hz, C4-H), 6.66 (1H, d, J=7.0 Hz, C3-H), 5.10-5.00 (1H, m, C8-H), 3.92 (3H, s, OCH_3), 3.83 (3H, s, CO_2CH_3), 3.51 (1H, dd, J=14.4, 6.3 Hz, C10-H), 3.35-3.15 (1H, m, C9-H), 3.22 (1H, d, J=14.4 Hz, C10-H), 3.10 (3H, s, OSO_2CH_3), 2.20-1.85 (3H, m, C6-H x 2, C7-H), 1.06 (3H, d, J=5.3 Hz, CH_3).

(+)-(5*S*,9*R*)-Methyl 9,10-dihydro-2-methoxy-7-methyl-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate [(+)-6]

a) Preparation of (+)-**6** from **9** (**Table 1**, entry 7). A solution of **9** (14.1 mg, 37 μmol) and NaOAc (4.0 mg, 49 μmol) in AcOH (1.0 mL) was heated at 120 °C for 24 h. After concentration *in vacuo*, the residue was diluted with sat. $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by preparative thin layer chromatography (C_6H_{14}/EtOAc, 4:1) to give (+)-**6** as a colorless oil (6.3 mg, 60%, 64% ee). The ester (+)-**6** (99 mg) prepared in the same manner as described above was recrystallized several times from C_6H_{14}, affording optically pure (+)-**6** as colorless crystals (21 mg, >99% ee), mp 139.5-141.5 °C. $[\alpha]_D^{20}$ +69.9° (c 1.37, $CHCl_3$). The enantiomeric excess was determined by HPLC with a chiral column [DAICEL OD-H, C_6H_{14}/2-propanol, 20:1 as an eluent, flow rate 0.5 mL/min, detection UV (254nm), Rt: (–)-**6**: 13.2 min; (+)-**6**: 16.9 min]. IR (KBr): 2960, 1740, 1730, 1605, 1570, 1480, 1430, 1320, 1285, 1260, 1025, 830 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.11 (1H, d, J=8,6 Hz, C4-H), 6.62 (1H, d, J=8.6 Hz, C3-H), 5.46-5.40 (1H, m, C8-H), 3.92 (3H, s, OCH_3), 3.76 (3H, s, CO_2CH_3), 3.66-3.37 (1H, m, C6-H), 3.38 (1H, dd, J=17.4, 5.1 Hz, C10-H), 3.18 (1H, d, J=17.4, 1.9 Hz, C10-H), 3.18-3.12 (1H, m, C9-H), 2.54 (1H, d, J=17.5 Hz, C6-H), 1.62 (3H, s, CH_3). EIMS (m/z): 287 (M^+), 255. HREIMS (m/z): Calcd. for $C_{16}H_{17}NO_4$ (M^+): 287.1157. Found: 287.1183. Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.85; H, 5.90; N, 4.75.

b) Preparation of (+)-**6** from (+)-**8**. [Compound (+)-**8** was prepared by the asymmetric palladium-catalyzed bicycloannulation reaction (*vide infra*).] Trifluoromethanesulfonic acid (64 μL, 0.73 mmol) was added to a solution of (+)-**8** (148 mg, 0.52 mmol, 64% ee) in 1,4-dioxane (2.0 mL) at room temperature under argon, and the mixture was heated at 95 °C for 6 h. After concentration *in vacuo*, the residue was diluted with sat. $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine. Concentration *in vacuo* followed by purification by flash column chromatography (C_6H_{14}/EtOAc, 5:1) gave (+)-**6** as a colorless oil (128 mg, 86%, 64% ee). This sample was recrystallized from C_6H_{14} to give optically pure (+)-**6** as a colorless crystals (67.0 mg, >99% ee), mp 139-140 °C, $[\alpha]_D^{20}$ +67.8° (c 0.52, $CHCl_3$). The spectral data were shown in a). The enantiomeric excess was estimated in a similar manner to that described in a).

(–)-(5*R*,9*S*)-Methyl 9,10-dihydro-2-methoxy-7-methyl-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate [(–)-6]

a) Preparation of (–)-**6** from **3** by way of *ent*-**5** and *ent*-**9** (**Table 1**, entry 5). Methacrolein (**4**) (88 μL, 1.0 mmol) and **26** (31.0 mg, 0.10 mmol) were added to a solution of **3**[8] (25.0 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) at -16 °C under argon, and the mixture was stirred at the same temperature for 384 h. The same treatments of the reaction mixture as described for the preparation of **5** gave *ent*-**5** (a mixture of three diastereomers) as a colorless oil (14.0 mg, 43%) after purification by preparative thin layer chromatography (C_6H_{14}/EtOAc, 3:2). Triethylamine (64 μL, 0.46 mmol) and DMAP (5.0 mg, 41 μmol) and methanesulfonyl chloride (15 μL, 0.19

mmol) were added to a solution of *ent*-**5** (14.0 mg, 46 μmol) in CH_2Cl_2 (1.5 mL) at 0 °C under argon. After stirring at room temperature for 2 h, the reaction mixture was treated in the same manner as described for the preparation of **9**, affording *ent*-**9** as a colorless oil (17.1 mg, 97%) after purification by preparative thin layer chromatography (C_6H_{14}/EtOAc, 3:2). A solution of *ent*-**9** (17.1 mg, 45 μmol) and NaOAc (4.0 mg, 49 μmol) in AcOH (1.0 mL) was heated at 120 °C for 24 h. Treatments of the reaction mixture in a similar manner as described for the preparation of (+)-**6** gave (–)-**6** as a colorless oil (3.7 mg, 29%, 61% ee) after purification by preparative thin layer chromatography (C_6H_{14}/EtOAc, 4:1). The partially optically active ester (–)-**6** (46 mg, 61% ee) prepared in the same manner to that described above was recrystallized several times from C_6H_{14}, affording optically pure (–)-**6** as colorless crystals (9.0 mg, >99% ee), mp 140.5-141.5 °C, $[\alpha]_D^{20}$ -69.9° (c 1.25, $CHCl_3$). The enantiomeric excess was estimated in a similar manner to that described for the preparation of (+)-**6**. Spectral properties (IR, ^{1}H-NMR, MS) of this sample were identical to those of (+)-**6**.

b) Preparation of (–)-**6** from (–)-**8**. [Compound (–)-**8** was prepared by the asymmetric palladium-catalyzed bicycloannulation reaction (*vide infra*).] The same treatments of (–)-**8** (179 mg, 0.62 mmol, 63% ee) with trifluoromethanesulfonic acid (77 μL, 0.87 mmol) in 1,4-dioxane (2.0 mL) as described for the preparation of (+)-**6** from (+)-**8** gave (–)-**6** as a colorless oil (136 mg, 76%, 63% ee) after purification by flash column chromatography (C_6H_{14}/EtOAc, 4:1). This was recrystallized from C_6H_{14} to give (–)-**4** as colorless crystals (42.0 mg, >99% ee), mp 139-140 °C. $[\alpha]_D^{20}$ -68.9° (c 0.21, $CHCl_3$). The enantiomeric excess was estimated in a similar manner to that described for the preparation of (+)-**6**. This sample showed the same spectral properties as described for (+)-**6**.

(*R*)-*N*-Methyl-*N*-(3-hydroxypropyl)-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine [(*R*)-(*S*)-36]

A solution of (*R*)-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl acetate (100 mg, 0.16 mmol) and *N*-methyl-3-aminopropanol (107 mg, 1.2 mmol) in MeOH (5.0 mL) was heated at reflux for 7 h under argon. After concentration *in vacuo*, the mixture was diluted with EtOAc, and the ethyl acetate solution was washed with H_2O and brine. After concentration *in vacuo*, the residue was purified by column chromatography on alumina (EtOAc/EtOH, 50:1) to give (*R*)-(*S*)-**36** as an orange amorphous powder (40.0 mg, 38%), $[\alpha]_D^{20}$ -294° (c 1.40, $CHCl_3$). IR (KBr): 3400, 3060, 2950, 2800, 1595, 1480, 1440, 1270, 1250, 1170, 1050, 830, 740 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.55-7.42 (2H, m), 7.30-7.03 (8H, m), 4.40 (1H, m), 4.31 (1H, m), 4.13 (1H, m), 4.12 (1H, m), 4.06 (1H, m), 3.79 (1H, m), 3.74 (1H, m), 3.38 (1H, m), 3.28-3.05 (2H, m), 2.63-2.48 (1H, m), 2.35-2.22 (1H, m), 1.95-1.77 (2H, m), 1.72 (3H, s), 1.24 (3H, d, J=6.9 Hz). EIMS (m/z): 669 (M^+), 610, 580, 503, 395, 329, 318, 305, 290, 275, 226, 212, 197, 183, 171, 133, 44. HREIMS (m/z): Calcd. for $C_{40}H_{41}FeNOP_2$ (M^+): 669.2010. Found: 669.2024.

(*R*)-*N*-Methyl-*N*-(4-hydroxybutyl)-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine [(*R*)-(*S*)-37]

In a similar manner to that described for the preparation of (*R*)-(*S*)-**36**, the reaction of (*R*)-1-[(*S*)-1',2-bis(diphenylphosphino)-ferrocenyl]ethyl acetate (300 mg, 0.47 mmol) and *N*-methyl-4-aminobutanol (330 mg, 3.2 mmol) gave (*R*)-(*S*)-**37** as an orange amorphous powder (253 mg, 79%) after purification by column chromatography, $[\alpha]_D^{20}$ -319° (c 0.60, $CHCl_3$). IR (KBr): 3400, 3060, 2950, 2800, 1595, 1480, 1440, 1270, 1250, 1170, 1030, 830, 740 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.55-7.42 (2H, m), 7.30-7.03 (8H, m), 4.38 (1H, m), 4.35 (1H, m), 4.13 (1H, m), 4.12 (1H, m), 4.06 (1H, m), 3.79 (1H, m), 3.75 (1H, m), 3.42 (1H, m), 3.36 (2H, t, J=6.0 Hz), 2.30-2.15 (2H, m), 1.91 (2H, br s), 1.72 (3H, s), 1.24 (3H, d, J=7.1 Hz), 1.20-0.95 (2H, m). EIMS (m/z): 683 (M^+), 610, 580, 503, 395, 329, 318, 305, 290, 275, 226, 212, 197, 183, 171, 133, 44. HREIMS (m/z): Calcd. for $C_{41}H_{43}FeNOP_2$ (M^+): 683.2166. Found: 683.2148.

(*S*)-*N*-Methyl-*N*-(4-hydroxybutyl)-1-[(*R*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine [(*S*)-(*R*)-37]

The reaction of (*S*)-1-[(*R*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl acetate (200 mg, 0.31 mmol) and *N*-methyl-4-aminobutanol (198 mg, 1.9 mmol) in a similar manner to that described for the preparation of (*R*)-(*S*)-**37** gave (*S*)-(*R*)-**37** as an orange amorphous powder (177 mg, 83%), $[\alpha]_D^{20}$ +320° (c 0.58, $CHCl_3$). Spectral properties of this sample were identical to those of (*R*)-(*S*)-**37**.

(*R*)-*N*-Methyl-*N*-(5-hydroxypentyl)-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine [(*R*)-(*S*)-38]

In a similar manner to that described for the preparation of (*R*)-(*S*)-**36**, the reaction of (*R*)-1-[(*S*)-1',2-bis(diphenylphosphino)-ferrocenyl]ethyl acetate (100 mg, 0.16 mmol) and *N*-methyl-5-aminopentanol (161 mg, 1.4 mmol) gave (*R*)-(*S*)-**38** as an orange amorphous powder (93.0 mg, 86%) after purification by column chromatography, $[\alpha]_D^{20}$ -311° (c 0.50, $CHCl_3$). IR (KBr): 3400, 3060, 2950, 2800, 1595, 1480, 1440, 1270, 1180, 1030, 830, 740 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.55-7.42 (2H, m), 7.30-7.03 (8H, m), 4.36 (1H, m), 4.34 (1H, m), 4.13 (1H, m), 4.06 (1H, m), 4.05 (1H, m), 3.89 (1H, m), 3.65 (1H, m), 3.45 (1H, m), 3.44 (2H, t, J=6.6 Hz), 2.40-2.10 (2H, m), 1.67 (3H, s), 1.40-1.25 (2H, m), 1.15 (3H, d, J=6.7 Hz), 1.05-0.85 (4H, m). EIMS (m/z): 697 (M^+), 610, 580, 503, 395, 329, 318, 305, 290, 275, 226, 183, 171, 44. HREIMS (m/z): Calcd. for $C_{42}H_{45}FeNOP_2$ (M^+): 697.2323. Found: 697.2304.

(+)-(5*S*,9*S*)-Methyl 7,8,9,10-tetrahydro-2-methoxy-7-methylene-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate [(+)-8] and its enantiomer [(–)-8]

a) Preparation of (+)-**8** (**Table 3**, entry 8). A solution of $Pd(OAc)_2$ (4.6 mg, 20 μmol) and (*R*)-(*S*)-**37** (27.3 mg, 40 μmol) in DME (0.5 mL) was stirred at room temperature for 30 min under argon. A solution of **3** (23.5 mg, 0.10 mmol), 2-methylene-1,3-propanediol diacetate (**7**) (16 μL, 0.10 mmol) and TMG (18 μL, 0.11 mmol) in DME (2.0 mL) was added at -30 °C. After stirring for 20 min, another amount of TMG (18 μL, 0.11 mmol) was added , and the resulting mixture was allowed to gradually warm to room temperature (15 °C) over 5 h and 40 min. After concentration *in vacuo*, the residue was purified by flash column

chromatography (C6H14/EtOAc, 6:1) to give (+)-**8** as a colorless oil (26.4 mg, 92%, 64% ee), $[\alpha]_D^{20}$ +20.3° (c 0.54, $CHCl_3$) (64% ee). The enantiomeric excess was determined by HPLC with a chiral column [DAICEL OD-H, C6H14/2-propanol, 20:1 as eluent, flow rate 0.5 mL/min. detection UV (254nm), Rt: (–)-**8**, 15.5 min; (+)-**8**, 20.3 min]. [When the same asymmetric reaction was carried out using $Pd(OAc)_2$ (7.6 mg, 34 μmol), (*R*)-(*S*)-**37** (46.3 mg, 68 μmol), **3** (70.5 mg, 0.30 mmol), 2-methylene-1,3-propanediol diacetate (**7**) (49 μL, 0.30 mmol), and TMG (53 μL, 0.33 mmol), (+)-**8** could be obtained as a colorless oil (78.9 mg, 92%, 64% ee by HPLC) after purification by column chromatography.] IR (neat): 2940, 1740, 1720, 1650, 1600, 1575, 1475, 1420, 1320, 1260, 1175, 1115, 1065, 1030 ,1005, 1000, 950, 905 ,875, 830, 775, 735, 700, 660, 575 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.98 (1H, d, J=8.6 Hz, C4-H), 6.59 (1H, d, J=8.6 Hz, C3-H), 4.87-4.82 (1H, m, C12-H), 4.53-4.48 (1H, m, C12-H), 3.90 (3H, s, OCH_3), 3.82 (3H, s, CO_2CH_3), 3.45 (1H, dd, J=18.2, 6.9 Hz, C10-H), 3.21-3.13 (1H, m, C6-H), 3.12 (1H, d, J=18.2 Hz, C10-H), 3.01-2.94 (1H, m, C9-H), 2.85-2.76 (1H, m, C8-H), 2.67-2.58 (1H, m, C6-H), 2.63-2.54 (1H, m, C8-H). These spectral properties were identical with those reported for (±)-**8**.[10b] EIMS (m/z): 287 (M^+), 255. HREIMS (m/z): Calcd. for $C_{16}H_{17}NO_4$ (M^+): 287.1156. Found: 287.1146.

b) Preparation of (–)-**8** (**Table 3**, entry 10). The reaction of **3** (23.5 mg, 0.10 mmol) performed by using (*R*)-(S)-**37** in place of (S)-(*R*)-**37** gave (–)-**8** as a colorless oil (26.1 mg, 91%, 63% ee) after purification by column chromatography. Spectral data of this sample was identical to those described for (+)-**8**.

(+)-(5*R*,9*R*,11*E*)-Methyl 11-ethylidene-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylate and its enantiomer [(+)- and (–)-39]

a) Preparation of (+)-**39**. A solution of butyllithium in C6H14 (1.64 M solution, 2.9 mL, 4.5 mmol) was added to a suspension of ethyltriphenylphosphonium bromide (2.00 g, 5.4 mmol) in THF (21 mL) at 0 °C under argon. The resulting orange suspension was stirred at room temperature for 70 min. After the mixture was cooled to 0 °C, a solution of (+)-**6** (340 mg, 1.2 mmol, >99% ee) in THF (7.0 mL) was slowly added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with H_2O. After THF was removed *in vacuo*, the aqueous residue was extracted with EtOAc. The combined organic extracts were washed with brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (C6H14/EtOAc, 10:1) to give a mixture of (+)-**39** and its 13(*Z*)-isomer (1:4) as a colorless oil (327 mg, 93%). The ratio of (+)-**39** to its 13(*Z*)-isomer was estimated by the ^{1}H-NMR spectrum. During the purification by flash column chromatography, a pure sample of major 13(*Z*)-isomer could be isolated in a small amount. $[\alpha]_D^{20}$ +46.6° (c 1.83, $CHCl_3$). IR (neat): 2940, 2910, 1720, 1595, 1575, 1470, 1420, 1320, 1300, 1260, 1200, 1030, 830, 630 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.09 (1H, d, J=8.6 Hz, C4-H), 6.54 (1H, d, J=8.6 Hz, C3-H), 5.51 (1H, q, J=7.3 Hz, C13-H), 5.44-5.39 (1H, m, C8-H), 3.89 (3H, s, OCH_3), 3.71 (3H, s, CO_2CH_3), 3.15 (1H, dd, J=16.9, 5.2 Hz, C10-H), 3.10-3.04 (1H, m, C9-H), 3.02 (1H, dd, J=17.0, 1.0 Hz, C6-H), 2.81 (1H, dd, J=16.9, 1.4 Hz, C10-H), 2.21 (1H, d, J=17.0 Hz, C6-H), 1.54 (3H, s, C12-H), 1.51 (3H, d, J=7.3 Hz, C14-H). EIMS (m/z): 299 (M^+), 240. HREIMS (m/z): Calcd. for $C_{18}H_{21}NO_3$ (M^+): 299.1520. Found: 299.1524. These spectral properties were identical with those reported.[8a] A solution of the olefin mixture, AIBN (125 mg, 1.1 mmol), and thiophenol (165 μL, 1.6 mmol) in C6H5Me (3.0 mL) was heated at 85 °C for 24 h. After concentration *in vacuo*, the residue was dissolved in Et_2O, washed with H_2O and brine. Concentration *in vacuo* followed by purification by flash column chromatography (C6H14/EtOAc, 20:1) gave a mixture of (+)-**36** and its 13(*Z*)-isomer (7:1) as a colorless oil (303 mg, 95%). The ratio of (+)-**39** to its 13(*Z*)-isomer was determined by the ^{1}H-NMR spectrum. Recrystallizations from C6H14 afforded an analytical sample of (+)-**39** as colorless needles, mp 145.5-147 °C. $[\alpha]_D^{20}$ +45.0° (c 0.83, $CHCl_3$). IR (KBr): 2895, 1730, 1600, 1580, 1475, 1430, 1320, 1270, 1240, 1075, 1020, 825 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.08 (1H, d, J=8.5 Hz, C4-H), 6.53 (1H, d, J=8.5 Hz, C3-H), 5.43-5.38 (1H, m, C8-H), 5.05 (1H, q, J = 6.7 Hz, C13-H), 3.89 (3H, s, OCH_3), 3.74 (3H, s, CO_2CH_3), 3.63-3.56 (1H, m, C9-H), 3.12-3.02 (2H, m, C6-H and C10-H), 2.85 (1H, dd, J=17.0, 1.7 Hz, C10-H), 2.15 (1H, d, J = 17.0 Hz, C6-H), 1.70 (3H, d, J = 6.7 Hz, C14-H), 1.54 (3H, s, C12-H). EIMS (m/z): 299 (M^+), 240. These spectral data (IR, ^{1}H-NMR, MS) were identical with those reported.[8a] HREIMS (m/z): Calcd. for $C_{18}H_{21}NO_3$ (M^+): 299.1520. Found: 299.1528. Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.43; H, 7.35; N, 4.59.

b) Preparation of (–)-**39**: Treatments of (–)-**6** (487 mg, 1.7 mmol, >99% ee) in a similar manner to that described in a), gave a mixture of (–)-**39** and its 13(*Z*)-isomer(1:4) as a colorless oil (463 mg, 91%). Subsequent isomerization of the double bond provided a mixture of (–)-**39** and its 13(*Z*)-isomer (7:1) (416 mg, 93%) as a colorless oil. Recrystallizations of this sample from C6H14 afforded an analytical sample of (–)-**39** as colorless needles, mp 145.5-146.5 °C, $[\alpha]_D^{20}$ -46.8° (c 0.81, $CHCl_3$). Spectral properties of this sample were identical to those described in a).

(+)-(5*R*,9*R*,11*E*)-11-Ethylidene-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic acid and its enantiomer [(+)- and (–)-40]

a) Preparation of (+)-**40**. A mixture of (+)-**39** and its 13(*Z*)-isomer (7:1) (250 mg, 0.84 mmol) was dissolved in MeOH-THF (1:2) (3.0 mL), and 20% NaOH (1.0 mL) was added. The mixture was heated at reflux for 36 h under argon. After cooling, the mixture was adjusted to pH 5-6 with 1N-HCl, and MeOH and THF were removed *in vacuo*. The aqueous residue was extracted with EtOAc. The combined organic extracts were washed with brine. After concentration *in vacuo*, the residue was purified by flash column chromatography (EtOAc) to give (+)-**40** as a colorless amorphous solid (153 mg, 64 %), $[\alpha]_D^{25}$ +42.8° (c 1.01, $CHCl_3$) [lit.[11] $[\alpha]_D^{25}$ +40.9° (c 4.4 x 10^{-3}, $CHCl_3$)]. IR (KBr): 3700-2200 (br), 2940, 1710, 1600, 1580, 1480, 1430, 1325, 1270, 1255, 1035, 820, 760 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.25 (1H, d, J=8.5 Hz, C4-H), 6.57 (1H, d, J=8.5 Hz, C3-H), 5.45-5.39 (1H, m, C8-H), 5.31 (1H, q, J=6.7 Hz, C13-H), 3.89 (3H, s, OCH_3), 3.66-3.60 (1H, m, C9-H), 3.08 (1H, dd, J=17.1, 5.1 Hz, C10-H), 3.03 (1H, br d, J=17.0 Hz, C6-H), 2.87 (1H, dd, J=17.0, 1.5 Hz, C10-H), 2.18 (1H, d, J=17.0 Hz, C6-H), 1.74 (3H, d, J=6.7 Hz,

C14-H), 1.54 (3H, s, C12-H). EIMS (m/z): 285 (M^+), 240. These spectral data were identical with those reported for (+)-**40**.[11] HREIMS (m/z): Calcd. for $C_{17}H_{19}NO_3$ (M^+): 285.1363. Found: 285.1345.

b) Preparation of (–)-**40**. Treatments of a mixture of (–)-**39** and its 13(Z)-isomer (7:1) (385 mg, 1.3 mmol) in a similar manner to that described in a), gave (–)-**40** as a colorless amorphous solid (298 mg, 81%) after purification by flash column chromatography, $[\alpha]_D^{25}$ -45.1° (c 1.11, $CHCl_3$). This sample showed identical spectral properties to those described in a).

(+)-(5*R*,9*R*,11*E*)-Methyl [11-ethylidene-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-yl]carbamate and its enantiomer [(+)- and (–)-41]

a) Preparation of (+)-**41**. A mixture of (+)-**40** (145 mg, 0.51 mmol), Et_3N (71 μL, 0.51 mmol), and diphenylphosphoryl azide (110 μL, 0.51 mmol) in C_6H_5Me (2.0 mL) was heated at 85 °C for 3 h under argon. After cooling, the reaction mixture was concentrated *in vacuo*, and the residue was dissolved in MeOH (2.0 mL). The resulting solution was heated at reflux for 27 h. After concentration *in vacuo*, the residue was purified by preparative thin layer chromatography (CH_2Cl_2/Et_2O, 20:1) to give (+)-**41** as a colorless caramel (106 mg, 66%), $[\alpha]_D^{25}$ +20.5° (c 1.20, $CHCl_3$) [lit.[11] $[\alpha]_D^{25}$ +20.6° (c 8.2 x 10^{-3}, $CHCl_3$)]. IR (neat): 3320, 2940, 1710, 1650, 1630, 1595, 1525, 1470, 1420, 1320, 1300, 1255, 1030, 825, $^{-1}$cm. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.56 (1H, d, J=8.6 Hz, C4-H), 6.55 (1H, d, J=8.6 Hz, C3-H), 5.49-5.43 (1H, m, C8-H), 5.36 (1H, q, J=6.8 Hz, C13-H), 5.02-4.90 (1H, br s, NH), 3.88 (3H, s, OCH_3), 3.70-3.60 (1H, m, C9-H), 3.62 (3H, br s, CO_2CH_3), 3.07 (1H, br d, J=16.7 Hz, C10-H), 2.83 (1H, dd, J=16.7, 1.9 Hz, C10-H), 2.58 (1H, br d, J=16.9 Hz, C6-H), 2.23 (1H, d, J=16.9 Hz, C6-H), 1.72 (3H, d, J=6.8 Hz, C14-H), 1.51 (3H, s, C12-H). EIMS (m/z): 314 (M^+), 224. These spectral data were identical with those reported for (+)-**41**.[11] HREIMS (m/z): Calcd. for $C_{17}H_{19}NO_3$ (M^+): 314.1628. Found: 314.1608.

b) Preparation of (–)-**41**. Treatments of (–)-**40** (205 mg, 0.72 mmol) in a similar manner to that described in a), gave (–)-**41** as a colorless amorphous solid (168 mg, 74%), $[\alpha]_D^{25}$ -23.1° (c 1.09, $CHCl_3$). This sample showed identical spectral properties to those described in a).

(–)-(5*R*,9*R*,11*E*)-5-Amino-11-ethylidene-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]pyridine-2(1*H*)-one and its enantiomer [natural (–)-huperzine A (1) and unnatural (+)-huperzine A (*ent*-1)]

a) Preparation of **1**. Iodotrimethylsilane (453 μL, 3.2 mmol) was added to a solution of (+)-**41** (100 mg, 0.32 mmol) in $CHCl_3$ (12 mL) at room temperature under argon, and the mixture was heated at reflux for 12 h. After cooling, MeOH (12 mL) was added, and the resulting mixture was further refluxed for 12 h. After concentration *in vacuo*, the residue was diluted with CH_2Cl_2, washed successively with 10% $Na_2S_2O_3$, sat. $NaHCO_3$, H_2O, and brine. The combined organic extracts were concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (EtOAc/MeOH, 20:3) to give (–)-**1** as colorless prisms (62.6 mg, 81%), mp 228.5-230 °C [lit.[11] 230 °C]. $[\alpha]_D^{25}$ -149° (c 1.78, $CHCl_3$) [lit.[11] $[\alpha]_D^{25}$ -150° (c 0.12, $CHCl_3$)]. IR (KBr): 3430, 3380, 2930, 1655, 1615, 1555, 1460, 1310, 1120, 930, 835, 660, 520 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 12.89 (1H, br s, NH), 7.90 (1H, d, J=9.4 Hz, C4-H), 6.42 (1H, d, J=9.4 Hz, C3-H), 5.49 (1H, q, J=6.7 Hz, C13-H), 5.41 (1H, br d, J=5.0 Hz, C3-H), 3.64-3.58 (1H, m, C9-H), 2.89 (1H, dd, J=16.9, 5.2 Hz, C10-H), 2.73 (1H, dd, J=16.9, 1.5 Hz, C10-H), 2.15 (1H, d, J=17.0 Hz, C3-H), 2.11 (1H, d, J=17.0 Hz, C6-H), 1.68 (3H, d, J=6.7 Hz, C14-H), 1.55 (3H, s, C12-H), 1.57-1.25 (2H, br s, NH_2). EIMS (m/z): 242 (M^+), 227, 213, 187. These spectral data were identical to those reported.[11] HREIMS (m/z): Calcd. for $C_{15}H_{18}N_2O$ (M^+): 242.1419. Found: 242.1423.

b) Preparation of *ent*-**1**. The same treatments of (–)-**41** (150 mg, 0.48 mmol) as described in a) gave (+)-**1** as colorless crystals (105 mg, 91%) after purification by preparative thin layer chromatography, mp 230-231.5 °C [lit.[11] mp 230 °C for (–)-**1**] $[\alpha]_D^{25}$ +153° (c 0.44, $CHCl_3$) [lit.[11] $[\alpha]_D^{25}$ +147° (c 0.72, $CHCl_3$)]. This sample showed identical spectral properties to those described in a).

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