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DEVELOPMENT OF NOVEL ASYMMETRIC REACTIONS AND THEIR APPLICATION TO THE SYNTHESIS OF NATURAL PRODUCTS

Manabu Node,* Tetsuya Kajimoto, and Minoru Ozeki

Kyoto Pharmaceutical University, 1 Shichono-cho, Misasagi, Yamashina-ku, Kyoto 607-8412, Japan
node@mb.kyoto-phu.ac.jp

Abstract – Asymmetric Michael addition of zinc enolate to a chiral nitroolefin was improved and the method was applied to the synthesis of (–)-$\Delta^{9(12)}$-Capnellene [**(–)-6**], (–)-aphanorphine [**(–)-7**], and (–)-eptazocine [**(–)-8**]. Whisky lactone (**28**) was also prepared by taking advantage of tandem Michael addition-MPV-reduction, which was capable of constructing three contiguous chiral centers of 1,3-mercaptoalcohols. In addition, (+)-negamycin [**(+)-35**] was synthesized by using the Michael addition of a chiral amine [**(–)-31**] as a key step with the best overall yield and with shortest steps to date. Efficient synthesis of galanthamine [**(-)-51**] was attained by a novel strategy of remote asymmetric control of intramolecular Michael addition of phenolic hydroxyl group to the dienone moiety. Moreover, epibatidine [**(–)-42**] was synthesized by using the Diels-Alder reaction, of which the dienophile, chiral allene dicarboxylate, was prepared by asymmetric crystallization. Finally, the first synthesis of naturally occurring form of dichroanal B (**71**), dichroanone (**72**), and taiwaniaquinone H (**73**) were achieved by using intramolecular asymmetric Heck reaction.

1. INTRODUCTION

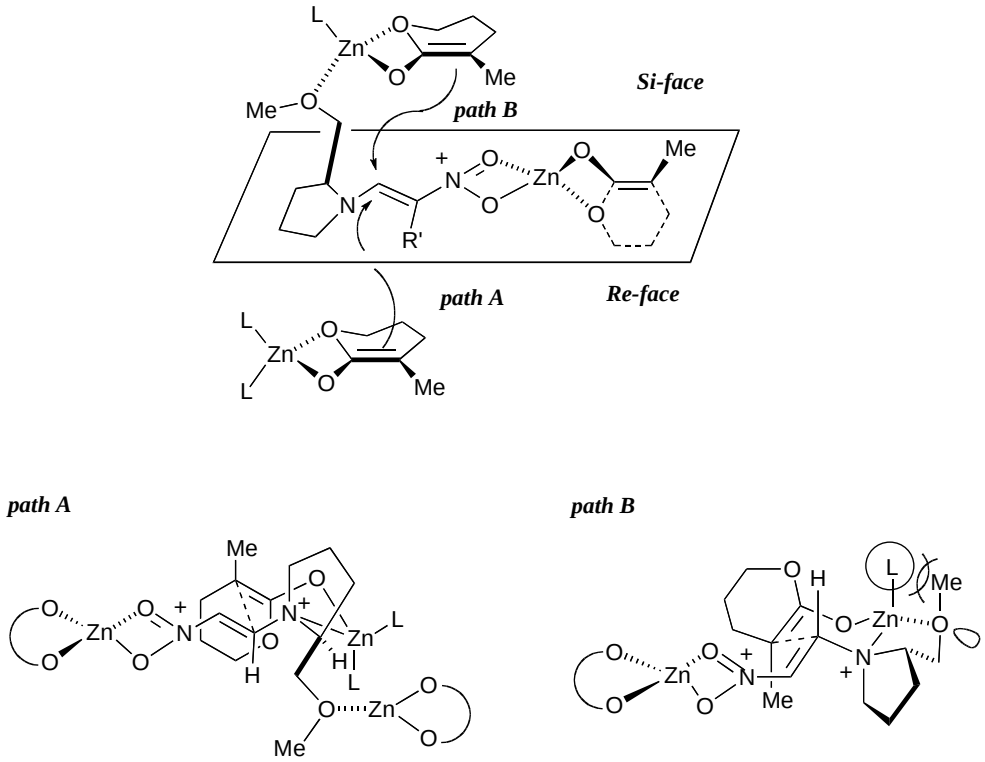
A number of asymmetric reactions have been developed to date and applied to the total synthesis of chiral forms of naturally occurring products having biological activity. The first author of the present article initially became interested in using Michael addition to develop a novel asymmetric reaction in 1990,

when he was appointed as a professor of Kyoto Pharmaceutical University (KPU). His research at KPU started with the improvement of the chiral nitroenamine **1**, the Michael acceptor of the asymmetric nitroolefination developed by Fuji *et al.*[1]

2. IMPROVEMENT OF ASYMMETRIC NITROOLEFINATION USING A CHIRAL NITROENAMINE

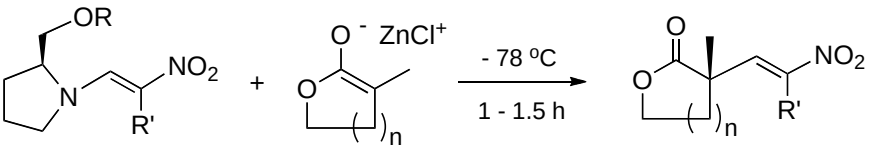
The nitroolefination initiated with Michael addition of an enolate prepared from the six-membered lactone **2** and the nitroolefine **1a**,**1b** proceeded in good yield with excellent ee.; however, reactions with the enolates of five-membered lactones afforded disappointing results. In the transition-state of the Michael addition, three molecules of the zinc enolate were supposed to coordinate to one molecule of **1a**, **1b** (Figure 1). The preference of the *Re*-face attack of the enolate (Figure 1, path A) afforded the products **4a** and **4b**, the ee values of which were decreased when the *Si*-face attack of the enolate (Figure 1, path B) was not effectively suppressed due to the relatively small steric hinderance between the ligand of the zinc ion and the methoxyl group in **1a** and **1b**. Thus, the methoxyl groups of **1a** and **1b** were substituted with a more bulky *tert*-butyldimethylsilyloxy group to overcome the defects of the Michael addition.

Figure 1. Transition-state of the Michael addition of the zinc enolate **2** to the nitroolefine **1a**[2,3]



As a result, the reaction of the zinc enolate of 2-methyl-γ-lactone (**5**) with **3a** produced **4a** in 92% yield with 88%ee, while that with **1a** provided **4a** in 56%ee (Table 1, entries 1 and 2). Moreover, the reaction of the enolate of 2-methyl-δ-lactone (**2**) with **3b** increased the chemical yield and ee, compared to the reaction with **1b** (Table 1, entries 3 and 4).[2,3]

Table 1. Micheal addition of enolate to the chiral nitroolefins **1** and **3**[2,3]



1a: R = Me, R' = H
1b: R = R' = Me
3a: R = TBS, R' = H
3b: R = TBS, R' = Me

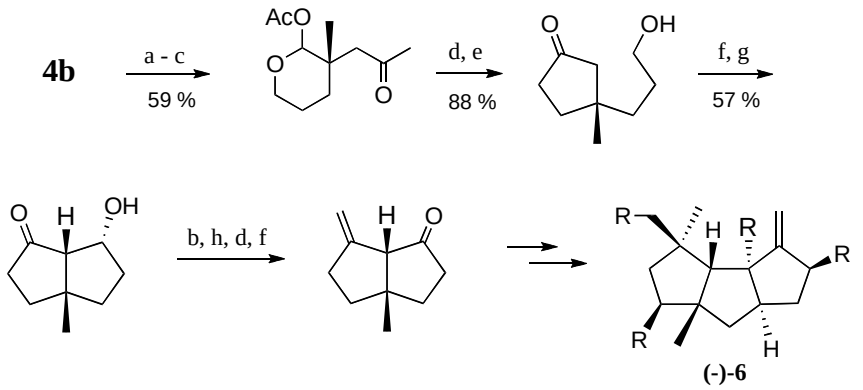
2: n = 2
5: n = 1

4a: R' = H, n = 1
4b: R' = Me, n = 2
4c: R' = H, n = 2

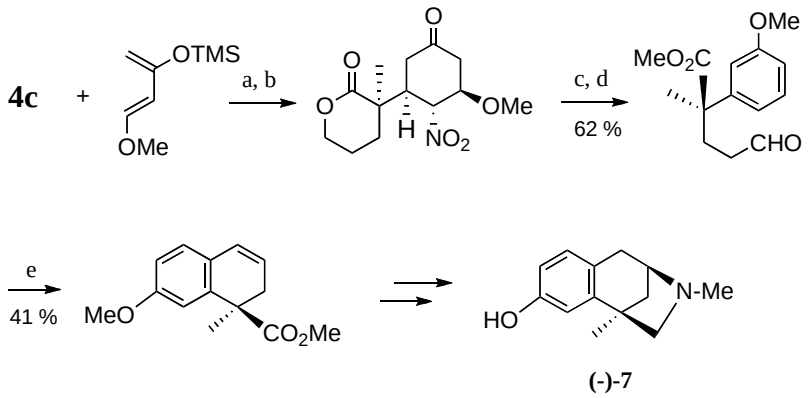
Entry	Substrate	Enolate	Solv.	Product	Yield (%)	Ee (%)
1	**1a**	**5**	DME	**4a**	82	56
2	**3a**	**5**	DME	**4a**	92	88
3	**1b**	**2**	DME	**4b**	85	94
4	**3b**	**2**	THF	**4b**	95	99
5	**3a**	**2**	THF	**4c**	99	99

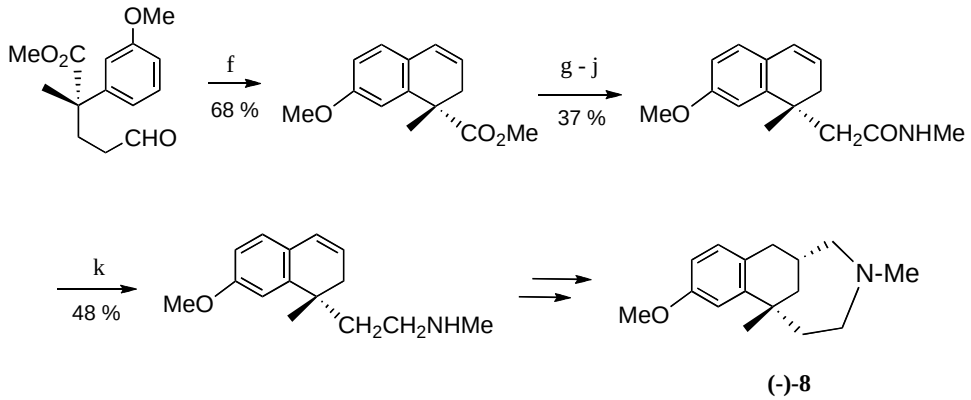
Taking advantage of the reaction, which used **3a** and **3b** as the chiral Michael acceptor to afford **4b** and **4c** in excellent chemical yield and ee (Table 1, entries 4 and 5), (–)-$\Delta^{9(12)}$-capnellene [**(–)-6**], (–)-aphanorphine [**(–)-7**], and (–)-eptazocine [**(–)-8**] were efficiently synthesized in short steps as shown in Scheme 1.[4,5]

Scheme 1. Synthesis of **(–)-6**, **(–)-7**, and **(–)-8** from the chiral nitroolefins **4b** and **4c**[4, 5]



a: DIBAL, **b**: Ac_2O, **c**: $TiCl_3$, **d**: KOH, **e**: Pd-C / H_2, **f**: PCC, **g**: HCl, **h**: CH_2Br_2 / Zn, $TiCl_4$





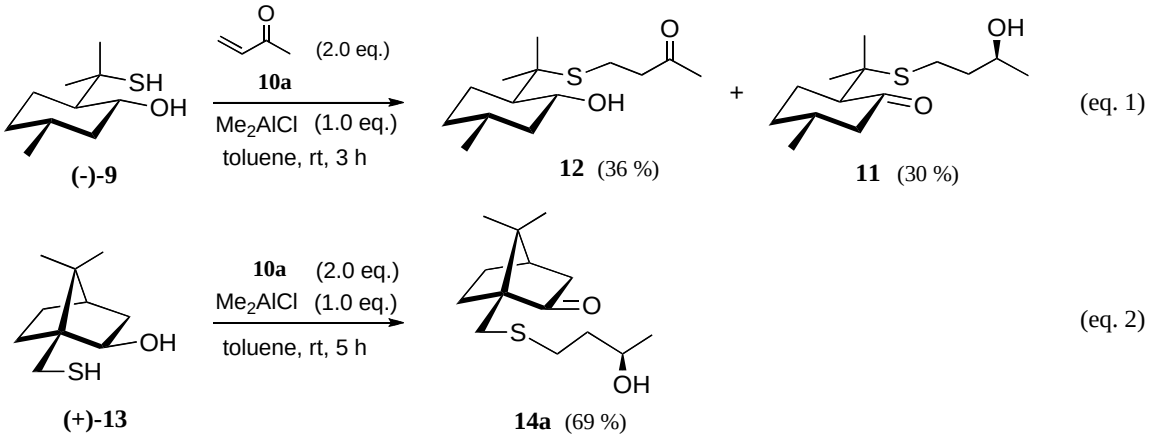
a: C_6H_6, reflux, **b**: HCl, **c**: *p*-TsOH, MeOH, **d**: Swern ox., **e**: BF_3 Et_2O, CH_2Cl_2,
f: $EtAlCl_2$, CH_2Cl_2, **g**: LiOH, **h**: $SOCl_2$, **i**: CH_2N_2, **j**: Ag_2O, $MeNH_2$, **k**: $LiAlH_4$, THF

3. TANDEM ASYMMETRIC MICHAEL ADDITION—MPV-REDUCTION

Asymmetric Michael addition using a chiral mercaptoalcohol such as (–)-(1*R*,3*R*,4*R*)-3-hydroxy-8-mercapto-*p*-menthane [**(–)-9**] as a nucleophile was first attempted, employing many kinds of α,β-unsaturated carbonyl compounds as the Micheal acceptors. The Michael addition of methyl vinyl ketone (**10a**) with **(–)-9** in the presence of dimethylaluminum chloride afforded

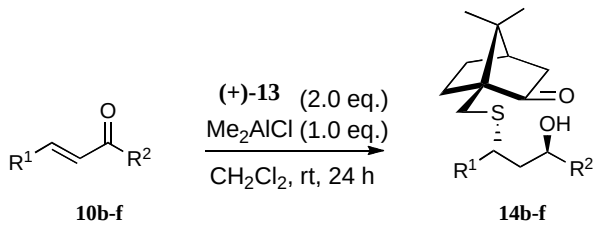
the MPV-reductant **11** as well as the Michael adduct **12** in 30% and 36% yield, respectively (Scheme 2, eq. 1). Since the equilibrium between acyclic ketone / cyclopentanol and secondary alcohol / cyclopentanone would incline to the right more than that of acyclic ketone / cyclohexanone and secondary alcohol / cyclohexanol, the Michael addition of **10a** was performed with the mercaptoalcohol **(+)-13** having cyclopetanol as a partial structure to afford the corresponding MPV-reductant **14a**. As expected, the MPV-reductant **14a** was obtained as a sole product in good yield (69%) (Scheme 2, eq. 2).[6]

Scheme 2. Michael addition of the chiral mercaptoalcohols **(–)-9** and **(+)-13**[7]



The stereochemistry of the Michael addition and MPV-reduction was investigated using several α,β-unsaturated ketones, **10b-f**, as the Michael acceptor. As shown in Table 2, the Michael addition-MPV-reduction of **10b** afforded **14b** as a single diastereomer, the absolute structure of which was determined by X-ray diffraction analysis after deriving to the sulfone.

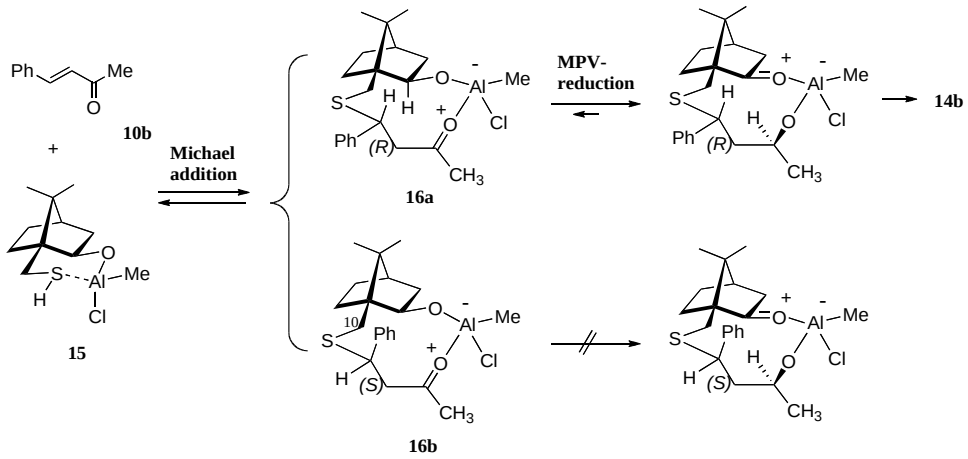
Table 2. Tandem Michael addition-MPV-reduction with the enones **10b-f**[6,7]



Entry		Substrates **10**		Products **14**	
		R^1	R^2	Yield (%)	De (%)
1	**b**	Ph	Me	95	99
2	**c**	Ph	*i*-Pr	96	99
3	**d**	Pr	Me	88	92
4	**e**	Pr	Hex	81	95
5	**f**	Pr	Ph	82	90

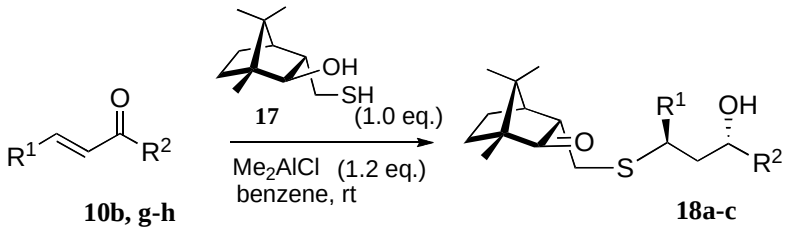
A plausible mechanism leading to the high diastereoselectivity is shown in Scheme 3.[7] Namely, the β-substituted α,β-unsaturated ketone **10b** reacted reversibly with the chiral aluminum complex **15** derived from **(+)-13** and Me_2AlCl to give two diastereomeric chelated adducts, **16a** and **16b**. The *R*-diastereomer **16a** was subsequently subjected to a reversible intramolecular MPV reduction. Since the distance between the migrating hydrogen and the carbonyl carbon in the chelated *R*-isomer **16a** was estimated about 3.1–3.4 Å from PM3 calculations, the *R*-isomer of the 10-membered ring could easily proceed to the rigid bicyclic transition-state. Meanwhile, the phenyl ring in the *S*-diastereomer **16b** lay close to the hydrogen at C-10 on the β-face of the 10-membered chelated ring, which greatly retarded the MPV-reduction. Thus, the production of a single isomer of **14b** was attributed to dynamic kinetic resolution[8] via reversible Michael addition and the kinetically controlled intramolecular MPV-reduction of one of the two Michael adducts (Scheme 3).

Scheme 3. Reaction mechanism of the tandem Michael addition-MPV reduction[7]



Interestingly, in the reaction using the chiral mercaptoalcohol **17** as a nucleophile, different facial selectivity from the reaction with **(+)-13** was observed in the Michael addition step (Table 3).[9]

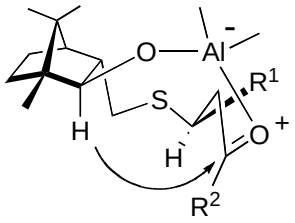
Table 3. Tandem Michael addition-MPV reduction[9]



Entry	Substrates **10**			Products **18**		
		R^1	R^2		Yield (%)	De (%)
1	**b**	Ph	Me	**a**	74	95
2	**g**	Ph	Oct	**b**	50	98
3	**h**	Ph	Ph	**c**	60	96

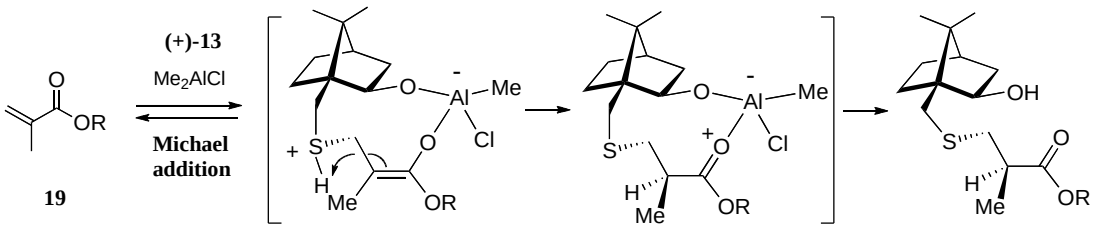
The inverted stereoselectivity of the products **18** in the tandem Michael addition-MPV reduction could be attributed to the plausible transition-state shown in Figure 2.

Figure 2. The plausible transition-state of the reaction of **10** with **17**[9]



Moreover, when the α-substituted α,β-unsaturated ester **19** was employed as the Michael acceptor, the enolate intermediate generated by the Michael addition was protonated by the proton on the sulfur atom to afford **20** with high diastereoselectivity (Scheme 4).[10]

Scheme 4. The mechanism in the reaction of **19** with **(+)-13**[10]

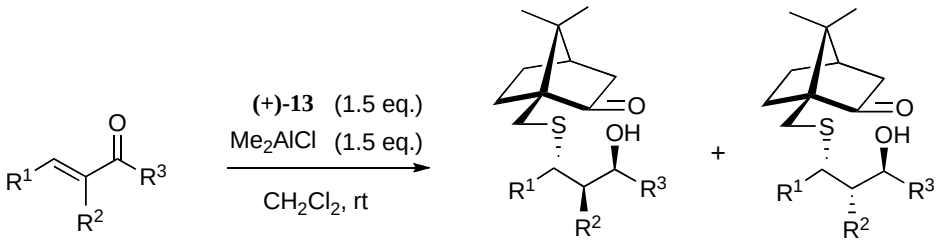


To expand the method for controlling three contiguous chiral centers, the reaction of α,β-disubstituted α,β-unsaturated ketone **21** with the chiral mercaptoalcohol **(+)-13** was scrutinized further.[11]

The results are summarized in Table 4, and show that the substrates having aromatic rings for both R^1 and R^3 were converted to the β-mercaptoalcohol in good yield with excellent dr (Table 4, entries 1-4). In addition, as the alkyl group at the α-position R^2 became more bulky, the yield became the less satisfactory; however, the dr increased (Table 4, entries 2-4). Unfortunately, the chemical yield and dr were both unsatisfactory when the substrates having an alkyl group for R^3 were used as the Michael acceptor (Table 4, entries 5-7).

Thus, several additives were tested to increase the yield and dr of the reaction using the substrate **21f** as a model Michael acceptor. A relationship between the *pKa* values of additives and chemical yield was clearly observed and adding pentafluorobenzoic acid (PFBA) (*pKa* = 1.7) was found to give the best yield (49%, **22Af**:**22f** = 93:2) (Figure 3).[11]

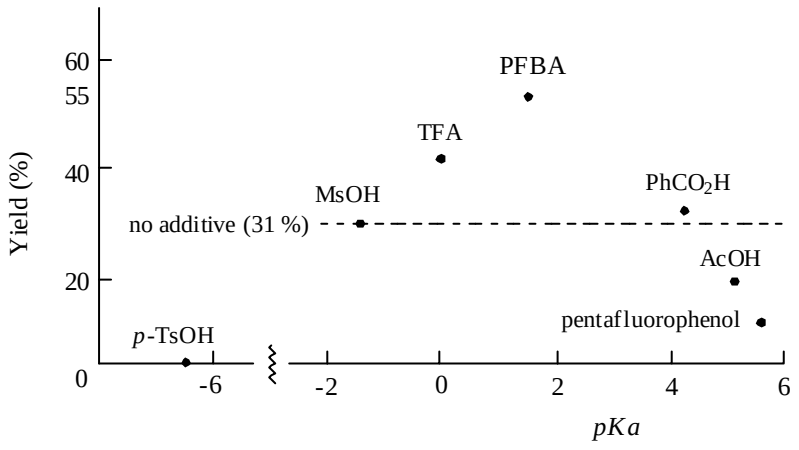
Table 4. Tandem Michael addition-MPV reduction with α,β-disubstituted α,β-unsaturated ketones[11]



21 **22A** **22B**

Entry		Substrates **21**			Time (day)	Products **22**	
		R^1	R^2	R^3		Yield (%)	Dr. (A : B)
1	**a**	Ph	Me	Ph	2	92	94 : 6
2	**b**	Ph	Et	Ph	2	60	97 : 3
3	**c**	Ph	Pr	Ph	2.5	44	99 : 1
4	**d**	Ph	Bn	Ph	3	37	99 : 1
5	**e**	Ph	Me	Et	3	78	58 : 42
6	**f**	Ph	Me	*c*-Hex	3	31	80 : 20
7	**g**	4-MeO-Ph	Me	*i*-Pr	3	37	72 : 28

Figure 3. The relationship between the pKa values of the additives (1.0 eq) and the chemical yield of **22**[11]



Next, the most suitable amount of PFBA was scrutinized in the reaction using **21f** as the acceptor substrate. The highest chemical yield of the product **22Af** was obtained in the case that 1.5 eq. of PFBA was added against the substrate (Figure 4). Moreover, the additive increased the ratio of **22A** : **22B**, compared to the reaction without PFBA (Table 4 and 5).

Figure 4. The relationship between the amount of PFBA and yield of **22**[11]

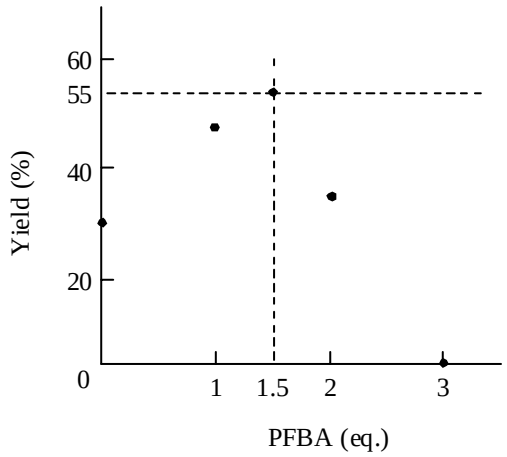
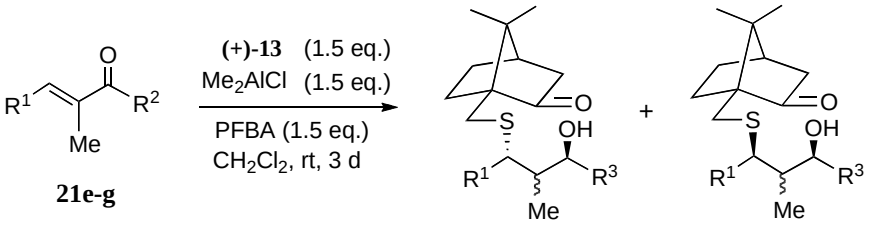


Table 5. Additive effect of PFBA in the reaction of **21e-g** with **(+)-13**[11]

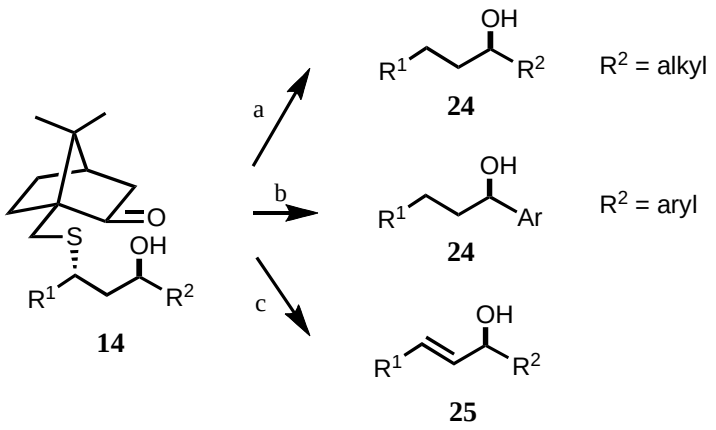


Entry		Substrates		Yield (%)[a] (Ratio)[b]	
		R^1	R^2	**22A : 22B**	**23A : 23B**
1	**e**	Ph	Et	71 (73 : 27)	14 (100 : 0)
2	**f**	Ph	*c*-Hex	50 (98 : 2)	5 (58 : 42)
3	**g**	4-MeO-Ph	*i*-Pr	52 (97 : 3)	6 (47 : 53)

a) Isolated yield. b) determined by ^{1}H-NMR

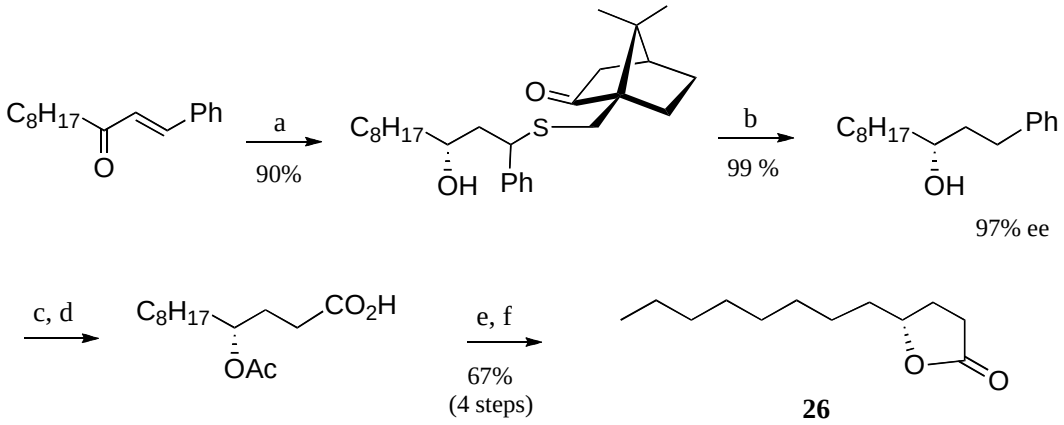
To improve the usefulness of the tandem Michael addition-MPV reduction in organic synthesis, desulfurization of the chiral sulfide moiety from **14** to provide chiral secondary alcohols **24a** and **24b** was tried using Raney nickel, the most common reagent for the reduction of carbon-sulfur bonds. Unexpectedly, racemization of the secondary alcohol was observed especially in the case of benzylic alcohols due to the occurrence of a set of oxidation-reduction reactions. Thus, sodium hypophosphite was used as a hydrogen source in the reduction with Raney Ni (W-2) in ethanolic acetate buffer to suppress the oxidation. In addition, elimination of the bornyl sulfide moiety, followed by the oxidation of sulfide to sulfoxide, was also carried out to give chiral allylic alcohols **25** (Scheme 5). As an application of the desulfurization, rove beetle pheromone **26** was synthesized in short steps (Scheme 6).

Scheme 5. Transformation of **14** to secondary alcohols **24** and allylic alcohol **25**[6,7]



a: Raney Ni, **b**: Raney Ni, $NaPH_2O_2$, **c**: 1) $NaIO_4$, 2) $CaCO_3$, toluene, Δ

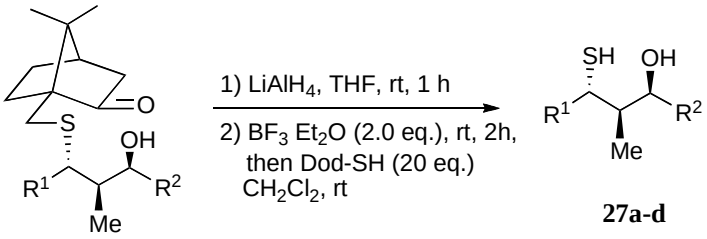
Scheme 6. Synthesis of rove beetle pheromone **26**[7]



a: (+)-13, Me_2AlCl, CH_2Cl_2, **b**: Raney Ni, $NaPH_2O_2$, **c**: Ac_2O, pyr., **d**: $RuCl_3$, HIO_4, **e**: 1 M NaOH, **f**: 10 % HCl

Finally, removal of the chiral auxiliary used in the tandem Michael addition-MPV reduction was performed. Needless to mention, treating **18a-c** with DBU facilely gave the corresponding *syn*-mercaptoalcohol in good yield; however, some effort had to be made to cleave the 10-camphonyl group from the products **22A**. Herein, the Wagner-Meerwein rearrangement, which occurs in the treatment of bornyl-type monoterpenes with Lewis acids, was chosen to cleave the chiral group from the products. Namely, the carbonyl group of **22Ae** was first reduced with lithium aluminum hydride to alcohol, which was then treated with $BF_3{\cdot}Et_2O$ followed by a thiol exchange reaction in the presence of $BF_3{\cdot}Et_2O$ and dodecanethiol to afford the desired 1,3-mercaptoalcohol **27a** in good yield (Table 6).[10-12]

Table 6. Cleavage of the chiral auxiliary of **22A**[11,12]

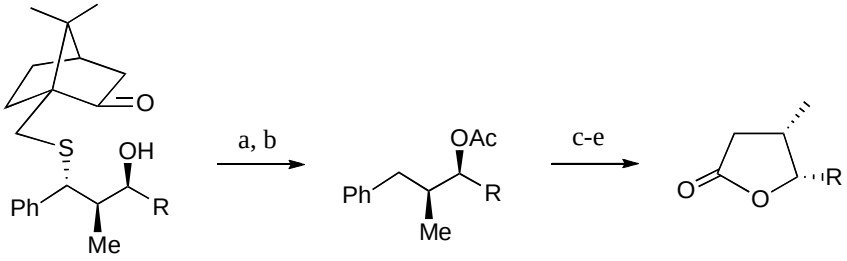


22Ae-h **27a-d**

Entry		Substrates **22**		Products **27**		
		R^1	R^2		Yield (%)	Ee (%)
1	**e**	Ph	Et	**a**	83	99
2	**f**	Ph	*c*-Hex	**b**	75	99
3	**h**	Ph	*i*-Pr	**c**	82	88
4	**i**	4-Me-Ph	*i*-Pr	**d**	58	99

As an application of the tandem Michael addition-MPV reduction, whisky lactone (**28a**) and cognac lactone (**28b**) were synthesized.[13] The carbon-sulfur bond in the products was reductively cleaved by Raney nickel after the protection of the hydroxyl group by conventional acetylation.[14] The resulting acetate **29** was oxidized with ruthenium tetroxide, saponified, and treated with acid to afford **28a** and **28b** (Scheme 7).

Scheme 7. Synthesis of whisky lactone **28a** and cognag lactones **28b**[13]



22A **29** **28**

a: R = *n*-Bu 89 % (99 % ee) 62 %

b: R = *n*-Pen 90 % (99 % ee) 70 %

a: Ac_2O (3 eq.), DMAP (cat), pyr.; **b**: Raney Ni (W-2), EtOH; **c**: $RuCl_3$, H_5IO_6, CCl_4 / MeCN / H_2O; **d**: 1 M NaOH aq.; **e**: 10% HCl aq.

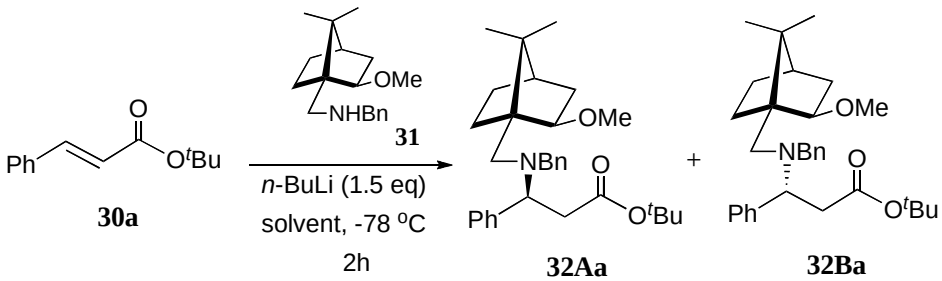
4. ASYMMETRIC MICHAEL ADDITION OF A CHIRAL AMINE.

Asymmetric Michael additions of amines to α,β-unsaturated esters are very promising reactions to afford units of β-amino acids, which are a part of a number of naturally occurring bioactive compounds.

Many methods of stereoselective Michael addition, with amines or amides utilized as nucleophiles, have been developed using either catalytic or stoichiometric approaches. For example, Davies employed a chiral phenethylamide as a nucleophile to attack α,β-unsaturated esters to afford derivatives of β-amino acids,[15] while Tomioka achieved the Michael addition of an achiral *N*-silylated lithium amide in the presence of a chiral ligand.[16] Enders developed a recyclable *N*-silylated amide carrying (*S*)-2-methoxymethylpyrrolidine as a nucleophile.[17] On the basis of these findings, we next embarked on the development of a novel asymmetric Michael addition to α,β-unsaturated esters **30** using the chiral bornylamine **(–)-31** as a nucleophile, which could be prepared from commercially available ketopinic acid,[18] for establishing an alternative way of providing both (*R*)- and (*S*)-β-amino acids.[19]

Initially, the Michael additions were scrutinized by fixing the reaction conditions, *i.e.*, adding the amide prepared from **(–)-31** (1.5 eq) and *n*-butyllithium (1.5 eq) to a solution of *tert*-butyl cinnamate **30a** in an appropriate organic solvent and stirring the mixture at -78 °C for 2 hours (Table 7). While the reaction conducted in a non-polar solvent, such as toluene or hexane, did not proceed well in terms of chemical yield and diastereoselectivity (Table 7, entries 5 and 6), that in diethyl ether (Table 7, entry 1) and in tetrahydrofuran (Table 7, entry 4) proceeded with satisfactory yields and an excellent contrast of product ratios. Interestingly, the diastereoselectivity was completely inverted by changing the solvent from diethyl ether to tetrahydrofuran (Table 7, entries 1 and 4).

Table 7. Michael additions of **(–)-31** and *tert*-butyl cinnamate (**30a**)[19]

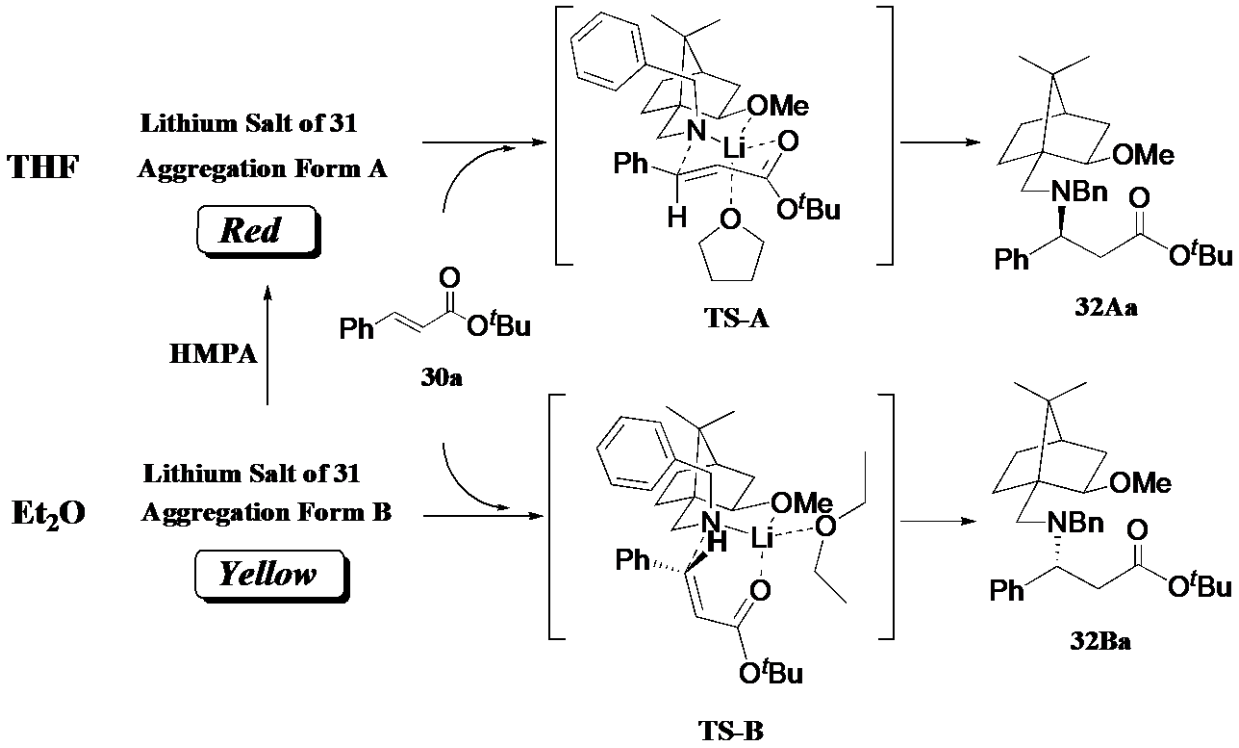


Entry	Solvent	Yield (%)[a)]	**32A** :	**32B**[b)]
1	Et_2O	74	15	85
2	Et_2O + HMPA (6 eq) [c)]	52	88	12
3	Et_2O + HMPA (30 eq) [d)]	61	94	6
4	THF	62	81	19
5	toluene	48	52	48
6	hexane	36	28	72

a) Isolated yield. b) Ratio was determined by ^{1}H-NMR. c) -50°C, d) -20°C

The reaction solution of tetrahydrofuran maintained a transparent red color during the reaction while that of diethyl ether remained transparent yellow. On the basis of this difference in color, the inversion of the diastereoslectivity could be attributed to differences in the aggregated forms of the lithium amide in the solutions, *i.e.*, forms A and B would be dissociated by adding *tert*-butyl cinnamate **30a** to construct the transition states TS-A and B (Scheme 8).

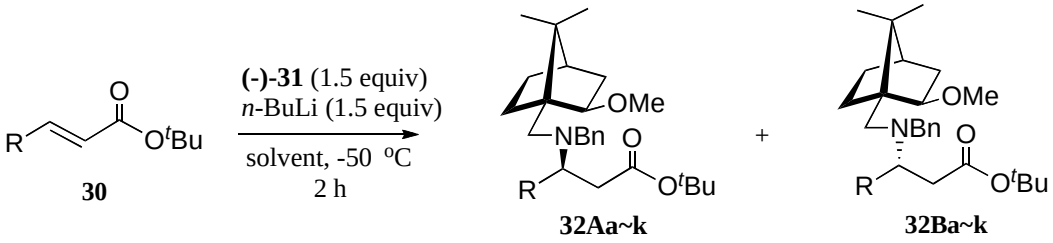
Scheme 8. Aggregated forms of the lithium amide in the transition-state[19]



Moreover, it was found that the addition of 0.5 equivalents of lithium salts, such as lithium trifluoroacetate and lithium trifluoromethanesulfonate, generally increased both chemical yield and diastereoselectivity. Notably, in the reaction with *p*-chlorocinnamate (**30b**), the chemical yield increased from 80% to 91% and the diastereoselectivity improved from 91 : 9 to 94 : 6 on adding lithium triflate (Table 8).

The newly generated chiral center was determined to have an *S*-configuration by X-ray diffraction analysis of **32Ad**, which was obtained in the reaction of *tert*-butyl *p*-methylcinnamate with **(–)-31**.

Table 8. Michael addition of **(–)-31** to the α,β-unsaturated esters **30a-k** in the presence of LiOTf[19]

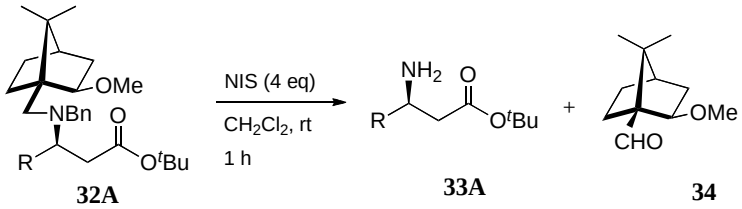


entry	substrates **30**		solvent			
			THF		Et_2O	
		R	yield (%)[b]	**32A** : **32B**	yield (%)[b]	**32A** : **32B**
1	**a**	Ph	90 (99)[a]	93 : 7 (94 : 6)[d]	74[a]	15 : 85[a]
2	**b**	4-Cl-Ph	80 (91)[a]	91 : 9 (94 : 6)[d]	50[a]	7 : 93[a]
3	**c**	4-MeO-Ph	90 (97)	94 : 6 (96 : 4)[d]	65	23 : 77
4	**d**	4-MePh	83 (80)	91 : 9 (94 : 6)[d]	79	22 : 78
5	**e**	2-Naph	70 (88)	92 : 8 (96 : 4)[d]	79	21 : 79
6	**f**	*n*-Hex	83[a] (81)[a]	95 : 5[a] (95 : 5)[d]	29	44 : 56
7	**g**	*c*-Hex	99 (92)	>99 : 1 (>99 : 1)[d]		
8	**h**	*i*-Pr	90 (95)	>99 : 1 (93 : 7)[d]		
9	**i**	*n*-Pr	83 (95)	91 : 9 (91 : 9)[d]		
10	**j**	3-Pen	76 (88)	92 : 8 (96 : 4)[d]		
11	**k**	*c*-Pen	99 (99)	97 : 3 (97 : 3)[d]		

[a] performed at -78 °C. [b] Isolated yield. [c] Ratio was determined by ^{1}H-NMR. [d] The value in the parentheses was the result of the reactions with LiOTf (0.5 equiv).

Next, in order to develop the Michael addition as a general method to synthesize β-amino acids or esters, the chiral auxiliary must be removed from the Michael adducts. Although cleavage reactions of the carbon-nitrogen bond are difficult in general, many methods have been developed. For example, the oxidative dealkylation of secondary amines with *N*-chlorosuccinimide (NCS) can be conducted facilely due to the ease of forming a Schiff base.[20] Thus, we tried to cleave the chiral auxiliary by using an excess amount of *N*-iodosuccinimide (NIS) to oxidize the tertiary amine into iminium salt.[21] Namely, the Michael adducts **32A** were treated with 4 equivalents of NIS to afford the β-amino esters **33** and 2-methoxybornyl aldehyde **34**, which can be reconverted to **(–)-31** by reductive amination with benzyl amine, in good yield (Table 9).

Table 9. Cleavage of the chiral auxiliary of **32A** with NIS[19]



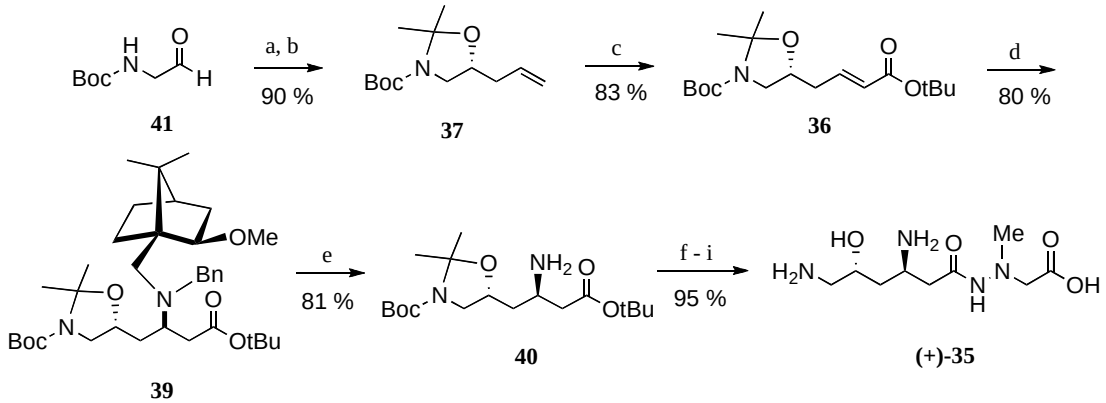
32A **33A** **34**

Entry	Substrate	R	Yield (%)	
			33A	**34**
1	**32Aa**	Ph	76	93
2	**32Ac**	4-Me-Ph	80	97
3	**32Ad**	4-MeO-Ph	84	99
4	**32Ae**	*c*-Hex	89	93
5	**32Af**	*i*-Pr*	68	88

* As adding four equivalents of NIS at once to the reaction mixture reduced the chemical yield, two equivalents of NIS was added twice at an interval of 1 hour.

The present method was used to synthesize (+)-negamycin [**(+)-35**],[22,23] an antibiotic isolated from *Streptomyces purperfuscus*. The Michael addition of **(–)-31** was applied to the α,β-unsaturated *tert*-butyl ester **36**, which was prepared by the metathesis reaction of oxazolidine **37** and *tert*-butyl acrylate (**38**) in the presence of Grubbs catalyst.[24] As expected, the amine was introduced in good yield with an excellent ee to afford **39**. After the cleavage of the chiral auxiliary with NIS, the resulting amine **40** was converted to **(+)-35** in 4 steps. The synthetic route starting from Boc-glycinal **41** provided **(+)-35** with an overall yield of 42% in eight steps (Scheme 9).[25]

Scheme 9. Synthesis of (+)-negamycin [**(+)-35**][25]



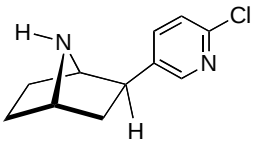
41 **37** **36** **39** **40** **(+)-35**

a: (-)-Ipc_2B(allyl), Et_2O, **b**: 2,2-dimethoxypropane, BF_3 Et_2O, **c**: Grubbs II, H_2C=CH-CO_2tBu (**38**), **d**: **(-)-31**, *n*-BuLi, THF, **e**: NIS CH_2Cl_2,**f**; $(Boc)_2O$, THF, **g**: KOH, MeOH, H_2O, **h**: H_2N-N(Me)-CH_2CO_2tBu, EDC, HOBt, Et_3N, CH_2Cl_2, **i**: 4 M HCl, dioxane

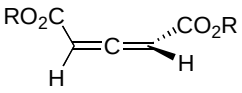
5. ASYMMETRIC CRYSTALLIZATION OF ALLENE-1,3-DICARBOXYLATE AND SYNTHESIS OF EPIBATIDINE

(–)-Epibatidine [**(–)-42**] is an alkaloid isolated from the skin of the poison frog *Epipedobates tricolor*,[26] the collection of which is forbidden by the international treaty for the protection of endangered species enacted in 1984. Although much progress has been made over last decade in establishing practical methods of synthesis,[27] optically pure **(–)-42** remains an attractive target because it is an excellent candidate for a non-opioidic analgesic agent for clinical use in accordance with the development of biological studies.[28] We succeeded in the asymmetric synthesis of **(–)-42** by means of the crystallization-induced asymmetric transformation of allene-1,3-dicarboxylates (**43-45**) (Figure 5).[29]

Figure 5. Structure of epibatidine **(–)-42** and allene-1,3-dicarboxylates (**43-45**)



(-)-42

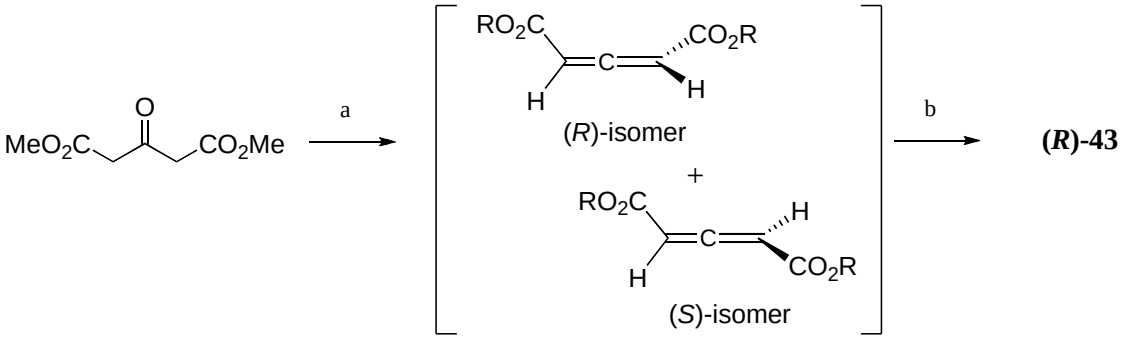


43 : R = (-)-menthyl
44 : R = (-)-bornyl
45 : R = (-)-isobornyl

A mixture of (*S*)- and (*R*)-isomers of di-(–)-menthyl allene-1,3-dicarboxylate (diastereo ratio = 5:4) (**43**) prepared from di-(–)-menthyl 1,3-acetonedicarboxylate by a reaction with 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and triethylamine was crystallized in the presence of triethylamine (0.01 eq.) at low temperature to afford di-(–)-menthyl (*R*)-allene-1,3-dicarboxylate [**(*R*)-43**] as a single crystal in pentane. Repeating the same procedure three times gave **(*R*)-43** in 90% total yield (Scheme 10).

Later, we found that (–)-bornyl and (–)-isobornyl allene-1,3-dicarboxylates (**44**, **45**) were more suitable substrates for the asymmetric crystallization because the procedure was attainable in hexane at room temperature (**44**, 89%; **45**, 89%). The absolute axis configuration of **44** and **45** obtained by the asymmetric crystallization was identical to that of **(*R*)-43**.[30]

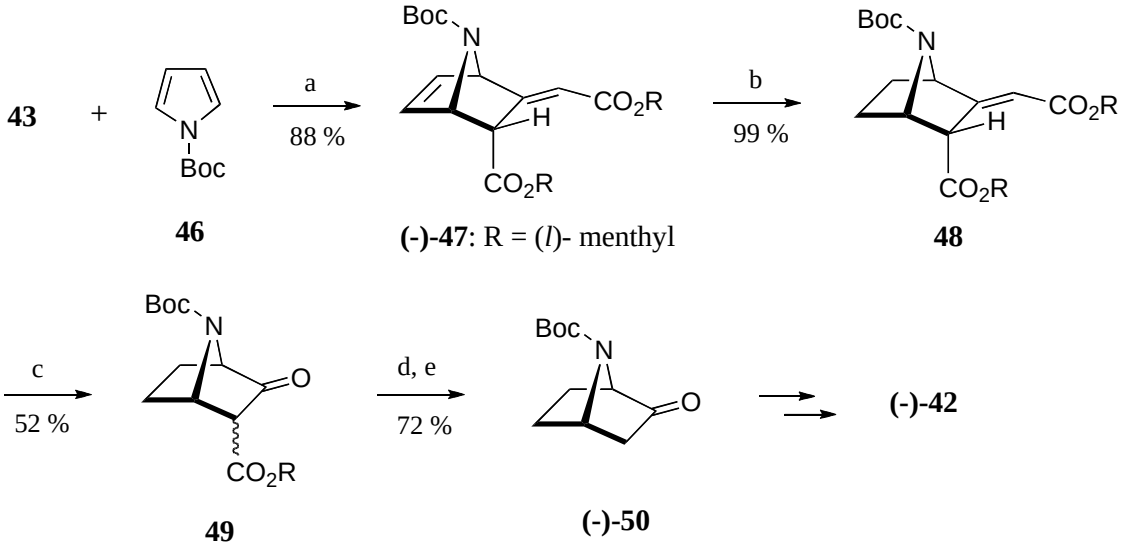
Scheme 10. Asymmetric crystallization of allene-1,3-dicarboxylate **(*R*)-43**[30]



a: (-)-menthol, DMC, Et_3N, **b**: Et_3N then crystallization

Being encouraged by obtaining the chiral allene-1,3-dicarboxylates **(*R*)-43**, we adopted it as a dienophile of the Diels-Alder reaction with *N*-Boc-pyrrole **46**. Fortunately, the Diels-Alder reaction conducted in the presence of $AlCl_3$ at –78 °C in CH_2Cl_2 afforded the *endo*-adduct **47** as the sole product in good yield.[31] After hydrogenation of the isolated double bond of the *endo* adduct **(–)-47**, the diester **48** was ozonolyzed to the β-ketoester **49**, which was converted to a known synthetic intermediate **(–)-50**[28c] of (–)-epibatidine by dealkoxycarbonylation and successive reprotection of the secondary amino group with $(Boc)_2O$ (Scheme 11).

Scheme 11. Synthesis of (–)-epibatidine [**(–)-42**][29,31]



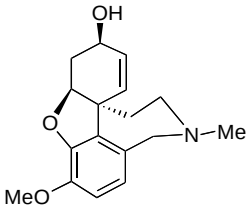
a: $AlCl_3$, CH_2Cl_2, - 78 °C; **b**: Pd-C / H_2, AcOEt; **c**: O_3 / Me_2S, CH_2Cl_2, - 78 °C; **d**: 10 % HCl,**e**: Boc_2O (3.0 eq.), Et_3N (5.0 eq.), CH_2Cl_2, r.t.

6. SYNTHESIS OF GALLANTHAMINE

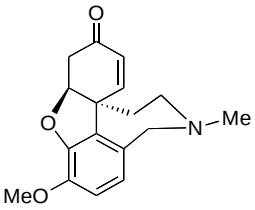
(–)-Galanthamine [**(–)-51**], an alkaloid isolated from *Galanthus woronowii*, referred to as Caucasian snow drop,[32] and *Lycoris radiate*[33] was developed as a medicine for Altzheimer's disease based on its biological actions as an allosteric modulator of the nicotinic receptor to secrete acetylcholine as well as a competitive inhibitor of acetylcholine esterase.[34]

The synthesis of **(±)-51**, where intramolecular oxidative phenol coupling of norbelladine (**52**) was adopted to afford narwedine (**53**), was first achieved by Barton and Kirby.[35] Thereafter, much effort was made to improve their method[36] since it was accompanied by the successful preparation of an enantiomerically pure form of **(–)-51** using the asymmetric crystallization of (–)-narwedine [**(–)-53**](Figure 6).[36] However, the yield of the intramolecular phenol coupling reaction in each route still remains less than 50%, which hinders the overall yield from reaching a satisfactory level.[37]

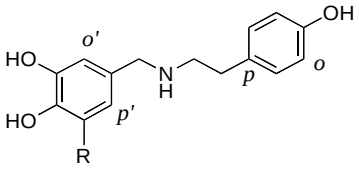
Figure 6. Structure of galanthamine [**(–)-51**] and related compounds



(-)-galanthamine [**(-)-51**]



narwedine (**53**)

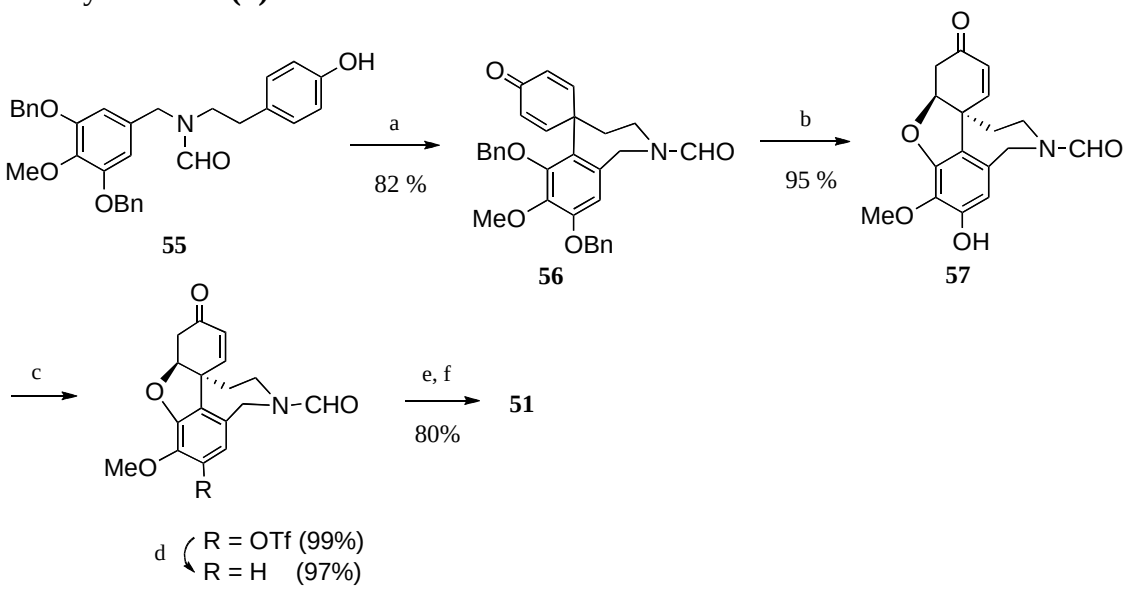


norbelladine (**52**): R = H
pyrogallol-type norbelladine (**54**): R = OH

While some excellent approaches to the synthesis of **(±)-51** or **(–)-51** using the intramolecular Heck reaction as a key step have been published,[38] such routes require multiple steps and their overall yields remain unsatisfactory. Based on this background, we succeeded in the asymmetric synthesis of **(–)-51**[39,40] by improving the biomimetic approach via the intramolecular phenol coupling reaction.

In advance of the asymmetric synthesis of **(–)-51**, a facile synthetic route for **(±)-51** was established using intramolecular phenol coupling.[40] The intramolecular phenol coupling of **52** was reported to yield a *p–p'* coupling product rather than the desired *p–o'* coupling product due to steric repulsion.[35] To overcome these disadvantages in the synthesis of **(±)-51**, we referred to Koga's procedure where the catechol moiety of **52** was replaced with a pyrogallol group because the symmetrical characteristic of the pyrogallol moiety in the precursor (**54**) made the *p–o'* coupling afford the only possible coupling product.[41] Improving the yield of the oxidative phenol coupling of **55** by employing phenyliodine(III) bis(trifluoroacetate) (PIFA) as the oxidative reagent, our scheme increased the overall yield of the total synthesis of (±)-galanthamine [**(±)-51**] (60% overall yield from the norbelladine derivative **55**, 6 steps) in comparison with yields reported to date (Scheme 12).

Scheme 12. Synthesis of **(±)-51**[40]

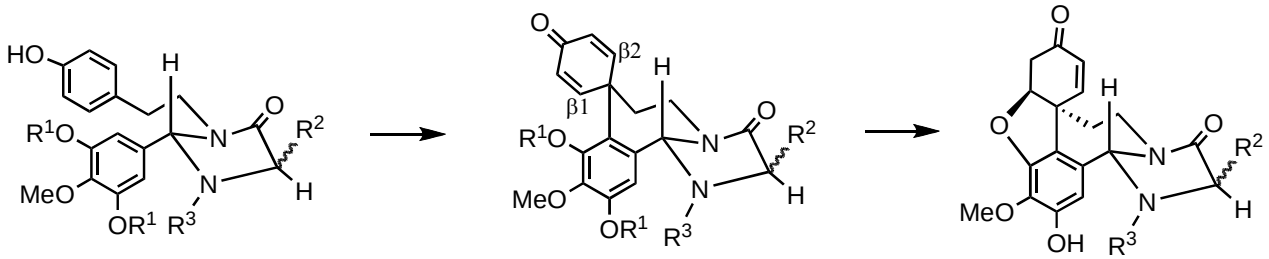


a: PIFA, CF_3CH_2OH, -40 ºC, **b**: BCl_3, CH_2Cl_2, -78 ºC, **c**: Tf_2O, pyridine, **d**: $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H, **e**: L-Selectride, **f:** $LiAlH_4$

Being encouraged by the success in the racemic synthesis of **(±)-51**, we next planned to establish a novel route for the asymmetric synthesis of **(–)-51** that could circumvent narwedine (**53**) in view of the severe allergic responses caused. In order to improve racemic synthesis for asymmetric synthesis, the phenolic hydroxyl group should preferentially attack one of the two β-olefinic carbons of the dienone in the intramolecular Michael addition since the symmetrical dienones (**56**) were converted to racemic mixtures (**57**) by a non-selective intramolecular reaction (Scheme 12).

Herein, remote axis asymmetric induction was used, restricting the conformation of the seven-membered ring of **56** by introducing chiral centers similar to Koga who put an alkoxycarbonyl group onto the seven-membered ring for chiral synthesis of (+)-galanthamine [**(+)-51**].[41] Our strategy was designed so as to introduce another C–N bond of the benzylic position of the gallyl amino moiety of **56** to take advantage of the easily cleavable properties of the benzylic C–N bond and the aza-acetal bond. We decided to link an optically pure α-amino acid on the benzylic C–N bond of **56** to afford a chiral imidazolidinone [**A**]. Specifically, the conformation of the seven-membered ring of the coupling product [**B**] would be restricted by the fused-imidazolidinone composed of an amino acid to afford [**C**] as a single Michael adduct (Scheme 13). Originally, synthesis of chiral 1,3-imidazolidin-5-one and its application to chiral induction was reported by Seebach, who proposed the concept as Self Regeneration of Stereocenters (SRS).[46] Among naturally abundant amino acids, phenylalanine and valine were chosen as the chiral auxiliary to form the fused imidazolidinone because the bulky isopropyl and benzyl groups on amino acid residues would provide promising stereoselectivities. In the beginning, we simply expected the spontaneous Michael addition after deprotection of R^1 in [**B**] to progress diastereoselectively to afford cyclic ether [**C**] with the desired configuration.

Scheme 13. Synthetic strategy of **(–)-51**

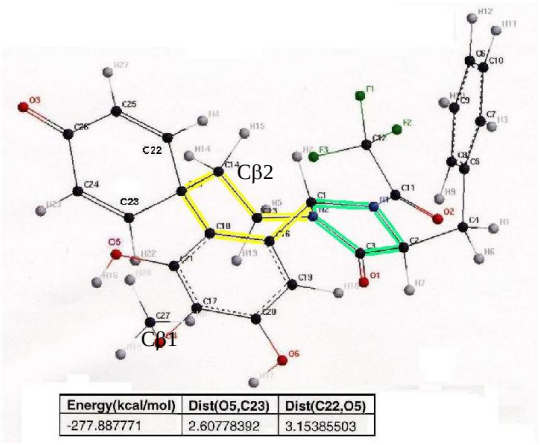


A **B** **C**

As expected, PM3 calculations revealed that the most stable conformer of **B** (R^1 = H, R^2 = Bn, R^3 = CF_3CO), where the chiral imidazolodinone moiety was composed of D-phenylalanine, had a shorter distance between the phenolic oxygen atom and Cβ1 (2.61 Å) than that between the oxygen and Cβ2 (3.15 Å) (Figure 7).

Moreover, the calculation showed that the Michael adduct from the former transition state was more stable than that from the latter transition state by 6.7 kcal/mol (Figure 8). These results supported our expectation that the Michael addition of phenolic hydroxyl groups in **B** bearing a D-amino acid as a chiral auxiliary, predominantly affords a diastereomer that could lead to the desired enantiomers of synthetic intermediates.

Figure 7. Result of PM3 calculations of the transition-state to afford the cyclic ether[39]



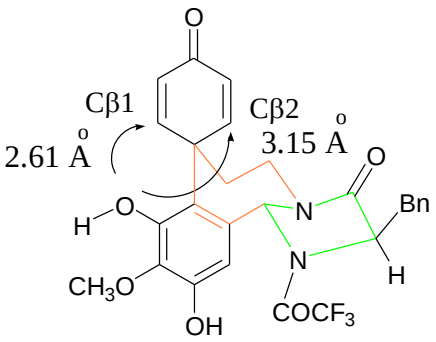
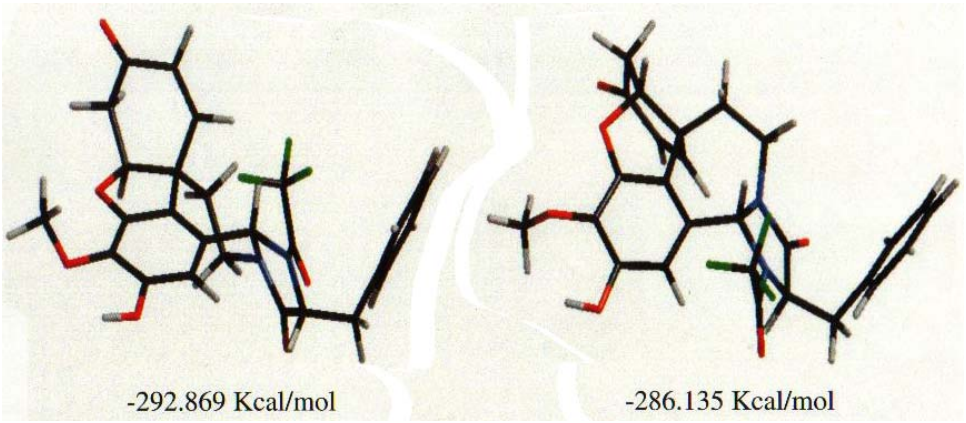
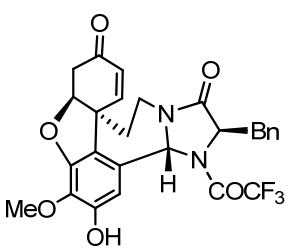
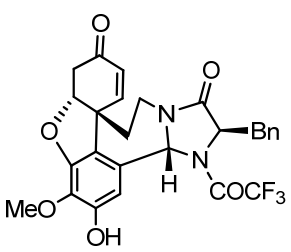


Figure 8. Heat of Formation of the Cyclic Ethers (PM3)[39]

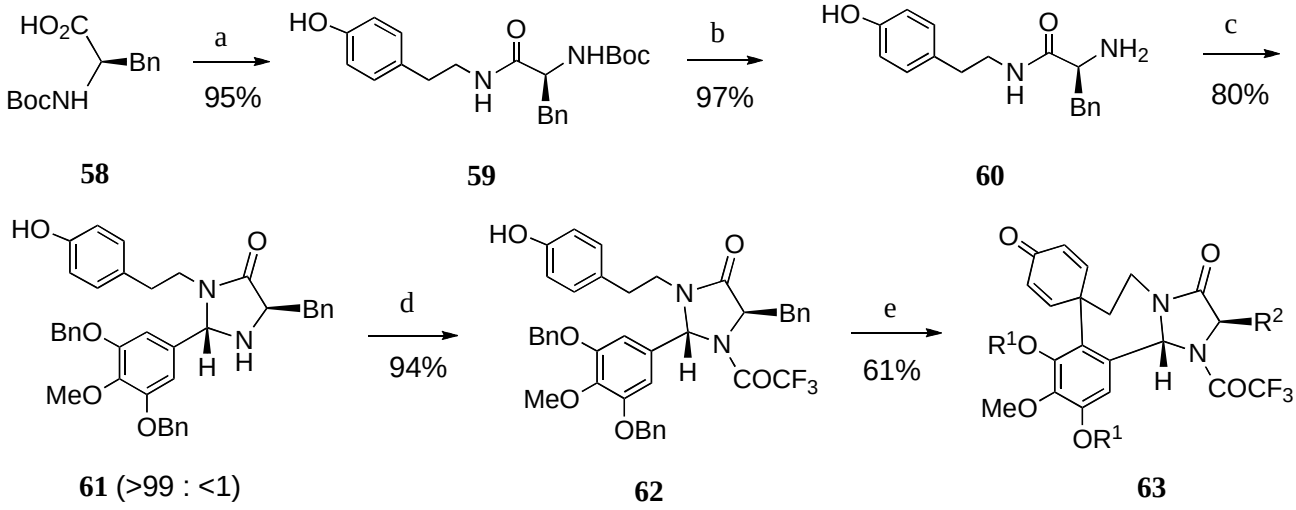






This approach began with the reaction of tyramine and *N*-Boc-D-phenylalanine (**58**) in the presence of EDC·HCl and HOBt to afford amides **59**. Removal of the Boc-group of **59** with methanesulfonic acid to afford amines **60**, the formation of a Schiff base with 3,5-dibenzyloxy-4-methoxybenzaldehyde, and successive treatment with acid yielded imidazolidinone (**61**). The diastereoselectivity in the reaction providing **61** (>98% de) was satisfactorily high.[46] The amino group of **61** was next protected with a trifluoroacetyl group to prepare **62**, a substrate of phenol coupling. The intramolecular oxidative coupling of **62** with PIFA in trifluoroethanol at –40 ºC afforded the highest yield of the corresponding spirodienone **63** (Scheme 14).

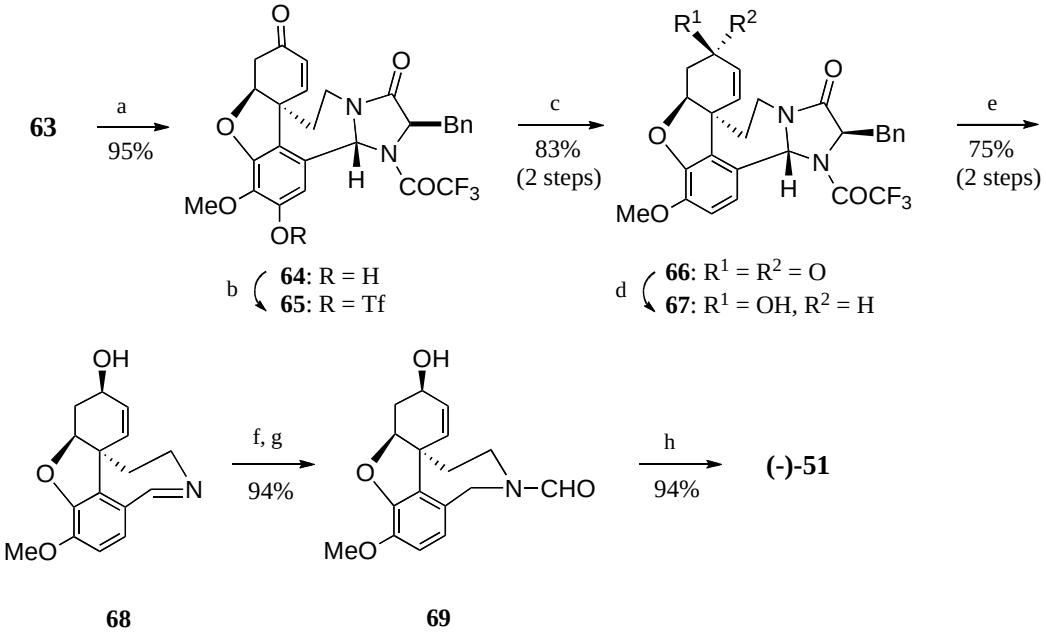
Scheme 14. Synthesis of the key intermediate **63**[39]



a: tyramine, EDC HCl, HOBt, **b**: MsOH in MeOH, **c**: 2,5-dibenzyloxy-4-methoxybenzaldehyde, and HCl, **d**: $(CF_3CO)_2O$, **e**: PIFA

Thus, deprotection of the benzyl group of **63** with boron trichloride at –78 ˚C afforded the desired **64** as a single diastereomer in excellent yield (95%), as expected.[43] In the transformation of **64** into **(–)-51**, we deoxygenated the phenolic hydroxyl group of **64** via the triflate **65** prior to the reduction of α,β-unsaturated ketone, *i.e.*, the cyclic ether **64** was converted to **65** which was reduced with a palladium catalyst in the presence of formate to afford the narwedine derivative **66**[44] and then, the conjugated ketone moiety of **66** was reduced with L-Selectride[45] resulting in the allyl alcohol **67**. The hydrolysis of **67** in an aqueous medium did not yield any imine **68** because of the low solubility of the deoxygenated intermediate **67**. Therefore, more drastic conditions were chosen to achieve hydrolysis and the hydrolysis with potassium hydroxide in aqueous ethanol under refluxed conditions in the presence of a phase transfer, tetrabutylammonium bromide (TBAB), resulted in the imine **68**. Optically pure (–)-galanthamine [**(–)-51**] (100% ee) was finally obtained by the reduction of **68** with sodium borohydride, followed by *N*-formylation using ethyl formate and the subsequent reduction of the formamide **69** with lithium aluminum hydride[39] (Scheme 15).

Scheme 15. Synthesis of **(–)-51**[39]

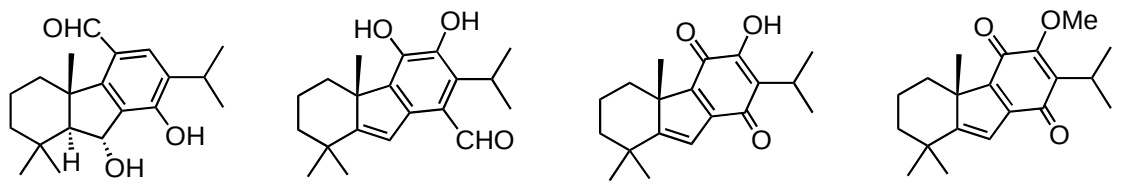


a: BCl_3, **b**: Tf_2O, pyr., **c**: $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H, **d**: L-selectride, **e**: KOH, TBAB, **f**: $NaBH_4$, **g**: HCO_2Et**, h**: $LiAlH_4$

7. ASYMMETRIC HECK REACTION AND SYNTHESIS OF ABEO-ABIETANE-TYPE DITERPENOIDS

Recently, diterpenes having an *abeo*-abietane (4a-methyltetrahydrofluorene) skeleton were identified as a new type of naturally occurring product. Among them, standishinal (**70**) isolated from *Thuja standishii* by Tanaka has been evaluated as a potential anti-tumor agent for treating breast cancer post-menopause because of its appreciable inhibitory activity against aromatase.[47] Thus, other diterpenes possessing the same skeleton are expected to have promising activities for the treatment of female hormone-dependent cancers (Figure 9). In spite of the success in the total synthesis of racemic forms of dichroanal B (**71**), dichroanone (**72**), taiwaniaquinol B, and taiwaniaquinone D and H (**73**),[48] no asymmetric synthesis has been reported to date, except for that by Stoltz and his colleagues.[49] However, it should be noted that **(+)-72** synthesized therein was the antipode of the naturally occurring compound. Against this background, we embarked on a synthetic study of natural form of *abeo*-abietane-type diterpenes using an intramolecular Heck reaction.

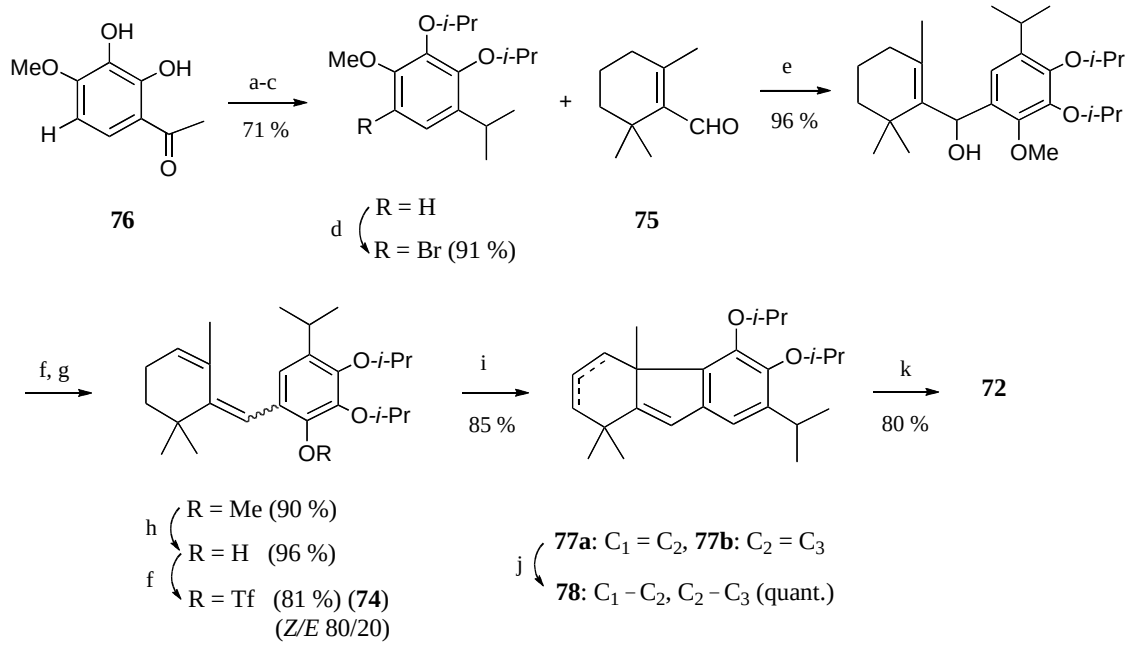
Figure 9. Structure of *abeo*-abietane-type diterpenoids



standishinal (70) **dichroanal B (71)** **dichroanone (72)** **taiwaniaquinone H (73)**

We started with the synthesis of **(±)-72** in advance of the asymmetric synthesis of the *abeo*-abietane-type diterpenoids.[50] The *o*-dienylphenyl triflate **74** was designed as the substrate of the intramolecular Heck reaction, and was prepared from β-cyclocitral (**75**) and 2',3'-dihydroxy-4'- methoxyacetophenone (**76**) (Scheme 16). The palladium-catalyzed reaction proceeded smoothly in DMF at 100 °C to afford the isomers **77a** and **77b**, the isolated double bond of which was selectively reduced with Wilkinson's catalyst providing the desired intermediate **78**. Subsequent dealkylation and formylation yielded **(±)-72** in short steps (Scheme 16).

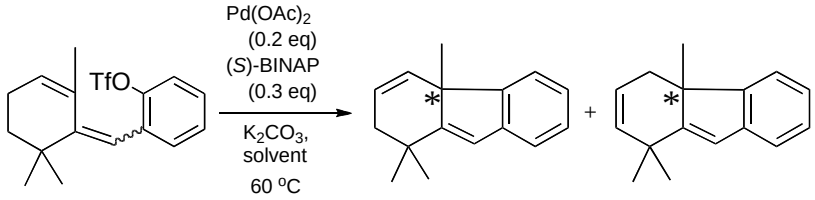
Scheme 16. Synthesis of **(±)-72**[50]



a: MeMgBr, Et_2O, **b**: Et_3SiH, BF_3-Et_2O, Et_2O, **c**: *i*-PrBr, Cs_2CO_3, CH_3CN, **d**: NBS, CH_2Cl_2, **e**: *n*-BuLi, THF, **f**: Tf_2O, pyr. **g**: DABCO, **h**: Dod-SH, NaH, DMF, 120 °C, **i**: $Pd(OAc)_2$ (0.2 eq.), dppp (0.4 eq.), K_2CO_3, DMF, **j**: $RhCl(PPh_3)_3$, H_2, **k**: BCl_3 then $MeOCHCl_2$

In order to apply the synthetic scheme to the asymmetric synthesis of abeo-abietanes, the asymmetric intramolecular Heck reaction of **79** (a mixture of *E*/*Z* isomers) was conducted as a model experiment under Shibasaki's condition where (*S*)-BINAP and potassium carbonate were adopted as a chiral ligand and base, respectively.[51] Fortunately, the cyclized products **80** and **81** were attained in 70% yield with 49% ee at 60 °C (Table 10, entry 1). Changing the solvent from toluene to aprotic polar solvents shortened the reaction period and increased both chemical and asymmetric yields at the same temperature (Table 10). The reaction in DMF gave the most satisfactory result, *i.e.*, 90% yield with 97% ee (Table 10, entry 4). Since the dissociation of palladium and triflate could accelerate the Heck reaction using DMF as a solvent, the high enatioselectivity could be obtained by a route involving a cation intermediate.[52]

Table 10. Solvent's effect in the intramolecular asymmetric Heck reaction of **79** [56]



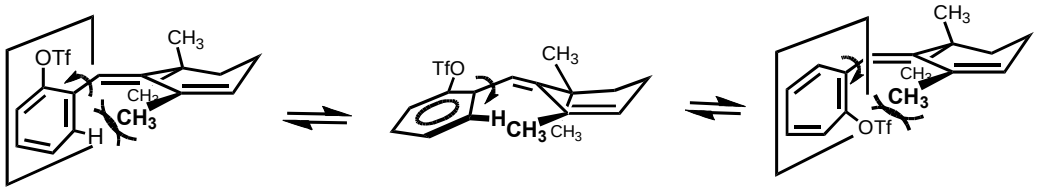
79 (a mixture of *Z*/*E*) **80** **81**

Entry [a]	Conditions		Products		
	Solv.	Time	Yield (%) [b]	**80** / **81**	% Ee (**80**)[c]
1	toluene	40 h	70	38 / 62	49
2	THF	18 h	90	12 / 88	58
3	MeCN	17 h	89	52 / 48	69
4	DMF	7.5 h	90	25 / 75	97

[a] The starting material **79** of *Z*/*E* 84/16 (entry 1, 3) and *Z*/*E* 91/9, (entry 2, 4) was used. [b] The yield was calculated from the *Z* isomer. [c] The ee valeu was determined by chiral HPLC.

Since the two atropisomers were observed at lower temperature than -70 ℃ in the ^{1}H-NMR spectroscopic analysis of the compound, in which the triflate group of **79** was replaced with *N*-Boc-L-phenylalanine, the present asymmetric Heck reaction should proceed under dynamic kinetic resolution via the equilibrium of two atropisomers (Scheme 17).[53]

Scheme 17. Equilibrium between two atropisomers of the substrate **79** of the intramolecular Heck reaction [56]

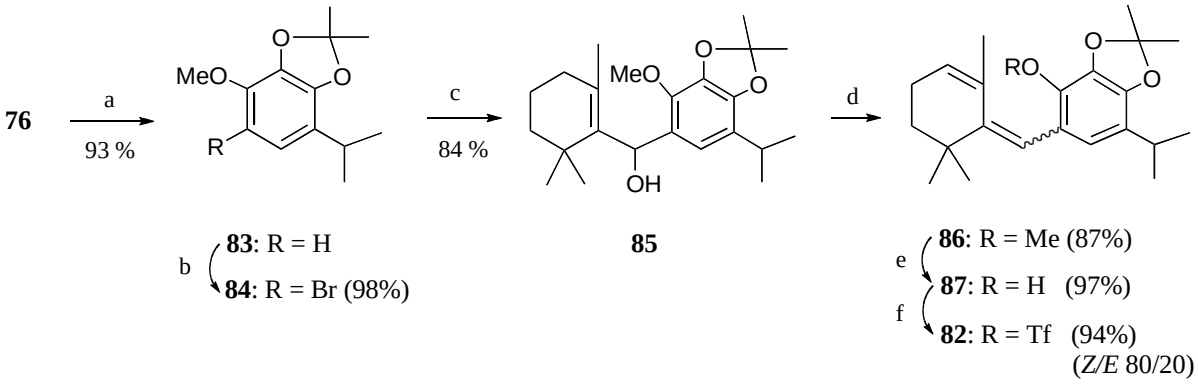


stable conformation **distorted boat form** **stable conformation**

Finally, we applied the intramolecular Heck reaction to the asymmetric synthesis of **(–)-71** and **(–)-72** isolated from roots of *Salvia dichroantha*,[54] and **(–)-73** from *Taiwania cryptomerioides*,[55] Initially, we designed the substrate **82** bearing a rigid acetonide group in the catechol moiety because the flexible

isopropyl group employed in the racemic synthesis of **(±)-72** retarded the access of the palladium complex to a bulky chiral ligand. Thus, **82** was prepared by modifying a previously reported method [50] as shown in Scheme 18. Namely, **76** was treated with acetone in the presence of $BF_3{\cdot}Et_2O$ to give the acetonide **83**, the bromination of which with NBS afforded **84** in excellent yield. After lithiation of the bromide **84** with *n*-butyllithium, the aryllithium generated was reacted with β-cyclocitral (**75**) to afford the benzylic alcohol **85**. Dehydration of **85** by treatment with methanolic hydrochloric acid gave the diene **86** as a mixture of *E* and *Z* isomers (*ca* 1:4). After the demethylation of the methyl ether in **86** with dodecane thiol (Dod-SH) and sodium hydride in DMF, the phenolic compound **87** was converted to the triflate **82**.

Scheme 18. Preparation of the substrate of the Heck reaction **82**[56]

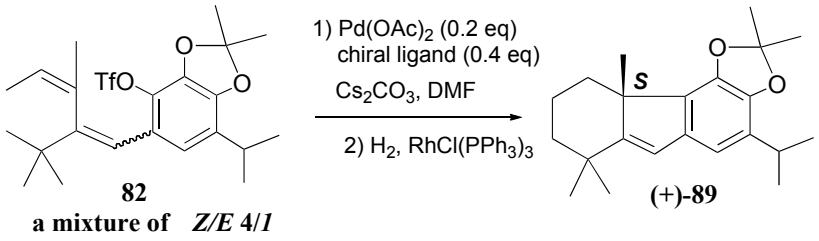


a: acetone, BF_3-Et_2O, Et_2O, **b**:NBS, CH_2Cl_2, **c**: *n*-BuLi, **75**, THF, **d**: HCl, MeOH, **e**: Dod-SH, NaH, DMF, 120 °C**, f**: Tf_2O, pyr.

The intramolecular asymmetric Heck reaction of the triflate **82** (a mixture of *E*/*Z* isomers) was tried using palladium (II) acetate, chiral BINAP, and cesium carbonate in DMF at 100 °C, the hydrogenated product of which showed 76% ee (Table 11, entry 1). A remarkable temperature-dependence to improve the ee was not observed in the Heck reaction with chiral BINAP (Table 11, entries 1-3). Among several other chiral phosphorous ligands having C_2-symmetry, Synphos (**88**) exhibited a further improvement in ee and reaction time (Table 11, entries 4-6). Moreover, temperature dependence was observed in the reaction. Finally, it was found that the Heck reaction of **82** and successive hydrogenation gave **89** in good yield (<86% in 2 steps) with excellent ee (94-98% ee) when (*R*)-**88** was used as a ligand.

The absolute configuration of **(+)-89** was confirmed to be *S* by a single-crystal X-ray diffraction analysis after deriving to **90** with NBS. Because the *E*-isomer of **82** also afforded the desired product in 46% yield under the Heck conditions, which meant the existence of equilibrium between the *E*/*Z* isomers, the *E*/*Z* mixture was used without any separation in the reactions.

Table 11. Heck reaction of **82** with chiral ligands having C_2-symmetry and ORTEP of **90**[56]

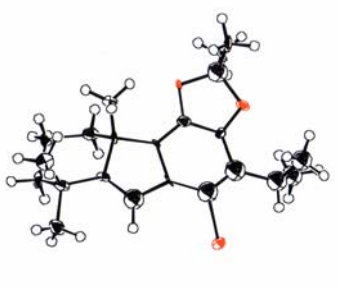


82
a mixture of *Z/E* 4/1

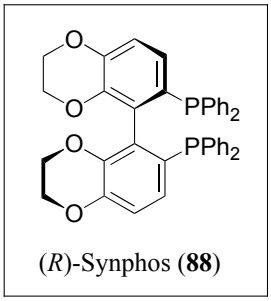
(+)-89

Entry	Chiral ligands	Temp.	Time (h)	Yield*	%Ee
1	(*R*)-BINAP	100 °C	25	83	76
2	(*R*)-BINAP	90 °C	45	84	76
3	(*R*)-BINAP	80 °C	90	83	77
4	(*R*)-Synphos	100 °C	6	85	94
5	(*R*)-Synphos	90 °C	9	72	97
6	(*R*)-Synphos	80 °C	26	72	98

* The numerical values show chemical yields (%) in the Heck reaction. The subsequent hydrogenation proceeded quantitatively.



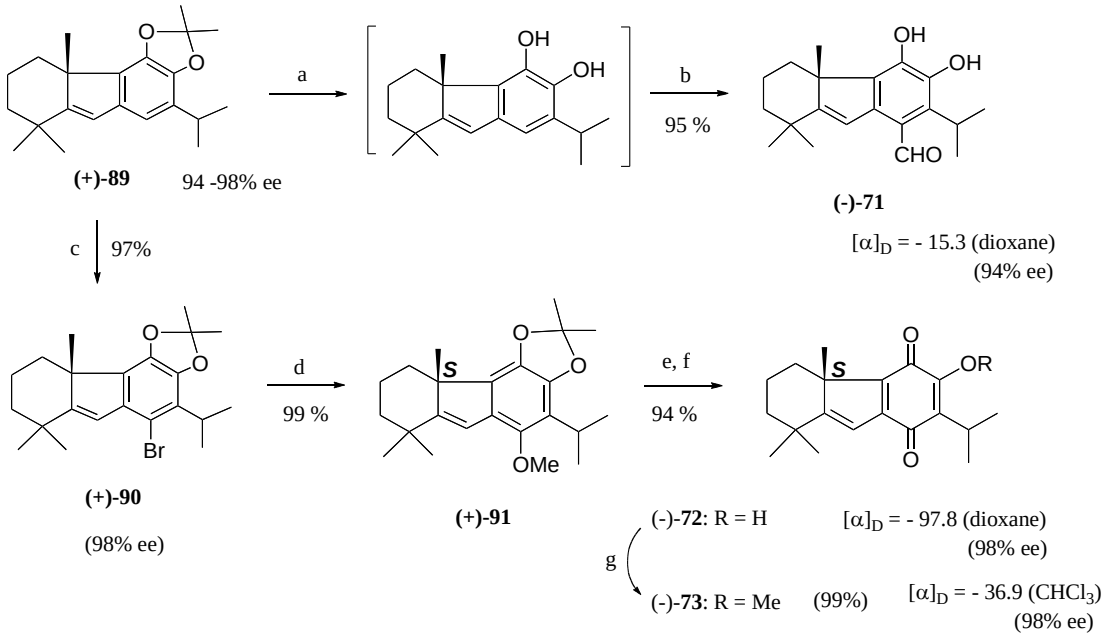
ORTEP of **90**



(*R*)-Synphos (**88**)

Finally, the acetonide of **(+)-89** (94.2% ee) was subjected to deprotection with HCl-MeOH followed by the Friedel-Crafts type reaction with dichloromethoxymethane in the presence of BCl_3 to give **(–)-71** in 92% yield. Treatment of **(+)-90** (98% ee) with sodium methoxide in the presence of CuI followed by removal of the acetonide and oxidation with DDQ afforded **(–)-72**, which was further transformed to **(–)-73** on treatment with Meerwein reagent (Scheme 19).[56]

Scheme 19. Synthetic routes of **(–)-71**, **(–)-72**, and **(–)-73**[56]



a: HCl, MeOH, 60 °C, **b**: BCl_3, $CHCl_2OCH_3$ (5 eq), CH_2Cl_2, 0 °C, **c**: NBS, **d**: CuI, NaOMe, DMF, MeOH, 100 °C, **e**: BBr_3 (4 eq), CH_2Cl_2, -78 ~0 °C, **f**: DDQ (1.1 eq), CH_2Cl_2, **g**: Me_3OBF_4, DIEA, CH_2Cl_2

We succeeded in the first asymmetric synthesis of naturally occurring *abeo*-abietane type diterpenoids, **(–)-71**, **(–)-72** and **(–)-73**, in 10, 12, and 13 steps with an overall yield of 50, 40, and 39%, respectively. Our routes gave a much higher overall yield and ee with fewer steps than those for racemic and antipodal forms reported to date.

8. CONCLUSION AND ACKNOWLEDGEMENTS

In conclusion, we succeeded in the asymmetric synthesis of physologically and pharmaceutically important compounds by developing novel asymmetric reactions, *i.e.*, tandem Michael addition-MPV reduction, Michael addition of the chiral amine, intramolecular Heck reaction, and asymmetric crystallization of allene 1,3-dicarboxylates. We thank the many coworkers and students involved in these studies. In addition, we acknowledge the financial supports from Grant-in-aid, the Frontier Research Program, and the 21st COE Program from the Ministry of Education, Culture, Sports and Technology, Japan.

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Manabu Node was born in 1945, and received his B.S. in 1967 from Tokushima University. He then moved to Kyoto University and received his M.S. in 1970 and Ph.D. in 1973. He was appointed as Assistant Professor of the Institute of Chemical Research in Dr. Fujita's group. After a year of postdoctoral study with Professor Jung at UCLA, he moved to Dr. Fuji's group as Associate Professor in 1983. He then moved to Kyoto Pharmaceutical University in 1990, where he is currently Professor of Pharmaceutical Manufacturing Chemistry. He was a recipient of Pharmaceutical Society of Japan for Young Scientist (1985) and Miyata Foundation Award (2000). His research interest is in the area of asymmetric synthesis.

Tetsuya Kajimoto was born in 1960, and received his B.S. in 1982 from Tokushima University. He then entered the Graduate School of Kyoto University and received his M.S. in 1984 and Ph.D. in 1989. He was then appointed as Assistant Professor of Kumamoto University. After two years of postdoctoral study with Professor Wong at The Scripps Research Institute (1990-1991), he moved to Frontier Research Program in the Institute of Physical and Chemical Research (RIKEN). He had experienced as Associate Professor in Showa University (1996-1999), Tokyo University of Agriculture and Technology (1999-2003), and Kyoto Pharmaceutical University (2004-2007). Then, he was appointed as Professor in Suzuka University of Medical Science in 2008. He is now Term-limited Professor in Osaka University of Pharmaceutical Sciences.

Minoru Ozeki was born in 1974, and received his Ph.D. in 2004 from Kyoto Pharmaceutical University. After nine months of postdoctoral study with Professor Manabu Node at Kyoto Pharmaceutical University, he worked in Sumitomo chemical Co., Ltd. as a researcher (2005-2007). Then, he was appointed as Assistant Professor of Kyoto Pharmaceutical University. He received The Pharmaceutical Society of Japan Award for Young Scientists (Kinki Branch) in 2008. His research interests are in the areas of asymmetric synthesis.