Biomimetic Synthesis of (±)-Galanthamine and Asymmetric Synthesis of (−)-Galanthamine Using Remote Asymmetric Induction

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(±)-Galanthamine (1) was synthesized in excellent yield by applying PIFA-mediated oxidative phenol coupling of *N*-(4-hydroxy)phenethyl-*N*-(3′,4′,5′-trialkoxy)benzyl formamide (15b) as a key step. Because of the symmetrical characteristics of the pyrogallol moiety in the substrate (15b), the phenol coupling resulted in a sole coupling product except for volatile components from the oxidizing agent. On the basis of the successful results of the above strategy, (−)-galanthamine (1) was synthesized by employing a novel remote asymmetric induction, where conformation of the seven-membered ring in the product of the phenol coupling was restricted by forming a fused-chiral imidazolidinone ring with D-phenylalanine on the benzylic C–N bond of the tri-*O*-alkylated gallyl amino moiety. The conformational restriction and successive debenzylation of the protected hydroxyl groups on the pyrogallol ring caused diastereoselective cyclization to yield a cyclic ether having the desired stereochemistry for the synthesis of (−)-1.

Key words galanthamine; norbelladine; remote asymmetric induction; intramolecular phenol coupling; phenyliodine(III) bis(trifluoroacetate) PIFA; biomimetic synthesis

(−)-Galanthamine (**1**), an alkaloid isolated from the Caucasian snow drop, *Galanthus woronowii*,[1] and another species of the Amaryllidaceae family, *Lycoris radiate*,[2,3] has been reported to have many biological activities, *e.g.*, acting as an allosteric modulator of the nicotinic receptor to secrete acetylcholine as well as a competitive inhibitor of acetylcholine esterase.[4] On the basis of these activities, (−)-**1** was developed as a medicine for Altzheimer's disease, which is considered to be caused by the functional deficiency of cholinergic neural networks, and has been already purchased for clinical use in Europe and the United States.[5] Owing to scarce supplies from the plant source and the significant increase in demand due to the increased average life span in developed countries, the need for a practical total synthesis of (−)-**1** and its stable supply has increased. Synthesis of **1**, where intramolecular oxidative phenol coupling of norbelladine (**2**) was adopted to afford narwedine (**3**), was first attained by Barton and Kirby.[6] Thereafter, much effort has been made to improve their method[7,8] since it was accompanied by the successful preparation of an enantiomerically pure form of (−)-**1** by using resolutional crystallization of (−)-narwedine (**3**).[9] However, the yield of the intramolecular phenol coupling reaction in each synthetic route still remains less than 50%, which hinders the overall yield from reaching a satisfactory level.

While some excellent synthetic approaches of (±)-**1** or (−)-**1** using intramolecular Heck reaction as a key step have been published recently,[10—20] such routes required multiple steps and their overall yields are unsatisfactory. Thus, biomimetic approaches *via* the intramolecular phenol coupling reaction still remain a promising strategy in terms of chemical yield and regioselectivities. Based on this background, we have recently published the total synthesis of (±)-**1** and the asymmetric synthesis of (−)-**1**.[21,22] Here, we would like to report the details of the synthesis.

Results and Discussion

A number of Amarylliaceae alkaloids were confirmed to be biosynthesized by the phenol coupling reaction of norbelladine (**2**), which was derived from L-tyrosine in plants, and the multiple styles of the phenol couplings afford structural diversities of the alkaloids.[23—25] For example, the coupling between the *p*-position of the phenol part and the *o′*-position of the catechol portion affords galanthamine (**1**) alkaloids while *p–p′* and *o–p′* couplings respectively afford crinine (**4**) and lycorine (**5**) alkaloids. The first synthesis of (±)-**1** employed the intramolecular phenol coupling of **2** with potassium ferricyanide but unfortunately preferentially yielded a *p–p′* coupling product rather than the desired *p–o′* coupling product due to steric repulsion.[6] In order to avoid the undesired coupling, the strategy was improved to mask the *p′*-position with a bromo or trimethylsilyl group. However, chemical yields of the coupling could not be increased to more than 50%.[26—42] In addition, the coupling reaction using metal oxidants had the practical disadvantages of releasing toxic chemicals as waste reagents, *e.g.*, cyanides from potassium ferricyanide or heavy metal ions.

To overcome these disadvantages in the synthetic strategies of (±)-**1**, we referred to Koga's procedure where the catechol moiety of **2** was replaced with a pyrogallol group because the symmetrical characteristic of the pyrogallol moiety in the precursor (**6**) made the *p–o′* coupling afford the only possible coupling product.[38,39] Moreover, phenyliodine(III) bis(trifluoroacetate) (PIFA) was chosen as the oxidative reagent for the phenol coupling based on reports that in addition to the coupling product only volatile products, *i.e.*, iodobenzene and trifluoroacetic acid, remained after the PIFA-induced reaction.[33—37,43—49]

At an initial stage of pretesting, we focused on the PIFA-induced phenol coupling of tri-*O*-methylated derivatives (**7a**, **b**) of pyrogallol-type norbelladine (**6**) to synthesize key intermediates **8a** and **8b**, and began with the preparation of

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7a and **7b**. 3,4,5-Trimethoxybenzaldehyde (**9**) was treated with tyramine in the presence of sodium borohydride to afford **10**, which was derived to trifluoroacetamide **7a** and formamide **7b**. Next, the PIFA-mediated intramolecular phenol couplings of **7a** and **7b** were attempted and were found to afford good yields (75 and 95%, respectively) of dienone (**11a**, **b**) when the reaction was carried out at −40 °C in trifluoroethanol, where low nucleophilicity is believed to increase in the chemical yield of the oxidative coupling (Chart 1).[33—37)]

Herein, we were able to show that the use of the PIFA-mediated phenol coupling, where the substrates had a tri-*O*-methyl pyrogallol ring instead of a catechol moiety in the norbelladine skeleton, could provide an excellent method for the synthesis of **1**. However, the attempted demethylation of **11a** and **11b** with boron tribromide at −78 °C to afford tetrahydrodibenzofuran derivatives (**8a**, **b**) was unsuccessful because of difficulties in the selective cleavage of methyl ethers and the occurrence of side-reactions such as dienone-phenol rearrangement.[50)]

Therefore, we considered the synthesis of a substrate (**12a**) that had no protecting groups on the hydroxyl groups at C-3′ and C-5′ of the pyrogallol moiety and could be directly transformed to tetrahydrodibenzofuran **8a** once the coupling reaction had proceeded smoothly. Namely, the *p*-hydroxyl group of methyl gallate (**13a**) was first methylated by conventional methods to afford monomethyl ether **13b** which was derived to aldehyde **14a** *via* primary alcohol **14b**. Reductive amination of **14a** with tyramine in the presence of sodium borohydride and successive treatment of the product **12b** with trifluoroacetic anhydride produced a good yield of trifluoroacetamide **12a**. However, solubility of **12a** in trifluoroethanol, the most suitable solvent for PIFA-mediated reaction,[33—37)] was quite poor and the reaction attained in trifluoroacetic acid produced a low yield (12%) of **8a** probably due to side-reactions triggered by the generation of a radical species on the pyrogallol moiety.

Thus, in order to increase solubility in trifluoroethanol and suppress side reactions, the derivatives **15a**—**g** in which the two hydroxyl groups on the pyrogallol moiety of **12a** were protected with benzyl (Bn), allyl, methoxymethyl (MOM), or *tert*-butyldimethylsilyl (TBS) groups were synthesized by first protecting of the hydroxyl groups in **13b**. First, monomethyl ether **13b** was derived to **16a**—**d** respectively, reduced with lithium aluminum hydride to primary alcohols **17a**—**d**, and oxidized with pyridium chlorochromate or oxygen in the presence of palladium acetate and molecular sieves resulting in aldehydes **18a**—**d**. The aldehydes were treated with tyramine under a reductive condition, *i.e.*, in the presence of sodium borohydride, to afford norbelladine derivatives **19a**—**d**. A formyl group as well as a trifluoroacetyl group were adopted to protecting the secondary amines **19a**—**d** to afford *N*-protected pyrogallol type-norbelladines **15a**—**g** (Chart 2).

After running the phenol coupling of norbelladine derivatives **15a**—**g** with PIFA in trifluoroethanol −40 °C to afford spirodienones **20a**—**g** (Table 1), it was found that allyl ethers **15c**—**d**, MOM ethers **15e**—**f**, and TBS ether **15g** were oxidized to the corresponding siprodienones **20c**—**g** in moderate yields (Table 1, Entries 3—7), and the reaction using benzyl ether **15b** as a substrate resulted in the highest yield (Table 1, Entry 2). The formyl group protected secondary amines better than the trifluoroacetyl group in the reactions with **15a** and **15b** with regard to chemical yield (Table 1, Entries 1, 2). The product **20b** was especially easy to crystallize, and was separated mainly by crystallization from a solution of the worked-up residue in ethyl acetate.

Since achieving phenol coupling attainable on a large scale and satisfying economical and environmental issues were crucial, reactions using dibenzyl ether **15b** as a substrate were attempted at 0 °C to room temperature by changing the solvent from trifluoroethanol to other polar solvents and by switching the oxidizing agent from PIFA to phenyliodine(III) diacetate (PIDA) (Table 2). The reaction with PIDA produced a moderate yield of **20b**, compared to the reaction with PIFA (Table 2, Entries 2, 3, 5). As previously predicted,[33—37)] considerable amounts of by-products **21a**—**d** were obtained in cases using acetic acid, acetonitrile, dimethoxyethane, and isopropanol as solvents due to the gen-

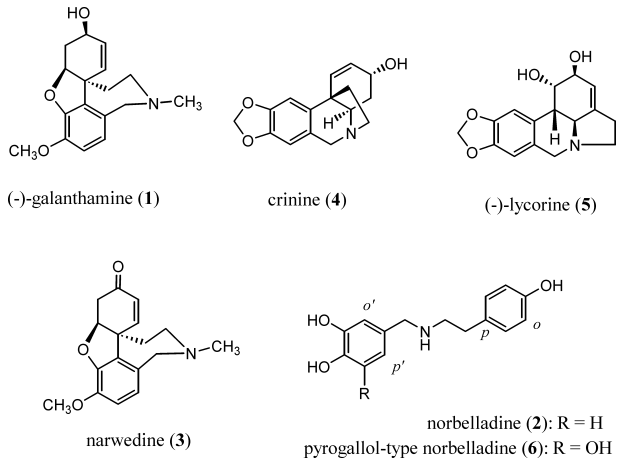


Fig. 1. Galanthamine (**1**) and Its Related Compounds

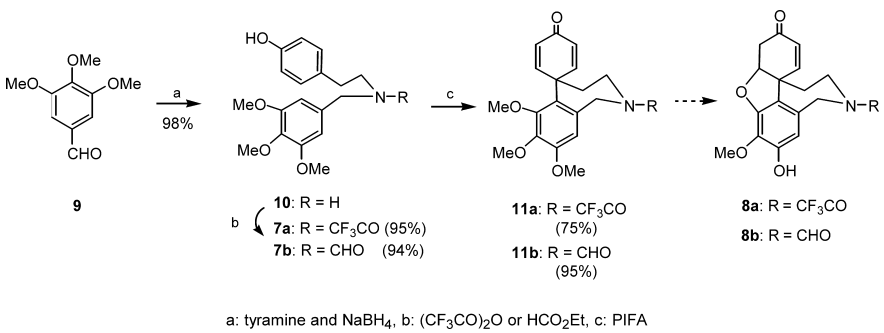


Chart 1. Synthesis of Norbelladine Derivatives (**10**, **7a**, **b**) and Successive Phenol Coupling with PIFA

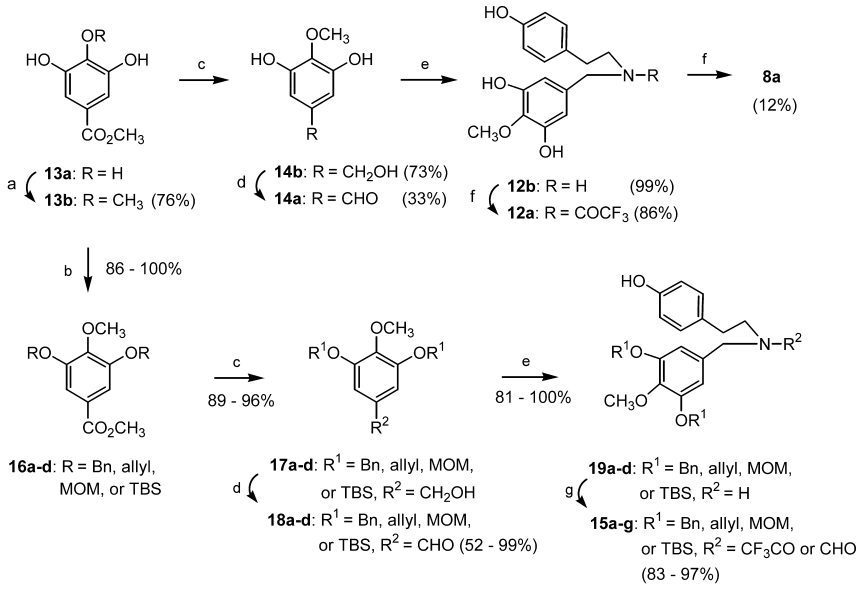
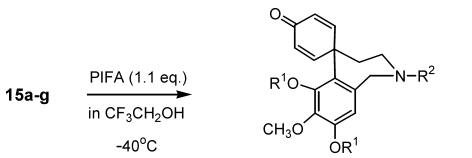


Chart 2. Synthesis of Norbelladine Derivatives (**15a**—**g**)

Table 1. Phenol Coupling Reaction of Norbelladine Derivatives (**15a**—**g**)



Entry	Substrate			Time	Product	Yield (%)
		R^1	R^2			
1	**15a**	Bn	$COCF_3$	1 h	**20a**	53
2	**15b**	Bn	CHO	1 h	**20b**	82
3	**15c**	Allyl	$COCF_3$	4 h	**20c**	60
4	**15d**	Allyl	CHO	15 min	**20d**	48
5	**15e**	MOM	$COCF_3$	15 min	**20e**	45
6	**15f**	MOM	CHO	15 min	**20f**	43
7	**15g**	TBS	$COCF_3$	1 h	**20g**	50

eration of a cation (**22**) or a radical followed by nucleophilic attack of the solvents (Table 2, Entries 4—8). Fortunately, the best yield (85%) was obtained in the reaction conducted with PIFA in trifluoroethanol at room temperature (Table 2, Entry 1). Needless to say, metal oxidants such as manganese(III) acetate and copper(II) acetate gave no productive results.

Next, debenzylation of dienones **20a** and **20b** was performed in order to afford cyclic ethers **8a** and **8b**, respectively, as the resulting products by spontaneous Michael addition of a deprotected hydroxyl group to the dienone moiety. Treatment of **20a** and **20b** with a combination of trifluoroacetic acid and dimethyl sulfide[51—53] afforded good yields (85 and 81%, respectively) of **8a** and **8b**, respectively (Table 3, Entries 1, 2) in spite of an extended reaction time. Replacing trifluoroacetic acid with a stronger acid such as methanesulfonic acid[54] resulted in a faster reaction period, but, the chemical yield (62%) was reduced (Table 3, Entry 4) due to undesired dienone-phenol rearrangements.[50] The use of an odorless sulfide instead of dimethyl sulfide made little difference (Table 3, Entries 3, 5). Deprotection of benzyl ethers with boron trichloride[55—58] could favorably afford in an excellent yield (95%) of **8b** (Table 3, Entry 6).

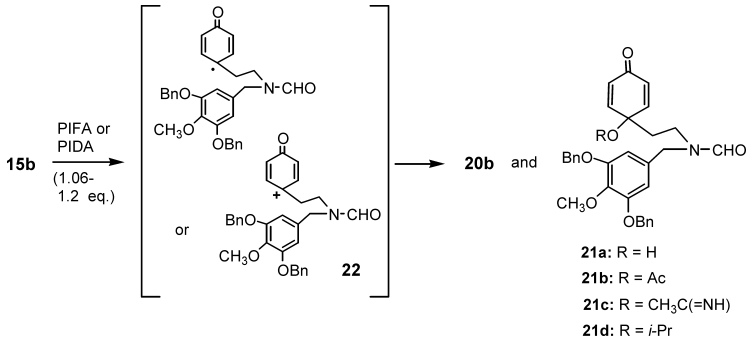
Finally, conversion of the cyclic ether **8b** in order to convert it to (±)-**1** was attained as follows. The extra phenolic hydroxyl group on **8b** was once transformed to triflate **23**, and successive reduction with palladium acetate in the presence of triphenylphosphine, triethylamine and formic acid afforded narwedine derivative **24**.[59] Reaction of **24** with L-Selectride[31,32] followed by reduction of the formyl group to a methyl group with lithium aluminum hydride resulted in a good yield of galanthamine (**1**) from **8b** (Chart 3).

Our synthetic scheme, where the phenol coupling reaction was especially revised by using a combination of the symmetrical substrate and PIFA, improved the overall yield from the norbelladine derivative (**19a**) to (±)-galanthamine (**1**) (44% overall yield, 7 steps).

Herein, it is noteworthy that the successful resolution of galanthamine (**1**) and narwedine (**3**) with di-*p*-toluoyl-D-tartaric acid has been reported.[30,60] Moreover, the synthetic intermediate **3** was found recently to exist as a racemic conglomerate, *i.e.*, a yield of more than 70% of an enantiomerically pure form of **3** could be obtained from a supersaturated solution of (±)-narwedine (**3**) in ethanol and triethylamine, by seeding not only optically pure crystals of **3** but also foreign substances such as (+)- and (−)-galanthamine (**1**).[61] Thus, conversion of **24** to **3** was also examined to find an alternative effective synthetic route of optically pure (−)-**1**. The carbonyl group of **24** was protected with ethylene glycol to give acetal **25**, which was reduced with lithium aluminum hydride, followed by deprotection of the acetal group with acid to achieve an overall good yield (76%) of (±)-**3**.

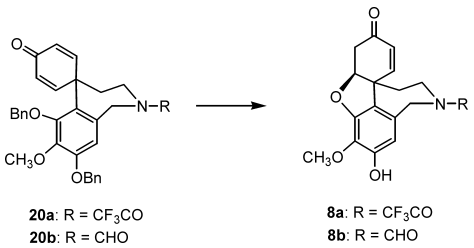
Encouraged by the success in the racemic synthesis of (±)-**1** and to provide an alternative synthesis of **3**, which is a key intermediate for the practical synthesis of (−)-galan-

Table 2. Phenol Coupling Reaction of **15b** in Several Kinds of Solvent



Entry	Oxidant	Solvent	Temp. (°C)	Time (min)	Product (%)					15b
					20b	**21a**	**21b**	**21c**	**21d**	
1	PIFA	CF_3CH_2OH	r.t.	15	85					
2	PIDA	CF_3CH_2OH	r.t.	30	54					
3	PIDA	CF_3CO_2H	r.t.	20	56	23				6
4	PIFA	CF_3CO_2H	0	40	50	13				8
5	PIDA	CF_3CO_2H	r.t.	20	36		20			
6	PIFA	CH_3CN	0	30	32			11		30
7	PIFA	DME	r.t.	15	5	13				14
8	PIFA	*i*-PrOH	0	45	24	5			11	34

Table 3. Debenzylation of **20a** and **20b**



Entry	Substrate	Reagent	Solvent	Temp.	Time	Product	Yield (%)
1	**20a**	CF_3CO_2H	CH_3SCH_3	r.t.	5 d	**8a**	85
2	**20b**	CF_3CO_2H	CH_3SCH_3	r.t.	4 d	**8b**	81
3	**20b**	CF_3CO_2H	$C_{12}H_{25}SCH_3$	r.t.	4 d	**8b**	77
4	**20b**	CH_3SO_3H	CH_3SCH_3	r.t.	2 h	**8b**	62
5	**20b**	CH_3SO_3H	$C_{12}H_{25}SCH_3$	r.t.	2 h	**8b**	57
6	**20b**	BCl_3	CH_2Cl_2	−78 °C	20 h	**8b**	95

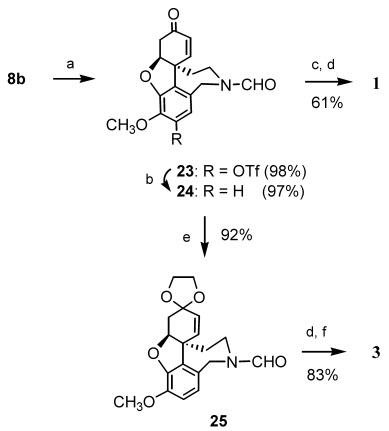


Chart 3. Synthesis of Galanthamine (**1**) and Narwedine (**3**)

thamine (**1**), we next planned to establish a novel route for the asymmetric synthesis of (−)-**1** that could circumvent narwedine (**3**) 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 (**20a**, **b**) were converted to racemic mixtures (**8a**, **b**) by non-selective intramolecular reaction (Table 3).

Remote asymmetric induction was used, restricting conformation of the seven-membered ring of **20a** by introducing chiral centers similar to Koga who put an alkoxycarbonyl group onto the seven-membered ring for chiral synthesis of (+)-galanthamine (**1**).[39] Our strategy was designed so as to introduce another C–N bond on the benzylic position of the gallyl amino moiety of **20a** to take advantage of the easily cleavable properties of the benzylic C–N bond and the aza-

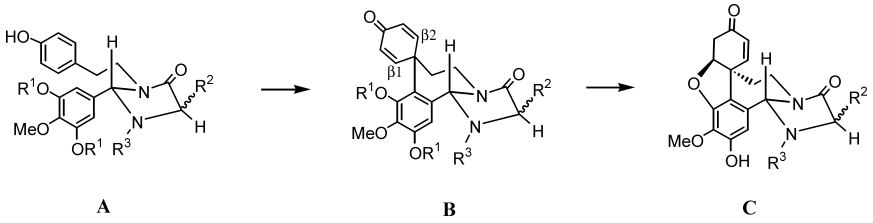


Chart 4

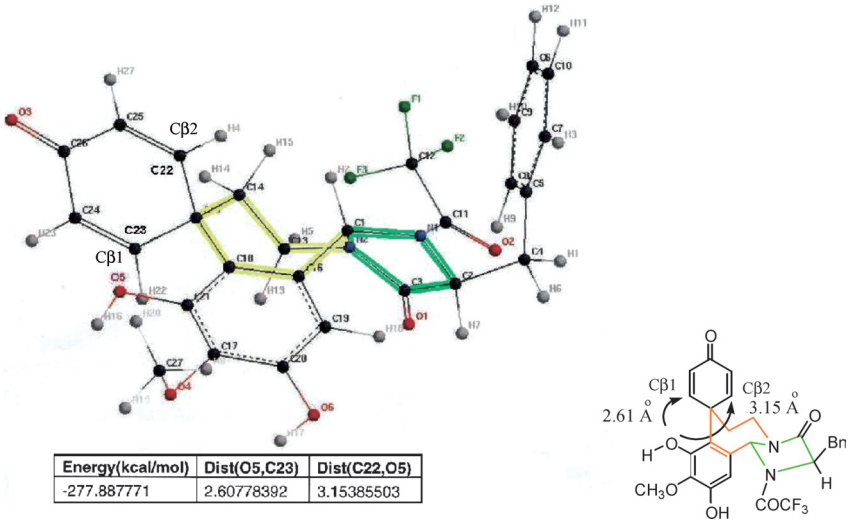


Fig. 2. PM3 Calculation of the Intermediate

acetal bond. We decided to link an optically pure α-amino acid on the benzylic C–N bond of **20a** 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 (Chart 4).

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).[62—64]

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 that the spontaneous Michael addition after deprotection of R^1 in **B** would progress diastereoselectively to afford cyclic ether (**C**) with the desired configuration. As expected, PM3 calculation 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 shorter distance between the phenolic oxygen atom and Cβ1 (2.61 Å) than that between the oxygen and Cβ2 (3.15 Å) (Fig. 2).

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 (Fig. 3). 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 be led to the desired enantiomers of synthetic intermediates.

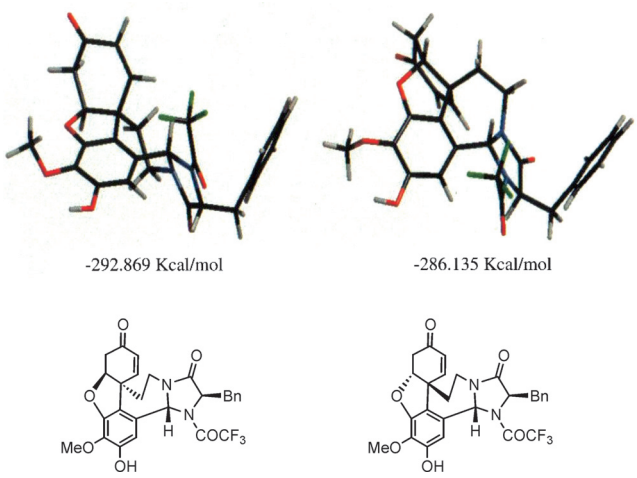


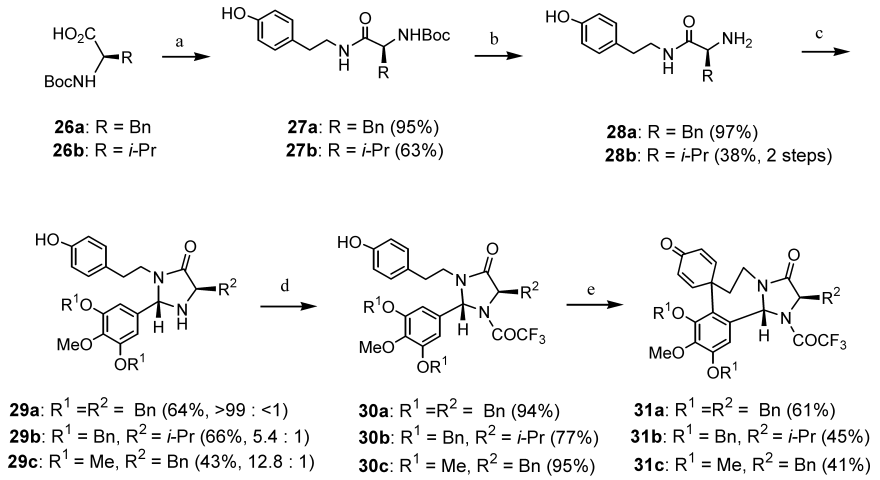
Fig. 3. Heat of Formation of the Cyclic Ether (PM3)

On the basis of foregoing, this synthetic strategy began with the reaction of tyramine and *N*-Boc-D-phenylalanine (**26a**) or *N*-Boc-D-valine (**26b**) in the presence of EDC·HCl and HOBt to afford amides **27a**, **b**. Removal of the Boc-group of **27a** and **27b** with methanesulfonic acid to afford amines **28a**, **b** and following the formation of a Schiff base with **18a**, and the successive treatment with acid yielded imidazolidinone (**29a**, **b**), respectively, while the acid treatment of **28a** followed by treatment with **9** under acidic condition resulted in **29c**. The diastereoselectivity in the reaction providing **29a** (>98% de) was much higher than those the others (69% de in **29b** and 86% de in **29c**) and the stereochem-

istry of the major isomers was determined to be *trans* based on the NOESY spectrum. The configuration of the major isomers was also supported by the experimental data in the synthesis of imidazolidinone derivatives, which was reported by Seebach.[62—64)]

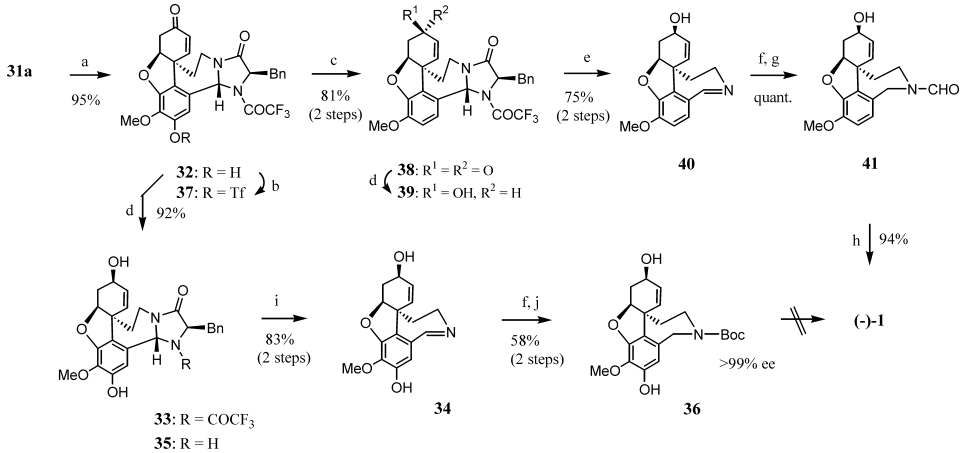
The amino group of **29a** was next protected with a trifluoroacetyl group to prepare **30a**, a substrate of the phenol coupling. The imidazolidinone derivatives **30b** and **30c** were also prepared from **29b** and **29c** in order to compare the coupling reactions. Among the intramolecular oxidative couplings of **30a**—**c** with PIFA in trifluoroethanol, the reaction of **30a** at −40 °C afforded the highest yield of corresponding spirodienone **31a**. When the reaction was conducted at room temperature similar to that in Table 2, entry 1, the imidazolidinone moiety seemed to decompose. In addition, the phenol coupling of the compound with a formyl group instead of a trifluoroacetyl group in **30a** with PIFA resulted only in a low yield (33%). Although the yield (61%; the best record in our experiments) was not satisfactory in comparison with that obtained in the reaction of **20b**, it was higher than any other reported reactions using norbelladine derivatives as substrates.[26—42)] Because of the high stereoselectivity on forming imidazolidinone and the good chemical yield in the successive phenol coupling, imidazolidinone **29a** with benzyl groups as the protecting groups (R^1) and a side chain (R^2) of α-amino acid is considered to be the most suitable synthetic intermediate (Chart 5).

Thus, deprotection of the benzyl group of **31a** with boron trichloride at −78 °C afforded an excellent yield (95%) of **32**.[55—58)] In the first strategy of transformation from **32** to (−)-**1**, we tried to remove the chiral imidazolidinone moiety in the early steps since the presence of a fused ring caused complexities and broadness of the NMR spectra, which interfered with structure analysis. Thus, **32** was first reduced with L-Selectride to afford allyl alcohol **33**, where hydrolysis with sodium hydroxide to imine **34** *via* secondary amine **35** proceeded smoothly at room temperature. Successive reduction of **34** with sodium borohydride and protection of the amino group with a Boc group resulted in **36**, with an optical purity of >99% e.e. could be secured by means of a chiral HPLC settled with a DAICEL CHIRALCEL OD column (Chart 6). The high optical purity of **36** confirmed that the intramolecular Michael addition progressed to afford cyclic ether **32** with high stereoselectivity. However, triflation of **36** with triflic



a: tyramine, EDC HCl, HOBt, **b**: MsOH in MeOH, **c**: **18a** or **9** and HCl, **d**: $(CF_3CO)_2O$, **e**: PIFA

Chart 5



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**: $LiAlH_4$, **i**: NaOH, **j**: $(Boc)_2O$

Chart 6

anhydride and successive reduction of triflate with a palladium catalyst in the presence of formate[59] reduced the double bond of the allylic alcohol moiety. In view negative results in the conversion of **32** to (−)-galanthamine (**1**), we revised the synthetic strategy to deoxygenate the phenolic hydroxyl group of **32** *via* triflate **37** prior to the reduction of α,β-unsaturated ketone, *i.e.*, cyclic ether **32** was converted to triflate **37** which was reduced with a palladium catalyst in the presence of formate to afford narwedine derivative **38**[59] and then, the conjugated ketone moiety of **38** was reduced with L-Selectride[31,32] resulting in allyl alcohol **39**. The hydrolysis of **39** under the same conditions adopted in the reaction of **33** did not yield any imine **40** because of the low solubility of the deoxygenated intermediate **39** in an aqueous medium. This was in good contrast with the fast hydrolysis of **33**, which could be explained by the higher solubility in an aqueous medium due to the presence of allylic and phenolic hydroxyl groups. 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), finally resulted in imine **40**. Imine **40** was reduced with sodium borohydride, and the final *N*-methylation to galanthamine (**1**) was attained by *N*-formylation using ethyl formate and successive reduction of formamide **41** with lithium aluminum hydride. All the spectral and physical data of synthesized (−)-galanthamine (**1**) were identical with those in publications.

Conclusions

In conclusion, we succeeded in the synthesis of (±)-**1** by using a biomimetic approach, which took advantage of PIFA-mediate oxidative phenol coupling of the structurally symmetrical norbelladine derivative **15b**. Moreover, an asymmetric synthesis of optically pure (−)-**1**, which could circumvent allergenic intermediate **3**, could be attained by using a new type of remote asymmetric induction as a key step. Our synthetic route of (−)-**1** provided the highest overall yield (22% from **26a**, 13 steps) among the asymmetric synthesis reported recently.

Experimental

General Infrared (IR) spectra were recorded on a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer and ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL JNM-AL300, Varian Unity INOVA-400 and Varian GEMINI 200 spectrometers with tetramethylsilane as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 (silica gel) (100—200 mesh, Wako) was used for open column chromatography. Flash column chromatography was performed by using Silica Gel 60N (Kanto Chemical Co., Inc.) as a solid support of immobile phase. Kieselgel 60 F-254 plates (Merck) were used for thin-layer chromatography (TLC). Preparative TLC (PTLC) was conducted with Kieselgel 60 F-254 plate (0.25 mm, Merck) or Silica gel 60 F-254 plate (0.5 mm, Merk). Unless purification with silica gel gave a pure enough compound, the compounds were further treated with a recycle HPLC (JAI LC-908) on GPC column (JAIGEL 1H and 2H). In the case it is possible, diastereomeric mixtures were also separated by a recycle HPLC (JAI LC-908) on silica gel column (Kusano Si-10) after the purification mentioned above.

***N*-(4-Hydroxy)phenethyl-*N*-(3,4,5-trimethoxy)benzylamine (10)** Tyramine (4.20 g, 30.6 mmol) was added to a solution of **9** (5.00 g, 25.5 mmol) in methanol (50 ml) and the mixture was stirred for 2 d at room temperature. After cooling the mixture at 0 °C, sodium borohydride (1.04 g, 27.5 mmol) was added to the reaction mixture, which was stirred for 24 h at room temperature. After the reaction, the reaction mixture was evaporated and crystallized from methanol to afford **10** (7.77 g, 98%) as colorless crystals; mp 161—163 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.77 (2H, t, J=6.9 Hz, Ar-C$\underline{H}_2$–CH_2–N), 2.89 (2H, t, J=6.9 Hz, CH_2–C$\underline{H}_2$–N), 3.74 (2H, s, Ar-C$\underline{H}_2$–N), 3.80 (6H, s, OCH_3×2), 3.82 (3H, s, OCH_3), 6.50 (2H, s, Ar-H), 6.70 (2H, d, J=8.5 Hz, Ar-H), 7.03 (2H, d, J=8.5 Hz, Ar-H). ^{13}C-NMR (50 MHz , $CDCl_3$) δ: 35.3, 50.8, 54.4, 56.4, 61.2, 105.4, 115.9, 130.0, 131.2, 135.5, 137.2, 153.5, 155.0. IR ($CHCl_3$) cm^{-1}: 3009, 1593, 1514, 1464, 1331, 1240, 1130, 1003. FAB-MS m/z: 318 (M+H$^+$). HR-MS m/z: 318.1701 (Calcd for $C_{18}H_{24}NO_4$: 318.1705). *Anal.* Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.99; H, 7.29; N, 4.45.

***N*-(4-Hydroxy)phenethyl-*N*-(3,4,5-trimethoxy)benzyltrifluoroacetamide (7a)** Trifluoroacetic anhydride (0.13 ml, 0.9 mmol) was added to a solution of **10** (110 mg, 0.56 mmol) in pyridine (1.0 ml) at 0 °C and the mixture was stirred for 1 h at room temperature. After the reaction, the reaction mixture was extracted with ethyl acetate and the organic layer was successively washed with 1 M hydrochloric acid, a saturated aqueous solution of sodium bicarbonate, and a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol=50 : 1) to afford **7a** (96.5 mg, 95%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.78 (1H, t, J=7.4 Hz, Ar-C$\underline{H}_2$–CH_2), 2.83 (1H, t, J=8.1 Hz, Ar-C$\underline{H}_2$–CH_2), 3.47 (1H, t, J=8.1 Hz, CH_2–C$\underline{H}_2$–N), 3.52 (1H, t, J=7.4 Hz), 3.83 (6H, s, OCH_3), 3.84 and 3.85 (3H, s, OCH_3), 4.33 and 4.58 (2H, s, Ar-CH_2N), 5.83 and 5.85 (1H, s, OH), 6.42 and 6.77 (2H, s, Ar-H), 6.78 and 6.80 (2H, d, J=8.5 Hz, Ar-H), 6.99 (d, J=8.5 Hz, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.3, 34.7, 48.8, 50.2, 51.9, 52.0, 56.5, 56.5, 61.2, 61.2, 104.7, 105.4, 115.9, 116.1, 118.3, 118.5, 129.4, 130.1, 130.2, 130.7, 131.3, 138.0, 138.1, 153.9, 154.0, 155.1, 155.3. IR ($CHCl_3$) cm^{-1}: 3009, 1686, 1595, 1516, 1464, 1240, 1196, 1167, 1150, 1132, 1001. FAB-MS m/z: 413 (M$^+$). HR-MS m/z: 413.1454 (Calcd for $C_{20}H_{22}F_3NO_5$: 413.1450).

***N*-(4-Hydroxy)phenethyl-*N*-(3,4,5-trimethoxy)benzylformamide (7b)** A suspension of **10** (2.00 g, 6.30 mmol) in ethyl formate (40 ml) was refluxed for 4 d. After the reaction, the organic solvent was evaporated and the residue was purified by recrystallization from ethyl acetate to afford **7b** (2.05 g, 94%) as colorless crystals; mp 117—119 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.72 and 2.75 (2H, t, J=6.9 Hz, Ar-C$\underline{H}_2$–CH_2–N), 3.38 and 3.48 (2H, t, J=6.9 Hz, Ar-CH_2–C$\underline{H}_2$–N), 3.83 (6H, s, OCH_3×2), 3.84 (3H, s, OCH_3), 4.20 and 4.48 (2H, s, Ar-CH_2–N), 6.33 and 6.48 (2H, s, Ar-H), 6.74 and 6.77 (2H, d, J=8.5 Hz, Ar-H), 6.91 and 7.01 (2H, d, J=8.5 Hz, Ar-H), 7.83 and 8.23 (1H, s, CHO). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.8. 34.1, 44.2, 46.3, 49.2, 52.4, 56.5, 56.5, 61.2, 104.7, 105.7, 115.8, 116.1, 129.1, 130.1, 130.2, 130.2, 131.7, 132.3, 137.9, 138.1, 153.8, 154.0, 155.4, 155.8, 163.4, 163.8. IR ($CHCl_3$) cm^{-1}: 3007, 1665, 1595, 1516, 1464, 1240, 1130, 1003. FAB-MS m/z: 346 (M+H$^+$). HR-MS m/z: 346.1657 (Calcd for $C_{19}H_{24}NO_5$: 346.1654). *Anal.* Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.14; H, 6.72; N, 4.32.

2-Trifluoroacetyl-6,7,8-trimethoxy-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (11a) A solution of PIFA (0.21 g, 0.50 mmol) in 2,2,2-trifluoroethanol (5.0 ml) was added to a solution of **7a** (0.19 g, 0.45 mmol) in 2,2,2-trifluoroethanol (3.0 ml) at −40 °C and the mixture was stirred for 2 h with keeping the temperature. After the reaction, the organic solvent in the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate=1 : 1) to afford **11a** (0.14 g, 75%) as colorless crystals; mp 185—187 °C (ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.34 (2H, t, J=6.1 Hz, C$\underline{H}_2$–CH_2–N), 3.63 and 3.64 (3H, s, OCH_3), 3.77 and 3.79 (3H, s, OCH_3), 3.87 and 3.89 (3H, s, OCH_3), 3.85 and 3.90 (2H, t, J=6.1 Hz, CH_2–C$\underline{H}_2$–N), 4.78 and 4.82 (2H, s, Ar-CH_2–N), 6.31 (2H, d, J=10.2 Hz), 6.45 and 6.63 (1H, s, Ar-H), 6.93 and 6.99 (2H, d, J=10.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.0, 38.5, 44.7, 45.5, 45.5, 47.3, 47.6, 48.4, 49.2, 56.3, 56.4, 60.8, 60.9, 61.35, 61.37, 109.3, 110.1, 115.3, 118.1, 123.0, 123.4, 126.95, 126.98, 131.5, 131.6, 142.4, 142.6, 153.1, 154.3, 154.4, 154.45, 154.53, 185.8, 185.9. IR ($CHCl_3$) cm^{-1}: 1670, 1661, 1620, 1595, 1466, 1332, 1184, 1150, 1128, 1001. FAB-MS m/z: 412 (M+H$^+$). HR-MS m/z: 412.1378 (Calcd for $C_{20}H_{21}F_3NO_5$: 412.1372).

2-Formyl-6,7,8-trimethoxy-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (11b) A solution of PIFA (47 mg, 0.11 mmol) in 2,2,2-trifluoroethanol (0.5 ml) was added to a solution of **7b** (35 mg, 0.1 mmol) in 2,2,2-trifluoroethanol (0.5 ml) at −40 °C and the mixture was stirred for 15 min with keeping the temperature. After the reaction, the organic solvent in the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane : acetone=15 : 1) to afford **11b** (32.8 mg, 95%) as colorless crystals; mp 157—159 °C (ethyl

acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.29 and 2.33 (2H, t, J=6.2 Hz, $C\underline{H}_2$–CH_2–N), 3.61 and 3.63 (3H, s, OCH_3), 3.68 and 3.73 (2H, t, J=6.2 Hz, CH_2–$C\underline{H}_2$–N), 3.76 and 3.78 (3H, s, OCH_3), 3.88 and 3.89 (3H, s, OCH_3), 4.64 and 4.70 (2H, s, Ar-CH_2–N), 6.31 (2H, d, J=10.1 Hz), 6.48 and 6.63 (1H, s, Ar-H), 6.96 and 7.01 (2H, d, J=10.1 Hz), 8.19 and 8.24 (1H, s, CHO). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.6, 38.8, 45.7, 45.9, 47.5, 50.6, 56.2, 56.3, 60.8, 60.9, 61.3, 61.4, 66.2, 108.4, 109.6, 123.4, 123.5, 126.6, 126.8, 133.3 133.5, 142.0, 142.3, 152.9, 153.0, 154.6, 154.7, 154.9, 162.1, 162.8, 186.1, 186.1. IR ($CHCl_3$) cm^{-1}: 1663, 1620, 1593, 1427, 1332, 1126. FAB-MS m/z: 344 ($M+H^+$). HR-MS m/z: 344.1494 (Calcd for $C_{19}H_{22}NO_5$: 344.1498). *Anal.* Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.22; H, 6.26; N, 4.33.

Methyl 3,5-Dihydroxy-4-methoxybenzoate (13b) Potassium carbonate (0.9 g, 6.5 mmol) was added to a solution of methyl gallate (**13a**) (1.0 g, 5.4 mmol) in *N*,*N*-dimethylformamide (10 ml) and the mixture was stirred for 1 h at 85 °C. After cooling the reaction mixture to 0 °C, methyl iodide (0.8 g, 5.6 mmol) was added and the reaction mixture was stirred for 30 min at 0 °C and kept stirring for another 24 h at room temperature. After the reaction, the mixture was filtered to remove precipitates and the filtrate was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol=50 : 1) to afford **13b** (819.5 mg, 76%) as colorless needles; mp 147—148 °C (toluene). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.75, 3.78 (each 3H, s, OMe), 6.96 (2H, d, J=0.7 Hz, Ar-H), 9.49 (2H, s, OH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 52.0, 59.7, 108.5 (2C), 124.5, 139.7, 150.7 (2C), 166.0. IR ($CHCl_3$) cm^{-1}: 3531, 3265, 2952, 1714, 1595, 1438, 1337, 1236, 1198. EI-MS m/z: 198 (M^+). HR-MS m/z: 198.0533 (Calcd for $C_9H_{10}O_5$: 198.0528). *Anal.* Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.78, H, 5.33.

3,5-Dihydroxy-4-methoxybenzyl Alcohol (14b) A solution of **13b** (11.9 g, 60.0 mmol) in tetrahydrofuran (45 ml) was added to a suspension of lithium aluminum hydride (9.1 g, 24.0 mmol) in tetrahydrofuran (240 ml) at 0 °C, and the mixture was stirred for 2 h at 55 °C. After the reaction, ethyl acetate and saturated aqueous solution of sodium sulfate were added. The mixture was filtered through celite, and the filtrate was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol=50 : 1) to afford **14b** (7.48 g, 73%) as colorless needles (chloroform); mp 171—173 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.64 (3H, s, OMe), 4.25 (2H, d, J=5.5 Hz, CH_2), 4.95 (1H, t, J=5.9 Hz, OH), 6.25 (2H, s, Ar-H), 8.90 (2H, s, OH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 60.1, 63.2, 105.9 (2C), 134.5, 138.3 (2C), 150.8 (2C). IR ($CHCl_3$) cm^{-1}: 3435, 1601, 1528, 1433, 1346, 991, 961. EI-MS m/z: 170 (M^+). HR-MS m/z: 170.0583 (Calcd for $C_8H_{10}O_4$: 170.0579).

3,5-Dihydroxy-4-methoxybenzaldehyde (14a) A solution of **14b** (3.4 g, 20.0 mmol) in tetrahydrofuran (50 ml) was added to a suspension of pyridinium chlorochromate (8.6 g, 40.0 mmol) and Celite® in tetrahydrofuran (50 ml) at 0 °C, and the mixture was stirred for 1 d at room temperature. After the reaction, the reaction mixture was filtered and the filtrate was evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=1 : 1) to afford **14a** (1.11 g, 33%) as colorless crystals; mp 148—150 °C (chloroform). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.77 (3H, s, OMe), 6.86 (2H, s, Ar-H), 9.62 (2H, s, OH), 9.71 (1H, s, CHO). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 59.7, 108.6 (2C), 131.7, 141.1, 151.3 (2C), 192.0. IR ($CHCl_3$) cm^{-1}: 3260, 1693, 1597, 1524, 1350, 1126. EI-MS m/z: 168 (M^+). HR-MS m/z: 168.0413 (Calcd for $C_{31}H_{29}NO_5$: 168.0422).

***N*-(3,5-Dihydroxyl-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethylamine (12b)** Tyramine (720 mg, 5.25 mmol) was added to a solution of **14a** (840 mg, 5 mmol) in methanol (15 ml) and the mixture was stirred for 25 min at room temperature. And then, sodium borohydride (190 mg, 5 mmol) was added to the reaction mixture, which was stirred for 20 min at 0 °C and for another 50 min at room temperature. After the reaction, dry ice was added to the reaction mixture and precipitates were filtered off. The filtrate was evaporated and the residue was purified by silica gel column chromatography (chloroform : methanol=1 : 1) to afford **12b** (1.43 g, 99%) as colorless crystals; mp 108—112 °C (methanol and diethyl ether). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.59—2.61 (4H, m, CH_2CH_2), 3.45 (2H, s, Ar-$C\underline{H}_2$–N), 3.62 (3H, s, OMe), 6.23 (2H, s, Ar-H), 6.64, 6.95 (each 2H, d, AB type, J=8.1 Hz, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 35.0, 50.8, 52.8, 56.0, 106.8, 115.0, 129.3, 130.4, 134.0, 136.2, 150.3, 155.4. IR ($CHCl_3$) cm^{-1}: 3628, 1601, 1514, 1437, 1364, 1169, 1047, 1016. EI-MS m/z: 289 (M^+). HR-MS m/z: 289.1317 (Calcd for $C_{16}H_{19}NO_4$: 289.1314).

***N*-(3,5-Dihydroxyl-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethyltrifluoroacetamide (12a)** Trifluoroacetic anhydride (0.15 ml, 1.04 mmol) was added to a solution of **12b** (100 mg, 0.35 mmol) in pyridine (1.5 ml) at 0 °C and the mixture was stirred for 20 min. After the reaction, methanol was added to the reaction mixture and the organic solvent was evaporated. The residue was extracted with ethyl acetate and the organic layer was successively washed with 1 M hydrochloric acid, a saturated aqueous solution of sodium bicarbonate, and a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol=50 : 1) to afford **12a** (114.2 mg, 86%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.96 and 2.81 (2H, t, J=6.6 Hz, Ar-$C\underline{H}_2$–CH_2), 3.45 and 3.50 (2H, t, J=6.6 Hz, CH_2–$C\underline{H}_2$–N), 3.87 and 3.88 (3H, s, OMe), 4.22 and 4.48 (2H, s, Ar-CH_2–N), 4.98 (1H, br s, OH), 5.67 and 5.90 (2H, br s, OH), 6.28 and 6.38 (2H, s, Ar-H), 6.75 and 6.78 (2H, d, J=8.8 Hz), 7.00 (2H, d, J=8.8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 29.7, 31.9, 34.3, 48.6, 49.4, 51.1, 61.15, 61.19, 107.0, 107.8, 115.6, 115.7, 118.4, 118.6, 129.3, 129.9, 130.0, 130.2, 131.6, 132.1, 134.3, 149.3, 149.4, 154.4, 154.6, 156.8, 157.2, 157.3, 157.7. IR ($CHCl_3$) cm^{-1}: 3312, 1686, 1599, 1516, 1458, 1439, 1366, 1263, 1192, 1165, 1061. EI-MS m/z: 385 (M^+). HR-MS m/z: 385.1132 (Calcd for $C_{18}H_{18}NO_5F_3$: 385.1137).

Methyl 3,5-Dibenzyloxy-4-methoxybenzoate (16a) Benzyl chloride (3.81 ml, 33.3 mmol) and potassium carbonate (7.02 g, 50.8 mmol) were added to a solution of **13b** (2.81 g, 14.2 mmol) in *N*,*N*-dimethylformamide (15 ml) and the mixture was stirred for 1.5 h at 150 °C. After the reaction, precipitates were removed by filtration and the filtrate was evaporated, and extracted with benzene. The organic layer was successively washed with 5% aqueous solution of sodium hydroxide and a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was recrystallized from methanol (5.07 g, 95%) as colorless needles; mp 116—118 °C (methanol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.88, 3.94 (3H, s, OMe), 5.16 (4H, s, 2×CH_2O), 7.32—7.48 (12-H, m, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 52.2, 61.0, 71.2 (2C), 109.2 (2C), 125.0, 127.4 (4C), 128.0 (2C), 128.5 (4C), 136.7 (2C), 143.6, 152.2 (2C), 166.6. IR ($CHCl_3$) cm^{-1}: 3010, 2953, 1715, 1591, 1429, 1336, 1236, 1113. EI-MS m/z: 378 (M^+). HR-MS m/z: 378.1469 (Calcd for $C_{23}H_{22}O_5$: 378.1467). *Anal.* Calcd for $C_{23}H_{22}O_5$: C, 73.00, H, 5.86. Found: C, 73.33; H, 6.10.

Methyl 3,5-Diallyloxy-4-methoxybenzoate (16b) Allyl bromide (4.0 ml, 46.0 mmol) and potassium carbonate (8.30 g, 60.0 mmol) were added to a solution of **13b** (3.95 g, 20.0 mmol) in *N*,*N*-dimethylformamide (168 ml) and the mixture was stirred for 90 min at 50 °C. After the reaction, the reaction mixture was evaporated to remove the organic solvent and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=2 : 1) to afford **16b** (5.9 g, quant.) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.89, 3.93 (3H, s, OMe), 4.62, 4.64 (4H, dt, J=5.4, 1.5 Hz, 2×CH_2O), 5.29 (2H, dq, J=10.6, 1.5 Hz, 2×$C\underline{H}_2$=CH–), 5.43 (2H, dq, J=17.2, 1.5 Hz, 2×$C\underline{H}_2$=CH–), 6.08 (2H, ddt, J=17.2, 10.6, 1.5 Hz, 2×CH_2=C$\underline{H}$–), 7.29 (2H, s, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 52.2, 60.9, 69.9, 100.6, 108.8 (2C), 117.9 (2C), 124.9, 132.9 (2C), 143.2, 152.0, 166.6. IR ($CHCl_3$) cm^{-1}: 2951, 1717, 1589, 1501, 1435, 1331, 1258, 1111, 1003. EI-MS m/z: 278 (M^+). HR-MS m/z: 278.1157 (Calcd for $C_{15}H_{18}O_5$: 278.1154).

Methyl 3,5-Dimethoxymethoxyl-4-methoxybenzoate (16c) Chloromethyl methyl ether (8.98 g, 111.0 mmol) and potassium carbonate (20.5 g, 148.0 mmol) were added to a solution of **13b** (7.37 g, 37.2 mmol) in *N*,*N*-dimethylformamide (168 ml) at 0 °C and the mixture was stirred for 15 h at 45 °C. After the reaction, the mixture was filtered and the filtrate was evaporated to remove the organic solvent and then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=2 : 1) to afford **16c** (9.35 g, 88%) as colorless needles; mp 69—79 °C (diethyl ether); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.53 (6H, s), 3.89 and 3.94 (each 3H, s, OMe), 5.26 (4H, s, 2×CH_2O), 7.53 (2H, s, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 52.2, 56.4 (2C), 61.1, 95.3 (2C), 111.9 (2C), 125.5, 144.2, 150.5 (2C), 166.3. IR ($CHCl_3$) cm^{-1}: 3020, 2955, 1717, 1593, 1501, 1435, 1331, 1231, 1049. EI-MS m/z: 286 (M^+). HR-MS m/z: 286.1063 (Calcd for $C_{13}H_{18}O_7$: 286.1052). *Anal.* Calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.53; H, 6.47.

Methyl 3,5-Di-*tert*-butyldimethylsilyloxy-4-methoxybenzoate (16d) A solution of *tert*-butyldimethylsilyl chloride (1.83 g, 12.1 mmol) and imidazole (1.38 g, 20.2 mmol) were stirred for 20 min at room temperature, and

13b (1.0 g, 5.05 mmol) was added to the solution. After stirring the reaction mixture for 3 h at room temperature, 1 M hydrochloric acid was added to the reaction mixture which was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to afford **16d** (2.0 g, 93%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.19 (12H, s), 1.01 (18H, s), 3.77, 3.87 (each 3H, s, OMe), 7.19 (2H, s, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: –4.7, 18.3 (2C), 25.7 (6C), 52.0, 60.0, 116.1 (2C), 125.1, 147.3, 149.6 (2C), 166.7. IR ($CHCl_3$) cm^{-1}: 2955, 1717, 1493, 1427, 1354, 1092, 1011. EI-MS *m/z*: 426 (M^+). HR-MS *m/z*: 426.2259 (Calcd for $C_{21}H_{38}O_5Si_2$: 426.2258).

3,5-Dibenzyloxy-4-methoxybenzyl Alcohol (17a) A suspension of **16a** (488 mg, 1.29 mmol) and lithium aluminum hydride (150 mg, 3.87 mmol) in tetrahydrofuran (6 ml) was stirred for 3 h at 60 °C. After the reaction, excess amount of lithium aluminum hydride was quenched with ethyl acetate and ice water, and then the mixture was extracted with ethyl acetate. The organic layer was successively washed with 1 M hydrochloric acid and saturated solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by recrystallization from a mixed solvent of hexane and ethyl acetate to afford **17a** (434 mg, 96%) as colorless needles; mp 103—105 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.87 (3H, s, OMe), 4.49 (2H, s, CH_2OH), 5.08 (4H, s, 2×PhC$\underline{H}_2$O), 6.61 (2H, s, Ar-H), 7.23—7.44 (10H, m, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 60.9, 65.1, 70.9 (2C), 106.2 (2C), 127.2 (4C), 127.8, 128.5 (4C), 136.6, 137.0 (2C), 138.5, 152.5 (2C). IR ($CHCl_3$) cm^{-1}: 3690, 3600, 1593, 1506, 1437, 1234. EI-MS *m/z*: 350 (M^+). HR-MS *m/z*: 350.1519 (Calcd for $C_{22}H_{22}O_4$: 350.1518). *Anal.* Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.67; H, 6.39.

3,5-Diallyloxy-4-methoxybenzyl Alcohol (17b) A solution of **16b** (7.00 g, 25.2 mmol) in tetrahydrofuran (110 ml) was added to a suspension of lithium aluminum hydride (2.86 g, 75.4 mmol) in tetrahedrofuran (25 ml) at 0 °C and the mixture was stirred for 3 h at room temperature. After the reaction, excess amount of lithium aluminum hydride was quenched with ethyl acetate and saturated aqueous solution of sodium sulfate, and then the mixture was filtered through Celite®. The filtrate was extracted with ethyl acetate and the organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to afford **17b** (5.60 g, 89%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.86 (3H, s, OMe), 4.58 (6H, dt, J=5.2, 1.5 Hz, 2×C$\underline{H}_2$–CH=CH+C$\underline{H}_2$Ar), 5.27 (2H, dq, J=10.4, 1.5 Hz, C$\underline{H}_2$=CH–), 5.41 (2H, dq, J=17.2, 1.5 Hz, C$\underline{H}_2$=CH–), 6.06 (2H, ddt, J=17.2, 10.4, 1.5 Hz, 2×CH$_2$=C$\underline{H}$–), 6.58 (2H, s, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 60.7, 65.3, 69.8 (2C), 105.8 (2C), 117.5 (2C), 133.3 (2C), 136.4, 138.3, 152.4. IR ($CHCl_3$) cm^{-1}: 3422, 2939, 1589, 1504, 1435, 1327, 1238, 1111, 1003. EI-MS *m/z*: 250 (M^+). HR-MS *m/z*: 250.1197 (Calcd for $C_{14}H_{18}O_4$: 250.1205).

3,5-Dimethoxymethoxy-4-methoxybenzyl Alcohol (17c) A solution of **16c** (9.30 g, 32.5 mmol) in tetrahydrofuran (35 ml) was added to a suspension of lithium aluminum hydride (3.70 g, 97.5 mmol) in tetrahydrofuran (35 ml) and the mixture was stirred for 80 min at 60 °C. After the reaction, the excess amount of lithium aluminum hydride was quenched with ethyl acetate and a saturated aqueous solution of sodium sulfate, and then the mixture was filtered through Celite®. The filtrate was evaporated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to afford **17c** (8.00 g, 95%) as a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.51(6H, s, 2×OMe), 3.87 (3H, s, OMe), 4.57 (2H, s, ArCH_2O), 5.21 (4H, s, 2×OCH_2O), 6.84 (2H, s, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 56.2 (2C), 61.0, 64.9, 95.1, 108.9, 136.9, 139.1, 150.8 (2C). IR ($CHCl_3$) cm^{-1}: 3456, 2909, 1589, 1497, 1450, 1396, 1315, 1250. EI-MS *m/z*: 258 (M^+). HR-MS *m/z*: 258.1104 (Calcd for $C_{12}H_{18}O_6$: 258.1103).

3,5-Di-*tert*-butyldimethylsilyloxy-4-methoxybenzyl Alcohol (17d) A solution of **16d** (1.00 g, 2.3 mmol) in tetrahydrofuran (15 ml) was added to a suspension of lithium aluminum hydride (266.8 mg, 7.0 mmol) in tetrahydrofuran (15 ml) and the mixture was stirred for 3 h at room temperature. After the reaction, the excess amount of lithium aluminum hydride was quenched with ice water and saturated aqueous solution of sodium sulfate, and then the mixture was filtered through Celite®. The filtrate was evaporated, dried over sodium sulfate, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to afford **17d** (931.9 mg, 94%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.17 (12H, s), 1.00 (18H, s), 3.70 (3H, s, OMe), 4.52 (2H, br s, CH_2), 6.51 (2H, s, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: −4.7 (4C), 18.3, 25.7 (6C), 59.9, 65.1, 113.2 (2C), 136.2, 142.3, 149.9 (2C). IR ($CHCl_3$) cm^{-1}: 2932, 1578, 1493, 1470, 1435, 1350, 1254, 1092, 1007. EI-MS *m/z*: 398 (M^+). HR-MS *m/z*: 398.2299 (Calcd for $C_{20}H_{38}O_4Si_2$: 398.2309).

3,5-Dibenzyloxy-4-methoxybenzaldehyde (18a) Pyridinium chlorochromate (1.32 g, 6.1 mmol) was added to a solution of **17a** (1.43 g, 4.1 mmol) in terahydrofuran (15 ml) and the mixture was stirred for 3 h at room temperature. After the reaction, the reaction mixture was filtered through Celite®, concentrated *in vacuo*, and the residue was extracted with ethyl acetate. The organic layer was successively washed with 1 M hydrochloric acid, a saturated aqueous solution of sodium bicarbonate, and a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by recrystallization from ethanol to afford **18a** (1.36 g, 96%) as colorless needles; mp 75—77 °C, ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.97 (3H, s, OMe), 5.19 (4H, s, 2×CH_2O), 7.17 (2H, s, Ar-H), 7.30—7.46 (10H, m, Ar-H), 9.78 (1H, s, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 61.0, 71.2, 109.0 (2C), 127.3 (4C), 128.1 (2C), 128.6 (4C), 131.5 (2C), 136.4 (2C), 145.0, 152.9 (2C), 190.9. IR ($CHCl_3$) cm^{-1}: 3010, 2943, 2359, 1693, 1585, 1499, 1439, 1327, 1115. EI-MS *m/z*: 348 (M^+). HR-MS *m/z*: 348.1356 (Calcd for $C_{22}H_{20}O_4$: 348.1361). *Anal.* Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.48; H, 5.50.

3,5-Diallyloxy-4-methoxybenzaldehyde (18b) Molecular sieves 3A (9.0 g) was added to a mixture of **17b** (4.50 g, 18.0 mmol), palladium acetate (0.20 g, 0.89 mmol) and pyridine (0.17 ml) in toluene (160 ml) and the mixture was stirred for 5 h at 90 °C under the atmosphere of oxygen. After the reaction, the reaction mixture was filtered and the filtrate was evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to afford recovered **17b** (1.65 g, 37%) and **18b** (2.30 g, 52%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.97 (3H, s, OMe), 4.66 (4H, dt, J=5.1, 1.5 Hz, 2×OC$\underline{H}_2$–CH=CH$_2$), 5.31 (2H, dq, J=10.5, 1.5 Hz, 2×C$\underline{H}_2$=CH–), 5.43 (2H, dq, J=17.3, 1.5 Hz, 2×C$\underline{H}_2$=CH–), 6.06 (2H, ddt, J=17.3, 10.5, 1.5 Hz, 2×CH$_2$=C$\underline{H}$–), 7.11 (2H, s, Ar-H), 9.82 (1H, s, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 61.0, 70.0 (2C), 108.6, 118.1 (2C), 131.5, 132.7 (2C), 152.7 (2C), 191.0. IR ($CHCl_3$) cm^{-1}: 3013, 1690, 1585, 1497, 1443, 1393, 1327, 1111. EI-MS *m/z*: 248 (M^+). HR-MS *m/z*: 248.1051 (Calcd for $C_{14}H_{16}O_4$: 248.1048).

3,5-Dimethoxymethoxy-4-methoxybenzaldehyde (18c) Molecular sieves 3A (10 g) was added to a mixture of **17c** (5.17 g, 20.0 mmol), palladium acetate (0.22 g, 1.00 mmol) and pyridine (0.16 g, 2.0 mmol) in toluene (150 ml) and the mixture was stirred for 2.5 h at 90 °C under the atmosphere of oxygen. After the reaction, the reaction mixture was filtered and the filtrate was evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to afford **18c** (5.05 g, quant.) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.53 (6H, s, 2×OCH_3), 3.98 (3H, s, OCH_3), 5.28 (4H, s, 2×OCH_2O), 7.41 (2H, s, Ar-H), 9.86 (1H, s, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 56.4 (2C), 61.2, 95.3 (2C), 111.7 (2C), 131.9, 151.3 (2C), 190.9. IR ($CHCl_3$) cm^{-1}: 2959, 1701, 1589, 1497, 1450, 1381, 1323, 1242, 1157. EI-MS *m/z*: 256 (M^+); HR-MS *m/z*: 256.0951 (Calcd for $C_{12}H_{16}O_6$: 256.0947).

3,5-Di-*tert*-butyldimethylsilyloxy-4-methoxybenzaldehyde (18d) Pyridinium chlorochromate (735.1 mg, 3.41 mmol) was added to a mixture of **17d** (679.8 mg, 1.70 mmol) and Celite® in chloroform (7 ml) and the mixture was stirred for 2 h at room temperature. After the reaction, the reaction mixture was filtered and the residue was washed with ethyl acetate. The filtrate was evaporated and the residue was purified by silica gel column chromatography (chloroform) to afford **18d** (570.5 mg, 85%) as colorless needles; mp 75—77 °C (methanol), ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.20 (12H, s), 1.01 (18H, s), 3.81 (3H, s, OMe), 7.03 (2H, s, Ar-H), 9.78 (1H, s, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: −4.6 (4C), 18.3, 25.7 (6C), 60.1, 115.9 (2C), 131.8, 148.9, 150.4 (2C), 191.1. IR ($CHCl_3$) cm^{-1}: 2932, 1693, 1574, 1489, 1439, 1389, 1346, 1258, 1231, 1092, 1007. EI-MS *m/z*: 396 (M^+). HR-MS *m/z*: 396.2161 (Calcd for $C_{20}H_{36}O_4Si_2$: 396.2152).

***N*-(3,5-Dibenzyloxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethylamine (19a)** Tyramine (2.05 g, 15.0 mmol) was added to a solution of **18a** (5.00 g, 14.4 mmol) in methanol (100 ml) and the mixture was stirred for 70 min at 70 °C. After cooling the mixture to 0 °C, sodium borohydride (0.60 g, 15.8 mmol) was added to the reaction mixture, which was stirred for 30 min at 0 °C and for another 40 min at room temperature. After the reaction, the reaction mixture was evaporated and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated, the residue was purified by recrystallization from methanol to afford **19a** (5.5 g, 81%) as colorless crytstals; mp 133—135 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.70 (2H, t, J=6.4 Hz, Ar-C$\underline{H}_2$CH$_2$), 2.78 (2H, t, J=6.4 Hz, CH$_2$C$\underline{H}_2$N), 3.64 (2H, s, Ar-C$\underline{H}_2$N), 3.86 (3H, s, OMe), 5.02 (4H, s, 2×CH_2O), 6.54 (2H, s, Ar-H), 6.66 (2H, d, J=8.4 Hz), 6.96 (2H, d, J=8.4 Hz), 7.26—7.41 (m, 10H). ^{13}C-NMR

(100 MHz, $CDCl_3$) δ: 34.8, 50.1, 53.8, 60.9, 70.9 (2C), 107.8 (2C), 115.6 (2C), 127.3 (4C), 127.8 (2C), 128.5 (4C), 129.8 (2C), 130.6, 134.8, 137.1 (2C), 138.4, 152.5 (2C), 155.0. IR ($CHCl_3$) cm^{-1}: 3310, 3013, 1593, 1512, 1435, 1327, 1111, 1007. EI-MS *m/z*: 469 (M^+). HR-MS *m/z*: 469.2257 (Calcd for $C_{30}H_{31}NO_4$: 469.2253). *Anal.* Calcd for $C_{30}H_{31}NO_4$: C, 76.73; H, 6.65; N, 2.98. Found: C, 76.82; H, 6.68; N, 3.13.

***N*-(3,5-Diallyloxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethylamine (19b)** Tyramine (0.58 g, 4.2 mmol) was added to a solution of **18b** (1.00 g, 4.0 mmol) in methanol (12 ml) and the mixture was stirred for 20 min at room temperature. After cooling the mixture to 0 °C, sodium borohydride (0.15 g, 4.0 mmol) was added to the reaction mixture, which was stirred for 20 min at room temperature. After the reaction, the reaction mixture was evaporated and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated, the residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1) to afford **19b** (1.29 g, 87%) as colorless plates; mp 91—94 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.88 (4H, br s, CH_2CH_2), 3.83 (3H, s, OMe), 3.84 (2H, s, Ar-CH_2N), 4.55 (4H, d, J=5.1 Hz, 2×CH_2O), 5.23 (2H, dd, J=10.5, 1.4 Hz, C$\underline{H}_2$=CH–), 5.38 (2H, dd, J=17.3, 1.4 Hz, C$\underline{H}_2$=CH–), 5.95—6.18 (2H, m, CH_2=C$\underline{H}$–), 6.64 (2H, s, Ar-H), 6.69, 6.92 (each 2H, d, AB type, J=8.4 Hz, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 34.7, 50.1, 53.8, 60.7, 69.5, 107.3, 115.7, 117.4, 129.7, 130.4, 133.4, 134.5, 138.0, 152.3, 155.1. IR ($CHCl_3$) cm^{-1}: 3310, 2932, 1593, 1512, 1435, 1327, 1242, 1107, 1003; EI-MS *m/z*: 369 (M^+). HR-MS *m/z*: 369.1951 (Calcd for $C_{22}H_{27}NO_4$: 369.1940). *Anal.* Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.48; H, 7.21; N, 4.05.

***N*-(3,5-Dimethoxymethoxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethylamine (19c)** Tyramine (1.40 g, 10.5 mmol) was added to a solution of **18c** (2.60 g, 10.1 mmol) in methanol (30 ml) and the mixture was stirred for 20 min at room temperature. After cooling the mixture to 0 °C, sodium borohydride (0.38 g, 10.0 mmol) was added to the reaction mixture, which was stirred for 50 min at room temperature. After the reaction, the reaction mixture was evaporated and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated, the residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1) to afford **19c** (3.80 g, quant) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.75 (2H, t, J=6.8 Hz, Ar-C$\underline{H}_2$$CH_2$), 2.86 (2H, t, J=6.8 Hz, CH_2C$\underline{H}_2$N), 3.50 (6H, s, 2×OMe), 3.70 (2H, s, ArCH_2N), 3.86 (3H, s, OMe), 5.18 (4H, s, 2×OCH_2O), 6.71 (2H, d, J=8.5 Hz, Ar-H), 6.76 (2H, s), 7.03 (2H, d, J=8.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 34.9, 50.3, 53.5, 56.2 (2C), 61.0, 95.3 (2C), 110.3 (2C), 115.5 (2C), 129.7 (2C), 131.0, 135.5, 138.9, 150.8 (2C), 154.7. IR ($CHCl_3$) cm^{-1}: 3314, 2935, 1593, 1512, 1435, 1323, 1242, 1111, 1042. EI-MS *m/z*: 377 (M^+). HR-MS *m/z*: 377.1837 (Calcd for $C_{20}H_{27}NO_6$: 377.1838).

***N*-(3,5-Di-*tert*-butyldimethylsilyloxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethylamine (19d)** Tyramine (328 mg, 2.39 mmol) was added to a solution of **18d** (950 mg, 2.39 mmol) in methanol (25 ml) and the mixture was stirred for 2 h at room temperature. After cooling the mixture to 0 °C, sodium borohydride (90.8 mg, 2.39 mmol) was added to the reaction mixture, which was stirred for 1 h at room temperature. After the reaction, the reaction mixture was evaporated and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated, the residue was purified by silica gel column chromatography (chloroform : methanol = 30 : 1) to afford **19d** (1.22 g, 98%) as colorless needles; mp 113—114 °C (*n*-hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.14 (12H, s), 0.98 (18H, s), 2.74 (2H, t, J=6.5 Hz, Ar-C$\underline{H}_2$$CH_2$), 2.84 (2H, t, J=6.3 Hz, CH_2C$\underline{H}_2$N), 3.64 (2H, s, Ar-CH_2N), 3.69 (3H, s, OMe), 6.42 (2H, s, Ar-H), 6.66 (2H, d, J=8.2 Hz, Ar-H), 6.99 (2H, d, J=8.2 Hz, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: −4.7 (4C), 18.3, 25.7 (6C), 35.0, 50.1, 53.2, 59.9, 114.4 (2C), 115.6 (2C), 129.7 (2C), 130.9, 134.7, 141.9, 149.7 (2C), 154.7. IR ($CHCl_3$) cm^{-1}: 2932, 1578, 1516, 1431, 1350, 1254, 1092, 1007. EI-MS *m/z*: 517 (M^+). HR-MS *m/z*: 517.3028 (Calcd for $C_{28}H_{47}NO_4Si_2$: 517.3043).

***N*-(3,5-Dibenzyloxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethyltrifluoroacetamide (15a)** Trifluoroacetic anhydride (0.36 ml, 2.56 mmol) was added to a solution of **19a** (500 mg, 1.06 mmol) in pyridine (5 ml) at 0 °C and the mixture was stirred for 10 min with keeping the temperature. After the reaction, the reaction was quenched by adding methanol (5 ml) and the reaction mixture was evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to afford **15a** (543 mg, 91%) as an amorphous powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.61 and 2.63 (2H, t, J=8.0 Hz), 3.26 and 3.30 (2H, t, J=8.0 Hz), 3.90 and 3.91 (3H, s, OMe), 4.17 and 4.45 (2H, s), 5.09 (4H, s, 2×OC$\underline{H}_2$Ph), 5.80 (1H, br, –OH), 6.30 and 6.42 (2H, s), 6.72—6.78 (2H, m), 6.84—6.88 (2H, m), 7.24—7.40 (10H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 31.7, 34.2, 48.3, 48.4, 49.7, 51.4, 60.9, 61.0, 71.0, 71.1, 107.0, 107.7, 115.0, 115.2, 115.5, 115.6, 117.9, 118.0, 127.16, 127.18, 127.9, 128.0, 128.5, 128.6, 128.9, 129.66, 129.73, 129.8, 129.9, 130.7, 136.6, 136.7, 138.95, 139.04, 152.57, 152.64, 154.7, 154.9, 156.6, 157.0, 157.2, 157.5. IR ($CHCl_3$) cm^{-1}: 3317, 3013, 1686, 1593, 1516, 1435, 1150, 1115. EI-MS *m/z*: 565 (M^+). HR-MS *m/z*: 565.2077 (Calcd for $C_{32}H_{30}F_3NO_5$: 565.2076).

***N*-(3,5-Dibenzyloxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethylformamide (15b)** A suspension of **19a** (1.96 g, 4.2 mmol) in ethyl formate (40 ml) was refluxed for 6 h. After the reaction, the organic solvent was evaporated and the residue was purified by silica gel column chromatography (chloroform : methanol = 20 : 1) to afford **15b** (2.0 g, 97%) as colorless crystals; mp 125—126 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.54 and 2.61 (2H, t, J=6.9 Hz), 3.14 and 3.30 (2H, t, J=6.9 Hz), 3.90 (3H, s, OMe), 4.06 and 4.36 (2H, s), 5.10 (4H, s, 2×OCH_2Ph), 6.33 and 6.48 (2H, s, Ar-H), 6.74 and 6.82 (2H, d, A part of AB, J=8.5 Hz), 6.71 and 6.92 (2H, d, B part of AB, J=8.5 Hz), 6.67 and 7.01 (1H, br s, –OH), 7.26—7.43 (10H, m), 7.74 and 8.13 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.3, 33.6, 43.5, 45.7, 48.6, 51.8, 60.9, 71.0, 71.1, 107.1, 108.1, 115.4, 115.6, 127.2, 127.3, 127.8, 128.0, 128.5, 128.6, 128.7, 129.6, 129.7, 129.8, 131.0, 131.5, 136.7, 136.9, 138.9, 139.1, 152.5, 152.7, 155.0, 155.4, 163.0, 163.3. IR ($CHCl_3$) cm^{-1}: 3310, 2939, 1663, 1593, 1516, 1435, 1238, 1115, 1007. EI-MS *m/z*: 497 (M^+). HR-MS *m/z*: 497.2207 (Calcd for $C_{31}H_{31}NO_5$: 497.2202).

***N*-(3,5-Diallyloxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethyltrifluoroacetamide (15c)** Trifluoroacetic anhydride (0.48 ml, 3.4 mmol) was added to a solution of **19b** (0.42 g, 1.13 mmol) in pyridine (4 ml) at 0 °C and the mixture was stirred for 10 min with keeping the temperature. After the reaction, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to afford **15c** (0.49 g, 93%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.75 and 2.80 (2H, t, J=7.6 Hz), 3.45 and 3.47 (2H, t, J=7.6 Hz), 3.86 and 3.87 (3H, s, OMe), 4.27 and 4.53 (2H, s), 4.55—4.58 (4H, m, 2×CH_2=CH–C$\underline{H}_2$O), 5.25 and 5.28 (2H, dq, J=10.4, 1.5 Hz, 2×C$\underline{H}_2$=CH–), 5.39 and 5.40 (2H, dq, J=17.3, 1.5 Hz, 2×C$\underline{H}_2$=CH–), 6.00 and 6.05 (2H, ddt, J=17.3, 1.5 Hz, CH_2–C$\underline{H}$=CH_2), 6.32 and 6.43 (2H, s, Ar-H), 6.78 and 6.79 (2H, d, J=8.5 Hz, Ar-H), 7.00 (2H, d, J=8.5 Hz, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 31.9, 34.3, 48.4, 49.7, 51.4, 60.80, 60.83, 69.9, 70.0, 106.6, 107.3, 115.5, 115.7, 117.7, 117.8, 129.2, 129.8, 129.90, 129.94, 130.1, 130.7, 133.0, 133.1, 138.8, 138.9, 152.6, 152.7, 154.5, 154.7. IR ($CHCl_3$) cm^{-1}: 2939, 1690, 1663, 1593, 1493, 1462, 1435, 1327, 1150. EI-MS *m/z*: 465 (M^+). HR-MS *m/z*: 465.1759 (Calcd for $C_{24}H_{26}F_3NO_5$: 465.1763).

***N*-(3,5-Diallyloxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethylformamide (15d)** A solution of **19b** (554 mg, 1.5 mmol) in ethyl formate (10 ml) was refluxed for 33 h. After the reaction, the organic solvent was evaporated and the residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1) to afford **15d** (570 mg, 97%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.69 and 2.71 (2H, t, J=7.4 Hz), 3.34 and 3.44 (2H, t, J=7.4 Hz), 3.86 (3H, s, OMe), 4.14 and 4.43 (2H, s), 4.56 and 4.57 (4H, dt, J=5.1, 1.5 Hz, 2×CH_2=CH–C$\underline{H}_2$), 5.26 and 5.27 (2H, dq, J=10.2, 1.5 Hz, 2×C$\underline{H}_2$=CH–), 5.39 (2H, dd, J=18.0, 1.5, 2×C$\underline{H}_2$=CH–), 5.99—6.05 (2H, m, 2×CH_2=C$\underline{H}$–), 6.32 and 6.46 (2H, s, Ar-H), 6.73 and 6.75 (2H, d, J=8.5 Hz), 6.91 and 7.01 (2H, d, J=8.4 Hz, Ar-H), 7.86 and 8.21 (1H, s, CHO). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.4, 33.8, 43.9, 45.8, 48.8, 52.0, 60.72, 60.74, 65.8, 67.9, 69.86, 69.90, 106.9, 107.5, 115.4, 115.7, 117.6, 117.7, 128.5, 129.5, 129.65, 129.71, 130.9, 131.5, 133.0, 133.1, 138.5, 138.7, 152.4, 152.6, 155.2, 155.5, 163.1, 163.3. IR ($CHCl_3$) cm^{-1}: 3316, 2936, 1663, 1593, 1516, 1423, 1238, 1111, 1103. EI-MS *m/z*: 397 (M^+). HR-MS *m/z*: 397.1892 (Calcd for $C_{22}H_{27}NO_5$: 397.1889).

***N*-(3,5-Dimethoxymethoxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)-ethyltrifluoroacetamide (15e)** Trifluoroacetic anhydride (5.35 ml, 37.9 mmol) was added to a solution of **19c** (4.77 g, 12.6 mmol) in pyridine (40 ml) at 0 °C and the mixture was stirred for 20 min. After the reaction, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1) to afford **15e** (5.1 g, 85%) as colorless needles; mp 95—97 °C (*n*-hexane–diethyl ether). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.76 and 2.81 (2H, t, J=7.8 Hz), 3.48 and 3.50 (2H, t, J=7.8 Hz), 3.50 (6H, s, 2×OMe), 3.87 and 3.88 (3H, s, OMe), 4.31 and 4.55 (2H, s), 5.18 (4H, s, 2×OCH_2O), 5.40 (1H, br s, OH), 6.63 and 6.71 (2H, s, Ar-H), 6.74 and 6.75 (2H, d, J=8.5 Hz), 6.99 and 7.00 (2H, d, J=8.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 31.9, 34.3, 48.4, 48.5, 49.5, 51.3, 56.26, 56.29, 61.05, 61.07, 95.4, 109.9, 110.4, 115.5, 115.7, 129.2,

129.8, 129.9, 130.1, 130.5, 131.0, 136.6, 139.8, 139.9, 151.2, 151.3, 154.5, 154.7, 156.7, 156.8. IR ($CHCl_3$) cm^{-1}: 3337, 2936, 1686, 1597, 1516, 1435, 1323, 1242, 1157, 1111, 1049, 1007. EI-MS *m/z*: 473 (M^+). HR-MS *m/z*: 473.1654 (Calcd for $C_{22}H_{26}F_3NO_7$: 473.1661). *Anal.* Calcd for $C_{22}H_{26}F_3NO_7$: C, 55.81; H, 5.54; N, 2.96. Found: C, 55.53; H, 5.61; N, 2.96.

***N*-(3,5-Dimethoxymethoxoxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)-ethylformamide (15f)** A solution of **19c** (4.28 g, 11.3 mmol) in ethyl formate (35 ml) was refluxed for 3.5 h. After the reaction, the organic solvent was evaporated and the residue was purified by silica gel column chromatography (chloroform : ethyl acetate = 1 : 1) to afford **15f** (3.8 g, 83%) as colorless crystals; mp 120—125 °C (ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.71 and 2.72 (2H, t, J=6.0 Hz), 3.37 and 3.46 (2H, t, J=6.0 Hz), 3.51 (6H, s, 2×OMe), 3.86 and 3.87 (3H, s, OMe), 4.16 and 4.46 (2H, s), 5.20 (4H, s), 6.63 and 6.73 (2H, s, Ar-H), 6.72 and 6.75 (2H, d, J=8.6 Hz), 6.90 and 7.00 (2H, d, J=8.6 Hz), 7.84 and 8.21 (1H, s, CHO). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.4, 33.8, 43.9, 45.6, 48.9, 51.8, 56.1, 56.3, 60.95, 61.03, 95.30, 95.34, 109.9, 110.5, 115.4, 115.7, 128.8, 129.7, 129.79, 129.81, 131.5, 131.9, 139.5, 139.8, 151.0, 151.2, 155.0, 155.4, 163.0, 163.3. IR ($CHCl_3$) cm^{-1}: 3321, 2936, 1666, 1597, 1516, 1435, 1396, 1157, 1049, 1107. EI-MS *m/z*: 405 (M^+). HR-MS *m/z*: 405.1797 (Calcd for $C_{21}H_{27}NO_7$: 405.1787). *Anal.* Calcd for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.34; H, 6.83; N, 3.27.

***N*-(3,5-Di-*tert*-butyldimethylsilyloxy-4-methoxy)benzyl-*N*-(4-hydroxyphenyl)ethyltrifluoroacetamide (15g)** Trifluoroacetic anhydride (0.98 ml, 7.0 mmol) was added to a solution of **19d** (1.2 g, 2.3 mmol) in pyridine (20 ml) at 0 °C and the mixture was stirred for 3 h at room temperature. After the reaction, the reaction mixture was evaporated and extracted with ethyl acetate. The organic layer was successively washed with 10% hydrochloric acid, saturated aqueous solution of sodium bicarbonate, and saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to afford **15g** (1.19 g, 84%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.15 (12H, s), 0.99 (18H, s), 2.75 and 2.80 (2H, t, J=7.2 Hz), 3.44 and 3.46 (2H, t, J=7.2 Hz), 3.71 and 3.72 (3H, s, OMe), 4.20 and 4.49 (2H, s), 4.95 (1H, br, –OH), 6.28 and 6.37 (2H, s, Ar-H), 6.75 and 6.77 (2H, d, J=8.6 Hz), 6.99 and 7.01 (2H, d, J=8.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: −4.7 (4C), 18.3, 25.7 (6C), 31.9, 34.3, 48.3, 49.1, 51.1, 51.2, 60.0, 113.8, 114.2, 115.5, 115.7, 129.3, 129.7, 129.8, 129.9, 130.1, 130.3, 142.6, 142.8, 150.1, 150.2, 154.5, 154.7, 156.61, 156.62, 157.1, 157.6. IR ($CHCl_3$) cm^{-1}: 3337, 2932, 1686, 1578, 1516, 1497, 1431, 1358, 1258, 1150, 1092, 1107. EI-MS *m/z*: 613 (M^+). HR-MS *m/z*: 613.2881 (Calcd for $C_{30}H_{46}F_3N_5Si_2$: 613.2866).

6,8-Dibenzyloxy-7-methoxy-2-trifluoroacetyl-2,3,4,5-tertahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-4′-one (20a) A solution of PIFA (1.70 g, 3.80 mmol) in 2,2,2-trifluoroethanol (15 ml) was added to a solution of **15a** (1.8 g, 3.20 mmol) in 2,2,2-trifluoroethanol (4 ml) at −40 °C and the mixture was stirred for 1 h with keeping the temperature. After the reaction, the organic solvent in the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to afford **20a** (960.7 mg, 53%) as colorless amorphous powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.28 (2H, m), 3.75 and 3.76 (3H, s), 3.80—3.88 (2H, m), 4.73 and 4.79 (2H, s), 4.89 and 4.91 (2H, s), 5.12 and 5.14 (2H, s), 6.12 (2H, d, J=10.1 Hz), 6.57 and 6.78 (1H, s), 6.94 and 7.01 (2H, d, J=10.1 Hz), 7.22—7.47 (10H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 37.2, 38.8, 44.3, 45.05, 45.10, 46.8, 47.08, 48.12, 48.85, 48.88, 60.6, 60.7, 70.7, 70.8, 75.4, 77.2, 111.2, 111.6, 114.1, 114.3, 117.9, 118.1, 121.7, 121.9, 123.6, 124.0, 126.52, 126.53, 127.1, 127.2, 127.5, 127.58, 127.61, 127.9, 128.0, 128.1, 128.4, 128.5, 131.1, 131.2, 136.1, 136.2, 136.6, 136.7, 142.5, 142.7, 151.7, 151.8, 152.9, 153.0, 153.7, 153.9, 155.7, 156.0, 156.2, 156.5, 184.66, 184.73. IR ($CHCl_3$) cm^{-1}: 1690, 1663, 1593, 1466, 1331, 1150, 1123. EI-MS *m/z*: 563 (M^+). HR-MS *m/z*: 563.1924 (Calcd for $C_{32}H_{28}F_3NO_5$: 563.1919).

6,8-Dibenzyloxy-2-formyl-7-methoxy-2,3,4,5-tertahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-4′-one (20b) (*s-cis* and *s-trans* = 2 : 1) A solution of PIFA (1.90 g, 4.4 mmol) in 2,2,2-trifluoroethanol (10 ml) was added to a solution of **15b** (2.00 g, 4.0 mmol) in trifluoroethanol (100 ml) at −40 °C and the mixture was stirred for 1 h with keeping the temperature. After the reaction, the organic solvent in the reaction mixture was evaporated and the residue was purified by recrystallization from ethyl acetate to afford **20b** (1.29 g, 65%) and the mother liquid was purified by silica gel column chromatography (chloroform : ethyl acetate = 20 : 1) to afford **20b** (341.5 mg, 17%) as colorless crystals; mp 187—189 °C (ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.26 and 2.29 (2H, t, J=6.2 Hz), 3.65 and 3.71 (2H, t, J=6.2 Hz), 3.74 and 3.75 (3H, s, OMe), 4.60 and 4.69 (2H, s), 4.84 and 4.88 (2H, s), 5.14 and 5.15 (2H, s), 6.14 and 6.15 (2H, d, J=10.2 Hz, A part of AB), 6.57 and 6.76 (1H, s, Ar-H), 6.98 and 7.05 (2H, d, B part of AB, J=10.2 Hz), 7.22—7.47 (10H, m), 8.19 and 8.21 (1H, s, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 38.1, 39.4, 40.8, 45.6, 45.7, 47.1, 50.4, 60.8, 60.9, 70.7, 71.0, 75.7, 110.3, 111.2, 124.2, 124.4, 126.5, 126.6, 127.3, 127.4, 127.7, 127.80, 127.82, 128.1, 128.2, 128.31, 128.33, 128.6, 128.7, 133.0, 133.3, 136.3, 136.4, 136.7, 136.8, 142.2, 142.6, 151.81, 151.84, 153.1, 153.6, 154.1, 154.4, 161.7, 162.4, 185.1, 185.2. IR ($CHCl_3$) cm^{-1}: 1663, 1620, 1593, 1493, 1329, 1123. EI-MS *m/z*: 495 (M^+). HR-MS *m/z*: 495.2052 (Calcd for $C_{31}H_{29}NO_5$: 495.2045). *Anal.* Calcd for $C_{31}H_{29}NO_5$: C, 75.13; H, 5.90; N, 2.83. Found: C, 75.26; H, 5.98; N, 2.92.

6,8-Diallyloxy-7-methoxy-2-trifluoroacetyl-2,3,4,5-tertahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-4′-one (20c) A solution of PIFA (47.3 mg, 0.12 mmol) in 2,2,2-trifluoroethanol (1 ml) was added to a solution of **15c** (50 mg, 0.11 mmol) in 2,2,2-trifluoroethanol (1.5 ml) at −40 °C and the mixture was stirred for 1 h with keeping the temperature. After the reaction, the organic solvent in the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to afford **20c** (30.0 mg, 60%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.31 (2H, t, J=5.5 Hz), 3.79 and 3.80 (3H, s, OMe), 3.84 and 3.88 (2H, t, J=6.2 Hz), 4.37 and 4.39 (2H, dt, J=4.4, 1.2 Hz, CH_2=CH–C$\underline{H}_2$), 4.59 and 4.61(2H, dt, J=4.4, 1.2 Hz, CH_2=CH–C$\underline{H}_2$), 4.76 and 4.80 (2H, s), 5.14 and 5.32 (2H, dm, J=10.4 Hz, 2×C$\underline{H}_2$=CH–), 5.20 and 5.43 (2H, dm, J=17.2 Hz, 2×CH_2=CH–), 5.80 and 6.06 (2H, m, 2×CH_2=C$\underline{H}$–), 6.27 (2H, d, J=10.0 Hz), 6.47 and 6.64 (1H, s, Ar-H), 6.95 and 7.00 (2H, d, J=10.0 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 37.2, 38.7, 44.4, 45.3, 47.0, 47.3, 48.2, 49.0, 60.67, 60.72, 69.6, 69.8, 111.0, 111.5, 117.9, 118.05, 118.10, 123.2, 123.6, 126.9, 131.0, 131.2, 132.6, 132.7, 133.0, 133.1, 142.5, 142.7, 151.7, 152.6, 152.7, 153.8, 154.1, 185.39, 185.44; IR ($CHCl_3$) cm^{-1}: 1690, 1663, 1620, 1593, 1466, 1327, 1150, 1092. EI-MS *m/z*: 463 (M^+). HR-MS *m/z*: 463.1600 (Calcd for $C_{24}H_{24}F_3NO_5$: 463.1606).

6,8-Diallyloxy-2-formyl-7-methoxy-2,3,4,5-tertahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-4′-one (20d) A solution of PIFA (155.8 mg, 0.36 mmol) in 2,2,2-trifluoroethanol (1.0 ml) was added to a solution of **15d** (120 mg, 0.3 mmol) in 2,2,2-trifluoroethanol (0.5 ml) at −40 °C and the mixture was stirred for 30 min with keeping the temperature. After the reaction, the organic solvent in the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to afford **20d** (57.0 mg, 48%) as colorless crystals. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.28 and 2.31 (2H, t, J=6.3 Hz), 3.67 and 3.72 (2H, t, J=6.0 Hz), 3.78 and 3.79 (3H, s, OMe), 4.33 and 4.37 (2H, dt, J=5.6, 1.2 Hz, 2×CH_2=CH–C$\underline{H}_2$), 4.59—4.61 (2H, m), 4.61 and 4.68 (2H, s), 5.13 and 5.33 (2H, dm, J=10.4 Hz, 2×C$\underline{H}_2$=CH–), 5.19 and 5.44 (2H, dm, J=17.2 Hz, 2×C$\underline{H}_2$=CH–), 5.80 and 6.06 (2H, m, 2×CH_2=C$\underline{H}$–), 6.26 (2H, d, J=10.0 Hz), 6.49 and 6.64 (1H, s, Ar-H), 6.98 and 7.03 (2H, d, J=10.0 Hz), 8.19, 8.22 (1H, s, CHO). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.8, 38.9, 40.8, 45.4, 45.6, 47.1, 50.3, 60.6, 60.7, 69.5, 69.7, 74.06, 74.13, 109.92, 110.93, 117.90, 117.93, 118.01, 118.03, 123.7, 123.8, 126.6, 126.7, 132.65, 132.71, 132.9, 133.0, 133.2, 142.1, 142.4, 151.5, 151.6, 152.5, 152.9, 154.2, 154.4, 161.7, 162.4, 185.6. IR ($CHCl_3$) cm^{-1}: 1666, 1620, 1593, 1493, 1466, 1331, 1215, 1123, 1092; EI-MS *m/z*: 395 (M^+). HR-MS *m/z*: 395.1740 (Calcd for $C_{23}H_{25}NO_5$: 395.1732).

6,8-Dimethoxymethoxy-7-methoxy-2-trifluoroacetyl-2,3,4,5-tertahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclo-hexa-2′,5′-diene-4′-one (20e) PIFA (72.6 mg, 0.16 mmol) was added to a solution of **15e** (72.7 mg, 0.15 mmol) in 2,2,2-trifluoroethanol (1.5 ml) at −40 °C and the mixture was stirred for 15 min with keeping the temperature. After the reaction, the organic solvent in the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to afford **20e** (32.3 mg, 45%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.33 (2H, m), 3.37 (3H, s, OMe), 3.52 (3H, s, OMe), 3.79 and 3.80 (3H, s, OMe), 3.82—3.90 (2H, m), 4.77 and 4.80 (2H, s), 4.91 and 4.92 (2H, s), 5.22 and 5.24 (2H, s), 6.32 (2H, d, J=10.1 Hz), 6.75 and 6.89 (1H, s, Ar-H), 6.95 and 7.00 (2H, d, J=10.1 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 37.1, 38.6, 44.4, 45.17, 45.22, 47.0, 47.2, 48.1, 48.89, 48.94, 56.3, 56.4, 57.67, 57.69, 60.70, 60.73, 95.0, 95.1, 99.2, 113.2, 113.8, 114.2, 114.4, 118.1, 118.2, 124.2, 124.5, 126.95, 126.99, 131.6, 131.8, 142.3, 142.4, 150.25, 150.29, 150.7, 150.8, 153.7, 154.0, 155.9, 156.3, 156.4, 156.7, 185.4, 185.5. IR ($CHCl_3$) cm^{-1}: 3013, 1690, 1663, 1620, 1153, 1049. EI-MS *m/z*: 471 (M^+). HR-MS *m/z*: 471.1499 (Calcd for $C_{22}H_{24}F_3NO_7$: 471.1504).

6,8-Dimethoxymethoxy-2-formyl-7-methoxy-2,3,4,5-tertahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-4′-one (20f) A solution

of PIFA (236 mg, 0.55 mmol) in 2,2,2-trifluoroethanol (2.5 ml) was added to a solution of **15f** (203 mg, 0.5 mmol) in 2,2,2-trifluoroethanol (1.5 ml) at −40 °C and the mixture was stirred for 10 min with keeping the temperature. After the reaction, the organic solvent in the reaction mixture was evaporated and partitioned between ethyl acetate and 5% aqueous solution of sodium bicarbonate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=2 : 3) to afford **20f** (87.0 mg, 43%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.29 and 2.32 (2H, t, J=6.5 Hz), 3.37 (3H, s, OMe), 3.52 and 3.53 (3H, s, OMe), 3.68 and 3.73 (2H, t, J=6.1 Hz), 3.78 and 3.79 (3H, s, OMe), 4.63 and 4.69 (2H, s), 4.86 and 4.90 (2H, s), 5.23 (2H, s), 6.30 (2H, d, J=10.3 Hz), 6.76 and 6.88 (1H, s, Ar-H), 6.98 and 7.04 (2H, d, J=10.3 Hz), 8.19 and 8.23 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 37.3, 37.8, 38.9, 40.3, 45.8, 45.6, 47.1, 47.2, 50.2, 56.3, 56.4, 57.69, 57.71, 60.7, 60.8, 95.0, 95.1, 99.26, 99.33, 112.1, 113.3, 124.8, 126.7, 126.8, 132.3, 133.0, 133.5, 133.7, 142.0, 142.1, 150.2, 150.3, 150.6, 151.1, 154.1, 154.4, 161.7, 162.5, 185.7. IR ($CHCl_3$) cm^{-1}: 3514, 2939, 1659, 1620, 1593, 1493, 1427, 1323, 1157, 1045. EI-MS m/z: 403 (M^+). HR-MS m/z: 403.1617 (Calcd for $C_{21}H_{25}NO_7$: 403.1631).

6,8-Di-*tert*-butyldimethylsilyloxy-7-methoxy-2-trifluoroacetyl-2,3,4,5-tertahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-4′-one (20g) A solution of PIFA (2.15 g, 5.0 mmol) in 2,2,2-trifluoroethanol (15 ml) was added to a solution of **15g** (2.90 g, 4.7 mmol) in 2,2,2-trifluoroethanol (15 ml) at −40 °C and the mixture was stirred for 1 h with keeping the temperature. After the reaction, the organic solvent in the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate=4 : 1) to afford **20g** (1.44 g, 50%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.07, 0.09, 0.17, and 0.19 (12H, s), 0.74, 0.80, 1.008, and 1.011 (18H, s), 2.24—2.30 (2H, m), 3.67 (3H, s), 3.80—3.84 (2H, m), 4.71 and 4.76 (2H, s), 6.26 (2H, d, J=10.1 Hz), 6.29 and 6.46 (1H, s), 6.96 (1H, d, J=10.1 Hz), 7.09 (1H, d, J=10.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: −4.6, −4.4, −1.42, −1.38, 18.1, 19.6, 19.8, 25.5, 25.6, 27.05, 27.09, 40.2, 42.1, 44.9, 45.8, 46.9, 47.3, 48.8, 49.6, 60.1, 60.2, 114.8, 114.9, 115.1, 116.6, 117.7, 117.8, 122.4, 122.6, 127.5, 127.6, 130.7, 131.3, 141.8, 141.9, 148.1, 148.2, 149.5, 150.1, 155.2, 155.4, 185.6, 185.7. IR ($CHCl_3$) cm^{-1}: 3275, 2932, 1659, 1616, 1585, 1470, 1431, 1385, 1254, 1150, 1115, 1088 1007. EI-MS m/z: 611 (M^+).

Oxidative Coupling of 15b with PIDA in Trifluoroethanol (Table 2, Entry 2) A solution of PIDA (177 mg, 0.55 mmol) in 2,2,2-trifluoroethanol (6 ml) was added dropwise to a solution of **15b** (250 mg, 0.5 mmol) in 2,2,2-trifluoroethanol (7 ml) and the mixture was stirred for 30 min at room temperature. The organic solvent of the reaction mixture was removed *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous solutions of sodium thiosulfate and sodium bicarbonate, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol=10 : 1) to afford **20b** (134 mg, 54%) as a colorless oil.

Oxidative Coupling of 15b with PIDA in Trifluoroacetic Acid (Table 2, Entry 3) A solution of PIDA (210 mg, 0.65 mmol) in trifluoroacetic acid (1 ml) was added dropwise to a solution of **15b** (250 mg, 0.5 mmol) in trifluoroacetic acid (6 ml) and the mixture was stirred for 45 min at room temperature. The organic solvent of the reaction mixture was removed *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous solutions of sodium thiosulfate and sodium bicarbonate, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol=10 : 1) to afford **15b** (15 mg, 6% recovered), **20b** (140 mg, 56%), and **21a** (44 mg, 23%) as a colorless oil.

21a: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.73 (2H, t, J=7.6 Hz), 3.04 and 3.15 (2H, t, J=7.6 Hz), 3.89 and 3.91 (3H, s), 4.21 and 4.33 (2H, s), 5.10 and 5.11 (4H, s), 6.11 and 6.13 (2H, d, J=10.3 Hz), 6.38 and 6.44 (2H, s), 6.65 and 6.73 (2H, d, J=10.3 Hz), 7.30—7.43 (10H, m), 8.06 and 8.13 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.6, 38.0, 38.7, 41.9, 45.7, 52.1, 61.30, 61.33, 68.5, 68.6, 71.3, 71.5, 107.5, 108.2, 127.56, 127.61, 128.2, 128.4, 128.5, 128.8, 128.9, 129.0, 131.0, 131.6, 137.1, 137.3, 139.3, 139.8, 150.1, 150.7, 152.9, 153.2, 163.1, 163.4, 185.1, 185.4. IR ($CHCl_3$) cm^{-1}: 3034, 1670, 1636, 1593, 1435, 1115, 1078. FAB-MS m/z: 513 (M^+). HR-MS m/z: 513.2146 (Calcd for $C_{31}H_{31}NO_6$: 513.2151).

Oxidative Coupling of 15b with PIFA in Trifluoroacetic Acid (Table 2, Entry 4) A solution of PIFA (220 mg, 0.525 mmol) in trifluoroacetic acid (1 ml) was added dropwise to a solution of **15b** (250 mg, 0.5 mmol) in trifluoroacetic acid (6 ml) and the mixture was stirred for 40 min at 0 °C. The organic solvent of the reaction mixture was removed *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous solutions of sodium thiosulfate and sodium bicarbonate, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol=10 : 1) to afford **15b** (20 mg, 8% recovered), **20b** (125 mg, 50%), and **21a** (33 mg, 13%) as a colorless oil.

Oxidative Coupling of 15b with PIDA in Acetic Acid (Table 2, Entry 5) A solution of PIDA (194 mg, 0.6 mmol) in acetic acid (3.7 ml) was added dropwise to a solution of **15b** (250 mg, 0.5 mmol) in acetic acid (10 ml) and the mixture was stirred for 40 min at room temperature. The organic solvent of the reaction mixture was removed *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous solutions of sodium thiosulfate and sodium bicarbonate, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol=20 : 1) to afford **20b** (88 mg, 35.5%), and **21b** (54 mg, 19.5%) as a colorless oil.

21b: ^{1}H-NMR (400 MHz,$CDCl_3$) δ: 1.82 and 1.85 (2H, t, J=7.9 Hz), 2.02 and 2.04 (3H, s), 3.01 and 3.13 (2H, t, J=7.9 Hz), 3.90 and 3.91 (3H, s), 4.19 and 4.34 (2H, s), 5.11 and 5.12 (4H, s), 6.23 and 6.25 (2H, d, J=10.2 Hz), 6.38 and 6.43 (2H, s), 6.66 and 6.73 (2H, d, J=10.2 Hz), 7.30—7.44 (10H, m), 8.09 and 8.15 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.46, 21.48, 36.2, 37.5, 38.1, 41.8, 45.8, 51.8, 61.29, 61.32, 71.4, 71.5, 75.3, 75.6, 107.4, 108.3, 127.55, 127.59, 128.2, 128.3, 128.9, 129.0, 129.5, 129.7, 131.0, 131.4, , 137.1, 137.3, 139.8, 147.1, 147.6, 153.0, 153.2, 162.9, 169.3, 169.5, 184.8, 185.1. IR ($CHCl_3$) cm^{-1}: 1751, 1670, 1593, 1435, 1371, 1240, 1115, 1007. FAB-MS m/z: 578 ($M+Na^+$). HR-MS m/z: 578.2159 (Calcd for $C_{33}H_{33}NO_7Na$: 578.2155).

Oxidative Coupling of 15b with PIFA in CH_3CN (Table 2, Entry 6) A solution of PIFA (225 mg, 0.525 mmol) in acetonitrile (2.5 ml) was added dropwise to a solution of **15b** (250 mg, 0.5 mmol) in acetonitrile (10 ml) at 0 °C and the mixture was stirred for 50 min with keeping the temperature. The organic solvent of the reaction mixture was removed *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous solutions of sodium thiosulfate and sodium bicarbonate, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol=10 : 1) to afford **15b** (75 mg, 30%), **20b** (80 mg, 32%), and **21c** (30 mg, 11%) as a colorless oil.

21c: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.69 (3H, t, J=7.2 Hz), 1.93 and 2.01 (3H, s), 2.88 and 3.09 (2H, t, J=7.2 Hz), 3.89 and 3.91 (3H, s), 4.21 and 4.33 (2H, s), 5.11 and 5.12 (4H, s), 6.23 (2H, d, J=10.2 Hz), 6.36 and 6.45 (2H, s), 6.71 (2H, d, J=10.2 Hz), 7.29—7.44 (10H, m), 8.02 and 8.16 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.7, 37.9, 38.4, 52.7, 54.9, 61.3, 71.4, 71.5, 107.5, 127.6, 127.7, 128.3, 128.4, 129.0, 129.3, 130.0, 130.6, 137.1, 139.9, 150.3, 153.2, 163.3, 170.5, 185.2. IR ($CHCl_3$) cm^{-1}: 3009, 1670, 1628, 1593, 1506, 1115, 1078. FAB-MS m/z: 555 (M^+). HR-MS m/z: 555.2500 (Calcd for $C_{33}H_{35}N_2O_6$: 555.2495).

Oxidative Coupling of 15b with PIFA in Dimethoxyethane (Table 2, Entry 7) A solution of PIFA (280 mg, 0.65 mmol) in dimethoxyethane (1.8 ml) was added dropwise to a solution of **15b** (250 mg, 0.5 mmol) in dimethoxyethane (6 ml) and the mixture was stirred for 60 min at room temperature. The organic solvent of the reaction mixture was removed *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous solutions of sodium thiosulfate and sodium bicarbonate, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol=10 : 1) to afford **15b** (34 mg, 14% recovered), **20b** (13 mg, 5%), and **21a** (33 mg, 13%) as a colorless oil.

Oxidative Coupling of 15b with PIFA in Isopropanol (Table 2, Entry 8) A solution of PIFA (225 mg, 0.525 mmol) in 2-propanol (3 ml) was added dropwise to a solution of **15b** (250 mg, 0.5 mmol) in 2-propanol (16 ml) at 0 °C and the mixture was stirred for 50 min with keeping the temperature. The organic solvent of the reaction mixture was removed *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous solutions of sodium thiosulfate and sodium bicarbonate, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol=20 : 1) to afford **15b** (84 mg, 33.6% recovered), **20b** (60 mg, 24%), and **21d** (30 mg, 10.8%), and **21a** (13 mg, 5%) as a colorless oil.

21d: ^{1}H-NMR (400 MHz,$CDCl_3$) δ: 1.07 and 1.09 (6H, d, J=6.2 Hz), 1.71 and 1.75 (2H, t, J=7.9 Hz), 3.04 and 3.10 (2H, t, J=7.9 Hz), 3.49 and

3.51 (1H, quint, J=6.2 Hz), 3.89 and 3.91 (3H, s), 4.20 and 4.33 (2H, s), 5.10 and 5.11 (4H, s), 6.26 and 6.27 (2H, d, J=10.3 Hz), 6.38 and 6.44 (2H, s), 6.66 and 6.71 (2H, d, J=10.3 Hz), 7.30—7.44 (10H, m), 8.09 and 8.13 (1H, s,). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 25.1, 37.0, 37.6, 38.9, 41.8, 45.6, 51.6, 61.30, 61.33, 68.4, 68.8, 71.4, 71.5, 74.1, 74.3, 107.4, 108.3, 127.57, 127.61, 128.2, 128.3, 128.9, 129.0, 130.8, 131.7, 137.1, 137.4, 150.8, 151.1, 153.0, 153.2, 162.9, 163.1, 185.5, 185.6. IR ($CHCl_3$) cm^{-1}: 1670, 1636, 1593, 1435, 1117, 1005. FAB-MS m/z: 555 (M^+). HR-MS m/z: 555.2626 (Calcd for $C_{34}H_{37}NO_6$: 555.2621).

(±)-3-Hydroxy-*N*-trifluoroacetyl-*N*-nornarwedine (8a) Trifluoroacetic acid (2 ml) was added to a solution of **20a** (284 mg, 0.5 mmol) in dimethyl sulfide (1 ml) at 0 °C and the mixture was stirred for 5 d at room temperature. After the reaction, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate=2 : 1) to afford **8a** (163 mg, 85%) as colorless needles; mp 250—251 °C (ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.08—2.23 (2H, m), 2.75 and 2.79 (1H, dd, J=17.6, 3.6 Hz), 3.13 (1H, br d, J=17.6 Hz), 3.33 and 3.70 (1H, br t, J=14.0 Hz), 3.95 and 3.97 (3H, s, OMe), 4.10 and 4.49 (1H, d, J=16.0 Hz, A part of AB type), 4.34 and 4.72 (1H, br d, J=15.4 Hz), 4.81 and 5.21 (1H, d, J=16.0 Hz, B part of AB type), 4.73 (2H, br s), 5.73 (1H, br s), 6.40 and 6.56 (1H, s, Ar-H), 6.07 and 6.09 (1H, d, A part of AB, J=10.3 Hz), 6.79 and 6.85 (1H, dd, B part of AB, J=10.3, 2.2 Hz). ^{13}C-NMR (400 MHz, $CDCl_3$) δ: 34.6, 37.37, 37.42, 37.6, 46.7, 46.9, 48.05, 48.09, 52.1, 52.9, 60.5, 88.3, 88.4, 107.7, 109.0, 114.8, 117.7, 121.6, 121.7, 127.2, 127.4, 128.3, 128.7, 131.3, 131.4, 142.8, 143.3, 148.8, 149.3, 193.94, 194.01. IR ($CHCl_3$) cm^{-1}: 3530, 1690, 1601, 1512, 1443, 1150, 1072. EI-MS m/z: 383 (M^+). HR-MS m/z: 383.0979 (Calcd for $C_{18}H_{16}F_3NO_5$: 383.0980). *Anal.* Calcd for $C_{18}H_{16}F_3NO_5$: C, 56.46; H, 4.21; N, 3.65. Found: C, 56.35; H, 4.47; N, 3.44.

(±)-3-Hydroxy-*N*-formyl-*N*-nornarwedine (8b) (*s-cis* and *s-trans*=3 : 2) Trifluoroacetic acid (1 ml) was added to a solution of **20b** (35.0 mg, 0.07 mmol) in dimethyl sulfide (0.5 ml) at 0 °C and the mixture was stirred for 4 d at room temperature. After the reaction, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (ethyl acetate) to afford **8b** (17.9 mg, 81%) as colorless plates; mp 249—251 °C (ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.94—2.24 (2H, m), 2.74—2.81 (1H, dm, J=17.0 Hz, A part of AB type), 3.09—3.15 (1H, dm, J=17.0 Hz, B part of AB type), 3.25 and 3.68 (1H, br t), 3.92 and 3.95 (3H, s), 4.01 (0.5H, d, J=17.0 Hz, A part of AB type), 5.16 (0.5H, d, J=17.0 Hz, B part of AB type), 4.49 (1H, s), 4.00 and 4.63 (1 H, br d, J=15.0 Hz), 4.70 (1H, br s), 6.06 and 6.07 (1H, d, J=10.3 Hz, A part of AB type), 6.40 and 6.53 (1H, s), 6.83 and 6.87 (1H, d, J=10.3 Hz, B part of AB type), 8.15 and 8.18 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 35.0, 37.4, 38.5, 41.3, 46.7, 47.0, 48.2, 48.3, 52.9, 60.5, 88.2, 88.4, 106.8, 108.6, 129.8, 130.3, 131.2, 143.4, 143.8, 148.9, 149.0, 149.3, 149.5, 162.0, 162.5, 194.1, 194.2. IR ($CHCl_3$) cm^{-1}: 1670, 1601, 1512, 1431, 1396, 1173, 1069. EI-MS m/z: 315 (M^+). HR-MS m/z: 315.1114 (Calcd for $C_{17}H_{17}NO_5$: 315.1106). *Anal.* Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.50; H, 5.57; N, 4.35.

Methanesulfonic acid (67.9 mg, 0.7 mmol) was added to a solution of **20b** (35.0 mg, 0.07 mmol) in dimethyl sulfide (0.5 ml) at 0 °C and the mixture was stirred for 2 h at room temperature. After the reaction, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (chloroform : methnol=10 : 1) to afford **8b** (13.6 mg, 62%).

Trifluoroacetic acid (1 ml) was added to a solution of **20b** (100 mg, 0.2 mmol) in dodecyl methyl sulfide (0.5 ml) at 0 °C and the mixture was stirred for 4 d at room temperature. After the reaction, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (chloroform : methanol=20 : 1) to afford **8b** (49.0 mg, 77%).

Methanesulfonic acid (96.1 mg, 1.0 mmol) was added to a solution of **20b** (50.0 mg, 0.1 mmol) in dodecyl methyl sulfide (2.0 ml) at 0 °C and the mixture was stirred for 2 h at room temperature. After the reaction, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (ethyl acetate) to afford **8b** (17.8 mg, 57%).

Boron tricloride (6.1 ml, 1 M solution in CH_2Cl_2, 6.1 mmol) was added to a solution of **20b** (1.0 g, 2.0 mmol) in dichloromethane (20 ml) at −78 °C and the mixture was stirred for 20 h with keeping the temperature. After the reaction, the reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by recrystallization from ethyl acetate to afford **8b** (605.3 mg, 95%).

(±)-3-Trifluoromethanesulfonyl-*N*-formyl-*N*-nornarwedine (23) Trifluoromethanesulfonic anhydride (0.26 ml, 1.5 mmol) was added to a solution of **8b** (200 mg, 0.634 mmol) in pyridine (4 ml) at 0 °C and the mixture was stirred for 1 h with keeping the temperature. After the reaction, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (chloroform : methanol=5 : 1) to afford **23** (278.3 mg, 98%) as colorless needles; mp 229—231 °C (methanol). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.00—2.34 (2H, m), 2.79 and 2.80 (1H, dd, J=3.7, 17.8 Hz,), 3.13 (1H, dm, J=17.8 Hz), 3.28 and 3.70 (1H, br t, J=10.0 Hz), 3.99 and 4.00 (3H, s, OMe), 4.01 and 4.62 (1H, br d, J=12.0 Hz), 4.02 (0.5H, d, J=15.2 Hz, A part of AB type), 5.19 (0.5H, d, J=15.2 Hz, B part of AB type), 4.52 (0.5H, d, J=17.0 Hz, A′ part of A′B′ type), 4.55 (0.5H, d, J=17.0 Hz, B′ part of A′B′ type), 4.80 (1H, m), 6.13 and 6.14 (1H, d, J=10.4 Hz), 6.81 and 6.87 (1H, dd, J=10.4, 2.0 Hz), 6.67 and 6.80 (1H, s), 8.16 and 8.19 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 34.8, 37.09, 37.11, 38.2, 41.0, 46.3, 46.4, 48.56, 48.60, 52.1, 60.6, 60.7, 88.6, 88.7, 113.7, 115.0, 117.0, 120.2, 128.2, 128.4, 129.3, 129.6, 130.9, 131.0, 136.95, 137.04, 140.8, 140.9, 142.0, 142.5, 150.3, 150.6, 161.8, 162.3, 193.3, 193.4. IR ($CHCl_3$) cm^{-1}: 1678, 1423, 1234, 1200, 1045, 1022. EI-MS m/z: 447 (M^+). HR-MS m/z: 447.0610 (Calcd for $C_{18}H_{16}F_3NO_7S$: 447.0599). *Anal.* Calcd for $C_{18}H_{16}F_3NO_7S$: C, 48.32; H, 3.60; N, 3.13. Found: C, 48.49; H, 3.84; N, 2.91.

(±)-*N*-Formyl-*N*-nornarwedine (24) Formic acid (6.17 mg, 0.134 mmol) and triethylamine (20 mg, 0.2 mmol) were added to a solution of **23** (30.0 mg, 0.067 mmol), palladium acetate (0.29 mg, 0.0013 mmol) and triphenylphosphine (0.7 mg, 0.0027 mmol) in *N*,*N*-dimethylformamide (0.5 ml) and the mixture was stirred for 3 h at 60 °C. After the reaction, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol=15 : 1) to afford **24** (19.4 mg, 97%) as colorless crystals; mp 193—195 °C (hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.98—2.12 (2H, m), 2.74 and 2.79 (1H, dd, J=5.4, 17.9 Hz), 3.20 (1H, dm, J=17.9 Hz), 3.23 and 3.68 (1H, br t, J=13.0 Hz), 3.85 and 3.86 (3H, s, OMe), 4.05 and 4.66 (each 0.5H, br d, J=10.1 Hz), 4.07 (0.5H, d, J=15.4 Hz, A part of AB type), 5.27 (0.5H, d, J=15.4 Hz, B part of AB type), 4.52 (0.5H, d, J=16.3 Hz, A′ part of A′B′ type), 4.59 (0.5H, d, J=16.3 Hz, B′ part of A′B′ type), 4.73 (1H, m), 6.08 and 6.10 (1H, d, J=10.5 Hz), 6.72—6.74 (1H, m), 6.88—6.90 (2H, m), 8.16 and 8.19 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 35.3, 37.2, 38.7, 41.3, 46.7, 46.9, 48.97, 49.00, 52.8, 56.05, 56.08, 87.6, 87.7, 112.0, 112.1, 120.2, 121.9, 127.6, 127.8, 127.9, 128.3, 129.5, 129.7, 142.7, 143.1, 144.6, 144.8, 147.5, 147.9, 161.8, 162.4, 193.8, 193.9. IR ($CHCl_3$) cm^{-1}: 1670, 1512, 1435, 1281, 1169, 1053. EI-MS m/z: 299 (M^+). HR-MS m/z: 299.1165 (Calcd for $C_{17}H_{17}NO_4$: 299.1157). *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 67.91; H, 5.82; N, 4.49.

(±)-Galanthamine (1) Lithium tri-*sec*-butylborohydride (L-Selectride) (0.4 ml, 1.0 M solution in tetrahydrofuran, 0.4 mmol) was added to a solution of **24** (40 mg, 0.17 mmol) in tetrahydrofuran (4 ml) at −78 °C and the mixture was stirred for 6 h with keeping the temperature. And then, a suspension of lithium aluminum hydride (15.2 mg, 0.40 mmol) in tetrahydrofuran (1.0 ml) was added to the reaction mixture, and the mixture was stirred for another 12 h at room temperature. After the reaction, an aqueous solution of sodium sulfate was added to the reaction mixture which was extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol=5 : 1) to afford (±)-**1** (23.4 mg, 61%) as colorless crystals; mp 123—124 °C (ethyl acetate) [lit. mp 121—123 °C].[26] ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.58 (1H, ddd, J=13.7, 4.0, 1.8 Hz), 2.01 (1H, ddd, J=15.7, 3.5, 1.8 Hz), 2.09 (1H, dt, J=13.3, 3.2 Hz), 2.42 (3H, s), 2.44 (1H, br s, OH), 2.69 (1H, ddt, J=15.7, 3.5, 1.8 Hz), 3.04 (1H, br d, J=13.7 Hz), 3.26 (1H, dt, J=13.7, 1.7 Hz), 3.68 (1H, d, A part of AB, J=15.2 Hz), 3.83 (3H, s), 4.09 (1H, d, B part of AB, J=15.2 Hz), 4.14 (1H, m), 4.61 (1H, br), 6.00 (1H, ddd, A part of AB, J=10.2, 5.0, 1.2 Hz), 6.07 (1H, dd, B part of AB, J=10.2, 1.2 Hz), 6.62 (1H, d, A part of AB, J=8.3 Hz), 6.66 (1H, d, B part of AB, J=8.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.3, 34.2, 42.5, 48.6, 54.2, 56.2, 61.0, 62.4, 89.1, 111.5, 122.4, 127.2, 129.8, 133.4, 144.4, 146.2. IR ($CHCl_3$) cm^{-1}: 3410, 2964, 2933, 1626, 1601, 1514, 1462, 1439, 1408, 1375, 1283, 1234, 1202, 1173, 1138, 1115, 1090, 1069, 1047, 1015. EI-MS m/z: 287 (M^+). HR-MS m/z: 287.1523 (Calcd for $C_{17}H_{21}NO_3$: 287.1521).

2-Hydroxy-3-methoxy-11-formyl-4α,5,9,10,11,12-hexahydro-6*H*-benzofuro[3α,3,2-ef][2]benzazepine-6-(1,2)-ethylenediol Ketal (25) Ethylene glycol and pyridinium *p*-toluenesulfonate were added to a solution of **24** (20.0 mg, 0.067 mmol) in benzene and the mixture was refluxed for 2 d.

After the reaction, the reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate, and condensed *in vacuo*. The residue was extracted with chloroform and the organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1) to afford **25** (21.2 mg, 92%) as colorless crystals; mp 253—254 °C (acetone). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.83—2.07 (2H, m), 2.19 (1H, dt, J=15.5, 3.7 Hz), 2.69 and 2.70 (1H, dd, J=15.5, 3.5 Hz), 3.15—3.23 (1H, m), 3.62—3.70 (1H, m), 3.82 and 3.83 (3H, s), 3.97—4.06 (4H, m), 4.48 and 4.54—4.62 (3H, m), 5.72 and 5.74 (1H, d, J=10.3 Hz), 6.10 and 6.15 (1H, d, J=10.4 Hz), 6.62—6.67 and 6.79 (2H, m), 8.10 and 8.14 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 33.2, 33.3, 36.4, 38.8, 41.1, 46.8, 48.0, 48.1, 52.9, 55.7, 64.4, 65.3, 86.9, 87.0, 102.5, 111.1, 111.2, 119.4, 121.2, 127.0, 127.2, 128.1, 128.4, 131.0, 131.2, 144.6, 144.8, 147.2, 147.6, 161.8, 162.4. IR ($CHCl_3$) cm^{-1}: 2935, 2889, 1668, 1626, 1591, 1510, 1465, 1431, 1286, 1171, 1132, 1057. EI-MS *m/z*: 343 (M^+). HR-MS *m/z*: 343.1435 (Calcd for $C_{19}H_{21}NO_5$: 343.1419).

(±)-Narwedine (3) A suspension of lithium aluminum hydride (9.95 mg, 0.262 mmol) in tetrahydrofuran (1.0 ml) was added to a solution of **25** (30.0 mg, 0.087 mmol) in tetrahydrofuran (0.5 ml) and the mixture was stirred for 24 h. After the reaction, a saturated aqueous solution of sodium sulfate was added to the reaction mixture, which was extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate and evaporated. The residue was dissolved in tetrahydrofuran (1 ml), to which 1 M hydrochloric acid was added, and the mixture was stirred for 24 h at room temperature. After the reaction, the reaction mixture was extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1) to afford (±)-**3** as colorless crystals (20.6 mg, 83%); mp 198—199 °C (ethyl acetate) [lit. mp 188—190 °C].[17] ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.84—1.89 (1H, m), 2.28 (1H, dt, J=13.2, 3.5 Hz), 2.45 (3H, s, NMe), 2.75 (1H, dd, J=17.9, 3.8 Hz), 3.19 (3H, m), 3.75 (1H, d, J=15.4 Hz, A part of AB type), 3.85 (3H, s, OMe), 4.10 (1H, d, J=15.4 Hz, B part of AB type), 4.73—4.75 (1H, m), 6.05 (1H, d, J=10.4 Hz), 6.66 (1H, d, J=8.2 Hz, Ar-H), 6.70 (1H, d, J=8.2 Hz, Ar-H), 6.95 (1H, d, J=10.4 Hz,). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 33.6, 37.7, 42.8, 49.3, 54.5, 56.4, 61.0, 88.3, 112.2, 122.3, 127.5, 129.8, 130.9, 144.3, 144.7, 147.3, 194.8. IR ($CHCl_3$) cm^{-1}: 1686, 1508, 1439, 1285, 1049. EI-MS *m/z*: 285 (M^+). HR-MS *m/z*: 285.1371 (Calcd for $C_{17}H_{19}NO_3$: 285.1365).

2-(*R*)-*tert*-Butoxycarbonylamino-*N*-2-(4-hydroxyphenethyl)-3-phenylpropionamide (27a) EDC·HCl (4.3 g, 22.6 mmol) was added to a mixture of *N*-Boc-D-phenylalanine (**26a**) (5.0 g, 18.9 mmol), tyramine (3.1 g, 22.0 mmol) and HOBt (254.6 mg, 1.88 mmol) in tetrahydrofuran (50 ml), and the mixture was stirred for 2 h at room temperature. After the reaction, the reaction mixture was concentrated *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was successively washed with 1 M hydrochloric acid, saturated aqueous solution of sodium bicarbonate, saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was recrystallized from diethyl ether to give **27a** (6.9 g, 95%) as colorless crystals; mp 102—104 °C (diethyl ether). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.39 (9H, s, *t*-Bu), 2.48—2.60 (2H, m), 3.00 (1H, d, J=6.2 Hz), 3.22—3.29 (1H, m), 3.35—3.42 (1H, m), 4.25 (1H, q, J=7.0 Hz), 5.16 (1H, s), 5.95 (1H, s), 6.73 (2H, d, J=8.4 Hz), 6.83—6.87 (2H, m), 7.16 (2H, d, J=8.4 Hz), 7.18—7.32 (3H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.2, 34.6, 38.8, 40.9, 56.1, 80.4, 115.5, 127.0, 128.6, 129.3, 129.4, 129.6, 129.9, 136.6, 154.9, 171.3. IR ($CHCl_3$) cm^{-1}: 3597, 3431, 3032, 1705, 1672, 1514, 1369, 1170. FAB-MS *m/z*: 385 (M+H$^+$). HR-MS *m/z*: 385.2120 (Calcd for $C_{22}H_{29}N_2O_4$: 385.2127).

2-(*R*)-*tert*-Butoxycarbonylamino-*N*-2-(4-hydroxyphenethyl)-3-methylbutylamide (27b) EDC·HCl (4.18 g, 21.8 mmol) was added to a mixture of *N*-Boc-D-valine (**26b**) (3.95 g, 18.2 mmol), tyramine (2.99 g, 21.8 mmol) and HOBt (246 mg, 1.82 mmol) in tetrahydrofuran (45 ml) at 0 °C, and the mixture was stirred for 24 h at room temperature. The reaction mixture was condensed *in vacuo*, and extracted with ethyl acetate. The organic layer was successively washed with 1 M hydrochloric acid, saturated aqueous solution of sodium bicarbonate, saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (chloroform : methanol = 50 : 1) to give **27b** (3.84 g, 63%) as colorless crystals; mp 99—102 °C (diethyl ether). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87, 0.89 (each 3H, d, J=7.7 Hz), 1.44 (9H, s), 1.71 (1H, m), 2.06 (1H, br), 2.71 (2H, t, J=7.0 Hz), 3.48 (2H, m), 3.77 and 3.80 (1H, d, J=7.0 Hz), 5.07 and 6.10 (each 1H, br s), 6.75 (2H, d, J=8.3 Hz), 7.00 (2H, d, J=8.3 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 18.0, 19.2 (2C), 28.3 (3C), 30.8, 34.8, 41.0, 60.2, 80.2, 115.6, 129.6 (2C), 129.8, 153.1, 155.1, 172.0. IR ($CHCl_3$) cm^{-1}: 3339, 2976, 1705, 1670, 1514, 1456, 1369, 1238, 1171. EI-MS *m/z*: 336 (M^+). HR-MS *m/z*: 336.2046 (Calcd for $C_{18}H_{28}N_2O_4$: 336.2049).

2-(*R*)-Amino-*N*-2-(4-hydroxyphenethyl)ethyl-3-phenylpropionamide (28a) Methanesulfonic acid (1.4 ml, 21.6 mmol) was added to a solution of **27a** (4.20 g, 10.8 mmol) in methanol (40 ml) at room temperature and the mixture was stirred at 40 °C for 3 h. The reaction mixture was then concentrated *in vacuo* and an aqueous solution of potassium carbonate was added and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated. The residue was recrystallized from diethyl ether to give **28a** (3.00 g, 97%) as colorless crystals, mp 87—88 °C (diethyl ether). $[\alpha]_D^{26}$ +39.5° (c=0.59, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.64 (2H, dd, J=13.7, 9.2 Hz), 2.71 (1H, t, J=7.2 Hz), 3.22 (1H, dd, J=13.7, 4.1 Hz), 3.45 (1H, dd, J=13.2, 7.2 Hz, A part of AB type), 3.50 (1H, dd, J=13.2, 7.2 Hz, B part of AB type), 3.56 (1H, dd, J=9.2, 4.1 Hz), 6.77 (2H, d, J=8.6 Hz), 6.98 (2H, d, J=8.6 Hz), 7.13—7.33 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 34.8, 40.5, 41.0, 56.4, 115.5 (2C), 126.8, 128.7 (2C), 129.3 (2C), 129.7 (2C), 130.2, 137.7, 154.8, 174.5; IR ($CHCl_3$) cm^{-1}: 3362, 1657, 1614, 1514, 1454, 1362, 1240, 1173, 1105. EI-MS *m/z*: 284 (M^+). HR-MS *m/z*: 284.1522 (Calcd for $C_{17}H_{20}N_2O_2$: 284.1525). *Anal.* Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.78; H, 7.06; N, 9.63.

2-(*R*)-Amino-*N*-2-(4-hydroxyphenyl)ethyl-3-methylbutyramide (28b) A mixture of **27b** (3.84 g, 11.4 mmol), methanesulfonic acid (1.48 ml, 22.8 mmol) in methanol (32 ml) was stirred at room temperature for 24 h. The reaction mixture was then concentrated *in vacuo* and an aqueous solution of potassium carbonate was added and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol = 5 : 1) to give **28b** (1.03 g, 38%) as colorless crystals; mp 134—136 °C (ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.77 (3H, d, J=7.0 Hz), 0.96 (3H, d, J=7.0 Hz), 2.24—2.32 (1H, m), 2.75 (2H, t, J=7.0 Hz), 3.19 (1H, d, J=3.7 Hz), 3.43—3.58 (2H, m), 6.77 (2H, d, J=8.4Hz), 7.05 (2H, d, J=8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.9 (2C), 19.7, 35.0, 40.3, 60.1, 115.4 (2C), 129.8 (2C), 130.7, 154.5, 174.4. IR ($CHCl_3$) cm^{-1}: 3342, 2964, 1655, 1614, 1597, 1514, 1466, 1369, 1252, 1173, 829. EI-MS *m/z*: 236 (M^+). HR-MS *m/z*: 236.1532 (Calcd for $C_{13}H_{20}N_2O_2$: 236.1525).

(2*S*,5*R*)-5-Benzyl-2-(3,5-dibenzyloxy-4-methoxyphenyl)-3-(4-hydroxyphenethyl)-imidazolidin-4-one (29a) A mixture of 3,5-dibenzyloxy-4-methoxybenzaldehyde (**18a**) (100 mg, 0.29 mmol) and **28a** (97.9 mg, 0.34 mmol) in dioxane (3.0 ml) was stirred at room temperature for 24 h. And then, 4.0 M HCl in dioxane (1.5 ml) was added to the reaction mixture at 0 °C, which was stirred at room temperature for another 24 h. The reaction mixture was then concentrated *in vacuo* and an aqueous solution of sodium bicarbonate was added and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give **29a** (115.4 mg, 64%) as an amorphous powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.38, 2.47 (each 1H, dd, J=13.7, 7.0 Hz, AB type), 2.59 (1H, dt, J=13.7, 7.2 Hz), 2.77 (1H, dd, J=13.7, 7.5 Hz, A part of AB type), 3.01 (1H, dd, J=13.7, 3.8 Hz, B part of AB type), 3.70 (1H, dt, J=13.7, 7.2 Hz), 3.80—3.93 (1H, m), 3.88 (3H, s, OCH_3), 4.73 (1H, s), 5.07 (4H, s, 2×$PhCH_2O$), 6.34 (2H, s), 6.71 (2H, d, J=8.6 Hz), 6.79 (2H, d, J=8.6 Hz), 7.10—7.41 (16H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.6, 38.1, 41.7, 59.7, 60.9, 71.1 (2C), 75.9, 106.2 (2C), 115.4 (2C), 126.7, 127.3 (4C), 128.0 (2C), 128.5 (2C), 128.6 (4C), 129.6 (2C), 129.7 (2C), 129.8, 134.3, 136.7 (2C), 137.3, 140.0, 152.8 (2C), 154.9, 174.1. IR ($CHCl_3$) cm^{-1}: 3595, 3007, 1686, 1595, 1516, 1445, 1327, 1240, 1113. FAB-MS *m/z*: 615 (M+H$^+$). HR-MS *m/z*: 615.2871 (Calcd for $C_{39}H_{39}N_2O_5$: 615.2859).

(2*S*,5*R*)-2-(3,5-Dibenzyloxy-4-methoxyphenyl)-3-(4-hydroxyphenethyl)-5-isopropylimidazolidin-4-one (29b) A mixture of 3,5-dibenzyloxy-4-methoxybenzaldehyde (**18a**) (653.9 mg, 1.90 mmol) and **28b** (300 mg, 1.27 mmol) in dioxane (6.0 ml) was stirred at room temperature for 24 h. And then, 4.0 M HCl in dioxane (6 ml) was added to the reaction mixture at 0 °C, which was stirred at room temperature for another 48 h. The reaction mixture was then concentrated *in vacuo* and an aqueous solution of sodium bicarbonate was added and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give **29b**

(473.9 mg, 66%) as an amorphous powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.74 (3H, d, J=6.8 Hz), 0.91 (3H, d, J=7.0 Hz), 1.70 (2H, br), 2.03—2.10 (1H, m), 2.46—2.68 (3H, m), 3.56 (1H, br s), 3.79—3.86 (1H, m), 3.92 (3H, s), 5.04 (1H, br s), 5.11 (4H, s, 2×OCH_2O), 6.43 (2H, s), 6.73 (2H, d, J=8.4 Hz), 6.91 (2H, d, J=8.4Hz), 7.28—7.43 (10H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 16.2, 19.4, 30.8, 32.5, 41.4, 60.9, 63.6, 71.1 (2C), 76.7, 106.2 (2C), 115.4 (2C), 127.3 (4C), 128.0 (2C), 128.6 (4C), 129.7 (2C), 134.9, 136.7 (2C), 140.1, 152.9 (2C), 154.9, 174.4. IR ($CHCl_3$) cm^{-1}: 3327, 2964, 1682, 1595, 1516, 1445, 1369, 1352, 1327, 1259, 1240, 1113, 1078, 1003, 827. EI-MS m/z: 566 (M^+). HR-MS m/z: 566.2784 (Calcd for $C_{35}H_{38}N_2O_5$: 566.2780).

(2*S*,5*R*)-5-Benzyl-3-(4-hydroxyphenethyl)-2-(3,4,5-trimethoxyphenyl)imidazolidin-4-one (29c) A mixture of 3,4,5-trimethoxybenzaldehyde (**9**) (2.6 g, 13.2 mmol) and **28a** (2.5 g, 8.8 mmol) in dioxane (30 ml) was stirred at room temperature for 12 h. And then, 4.0 M HCl in dioxane (20 ml) was added to the reaction mixture at 0 °C, which was stirred at room temperature for another 12 h. The reaction mixture was then concentrated *in vacuo* and an aqueous solution of sodium bicarbonate was added and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=2 : 1) to give **29c** (1.75 g, 43%) as an amorphous powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.48—2.61 (2H, m), 2.78 (1H, m), 2.85 (1H, dd, J=13.8, 7.2 Hz, A part of AB), 3.05 (1H, dd, J=13.8, 3.9 Hz, B part of AB type), 3.67 (1H, s), 3.80 (6H, s), 3.81 (3H, s), 3.74—3.93 (1H, m), 4.02—4.05 (1H, m), 4.85 (1H, d, J=1.5 Hz), 6.34 (2H, s), 6.75 (2H, d, J=8.6 Hz), 6.86 (2H, d, J=8.6 Hz), 7.22—7.38 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.7, 38.1, 42.1, 56.1 (2C), 59.9, 60.8, 76.3, 106.2 (2C), 115.5 (2C), 126.8, 128.5 (2C), 129.6 (2C), 129.66, 129.70 (2C), 134.5, 136.7, 138.5, 153.7 (2C), 155.1, 174.4. IR ($CHCl_3$) cm^{-1}: 1686, 1597, 1516, 1447, 1425, 1329, 1238, 1130. EI-MS m/z: 462 (M^+). HR-MS m/z: 462.2158 (Calcd for $C_{27}H_{30}N_2O_5$: 462.2154).

(2*S*,5*R*)-5-Benzyl-2-(3,5-dibenzyloxy-4-methoxyphenyl)-3-(4-hydroxyphenethyl)-1-(2,2,2-trifluoroacetyl)imidazolidin-4-one (30a) *s-cis* and *s-trans*=2 : 1 Trifluoroacetic anhydride (0.89 ml, 6.33 mmol) was added to a solution of **29a** (1.63 g, 2.64 mmol) in pyridine (10 ml) at 0 °C and the mixture was stirred for 15 min. After the reaction, methanol (10 ml) was added to the mixture, which was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 1 M hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane : ethyl acetate=2 : 1) to give **30a** (1.77 g, 94%) as colorless crystals; mp 118—135 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.96—2.09 (1H, m), 2.14—2.32 (2H, m), 3.25—3.33 (1H, m), 3.39—3.46 (1H, m), 3.53—3.60 (1H, m), 3.65 and 3.68 (1H, d, J=5.2 Hz), 3.86 and 3.87 (3H, s, OMe), 4.85 and 4.91 (1H, br s), 4.97—5.07 (4H, m, 2×Ph$C\underline{H}_2$O), 5.47 and 5.53 (1H, br s, –OH), 6.02 and 6.24 (2H, s), 6.47 (1H, d, J=8.5 Hz), 6.54 (1H, d, J=8.5 Hz), 6.63 and 6.65 (2H, d, J=8.5 Hz), 7.11—7.13 (1H, m), 7.18—7.20 (1H, m), 7.27—7.38 (13H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.3, 33.0, 33.2, 38.6, 41.6, 60.8, 60.9, 61.0, 61.2, 71.2, 71.3, 76.0, 107.4, 113.5, 114.1, 115.4, 116.4, 116.7, 127.2, 127.2, 127.5, 127.9, 128.0, 128.1, 128.6, 128.6, 128.9, 129.6, 129.8, 130.0, 130.1, 130.2, 130.3, 131.2, 133.6, 134.6, 136.2, 136.6, 140.4, 141.2, 152.6, 154.6, 154.7, 155.2, 155.7, 156.1, 166.4, 167.0. IR ($CHCl_3$) cm^{-1}: 3314, 1701, 1597, 1454, 1443, 1327, 1169, 1115. FAB-MS m/z: 711 (M+H^+). HR-MS m/z: 711.2690 (Calcd for $C_{41}H_{38}F_3N_2O_6$: 711.2682). *Anal*. Calcd for $C_{41}H_{37}F_3N_2O_6$: C, 69.29; H, 5.25; N, 3.94. Found: C, 69.13; H, 5.20; N, 3.82.

(2*S*,5*R*)-2-(3,5-Benzyloxy-4-methoxyphenyl)-3-(4-hydroxyphenethyl)-5-isopropyl-1-(2,2,2-trifluoroacetyl)imidazolin-4-one (30b) Trifluoroacetic anhydride (0.02 ml, 0.147 mmol) was added to an ice-cooled solution of **29b** (34.8 mg, 0.06 mmol) in pyridine (1.0 ml) at 0 °C and the mixture was stirred for 3 h. After the reaction, methanol (1.0 ml) was added to the mixture, which was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 1 M hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (chloroform : methanol=10 : 1) to give **30b** (30.5 mg, 77%) as colorless crystals. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.66 and 0.73 (3H, d, J=6.9 Hz), 1.19 and 1.23 (3H, d, J=7.1 Hz), 2.13 and 2.43 (1H, m), 2.35—2.49 (1H, m), 2.50—2.60 (1H, m), 3.71—3.82 (2H, m), 3.91 and 3.92 (3H, s, OMe), 4.43 and 4.52 (1H, br s), 5.10 (2H, s, OCH_2Ph), 5.06 (1H, d, J=12.4 Hz, A part of AB type, OCH_2Ph), 5.14 (1H, d, J=12.4 Hz, B part of AB, OCH_2Ph), 5.56 and 5.68 (1H, br s), 6.25 and 6.40 (2H, s), 6.72 and 6.75 (2H, d, J=8.5 Hz), 6.87 and 6.90 (2H, d, J=8.6 Hz), 7.26—7.41 (10H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.9, 15.9, 18.1, 18.6, 28.2, 32.4, 32.8, 34.2, 40.9, 40.9, 60.9, 61.1, 63.9, 64.2, 71.1, 71.4, 76.1, 107.5, 115.5, 127.2, 128.0, 128.3, 128.6, 128.7, 129.4, 129.7, 129.8, 130.2, 131.5, 136.3, 136.6, 140.5, 141.3, 152.7, 154.8, 154.8, 166.4, 166.8. IR ($CHCl_3$) cm^{-1}: 3325, 2936, 1697, 1597, 1516, 1504, 1445, 1420, 1371, 1346, 1327, 1292, 1259, 1238, 1167, 1115, 1078, 1003, 826. FAB-MS m/z: 662 (M^+). HR-MS m/z: 662.2608 (Calcd for $C_{37}H_{37}F_3N_2O_6$: 662.2604).

(2*S*,5*R*)-5-Benzyl-3-(4-hydroxyphenethyl)-1-(2,2,2-trifluoroacetyl)-2-(3,4,5-trimethoxyphenyl)-imidazolin-4-one (30c) Trifluoroacetic anhydride (0.23 ml, 1.62 mmol) was added to a solution of **29c** (311.6 mg, 0.67 mmol) in pyridine (3.0 ml) at 0 °C and the mixture was stirred for 60 min. After the reaction, methanol (3 ml) was added to the mixture, which was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 1 M hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane : ethyl acetate=1 : 1) to give **30c** (358 mg, 95%) as colorless crystals. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.17 (1H, br t, J=8.8 Hz), 2.26—2.50 (3H, m), 3.34 (0.5H, dd, J=14.5, 4.6 Hz, A part of AB), 3.46 (0.5 H, dd, J=14.5, 2.2 Hz, B part of AB), 3.36 (0.5H, dd, J=14.0, 2.2 Hz, A′ part of AB), 3.58 and 3.73 (1H, m), 3.72 (0.5H, dd, J=14.0, 4.9 Hz, B′ part of A′B′), 3.76 (3H, s), 3.77 (3H, s), 3.82 (3H, s), 5.01 and 5.08 (1H, m), 5.52 and 5.59 (1H, br s), 6.04 and 6.21 (2H, s), 6.57 and 6.61 (2H, d, J=8.4 Hz), 6.67 (2H, d, J=8.4 Hz), 7.17 and 7.23 (2H, dd, J=7.4, 1.9 Hz), 7.36—7.40 (3H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.5, 33.1, 33.3, 38.7, 41.7, 41.8, 56.2, 56.3, 60.8, 60.9, 61.3, 76.2, 76.3, 104.2, 115.4, 127.6, 127.9, 128.7, 129.0, 129.6, 129.8, 130.15, 130.23, 130.3, 130.4, 131.6, 133.6, 134.7, 138.9, 139.6, 153.5, 153.7, 154.6, 154.7, 166.5, 167.1. IR ($CHCl_3$) cm^{-1}: 3323, 1701, 1597, 1516, 1466, 1425, 1350, 1329, 1240, 1169, 1130. EI-MS m/z: 558 (M^+). HR-MS m/z: 558.1977 (Calcd for $C_{29}H_{29}F_3N_2O_6$: 558.1975). *Anal.* Calcd for $C_{29}H_{29}F_3N_2O_6$: C, 62.36; H, 5.23; N, 5.02. Found: C, 62.27; H, 5.14; N, 4.90.

Oxidative Coupling Reaction of 30a with PIFA PIFA (57.8 mg, 0.13 mmol) in 2,2,2-trifluoroethanol (3 ml) was added to a solution of **30a** (86.8 mg, 0.12 mmol) in 2,2,2-trifluoroethanol (3.0 ml) at −40 °C and the mixture was stirred for 10 min. After the reaction, the mixture was concentrated *in vacuo* and the residue was purified by silica gel colum chromatography (hexane : ethyl acetate=2 : 1) to give **31a** (51.8 mg, 61%) as an amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.47 (0.5H, dd, J=16.5, 12.3 Hz, A part of AB type), 1.75 (0.5H, dd, J=16.5, 5.7 Hz, B part of AB type), 1.88 (0.5H, dd, J=16.5, 5.5 Hz, A′ part of A′B′), 2.10 (0.5H, dd, J=15.7, 12.6 Hz, B′ part of A′B′), 2.90 and 3.15 (1H, t, J=13.2 Hz), 3.27—3.45 (1H, m), 3.57 (1H, dd, J=13.2, 5.2 Hz), 3.76 and 3.80 (3H, s, OMe), 3.75—3.85 (1H, m), 4.47 and 4.90 (1H, br s), 4.61 and 4.70 (1H, d, J=10.6 Hz), 4.82 and 4.89 (1H, d, J=10.6 Hz), 4.99 and 5.04 (1H, d, J=12.1 Hz), 5.08 and 5.21 (1H, d, J=12.1 Hz), 5.91 and 5.96 (1H, dd, J=10.1, 1.7 Hz), 5.60 and 6.06 (1H, s), 6.14 and 6.15 (1H, d, J=10.1 Hz), 6.29 and 6.36 (1H, s), 6.69 and 6.78 (1H, dd, J=9.9, 3.0 Hz), 7.08—7.52 (15H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.6, 36.7, 37.2, 37.3, 39.1, 46.1, 46.5, 60.9, 62.7, 62.8, 70.4, 70.7, 70.9, 71.0, 75.8, 77.2, 104.4, 104.5, 121.4, 121.9, 122.6, 123.4, 126.0, 127.1, 127.2, 127.4, 127.5, 128.0, 128.1, 128.3, 128.4, 128.7, 128.9, 129.6, 129.8, 130.3, 133.2, 134.1, 136.0, 136.0, 136.2, 136.4, 143.7, 150.9, 152.5, 152.6, 153.4, 153.7, 155.9, 156.3, 156.8, 157.2, 164.7, 165.5, 184.6, 184.9. IR ($CHCl_3$) cm^{-1}: 1707, 1660, 1456, 1333, 1184, 1171, 1117. FAB-MS m/z: 709 (M+H^+). HR-MS m/z: 709.2530 (Calcd for $C_{41}H_{36}F_3N_2O_6$: 709.2525).

Oxidative Coupling Reaction of 30b with PIFA PIFA (7.14 mg, 0.017 mmol) in 2,2,2-trifluoroethanol (0.5 ml) was added to a solution of **30b** (10.0 mg, 0.015 mmol) in 2,2,2-trifluoroethanol (0.5 ml) at −40 °C and the mixture was stirred for 15 min. After the reaction, the mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (chloroform : methanol=1 : 1) to give **31b** (4.5 mg, 45%) as an amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.86 and 0.94 (3H, d, J=6.8 Hz), 1.23 and 1.30 (3H, d, J=7.0 Hz), 2.09 (1H, td, J=16.0, 5.5 Hz), 2.33 and 2.96 (1H, m), 2.59 (1H, dt, J=16.0, 5.5 Hz) , 3.17 and 3.20 (1H, t, J=13.0 Hz), 3.74 and 3.90 (2H, dd, J=14.0, 5.5 Hz) 3.79 and 3.82 (3H, s), 4.06 and 4.41 (1H, br s), 4.72 and 4.73 (1H, d, J=10.5 Hz), 4.89 and 4.92 (1H, d, J=10.5 Hz), 5.01 and 5.03 (1H, d, J=12.5 Hz), 5.10 and 5.23 (1H, d, J=12.5 Hz), 6.02 (1H, dd, J=10.1, 1.8 Hz), 6.22 and 6.24 (1H, dd, J=9.1, 1.8 Hz), 6.31 and 6.32 (1H, s), 6.71 and 6.75 (1H, s), 6.90 and 7.13 (1H, dd, J=10.0, 3.0 Hz), 7.20—7.43 (10H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.0, 15.4, 17.9, 18.4, 25.8, 34.1, 36.9, 37.3, 37.4, 37.6, 46.7, 46.7, 60.9, 61.0, 65.6, 65.8, 70.5, 70.7, 70.8, 70.9, 75.8, 75.9, 104.3, 104.6, 121.6,

122.3, 123.2, 123.4, 126.5, 127.1, 127.2, 127.5, 127.6, 128.0, 128.1, 128.3, 128.4, 128.4, 128.7, 128.9, 130.8, 135.9, 136.0, 136.3, 136.4, 143.6, 151.1, 151.4, 152.6, 153.7, 157.0, 157.2, 164.6, 165.7, 184.7, 184.9. IR ($CHCl_3$) cm^{-1}: 3007, 1707, 1661, 1622, 1593, 1487, 1456, 1437, 1423, 1366, 1321, 1238, 1186, 1171, 1119, 1061, 1005, 854. EI-MS *m/z*: 660 (M^+). HR-MS *m/z*: 660.2254 (Calcd for $C_{37}H_{35}F_3N_2O_6$: 660.2247).

Oxidative Coupling Reaction of 30c with PIFA PIFA (84.0 mg, 0.20 mmol) in 2,2,2-trifluoroethanol (3.5 ml) was added to a solution of **30c** (100 mg, 0.18 mmol) in 2,2,2-trifluoroethanol (3.0 ml) at −40 °C and the mixture was stirred for 90 min. After the reaction, the mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give **31c** (41.0 mg, 41%) as a colorless powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.55 (0.5H, t, J=13.9 Hz), 1.75 (0.5H, dd, J=16.3, 5.7 Hz), 1.91 (0.5H, dd, J=16.1, 5.1 Hz,), 2.13 (0.5H, t, J=13.2 Hz), 3.00 and 3.24 (1H, t, J=13.2 Hz), 3.54 and 3.59 (3H, s), 3.76 and 3.77 (3H, s), 3.79 and 3.81 (3H, s), 3.31—3.86 (4H, m), 4.86 and 5.04 (1H, br s), 5.63 and 6.09 (1H, s), 6.20 and 6.31 (1H, s), 6.17—6.25 (2H, m), 6.68 and 6.74 (1H, dd, J=10.1, 2.7 Hz), 7.04—7.33 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 32.8, 36.0, 36.5, 36.8, 37.3, 39.3, 46.3, 46.7, 55.5, 55.9, 60.6, 60.7, 60.8, 62.8, 63.0, 70.7, 102.1, 122.7, 123.5, 126.0, 127.2, 127.4, 127.6, 128.1, 128.5, 128.8, 129.6, 129.8, 130.4, 133.3, 134.1, 151.1, 153.2, 153.5, 156.7, 157.2, 164.9, 165.5, 185.1. IR ($CHCl_3$) cm^{-1}: 1709, 1661, 1464, 1323, 1173, 1124. EI-MS *m/z*: 556 (M^+). HR-MS *m/z*: 556.1824 (Calcd for $C_{29}H_{27}F_3N_2O_6$: 556.1821).

Debenzylation Reaction of 31a with BCl_3 One molar solution of boron trichloride in CH_2Cl_2 (0.085 ml, 0.085 mmol) was added to a solution of **31a** (20.0 mg, 0.028 mmol) in CH_2Cl_2 (0.5 ml) at −78 °C and the mixture was stirred for 20 h. The reaction was quenched by adding chilled water and the mixture was stirred at room temperature for another 30 min. The reaction mixture was extracted with chloroform and the organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1) to give **32** (14.1 mg, 95%) as an amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.26—1.37 and 1.84—1.94 (2H, m), 2.01—2.06 (1H, m), 2.74 (1H, t, J=19.5 Hz), 3.07 (1H, t, J=18.0 Hz), 3.38 (2H, t, J=10.8 Hz), 3.46 (1H, t, J=11.8 Hz), 3.84—4.00 (1H, m), 3.92 and 4.00 (3H, s), 4.65—4.70 (1.5H, m), 4.94 and 5.42 (0.5H, s), 5.93 and 6.20 (1H, s), 5.97 and 6.03 (1H, d, J=9.3 Hz), 6.32 and 6.54 (1H, d, J=9.3 Hz), 7.13—7.34 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.3, 32.3, 33.0, 36.5, 37.0, 37.6, 38.9, 46.8, 47.4, 60.4, 61.2, 62.0, 71.3, 72.2, 77.2, 87.5, 88.0, 102.9, 103.4, 119.4, 125.7, 127.4, 127.9, 128.3, 128.4, 129.7, 129.9, 132.3, 133.5, 134.3, 142.9, 144.2, 149.3, 149.5, 166.2, 167.2, 193.6. IR ($CHCl_3$) cm^{-1}: 3526, 1693, 1510, 1456, 1437, 1238, 1169. EI-MS *m/z*: 528 (M^+). HR-MS *m/z*: 528.1508 (Calcd for $C_{27}H_{23}F_3N_2O_4$: 528.1514).

Reduction of 32 with L-Selectride One molar solution of lithium tri-*sec*-butylborohydride in tetrahydrofuran (0.64 ml, 0.64 mmol) was added to a solution of **32** (141.2 mg, 0.27 mmol) in tetrahydrofuran (2.0 ml) at −78 °C and the mixture was stirred for 24 h with keeping the temperature. The reaction was quenched by adding a saturated aqueous solution of sodium sulfate to the reaction mixture, which was extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated until a solid powder appeared, which was collected by vacuum filtration and purified by silica gel column chromatography (chloroform : methanol = 50 : 1) to give **33** (131.7 mg, 92%) as a colorless crystalline powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.18—1.39 (1H, m), 1.66—2.04 (3H, m), 2.18 (1H, d, J=10.8 Hz), 2.62 (1H, t, J=15.3 Hz,), 3.34—3.43 (2H, m), 3.82—3.93 (1H, m), 3.96 (3H, s), 4.11—4.14 (1H, m), 4.51 and 4.57 (1H, br s), 4.63 and 4.92 (1H, br s), 5.44 and 5.69 (1H, d, J=10.4Hz), 6.02 (1H, dd, J=9.9, 4.8 Hz), 5.92 and 6.17 (1H, s), 7.13—7.33 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.3, 29.7, 31.7, 32.4, 34.2, 37.7, 38.8, 46.3, 47.1, 60.4, 61.2, 61.6, 61.9, 71.6, 72.4, 88.8, 102.8, 103.2, 114.0, 116.8, 121.9, 126.5, 127.3, 127.9, 128.3, 128.7, 129.7, 132.3, 133.5, 134.3, 148.7, 148.8, 155.6, 156.0, 166.3, 167.1. IR ($CHCl_3$) cm^{-1}: 3530, 2939, 1709, 1603. EI-MS *m/z*: 530 (M^+). HR-MS *m/z*: 530.1660 (Calcd for $C_{27}H_{25}F_3N_2O_6$: 530.1664).

Hydrolysis of 33 A solution of **33** (50.0 mg, 0.094 mmol) in a mixed solvent composed of 10% aqueous solution of sodium hydroxide (0.5 ml) and tetrahydrofuran (0.5 ml) was stirred at room temperature for 12 h. After the reaction, the mixture was neutralized by 1 M hydrochloric acid and extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1) to give the **35** (40.9 mg, quant.), to which 10% aqueous solution of sodium hydroxide (9.0 ml) was added. After being stirred for 7 d, the mixture was neutralized with 1 M hydrochloric acid and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (chloroform : methano = 10 : 1) to afford **34** (22.0 mg, 83%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.00—2.08 (3H, m), 2.66 (1H, br d, J=15.6 Hz), 4.06 (3H, s), 4.01—4.16 (2H, m), 4.17 (1H, t, J=5.0 Hz), 4.71 (1H, br s), 5.56 (1H, d, J=9.9 Hz), 5.89 (1H, dd, J=9.9, 5.0 Hz), 6.63 (1H, s), 8.28 (1H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.8, 36.8, 47.0, 50.0, 60.5, 61.9, 70.7, 89.8, 111.4, 127.0, 127.7, 129.9, 133.9, 146.7, 148.8, 159.6. IR ($CHCl_3$) cm^{-1}: 3533, 2934, 1601, 1504, 1404, 1369, 1269. EI-MS *m/z*: 287 (M^+). HR-MS *m/z*: 287.1151 (Calcd for $C_{16}H_{17}NO_4$: 287.1157).

***N*-*tert*-Butoxycarbonyl-7-hydroxy-*N*-norgalanthamine (36) *s-cis* and *s-trans* = 2 : 1** Sodium borohydride (4.6 mg, 0.123mmol) was added to a solution of **34** (8.8 mg, 0.031 mmol) in methanol (0.5 ml) at 0 °C and the mixture was stirred at room temperature for 4 h. After the reaction, the reaction mixture was concentrated and the residue was extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. Di-*tert*-butyl dicarbonate (21.1 mg, 0.096 mmol) was added to a solution of the residue in tetrahydrofuran (0.5 ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and extracted with chloroform. The organic layer was washed with satureated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate) to give **36** (7.0 mg, 58%) as a colorless oil. [100% ee, chiral HPLC analysis; DICEL CHIRALCEL OD (25×0.46); eluent: *n*-hexane : *iso*-propanol = 1 : 9; flow rate: 1 ml/min; temp. 25 °C; detector; 254 nm, (−)-**36**: 50.2 min, (+)-**36**: 74.0 min]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.39 and 1.43 (9H, s), 1.65—1.77 (2H, m), 1.90 (1H, dt, J=13.1, 3.1 Hz), 2.00 and 2.04 (1H, dt, J=15.7, 2.4 Hz), 2.32 (1H, br), 2.65 (1H, d, J=15.7 Hz), 3.28 and 3.37 (1H, t, J=13.0 Hz), 3.93 and 3.96 (3H, s, OMe), 4.09 and 4.28 (1H, br d, J=16.0 Hz, A part of AB type), 4.15 (1H, s), 4.27 (1H, d, J=14.8 Hz), 4.58 (1H, s), 4.60 and 4.79 (1H, d, J=16.0 Hz, B part of AB type), 5.71 and 5.95 (1H, br d, J=10.4 Hz), 5.72 and 5.98 (1H, br s), 6.34 and 6.45 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.3, 28.5, 30.0, 36.3, 37.3, 45.3, 46.0, 47.6, 51.4, 52.0, 60.5, 62.0, 80.0, 89.0, 89.2, 107.5, 108.2, 124.4, 127.0, 127.2, 127.5, 130.8, 132.0, 147.8, 148.2, 154.9. IR ($CHCl_3$) cm^{-1}: 3531, 2937, 1686, 1601, 1508, 1462, 1441, 1416, 1367, 1251, 1169. EI-MS *m/z*: 389 (M^+). HR-MS *m/z*: 389.1836 (Calcd for $C_{21}H_{27}NO_6$: 389.1838).

Trifluoromethanesulfonation of 32 Trifluoromethanesulfonic anhydride (0.13 ml, 0.78 mmol) was added to a solution of **32** (343 mg, 0.65 mmol) in pyridine (1.5 ml) at 0 °C and the mixture was stirred at the temperature for 3 h. The reaction was quenched by adding methanol (3.0 ml) and the mixture was concentrated *in vacuo*. The residue was extracted with ethyl acetate and the organic layer was successively washed with 1 M hydrochloric acid and a saturated aqueous solution of sodium bicarbonate, a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate) to afford triflate **37** (354.3 mg, 83%) as a crystalline powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.46 and 1.95 (2H, m), 2.76 (1H, t, J=15.8 Hz), 3.07—3.52 (4H, m), 3.89 (1H, m), 3.99 (3H, br s), 4.68 and 4.79 (1H, s), 4.73 and 4.95 (1H, s), 5.41 and 5.93 (1H, s), 6.08—6.54 (3H, m), 7.16—7.35 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.8, 32.4, 33.2, 36.3, 36.7, 37.7, 38.7, 39.0, 47.4, 48.2, 60.8, 61.1, 61.9, 71.0, 71.6, 88.0, 88.5, 110.3, 117.0, 120.2, 122.7, 123.4, 127.6, 128.0, 128.4, 128.8, 129.9, 133.3, 133.9, 141.3, 142.6, 150.2, 150.6, 166.3, 167.0, 192.7. IR ($CHCl_3$) cm^{-1}: 1709, 1697, 1508, 1456, 1429, 1312, 1256, 1240, 1169, 1140, 1038, 1007. EI-MS *m/z*: 660 (M^+). HR-MS *m/z*: 660.1000 (Calcd for $C_{28}H_{22}F_6N_2O_8S$: 660.0996).

Detrifluoromethanesulfonation of 37 Formic acid (0.064 ml, 1.7 mmol) and triethylamine (0.355 ml, 2.55 mmol) were added to a solution of **37** (114.4 mg, 0.17 mmol), palladium acetate (7.86 mg, 0.035 mmol) and triphenylphosphine (18.17 mg, 0.069 mmol) in *N*,*N*-dimethylformamide (1.5 ml), and the mixture was stirred at 60 °C for 3 d. After the reaction, the mixture was concentrated *in vacuo* and the residue was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate) to give **38** (85.6 mg, 98%) as a colorless crystalline powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.42—1.49 and 1.83—2.17 (2H, m), 2.76 (1H, dd, J=17.6, 3.4 Hz), 2.70 and 3.20 (1H, m), 3.17 (1H, d, J=17.6 Hz), 3.37—3.48 (2H, m), 3.86 (3H, br s), 4.02 (1H, m), 4.65 and 4.72 (1.5H, br s), 4.96

and 5.50 (0.5H, s), 6.03 and 6.06 (1.5H, d, J=10.0 Hz), 6.29 and 6.34 (0.5H, d, J=10.0 Hz), 6.53 and 6.59 (1H, d, J=9.3 Hz), 6.52 and 6.59 (1H, d, J=9.0 Hz), 6.78 (1H, d, J=9.0 Hz), 7.14—7.35 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 30.9. 32.3, 33.6, 35.1, 36.3, 36.8, 37.8, 38.9, 39.8, 47.7, 48.6, 55.9, 56.1, 61.1, 61.9, 71.8, 72.6, 77.2, 87.0, 87.5, 88.0, 111.3, 112.1, 112.6, 116.4, 121.2, 123.5, 126.6, 127.4, 127.9, 128.1, 128.3, 128.7, 129.7, 129.9, 133.4, 134.2, 141.9, 143.3, 145.2, 145.8, 148.0, 155.8, 156.5, 166.4, 167.1, 193.2. IR ($CHCl_3$) cm^{-1}: 2937, 1693, 1510, 1456, 1437, 1286, 1167, 1055. EI-MS m/z: 512 (M^+); HR-MS m/z: 512.1553 (Calcd for $C_{27}H_{23}F_3N_2O_5$: 512.1559).

Reduction of 38 with L-Selectride One molar solution lithium tri-*sec*-butylborohydride in tetrahydrofuran (0.937 ml, 0.937 mmol) was added to a solution of **38** (200 mg, 0.39 mmol) in tetrahydrofuran (2 ml) at −78 °C and the mixture was stirred at the temperature for 3 h. The reaction was quenched by adding a saturated aqueous solution of sodium sulfate, and the mixture was extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate) to give **39** (156.3 mg, 78%) as an amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.56—2.03 (4H, m), 2.67 (1H, t, J=16.7 Hz), 3.40 (2H, t, J=12.5 Hz), 3.85 and 3.87 (3H, s), 3.80—3.89 (1H, m), 3.98—4.03 (1H, m), 4.16 (1H, br s), 4.51 and 4.58 (1H, s), 4.63 and 4.93 (1H, br s), 5.73 (1H, d, J=8.6 Hz), 5.99 (1H, s), 6.05 and 6.07 (1H, d, J=8.6 Hz), 6.26 and 6.49 (1H, d, J=8.2 Hz), 6.73 (1H, d, J=8.2 Hz), 7.12—7.36 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.1, 29.6, 32.4, 34.6, 37.9, 38.8, 47.3, 48.1, 55.9, 60.7, 61.1, 61.5, 61.9, 72.1, 72.7, 88.1, 111.3, 111.8, 114.0, 116.3, 125.6, 126.8, 127.3, 128.3, 128.7, 129.2, 129.7, 129.9, 134.4, 134.4, 145.9, 147.0, 167.1. IR ($CHCl_3$) cm^{-1}: 3568, 2937, 1709, 1508, 1456, 1437, 1286, 1238, 1194, 1167, 1060. EI-MS m/z: 514 (M^+). HR-MS m/z: 514.1711 (Calcd for $C_{27}H_{25}F_3N_2O_5$: 514.1715).

Hydrolysis of 39 A mixture of **39** (93.7 mg, 0.18 mmol), TBAB (29.4 mg, 0.09 mmol) and 10% solution of potassium hydroxide in methanol (3.0 ml) was stirred at 80 °C for 24 h. After the reaction, the mixture was neutralized with 1 M hydrochloric acid and concentrated *in vacuo*. The residue was extracted with chloroform, and the organic layer was washed with saturated aqueous solution of sodium chloride, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography (chloroform : methanol=10 : 1) to afford **40** (46.7 mg, 96%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.98—2.09 (3H, m), 2.68—2.73 (1H, m), 3.91 (3H, s, OMe), 4.01—4.18 (2H, m), 4.17 (1H, t, J=5.0 Hz), 4.72 (1H, br s), 5.59 (1H, d, J=10.0 Hz), 6.01 (1H, ddd, J=10.0, 5.0, 1.1 Hz), 6.85 (1H, d, J=8.2 Hz), 7.04 (1H, d, J=8.4 Hz), 8.35 (1H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.5, 35.9, 47.6, 49.7, 56.0, 61.7, 88.9, 111.7, 122.6, 126.4, 127.6, 128.7, 134.6, 145.2, 146.5, 158.9. IR ($CHCl_3$) cm^{-1}: 3564, 2930, 1620, 1506, 1454, 1437, 1406, 1286, 1173, 1090, 1063, 991. EI-MS m/z: 271 (M^+). HR-MS m/z: 271.1214 (Calcd for $C_{16}H_{17}NO_3$: 271.1208).

***N*-Formyl-*N*-norgalanthamine (41)** Sodium borohydride (13.4 mg, 0.35 mmol) was added to a solution of **40** (40.0 mg, 0.15 mmol) in methanol (1.0 ml) at 0 °C, and the mixture was stirred at room temperature for 24 h. After the reaction, the mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate and concentrated *in vacuo*. And then, ethyl formate (7.5 ml) was added to the residue, and the mixture was refluxed for 2 d. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (chloroform : methanol=10 : 1) to give **41** (46.3 mg, quant.) as colorless crystals; mp 117—118 °C (methanol). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.77—1.92 (2H, m), 1.94—2.07 (2H, m), 2.68—2.75 (1H, dm, J=16.0 Hz), 3.21—3.28 (1H, br t, J=12.4 Hz), 3.66—3.74 (1H, br t, J=13.6 Hz), 3.84 and 3.85 (3H, s), 4.03 (0.5H, d, J=15.0 Hz, A part of AB type), 4.17 (1H, t, J=4.6 Hz), 4.51 (1H, br s), 4.59 (1H, br s), 5. 21 (0.5H, d, J=15.0 Hz, B part of AB type), 5.97—6.11 (2H, m), 6.69 and 6.86 (1H, d, J=8.2 Hz), 6.70 (1H, s), 8.12 and 8.16 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.7, 29.8, 36.0, 39.3, 41.0, 46.5, 46.8, 48.2, 48.3, 52.8, 55.9, 61.8, 88.1, 88.2, 111.3, 111.4, 120.1, 121.8, 125.8, 126.1, 127.7, 128.4, 128.4, 128.6, 132.0, 132.1, 144.6, 144.8, 146.3, 146.7, 161.8, 162.4. IR ($CHCl_3$) cm^{-1}: 3564, 2936, 1668, 1628, 1591, 1510, 1456, 1435, 1396, 1375, 1281, 1240, 1194, 1171, 1132, 1059, 1063, 993, 966. EI-MS m/z: 301 (M^+). HR-MS m/z: 301.1317 (Calcd for $C_{17}H_{19}NO_4$: 301.1314).

(−)-Galanthamine (1) Compound **41** (10.5 mg, 0.035 mmol) was added to a suspension of lithium aluminum hydride (3.2 mg, 0.084 mmol) in THF (1.0 ml) and the mixture was stirred at room temperature for 7 h. The reaction was quenched by adding a saturated aqueous solution of sodium sulfate to the reaction mixture, which was extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (chloroform : methanol=10 : 1) to give (−)-**1** (9.5 mg, 94%) as colorless crystals, $[\alpha]_D^{22}$ −121.7° (c=0.30, ethanol) [lit. $[\alpha]_D$ −121.4° (c=0.99, ethanol)].[7] ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.60—1.70 (1H, m), 1.89—2.04 (1H, m), 2.06—2.31 (1H, m), 2.43 (3H, s, NCH_3), 2.67—2.72 (1H, m), 3.09 (1H, d, J=14.5 Hz), 3.32 (1H, t, J=13.0 Hz), 3.73 (1H, d, J=14.7 Hz), 3.84 (3H, s, OCH_3), 4.14 (1H, d, J=15.4 Hz), 4.15 (1H, t, J=4.8 Hz), 4.62 (1H, br s), 6.02 (1H, dd, J=10.5, 4.1 Hz), 6.06 (1H, d, J=10.3 Hz), 6.64 (1H, d, J=8.2 Hz), 6.68 (1H, d, J=8.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.8, 33.6, 41.8, 48.1, 53.6, 55.8, 60.4, 61.9, 88.6, 111.1, 122.0, 126.7, 127.6, 128.9, 132.9, 144.0, 145.5. IR ($CHCl_3$) cm^{-1}: 3410, 2964, 2933, 1626, 1601, 1514, 1462, 1439, 1408, 1375, 1283, 1234, 1223, 1202, 1173, 1138, 1115, 1090, 1069, 1047, 1015, 988, 943, 922, 870, 826. EI-MS m/z: 287 (M^+). HR-MS m/z: 287.1515 (Calcd for $C_{17}H_{21}NO_3$: 287.1521).

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