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Synthesis of phenserine analogues and evaluation of their cholinesterase inhibitory activities

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This work is dedicated to Dr. Masanori SAKAMOTO, Professor Emeritus of Meiji Pharmaceutical University, on the occasion of his 77th birthday (KIJU)

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Substituent effect

ABSTRACT

Phenserine is a potentially attractive drug for Alzheimer's disease. In order to further expand SAR study for inhibitions of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), the methyl group at the 3a-position of phenserine was replaced with an alkyl or alkenyl group, and its phenylcarbamoyl moiety was substituted at the *o*- or *p*-position. The synthetic methodology for these phenserine analogues includes the efficient cascade reactions for introduction of the 3a-substituent and assembly of the quaternary carbon center followed by reductive cyclization to the key pyrroloindoline structure. The bulkiness of the substituent at 3a-position of phenserine derivatives tends to reduce the inhibitory effect on AChE activity in the following order: methyl > ethyl > vinyl > propyl ≈ allyl > reverse-prenyl groups. Among the series synthesized, the 3a-ethyl derivative demonstrated the highest AChE selectivity. In construct, the 3a-reverse-prenyl derivative indicated modest BuChE selectivity.

1. Introduction

Alzheimer's disease (AD) is the most common form of elderly-onset dementia. Progressive AD is a neurodegenerative disease characterized by deficiency of cholinergic neurotransmission,[1] the formation of senile plaques including amyloid-β peptide (Aβ),[2] and the development of neurofibrillary tangles.[3] For enhancement of cholinergic neurotransmission by increasing acetylcholine (ACh) availability, development of selective acetylcholinesterase inhibitors (AChEIs) created several medicines such as donepezil and galantamine approved for AD treatment.[4] These medicines are prescribed to ease only AD symptoms, but they could not halt the progress of dementia. The approved AD medicine rivastigmine[5] and the experimental AD drug phenserine (**1**)[6] show non-selective inhibition of AChE and butyrylcholinesterase (BuChE). Since overexpression of BuChE in neuritic amyloid β Aβ plaques in AD brain was observed,[7] the presence of BuChE amplifies the toxicity of Aβ. On re-examining the non-selective ChEIs, phenserine (**1**) was found to be the most attractive drug to show dual action–inhibition of ChEs and reduction in the production of Aβ precursor protein.[8] Therefore, this drug has been expected to both ameliorate the symptoms of AD and control its progression. The structure–activity relationship (SAR) of phenserine analogues **2** has been developed (Fig. 1); for example, tolserine (R = Me, R^1 = 2-Me) indicated potent cholinesterase inhibition with a high selectivity for AChE, while cymserine (R = Me, R^1 = 4-*i*-Pr) showed potent and selective BuChE inhibition.[9] A variety of N^1- and N^8-substituents (R^2 and R^3) in phenserine (**1**), tolserine, and cymserine have also been well studied. However, to the best of our knowledge, there has been little research on the synthesis and SAR of various 3a-substituted (R) phenserine analogues.[9–11] Recently, we have developed a concise and efficient synthetic methodology for a series of pyrroloindole alkaloids.[12] On the basis of structural attractiveness and synthetic accessibility, we began to investigate SAR of novel phenserine analogues having a bulkier group (R) than methyl group at 3a-position and a substituent (R^1) on the phenyl moiety. Herein, we describe the efficient and versatile synthesis of the phenserine analogues **3**–**13** and their biological evaluation.

2. Results and discussion

2.1. Chemistry

The syntheses of target compounds **3**–**13** was accomplished by the synthesis of 3a-substituted pyrrolo[2,3-*b*]indolines **14** from **15**

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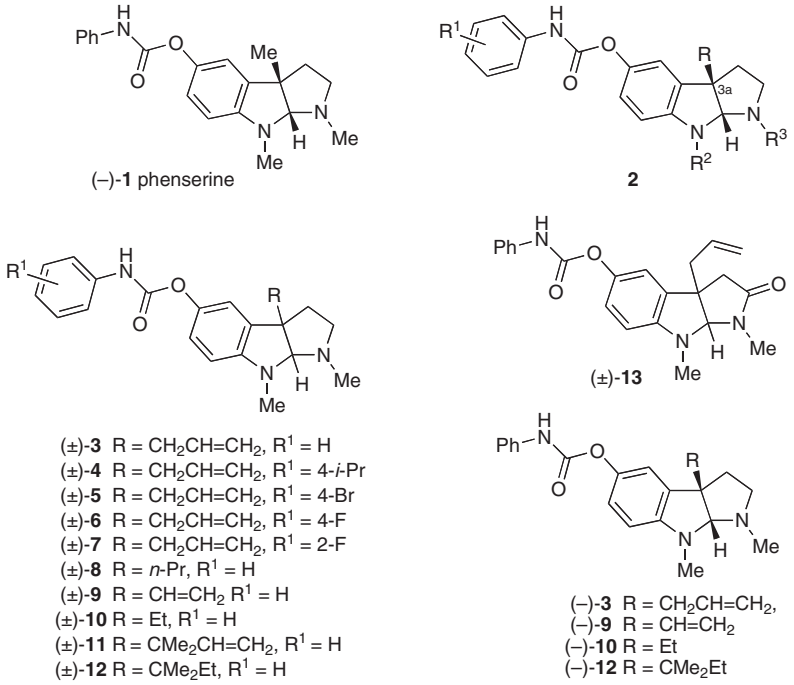


Figure 1. Phenserine (**1**), its analogues **2** used in SAR of ChEIs: e.g. cymserine (R = R^2 = R^3 = Me, R^1 = 4-*i*-Pr) and tolserine (R = R^2 = R^3 = Me, R^1 = 2-Me), and target compounds **3**–**13**.

using our previously developed methodology[12,13] and the transformation of **14** to **3–13** according to the known procedure for phenserine (**1**)[14] (Scheme 1).

2.1.1. Synthesis of racemic compounds (±)-3–13

The key synthetic intermediate **22** for the target molecules **3–8** was obtained starting from 5-methoxy-1-acetylindolin-3-one (**16**)[15] as shown in Scheme 2. Bromination of **16** at C2 followed by substitution with allyl alcohol afforded ether **17**. The Horner–Wadsworth–Emmons olefination of **17** with diethyl cyanomethylphosphonate in the presence of *t*-BuOK at a low temperature proceeded with the cascade of isomerization/deacylation/Claisen rearrangement to produce oxindole **18** in 87% yield. Methylation of **18**, followed by hydrolysis of nitrile **19** and condensation of carboxylic acid **20** with methylamine, gave methylamide **21** in 67% yield (three steps). The reductive cyclization of **21** with $LiAlH_4$ furnished the key pyrroloindoline **22**. Using conditions optimized by Brossi,[14a] sequential demethylation of **22** with BBr_3 and reaction with phenyl isocyanate were performed to produce the allyl target (±)-**3** in 76% yield (entry 1). To investigate the role of the substituent on the aromatic ring, some analogues (±)-**4**–**7** were prepared in good yields from **22** using conditions reported by Overman[14b] (entries 2–5). The propyl derivative (±)-**8** was obtained by hydrogenation of **3**.

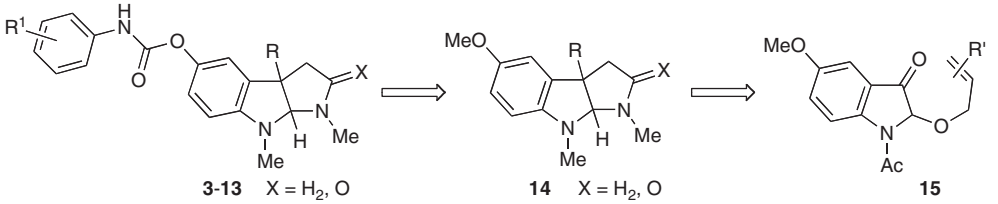
The target **13** was prepared from **21**. Thus, AlH_3-reduction of **21** proceeded with cyclization to give **23**, which was converted to (±)-**13** in the same manner as (±)-**3** (Scheme 3).

The target compounds **9** and **10** were obtained by conversion of the allyl group of **19** to both vinyl and ethyl groups (Scheme 4). Thus, OsO_4-oxidation of **19** followed by reduction gave alcohol **24**. Subsequent arylselenation and oxidative elimination of **24** afforded 3-vinyloxindole **25**. In the same way as (±)-**3**, synthesis of vinyl derivative (±)-**9** from **25** was achieved through hydrolysis, condensation with methylamine, reductive cyclization, demethylation, and carbamoylation. The ethyl derivative (±)-**10** was obtained by hydrogenation of **9**.

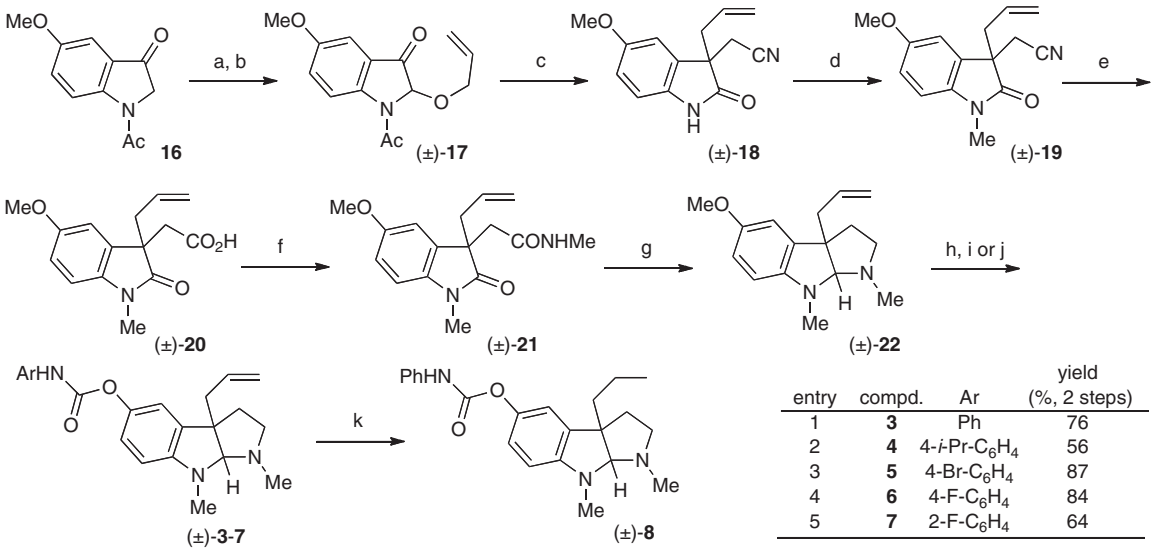
To synthesize the targets **11** and **12** with the bulky reverse-prenyl group at the 3a-position (Scheme 5), methylamide **33** was produced in 42% yield (six steps) from **16** and prenyl alcohol by the procedure similar to the preparation of **21**. Reduction of **33** with $LiAlH_4$ proceeded with cyclization to give both pyrroloindolin-2-one **34** and pyrroloindoline **35**. The indolin-2-one **34** was further reduced to afford **35** in 85% overall yield from **33**. In the case of **35**, demethylation with BBr_3 gave a miserable result due to its acid lability. For this reason, the dihydro-derivative **12** was prepared instead of **11**. After hydrogenation of **35**, demethylation of **36** with BBr_3 proceeded successfully, and subsequent carbamoylation with phenyl isocyanate afforded the target (±)-**12**.

2.1.2. Synthesis of optically active compounds (−)-3, (−)-9, (−)-10, (−)-12

To prepare the (3a*R*,8a*R*)-enantiomers (−)-**3**, (−)-**9**, (−)-**10**, and (−)-**12** having the same absolute configuration with (−)-phenserine

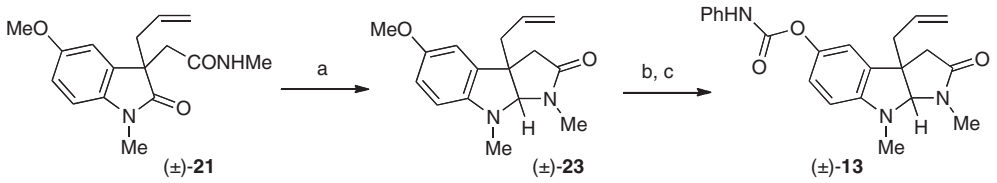


Scheme 1. Retrosynthetic approach to compounds **3**–**13**.

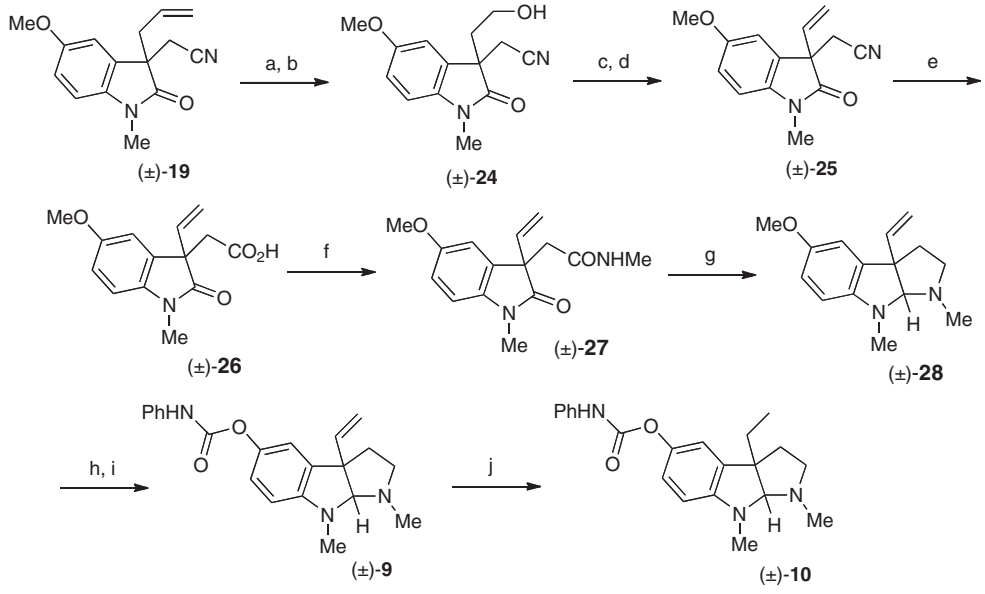


entry	compd.	Ar	yield (%, 2 steps)
1	**3**	Ph	76
2	**4**	4-*i*-Pr-C_6H_4	56
3	**5**	4-Br-C_6H_4	87
4	**6**	4-F-C_6H_4	84
5	**7**	2-F-C_6H_4	64

Scheme 2. Reagents and conditions: (a) Br_2, CH_2Cl_2, 0 °C, (b) allyl alcohol, MS 4A, MeCN, rt, 79% (2 steps); (c) $(EtO)_2P(O)CH_2CN$, *t*-BuOK, DMF, −78 °C to rt, 87%; (d) MeI, NaH, DMF, 0 °C, 98%; (e) NaOH, MeOH, reflux, 85%; (f) EDC, C_6F_5OH, Et_3N, THF, rt, then $MeNH_2$, 81%; (g) $LiAlH_4$, THF, reflux, 86%; (h) BBr_3, CH_2Cl_2, 0 °C; (i) Na, Et_2O, rt, then PhNCO, entry 1; (j) NaH, THF, rt, then ArNCO, entries 2–5; (k) Pd/C, H_2, rt, 96%.

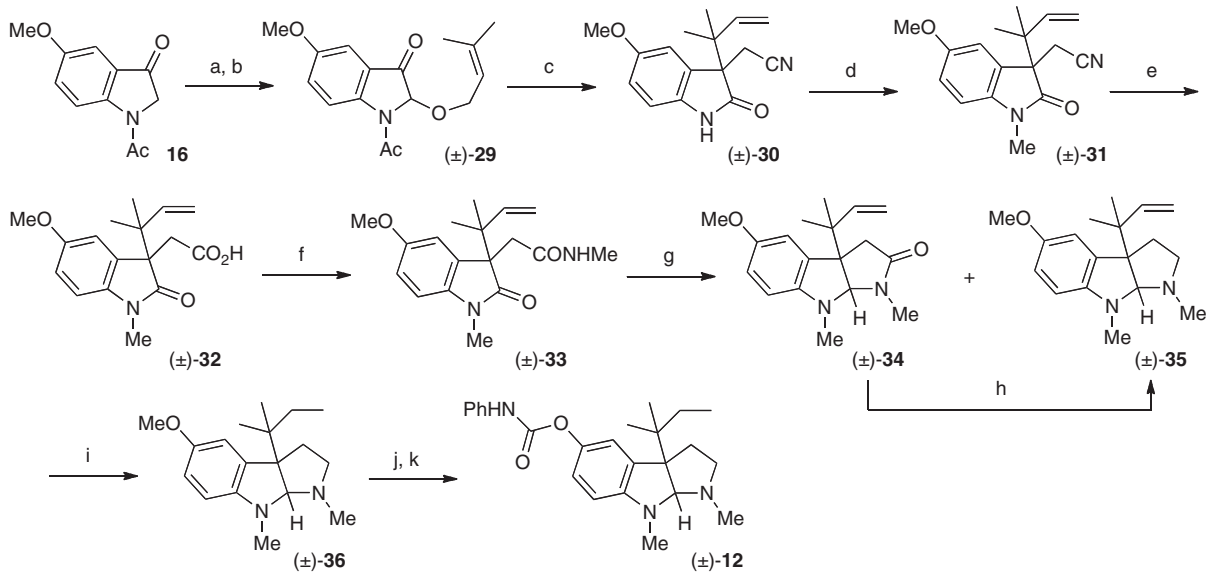


Scheme 3. Reagents and conditions: (a) $AlH_3{\cdot}EtNMe_2$, toluene/THF, −15 °C, 94%; (b) BBr_3, CH_2Cl_2, 0 °C; (c) NaH, THF, rt, then PhNCO, 69% (2 steps).



Scheme 4. Reagents and conditions: (a) OsO_4, NMO, MeCN, rt, then $NaIO_4$, 1,4-dioxane–H_2O, rt; (b) $NaBH_4$, MeOH, 0 °C, 65% (2 steps); (c) *o*-nitrophenyl selenocyanate, *n*-Bu_3P, THF, rt; (d) H_2O_2, THF, rt, 73% (2 steps); (e) NaOH, MeOH, reflux, quant.; (f) EDC, C_6F_5OH, Et_3N, THF, rt, then $MeNH_2$, 90%; (g) $LiAlH_4$, THF, reflux, 75%; (h) BBr_3, CH_2Cl_2, rt; (i) Na, Et_2O, rt, then PhNCO, 57% (2 steps); (j) Pd/C, H_2, EtOH, rt, 98%.

(**1**), the optical resolution of the respective carboxylic acids (±)-**20**, (±)-**26**, and (±)-**32** through (*R*)-4-phenyloxazolin-2-one derivatives **37a–c** was implemented (Scheme 6). The carboxylic acids (±)-**20**, (±)-**26**, and (±)-**32** were condensed with (*R*)-4-phenyloxazolin-2-one to give two diastereoisomers **37** and **38** (ca. 1:1). Hydrolysis of oxazolin-2-one derivatives **38a–c** with LiOH and H_2O_2 produced (−)-**20**, (+)-**26**, and (−)-**32** in 28–43% yield (three steps), respectively.[16] The optically pure (−)-**3**, (−)-**9**, (−)-**10**, and (−)-**12** were obtained from (−)-**20**, (+)-**26**, and (−)-**32** in the same manner as the racemic version.[17]

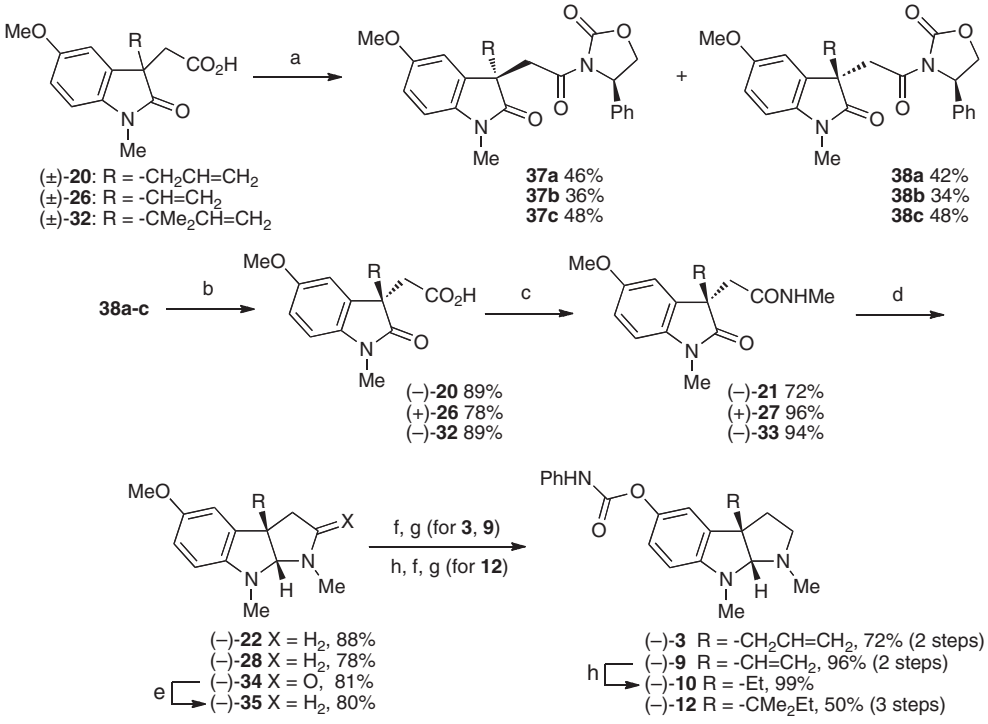


Scheme 5. Reagents and conditions: (a) Br_2, CH_2Cl_2, 0 °C, (b) prenyl alcohol, MS 4A, MeCN, rt, 74% (2 steps); (c) $(EtO)_2P(O)CH_2CN$, *t*-BuOK, DMF, −78 °C to rt, 91%; (d) MeI, NaH, DMF, rt, 75%; (e) NaOH, MeOH, reflux, 88%; (f) EDC, C_6F_5OH, Et_3N, THF, rt, then $MeNH_2$, 95%; (g) $LiAlH_4$, THF, reflux, **34** (52%) and **35** (41%); (h) $LiAlH_4$, THF, reflux, 85%; (i) Pd/C, H_2, rt, 99%; (j) BBr_3, CH_2Cl_2, 0 °C; (k) Na, Et_2O, rt, then PhNCO, 63% (2 steps).

2.2. Biological activity

2.2.1. Inhibitory effects of racemic phenserine derivatives on AChE and BuChE activity in vitro

The Ogura et al.[18]-modified spectrophotometric method of Ellman et al.[19] was used to evaluate 10 racemic and four optically active derivatives along with phenserine (−)-**1** and physostigmine as reference compounds. All of the test compounds inhibited the activities of AChE and BuChE in a concentration-dependent manner in 3×10^{-5} M (Fig. 2). The IC_{50} values for AChE and BuChE inhibition of new compounds (±)-**3–13** and phenserine (−)-**1** are shown in Table 1. A slight difference in the AChE inhibitory effect between the alkenyl and alkyl groups at 3a-site [e.g. vinyl **9** vs ethyl **10** (entries 7, 8)] was observed. A bulkier substituent (R) at the 3a-position of the phenserine derivatives tends to exert a weaker inhibitory effect on AChE activity in the following order: methyl (−)-**1** > ethyl (±)-**10** > vinyl (±)-**9** > propyl (±)-**8** ≈ allyl (±)-**3** > reverse-prenyl derivative (±)-**12** (entries 1, 6–11). The inhibitory activities of 4- and 2-fluoride derivatives (±)-**6** and (±)-**7** was comparable to that of (±)-**3** (entries 4, 5 vs 1), but 4-bromo- and



Scheme 6. Reagents and conditions: (a) EDC, C_6F_5OH, NEt_3, rt, then (*R*)-(−)-4-phenylisoxazolin-2-one, *n*-BuLi or NaH, 0 °C; (b) LiOH, H_2O_2, THF, H_2O, rt; (c) EDC, C_6F_5OH, NEt_3, THF, rt, then $MeNH_2$; (d) $LiAlH_4$, THF, reflux, 1 h; (e) $LiAlH_4$, THF, rt, 0.5 h; (f) BBr_3, CH_2Cl_2, rt; (g) Na, Et_2O, rt, then PhNCO; (h) Pd/C,H_2, EtOH, rt.

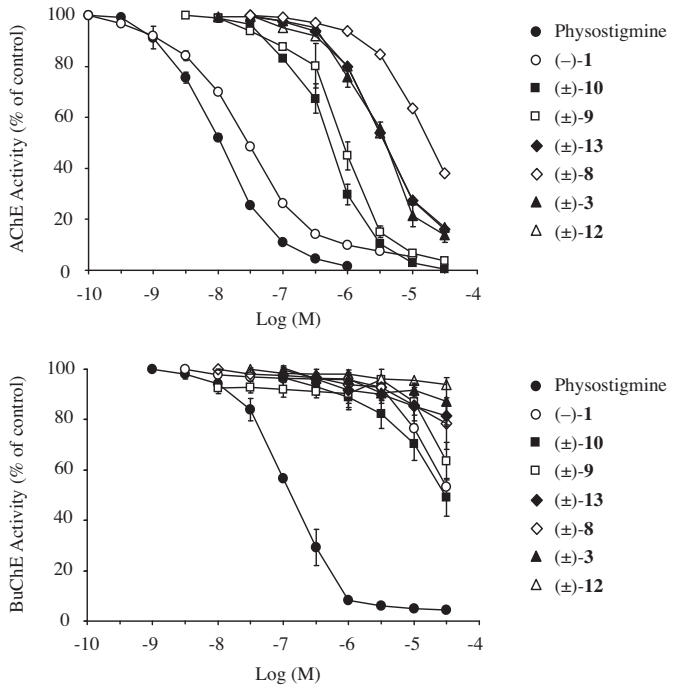


Figure 2. Effect of physostigmine, phenserine (−)-**1** and phenserine derivatives (±)-**3**–**13** on rat brain AChE and rat plasma BuChE activity. Data are presented as mean ± SE values from four experiments.

isopropyl derivatives (±)-**5** and (±)-**4** showed considerably poorer inhibitory effects than **3** (entries 2, 3). The 2- or 4-substituent of the phenyl ring of (±)-**3** had little effect on AChE and BuChE inhibitory activity. In terms of AChE selectivity (BuChE/AChE ratio), phenserine (−)-**1** has the highest value of more than 1000-fold, while (±)-**3** and (±)-**6–12** exhibit moderate selectivity for AChE (>5.4 to 76-fold), respectively. The AChE inhibitory activity and selectivity of lactam derivative (±)-**13** was lower than that of amine (±)-**3** (entries 1 vs 10).

IC_{50} and AChE selectivity of optically active allyl (−)-**3**, vinyl (−)-**9**, ethyl (−)-**10** and reverse-prenyl derivatives (−)-**12**, phenserine (−)-**1** and (−)-physostigmine are shown in Table 2. The IC_{50} values for AChE inhibition of the optically active compounds were lower than those of the racemic derivatives (Tables 1 vs 2). The AChE selectivity of optically active derivatives tends to be higher than that of the corresponding racemic derivatives. The effect of substituent (R) on AChE inhibitory activity and selectivity has the same tendency as the racemic version indicated above.

3. Conclusion

Several series of phenserine analogues with an alkyl or alkenyl group at the 3a-position were synthesized starting from 5-methoxy-1-acetylindolon-3-one in the following key steps: the cascade of olefination/isomerization/deacylation/Claisen rearrangement of 2-allyloxyindolin-3-ones to 3,3-disubstituted oxindoles, reductive cyclization of 3-allyl-3-carbamoylmethyloxindoles to 3a-allyl-pyrrolo[2,3-*b*]indolines, the substituent variation at the allylic moiety, and conventional carbamoylation. The phenserine analogues were assessed by AChE and BuChE inhibition assays. The bulkiness of the substituent at the 3a-position of phenserine analogues tends to reduce the inhibitory effect on AChE activity. Of the series synthesized, the 3a-ethyl derivative demonstrated the highest AChE selectivity. In construct, the 3a-reverse-prenyl derivative indicated modest BuChE selectivity.

4. Experimental section

4.1. Chemistry

All melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were obtained using a JASCO P-2200 polarimeter. Optical purities were determined on a JASCO HPLC (PU-2089 plus, MD-2015 plus) instrument equipped with Daisel Chemical chiral columns. CD spectra were measured with JASCO J-820 equipment with distilled CH_2Cl_2 in 10 mm of quarts cell at 25 °C. IR spectra were recorded on a Shimadzu IRPrestige-21 spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a JEOL JNM-AL300 (300 MHz), JEOL JMN-AL400 (400 MHz) or JEOL JNM-LA500 (500 MHz) spectrometer with tetramethylsilane as an internal standard. *J*-Values are given in Hertz. Mass spectra were recorded on a JEOL JMS-DX302 or JEOL JMS 700 instrument with a direct inlet system. Elemental analysis was performed using a Yanaco MT-6 elemental analyzer. Column chromatography was carried out on silica gel [Kanto Chemical Co. Inc. (Silica Gel 60N, Spherical, neutral 40–50 μm) and Merck Ltd. gel (Silica Gel 60, 230–400 mesh)].

4.1.1. 1-Acetyl-2-allyloxy-5-methoxyindolin-3-one (±)-(17)

Under N_2 atmosphere, to a solution of **16** (1.0 g, 4.9 mmol) in CH_2Cl_2 (35 mL) was added a solution of Br_2 in CH_2Cl_2 (11 mL, 1.0 M, 11 mmol) at 0 °C and the solution was stirred for 2 h. Starting material consumption was determined by TLC, and the reaction mixture was neutralized with satd. aqueous $NaHCO_3$. The organic layer was washed with brine and dried over $MgSO_4$. The concentrated residue (1.4 g) was used without further purification. Under

Table 1
Inhibitory effects of racemic phenserine derivatives on rat brain AChE and rat plasma BuChE

Entry	Compound			IC_{50} (μM)[a]		Selectivity
	No.	R	R^1	AChE	BuChE	BuChE/AChE
1	(±)-**3**	CH_2=$CHCH_2$–	H	3.77 ± 0.12	>100	>27
2	(±)-**4**	CH_2=$CHCH_2$–	4-*i*-Pr	>10	>10	–
3	(±)-**5**	CH_2=$CHCH_2$–	4-Br	>10	>10	–
4	(±)-**6**	CH_2=$CHCH_2$–	4-F	4.36 ± 0.26	>100	>23
5	(±)-**7**	CH_2=$CHCH_2$–	2-F	3.55 ± 0.06	87.3 ± 2.7	25
6	(±)-**8**	*n*-Pr–	H	3.66 ± 0.11	>100	>27
7	(±)-**9**	CH_2=CH–	H	0.749 ± 0.12	>30	>40
8	(±)-**10**	Et–	H	0.397 ± 0.005	~30	76
9	(±)-**12**	$EtMe_2C$–	H	18.4 ± 0.6	>100	>5.4
10	(±)-**13** [b]	CH_2=$CHCH_2$-	H	4.73 ± 0.001	65.3 ± 5.4	14
11	(−)-**1**	Me–	H	0.0283 ± 0.0013	~30	1100

[a] Data are presented as mean±SE values from 4 dose-response curves for each test compound.
[b] Lactam compound.

Table 2
Inhibitory effects of optically active phenserine derivatives on rat brain AChE and rat plasma BuChE

Entry	Compound			IC_{50} (μM)[a]		Selectivity
	No.	R	R^1	AChE	BuChE	BuChE/AChE
1	(−)-**3**	CH_2=$CHCH_2$–	H	1.26 ± 0.06	>100	>79
2	(−)-**9**	CH_2=CH–	H	0.644 ± 0.005	41.9 ± 1.2	65
3	(−)-**10**	Et–	H	0.373 ± 0.008	36.2 ± 0.8	97
4	(−)-**12**	$EtMe_2C$–	H	9.50 ± 0.71	>100	>11
5	(−)-**1**	Me–	H	0.0283 ± 0.0013	~30	1100
6	(−)-Physostigmine			0.0110 ± 0.0050	0.0584 ± 0.0070	5.3

[a] Data are presented as mean ± SE values from four dose-response curves for each test compound.

N_2 atmosphere, to a suspension of above residue (1.4 g) and molecular sieves 4A (6.9 g, powder) in CH_3CN (50 mL) was added allyl alcohol (1.6 mL, 24 mmol) and the mixture was stirred for 1 day. The reaction mixture was filtrated through a Celite pad and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/2.5) to give (±)-**17** (1.0 g, 79%) as pale yellow needles.

Mp: 99–102 °C (AcOEt); IR ($CHCl_3$): 1726, 1682, 1489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.38 (3H, s), 3.83 (3H, s), 4.05 (1H, ddt, *J* = 11.9, 5.7, 1.2 Hz), 4.19 (1H, ddt, *J* = 11.9, 5.7, 1.2 Hz), 5.20 (1H, ddt, *J* = 10.8, 2.5, 1.2 Hz), 5.24 (1H, s), 5.28 (1H, ddt, *J* = 17.4, 3.1, 1.2 Hz), 5.89 (1H, ddt, *J* = 17.4, 10.8, 5.7 Hz), 7.12 (1H, d, *J* = 2.7 Hz), 7.25 (1H, dd, *J* = 9.0, 2.7 Hz), 8.41 (1H, d, *J* = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 23.5, 55.8, 66.4, 85.7, 105.0, 118.4, 119.2, 123.0, 126.4, 132.5, 147.8, 156.4, 168.8, 194.6; MS (EI): *m/z* (%) 262 (13), 261 (M^+, 81), 218 (42), 205 (20), 191 (15), 178 (100), 162 (45), 150 (21), 106 (13), 43 (20), 41 (13); HRMS (EI): *m/z* Calcd for $C_{14}H_{15}NO_4$: 261.1001; Found: 261.1004; Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.11; H, 5.76; N, 5.28.

4.1.2. 2-(3-Allyl-5-methoxy-2-oxoindolin-3-yl)acetonitrile (±)-(18)

Under N_2 atmosphere, to a solution of *t*-BuOK (4.5 g, 41 mmol) in DMF (48 mL) was added $(EtO)_2P(O)CH_2CN$ (7.7 mL, 44 mmol) at 0 °C and the mixture was stirred at room temperature for 0.5 h. After cooling at −78 °C, to the mixture was added slowly a solution of (±)-**17** (3.5 g, 14 mmol) in DMF (20 mL) at the same temperature. After consumption of (±)-**17** (0.5 h), the stirred reaction mixture was warmed to room temperature for 2 h. The reaction mixture was diluted with Et_2O, neutralized with 10% HCl and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1) to give (±)-**18** (2.8 g, 87%) as colorless crystals.

Mp: 131.5–133.0 °C (AcOEt/*n*-hexane); IR ($CHCl_3$): 3436, 2257, 1710, 1605, 1493 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.63 (1H, dd, *J* = 15.4, 7.9 Hz), 2.69 (1H, dd, *J* = 15.4, 8.8 Hz), 2.69 (1H, d, *J* = 16.7 Hz), 2.86 (1H, d, *J* = 16.7 Hz), 3.80 (3H, s), 5.03 (1H, dd, *J* = 10.3, 1.3 Hz), 5.13 (1H, dd, *J* = 16.8, 1.3 Hz), 5.48 (1H, dddd, *J* = 16.8, 10.3, 8.8, 7.9 Hz), 6.80 (1H, dd, *J* = 8.4, 2.4 Hz), 6.88 (1H, *J* = 8.4 Hz), 7.00 (1H, d, *J* = 2.4 Hz), 9.25 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 40.2, 49.7, 55.8, 110.8, 110.9, 113.8, 116.3, 120.5, 130.4, 130.6, 133.7, 156.1, 178.8; MS (EI): *m/z* (%) 242 (M^+, 59), 201 (100), 158 (28); HRMS (EI): *m/z* Calcd for $C_{14}H_{14}N_2O_2$: 242.1055; Found: 242.1060; Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.28; H, 5.96; N, 11.46.

4.1.3. 2-(3-Allyl-5-methoxy-1-methyl-2-oxoindolin-3-yl)acetonitrile (±)-(19)

Under N_2 atmosphere, to a suspension of NaH (0.28 g, 60%, 7.0 mmol, washed with *n*-hexane) in DMF (40 mL) was added a solution of (±)-**18** (1.4 g, 5.9 mmol) in DMF (20 mL) with ice-bath cooling. After 1 h stirring at room temperature, MeI (0.43 mL, 7.0 mmol) was added to the mixture with ice-bath cooling. After 15 min stirring at room temperature, water (100 mL) was added to the reaction mixture. The mixture was extracted by Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1) to give (±)-**19** (1.5 g, 98%) as colorless crystals.

Mp: 115 °C (AcOEt/*n*-hexane); IR ($CHCl_3$): 3020, 1713, 1603, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.62 (1H, dd, *J* = 13.5, 7.9 Hz), 2.64 (1H, d, *J* = 16.7 Hz), 2.68 (1H, dd, *J* = 13.5, 6.8 Hz), 2.74 (1H, d, *J* = 16.5 Hz), 3.20 (3H, s), 3.82 (3H, s), 5.04 (1H, dd, *J* = 10.2, 1.8 Hz), 5.10 (1H, dd, *J* = 17.1, 1.8 Hz), 5.42 (1H, dddd, *J* = 17.1, 10.2, 7.8, 6.9 Hz), 6.78 (1H, d, *J* = 8.4 Hz), 6.87 (1H, *J* = 8.4, 2.4 Hz), 7.06 (1H, d, *J* = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 26.4, 40.2, 49.1, 55.8, 108.9, 110.9, 113.4, 116.3, 120.3, 130.1, 130.5, 136.6, 156.3, 175.9; MS (EI): *m/z* (%) 256 (M^+, 48), 215 (100); HRMS (EI): *m/z* Calcd for $C_{15}H_{16}N_2O_2$: 256.1212; Found: 256.1211; Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.58; H, 6.50; N, 10.80.

4.1.4. 2-(3-Allyl-5-methoxy-1-methyl-2-oxoindolin-3-yl)acetic acid (±)-(20)

To a solution of (±)-**19** (1.3 g, 5.0 mmol) in MeOH (20 mL) was added 35% aqueous NaOH (11 mL, 0.10 mol) and the mixture was stirred under reflux for 3 days. The mixture was concentrated and acidified with 1 N aqueous HCl and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated to give (±)-**20** (1.2 g, 85%) as a pale yellow oil.

IR ($CHCl_3$): 3010, 1710, 1601, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.34–2.49 (2H, m), 2.64 (1H, d, *J* = 16.0 Hz), 2.80 (1H, d, *J* = 16.0 Hz), 3.02 (3H, s), 3.75 (3H, s), 4.90 (1H, d, *J* = 10.2 Hz), 4.98 (1H, d, *J* = 16.2 Hz), 5.28–5.40 (1H, m), 6.66 (1H, d, *J* = 8.4 Hz), 6.70–6.79 (2H, m), 9.88 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 41.1, 41.8, 50.2, 55.7, 108.3, 110.6, 112.1, 119.3, 131.4, 132.5, 137.3, 155.9, 174.4, 179.4; MS (EI): *m/z* (%) 275 (M^+, 48), 191 (12), 190 (100), 174 (15); HRMS (EI): *m/z* Calcd for $C_{15}H_{17}NO_4$: 275.1158; Found: 275.1152; Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.27; H, 6.36; N, 5.14.

4.1.5. 2-(3-Allyl-5-methoxy-1-methyl-2-oxoindolin-3-yl)-*N*-methylacetamide (±)-(21) and (*S*)-derivative (−)-21

Under N_2 atmosphere, to a solution of (±)-**20** (0.20 g, 0.73 mmol) in THF (10 mL) was added pentafluorophenol (0.40 g, 2.2 mmol), Et_3N (0.20 mL, 1.5 mmol), and EDC·HCl (0.21 g, 1.1 mmol). After 2 h stirring at room temperature, $MeNH_2$ gas which was generated by the reaction of aqueous $MeNH_2$·HCl and NaOH pellet, was bubbled through the reaction mixture. After consumption of mixed anhydride, the reaction mixture was neutralized by 10% aqueous HCl and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The concentrated residue was purified

by silica gel column chromatography (AcOEt/*n*-hexane = 1/1 to 100/0) to give (±)-**21** (0.17 g, 81%) as colorless crystals.

Mp: 131 °C (AcOEt/*n*-hexane); IR ($CHCl_3$): 3462, 3030, 1690, 1603, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.52 (1H, dd, J = 13.4, 7.1 Hz), 2.58 (1H, dd, J = 13.4, 7.1 Hz), 2.62 (1H, d, J = 15.0 Hz), 2.63 (3H, d, J = 4.5 Hz), 2.80 (1H, d, J = 15.0 Hz), 3.20 (3H, s), 3.79 (3H, s), 4.94 (1H, d, J = 10.2 Hz), 4.99 (1H, dd, J = 17.0 Hz), 5.40 (1H, ddt, J = 17.0, 10.2, 7.1 Hz), 6.36 (1H, br s), 6.73 (1H, d, J = 8.4 Hz), 6.80 (1H, J = 8.4, 2.4 Hz), 6.86 (1H, d, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 26.5, 41.4, 42.6, 50.6, 55.8, 108.3, 110.8, 112.2, 119.3, 131.3, 132.3, 136.7, 155.8, 169.3, 178.9; MS (EI): *m/z* (%) 288 (M^+, 57), 216 (14), 215 (11), 191 (12), 190 (100), 174 (10); HRMS (EI): *m/z* Calcd for $C_{16}H_{20}N_2O_3$: 288.1474; Found: 288.1468; Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.60; H, 7.01; N, 9.65.

Optically active compound (−)-**21** was obtained from (−)-**20** in a procedure similar to that above. The enantiomer excess (>99% ee) was determined by HPLC (CHIRALCEL OD, flow = 0.5 mL/min, *i*-PrOH / *n*-hexane = 1/5). The spectral data of (−)-**21** were identical to those of (±)-**21**, other than for specific optical rotation: $[\alpha]_D^{25}$ −1.4 (*c* 1.14, $CHCl_3$).

4.1.5.1. 3a-Allyl-5-methoxy-1,8-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (±)-(22) and (*S*)-derivative (−)-22. Under N_2 atmosphere, to a solution of (±)-**21** (30 mg, 0.11 mmol) in THF (18 mL) was added $LiAlH_4$ (1.1 mL, 1.0 M in THF, 1.1 mmol) and the solution was stirred under reflux for 2.5 h. Excess $LiAlH_4$ was quenched by THF/H_2O (1:1) and filtered through Celite pad. The filtrate was extracted with AcOEt and washed with satd aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to give (±)-**22** (23 mg, 86%) as a pale yellow oil.

(±)-**22**: IR ($CHCl_3$): 2938, 1640, 1595, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.91 (1H, ddd, J = 12.1, 6.0, 3.1 Hz), 2.05 (1H, ddd, J = 12.1, 9.2, 6.8 Hz), 2.39 (1H, dd, J = 13.9, 8.4 Hz), 2.52 (3H, s), 2.57 (1H, dd, J = 13.9, 5.9 Hz), 2.57 (1H, ddd, J = 7.8, 6.8, 6.0 Hz), 2.73 (1H, ddd, J = 9.2, 7.8, 3.1 Hz), 2.86 (3H, s), 3.74 (3H, s), 4.16 (1H, s), 4.99–5.11 (2H, m), 5.58 (1H, dddd, J = 18.5, 10.1, 8.4, 5.9 Hz), 6.36 (1H, d, J = 8.4 Hz), 6.63–6.66 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.5, 38.0, 39.1, 44.4, 52.7, 56.1, 56.9, 94.6, 107.5, 110.1, 112.4, 117.6, 135.0, 136.0, 147.2, 152.8; MS (EI): *m/z* (%) 258 (M^+, 100), 243 (12), 217 (64), 202 (24), 187 (11), 174 (36); HRMS (EI): *m/z* Calcd for $C_{16}H_{22}N_2O$: 258.1732; Found: 258.1737.

Optically active compound (−)-**22** was obtained from (−)-**21** in a procedure similar to that above. The spectral data of (−)-**22** were identical to those of (±)-**22**, other than for specific optical rotation: $[\alpha]_D^{25}$ −30.8 (*c* 1.05, $CHCl_3$).

4.1.5.2. 3a-Allyl-1,8-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl phenylcarbamate (±)-(3) and (3a*R*,8a*R*)-derivative (−)-3. Under N_2 atmosphere, to a solution of (±)-**22** (0.16 g, 0.62 mmol) in CH_2Cl_2 (16 mL) was added a CH_2Cl_2 solution of BBr_3 (3.1 mL, 1.0 M, 3.1 mmol) at 0 °C. After 1.5 h stirring at room temperature, the reaction mixture was concentrated. MeOH (10 mL) was added to the residue and the mixture was stirred for 0.5 h. The mixture was added satd. $NaHCO_3$ and extracted by Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give crude alcohol. Under N_2 atmosphere, to a solution of above alcohol (0.15 g, 0.62 mmol) in Et_2O (35 mL) added Na (3.3 mg, 0.14 mmol) at room temperature. After stirring for 15 min, PhNCO (81 μL, 0.74 mmol) was added and stirred for 0.5 h. The reaction mixture was filtrated and the filtrate was concentrated. The residue was dissolved in Et_2O and the solution was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to give (±)-**3** (0.17 g, 76%) as a white powder.

Mp: 138–140 °C; IR ($CHCl_3$): 3433, 2934, 1748, 1602, 1526 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.94 (1H, ddd, J = 11.9, 6.0, 3.5 Hz), 2.04 (1H, ddd, J = 11.9, 9.0, 6.6 Hz), 2.40 (1H, dd, J = 14.0, 8.5 Hz), 2.51 (3H, s), 2.61 (1H, dd, J = 14.0, 6.1 Hz), 2.61 (1H, ddd, J = 9.4, 9.0, 6.0 Hz), 2.73 (1H, ddd, J = 9.4, 6.6, 3.5 Hz), 2.90 (3H, s), 4.22 (1H, s), 5.01–5.09 (2H, m), 5.58 (1H, dddd, J = 16.5, 10.1, 8.4, 6.1 Hz), 6.36 (1H, d, J = 8.4 Hz), 6.83 (1H, d, J = 2.4 Hz), 6.84 (1H, br s), 6.87 (1H, dd, J = 8.4, 2.4 Hz), 7.09 (1H, t, J = 7.2 Hz), 7.33 (2H, d, J = 7.2 Hz), 7.44 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.0, 37.9, 39.1, 44.4, 52.7, 56.7, 94.4, 106.5, 116.6, 117.8, 118.6, 120.5, 123.6, 129.0, 134.7, 135.5, 137.5, 142.4, 150.3; MS (EI): *m/z* (%) 363 (M^+, 8), 244 (100), 203 (67), 188 (23), 160 (53), 119 (38), 91 (19); HRMS (EI): *m/z* Calcd for $C_{22}H_{25}N_3O_2$: 363.1947; Found: 363.1948.

Optically active compound (−)-**3** was obtained from (−)-**22** in a procedure similar to that above. The spectral data of (−)-**3** were identical to those of (±)-**3**, other than for specific optical rotation: $[\alpha]_D^{25}$ −25.8 (*c* 0.96, $CHCl_3$) and CD λ_{max} (nm) [$\Delta\varepsilon$ (M^{-1} cm^{-1})] 307 (−1.35), 268 (−3.09).

4.1.6. General procedure for preparation of carbamates (±)-4–7

Under N_2 atmosphere, to a solution of (±)-**22** (1.0 mmol) in CH_2Cl_2 (10 mL) was added a BBr_3 (4.9 mmol) at 0 °C. After 2 h stirring, the reaction mixture was neutralized with satd aqueous $NaHCO_3$. The mixture was extracted by AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10/1) to give 5-hydroxy derivative. Under N_2 atmosphere, to a mixture of above 5-hydroxy derivative in THF (18 mL) added NaH (60%, 0.094 mmol) at room temperature. After stirring for 15 min, the corresponding arylisocyanate (1.0 mmol) was added and stirred for 0.5 h. The concentrated residue was dissolved in AcOEt and the solution was washed with water and brine. The extract was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10/1) to give carbamate (±)-**4**-(±)-**7**, respectively. The yields are listed in Scheme 2.

4.1.6.1. 3a-Allyl-1,8-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl (4-isopropylphenyl)carbamate (±)-(4). IR ($CHCl_3$): 3433, 1744, 1612, 1524, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (3H, s), 1.24 (3H, s), 1.93 (1H, ddd, J = 11.9, 6.0, 3.3 Hz), 2.05 (1H, ddd, J = 11.9, 9.1, 6.6 Hz), 2.39 (1H, dd, J = 14.0, 8.4 Hz), 2.50 (3H, s), 2.58 (1H, dd, J = 14.0, 5.8 Hz), 2.58 (1H, ddd, J = 9.4, 9.1, 6.0 Hz), 2.71 (1H, ddd, J = 9.4, 6.6, 3.3 Hz), 2.86 (1H, sep), 2.90 (3H, s), 4.23 (1H, s), 5.01–5.08 (2H, m), 5.59 (1H, dddd, J = 16.5, 10.1, 8.4, 5.8 Hz), 6.35 (1H, d, J = 8.4 Hz), 6.82 (1H, d, J = 2.3 Hz), 6.87 (1H, dd, J = 8.4, 2.3 Hz), 6.94 (1H, br s), 7.17 (2H, d, J = 8.4 Hz), 7.33 (2H, d, J = 8.4 Hz); ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.0, 33.5, 37.0, 37.7, 39.0, 44.2, 52.6, 56.6, 94.4, 106.6, 116.7, 117.9, 118.9, 120.6, 127.0, 134.9, 135.3, 135.6, 142.6, 144.4, 150.5, 152.6; MS (EI): *m/z* (%) 405 (M^+, 8), 245 (17), 244 (100), 203 (59), 188 (19), 187 (15), 161 (30), 160 (44), 146 (76), 128 (16); HRMS (EI): *m/z* Calcd for $C_{25}H_{31}N_3O_2$: 405.2416; Found: 405.2409.

4.1.6.2. 3a-Allyl-1,8-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl (4-bromophenyl)carbamate (±)-(5). Mp: 159–163 °C (AcOEt); IR ($CHCl_3$): 3431, 1748, 1593, 1520, 1493 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.93 (1H, ddd, J = 3.3, 6.0, 9.6 Hz), 2.04 (1H, ddd, J = 6.6, 8.7, 12.0 Hz), 2.39 (1H, dd, J = 8.4, 13.8 Hz), 2.50 (3H, s), 2.56 (1H, ddd, J = 6.0, 8.7, 9.9 Hz),

2.58 (1H, dd, J = 6.0, 13.8 Hz), 2.69 (1H, ddd, J = 3.3, 6.6, 9.9 Hz), 2.91 (3H, s), 4.22 (1H, s), 5.02–5.09 (2H, m), 5.59 (1H, dddd, J = 6.0, 8.4, 10.2, 16.2 Hz), 6.35 (1H, d, J = 8.4 Hz), 6.81 (1H, d, J = 2.4 Hz), 6.86 (1H, dd, J = 2.4, 8.4 Hz), 6.84–6.87 (1H, s), 7.32 (2H, d, J = 9.0 Hz), 7.42 (2H, d, J = 9.0 Hz); ^{13}C NMR (68 MHz, $CDCl_3$): δ 36.8, 37.8, 38.9, 44.2, 52.6, 56.6, 94.4, 106.5, 116.1, 116.6, 117.9, 120.3, 120.6, 132.0, 134.8, 135.8, 136.8, 142.3, 150.6, 152.4; MS (EI): m/z (%) 443 (2), 441 (M^+, 2), 245 (17), 244 (100), 203 (63), 199 (43), 197 (44), 188 (20), 187 (15), 160 (44), 90 (16); HRMS (EI): m/z Calcd for $C_{22}H_{24}BrN_3O_2$: 441.1052; Found: 441.1051; Anal. Calcd for $C_{22}H_{24}BrN_3O_2$: C, 59.73; H, 5.47; N, 9.50; Found: C, 59.47; H, 5.54; N, 9.37.

4.1.6.3. 3a-Allyl-1,8-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl (4-fluorophenyl)carbamate (±)-(6).

Mp: 170–181 °C (AcOEt); IR ($CHCl_3$): 3433, 1746, 1526, 1510, 1493 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92 (1H, ddd, J = 3.3, 6.0, 12.1 Hz), 2.04 (1H, ddd, J = 6.8, 9.0, 12.1 Hz), 2.39 (1H, dd, J = 8.5, 13.9 Hz), 2.50 (3H, s), 2.58 (1H, ddd, J = 6.0, 9.0, 9.6 Hz), 2.58 (1H, dd, J = 5.9, 13.9 Hz), 2.70 (1H, ddd, J = 3.3, 6.8, 9.6 Hz), 4.22 (1H, s), 5.01–5.09 (2H, m), 5.60 (1H, dddd, J = 5.9, 8.5, 10.0, 14.3 Hz), 6.35 (1H, d, J = 8.4 Hz), 6.81 (1H, d, J = 2.4 Hz), 6.86 (1H, dd, J = 2.4, 8.4 Hz), 6.81–6.88 (1H, br s), 7.02 (2H, t, J = 8.6 Hz), 7.40 (2H, dd, J = 4.6, 8.6 Hz); MS (EI): m/z (%) 381 (M^+, 5), 245 (17), 244 (100), 203 (63), 202 (12), 200 (14), 188 (21), 187 (15), 186 (11), 160 (45), 137 (40), 109 (19); HRMS (EI): m/z Calcd for $C_{22}H_{24}FN_3O_2$: 381.1853; Found: 381.1855.

4.1.6.4. 3a-Allyl-1,8-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl (2-fluorophenyl)carbamate (±)-(7).

Mp: 120–124 °C (AcOEt); IR ($CHCl_3$): 3433, 1749, 1535, 1497, 1456 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94 (1H, ddd, J = 3.1, 6.1, 11.9 Hz), 2.06 (1H, ddd, J = 7.0, 8.8, 11.9 Hz), 2.40 (1H, dd, J = 8.5, 14.0 Hz), 2.51 (3H, s), 2.57 (1H, ddd, J = 6.1, 8.8, 9.4 Hz), 2.60 (1H, dd, J = 5.9, 14.0 Hz), 2.71 (1H, ddd, J = 3.1, 7.0, 9.4 Hz), 2.90 (3H, s), 4.23 (1H, s), 5.02–5.09 (2H, m), 5.59 (1H, dddd, J = 5.9, 8.5, 9.3, 17.0 Hz), 6.36 (1H, d, J = 8.3 Hz), 6.84 (1H, d, J = 2.4 Hz), 6.88 (1H, ddd, J = 0.9, 2.4, 8.2 Hz), 6.93–7.16 (4H, m), 8.05–8.15 (1H, m); ^{13}C NMR (68 MHz, $CDCl_3$): δ 36.8, 37.8, 38.9, 44.2, 52.6, 56.6, 94.4, 106.5, 114.7, 115.0, 116.5, 117.9, 120.5, 123.7, 124.7, 126.3, 134.8, 135.7, 142.3, 150.6, 152.2, 154.0; MS (EI): m/z (%) 381 (M^+, 8), 245 (17), 244 (100), 229 (10), 203 (64), 202 (13), 200 (14), 188 (20), 187 (16), 186 (11), 160 (46), 137 (43), 109 (18); HRMS (EI): m/z Calcd for $C_{22}H_{24}FN_3O_2$: 381.1853; Found: 381.1844; Anal. Calcd for $C_{22}H_{24}FN_3O_2$: C, 69.27; H, 6.34; N, 11.02; Found: C, 69.02; H, 6.50; N, 10.86.

4.1.7. 1,8-Dimethyl-3a-propyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl phenylcarbamate (±)-(8)

To a solution of (±)-**3** (50 mg, 0.14 mmol) in EtOH (3.0 mL) was added 10% Pd/C (10 mg) and the solution was stirred vigorously at room temperature under H_2 bubbling for 3 h. The reaction mixture was filtrated and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to give (±)-**8** (48 mg, 96%) as a white powder.

Mp: 154–158 °C; IR ($CHCl_3$): 3433, 1748, 1603, 1526, 1495 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, t, J = 7.2 Hz), 1.06–1.22 (2H, m), 1.59–1.75 (2H, m), 1.91–2.00 (2H, m), 2.52 (3H, s), 2.51–2.59 (1H, m), 2.67–2.73 (1H, m), 2.91 (3H, s), 4.21 (1H, s), 6.35 (1H, d, J = 8.4 Hz), 6.78 (1H, d, J = 2.4 Hz), 6.87 (1H, dd, J = 8.4, 2.4 Hz), 7.07(1H, br s), 7.08 (1H, d, J = 7.4 Hz), 7.30 (2H, t, J = 8.4 Hz), 7.42 (2H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 19.2, 36.9, 37.9, 39.6, 42.5, 52.6, 57.2, 94.8, 106.3, 116.4, 118.6, 120.3, 123.5, 128.9, 135.8, 137.5, 142.4, 150.2, 152.3; MS (EI): m/z (%) 365 (M^+, 6), 246 (100), 203 (29), 202 (32), 188 (25), 174 (26), 160 (59), 119 (37), 91 (19); HRMS (EI): m/z Calcd for $C_{22}H_{27}N_3O_2$: 365.2103; Found: 365.2110.

4.1.7.1. 3a-Allyl-5-methoxy-1,8-dimethyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (±)-(23).

Under N_2 atmosphere, to a solution of (±)-**21** (78 mg, 0.27 mmol) in THF (13 mL) was added AlH_3·$EtNMe_2$ (2.7 mL, 5.0 M in toluene, 1.4 mmol) at −15 °C and the solution was stirred for 5 min. Excess AlH_3·$EtNMe_2$ was quenched by THF/H_2O (1:1) and filtered through Celite pad. The filtrate was basified by satd aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1) to give (±)-**23** (69 mg, 94%).

IR ($CHCl_3$): 1682, 1499 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (1H, dd, J = 8.2, 13.9 Hz), 2.54 (1H, dd, J = 6.1, 13.9 Hz), 2.63 (1H, d, J = 17.2 Hz), 2.70 (1H, d, J = 17.2 Hz), 2.91 (3H, s), 2.99 (3H, s), 3.75 (3H, s), 4.62 (1H, s), 5.05–5.15 (2H, m), 5.46–5.60 (1H, m), 6.43 (1H, d, J = 8.4 Hz), 6.65 (1H, d, J = 2.6 Hz), 6.71 (1H, dd, J = 2.6, 8.4 Hz); ^{13}C NMR (76 MHz, $CDCl_3$): δ 28.0, 37.2, 42.3, 43.8, 49.7, 56.0, 90.5, 109.0, 110.3, 113.5, 119.1, 133.1, 135.5, 144.4, 153.8, 172.7; MS (EI): m/z (%) 272 (M^+, 100), 231 (60), 174 (38); HRMS (EI): m/z Calcd for $C_{16}H_{20}N_2O_2$: 272.1525. Found: 272.1524.

4.1.7.2. 3a-Allyl-1,8-dimethyl-2-oxo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl phenylcarbamate (±)-(13).

Under N_2 atmosphere, to a solution of (±)-**23** (50 mg, 0.18 mmol) in CH_2Cl_2 (1.8 mL) was added a BBr_3 (0.17 mL, 1.8 mmol) at 0 °C. After 2 h stirring, the reaction mixture was neutralized with satd aqueous $NaHCO_3$ and was extracted by CH_2Cl_2. The organic layer was concentrated under reduced pressure and the residue was added Et_2O. The solution was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give crude phenol. Under N_2 atmosphere, to a mixture of above phenol (47 mg, 0.18 mmol) in THF (4.0 mL) added NaH (8.7 mg, 60%, 0.22 mmol) at room temperature. After stirring for 5 min, phenylisocyanate (24 μL, 0.22 mmol) was added and the solution was stirred for 15 min. The concentrated residue was dissolved in AcOEt and the solution was washed with water and brine. The extract was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1 to 3/1) to give (±)-**13** (47 mg, 69%) as a white powder.

Mp: 203–206 °C; IR ($CHCl_3$): 3431, 1749, 1682, 1603, 1526, 1497 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (1H, dd, J = 8.1, 13.8 Hz), 2.53 (1H, dd, J = 6.3, 13.8 Hz), 2.64 (1H, d, J = 17.1 Hz), 2.73 (1H, d, J = 17.1 Hz), 2.93 (3H, s), 3.04 (3H, s), 4.71 (1H, s), 5.09–5.15 (2H, m), 5.49–5.64 (1H, m), 6.44 (1H, d, J = 8.4 Hz), 6.86 (1H, br s), 6.87 (1H, d, J = 2.4 Hz), 6.95 (1H, dd, J = 2.4, 8.4 Hz), 7.09 (1H, t, J = 7.5 Hz), 7.30–7.46 (4H, m); ^{13}C NMR (68 MHz, $CDCl_3$): δ 28.4, 36.3, 42.2, 43.8, 49.4, 90.1, 107.8, 116.9, 118.6, 119.3, 121.7, 123.5, 128.9 (C2), 132.6, 134.7, 137.5, 143.2, 147.5, 152.3, 172.5; MS (EI): m/z (%) 377 (M^+, 0.97), 258 (100), 217 (62), 176 (11), 160 (41), 119 (36), 91 (13); HRMS (EI): m/z Calcd for $C_{22}H_{23}N_3O_3$: 377.1739; Found: 377.1738.

4.1.8. 2-[3-(2-Hydroxyethyl)-5-methoxy-1-methyl-2-oxoindolin-3-yl]acetonitrile (±)-(24)

To a solution of (±)-**19** (0.88 g, 3.4 mmol) in CH_3CN (6.3 mL) was added OsO_4 (1.1 mL, 4% aq, 0.17 mmol) and NMO (1.6 mL, 50% aq, 6.8 mmol) and the mixture was stirred for 12 h at room temperature. The concentrated residue was dissolved in 1,4-dioxane/H_2O (2/1, 23 mL) and added $NaIO_4$ (0.88 g, 4.1 mmol). After 10 min stirring, the mixture was filtrated through by Celite pad and the filtrate was concentrated under reduced pressure. The mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. The concentrated residue was purified by

silica gel column chromatography (AcOEt/*n*-hexane = 1/1 to 100/0) to give aldehyde (0.73 g, 83%) as a colorless oil.

IR ($CHCl_3$): 3021, 2837, 2255, 1713, 1601, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.60 (1H, d, J = 16.5 Hz), 2.93 (1H, d, J = 16.5 Hz), 3.09 (1H, d, J = 17.8 Hz), 3.26 (3H, s), 3.29 (1H, d, J = 17.8 Hz), 3.80 (3H, s), 6.84 (1H, d, J = 8.4 Hz), 6.89 (1H, dd, J = 8.4, 2.4 Hz), 7.04 (1H, d, J = 2.4 Hz), 9.51 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 26.9, 45.8, 55.9, 109.3, 110.7, 113.7, 115.6, 129.3, 136.7, 156.2, 175.3, 196.2; MS (EI): *m/z* (%): 258 (M^+, 64), 229 (47), 215 (11), 203 (10), 190 (100), 191 (12), 189 (13), 175 (13), 174 (24); HRMS (EI): *m/z* Calcd for $C_{14}H_{14}N_2O_3$: 258.1005; Found: 258.1003.

To a solution of aldehyde (1.5 g, 6.6 mmol) in MeOH (30 mL) was added $NaBH_4$ (2.5 g, 66 mmol) at 0 °C and the mixture was stirred for 0.5 h at the same temperature. After addition of satd aqueous NH_4Cl, the mixture was stirred for 1 h and then concentrated under reduced pressure. The residue was extracted with AcOEt and the organic layer was washed with brine and dried over $MgSO_4$. The concentrated residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1 to 100/0) to give (±)-**24** (1.2 g, 78%) as colorless crystals.

Mp: 102–106 °C (AcOEt); IR ($CHCl_3$): 3599, 3445, 3021, 2941, 2253, 1705, 1601, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.94 (1H, br s), 2.17 (1H, dt, J = 14.3, 5.5 Hz), 2.26 (1H, ddd, J = 14.3, 7.7, 5.5 Hz), 2.62 (1H, d, J = 16.7 Hz), 2.91 (1H, d, J = 16.7 Hz), 3.22 (3H, s), 3.41–3.52 (1H, m), 3.58–3.67 (1H, m), 3.82 (3H, s), 6.82 (1H, d, J = 8.4 Hz), 6.88 (1H, dd, J = 8.4, 2.4 Hz), 7.04 (1H, d, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 26.8, 38.1, 47.9, 55.9, 58.7, 109.2, 110.7, 113.6, 116.2, 130.1, 136.4, 156.3, 176.9; MS (EI): *m/z* (%) 260 (M^+, 60), 190 (100), 174 (18); HRMS (EI): *m/z* Calcd for $C_{14}H_{16}N_2O_3$: 260.1161; Found: 260.1163; Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.76; H, 6.31; N, 10.85.

4.1.9. (5-Methoxy-1-methyl-2-oxo-3-vinylindolin-3-yl)acetonitrile (±)-(25)

Under N_2 atmosphere, to a solution of (±)-**24** (1.7 g, 6.5 mmol) and *o*-nitrophenyl selenocyanate (1.8 g, 7.8 mmol) in THF (65 mL) was added tributylphosphine (2.0 mL, 7.8 mmol) and the solution was stirred at room temperature for 1.5 h. The concentrated residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1) to give arylselenide (2.3 g, 79%) as yellow amorphous.

IR ($CHCl_3$): 3021, 2255, 1707, 1593, 1516, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.31–2.64 (4H, m), 2.62 (1H, d, J = 16.7 Hz), 2.85 (1H, d, J = 16.7 Hz), 3.28 (3H, s), 3.85 (3H, s), 6.87 (1H, d, J = 8.4 Hz), 6.93 (1H, dd, J = 8.4, 2.4 Hz), 7.08 (1H, d, J = 2.4 Hz), 7.24–7.36 (2H, m), 7.53 (1H, ddd, J = 8.4, 7.7, 1.8 Hz), 8.29 (1H, dd, J = 8.8, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 25.9, 26.7, 35.2, 49.9, 55.9, 109.3, 110.6, 113.7, 115.8, 125.5, 126.3, 128.3, 129.0, 131.7, 133.6, 136.7, 146.5, 156.4, 175.2; MS (EI): *m/z* (%) 445 (M^+, 72), 259 (11), 243 (15), 216 (100), 189 (83), 174 (15), 106 (13); HRMS (EI): *m/z* Calcd for $C_{20}H_{19}N_3O_4Se$: 445.0541; Found: 445.0543.

To THF (2.4 mL) solution of arylselenide (0.11 g, 0.24 mmol) was added 30% aqueous H_2O_2 (65 μL, 0.58 mmol) at 0 °C and the mixture was stirred for 12 h at room temperature. The mixture was diluted with water and extracted with AcOEt. The organic layer was washed with 3% aqueous sodium hydrogen sulfite and brine. After dried over $MgSO_4$, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1) to give (±)-**25** (54 mg, 93%) as colorless needles.

Mp: 68–72 °C; IR ($CHCl_3$): 3016, 2255, 1713, 1601, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.73 (1H, d, J = 16.7 Hz), 3.01 (1H, d, J = 16.7 Hz), 3.22 (3H, s), 3.83 (3H, s), 5.25 (1H, d, J = 17.2 Hz), 5.36 (1H, d, J = 10.5 Hz), 5.98 (1H, dd, J = 17.2, 10.5 Hz), 6.84 (1H, d, J = 8.7 Hz), 6.91 (1H, dd, J = 8.7, 2.4 Hz), 7.09 (1H, d, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 26.8, 52.0, 55.9, 109.3, 111.9, 113.8, 116.1, 118.7, 128.9, 133.9, 136.3, 156.2, 174.4; MS (EI): *m/z* (%) 242 (M^+, 53), 202 (100), 174 (17), 159 (10); HRMS (EI): *m/z* Calcd for $C_{14}H_{14}N_2O_2$: 242.1056; Found: 242.1062; Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.38; H, 5.56; N, 11.45.

4.1.10. 2-(5-Methoxy-1-methyl-2-oxo-3-vinylindolin-3-yl)acetic acid (±)-(26)

A solution of (±)-**25** (1.2 g, 4.7 mmol) in MeOH (47 mL) was added 35% aqueous NaOH (8.1 mL, 71 mmol) and the mixture was stirred under reflux for 3 days. The mixture was acidified with 1 N aqueous HCl and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated to give (±)-**26** (1.2 g, quant.) as brownish powders.

IR ($CHCl_3$): 3505, 3383, 3092, 3010, 1711, 1602, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.89 (1H, d, J = 16.5 Hz), 3.15 (1H, d, J = 16.5 Hz), 3.19 (3H, s), 3.79 (3H, s), 5.08 (1H, d, J = 17.4 Hz), 5.17 (1H, d, J = 10.3 Hz), 5.90 (1H, dd, J = 17.2, 10.3 Hz), 6.76–6.85 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 40.3, 52.8, 55.8, 108.9, 111.4, 112.7, 116.7, 130.7, 135.7, 136.9, 155.9, 172.8, 177.2; MS (EI): *m/z* (%) 261 (M^+, 100), 246 (10), 202 (84), 174 (17); HRMS (EI): *m/z* Calcd for $C_{14}H_{15}NO_4$: 261.1001; Found: 261.1000.

4.1.11. (5-Methoxy-1-methyl-2-oxo-3-vinylindolin-3-yl)-*N*-methylacetamide (±)-(27) and (*S*)-derivative (+)-27

Under N_2 atmosphere, to a solution of (±)-**26** (1.2 g, 4.6 mmol) in THF (46 mL) was added pentafluorophenol (1.3 g, 6.9 mmol), Et_3N (1.3 mL, 9.2 mmol), and EDC·HCl (1.3 g, 6.9 mmol). After 2 h stirring, $MeNH_2$ gas, which was generated by the reaction of aqueous $MeNH_2$·HCl and NaOH pellet, was bubbled through the reaction mixture. After consumption of mixed anhydride, the reaction mixture was neutralized by 10% aqueous HCl and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The concentrated residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1 to 100/0) to give (±)-**27** (1.1 g, 90%) as colorless crystals.

Mp: 122–124 °C (AcOEt); IR ($CHCl_3$): 3460, 3312, 3009, 1690, 1603, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.68 (3H, d, J = 4.8 Hz), 2.86 (1H, d, J = 15.0 Hz), 2.95 (1H, d, J = 15.0 Hz), 3.22 (3H, s), 3.79 (3H, s), 5.08 (1H, d, J = 17.2 Hz), 5.15 (1H, d, J = 10.5 Hz), 5.96 (1H, dd, J = 17.2, 10.5 Hz), 6.58 (1H, br s), 6.76 (1H, d, J = 8.4 Hz), 6.81 (1H, dd, J = 8.4, 2.4 Hz), 6.87 (1H, d, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 26.6, 42.2, 53.5, 55.7, 108.6, 111.4, 112.2, 116.0, 131.2, 136.3, 136.6, 155.7, 169.1, 177.3; MS (EI): *m/z* (%) 274 (M^+, 100), 202 (71), 189 (13), 174 (15); HRMS (EI): *m/z* Calcd for $C_{15}H_{18}N_2O_3$: 274.1317; Found: 274.1319; Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.80; H, 6.63; N, 10.15.

Optically active compound (+)-**27** was obtained from (+)-**26** in a procedure similar to that above. The spectral data of (+)-**27** were identical to those of (±)-**26**, other than for specific optical rotation: $[\alpha]_D^{23}$ +10.2 (*c* 1.66, $CHCl_3$).

4.1.12. 5-Methoxy-1,8-dimethyl-3a-vinyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (±)-(28) and (3a*R*,8a*R*)-derivative (−)-28

Under N_2 atmosphere, to a solution of (±)-**27** (0.37 g, 1.4 mmol) in THF (50 mL) was added $LiAlH_4$ (14 mL, 1.0 M in THF, 14 mmol) and the solution was stirred under reflux for 3 h. Excess $LiAlH_4$ was quenched by THF/H_2O (1:1) and filtered through Celite pad. The filtrate was extracted with AcOEt and washed with satd aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to give (±)-**28** (0.28 g, 75%) as a pale yellow oil.

IR ($CHCl_3$): 2939, 1635, 1595, 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.98 (1H, ddd, J = 12.1, 5.9, 3.7 Hz), 2.28 (1H, ddd, J = 12.1, 9.4, 6.8 Hz), 2.52 (3H, s), 2.67 (1H, dt, J = 9.4, 5.9 Hz), 2.78 (1H, ddd, J = 9.4, 6.8, 3.7 Hz), 2.89 (3H, s), 3.74 (3H, s), 4.25 (1H, s), 5.04 (1H, d, J = 17.3 Hz), 5.09 (1H, d, J = 10.5 Hz), 6.09 (1H, dd, J = 17.3, 10.5 Hz), 6.38 (1H, d, J = 8.4 Hz), 6.60 (1H, d, J = 2.6 Hz), 6.68 (1H, dd, J = 8.4, 2.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.8, 38.3, 38.6, 53.1, 56.1, 59.8, 97.1, 107.7, 111.2, 112.9, 113.0, 134.5, 142.7, 146.7, 152.8; MS (EI): m/z (%) 244 (M^+, 100), 229 (17), 200 (37), 187 (13), 174 (22), 172 (15); HRMS (EI): m/z Calcd for $C_{15}H_{20}N_2O$: 244.1576; Found: 244.1578.

Optically active compound (−)-**28** was obtained from (+)-**27** in a procedure similar to that above. The spectral data of (−)-**28** were identical to those of (±)-**28**, other than for specific optical rotation: $[\alpha]_D^{23}$ −15.0 (c 0.43, $CHCl_3$).

4.1.13. 1,8-Dimethyl-3a-vinyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl phenylcarbamate (±)-(9) and (3a*R*,8a*R*)-derivative (−)-9

Under N_2 atmosphere, to a solution of (±)-**28** (0.28 g, 1.2 mmol) in CH_2Cl_2 (12 mL) was added BBr_3 (0.55 mL, 5.8 mmol) at 0 °C. After 1.5 h stirring at room temperature, the reaction mixture was quenched with satd $NaHCO_3$ and extracted by Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give crude phenol. Under N_2 atmosphere, to a solution of above phenol in Et_2O (20 mL) added Na (3.0 mg, 0.13 mmol) at room temperature. After stirring for 5 min, PhNCO (0.15 mL, 1.4 mmol) was added and stirred for 15 min. The reaction mixture was filtrated and the filtrate was concentrated. The residue was dissolved in Et_2O and the solution was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to give (±)-**9** (0.23 g, 57%) as a white powder.

Mp: 122–128 °C; IR ($CHCl_3$): 3433, 2940, 1749, 1602, 1526, 1495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.99 (1H, ddd, J = 12.1, 5.7, 3.9 Hz), 2.27 (1H, ddd, J = 12.1, 8.6, 7.0 Hz), 2.53 (3H, s), 2.66–2.81 (2H, m), 2.93 (3H, s), 4.32 (1H, s), 5.06 (1H, d, J = 17.4 Hz), 5.09 (1H, d, J = 10.8 Hz), 6.08 (1H, dd, J = 17.4, 10.8 Hz), 6.38 (1H, d, J = 8.4 Hz), 6.79 (1H, d, J = 2.4 Hz), 6.89 (1H, dd, J = 8.4, 2.4 Hz), 6.91 (1H, br s), 7.08 (1H, t, J = 7.2 Hz), 7.31 (2H, dd, J = 7.7, 7.2 Hz), 7.42 (2H, d, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.6, 38.69, 38.72, 53.1, 59.5, 97.0, 106.5, 113.2, 117.8, 118.6, 120.8, 123.6, 128.9, 133.9, 137.5, 142.2, 142.4, 149.9, 152.6; MS (EI): m/z (%) 349 (M^+, 3), 230 (100), 186 (47), 173 (20), 160 (25), 119 (50), 91 (19); HRMS (EI): m/z Calcd for $C_{21}H_{23}N_3O_2$: 349.1790; Found: 349.1789.

Optically active compound (−)-**9** was obtained from (−)-**28** in a procedure similar to that above. The spectral data of (−)-**9** were identical to those of (±)-**9**, other than for specific optical rotation: $[\alpha]_D^{23}$ −53.5 (c 1.07, $CHCl_3$) and CD λ_{max} (nm) [$\Delta\varepsilon$ (M^{-1} cm^{-1})] 309 (−0.81), 276 (−0.53).

4.1.14. 1,8-Dimethyl-3a-ethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl phenylcarbamate (±)-(10) and (3a*R*,8a*R*)-derivative (−)-10

Under H_2 atmosphere, to a solution of (±)-**9** (0.14 g, 0.40 mmol) in EtOH (4.0 mL) was added 10% Pd/C (10 mg, Aldrich) and the solution was stirred vigorously at room temperature for 3 h. The reaction mixture was filtrated with Celite pad and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to give (±)-**10** (0.14 g, 98%) as a white powder.

Mp: 154–157 °C; IR ($CHCl_3$): 3433, 1748, 1602, 1526, 1495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (3H, t, J = 7.5 Hz), 1.69 (1H, dq, J = 16.1, 7.5 Hz), 1.81 (1H, dq, J = 16.1, 7.5 Hz), 1.91 (1H, ddd, J = 12.0, 6.4, 3.5 Hz), 2.01 (1H, ddd, J = 12.0, 9.0, 6.4 Hz), 2.52 (3H, s), 2.56 (1H, ddd, J = 9.8, 9.0, 6.4 Hz), 2.70 (1H, ddd, J = 9.8, 6.4, 3.5 Hz), 2.92 (3H, s), 4.18 (1H, s), 6.35 (1H, d, J = 8.4 Hz), 6.78 (1H, d, J = 2.4 Hz), 6.86 (1H, dd, J = 8.4, 2.4 Hz), 6.91 (1H, br s), 7.10 (1H, t, J = 7.5 Hz), 7.32 (2H, t, J = 7.5 Hz), 7.43 (2H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.2, 32.6, 36.9, 38.0, 39.4, 52.7, 57.6, 94.4, 106.3, 116.5, 118.6, 120.3, 123.5, 128.9, 135.5, 137.5, 142.4, 150.5, 152.5; MS (EI): m/z (%) 351 (M^+, 9), 232 (100), 203 (22), 188 (45), 175 (16), 174 (29), 160 (47), 119 (36), 91 (15); HRMS (EI): m/z Calcd for $C_{21}H_{25}N_3O_2$: 351.1947; Found: 351.1947.

Optically active compound (−)-**10** was obtained from (−)-**9** in a procedure similar to that above. The spectral data of (−)-**10** were identical to those of (±)-**10**, other than for specific optical rotation: $[\alpha]_D^{23}$ −53.6 (c 1.02, $CHCl_3$) and CD λ_{max} (nm) [$\Delta\varepsilon$ (M^{-1} cm^{-1})] 332 (0.43), 266 (−2.96).

4.1.15. 1-Acetyl-5-methoxy-2-(3-methylbut-2-enyloxy)indolin-3-one (±)-(29)

Under N_2 atmosphere, to a solution of **16** (2.5 g, 12 mmol) in CH_2Cl_2 (70 mL) was added a solution of Br_2 in CH_2Cl_2 (24 mL, 1.0 M, 24 mmol) at 0 °C and the solution was stirred for 1 h. Starting material consumption was determined by TLC and the reaction mixture was neutralized with satd aqueous $NaHCO_3$. The organic layer was washed with brine and dried over $MgSO_4$. The concentrated residue was used without further purification. Under N_2 atmosphere, a suspension of above residue and molecular sieves 4A (17 g, powder) in CH_3CN (85 mL) was added prenyl alcohol (6.2 mL, 61 mmol) and the mixture was stirred for 1 day. The reaction mixture was filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/n-hexane = 1/3) to give (±)-**29** (2.7 g, 74%) as pale yellow needles.

Mp: 75–78 °C (AcOEt/n-hexane); IR ($CHCl_3$): 1724, 1678, 1620, 1589, 1489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.65 (3H, s), 1.71 (3H, s), 2.38 (3H, s), 3.83 (3H, s), 4.09 (1H, dd, J = 10.8, 7.5 Hz), 4.18 (1H, dd, J = 10.8, 7.5 Hz), 5.21 (1H, s), 5.32 (1H, tt, J = 7.5, 1.5 Hz), 7.14 (1H, d, J = 2.7 Hz), 7.25 (1H, dd, J = 8.4, 2.7 Hz), 8.43 (1H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 23.6, 25.8, 55.8, 62.0, 85.6, 104.9, 119.1, 119.3, 123.2, 126.3, 139.6, 147.8, 156.4, 168.9, 195.1; MS (EI): m/z (%) 289 (M^+, 13), 205 (17), 178 (100), 69 (12), 43 (8); HRMS (EI): m/z Calcd for $C_{16}H_{19}NO_4$: 289.1314; Found: 289.1312; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.46; H, 6.82; N, 4.83.

4.1.16. 2-[5-Methoxy-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetonitrile (±)-(30)

Under N_2 atmosphere, to a suspension of t-BuOK (0.58 g, 5.2 mmol) in DMF (10 mL) was added $(EtO)_2P(O)CH_2CN$ (1.0 mL, 5.6 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. After cooling at −78 °C, to the mixture was added (±)-**29** (0.50 g, 1.7 mmol) and the solution was stirred at the same temperature for 1 h. After consumption of (±)-**29**, the reaction mixture was warmed to room temperature and stirred for 3 h. To the reaction mixture was added H_2O, neutralized with 10% HCl, and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/n-hexane = 1/3) to give (±)-**30** (0.43 g, 91%) as colorless crystals.

Mp: 150 °C (AcOEt/n-hexane); IR ($CHCl_3$): 3435, 2250, 1727, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (3H, s), 1.17 (3H, s), 2.81 (1H, d, J = 16.5 Hz), 3.00 (1H, d, J = 16.5 Hz), 3.80 (3H, s),

5.10 (1H, dd, J = 17.4, 0.9 Hz), 5.22 (1H, dd, J = 10.8, 0.9 Hz), 6.10 (1H, dd, J = 17.4, 10.8 Hz), 6.82–6.88 (3H, m), 7.78 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 22.01, 22.04, 41.6, 55.78, 55.84, 110.3, 113.1, 113.3, 115.2, 116.7, 129.4, 134.8, 141.6, 155.1, 178.2; MS (EI): m/z (%) 270 (M^+, 16), 202 (100), 175 (86), 158 (10), 69 (49), 41 (14); HRMS (EI): m/z Calcd for $C_{16}H_{18}N_2O_2$: 270.1368; Found: 270.1366; Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.22; H, 6.83; N, 10.10.

4.1.17. 2-[5-Methoxy-1-methyl-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetonitrile (±)-(31)

Under N_2 atmosphere, to a suspension of NaH (0.23 g, 60%, 5.7 mmol) in DMF (9.0 mL) was added (±)-**30** (0.61 g, 2.3 mmol) with cooling by ice bath. After 1 h stirring at room temperature, MeI (0.42 mL, 6.8 mmol) was added to the mixture with ice-bath. After 15 min stirring at room temperature, water (100 mL) was added to the reaction mixture. The mixture was extracted by Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/n-hexane = 1/3) to give (±)-**31** (0.48 g, 75%) as colorless crystals.

Mp: 180–184 °C (AcOEt/n-hexane); IR ($CHCl_3$): 2250, 1705, 1600, 1498 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (3H, s), 1.14 (3H, s), 2.81 (1H, d, J = 16.2 Hz), 2.98 (1H, d, J = 16.2 Hz), 3.21 (3H, s) 3.81 (3H, s), 5.08 (1H, dd, J = 17.4, 0.9 Hz), 5.20 (1H, dd, J = 10.8, 0.9 Hz), 6.06 (1H, dd, J = 10.8, 17.4 Hz), 6.78 (1H, d, J = 8.4 Hz), 6.87 (1H, dd, J = 2.4, 8.4 Hz), 6.91 (1H, d, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 22.0, 22.1, 26.4, 41.7, 55.3, 55.8, 108.3, 112.8, 113.5, 115.0, 116.6, 128.9, 137.7, 141.8, 155.3, 175.6; MS (EI): m/z (%) 284 (M^+, 20), 216 (96), 189 (100), 174 (14), 69 (36), 41 (12); HRMS (EI): m/z Calcd for $C_{17}H_{20}N_2O_2$: 284.1525; Found: 284.1519; Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.92; H, 7.19; N, 9.74.

4.1.18. 2-[5-Methoxy-1-methyl-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetic acid (±)-(32)

A solution of (±)-**31** (0.33 g, 1.2 mmol) in MeOH (29 mL) was added 35% aqueous NaOH (1.7 mL, 15 mmol) and the mixture was stirred under reflux for 3 days. The mixture was acidified with 1 N aqueous HCl and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated to give (±)-**32** (0.31 g, 88%) as a pale yellow oil.

IR ($CHCl_3$): 3501, 1709, 1601, 1500 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, s), 1.10 (3H, s), 2.84 (1H, d, J = 16.2 Hz), 3.17 (1H, d, J = 16.2 Hz), 3.17 (3H, s), 3.78 (3H, s), 5.02 (1H, dd, J = 17.4, 1.2 Hz), 5.12 (1H, dd, J = 10.8, 1.2 Hz), 6.01 (1H, dd, J = 17.4, 10.8 Hz), 6.68 (1H, d, J = 8.4 Hz), 6.77 (1H, dd, J = 8.4, 2.4 Hz), 6.80 (1H, d, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 21.9, 26.4, 36.8, 41.7, 54.8, 55.8, 107.6, 111.8, 112.7, 114.1, 130.6, 138.5, 142.5, 154.7, 174.8, 177.9; MS (EI): m/z (%) 303 (M^+, 29), 235 (85), 190 (93), 189 (100), 174 (26), 69 (15); HRMS (EI): m/z Calcd for $C_{17}H_{21}NO_4$: 303.1471; Found: 303.1471; Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.40; H, 7.26; N, 4.45.

4.1.19. 2-[5-Methoxy-1-methyl-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]-*N*-methylacetamide (±)-(33) and (*S*)-derivative (−)-33

Under N_2 atmosphere, to a solution of (±)-**32** (0.21 g, 0.70 mmol) in THF (10 mL) was added pentafluorophenol (0.39 g, 2.1 mmol), Et_3N (0.20 mL, 1.1 mmol), and EDC·HCl (0.20 g, 1.1 mmol). After 2 h stirring, $MeNH_2$ gas which was generated by the reaction of aqueous $MeNH_2$·HCl and NaOH pellet) was bubbled through the reaction mixture. After consumption of mixed anhydride, the reaction mixture was neutralized by 10% aqueous HCl and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The concentrated residue was purified by silica gel column chromatography (AcOEt/n-hexane = 1/1 to 100/0) to give (±)-**33** (0.21 g, 95%) as colorless crystals.

Mp: 167 °C (AcOEt/n-hexane); IR ($CHCl_3$): 3019, 1690, 1601, 1499 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, s), 1.10 (3H, s), 2.51 (3H, d, J = 5.1 Hz), 2.64 (1H, d, J = 14.4 Hz), 3.02 (1H, d, J = 14.4 Hz), 3.19 (3H, s), 3.78 (3H, s), 4.98 (1H, dd, J = 17.4, 1.2 Hz), 5.10 (1H, dd, J = 10.8, 1.2 Hz), 5.38 (1H, br s), 6.03 (1H, dd, J = 17.4, 10.8 Hz), 6.68 (1H, d, J = 8.4 Hz), 6.76 (1H, d, J = 2.4 Hz), 6.79 (1H, dd, J = 8.4, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.1, 26.2, 26.3, 38.8, 41.9, 55.8, 56.0, 107.4, 111.5, 113.3, 113.7, 130.9, 138.3, 143.0, 154.6, 169.6, 178.3; MS (EI): m/z (%) 316 (M^+, 23), 248 (61), 190 (100), 189 (65), 174 (16); HRMS (EI): m/z Calcd for $C_{18}H_{24}N_2O_3$: 316.1787; Found: 316.1783; Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.13; H, 7.83; N, 8.65.

Optically active compound (−)-**33** was obtained from (−)-**32** in a procedure similar to that above. The enantiomer excess (>99% ee) was determined by HPLC (CHIRALPAK AD, flow = 0.5 mL/min, i-PrOH/n-hexane = 1/20). The spectral data of (−)-**33** were identical to those of (±)-**32**, other than for specific optical rotation: $[\alpha]_D^{25}$ −90.2 (c 0.24, $CHCl_3$).

4.1.20. 1,8-Dimethyl-5-methoxy-3a-(2-methylbut-3-en-2-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (±)-(34), 1,8-Dimethyl-5-methoxy-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydro pyrrolo[2,3-*b*]indole (±)-(35), and (3a*R*,8a*R*)-derivatives (−)-34 and (−)-35

Under N_2 atmosphere, to a solution of (±)-**33** (0.50 g, 1.6 mmol) in THF (100 mL) was added $LiAlH_4$ (16 mL, 1.0 M in THF, 16 mmol) and the solution was stirred under reflux for 10 h. Excess $LiAlH_4$ was quenched by THF/H_2O (1:1) and filtered through a Celite pad. The filtrate was extracted with AcOEt and washed with satd aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 15/1) to give (±)-**34** (0.25 g, 52%) as a colorless oil and (±)-**35** (0.19 g, 41%) as a pale yellow oil. Under N_2 atmosphere, to a solution of (±)-**34** (0.36 g, 1.2 mmol) in THF (20 mL) was added $LiAlH_4$ (5.9 mL, 1.0 M in THF, 5.9 mmol) and the solution was stirred under reflux for 1 h. The same work-up and purification procedure as that above was applied to this reaction to give (±)-**35** (0.29 g, 85%).

(±)-**34**; IR ($CHCl_3$): 3007, 2970, 2936, 1677, 1637, 1499 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (3H, s), 1.04 (3H, s), 2.56 (1H, d, J = 17.4 Hz), 2.85 (1H, d, J = 17.4 Hz), 2.86 (3H, s), 3.01 (3H, s), 3.74 (3H, s), 4.67 (1H, s), 5.05 (1H, dd, J = 17.2, 1.1 Hz), 5.11 (1H, dd, J = 10.8, 1.1 Hz), 5.78 (1H, dd, J = 17.4, 10.8 Hz), 6.36 (1H, m), 6.71–6.74 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 22.9, 27.6, 36.4, 39.5, 40.9, 56.0, 56.3, 88.2, 108.3, 112.5, 113.4, 114.1, 133.7, 143.4, 144.5, 152.8, 172.2; MS (EI): m/z (%) 300 (M^+, 36), 231 (100), 174 (50), 159 (8), 131 (6); HRMS (EI): m/z Calcd for $C_{18}H_{24}N_2O_2$: 300.1838; Found: 300.1841.

(±)-**35**; IR ($CHCl_3$): 1636, 1595, 1499 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, s) 1.01 (3H, s), 1.80 (1H, ddd, J = 11.8, 5.3, 2.9 Hz), 2.26 (1H, ddd, J = 11.8, 9.5, 6.6 Hz), 2.44 (3H, s), 2.44 (1H, ddd, J = 9.5, 9.0, 5.3 Hz), 2.67 (1H, ddd, J = 9.0, 6.6, 2.9 Hz), 2.89 (3H, s), 3.73 (3H, s), 4.16 (1H, s), 5.01 (1H, dd, J = 17.4, 1.4 Hz), 5.07 (1H, dd, J = 10.8, 1.4 Hz), 5.96 (1H, dd, J = 17.4, 10.8 Hz), 6.31 (1H, d, J = 8.4 Hz), 6.66 (1H, dd, J = 8.4, 2.4 Hz), 6.73 (1H, d, J = 2.4 Hz); MS (EI): m/z (%) 286 (M^+, 34), 217 (100), 202 (14), 187 (7), 174 (24), 159 (6), 131 (5); HRMS (EI): m/z Calcd for $C_{18}H_{26}N_2O$: 286.2045; Found: 286.2047.

Under N_2 atmosphere, to a solution of (−)-**33** (0.50 g, 1.6 mmol) in THF (16 mL) was added $LiAlH_4$ (16 mL, 1.0 M in THF, 16 mmol) and the solution was stirred under reflux for 1 h. Excess $LiAlH_4$ was quenched by THF/H_2O (1:1) and filtered through a Celite

pad. The filtrate was extracted with AcOEt and washed with satd. aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 30/1) to give (−)-**34** (0.38 g, 81%) as a colorless oil. The spectral data of (−)-**34** were identical to those of (±)-**34**, other than for specific optical rotation: $[\alpha]_D^{22}$ −108.7 (*c* 1.09, $CHCl_3$).

Under N_2 atmosphere, to a solution of (−)-**34** (0.35 g, 1.2 mmol) in THF (16 mL) was added $LiAlH_4$ (3.5 mL, 1.0 M in THF, 3.5 mmol) and the solution was stirred at room temperature for 0.5 h. Excess $LiAlH_4$ was quenched by THF/H_2O (1:1) and filtered through a Celite pad. The filtrate was extracted with AcOEt and washed with satd. aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to give (−)-**35** (0.27 g, 80%) as a pale yellow oil. The spectral data of (−)-**35** were identical to those of (±)-**35**, other than for specific optical rotation: $[\alpha]_D^{21}$ −78.4 (*c* 2.60, $CHCl_3$).

4.1.21. 1,8-Dimethyl-5-methoxy-3a-*tert*-pentyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (±)-(36)

Under H_2 atmosphere, to a solution of (±)-**35** (0.21 g, 0.74 mmol) in EtOH (3.0 mL) was added 10% Pd/C (10 mg, Aldrich) and the solution was stirred vigorously at room temperature for 3 h. The reaction mixture was filtrated with Celite pad and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to give (±)-**36** (0.21 g, 99%) as a pale yellow oil.

IR ($CHCl_3$): 2968, 2938, 2880, 2831, 1593, 1499, 1427 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.80 (3H, t, *J* = 7.6 Hz), 0.86 (3H, s), 0.90 (3H, s), 1.25 (2H, m), 1.80 (1H, ddd, *J* = 11.8, 5.3, 2.4 Hz), 2.26 (1H, ddd, *J* = 11.8, 9.7, 6.4 Hz), 2.43 (1H, ddd, *J* = 9.7, 9.0, 5.3 Hz), 2.44 (3H, s), 2.70 (1H, ddd, *J* = 9.0, 6.4, 2.4 Hz), 2.90 (3H, s), 3.76 (3H, s), 4.23 (1H, s), 6.29 (1H, d, *J* = 8.4 Hz), 6.65 (1H, dd, *J* = 8.4, 2.4 Hz), 6.72 (1H, d, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.6, 21.5, 21.7, 29.8, 34.3, 36.7, 37.1, 37.8, 53.2, 56.0, 65.7, 91.5, 106.2, 111.8, 112.7, 134.9, 147.6, 151.9; MS (EI): *m/z* (%) 288 (M^+, 65), 217 (100), 202 (18), 187 (7), 174 (34), 160 (7), 131 (4); HRMS (EI): *m/z* Calcd for $C_{18}H_{28}N_2O$: 288.2202; Found: 288.2201.

4.1.22. 1,8-Dimethyl-3a-*tert*-pentyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-5-yl phenylcarbamate (±)-(12) and (3a*R*,8a*R*)-derivative (−)-12

Under N_2 atmosphere, to a solution of (±)-**36** (55 mg, 0.19 mmol) in CH_2Cl_2 (6.3 mL) was added a CH_2Cl_2 solution of BBr_3 (0.59 mL, 6.3 mmol) at 0 °C. After 1.5 h stirring, the reaction mixture was added satd $NaHCO_3$ and extracted by Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give crude phenol (51 mg). Under N_2 atmosphere, to a solution of above phenol (51 mg) in Et_2O (4.0 mL) added Na (3.0 mg, 0.13 mmol) at room temperature. After stirring for 5 min, PhNCO (25 μL, 0.23 mmol) was added and stirred for 15 min. The reaction mixture was filtrated and the filtrate was concentrated. The residue was dissolved in Et_2O and the solution was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) to give (±)-**12** (47 mg, 63%) as a white powder.

Mp: 143–147 °C; IR ($CHCl_3$): 3433, 1748, 1603, 1526, 1497, 1443 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.80 (3H, t, *J* = 7.5 Hz), 0.86 (3H, s), 0.90 (3H, s), 1.14–1.38 (2H, m), 1.80 (1H, ddd, *J* = 11.8, 5.3, 2.4 Hz), 2.25 (1H, ddd, *J* = 11.8, 9.7, 6.4 Hz), 2.45 (3H, s), 2.46 (1H, ddd, *J* = 9.7, 9.0, 5.3 Hz), 2.68 (1H, ddd, *J* = 9.0, 6.4, 2.4 Hz), 2.94 (3H, s), 4.27 (1H, s), 6.29–6.32 (1H, m), 6.86–6.92 (3H, m), 7.08 (1H, t, *J* = 7.5 Hz), 7.31 (2H, t, *J* = 7.5 Hz), 7.43 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.7, 21.5, 21.6, 29.8, 34.3, 36.0, 37.4, 37.9, 53.4, 65.7, 91.4, 105.6, 118.5, 118.6, 120.4, 123.5, 128.9, 134.3, 137.5, 141.7, 150.6, 152.3; MS (EI): *m/z* (%) 393 (M^+, 4), 274 (68), 203 (100), 188 (14), 160 (40), 119 (25), 91 (12); HRMS (EI): *m/z* Calcd for $C_{24}H_{31}N_3O_2$: 393.2416; Found: 393.2423.

Optically active compound (−)-**12** was obtained in three steps from (−)-**35** in a procedure similar to that above. The spectral data of (−)-**12** were identical to those of (±)-**12**, other than for specific optical rotation: $[\alpha]_D^{21}$ −85.1 (*c* 1.10, $CHCl_3$) and CD λ_{max} (nm) [$\Delta\varepsilon$ (M^{-1} cm^{-1})] 312 (−1.95), 265 (−6.67).

4.1.23. General procedure for 3-{2-[(3*R*)-2-oxoindolin-3-yl]acetyl}-4(*R*)-phenyloxazolidin-2-ones 37 and 3-{2-[(3*S*)-2-oxoindolin-3-yl]acetyl}-4(*R*)-phenyloxazolidin-2-ones 38

Under N_2 atmosphere, to a solution of (±)-**20**, (±)-**26**, (±)-**32** (5 mmol) in THF (45 mL) was added pentafluorophenol (7.5 mmol), Et_3N (9.5 mmol), and EDC·HCl (7.5 mmol). After 2 h stirring, the mixture was concentrated under reduced pressure and dissolved in AcOEt. The solution was washed with satd aqueous Na_2CO_3 and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a crude ester. To a solution of (*R*)-(−)-4-phenyl-2-oxazolidinone (5.5 mmol) in THF (37 mL) was added NaH (60%, 5.5 mmol, for **20** and **26**) or *n*-BuLi (1.6 M in hexane, 5.5 mmol, for **38**) at 0 °C and the mixture was stirred for 2 h. To this solution was added above crude ester and the mixture was stirred for 0.5 h. After consumption of ester, the reaction mixture was neutralized by 1 N aqueous HCl and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The concentrated residue was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/2) to give **37** and **38**.

4.1.23.1. 3-{2-[3(*R*)-Allyl-5-methoxy-1-methyl-2-oxoindolin-3-yl]acetyl}-4(*R*)-phenyloxazolidin-2-one (37a) and 3-{2-[3(*S*)-Allyl-5-methoxy-1-methyl-2-oxoindolin-3-yl]acetyl}-4(*R*)-phenyloxazolidin-2-one (38a).

Carboxylic acid (±)-**20** (1.2 g, 4.5 mmol), pentafluorophenol (1.2 g, 6.7 mmol), Et_3N (1.2 mL, 8.9 mmol), EDC·HCl (1.3 g, 6.7 mmol), (*R*)-(−)-4-phenyl-2-oxazolidinone (1.1 g, 6.7 mmol), and NaH (0.23 g, 60%, 5.8 mmol) gave **37a** (0.86 g, 46%) as a pale yellow oil and **38a** (0.80 g, 42%) as a pale yellow oil.

Compound **37a**; IR ($CHCl_3$): 1780, 1707, 1603, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.47 (3H, dd, *J* = 13.2, 7.5 Hz), 2.53 (3H, dd, *J* = 13.2, 7.0 Hz), 3.11 (3H, s), 3.35 (1H, d, *J* = 17.1 Hz), 3.77 (3H, s), 4.00 (1H, d, *J* = 17.1 Hz), 4.13 (1H, dd, *J* = 8.8, 3.3 Hz), 4.59 (1H, dd, *J* = 8.8, 8.6 Hz), 4.96 (1H, dd, *J* = 10.1 Hz), 5.01 (1H, dd, *J* = 17.1 Hz), 5.26 (1H, dd, *J* = 8.6, 3.3 Hz), 5.44 (1H, dddd, *J* = 17.4, 10.1, 7.5, 7.0 Hz), 6.59 (1H, d, *J* = 8.4 Hz), 6.71 (1H, dd, *J* = 8.4, 2.4 Hz), 6.81 (1H, d, *J* = 2.4 Hz), 6.86–6.89 (2H, m), 7.18–7.21 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 40.8, 42.4, 50.2, 55.8, 57.2, 70.0, 108.1, 109.9, 112.2, 119.4, 125.0, 128.0, 128.7, 131.1, 131.8, 137.6, 138.1, 153.5, 155.4, 168.3, 178.2; MS (EI): *m/z* (%) 420 (M^+, 72), 216 (100), 174 (8); HRMS (EI): *m/z* Calcd for $C_{24}H_{24}N_2O_5$: 420.1685. Found: 420.1689.

Compound **38a**; IR ($CHCl_3$): 3009, 1782, 1709, 1603, 1501 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.45–2.55 (2H, m), 3.11 (3H, s), 3.34 (1H, d, *J* = 17.4 Hz), 3.77 (3H, s), 3.92 (1H, d, *J* = 17.4 Hz), 4.16 (1H, dd, *J* = 9.0, 3.3 Hz), 4.56 (1H, dd, *J* = 9.0, 8.7 Hz), 4.96–5.04 (2H, m), 5.20 (1H, dd, *J* = 8.7, 3.3 Hz), 5.42–5.46 (1H, m), 6.69–6.79 (3H, m), 7.13–7.16 (2H, m), 7.28–7.33 (3H, m).

4.1.23.2. 3-{2-[5-Methoxy-1-methyl-2-oxo-3(*S*)-vinylindolin-3-yl]acetyl}-4(*R*)-phenyloxazolidin-2-one (37b) and 3-{2-[5-Methoxy-1-methyl-2-oxo-3(*R*)-vinylindolin-3-yl]acetyl}-4(*R*)-phenyloxazolidin-2-one (38b).

Carboxylic acid (±)-**26** (1.3 g, 5.0 mmol), pentafluorophenol (1.4 g, 7.8 mmol), Et_3N (1.4 mL, 10 mmol), EDC·HCl (1.5 g, 7.8 mmol), (*R*)-(−)-4-phenyl-2-oxazolidinone

(1.3 g, 7.8 mmol), and NaH (0.31 g, 60%, 7.8 mmol) gave **37b** (0.75 g, 36%) as colorless crystals and **38b** (0.72 g, 34%) as a colorless oil.

37b; IR ($CHCl_3$): 1782, 1705, 1605, 1499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.12 (3H, s), 3.53 (1H, d, J = 17.6 Hz), 3.75 (3H, s), 4.04 (1H, d, J = 16.9 Hz), 4.13 (1H, dd, J = 3.2, 8.8 Hz), 4.59 (1H, t, J = 8.8 Hz), 5.06 (1H, d, J = 17.2 Hz), 5.15 (1H, d, J = 10.0 Hz), 5.27 (1H, dd, J = 3.6, 8.4 Hz), 5.91 (1H, dd, J = 10.4, 17.2 Hz), 6.62 (1H, d, J = 8.4 Hz), 6.73 (1H, dd, J = 2.8, 8.4 Hz), 6.78–6.81 (1H, m), 6.88–6.91 (2H, m), 7.16–7.22 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 40.7, 53.3, 55.8, 57.2, 70.1, 108.6, 110.7, 112.6, 116.2, 125.0, 128.0, 128.7, 130.7, 136.6, 137.5, 138.1, 153.5, 155.4, 168.1, 176.7; MS (EI): m/z (%) 407 (25), 406 (M^+, 100), 216 (16), 215 (12), 202 (55); HRMS (EI): m/z Calcd for $C_{23}H_{22}N_2O_5$: 406.1529; Found: 406.1522; $[\alpha]_D^{23}$ −140.7 (c 2.33, $CHCl_3$).

Compound **38b**; Mp: 166–168 °C (AcOEt/*n*-hexane); IR ($CHCl_3$): 1782, 1711, 1603, 1499 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.12 (3H, s), 3.54 (1H, d, J = 17.4 Hz), 3.80 (3H, s), 3.94 (1H, d, J = 17.4 Hz), 4.16 (1H, dd, J = 3.6, 8.8 Hz), 4.56 (1H, t, J = 8.8 Hz), 5.06 (1H, d, J = 17.2 Hz), 5.15 (1H, d, J = 10.4 Hz), 5.20 (1H, dd, J = 3.6, 8.4 Hz), 5.93 (1H, dd, J = 10.4, 17.2 Hz), 6.72–6.83 (3H, m), 7.14 (2H, d, J = 6.4 Hz), 7.26–7.36 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 41.1, 53.0, 55.8, 57.2, 70.1, 108.5, 111.0, 112.3, 116.1, 125.4, 128.4, 129.0, 131.2, 136.7, 137.6, 138.2, 153.6, 155.4, 168.1, 176.4; MS (EI): m/z (%) 406 (M^+, 100), 216 (13), 202 (57); HRMS (EI): m/z Calcd for $C_{23}H_{22}N_2O_5$: 406.1529; Found: 406.1523; Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 67.94; H, 5.66; N, 6.84; $[\alpha]_D^{23}$ −102.9 (c 1.18, $CHCl_3$).

4.1.23.3. 3-{2-[5-Methoxy-1-methyl-3(*S*)-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetyl}-4(*R*)-phenyloxazolidin-2-one (37c) and (*R*)-3-{2-[5-Methoxy-1-methyl-3(*R*)-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetyl}-4(*R*)-phenyloxazolidin-2-one (38c).

Carboxylic acid (±)-**32** (2.0 g, 6.7 mmol), pentafluorophenol (1.8 g, 9.9 mmol), Et_3N (1.8 mL, 13 mmol), EDC·HCl (1.9 g, 9.9 mmol), (*R*)-(−)-4-phenyl-2-oxazolidinone (1.2 g, 7.2 mmol), and *n*-BuLi (4.6 mL, 1.6 M in hexane, 7.2 mmol) gave **37c** (1.4 g, 48%) as a pale yellow oil and **38c** (1.4 g, 48%) as a pale yellow oil.

Compound **37c**; IR ($CHCl_3$): 3023, 3017, 1781, 1705, 1603, 1501, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, s), 1.13 (3H, s), 3.09 (3H, s), 3.39 (1H, d, J = 16.9 Hz), 3.76 (3H, s), 4.11 (1H, dd, J = 8.4, 3.5 Hz), 4.19 (1H, d, J = 16.9 Hz), 4.57 (1H, dd, J = 8.6, 8.4 Hz), 5.04 (1H, dd, J = 17.4, 1.1 Hz), 5.13 (1H, dd, J = 10.8, 1.1 Hz), 5.21 (1H, dd, J = 8.6, 3.5 Hz), 6.05 (1H, dd, J = 17.4, 10.8 Hz), 6.52 (1H, d, J = 8.4 Hz), 6.67 (1H, dd, J = 8.4, 2.4 Hz), 6.76–6.79 (3H, m), 7.11–7.18 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 21.9, 25.8, 36.9, 41.5, 54.9, 55.3, 56.7, 69.6, 107.2, 111.6, 111.7, 113.7, 124.4, 127.3, 128.1, 130.3, 137.9, 138.3, 142.3, 153.3, 154.2, 168.7, 177.5; MS (EI): m/z (%) 448 (M^+, 33), 380 (98), 216 (100), 189 (64), 174 (22), 160 (8); HRMS (EI): m/z Calcd for $C_{26}H_{28}N_2O_5$: 448.1998; Found: 448.2005.

Compound **38c**; IR ($CHCl_3$): 3023, 1781, 1709, 1601, 1538, 1518, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (3H, s), 1.11 (3H, s), 3.07 (3H, s), 3.43 (1H, d, J = 12.9 Hz), 3.76 (3H, s), 4.05 (1H, dd, J = 8.8, 3.4 Hz), 4.11 (1H, d, J = 12.9 Hz), 4.41 (1H, dd, J = 8.8, 8.5 Hz), 4.98 (1H, dd, J = 8.5, 3.4 Hz), 5.03 (1H, dd, J = 17.3, 0.9 Hz), 5.12 (1H, dd, J = 10.8, 0.9 Hz), 6.03 (1H, dd, J = 17.3, 10.8 Hz), 6.66 (1H, d, J = 8.3 Hz), 6.77 (1H, dd, J = 8.3, 2.3 Hz), 6.80 (1H, d, J = 2.3 Hz), 7.06 (2H, d, J = 6.4 Hz), 7.20–7.28 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 22.2, 26.2, 37.5, 41.9, 55.1, 55.6, 57.0, 69.9, 107.4, 111.6, 112.1, 114.1, 125.2, 128.2, 128.7, 131.1, 138.1, 138.6, 142.4, 153.6, 154.5, 169.0, 177.7; MS (EI): m/z (%) 448 (M^+, 31), 380 (99), 216 (100), 189 (66), 174 (22), 160 (8), 69 (5); HRMS (EI): m/z Calcd for $C_{26}H_{28}N_2O_5$: 448.1998; Found: 448.2000.

4.1.24. General procedure for (*S*)-2-(2-oxoindolin-3-yl)acetic acids (−)-20, (+)-26, (−)-32

A mixture of **38** (1.0 mmol), 30% aqueous H_2O_2 (4.0 mmol) and $LiOH{\cdot}H_2O$ (2.0 mmol) in THF/H_2O (2:1, 6–10 mL) was stirred at room temperature for 3 days. The concentrated residue was basified with 10% aqueous Na_2CO_3 and washed with Et_2O. The water layer was then acidified with 20% aqueous HCl and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated to give (−)-**20,** (+)-**26,** (−)-**32**.

4.1.24.1. (*S*)-2-(3-Allyl-5-methoxy-1-methyl-2-oxoindolin-3-yl)acetic acid (−)-(20).

Oxazolidin-2-one **38a** (0.80 g, 1.9 mmol), 30% aqueous H_2O_2 (0.75 mL, 7.6 mmol), and $LiOH{\cdot}H_2O$ (0.16 g, 3.8 mmol) in THF/H_2O (2:1, 12 mL) gave (−)-**20** (0.46 g, 89%). The spectral data of (−)-**20** were identical to those of (±)-**20**, other than for specific optical rotation: $[\alpha]_D^{25}$ −11.0 (c 1.90, $CHCl_3$).

4.1.24.2. (*R*)-2-(5-Methoxy-1-methyl-2-oxo-3-vinylindolin-3-yl)acetic acid (+)-(26).

Oxazolidin-2-one **38b** (0.70 g, 1.7 mmol), 30% aqueous H_2O_2 (0.78 mL, 6.9 mmol), and $LiOH{\cdot}H_2O$ (0.15 g, 3.5 mmol) in THF/H_2O (2:1, 15 mL) gave (+)-**26** (0.35 g, 78%). The spectral data of (+)-**26** were identical to those of (±)-**26**, other than for specific optical rotation: $[\alpha]_D$ ^{23} +2.3 (c 2.46, $CHCl_3$).

4.1.24.3. 2-[(*R*)-5-Methoxy-1-methyl-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetic acid (−)-(32).

Oxazolidin-2-one **38c** (1.4 g, 3.1 mmol), 30% aqueous H_2O_2 (1.3 mL, 13 mmol), and $LiOH{\cdot}H_2O$ (0.26 g, 6.2 mmol) in THF/H_2O (2:1, 30 mL) gave (−)-**32** (0.83 g, 88%) as a pale yellow oil. The spectral data of (−)-**32** were identical to those of (±)-**32** other than for specific optical rotation: $[\alpha]_D^{25}$ −80.1 (c 0.70, $CHCl_3$).

4.2. Biological methods

4.2.1. Animals

Male Wistar ST rats (8−10 weeks old) were purchased from Sankyo Labo Service Co. (Tokyo, Japan) and given free access to water and commercial food pellets (MF: Oriental Yeast Co., Tokyo, Japan). They were kept in a temperature—(24 ± 1 °C) and humidity—(55 ± 5%) controlled room with a 12-h day-night cycle. All experiments were performed in accordance with the guidelines of the Animal Research Committee of Toho University.

4.2.2. Measurement of AChE and BuChE activities

Rat brain homogenates and plasma were used as the sources of AChE and BuChE, respectively. Rat whole forebrain was homogenized in 20 volumes of ice-cold 0.1 M phosphate buffer (pH 8.0 or 7.4) containing 0.5% Triton-X. The homogenate was centrifuged at 1500×g at 4 °C for 10 min and the supernatant was used as the source of AChE. AChE and BuChE activities were measured using the Ogura[18] modified spectrophotometric method of Ellman[19] with acetylthiocholine iodide (AthCh) and butyrylthiocholine iodide (ButhCh) as the substrates for AChE and BuChE, respectively. The AChE assay mixture consisted of 0.1 M phosphate buffer (2.75 mL), 10 mM 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB) (0.10 mL), 75 mM AthCh (0.02 mL), ChE inhibitor (0.03 mL) and brain homogenates (0.10 mL). The BuChE assay mixture consisted of 0.1 M phosphate buffer (2.55 mL), 10 mM DTNB (0.10 mL), 150 mM ButhCh (0.02 mL), ChE inhibitor (0.03 mL) and plasma (0.30 mL). After mixing for 1 min with agitation, changes in absorbance at 412 nm were continuously recorded for 2 min at 25 °C

using a spectrophotometer (Hitachi, Tokyo, Japan). The ChE activity was determined as the change in absorbance during the last minute. Each ChE inhibitor was mixed with brain homogenate (3:10, v/v) or plasma (3:30, v/v) and incubated for 0.5 h at 37 °C. Aliquots of 0.13 or 0.33 mL of the preincubation mixture were used to assay ChE activity.

4.2.3. Statistical analysis

IC_{50} values were determined by 4-parameter logistic regression analysis using Stat View version 5.0 (SAS Institute Inc., Tokyo, Japan). Differences at $P < 0.05$ were considered statistically significant.

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