Toward General Access to the *Aspidosperma*-Type Terpenoid Indole Alkaloids: Synthesis of the Key 3,3-Disubstituted Piperidones through Enantioselective Intramolecular Heck-Type Reaction of Chloroformamides

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An enantioselective intramolecular Heck-type reaction of chloroformamides has been developed for the synthesis of 3,3-disubstituted piperidones. The desired piperidone was formed in the presence of a palladium catalyst, an optically active phosphoramidite ligand, K_3PO_4 and Ag_3PO_4. The obtained piperidone was converted to epieburnamonine.

Key words enantioselective reaction; total synthesis; terpenoid indole alkaloid

The terpenoid indole alkaloids are a class of natural products that are biosynthetically derived from tryptamine and a monoterpene unit.[1] Classification has been made by the feature of the terpenoid origin part.[2] A group of compounds with a quaternary carbon in the terpenoid region forms a large subclass that are called *aspidosperma*-type alkaloids (Fig. 1). Motivated by their bioactivities and attractive polycyclic structures, enormous synthetic studies on this class of compounds have been carried out.[3—9] Since the bond formation between the indole and the terpenoid moiety had been well resolved, much effort has been made to enhance the stereoselective construction of the quaternary carbon. Among these studies, strategies based on chiral auxiliary are dominant, and catalytic enantioselective method remains as a challenging task.[10—13]

Enantioselective Heck reaction has been well recognized as a powerful method to construct quaternary carbon centers (Fig. 2a).[14] Scope of this reaction is a limitation on the substrates: usually, the reaction needs to start from aryl or vinyl halides. In context of our recent studies on transition-metal-catalyzed reactions of carbamoyl derivatives,[15—18] we planned to develop an enantioselective Heck-type reaction of carbamoyl chlorides (Fig. 2b). By this reaction, a lactam ring with a quaternary carbon was expected to be obtained. Though racemic Heck-type reaction of carbamoyl chlorides was reported briefly in 1986,[19] further study does not exist.

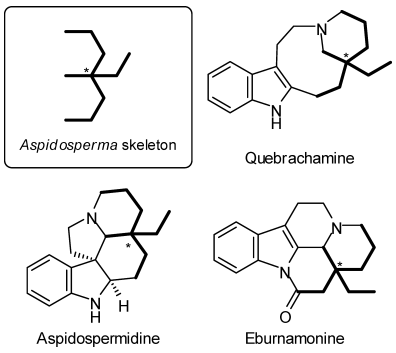

Fig. 1. Examples of the *Aspidosperma*-Type Terpenoid Indole Alkaloids

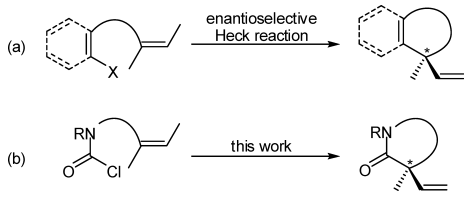

Fig. 2. Comparison of Heck Reaction and Heck-Type Reaction of Chloroformamides

We set up our goal to synthesize formyl piperidone **1** that could be a useful intermediate for the synthesis of the *aspidosperma*-type terpenoid indole alkaloids (Fig. 3). Chloroformamide **2** possessing an allyl ether moiety was designed as a substrate for the key Heck-type cyclization. Compound **2** can be synthesized from Boc-protected tryptamine **3** and alkenyl acetal **4**.

At the initial stage of this project, the key Heck-type reaction was tested with simple chloroformamide **8** (Fig. 4). Compound **8** was obtained from known allyl alcohol **5**[20] through Johnson–Claisen rearrangement, reduction of the resultant ester to alcohol, oxidation with IBX,[21] reductive amination, and chlorocarbonylation with triphosgene. Chloroformamide **8** was found to be stable for aqueous extraction, silica gel column chromatography and storage in refrigerator for several weeks, as expected.

Heck reaction of chloroformamide **8** was performed with $Pd(PPh_3)_4$ (10 mol%) and a base in xylene at 130 °C (Table 1). In contrast to the previously reported 5-*exo* cyclization,[19] the desired 6-membered lactam **9** was formed in poor yield

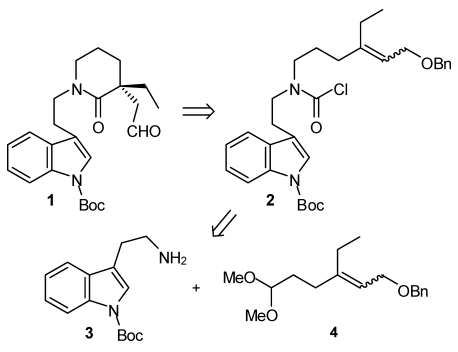

Fig. 3. Synthetic Plan

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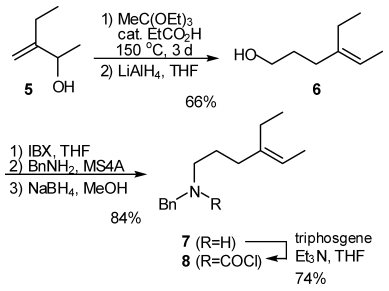


Fig. 4. Synthesis of Chloroformamide **8**

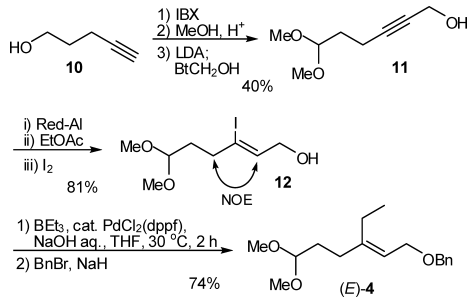
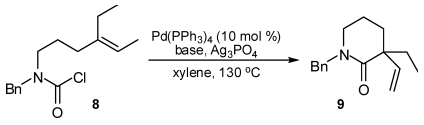


Fig. 5. Synthesis of Alkene (*E*)-**4**

Table 1. Heck-Type Reaction of Chloroformamide **8**



Entry	Base (eq)	Ag_3PO_4 (eq)	Yield (%)[a]
1	Bu_3N (1.5)	—	7 (61)
2	K_3PO_4 (1.2)	—	16 (49)
3	Collidine (2.6)	—	10 (64)
4	K_3PO_4 (1.5)	0.5	60
5[b]	K_3PO_4 (2.0)	0.5	59
6[c]	Collidine (1.7)	0.5	—

a) The yield in parentheses shows the recovered yield of compound **8**. *b*) Instead of $Pd(PPh_3)_4$, $Pd_2(dba)_3$ (5 mol%) and (*S*)-BINAP (15 mol%) were used. *c*) Instead of $Pd(PPh_3)_4$, $Pd(OAc)_2$ (10 mol%) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (10 mol%) were used.

under normal conditions (entries 1—3). However, lactam **9** was isolated in 60% yield when Ag_3PO_4 was added to the reaction (entry 4). The combination of $Pd_2(dba)_3$ and BINAP was also able to promote the cyclization in the presence of Ag_3PO_4 (entry 5). Nolan's NHC catalyst was not effective (entry 6).

With these results in hand, syntheses of each *cis–trans* isomer of alkenyl chloroformamide **2** were performed. Alkene (*E*)-**4** was synthesized through hydroalumination as a key step (Fig. 5). 4-Pentyn-1-ol (**10**) was transformed into alcohol **11** through oxidation, acetalization, and hydroxymethylation using benzotriazolylmethanol ($BtCH_2OH$).[22] Alcohol **11** was then subjected to the hydroalumination–iodination sequence[23,24] to give (*Z*)-iodo alkene **12**, whose configuration was confirmed by NOE experiment. Ethylation by Suzuki coupling, followed by benzylation gave the desired alkene (*E*)-**4**.

Change of the starting material afforded the alternative stereoisomer (Fig. 6). (*Z*)-Iodoalkene **14** was synthesized from 2-pentyn-1-ol (**13**) through hydroalumination and iodination. Since benzylation of the hydroxy group under either basic or acidic conditions competed with decomposition of the starting material, protection by THP group was carried out. The resultant THP ether **15** underwent Negishi coupling with 3,3-(dimethoxy)propylzinc chloride **16**.[25] Selective hydrolysis of the THP ether and benzylation afforded the desired alkene (*Z*)-**4**.

Alkenyl acetals (*E*)-**4** and (*Z*)-**4** were coupled with tryptamine **3**[26] through hydrolysis and reductive amination to give amines (*E*)-**17** and (*Z*)-**17**, respectively (Fig. 7). These compounds were converted to the corresponding chloroformamides (*E*)-**2** and (*Z*)-**2** by treating with triphosgene and Et_3N.

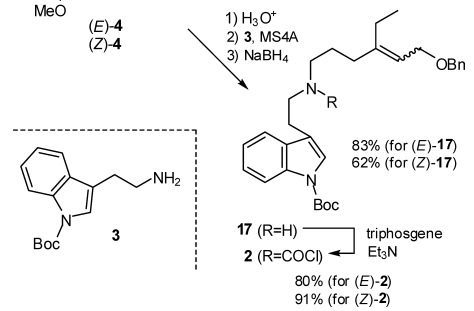
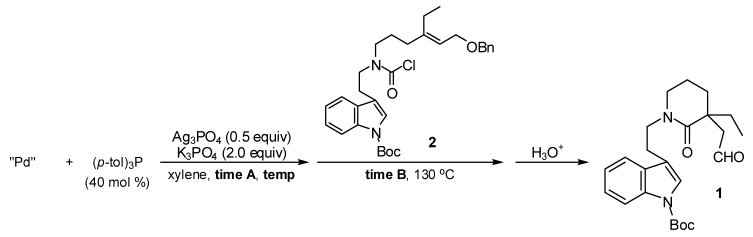


Fig. 6. Synthesis of Alkene (*Z*)-**4**

Fig. 7. Synthesis of Chloroformamides

Before the enantioselective Heck-type reaction, a racemic reaction was attempted to find out a suitable palladium source (Table 2). The cyclized product **1** was isolated after hydrolysis of the resultant enol ether. At the early stage, poor reproducibility was a serious problem. After several attempts, it was found that the activity of the catalyst is highly associated with the conditions used to mix palladium sources and ligands prior to the addition of chloroformamide **2**. When $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was premixed with $(p\text{-tol})_3P$ at 30 °C for 30 min, the disappearance of **2** was slow and the yield was 30% after 24 h (entry 1). In contrast, the starting material disappeared in 3 h and yield reached 49% when premixing was performed at 40 °C for 30 min (entry 2). Longer time and higher temperature gave less-active catalyst (entry 3). $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was found to be a better source than $Pd_2(dba)_3 \cdot CHCl_3$ or $PdCl_2(MeCN)_2$ (entries 4, 5).

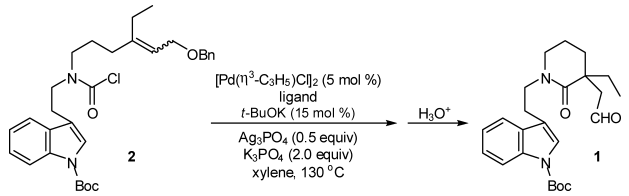
Table 2. The Effects of Premixing Conditions of Palladium Sources and $(p\text{-tol})_3P$



Entry	"Pd"	Time A (h)	Temp. (°C)	Time B (h)	Yield (%)
1[a]	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$[b]	0.5	30	24	30
2[a]	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$[b]	0.5	40	3	49
3[a]	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$[b]	1	80	24	29
4	$Pd_2(dba)_3\cdot CHCl_3$[b]	0.5	40	4	31
5	$PdCl_2(MeCN)_2$[c]	0.5	40	24	8

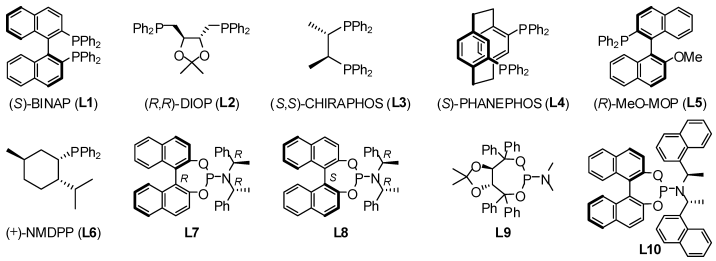
a) *t*-BuOK (0.11—0.15 mol%) was added. *b*) 5 mol%. *c*) 10 mol%.

Table 3. Enantioselective Heck-Type Reaction of Chloroformamide **2**[a]



Entry	Configuration of **2**	Ligand (mol%)	Time (h)	Yield (%)	Dominant enantiomer of **1**	ee (%)
1	*E*	**L1** (20)	24	16	*R*	3
2	*E*	**L2** (20)	9	32	*R*	8
3	*E*	**L3** (20)	22	35	*S*	5
4	*E*	**L4** (20)	6	50	*S*	18
5	*E*	**L5** (40)	3	51	—	0
6	*E*	**L6** (40)	3	31	*R*	5
7	*E*	**L7** (40)	11	52	*R*	43
8	*Z*	**L7** (40)	24	16	*S*	43
9	*E*	**L8** (40)	4	43	*S*	21
10	*Z*	**L8** (40)	23	24	*R*	64
11	*E*	**L9** (40)	11	30	*R*	47
12	*E*	**L10** (40)	5	30	*R*	52

a) $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, ligand, *t*-BuOK, Ag_3PO_4 and K_3PO_4 were premixed at 40 °C for 30 min prior to the addition of chloroformamide **2**.



The enantioselective Heck-type reaction of chloroformamide **2** was performed by combining $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ with optically active phosphorous ligands in the presence of Ag_3PO_4 and K_3PO_4 (Table 3). Initial attempts to react (*E*)-**2** by using bisphosphine ligands (**L1**—**L4**)[27—29] gave poor selectivity, though these ligands have been shown to be effective for normal enantioselective Heck reactions (entries 1—4).[14] Representative optically active monophosphines, (*R*)-MeO-MOP (**L5**)[30] and (+)-NMDPP (**L6**),[31] did not improve the selectivity (entries 5, 6). However, when the reaction was performed with phosphoramidite **L7**[32] that was synthesized from (*R*)-BINOL and bis[(*R*)-1-phenylethyl]amine, piperidone (*R*)-**1** was isolated in 52% and the selectivity reached to 43% ee (entry 7). By changing the starting material to (*Z*)-**2**, the opposite enantiomer, (*S*)-**1**, was obtained dominantly (entry 8). The corresponding diastereomeric ligand, **L8**, gave (*S*)-**1** in 21% ee from (*E*)-**2**, and (*R*)-**1** in 64% ee from (*Z*)-**2** (entries 9, 10). Though *Z*-isomer of chloroformamide **2** showed better selectivities in some cases, the reactions took longer period and the yields were lower than those of the *E*-

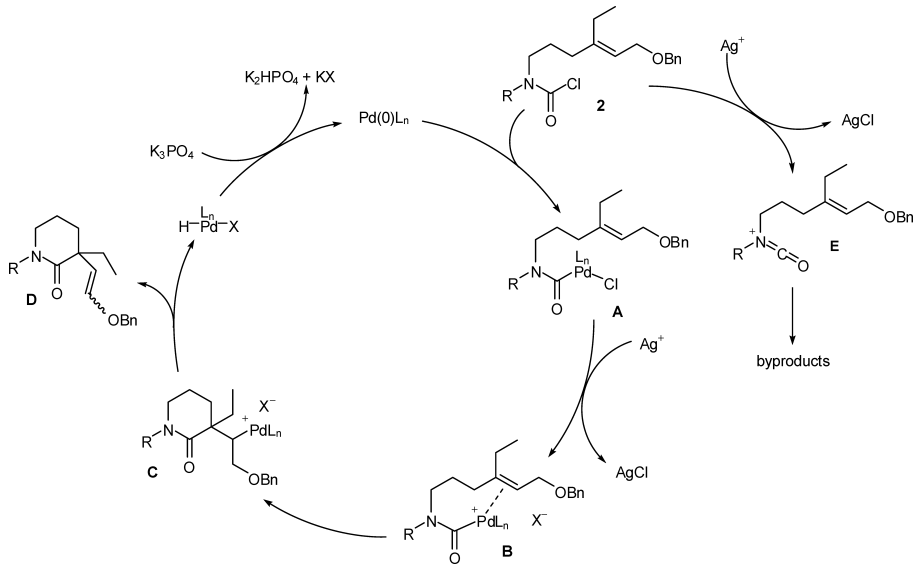


Fig. 8. Proposed Reaction Mechanism

isomer. Further screening of phosphoramidites[33,34] did not give dramatic improvements (entries 11, 12).

A reaction mechanism similar to that of the normal Heck reaction with halogen scavengers is proposed (Fig. 8). Oxidative addition followed by chloride abstraction generates cationic intermediate **B**. The side reactions are likely to occur by direct reaction of the silver salt with the starting chloroformamide **2**, which generates highly reactive intermediates such as **E**. Achieving the selective chloride abstraction from the complex **A** or avoiding the use of halogen scavengers will be a key for further improvements.

The utility of piperidone **1** as an intermediate for the terpenoid indole alkaloid synthesis was briefly demonstrated by converting **1** to epieburnamonine (Fig. 9). Oxidation and methylation followed by removal of the Boc group under microwave irradiation afforded methyl ester **19**, from which syntheses of eburnamonine, eburnamine and vincamine have been reported.[35—37] Methyl ester **19** was converted to epieburnamonine (**20**) through Bischler–Napieralski reaction and reduction with $NaBH_4$. It is known that reduction of the related compounds with $NaBH_4$ gives a mixture in which the *trans* isomer is in excess of the *cis* isomer.[38—41] In our system, *trans* isomer **20** was obtained as a sole product. Comparison of the optical rotation with that reported[42] showed that the product was (−)-epieburnamonine (**20**).

In conclusion, an enantioselective Heck-type reaction of chloroformamides has been developed for the construction of 3,3-disubstituted piperidones, and applied toward the synthesis of monoterpene indole alkaloids. The addition of silver salts was essential for the 6-*exo* cyclization. Phosphoramidite **L7** that was synthesized from (*R*)-BINOL and bis[(*R*)-1-phenylethyl]amine showed the best yield and selectivity. Further improvements of the current Heck-type reaction will lead to convenient and efficient access to a variety of compounds containing quaternary carbons.

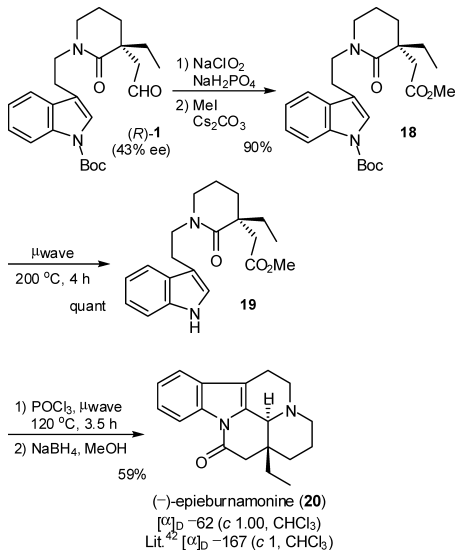


Fig. 9. Conversion of **1** to Epieburnamonine

Experimental

All reactions were performed under argon. $Pd(PPh_3)_4$ was prepared by using the reported protocol.[43] K_3PO_4 was dried by heating under vacuum. Bu_3N, diisopropylamine and xylene were distilled from CaH_2. Phosphoramidites were synthesized according to the literatures.[32—34] Other commercially available reagents and solvents were used as received without further purification.

Analytical thin-layer chromatography was performed with Merck silica gel 60 F_{254} and Merck 25 DC-Alufolein (alumina). Flash silica gel column chromatography was performed with Kanto silica gel 60 (particle size 0.063—0.210 mm). Flash alumina column chromatography was performed with deactivated (5% water) Merck aluminum oxide 90 (particle size 0.063—0.200 mm). Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-LA500 at 500 MHz or JEOL JNM-AL400 at 400 MHz, and chemical shifts were reported relative to Me_4Si (δ 0.00). Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a JNM-ECA500 at 125 MHz or JNM-AL400 at 100 MHz, and chemical shifts were reported relative to $CDCl_3$ (δ 77.2). Infrared spectra were recorded on a JASCO FT/IR-410. Optical rotations were recorded on a JASCO DIP-360 polarimeter. Enantiomeric excess (ee) was determined by HPLC analysis on a SHIMADZU SCL-10A. All microwave irradiation experiments were carried out in a CEM Discover microwave apparatus.

(*E*)-4-Ethylhex-4-en-1-ol (6) A mixture of 3-ethylbut-3-en-2-ol (**5**) (3.92 g, 39.2 mmol), $MeC(OEt)_3$ (25.0 ml, 137 mmol) and propionic acid (0.30 ml, 4.03 mmol) in a sealed tube was stirred at 150 °C for 3 d, and the solution was poured into a mixture of MeOH (30 ml) and aqueous 1 M HCl (30 ml).The resulting mixture was stirred for 2 h at room temperature. After adding brine, the mixture was extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4,

and concentrated *in vacuo*. The resulting residue was dissolved in THF (135 ml), and $LiAlH_4$ (80% purity, 2.42 g, 63.7 mmol) was added portion wise at 0 °C. After stirring for 15 min at 0 °C, the mixture was diluted with Et_2O. Potassium sodium tartrate tetrahydrate was added, and the mixture was stirred for 3 h at room temperature. Insoluble materials were removed by filtration, and the filtrate was concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/Et_2O=1/0→6/4) afforded alcohol **6** (3.33 g, 66%) as a colorless oil. *Rf* 0.59 (silica gel, hexane/EtOAc=8/2). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 5.22 (1H, q, J=6.8 Hz), 3.64 (2H, q, J=6.4 Hz), 2.08—2.03 (4H, m), 1.66 (2H, tt, J_1=J_2=6.4 Hz), 1.59 (3H, d, J=6.8 Hz), 1.30—1.27 (1H, m), 0.97 (3H, t, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 141.5, 118.4, 62.9, 32.9, 31.1, 22.7, 13.0, 12.8. IR (NaCl) cm^{-1}: 3332, 2964, 2935, 2872, 1456. LR-MS (EI) m/z=128 (M^+). *Anal.* Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.98; H, 12.84.

(*E*)-*N*-Benzyl-4-ethylhex-4-en-1-amine (7) A suspension of alcohol **6** (713 mg, 5.57 mmol) and IBX (2.35 g, 8.39 mmol) in THF (20 ml) was refluxed for 2.5 h. The reaction mixture was diluted with Et_2O, filtered through alumina pad, and concentrated *in vacuo*. The residue was dissolved in THF (19.3 ml), and benzylamine (0.65 ml, 5.96 mmol) and MS4A (3.39 g) were added. After stirring for 2.5 h at room temperature, insoluble materials were removed by filtration. To the filtrate was added a solution of $NaBH_4$ (95% purity, 264 mg, 6.60 mmol) in MeOH (22 ml) at 0 °C. After stirring for 1 h at room temperature, water was added, and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc/EtOH=1/0/0→0/5/5) afforded amine **7** (1.02 g, 84%) as a light yellow oil. *Rf* 0.35 (alumina, CH_2Cl_2/MeOH=9/1). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.34—7.30 (4H, m), 7.27—7.22 (1H, m), 5.17 (1H, q, J=6.7 Hz), 3.78 (2H, s), 2.62 (2H, t, J=7.1 Hz), 2.05—2.00 (4H, m), 1.60 (2H, tt, J_1=J_2=7.1 Hz), 1.57 (3H, d, J=6.7 Hz), 0.95 (3H, t, J=7.6 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 141.7, 140.8, 128.6 128.3, 127.1, 118.2, 54.2, 49.4, 34.4, 28.6, 22.7, 13.1, 12.9. IR (NaCl) cm^{-1}: 2963, 2931, 1454. LR-MS (EI) m/z=217 (M^+). *Anal.* Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.82; H, 10.88; N, 6.31.

(*E*)-*N*-Benzyl-*N*-(4-ethylhex-4-enyl)chloroformamide (8) To a solution of amine **7** (597 mg, 2.75 mmol) and Et_3N (0.55 ml, 4.2 mmol) in THF (6.0 ml) was added a solution of triphosgene (317 mg, 1.07 mmol) in THF (4.0 ml) at −78 °C. The reaction mixture was warmed to room temperature, followed by stirring for 2.5 h at 60 °C. EtOAc, water, and aqueous 1 M HCl were added successively at 0 °C. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined extracts were washed with aqueous 1 M HCl, water, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/Et_2O=1/0→9/1) afforded chloroformamide **8** (565 mg, 74%) as a light yellow oil. *Rf* 0.40 (silica gel, hexane/Et_2O=9/1). ^{1}H-NMR* ($CDCl_3$, 500 MHz) δ: 7.40—7.30 (3H, m), 7.27—7.25 (2H, m), 5.14 (1H, m), 4.71 (2H, s), 4.57 (s), 3.32 (2H, m), 2.03—1.94 (4H, m), 1.72—1.64 (2H, m), 1.56 (3H, m), 0.95—0.91 (3H, m). ^{13}C-NMR* ($CDCl_3$, 100 MHz) δ: 150.4, 149.5, 140.4, 140.2, 136.1, 135.9, 129.1, 129.0, 128.8, 128.30, 128.25, 128.19, 127.3, 119.1, 118.9, 54.5, 52.5, 50.3, 49.5, 33.6, 33.5, 26.2, 25.4, 22.6, 13.0, 12.8. IR (NaCl) cm^{-1}: 2964, 2933, 2872, 1735. LR-MS (EI) m/z=279 (M^+). *Anal.* Calcd for $C_{16}H_{22}ClNO$: C, 68.68; H, 7.93; N, 5.01. Found: C, 68.88; H, 7.84; N, 5.00 (* *ca.* 1 : 1 mixture of rotamers).

1-Benzyl-3-ethyl-3-vinylpiperidin-2-one (9) A suspension of chloroformamide **8** (58.7 mg, 0.210 mmol), K_3PO_4 (106 mg, 0.490 mmol), Ag_3PO_4 (45.5 mg, 0.107 mmol) and $Pd(PPh_3)_4$ (24.3 mg, 0.0210 mmol) in xylene (3.0 ml) were stirred for 2 h at 130 °C. After cooling to 0 °C, aqueous 1 M HCl were added, and the mixture was extracted with EtOAc. The combined extracts were washed with aqueous 1 M HCl, water, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/Et_2O=1/0→8/2) afforded piperidone **9** (30.6 mg, 60%) as a yellow oil. *Rf* 0.38 (silica gel, hexane/EtOAc=8/2). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.31 (2H, dd, J_1=J_2=7.0 Hz), 7.27—7.23 (3H, m), 5.94 (1H, dd, J_1=10.7 Hz, J_2=17.5 Hz), 5.16 (1H, d, J=10.7 Hz), 5.08 (1H, d, J=17.5 Hz), 4.62 (1H, d, J_1=14.7 Hz), 4.57 (1H, d, J_1=14.7 Hz), 3.24—3.13 (2H, m), 1.94—1.63 (6H, m), 0.86 (3H, t, J=7.4 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 173.2, 142.8, 137.9, 128.8, 128.3, 127.5, 114.2, 50.6, 49.4, 47.8, 31.8, 28.8, 19.3, 8.6. IR (NaCl) cm^{-1}: 2966, 2939, 2874, 2240, 1628. LR-MS (EI) m/z=243 (M^+). *Anal.* Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.81; H, 8.92; N, 5.49.

6,6-Dimethoxyhex-2-yn-1-ol (11) A mixture of 4-pentyn-1-ol (**10**) (7.00 ml, 73.5 mmol), DMSO (1.04 ml) and IBX (31.3 g, 112 mmol) in THF (75 ml) was refluxed for 22 h. After adding Et_2O, insoluble materials were removed by filtration. To the filtrate, MeOH (60 ml) and *p*-TsOH·H_2O (557 mg, 2.93 mmol) were added, and resultant solution was stirred for 3 h at 40 °C. After adding aqueous $NaHCO_3$, the mixture was extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and resulting solution was filtered through silica gel pad. Et_2O was removed by distillation to afford a solution of dimethyl acetal in THF. This solution was added to a solution of LDA at −78 °C, which was generated from diisopropylamine (41.1 ml, 294 mmol) and *n*-butyl lithium (1.63 M in hexane, 185 ml, 301 mmol) in anhydrous THF (16 ml). After stirring for 15 min at −78 °C, 1*H*-benzotriazole-methanol (18.6 g, 125 mmol) in anhydrous THF (500 ml) was added dropwise over 45 min. After stirring for 4 h at room temperature, aqueous NaOH was added at 0 °C and the mixture was extracted with EtOAc. The combined extracts were washed with aqueous 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc=6/4) afforded alcohol **11** (4.61 g, 40%) as a yellow oil. *Rf* 0.24 (silica gel, hexane/EtOAc=6/4). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 4.48 (1H, t, J=5.8 Hz), 4.25 (2H, dt, J_1=2.2 Hz, J_2=6.1 Hz), 3.34 (6H, s), 2.29 (2H, tt, J_1=2.2 Hz, J_2=7.3 Hz), 1.81 (2H, dt, J_1=5.8 Hz, J_2=7.3 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 103.3, 84.7, 79.0, 53.0, 50.9, 31.4, 14.2. IR (NaCl) cm^{-1}: 3426, 2940, 2225. LR-MS (FAB) m/z=157 (M^+−1). *Anal.* Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.51; H, 8.64.

(*Z*)-3-Iodo-6,6-dimethoxyhex-2-en-1-ol (12) To a solution of Red-Al (3.05 M in toluene, 28.9 ml, 88.1 mmol) in anhydrous Et_2O (30 ml) was added alcohol **11** (5.57 g, 35.3 mmol) in Et_2O (75 ml) at 0 °C. After stirring for 4.5 h at 30 °C, EtOAc (8.6 ml, 88.2 mmol) and a solution of iodine (10.7 g, 42.2 mmol) in THF (90 ml) were added successively at 0 °C. Reaction mixture was stirred for 2 h at room temperature, and was added saturated aqueous potassium sodium tartrate tetrahydrate and 10% aqueous sodium thiosulfate at 0 °C. The mixture was extracted with EtOAc, and the combined extracts were washed with 10% aqueous sodium thiosulfate and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc=6/4→4/6) afforded iodide **12** (8.21 g, 81%) as a yellow oil. *Rf* 0.28 (silica gel, hexane/EtOAc=6/4). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.89 (1H, tt, J_1=1.2 Hz, J_2=5.9 Hz), 4.37 (1H, t, J=5.8 Hz), 4.19 (2H, t, J=5.9 Hz), 3.33 (6H, s), 2.57 (2H, dt, J_1=1.2 Hz, J_2=7.7 Hz), 1.87—1.82 (2H, m). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 134.6, 108.1, 103.0, 67.1, 52.9, 40.3, 32.1. IR (NaCl) cm^{-1}: 3406, 2934, 1127, 1055. LR-MS (FAB) m/z=285 (M^+−1). *Anal.* Calcd for $C_8H_{15}IO_3$: C, 33.58; H, 5.28. Found: C, 33.72; H, 5.13.

(*E*)-1-Benzyloxy-3-ethyl-6,6-dimethoxyhex-2-ene (4) A mixture of iodide **12** (3.59 g, 12.6 mmol), triethylborane (1.0 M in hexane, 15.0 ml, 15.0 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (317 mg, 0.388 mmol) and NaOH (1.13 g, 28.3 mmol) in THF (27 ml) and water (5.5 ml) was stirred for 2 h at 30 °C. After adding aqueous H_2O_2 at 0 °C, the mixture was extracted with EtOAc. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Filtration through silica gel pad (hexane/EtOAc=5/5) and concentration *in vacuo* afforded crude olefin. This crude material was dissolved with DMF (40 ml) and water (1.0 ml), and sodium hydride (55% purity, 1.64 g, 37.6 mmol) was added portion wise at 0 °C. After stirring for 10 min, benzyl bromide (97% purity, 1.85 ml, 15.1 mmol) was added and the suspension was stirred for 1 h at 30 °C. Water was added at 0 °C, and the mixture was extracted with Et_2O. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc=1/0→9/1) afforded benzyl ether (*E*)-**4** (2.57 g, 74%) as a colorless oil. *Rf* 0.49 (silica gel, hexane/EtOAc=8/2). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.35—7.25 (5H, m), 5.38 (1H, t, J=6.7 Hz), 4.50 (2H, s), 4.37 (1H, t, J=5.7 Hz), 4.04 (2H, d, J=6.7 Hz), 3.32 (6H, s), 2.12—2.03 (4H, m), 1.76—1.70 (2H, m), 0.97 (3H, t, J=7.7 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 145.3, 138.6, 128.3, 127.7, 127.5, 120.7, 104.2, 72.1, 66.3, 52.6, 31.2, 30.9, 23.8, 13.4. IR (NaCl) cm^{-1}: 2933, 1454, 1365, 1126, 1067. LR-MS (FAB) m/z=277 (M^+−1). *Anal.* Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.44; H, 9.38.

(*Z*)-3-Iodopent-2-en-1-ol (14) To a solution of Red-Al (3.05 M in toluene, 19.9 ml, 60.7 mmol) in anhydrous Et_2O (20 ml) at 0 °C, was added a solution of 2-pentyn-1-ol (**13**) (2.04 g, 24.3 mmol) in Et_2O (30 ml). After stirring for 2.5 h at 30 °C, EtOAc (6.0 ml, 61.5 mmol) and a solution of iodine (7.44 g, 29.3 mmol) in THF (60 ml) was added at 0 °C. The reaction mixture was stirred for 2 h at room temperature, cooled to 0 °C, and saturated aqueous potassium sodium tartrate tetrahydrate and 10% aqueous sodium thiosulfate were added successively. The mixture was extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4,

and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc=1/0→7/3) afforded iodide **14** (4.18 g, 81%) as a light yellow oil. *Rf* 0.58 (silica gel, hexane/EtOAc=6/4). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.84 (1H, t, J=5.9 Hz), 4.20 (2H, d, J=5.9 Hz), 2.55 (2H, q, J=7.3 Hz), 1.10 (3H, t, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 132.6, 111.7, 67.2, 39.0, 14.8. IR (NaCl) cm^{-1}: 3320, 2969, 1644, 1019. *Anal.* Calcd for C_5H_9IO: C, 28.32; H, 4.28. Found: C, 28.37; H, 4.21.

(*Z*)-2-(3-Iodopent-2-enyloxy)tetrahydro-2*H*-pyran (15) A solution of iodide **14** (2.44 g, 11.5 mmol), dihydropyran (1.57 ml, 17.2 mmol) and *p*-TsOH·H_2O (222 mg, 1.17 mmol) in CH_2Cl_2 (38 ml) was stirred for 1.5 h at 30 °C. After adding aqueous $NaHCO_3$, the mixture was extracted with $CHCl_3$. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc=1/0→94/6) afforded THP ether **15** (3.05 g, 89%) as a colorless oil. *Rf* 0.36 (silica gel, hexane/EtOAc=94/6). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.82 (1H, tdd, J_1=1.2 Hz, J_2=5.6 Hz, J_3=7.6 Hz), 4.65 (1H, dd, J_1=2.9 Hz, J_2=3.9 Hz), 4.29 (1H, tdd, J_1=1.2 Hz, J_2=5.6 Hz, J_3=13.2 Hz), 4.06 (1H, tdd, J_1=1.2 Hz, J_2=7.6 Hz, J_3=13.2 Hz), 3.89 (1H, ddd, J_1=3.2 Hz, J_2=7.8 Hz, J_3=11.4 Hz), 3.56—3.51 (1H, m), 2.54 (2H, dddq, J_1=J_2=J_3=1.2 Hz, J_4=7.3 Hz), 1.87—1.79 (1H, m), 1.76—1.69 (1H, m), 1.64—1.50 (4H, m), 1.10 (3H, t, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 130.7, 111.8, 98.4, 71.8, 62.3, 39.1, 30.6, 25.5, 19.5, 14.7. IR (NaCl) cm^{-1}: 2938, 1648, 1455, 1121, 1028. LR-MS (FAB) m/z=297 ($M+H^+$). *Anal.* Calcd for $C_{10}H_{17}IO_2$: C, 40.56; H, 5.79. Found: C, 40.78; H, 5.59.

(*Z*)-2-(3-Ethyl-6,6-dimethoxyhex-2-enyloxy)tetrahydro-2*H*-pyran To a mixture of magnesium turning (455 mg, 18.7 mmol) in anhydrous THF (3.0 ml), was added a small portion of 1-bromo-3,3-dimethoxypropane (3.23 g, 17.7 mmol) in anhydrous THF (8.0 ml) and 3 drops of 1,2-dibromethane. As soon as the reaction started, remainder of the bromide solution is added dropwise, and the resulting mixture was stirred for 1 h at room temperature. This solution was diluted with anhydrous THF (8.0 ml), and added to a solution of anhydrous $ZnCl_2$ (2.57 g, 18.5 mmol) in anhydrous THF (48 ml) at −78 °C. The reaction mixture was warmed up to room temperature, and added to a solution of THP ether **15** (2.64 g, 8.92 mmol) and $Pd(PPh_3)_4$ (836 mg, 0.723 mmol) in anhydrous THF (10 ml). After stirring for 20 h at 30 °C, water was added, and the mixture was extracted with EtOAc. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc=1/0→8/2) afforded (*Z*)-2-(3-ethyl-6,6-dimethoxyhex-2-enyloxy)tetrahydro-2*H*-pyran (1.43 g, 59%) as a yellow oil. *Rf* 0.42 (silica gel, hexane/EtOAc=8/2). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.37 (1H, t, J=6.8 Hz), 4.63 (1H, t, J=3.7 Hz), 4.33 (1H, t, J=5.6 Hz), 4.27 (1H, dd, J_1=6.8 Hz, J_2=11.9 Hz), 4.04 (1H, dd, J_1=6.8 Hz, J_2=11.9 Hz), 3.89 (1H, ddd, J_1=3.4 Hz, J_2=7.6 Hz, J_3=11.2 Hz), 3.54—3.51 (1H, m), 3.32 (6H, s), 2.19—2.04 (4H, m), 1.89—1.76 (1H, m), 1.76—1.48 (7H, m), 1.03 (3H, t, J=7.5 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 144.9, 120.3, 104.1, 98.0, 63.5, 62.2, 52.6, 31.4, 30.8, 29.5, 25.7, 25.6, 19.6, 12.4. IR (NaCl) cm^{-1}: 2941, 1459, 1383, 1127, 1025. LR-MS (FAB) m/z=271 (M^+-1). *Anal.* Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.23; H, 10.65.

(*Z*)-1-Benzyloxy-3-ethyl-6,6-dimethoxyhex-2-ene (4) To a solution of (*Z*)-2-(3-ethyl-6,6-dimethoxyhex-2-enyloxy)tetrahydro-2*H*-pyran (913 mg, 3.35 mmol) and $Sc(OTf)_3$ (48.4 mg, 98.4 μmol) in MeOH (22.0 ml) and water (0.5 ml) was stirred for 3 h at 40 °C. The solution was poured onto ice-cooled saturated aqueous $NaHCO_3$, and the resultant mixture was extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. This residue was dissolved with DMF (11 ml), and cooled to 0 °C. Sodium hydride (55% purity, 297 mg, 6.81 mmol) and benzyl bromide (97% purity, 0.49 ml, 4.00 mmol) were added and stirred for 1 h at room temperature. After adding water at 0 °C, the mixture was extracted with Et_2O. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/Et_2O=1/0→9/1) afforded benzyl ether (*Z*)-**4** (546 mg, 59%) as a colorless oil. *Rf* 0.50 (silica gel, hexane/EtOAc=8/2). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.36—7.27 (5H, m), 5.41 (1H, t, J=6.7 Hz), 4.51 (2H, s), 4.29 (1H, t, J=5.8 Hz), 4.05 (2H, d, J=6.7 Hz), 3.29 (6H, s), 2.11—2.04 (4H, m), 1.67—1.62 (2H, m), 1.03 (3H, t, J=7.4 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 145.2, 138.7, 128.5, 128.0, 127.7, 120.6, 104.2, 72.4, 66.6, 52.8, 31.4, 29.5, 25.9, 12.6. IR (NaCl) cm^{-1}: 2962, 1455, 1126, 1067. LR-MS (FAB) m/z=277 (M^+-1). *Anal.* Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.07; H, 9.20.

2-[2-(1*H*-indol-3-yl)ethyl]isoindoline-1,3-dione A mixture of tryptamine (9.26 g, 57.9 mmol), phthalic anhydride (9.01 g, 60.9 mmol) and DMF (9 ml) was divided into six microwave reactor vials. Each vial was irradiated with microwave at 180 °C for 25 min with 50 W as max irradiation power. The combined reaction mixtures were added aqueous 1 M HCl and extracted with $CHCl_3$. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$ and brine, dried Na_2SO_4, and concentrated *in vacuo*. Recrystallization from $CHCl_3$ and hexane afforded 2-[2-(1*H*-indol-3-yl)ethyl]isoindoline-1,3-dione (14.9 g, 89%) as a yellow solid. *Rf* 0.31 (alumina, CH_2Cl_2). mp 167.0—167.8 °C (lit. 164 °C).[44] ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.99 (1H, br s), 7.84 (2H, dd, J_1=3.0 Hz, J_2=5.4 Hz), 7.74 (1H, d, J=7.6 Hz), 7.70 (2H, dd, J_1=3.0 Hz, J_2=5.4 Hz), 7.35 (1H, d, J=7.6 Hz), 7.19 (1H, dd, J_1=J_2=7.6 Hz), 7.13 (1H, dd, J_1=J_2=7.6 Hz), 7.10 (1H, s), 4.01 (2H, t, J=7.8 Hz), 3.16 (2H, t, J=7.8 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 168.7, 136.4, 134.1, 132.4, 127.6, 123.4, 122.33, 122.25, 119.7, 119.1, 112.6, 111.3, 38.6, 24.6. IR (KBr) cm^{-1}: 3355, 1707, 1396, 1103, 745, 713. LR-MS (FAB) m/z=290 (M^+).

***tert*-Butyl 3-[2-(1,3-Dioxoisoindolin-2-yl)ethyl]-1*H*-indole-1-carboxylate** A solution of 2-[2-(1*H*-indol-3-yl)ethyl]isoindoline-1,3-dione (5.33 g, 18.4 mmol) in DMF (60 ml) was added sodium hydride (55% purity, 1.08 g, 24.8 mmol) at 0 °C. After stirring for 20 min, di-*tert*-butyl dicarbonate (4.87 g, 22.3 mmol) and DMF (20 ml) was added. The suspension was stirred for 45 min at 40 °C, cooled to 0 °C, and then hexane and water were added. The appeared brown solid was collected by filtration and dissolved with $CHCl_3$. This solution was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Recrystallization from $CHCl_3$ and Et_2O afforded *tert*-butyl 3-[2-(1,3-dioxoisoindolin-2-yl)ethyl]-1*H*-indole-1-carboxylate (4.48 g, 62%) as a light brown crystal. *Rf* 0.44 (alumina, CH_2Cl_2). mp 149.0—149.8 °C. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 8.13 (1H, br d, J=7.7 Hz), 7.86 (2H, dd, J_1=3.0 Hz, J_2=5.5 Hz), 7.73 (2H, dd, J_1=3.0 Hz, J_2=5.5 Hz), 7.68 (1H, d, J=7.7 Hz), 7.48 (1H, br s), 7.32 (1H, ddd, J_1=0.9 Hz, J_2=J_3=7.7 Hz), 7.26 (1H, ddd, J_1=0.9 Hz, J_2=J_3=7.7 Hz), 4.00 (2H, t, J=7.9 Hz), 3.08 (2H, t, J=7.9 Hz), 1.66 (9H, s). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 168.5, 149.9, 135.8, 134.2, 132.4, 130.5, 124.7, 123.6, 123.5, 122.8, 119.2, 117.1, 115.5, 83.6, 37.8, 28.3, 24.4. IR (KBr) cm^{-1}: 1773, 1737, 1712, 1395, 1371, 765, 744, 716. LR-MS (FAB) m/z=390 (M^+). *Anal*. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17. Found: C, 70.51; H, 5.61; N, 7.17.

Tryptamine 3 A solution of *tert*-butyl 3-[2-(1,3-dioxoisoindolin-2-yl)ethyl]-1*H*-indole-1-carboxylate (2.41 g, 6.17 mmol) and hydrazine monohydrate (0.46 ml, 9.3 mmol) in 2-propanol (40 ml) and THF (10 ml) was refluxed. After 4 h, hydrazine monohydrate (0.095 ml, 1.92 mmol) was added and reflux was continued for additional 3.5 h. The reaction mixture was diluted with $CHCl_3$, insoluble materials were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was solved with $CHCl_3$, and aqueous $NaHCO_3$ was added. The layers were separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by alumina column chromatography (hexane/$CHCl_3$/MeOH=1/1/0→0/9/1) afforded tryptamine **3**[45] (1.50 g, 94%) as a yellow oil. *Rf* 0.22 (alumina, CH_2Cl_2/MeOH=5/5). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 8.13 (1H, br s), 7.54 (1H, d, J=7.9 Hz), 7.43 (1H, br s), 7.32 (1H, dd, J_1=J_2=7.9 Hz), 7.24 (1H, dd, J_1=J_2=7.9 Hz), 3.05 (2H, t, J=6.8 Hz), 2.84 (2H, t, J=6.8 Hz), 1.67 (9H, s), 1.25 (2H, br s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 150.0, 135.8, 130.8, 124.6, 123.4, 122.6, 119.2, 118.5, 115.5, 83.6, 41.7, 29.3, 28.3. IR (NaCl) cm^{-1}: 3372, 1732, 1607, 1454, 1379, 1255, 1159, 1090, 746. LR-MS (FAB) m/z=261 ($M+H^+$).

Amine (*E*)-17 A solution of benzyl ether (*E*)-**4** (751 mg, 2.70 mmol) and *p*-TsOH·H_2O (1.03 g, 5.42 mmol) in acetone (15 ml) and water (1.0 ml) was stirred for 3.5 h at 40 °C. After aqueous $NaHCO_3$ was added, the mixture was extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. This residue was dissolved with THF (9.0 ml), and added tryptamine **3** (857 mg, 3.30 mmol) and MS4A (3.77 g). After stirring for 2 h at 40 °C, MS4A was removed by filtration. To the filtrate, was added a solution of $NaBH_4$ (158 mg, 4.07 mmol) in MeOH (10 ml) at 0 °C. After stirring for 20 min at room temperature, water was added, and the mixture was extracted with EtOAc. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by alumina column chromatography (hexane/$CHCl_3$=5/5→0/1) afforded amine (*E*)-**17** (1.07 g, 83%) as a colorless oil. *Rf* 0.39 (alumina, CH_3Cl/MeOH=9/1). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.13 (1H, br d, J=8.0 Hz), 7.55 (1H, d, J=7.6 Hz), 7.42 (1H, br s), 7.34—7.21 (7H, m), 5.34 (1H, t, J=6.6 Hz), 4.49 (2H, s), 4.02 (2H, d, J=6.6 Hz), 2.95 (2H, t, J=5.8 Hz), 2.89 (2H, t, J=5.8 Hz), 2.64 (2H, t, J=7.4 Hz), 2.08—2.01 (4H, m), 1.66—1.57 (11H, m), 0.94 (3H, t, J=7.6 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 149.9, 146.0, 138.7, 135.7, 130.8, 128.5, 127.9, 127.6, 124.5, 123.1, 122.5, 120.7, 119.1, 118.9, 115.4,

83.5, 72.1, 66.4, 49.9, 49.3, 34.3, 28.5, 28.4, 25.9, 23.7, 13.5. IR (NaCl) cm^{-1}: 2932, 1730, 1453, 1374, 1254, 1159, 1088. LR-MS (FAB) m/z=477 ($M+H^+$). *Anal.* Calcd for $C_{30}H_{40}N_2O_3$: C, 75.59; H, 8.46; N, 5.88. Found: C, 75.41; H, 8.65; N, 5.89.

Amine (*Z*)-17 A solution of benzyl ether (*Z*)-**4** (425 mg, 1.53 mmol) and *p*-TsOH·H_2O (576 mg, 3.03 mmol) in acetone (10 ml) and water (0.5 ml) was stirred for 3 h at 40 °C. After adding aqueous $NaHCO_3$, the mixture was extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. To a solution of this residue in THF (5.1 ml), were added tryptamine **3** (615 mg, 2.37 mmol) and MS4A (2.12 g). After stirring for 2 h at 40 °C, MS4A was removed by filtration. To the filtrate, was added a solution of $NaBH_4$ (98% purity, 88.6 mg, 2.28 mmol) in MeOH (8.0 ml) at 0 °C. After stirring for 1 h at room temperature, water was added, and the mixture was extracted with EtOAc. The combined extracts were washed with water, brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by alumina column chromatography (hexane/$CHCl_3$=5/5→$CHCl_3$/MeOH=9/1) afforded amine (*Z*)-**17** (451 g, 62%) as a colorless oil. *Rf* 0.45 (alumina, CH_3Cl/MeOH=9/1). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.13 (1H, br d, J=7.8 Hz), 7.54 (1H, d, J=7.8 Hz), 7.41 (1H, br s), 7.35—7.22 (7H, m), 5.38 (1H, t, J=6.7 Hz), 4.48 (2H, s), 4.01 (2H, d, J=6.7 Hz), 2.95—2.86 (4H, m), 2.58 (2H, t, J=7.2 Hz), 2.07—2.01 (4H, m), 1.66 (9H, s), 1.58—1.49 (2H, m), 1.01 (3H, t, J=7.5 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 149.8, 145.7, 138.6, 135.6, 130.7, 128.4, 127.9, 127.6, 124.4, 123.0, 122.4, 120.1, 119.0, 118.8, 115.4, 83.4, 72.2, 66.4, 49.8, 49.3, 29.4, 29.0, 28.5, 28.3, 25.8, 12.5. IR (NaCl) cm^{-1}: 2932, 1731, 1453, 1373, 1254, 1159, 1088. LR-MS (FAB) m/z=477 ($M+H^+$). *Anal.* Calcd for $C_{30}H_{40}N_2O_3$: C, 75.59; H, 8.46; N, 5.88. Found: C, 75.85; H, 8.55; N, 5.83.

Chloroformamide (*E*)-2 To a solution of triphosgene (349 mg, 1.18 mmol) in THF (10 ml) was added triethylamine (0.59 ml, 4.22 mmol) followed by amine (*E*)-**17** (1.42 g, 2.98 mmol) in THF (10 ml) at −78 °C. The reaction mixture was warmed to room temperature, stirred for 1.5 h at 70 °C, and aqueous 1 M HCl was added at 0 °C. The mixture was extracted with EtOAc, and the combined organic extracts were washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc=1/0→9/1) afforded chloroformamide (*E*)-**2** (1.29 g, 80%) as a colorless oil. *Rf* 0.45 (silica gel, hexane/EtOAc=8/2). ^{1}H-NMR* ($CDCl_3$, 400 MHz) δ: 8.14 (1H, br d, J=7.3 Hz), 7.56 (1H, dd, J_1=7.8 Hz, J_2=10.5 Hz), 7.42 (1H, br s), 7.34—7.22 (7H, m), 5.35 (1H, t, J=6.8 Hz), 4.50 (2H, s), 4.02 (2H, d, J=6.8 Hz), 3.72—3.61 (2H, m), 3.38—3.32 (2H, m), 3.06—3.00 (2H, m), 2.06—2.00 (4H, m), 1.78—1.70 (2H, m), 1.67 (9H, s), 0.95 (3H, t, J=7.6 Hz). ^{13}C-NMR* ($CDCl_3$, 125 MHz) δ: 149.8, 149.3, 149.1, 144.7, 144.4, 138.6, 138.6, 135.7, 130.3, 130.2, 128.5, 127.9, 127.7, 124.83, 124.76, 123.5, 122.8, 121.6, 121.4, 118.9, 118.7, 116.9, 116.6, 115.6, 115.5, 83.9, 83.8, 72.43, 72.36, 66.3, 51.9, 51.4, 50.4, 50.3, 33.4, 33.3, 28.4, 26.7, 25.8, 24.7, 23.7, 23.4, 13.5. IR (NaCl) cm^{-1}: 2971, 1733, 1454, 1375, 1255, 1157, 1088. LR-MS (FAB) m/z=538 (M^+). *Anal.* Calcd for $C_{31}H_{39}ClN_2O_4$: C, 69.06; H, 7.29; N, 5.20. Found: C, 69.08; H, 7.09; N, 5.18 (* *ca.* 1 : 1 mixture of rotamers).

Chloroformamide (*Z*)-2 To a solution of triphosgene (69.8 mg, 0.235 mmol) in THF (1.0 ml) was added a solution of triethylamine (0.11 ml, 0.786 mmol) and amine (*Z*)-**17** (273 mg, 0.573 mmol) in THF (4.0 ml) at −78 °C. The reaction mixture was warmed up to 70 °C, and stirred for 2 h. After successive addition of water and 1 M HCl at 0 °C, the mixture was extracted with EtOAc. The combined organic extracts were washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc=1/0→9/1) afforded chloroformamide (*Z*)-**2** (282 mg, 91%) as a colorless oil. *Rf* 0.46 (silica gel, hexane/EtOAc=8/2). ^{1}H-NMR* ($CDCl_3$, 400 MHz) δ: 8.14 (1H, br d, J=7.1 Hz), 7.54 (1H, dd, J_1=7.8 Hz, J_2=10.7 Hz), 7.41 (1H, br s), 7.36—7.23 (7H, m), 5.45—5.40 (1H, m), 4.49 (2H, s), 3.98—3.94 (2H, m), 3.67—3.56 (2H, m), 3.29—3.25 (2H, m), 3.02—2.97 (2H, m), 2.05—1.99 (4H, m), 1.67 (11H, s), 1.01 (3H, t, J=7.4 Hz). ^{13}C-NMR* ($CDCl_3$, 125 MHz) δ: 149.7, 149.2, 148.9, 144.7, 144.5, 138.4, 138.4, 135.6, 130.2, 130.1, 128.4, 127.9, 127.70, 127.66, 124.76, 124.68, 123.4, 122.8, 120.9, 120.8, 118.8, 118.6, 116.8, 116.5, 115.54, 115.45, 83.8, 83.7, 72.4, 66.2, 66.1, 51.8, 51.2, 50.3, 50.2, 29.3, 28.29, 28.26, 27.8, 27.7, 27.2, 26.3, 24.6, 23.3, 12.5. IR (NaCl) cm^{-1}: 2968, 1734, 1454, 1376, 1256, 1158, 1088. LR-MS (FAB) m/z=538 (M^+). *Anal.* Calcd for $C_{31}H_{39}ClN_2O_4$: C, 69.06; H, 7.29; N, 5.20. Found: C, 69.06; H, 7.35; N, 5.19 (* *ca.* 1 : 1 mixture of rotamers).

Piperidone 1 A suspension of [Pd(η^3-C_3H_5)Cl]$_2$ (3.63 mg, 9.72 μmol), *t*-BuOK (90% purity, 3.59 mg, 28.8 mmol), phosphoramidite **L7** (39.8 mg, 73.8 μmol), K_3PO_4 (83.2 mg, 0.385 mmol) and Ag_3PO_4 (39.1 mg, 91.5 μmol) in xylene (1.0 ml) was stirred for 30 min at 40 °C. To this suspension, a solution of chloroformamide (*E*)-**2** (100 mg, 0.186 mmol) in xylene (3.0 ml) was added. After stirring for 5 h at 130 °C, the reaction mixture was cooled to room temperature, and water was added, and the product was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/$CHCl_3$/Et_2O=1/0/0→60/16/24) afforded a mixture containing enol ether, which was added acetone (3.0 ml), water (0.1 ml) and *p*-TsOH·H_2O (36.5 mg, 0.192 mmol). After stirring for 100 min at 30 °C, aqueous $NaHCO_3$ was added, and the product was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc=1/0→6/4) afforded piperidone **1** (39.8 mg, 52%) as a light yellow oil. Enantiomeric excess (ee) was measured by HPLC analysis with chiralcel AS-H column (hexane/2-propanol=95/5, 0.5 ml/min, 254 nm) t_R: 36.9 min (*S*, minor), 44.9 min (*R*, major) (43% ee). *Rf* 0.30 (silica gel, hexane/EtOAc=6/4). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 9.79 (1H, dd, J_1=1.2 Hz, J_2=2.4 Hz), 8.13 (1H, br d, J=7.8 Hz), 7.62 (1H, d, J=7.8 Hz), 7.43 (1H, br s), 7.31 (1H, dd, J_1=J_2=7.8 Hz), 7.24 (1H, dd, J_1=J_2=7.8 Hz), 3.69—3.57 (2H, m), 3.40—3.34 (1H, m), 3.25—3.20 (1H, m), 2.96 (2H, t, J=7.6 Hz), 2.86 (1H, dd, J_1=1.2 Hz, J_2=16.4 Hz), 2.43 (1H, dd, J_1=2.4 Hz, J_2=16.4 Hz), 1.85—1.68 (6H, m), 1.66 (9H, s), 0.90 (3H, t, J=7.5 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 201.7, 173.8, 149.9, 135.7, 130.7, 124.5, 123.3, 122.7, 119.2, 118.0, 115.4, 83.5, 51.5, 49.0, 48.3, 43.7, 31.0, 30.1, 28.3, 22.8, 19.6, 8.3. IR (NaCl) cm^{-1}: 2937, 1727, 1629, 1454, 1377, 1255, 1158. LR-MS (FAB) m/z=413 ($M+H^+$). $[\alpha]_D$ −0.9 (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.58; H, 8.00; N, 6.56.

Methyl Ester 18 A mixture of piperidone **1** (149 mg, 0.361 mmol), 2-methyl-2-butene (1.0 ml), $NaClO_2$ (80% purity, 143 mg, 1.27 mmol), NaH_2PO_4·$2H_2O$ (141 mg, 0.904 mmol) in *t*-BuOH (3.0 ml) and water (1.5 ml) was stirred for 2 h. After adding saturated aqueous NH_4Cl, the mixture was extracted with $CHCl_3$. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. This residue was dissolved in CH_3CN (3.0 ml), and Cs_2CO_3 (142 mg, 0.436 mmol) and MeI (0.025 ml, 0.40 mmol) were added at 0 °C. After stirring for 2.5 h, water was added, and. the mixture was extracted with $CHCl_3$. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/EtOAc=1/0→6/4) afforded methyl ester **18** (144 mg, 90%) as a colorless oil. *Rf* 0.41 (silica gel, hexane/EtOAc=6/4). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.13 (1H, br d, J=7.5 Hz), 7.65 (1H, d, J=7.5 Hz), 7.44 (1H, br s), 7.31 (1H, dd, J_1=J_2=7.5 Hz), 7.24 (1H, dd, J_1=J_2=7.5 Hz), 3.71—3.57 (5H, m), 3.46—3.40 (1H, m), 3.22—3.18 (1H, m), 3.02—2.91 (3H, m), 2.43 (1H, d, J=16.1 Hz), 1.98—1.55 (15H, m), 0.89 (3H, t, J=7.6 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 174.1, 172.6, 149.9, 135.7, 130.7, 124.5, 123.3, 122.6, 119.3, 118.3, 115.3, 83.4, 51.5, 49.1, 48.5, 43.5, 42.2, 31.6, 29.4, 28.4, 22.8, 20.0, 8.7. IR (NaCl) cm^{-1}: 2942, 1733, 1635, 1454, 1377, 1255, 1160. LR-MS (FAB) m/z=443 ($M+H^+$). $[\alpha]_D$ −0.4 (c=0.99, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{34}N_2O_5$: C, 67.85; H, 7.74; N, 6.33. Found: C, 67.42; H, 7.78; N, 6.24.

Indole 19 A solution of methyl ester **18** (144 mg, 0.325 mmol) in CH_3CN (4.0 ml) was irradiated microwave for 4 h at 200 °C, using a maximum irradiation power of 150 W. The reaction mixture was concentrated *in vacuo*, and purification by silica gel column chromatography (hexane/EtOAc=1/0→6/4) afforded indole **19** (110 mg, 99%) as a colorless oil. *Rf* 0.53 (silica gel, hexane/EtOAc=3/7). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.19 (1H, br s), 7.68 (1H, d, J=7.8 Hz), 7.35 (1H, d, J=7.8 Hz), 7.18 (1H, dd, J_1=J_2=7.8 Hz), 7.11 (1H, dd, J_1=J_2=7.8 Hz), 7.06 (1H, s), 3.67—3.63 (5H, m), 3.42—3.36 (1H, m), 3.22—3.17 (1H, m), 3.03 (2H, t, J=7.7 Hz), 2.96 (1H, d, J=16.1 Hz), 2.35 (1H, d, J=16.1 Hz), 1.99—1.60 (6H, m), 0.88 (3H, t, J=7.7 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 174.0, 172.7, 136.5, 127.7, 122.3, 122.1, 119.4, 119.1, 113.6, 111.3, 51.6, 49.1, 49.0, 43.6, 42.2, 31.7, 29.4, 23.1, 20.1, 8.8. IR (NaCl) cm^{-1}: 3268, 2946, 1736, 1615, 1492, 1457, 1435, 1355, 1198, 742. LR-MS (FAB) m/z=343 ($M+H^+$). $[\alpha]_D$ −1.9 (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 69.92; H, 7.83; N, 7.88.

(−)-Epieburnamonine (20) A solution of indole **19** (110 mg, 0.321 mmol) and $POCl_3$ (0.120 ml, 1.28 mmol) in anhydrous CH_3CN (4.0 ml) was irradiated microwave for 3.5 h at 120 °C, using a maximum irradiation power of 150 W. Then the reaction mixture was added dropwise into a solution of $NaBH_4$ (248 mg, 6.40 mmol) in MeOH (16 ml) at 0 °C. After stirring for 25 min, water was added, and the mixture was extracted

with $CHCl_3$. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexane/$CHCl_3$=2/8→0/1) afforded (−)-epieburnamonine (**20**) (55.8 mg, 59%) as a light yellow solid. *Rf* 0.51 (silica gel, hexane/EtOAc=6/4). mp 125.7—127.0 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.33 (1H, dd, J_1=2.0 Hz, J_2=6.3 Hz), 7.41 (1H, dd, J_1=2.0 Hz, J_2=6.3 Hz), 7.31—7.06 (2H, m), 3.12—3.05 (3H, m), 2.92—2.83 (1H, m), 2.80 (1H, d, J=15.6 Hz), 2.66 (1H, br d, J=15.9 Hz), 2.53 (1H, ddd, J_1=4.4 Hz, J_2=J_3=11.4 Hz), 2.36 (1H, dd, J_1=1.9 Hz, J_2=15.6 Hz), 2.31 (1H, dd, J_1=2.9 Hz, J_2=11.0 Hz), 1.95—1.83 (3H, m), 1.66—1.57 (1H, m), 1.24—1.16 (1H, m), 0.87—0.76 (4H, m). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 167.8, 135.2, 133.5, 130.1, 124.2, 124.0, 118.3, 116.4, 113.1, 66.1, 55.6, 52.4, 44.4, 39.6, 32.0, 21.7, 21.4, 20.9, 7.5. IR (KBr) cm^{-1}: 2928, 1706, 1655, 1457, 1365, 751. LR-MS (FAB) m/z=295 (M+H$^+$). $[\alpha]_D$ −62.3 (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.24; H, 7.52; N, 9.23.

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