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A CONCISE APPROACH TO (±)-TUBIFOLINE BASED ON THE PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF INDOLYLBORATE

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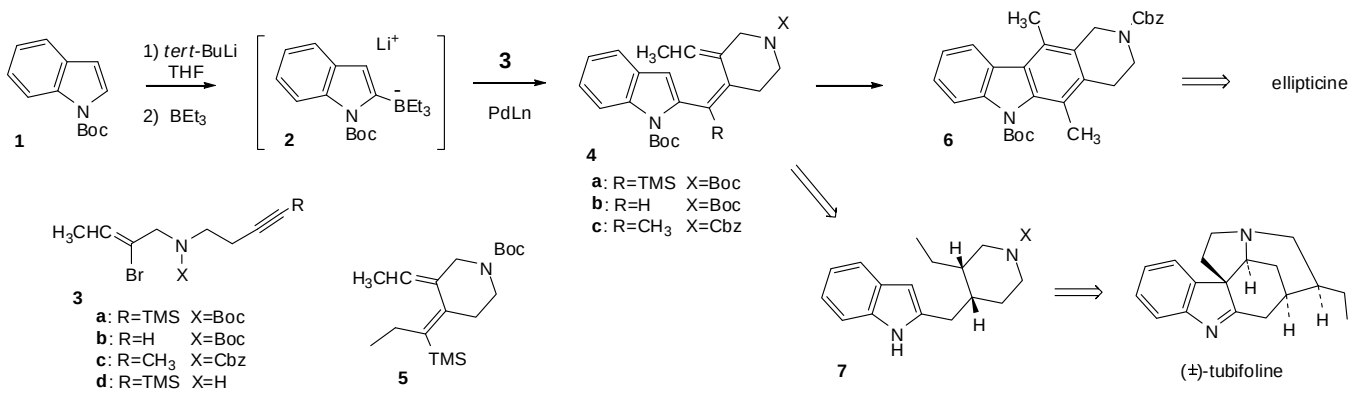
Abstract – The palladium-catalyzed tandem cyclization-cross-coupling protocol using 1*H*-indol-2-yltrialkylborate (indolylborate) proved to be a versatile approach to the generation of 2-(4-piperidylmethyl)indole, which was successfully used for the preparation of (±)-tubifoline.

The synthesis of *Strychnos* indole alkaloids has been an area of intensive research, and there are a numerous reports of the synthesis of this alkaloid group.[1] Among them, 2-(4-piperidylmethyl)indole **7** has been developed as a profitable synthetic intermediate for further construction of the pentacyclic skeleton of *Strychnos* alkaloids.[2] In the course of our continuous investigation of the synthetic potential of 1*H*-indol-2-yltrialkylborates (indolylborates) generated from the corresponding indoles and trialkylboranes *in situ*,[3] we have previously disclosed the high reactivity of indolylborate **2** in the palladium-catalyzed cross-coupling reaction.[4] During these studies, the palladium-catalyzed tandem cyclization-cross-coupling reaction of **2** with bromide **3c** was successfully used for the novel synthesis of



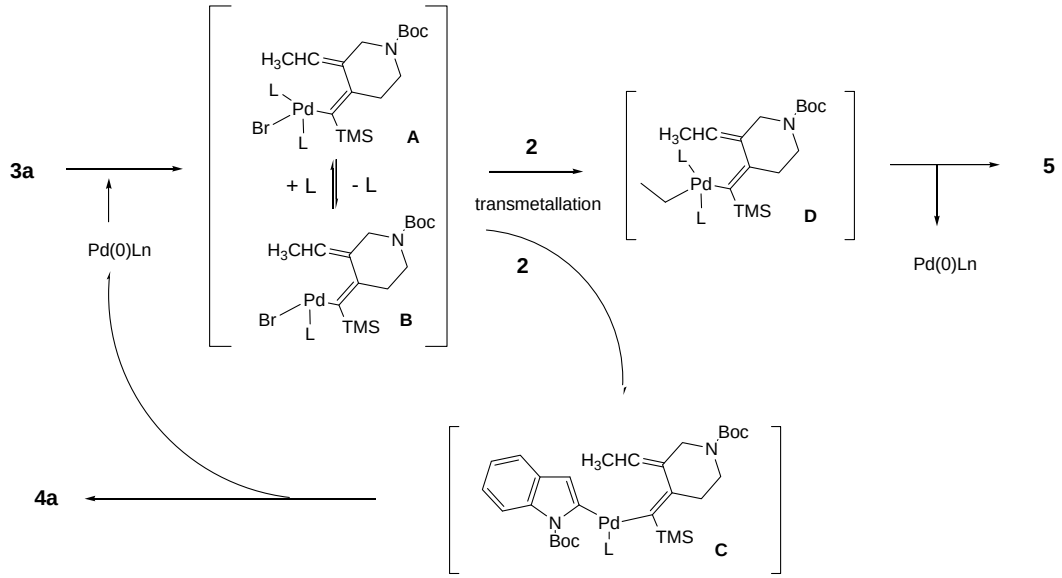
Scheme 1

ellipticine through the one-pot generation of hexatriene **4c** and the subsequent ring-closure of **4c** to pyridocarbazole core **6** as key features[5] (Scheme 1).

From a structural perspective, a concise alternative for the formation of 2-(4-piperidylmethyl)indole **7** was envisioned *via* the catalytic hydrogenation of **4**. Herein, we describe a concise approach to (±)-tubifoline based on **4** readily available from the cross-coupling reaction of **2** with **3**.

In accordance with our preliminary investigation,[6] the successful route to **7** was assumed to involve the catalytic hydrogenation of **4b** (R=H) having no substituents on the olefinic carbon. Thus, the straightforward approach to obtaining the requisite **4b** was the subjection of **3b** to the cross-coupling reaction with **2**, but this approach was not practicable due to the formation of a complex mixture. Alternatively, the reaction of **2** with **3a** having TMS group on the alkyne terminus was undertaken in the presence of Pd complex (5 mol%) with or without triphenylphosphine (PPh_3) in THF at 60°C according to the previous conditions.[5] However, we were confronted with the serious problem of the significant suppression of the reaction, ascribable to the intervention of severe steric repulsion between the TMS group and the *N*-Boc group of the indole ring (N^a-Boc group) in the transmetallation step, resulting in the formation of only trace amounts of **4a** along with substantial amounts of **5**. After efforts to influence the reaction by varying solvent, temperature, and Pd catalyst, a profound improvement in the yield of **4a** was realized by the use of $Pd(OAc)_2$ (5 mol%) with tri-*o*-tolylphosphine [(*o*-Tol)$_3$P] (10 mol%) in DME at 85°C (Table). Under the microwave irradiation, the reaction of **2** with **3a** using $PdCl_2[(o\text{-Tol})_3P]_2$ in dioxane inefficiently resulted in a low yield of **4a** with the predominant formation of **5**.

In terms of a common mechanistic feature (Scheme 2),[7] the coordination-transmetallation step is presumed to proceed through complex **A** when L is a moderately bulky ligand or through complex **B**,



Scheme 2

generated by prior dissociation of one ligand, when L is a bulky ligand. The ligation of bulky (*o*-Tol)$_3$P to the Pd displaces the equilibrium between **A** and **B** in favor of the less crowded complex **B**, which promptly promotes the transfer of the indole ring of **2** in the reaction with **3a**, leading to **4a** *via* complex **C**. Otherwise, competitive transfer of the less bulky ethyl group in the transmetallation between **A** and **2** might allow the formation of **5** *via* complex **D**.

Table Cross-coupling reaction of **2** with **3a**

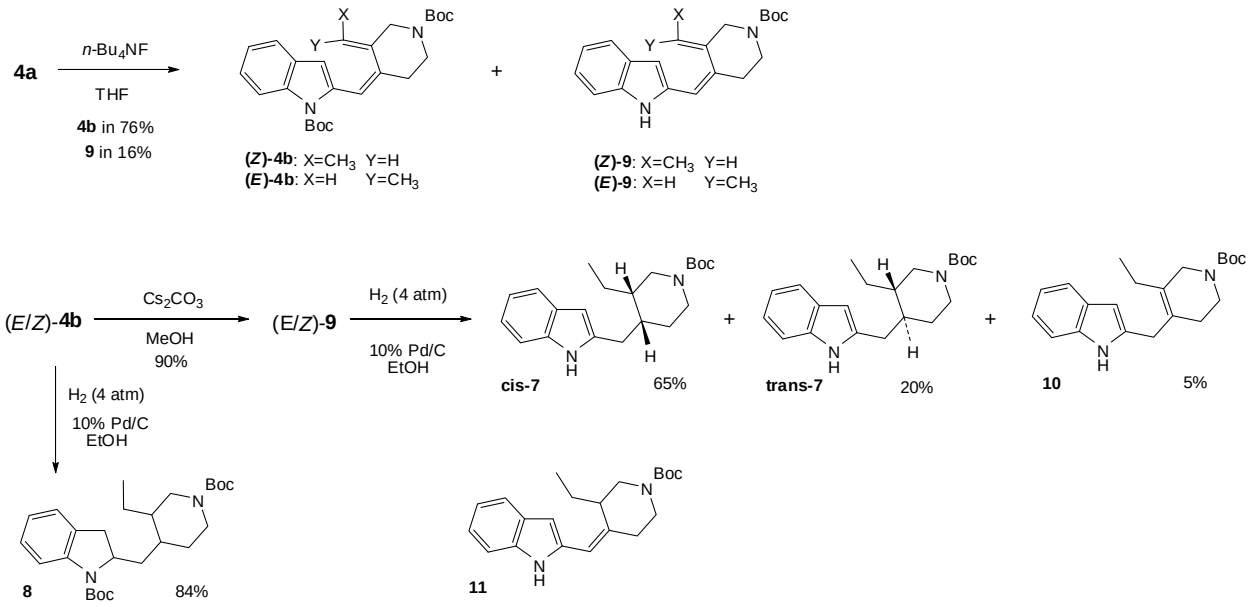
			yield (%)[a]	
solvent	PdLn	conditions	**4**	**5**
THF	$Pd(OAc)_2$	60 °C / 3 h	7	56
THF	$Pd(OAc)_2$+2PPh_3	60 °C / 3 h	8	50
THF	$PdCl_2(PPh_3)_2$	60 °C / 3 h	6	55
DME	$Pd(OAc)_2$	85 °C / 3 h	14	35
DME	$PdCl_2(CH_3CN)_2$	85 °C / 3 h	16	24
DME	$Pd(OAc)_2$+2PPh_3	85 °C / 3 h	10	45
DME	$PdCl_2(PPh_3)_2$	85 °C / 3 h	11	50
DME	$PdCl_2$[(*o*-Tol)$_3$P]$_2$	85 °C / 3 h	48	20
DME	$Pd(OAc)_2$+2(*o*-Tol)$_3$P	85 °C / 3 h	55	18
DME	$PdCl_2$[(*c*-Hex)$_3$P]$_2$	85 °C / 3 h	14	33
DME	$Pd(OAc)_2$+Ln1[b]	85 °C / 3 h	29	18
DME	$Pd(OAc)_2$+Ln2[c]	85 °C / 3 h	19	47
DMF	$PdCl_2$[(*o*-Tol)$_3$P]$_2$	100 °C / 3 h	35	32
toluene	$PdCl_2$[(*o*-Tol)$_3$P]$_2$	100 °C / 3 h	15	40
dioxane	$PdCl_2$[(*o*-Tol)$_3$P]$_2$	100 °C / 3 h	24	35
dioxane[d]	$PdCl_2$[(*o*-Tol)$_3$P]$_2$	100 °C / 1 h	10	50

[a] based on bromide (**3a**)
[b] Ln1: 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl[8]
[c] Ln2:1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride[9]
[d] microwave irradiation

With optimized conditions to obtain the requisite **4a** in hand, we next set about the conversion of **4a** to **7** (Scheme 3). Removal of the TMS group of **4a** was readily effected by treatment with *n*-Bu_4NF in THF at room temperature for 10 min to produce (*E*)- and (*Z*)-**4b** in 76% yield along with a small amount of (*E*)- and (*Z*)-**9** in 16% yield.

Attempted catalytic hydrogenation of **4b** using 10% Pd/C in EtOH even under medium pressure (4 atm) resulted in the formation of indoline **8** as a mixture of stereoisomers. As the precedent for the catalytic hydrogenation of *N*-acylindoles into *N*-acylindolines under high-pressure (50 atm) conditions exists in the literature,[10] the N^a-Boc group of **4b** was removed, prior to catalytic reduction, by treatment with Cs_2CO_3

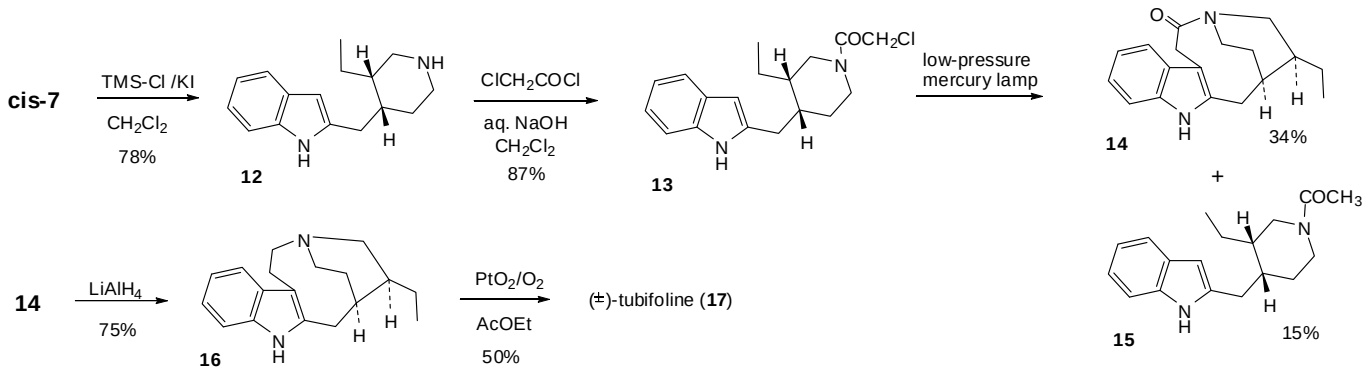
in MeOH under reflux, affording **9**. Treatment of **4a** with excess amounts of *n*-Bu_4NF in THF under reflux overnight also afforded **9** but in slightly smaller amounts (65% yield). Then, the exposure of **9** to



Scheme 3

the catalytic hydrogenation produced ***cis*-7** and ***trans*-7** along with a minor amount of **10**.[6] The use of PtO_2 as a hydrogenation catalyst did not improve the ratio of products in favor of ***cis*-7**. Moreover, a small amount of **11** was incidentally isolated along with **7** and **10** on the reduction performed using a large amount of **9**. Since the catalytic hydrogenation of **11** under the same conditions reproduced ***cis*-7**, ***trans*-7** and **10** in the same ratio, the reduction of the diene moiety of **9** is assumed to take place through the initial reduction of the ethylidene group, followed by reduction or isomerization of the intact double bond remained, leading to **7** and **10**, respectively.

Removal of the *N*-Boc group of ***cis*-7** was effected by treatment with chlorotrimethylsilane and potassium



Scheme 4

iodide in CH_2Cl_2 at room temperature, smoothly leading to **12** (Scheme 4).

Next, the conversion of **12** to (±)-tubifoline (**17**) was undertaken according to the literature.[2e] Exposure of **12** to the reaction with chloroacetyl chloride produced **13**. Then, irradiation of **13** with a low-pressure mercury lamp in MeOH-H_2O at room temperature afforded **14** along with **15**. Subsequent reduction of **14** with $LiAlH_4$ in THF under reflux afforded **16**, and the oxidation of **16** led to (±)-tubifoline (**17**).

We have described herein a concise protocol for the generation of 2-(4-piperidylmethyl)indole **7** based on the palladium-catalyzed tandem cyclization-cross-coupling reaction of indolylborate **2** with **3a**, and the subsequent conversion of ***cis*-7** to (±)-tubifoline.

EXPERIMENTAL

Melting points were recorded on a Yamato MP21 and are uncorrected. MS and high-resolution MS spectra were recorded on a Micromass AutoSpec 3100 mass spectrometer. IR spectra were measured on a Hitachi Model 270-30 spectrometer. The NMR experiments were performed with a JEOL JNM-ECA500 spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference. Flash chromatography and medium pressure liquid chromatography (MPLC) were performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd.). Anhydrous THF and DME were purchased from Kanto Chemical Co., Ltd.

Preparation of 3a:

According to our previous report,[5] alkylation of (2*E*/2*Z*)-2-bromobut-2-en-1-amine with 4-(trimethylsilyl)but-3-yn-1-yl trifluoromethanesulfonate produced **3d** in 75% yield, and the subsequent treatment of **3d** with $(Boc)_2O$ afforded **3a** in 80% yield.

[(2*E*/2*Z*)-2-Bromobut-2-en-1-yl][4-(trimethylsilyl)but-3-yn-1-yl]amine 3d:

bp 95 °C / 1 mmHg. IR (neat): 2956, 2172, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (s, 9H), 1.66 &1.72 (two d, 3H, *J* = 6.9 Hz), 1.86 (br s, 1H), 2.37 (t, 2H, *J* = 6.8 Hz), 2.61 (t, 2H, *J* = 6.8 Hz), 3.44 (s, 2H), 5.89 (q, 1H, *J* = 6.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 0.18, 16.6, 21.1, 46.0, 86.1, 104.8, 125.2, 129.3. HR-MS *m/z*: Calcd for $C_{11}H_{20}BrNSi$: 273.0548. Found: 273.0547.

(2*E*/2*Z*)-*tert*-Butyl (2-Bromobut-2-en-1-yl)[4-(trimethylsilyl)but-3-yn-1-yl]carbamate 3a:

bp 125 °C / 1 mmHg. IR (neat): 2172, 1704 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (s, 9H), 1.41 and 1.44 (two s, 9H), 1.73 (d, 3H, *J* = 6.9 Hz), 2.38-2.48 (m, 2H), 3.28 and 3.33 (two t, 2H, *J* = 6.8 Hz), 4.13 and 4.18 (two s, 2H), 5.81-5.89 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ: 0.1, 15.1, 16.5, 19.6, 20.0, 28.3, 28.4, 45.3, 45.4, 55.1, 55.8, 80.2, 86.0, 86.1, 104.5, 104.9, 124.8, 124.9, 125.3, 154.9, 155.2. HR-MS *m/z*: Calcd for $C_{16}H_{28}BrNO_2Si$: 373.1072. Found: 373.1090.

Cross-coupling reaction of 2 with 3a in the presence of $Pd(OAc)_2$ and (*o*-Tol)$_3$P in DME:

To a THF (15 mL) solution of **1** (434 mg, 2 mmol) was added *tert*-BuLi (1.5M solution in *n*-pentane, 1.7

mL) at -78 °C under an argon atmosphere, and the mixture was stirred for 1 h. After BEt_3 (1M solution in hexane, 2.4 mL) was added, the mixture was gradually warmed to room temperature over 1 h and stirred for 30 min, generating a THF solution of **2**. The solvent was removed from the solution of **2** under reduced pressure, and DME (15 mL) was added under an argon atmosphere. Bromide (**3a**) (373 mg, 1 mmol), $Pd(OAc)_2$ (12 mg, 0.05 mmol) and P(*o*-Tol)$_3$ (28 mg, 0.1 mmol) were added, and the mixture was heated at 85 °C for 3 h. After cooling, 10% aq. NaOH (10 mL) and 30% aq. hydrogen peroxide (2 mL) solutions were added to the mixture under ice-cooling, and the mixture was stirred for 10 min. The mixture was diluted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by MPLC with AcOEt/hexane (7:1) as an eluent, giving **4a** and **5** as shown in Table.

(3*E*/3*Z*)-*tert*-Butyl 2-[(*E*)-[1-(*tert*-Butoxycarbonyl)-3-ethylidenepiperidin-4-ylidene](trimethylsilyl)-methyl]-1*H*-indole-1-carboxylate 4a:

mp 146-149 °C (hexane-AcOEt). IR ($CHCl_3$): 1724, 1628 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (s, 9H), 1.28 (d, 3H, *J* = 6.8 Hz), 1.45 (s, 9H), 1.66 (s, 9H), 2.36-2.42 (m, 1H), 2.68-2.78 (m, 1H), 3.00-3.30 (m, 1H), 3.42-3.60 (m, 1H), 3.90-4.10 (m, 1H), 4.10-4.32 (m, 1H), 5.15 (br s, 1H), 5.98 (s, 1H), 7.12-7.18 (m, 2H), 7.40 (d, 1H, *J* = 7.8 Hz), 7.89 (d, 1H, *J* = 8.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 0.4, 13.9, 28.3, 28.5, 35.5, 45.3, 55.0, 79.6, 83.5, 105.8, 115.5, 119.9, 121.7, 122.5, 122.7, 130.2, 133.9, 135.0, 136.1, 143.4, 146.7, 150.4, 154.8. MS *m/z*: 510 (M^+). *Anal.* Calcd for $C_{29}H_{42}N_2O_4Si$: C, 68.20; H, 8.29; N, 5.48. Found: C, 68.22; H, 8.53; N, 5.39.

(3*Z*/3*E*)-*tert*-Butyl (4*E*)-3-Ethylidene-4-[1-(trimethylsilyl)propylidene]piperidine-1-carboxylate 5:

IR (neat): 1674 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.16 and 0.17 (two s, 9H), 0.82 and 0.87 (two t, 3H, *J* = 7.5 Hz), 1.44 (s, 9H), 1.48 and 1.75 (two d, 3H, *J* = 7.4 Hz), 2.19 (q, 2H, *J* = 7.5 Hz), 2.10-2.19 (m, 0.5H), 2.35 (t, 1H, *J* = 5.5 Hz), 2.49-2.52 (m, 0.5H), 2.83-2.96 (m, 0.5H), 3.31-3.45 (m, 0.5H), 3.47 (t, 1H, *J* = 5.5 Hz), 3.97 (br s, 0.5H), 4.02-4.47 (m, 0.5H), 5.29-5.37 (m, 0.5H), 5.42-5.51 (m, 0.5H). ^{13}C-NMR ($CDCl_3$) δ: 1.1, 13.2, 14.8, 15.8, 16.7, 25.4, 25.9, 28.5, 36.1, 45.2, 46.2, 53.6, 55.1, 79.4, 120.3, 135.6, 136.3, 137.8, 144.4, 148.4, 154.8. HR-MS *m/z*: Calcd for $C_{18}H_{33}NO_2Si$: 323.2280. Found: 323.2265.

Reaction of 4a with *n*-Bu$_4$NF in THF:

n-Bu_4NF (1M solution in THF, 2 mL) was added to **4a** (500 mg, 0.98 mmol) in THF (25 mL), and the mixture was stirred at room temperature for 10 min. The mixture was then diluted with AcOEt, washed with brine, and dried over $MgSO_4$. The solvent was removed, and separation of the residue by MPLC with hexane/AcOEt (5:1) as an eluent allowed the isolation of **(*Z*)**- and **(*E*)-4b** (326 mg, 76%), and **(*Z*)**- and **(*E*)-9** (53 mg, 16%).

***tert*-Butyl 2-{(*Z*)-[(3*Z*)-1-(*tert*-Butoxycarbonyl)-3-ethylidenepiperidin-4-ylidene]methyl}-1*H*-indole-1-carboxylate (*Z*)-4b:**

IR ($CHCl_3$): 1724, 1678 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.64 (s, 9H), 1.83 (d, 3H, *J* = 6.9 Hz), 2.66 (t, 2H, *J*=5.1 Hz), 3.47 (br s, 2H), 3.98 (br s, 2H), 5.61 (br s, 1H), 6.50 (s, 1H), 6.68 (s, 1H), 7.20 (t, 1H, *J* = 7.5 Hz), 7.26 (t, 1H, *J* = 7.5 Hz), 7.49 (d, 1H, *J* = 7.5 Hz), 8.09 (d, 1H, *J* = 7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.7, 28.3, 28.5, 30.7, 44.5, 54.1, 79.6, 83.9, 110.1, 115.6, 120.3, 120.9, 122.9, 124.1, 129.3, 135.7, 136.1, 136.2, 150.4, 154.7. HRMS *m/z*: Calcd for $C_{26}H_{34}N_2O_4$: 438.2519. Found: 438.2518.

***tert*-Butyl 2-{(*Z*)-[(3*E*)-1-(*tert*-Butoxycarbonyl)-3-ethylidenepiperidin-4-ylidene]methyl}-1*H*-indole-1-carboxylate (*E*)-4b:**

mp 139-140 °C (hexane-AcOEt). IR ($CHCl_3$): 1724, 1676 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (d, 3H, *J* = 6.9 Hz), 1.47 (s, 9H), 1.66 (s, 9H), 2.38-2.42 (m, 2H), 3.61-3.68 (m, 2H), 4.10-4.19 (m, 2H), 5.32-5.43 (m, 1H), 6.41 (br s, 1H), 6.65 (s, 1H), 7.18 (t, 1H, *J* = 7.5 Hz), 7.23 (t, 1H, *J* = 7.5 Hz), 7.41 (d, 1H, *J* = 7.5 Hz), 8.08 (d, 1H, *J* = 7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.2, 28.3, 28.5, 37.5, 45.3, 53.5, 79.7, 83.9, 108.8, 115.5, 119.1, 120.2, 122.5, 122.8, 123.8, 129.6, 133.1, 136.0, 136.4, 137.0, 150.5, 154.7. MS *m/z*: 438 (M^+). *Anal.* Calcd for $C_{26}H_{34}N_2O_4$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.26; H, 7.97; N, 6.25.

***tert*-Butyl (3*E*,4*Z*)-3-Ethylidene-4-(1*H*-indol-2-ylmethylene)piperidine-1-carboxylate (*E*)-9:**

IR ($CHCl_3$): 3396, 1686 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.53 (d, 3H, *J* = 6.8 Hz), 2.90-3.10 (m, 2H), 3.45-3.65 (m, 2H), 4.10-4.35 (m, 2H), 5.82 (s, 1H), 6.39 (s, 1H), 6.42 (s, 1H), 7.05 (t, 1H, *J* = 8.0 Hz), 7.13 (t, 1H, *J* = 7.5 Hz), 7.25 (d, 1H, *J* = 7.8 Hz), 7.53 (d, 1H, *J* = 7.5 Hz), 8.70 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 14.9, 29.4, 38.4, 45.9, 46.4, 52.3, 53.5, 79.9, 104.7, 110.5, 116.4, 119.9, 120.4, 122.5, 124.6, 128.0, 134.4, 135.4, 136.2, 136.6, 154.6. HR-MS *m/z*: Calcd for $C_{21}H_{26}N_2O_2$: 338.1994. Found: 338.2000.

***tert*-Butyl (3*Z*,4*Z*)-3-Ethylidene-4-(1*H*-indol-2-ylmethylene)piperidine-1-carboxylate (*Z*)-9:**

mp 156-157 °C (hexane-AcOEt). IR ($CHCl_3$): 3396, 1686 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.83 (d, 3H, *J* = 7.5 Hz), 2.77-2.85 (m, 2H), 3.49-3.60 (m, 2H), 3.99 (br s, 2H), 5.60-5.69 (m, 1H), 6.32 (s, 1H), 6.53 (s, 1H), 7.09 (t, 1H, *J* = 7.8 Hz), 7.16 (t, 1H, *J* = 7.5 Hz), 7.33 (d, 1H, *J* = 8.0 Hz), 7.58 (d, 1H, *J* = 8.0 Hz), 8.05 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 14.9, 28.5, 31.5, 42.0, 53.5, 79.7, 96.2, 103.4, 110.6, 118.7, 120.2, 120.5, 122.5, 123.1, 128.9, 134.8, 135.9, 154.6. MS *m/z*: 338 (M^+). *Anal.* Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.30; H, 7.89; N, 8.17.

***tert*-Butyl 4-(2,3-Dihydro-1*H*-indol-2-ylmethyl)-3-ethylpiperidine-1-carboxylate 8:**

Catalytic hydrogenation of **4b** (100 mg) was carried out using 10% Pd/C (10 mg) in EtOH (15 mL) under hydrogen (4 atm) for 12 h. The catalyst and solvent were removed, and the residue was separated by MPLC with hexane/AcOEt (5:1) as an eluent to give **8** (85 mg, 84%).

IR (neat): 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 and 0.96 (two t, 3H, *J* = 7.5 Hz), 1.15-1.28 (m, 2H), 1.31-1.49 (m, 6H), 1.47 (s, 9H), 1.55 (s, 9H), 1.70-2.10 (m, 2H), 2.60-3.00 (m, 2H), 3.21-3.35 (m, 1H), 3.55-4.10 (m, 1H), 4.36-4.60 (m, 1H), 6.93 (t, 1H, *J* = 8.0 Hz), 7.11-7.18 (m, 2H), 7.65-7.75 (m, 1H).

^{13}C-NMR ($CDCl_3$) δ: 11.1, 12.4, 13.2, 23.6, 28.5, 32.5, 33.2, 34.6, 36.2, 37.1, 39.4, 41.8, 43.5, 46.5, 46.8, 57.3, 79.2, 80.9, 115.8, 122.5, 124.9, 127.4, 130.5, 142.1, 152.4, 154.9, 155.2. HR-MS *m/z*: Calcd for $C_{26}H_{40}N_2O_4$: 444.2988. Found: 444.2988.

Removal of the *N*-Boc group of 4b:

A mixture of **4b** (560 mg, 1.28 mmol) and Cs_2CO_3 (1.3 g) in MeOH (20 mL) and THF (40 mL) was heated under reflux for 2 h. After cooling, the solvent was removed on a rotary evaporator, and the residue was diluted with AcOEt. The organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was separated by MPLC with hexane/AcOEt (10:1) as an eluent to give **9** (389 mg, 90%).

Catalytic hydrogenation of 9:

Catalytic hydrogenation of **9** (480 mg) was carried out using 10% Pd/C (40 mg) in EtOH (15 mL) under hydrogen (4 atm) overnight. The catalyst and solvent were removed, and the residue was separated by MPLC with hexane/AcOEt (10:1) as an eluent to give ***cis*-7** (485 mg, 65%), ***trans*-7** (97 mg, 20%) and **10** (24 mg, 5%).

***rel*-*tert*-Butyl (3*R*,4*S*)-3-Ethyl-4-(1*H*-indol-2-ylmethyl)piperidine-1-carboxylate *cis*-7:**

mp 155-156 °C (hexane-AcOEt). IR ($CHCl_3$): 3468, 3372, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (t, 3H, *J* = 7.4 Hz), 1.23-1.35 (m, 1H), 1.35-1.50 (m, 1H), 1.41-1.49 (m, 2H), 1.42 (s, 9H), 1.54-1.56 (m, 1H), 2.00 (br s, 1H), 2.67 (dd, 1H, *J* = 8.3, 15.0 Hz), 2.75 (dd, 1H, *J* = 6.5, 15.0 Hz), 2.70-3.10 (m, 2H), 3.68-3.90 (m, 1H), 3.90-4.05 (m, 1H), 6.23 (s, 1H), 7.06 (t, 1H, *J* = 7.5 Hz), 7.11 (t, 1H, *J* = 7.5 Hz), 7.29 (d, 1H, *J* = 8.0 Hz), 7.52 (d, 1H, *J* = 7.5 Hz), 7.86 (br s, 1H,). ^{13}C-NMR ($CDCl_3$) δ: 12.4, 17.0, 18.5, 27.2, 28.5, 29.5, 31.5, 39.7, 40.3, 43.3, 45.4, 46.6, 79.4, 100.5, 110.5, 119.6, 119.8, 121.0, 128.9, 136.0, 137.9, 155.3. MS *m/z*: 342 (M^+). *Anal.* Calcd for $C_{21}H_{30}N_2O_2$: C, 73.65; H, 8.83; N, 8.18. Found: C, 73.44; H, 9.02; N, 8.11.

***rel*-*tert*-Butyl (3*R*,4*R*)-3-Ethyl-4-(1*H*-indol-2-ylmethyl)piperidine-1-carboxylate *trans*-7:**

mp 127-128 °C (hexane-AcOEt). IR ($CHCl_3$): 3412, 3320, 1682 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (t, 3H, *J* = 7.5 Hz), 1.15-1.32 (m, 3H), 1.44 (s, 9H), 1.51-1.67 (m, 2H), 1.67-1.77 (m, 1H), 2.47 (t, 1H, *J* = 5.5 Hz), 2.69-2.80 (m, 1H), 2.40-2.82 (m, 1H), 3.09 (d, 1H, *J* = 14.3 Hz), 3.89 (d, 1H, *J* = 13.1 Hz), 3.85-4.25 (m, 1H,), 6.22 (s, 1H), 7.06 (t, 1H, *J* = 7.5 Hz), 7.11 (t, 1H, *J* = 7.5 Hz), 7.29 (d, 1H, *J* = 7.5 Hz), 7.52 (d, 1H, *J* = 7.5 Hz), 7.92 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 11.0, 23.6, 28.5, 30.8, 31.9, 40.5, 41.7, 43.0, 47.3, 79.4, 100.9, 110.4, 119.7, 119.8, 121.1, 128.9, 135.9, 137.6, 154.9. MS *m/z*: 342 (M^+). *Anal.* Calcd for $C_{21}H_{30}N_2O_2$: C, 73.65; H, 8.83; N, 8.18. Found: C, 73.62; H, 9.06; N, 8.08.

***tert*-Butyl 5-Ethyl-4-(1*H*-indol-2-ylmethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate 10:**

IR (neat): 1686 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.09 (t, 3H, *J* = 7.4 Hz), 1.46 (s, 9H), 2.02 (br s, 2H), 2.19 (q, 2H, *J* = 7.4 Hz), 3.41 (t, 2H, *J* = 3.4 Hz), 3.54 (s, 2H), 3.88 (br s, 2H), 6.23 (s, 1H), 7.06 (t, 1H, *J* = 7.5

Hz), 7.11 (t, 1H, *J* = 7.5 Hz), 7.29 (d, 1H, *J* = 8.0 Hz), 7.51 (d, 1H, *J* = 7.5 Hz), 7.81 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 13.6, 23.8, 28.1, 28.6, 31.3, 40.2, 45.6, 79.7, 100.6, 110.5, 119.7, 119.8, 121.2, 125.6, 128.9, 132.3, 136.1, 137.0, 155.0. HR-MS *m/z*: Calcd for $C_{21}H_{28}N_2O_2$: 340.2151. Found: 340.2150.

***tert*-Butyl (4*Z*)-3-Ethyl-4-(1*H*-indol-2-ylmethylene)piperidine-1-carboxylate 11:**

IR ($CHCl_3$): 3392, 1666 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 and 1.09 (two t, 3H, *J* = 7.5 Hz), 1.50 and 1.52 (two s, 9H), 1.68-1.74 (m, 2H), 2.06-2.20 (m, 2H), 2.44-2.55 (m, 1H), 2.55-2.65 (m, 1H), 3.01-3.09 (m, 1H), 3.25-3.33 (m, 1H), 3.63 and 3.71 (two dt, 1H, *J* = 12.6, 4.5 Hz), 6.27 (s, 1H), 6.61 and 6.78 (two s, 1H), 7.08 (t, 1H, *J* = 7.0 Hz), 7.13 (t, 1H, *J* = 7.0 Hz), 7.30 (d, 1H, *J* = 8.0 Hz), 7.54 (d, 1H, *J* = 7.5 Hz), 8.13 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 12.9, 13.1, 25.8, 26.0, 28.4, 31.7, 34.1, 38.0, 38.9, 80.7, 119.7, 119.8, 120.1, 120.5, 121.2, 121.8, 128.8, 136.1, 137.6, 152.4, 152.9. HR-MS *m/z*: Calcd for $C_{21}H_{28}N_2O_2$: 340.2151. Found: 340.2155.

***rel*-2-{[(3*R*,4*S*)-3-Ethylpiperidin-4-yl]methyl}-1*H*-indole 12:**

To a solution of ***cis*-7** (2.37 g, 6.9 mmol), powdered potassium iodide (23.3 g, 140 mmol) and a catalytic amount of 18-crown-6-ether in CH_2Cl_2 (200 mL), chlorotrimethylsilane (7.6 mL, 60 mmol) was added at room temperature, and the whole was stirred overnight. The mixture was concentrated on a rotary evaporator, and the residue was made alkaline with 10% aq. NaOH solution. The mixture was diluted with AcOEt, washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was washed with ether to give **12** (1.3 g, 78%) as crystals, which were used without further purification.

IR (neat): 3476 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (t, 3H, *J* = 7.5 Hz), 1.36-1.45 (m, 1H), 1.45-1.51 (m, 3H), 1.51-1.57 (m, 1H), 2.04-2.12 (m, 1H), 2.63-2.79 (m, 5H), 2.93 (dd,1H, *J* = 5.1, 12.5 Hz), 3.00 (dt, 1H, *J* = 12.5, 4.5 Hz), 6.23 (s, 1H), 7.06 (t, 1H, *J* = 7.5 Hz), 7.11 (t, 1H, *J* = 7.5 Hz), 7.29 (d, 1H, *J* = 7.5 Hz), 7.52 (d, 1H, *J* = 7.5 Hz), 8.04 (br s, 1H,). ^{13}C-NMR ($CDCl_3$) δ: 12.1, 19.2, 28.4, 29.7, 38.7, 39.9, 44.8, 47.9, 100.5, 110.4, 119.6, 119.8, 121.0, 128.9, 136.0, 138.2. HR-MS *m/z*: Calcd for $C_{16}H_{22}N_2$: 242.1783. Found: 242.1782.

***rel*-2-{[(3*R*,4*S*)-1-(Chloroacetyl)-3-ethylpiperidin-4-yl]methyl}-1*H*-indole 13:**

Chloroacetyl chloride (0.55 mL, 6.8 mmol) was added slowly to **12** (880 mg, 3.6 mmol) in CH_2Cl_2 (200 mL) and 10% aq. NaOH solution (100 mL) under ice-cooling, and the mixture was stirred for 1 h. The mixture was diluted with AcOEt, washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was separated by MPLC with hexane/AcOEt (1:1) as an eluent to give **13** (995 mg, 87%).

IR ($CHCl_3$): 3292, 1634 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 and 0.99 (two t, 3H, *J* = 7.4 Hz), 1.20-1.34 (m, 1H), 1.37-1.51 (m, 1H), 1.53-1.61 (m, 2H), 1.61-1.67 (m, 1H), 2.09-2.17 (m, 1H), 2.70 and 2.73 (two dd, 1H, *J* = 9.1, 14.7 Hz), 2.79 (dd, 1H, *J* = 6.3, 14.7 Hz), 3.10-3.18 (m, 1H), 2.95 and 3.26 (two dd, 1H, *J* = 3.4, 13.6 Hz), 3.55 and 4.24 (two dd,1H, *J* = 5.7, 13.6 Hz), 3.73 and 4.06 (two dt, 1H, *J* = 3.4, 13.6 Hz), 4.03 and 4.04 (two d, 1H, *J* = 11.9 Hz), 4.09 and 4.10 (two d, 1H, *J* = 11.9 Hz), 6.25 (s, 1H), 7.07 (t, 1H,

J = 7.5 Hz), 7.13 (dt, 1H, *J* = 1.2, 7.5 Hz), 7.30 (d, 1H, *J* = 8.5 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.90 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 12.5, 12.6, 18.0, 18.5, 27.0, 27.7, 29.5, 30.5, 38.9, 39.6, 40.0, 40.3, 41.1, 41.3, 41.4, 44.6, 46.1, 48.4, 100.9, 101.0, 110.4, 119.9, 121.3, 128.8, 136.0, 137.1, 137.3, 165.5, 165.7. HR-MS *m/z*: Calcd for $C_{18}H_{23}ClN_2O$: 318.1498. Found: 318.1491.

Irradiation of 13 with low-pressure mercury lamp:

A mixture of **13** (100 mg) and $NaHCO_3$ (200 mg) in MeOH (150 mL) and H_2O (150 mL) was irradiated with a low-pressure mercury lamp at room temperature for 1 h. The solvent was removed, and the residue was diluted with AcOEt, washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was separated by flash chromatography with CH_2Cl_2/MeOH (50:1) as an eluent to give **14** (30 mg, 34%) and **15** (13 mg, 15%).

***rel*-(5*S*,6*R*)-5-Ethyl-1,4,5,6,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indol-2-one 14:**

mp 274-275 °C (MeOH-AcOEt). IR ($CHCl_3$): 3470, 1616 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (t, 3H, *J* = 7.3 Hz), 1.26-1.38 (m, 2H), 1.45-1.56 (m, 2H), 1.80-1.87 (m, 1H), 2.13-2.20 (m, 1H), 2.62 (dd, 1H, *J* = 11.4, 15.9 Hz), 2.84 (dd, 1H, *J* = 6.3, 15.9 Hz), 3.04 (dd, 1H, *J* = 9.0, 13.0 Hz), 3.01-3.08 (m, 1H), 3.57 (ddt, 1H, *J* = 3.4, 10.2, 13.5 Hz), 3.67 (d, 1H, *J* = 15.9 Hz), 4.12 (d, 1H, *J* = 15.9 Hz), 4.37 (ddd, 1H, *J* = 2.8, 7.4, 13.0 Hz), 7.10 (dt, 1H, *J* = 1.2, 7.8 Hz), 7.15 (dt, 1H, *J* = 1.1, 7.8 Hz), 7.28 (d, 1H, *J* = 8.0 Hz), 7.41 (d, 1H, *J* = 8.0 Hz), 7.80 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 12.1, 25.1, 27.0, 27.5, 30.2, 33.1, 42.1, 42.6, 45.2, 105.8, 110.4, 117.8, 119.5, 121.7, 128.6, 133.8, 134.7, 172.8. MS *m/z*: 282 (M^+). *Anal.* Calcd for $C_{18}H_{22}N_2O$+1/10H_2O: C, 76.07; H, 7.87; N, 9.85. Found: C, 76.06; H, 7.95; N, 9.81.

***rel*-2-{[(3*R*,4*S*)-1-Acetyl-3-ethylpiperidin-4-yl]methyl}-1*H*-indole 15:**

IR ($CHCl_3$): 3404, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 and 0.99 (two t, 3H, *J* = 7.4 H), 1.21-1.29 (m, 1H), 1.34-1.61 (m, 4H), 2.07-2.11 (m, 1H), 2.10 and 2.11 (two s, 3H), 2.63-2.70 (m, 1H), 2.71-2.79 (m, 1H), 2.85 (ddd, 0.5H, *J* = 3.5, 10.9, 13.2 Hz), 2.99 (dd, 0.5H, *J* = 2.9, 13.2 Hz), 3.05-3.13 (m, 1H), 3.60-3.65 (m, 1H), 4.90 (dd, 0.5H, *J* = 4.0, 13.2 Hz), 4.31 (td, 0.5H, *J* = 4.0, 13.2 Hz), 6.23 (s, 1H), 7.08 (t, 1H, *J* = 7.5 Hz), 7.13 (t, 1H, *J* = 7.5 Hz), 7.30 (d, 1H, *J* = 7.5 Hz), 7.55 (d, 1H, *J* = 8.0 Hz), 8.71 and 8.73 (two s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 12.5, 12.7, 17.5, 18.3, 21.6, 21.7, 27.1, 27.8, 30.1, 30.5, 39.2, 39.7, 40.0, 40.2, 40.4, 41.2, 43.8, 45.8, 48.8, 100.4, 100.5, 110.6, 119.6, 119.8, 121.0, 128.8, 136.1, 136.2, 137.7, 137.9, 169.4, 169.7. HR-MS *m/z*: Calcd for $C_{18}H_{24}N_2O$: 284.188. Found: 284.1890.

***rel*-(5*S*,6*R*)-5-Ethyl-1,4,5,6,7,8-hexahydro-2*H*-3,6-ethanoazonino[5,4-*b*]indole 16:**

A mixture of **14** (92 mg, 0.32 mmol) and $LiAlH_4$ (15 mg, 40 mmol) in THF (5 mL) was heated under reflux for 3 h. After the mixture was treated with saturated aq. NH_4Cl solution under ice-cooling, insoluble materials were removed by filtration under suction. The filtrate was extracted with AcOEt, and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was separated by flash chromatography with AcOEt/diethylamine (50:1) as an eluent to give **16** (66 mg,

75%).

IR ($CHCl_3$): 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (t, 3H, *J* = 7.5 Hz), 1.29-1.38 (m, 2H), 1.73-1.89 (m, 3H), 2.40-2.48 (m, 1H), 2.52 (t, 1H, *J* = 12.0 Hz), 2.50-2.58 (m, 1H), 2.79 (dd, 1H, *J* = 6.9, 16.0 Hz), 2.85-3.04 (m, 3H), 2.99 (dd, 1H, *J* = 7.5, 12.0 Hz), 3.10 (dd, 1H, *J* = 7.5, 12.0 Hz), 3.12-3.26 (m, 2H), 7.09 (dt, 1H, *J* = 1.1, 7.5 Hz), 7.12 (dt, 1H, *J* = 1.7, 7.5 Hz), 7.29 (d, 1H, *J* = 7.5 Hz), 7.48 (d, 1H, *J* = 8.0 Hz), 8.05 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 12.1, 23.8, 24.8, 28.6, 30.1, 30.4, 38.2, 45.2, 48.6, 56.0, 110.4, 117.4, 119.1, 121.0, 128.5, 135.0, 135.9. HR-MS *m/z*: Calcd for $C_{18}H_{24}N_2$: 268.1939. Found: 268.1940.

(±)-Tubifoline (17)[2e]

After treatment of PtO_2 (30 mg) in AcOEt (5 mL) under hydrogen for 10 min, **16** (36 mg) was added, and hydrogen was replaced with oxygen. The mixture was stirred at room temperature for 3 h, and the catalyst was removed by filtration. The filtrate was concentrated on a rotary evaporator, and the residue was separated by flash chromatography with AcOEt/diethylamine (30:1) as an eluent to give (±)-**17** (18 mg, 50%).

^{1}H-NMR ($CDCl_3$) δ: 0.94 (t, 3H, *J* = 7.9 Hz), 1.17 (ddd, 1H, *J* = 2.3, 4.5, 14.2 Hz), 1.32 (dt, 2H, *J* = 2.3, 7.9 Hz), 1.61 (ddd, 1H, *J* = 2.2, 3.5, 13.6 Hz), 1.71-1.75 (m, 1H), 1.92 (dd, 1H, *J* = 5.6, 13.6 Hz), 2.33-2.38 (m, 1H), 2.54 (t, 1H, *J* = 12.4 Hz), 2.57 (dd, 1H, *J* = 2.3, 13.1 Hz), 2.79 (ddd, 1H, *J* = 7.8, 11.9, 13.0 Hz), 2.82 (dd, 1H, *J* = 10.0, 14.0 Hz), 3.13 (dd, 1H, *J* = 4.5, 11.9 Hz), 3.17 (dd, 1H, *J* = 6.8, 11.9 Hz), 3.25 (dt, 1H, *J* = 6.2, 11.9 Hz), 3.74 (s, 1H), 7.19 (dt, 1H, *J* = 1.1, 7.3 Hz), 7.29 (dt, 1H, *J* = 1.1, 7.3 Hz), 7.31 (d, 1H, *J* = 7.5 Hz), 7.52 (d, 1H, *J* = 7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.4, 24.9, 26.3, 28.5, 32.1, 33.1, 41.6, 50.8, 57.4, 65.9, 70.0, 119.9, 120.9, 125.4, 127.7, 145.4, 154.6, 190.7. HR-MS *m/z*: Calcd for $C_{18}H_{22}N_2$: 266.1783. Found: 266.1781.

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