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Synthesis of febrifugine derivatives and a solution to the puzzle of the structural determination of febrifugine

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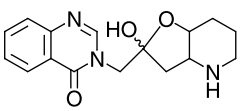
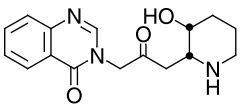
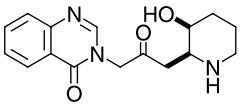
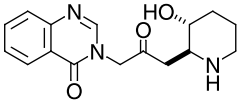
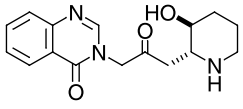
Abstract—The stereo-structure of piperidine lactone (**3**), a synthetic intermediate of the antimalarial agent febrifugine ((+)-**1**) with a piperidine ring in the *trans* relative configuration, was re-revised to the *cis*-form. We determined that isomerization to the *trans*-form from the *cis*-form occurred in the stage (**6** from **5**) of deprotection in Baker's synthesis.

1. Introduction

Febrifugine ((+)-**1**) is an antimalarial agent that has been isolated from *Dichroa febrifuga* and *Hydrangea umbellate*.[1] The plane structure of (+)-**1** was first proposed in 1950.[2] Subsequently, their relative[3] and absolute[4] structures were proposed, based on Baker's synthetic work.[5] The relative configuration[6] of (+)-**1** was corrected in 1973 and then the absolute structure[7] of (+)-**1** was corrected in 1999 (Table 1). Currently, dramatic medical[8] and synthetic[9] studies of (+)-**1** are in progress.

Baker et al. synthesized *dl*-febrifugine (**1**) from furfural (**2**) in 1953 and proposed that the configuration of the 2 and 3 positions on the piperidine ring of **1** was the *cis*-form.[5b] The key intermediates in the structural determination were piperidine lactone (**3**) and its ring-opening product (**4**), which were easily transformed into each other. However, Barringer et al.[6] corrected the configuration of **3** and **1** to the *trans*-form from the *cis*-form in 1973, based on an analysis of the ^{1}H NMR spectra of **3**. The protons of H_{3a} and H_{7a} on the bridgehead of **3** were observed at δ 5.15 and 4.69 ppm with a coupling constant of 8.5 Hz (Scheme 1). It is presently accepted without doubt that the configuration of the substituents on the piperidine ring in (+)-**1** are in the *trans* configuration, while we doubt Barringer's conclusion about the structural determination of **3**. The molecular calculation indicates that even if the configuration of **3** was *cis*, the coupling constant between H_{3a} and H_{7a} would reasonably be 8.5 Hz.[10] A result that supports our view has been reported. Recently, Kobayashi et al. synthesized a *trans* dimethyl derivative (**3′**) in which each proton on the bridgehead was observed at δ 3.09 and 4.09 ppm with a coupling constant of 10.4 Hz.[11a,b] From these results, we thought that the configuration of **3** would be the *cis*-form and that isomerization of the *cis*-form to the *trans*-form must have occurred after **3** in Baker's synthesis of **1**.

Table 1. Proposed structures of febrifugine ((+)-**1**)

Structure	Year	Proposer
	1950	Koepfli et al.[2]
	1953	Baker et al.[3]
	1962	Hill and Edwards[4]
	1973	Barringer Jr. et al.[6]
	1999	Kobayashi et al.[7]

2. Results and discussion

First, we attempted to synthesize *cis*- (*cis*-**3**) and *trans*-piperidine lactone (*trans*-**3**) (Scheme 2). Piperidine-2,3-diol

Keywords: febrifugine; antimalarial compounds; structural determination; isomerization.

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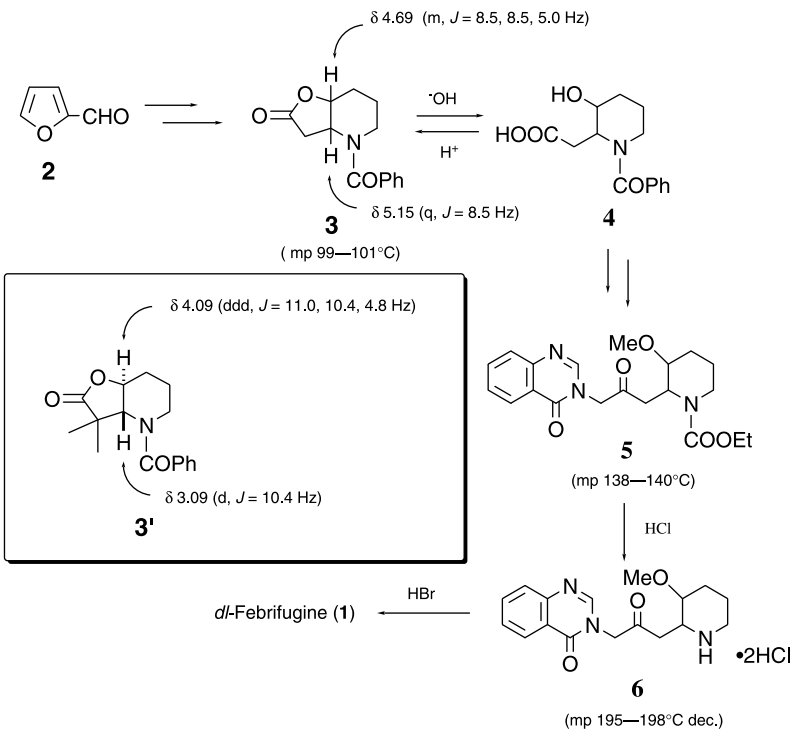
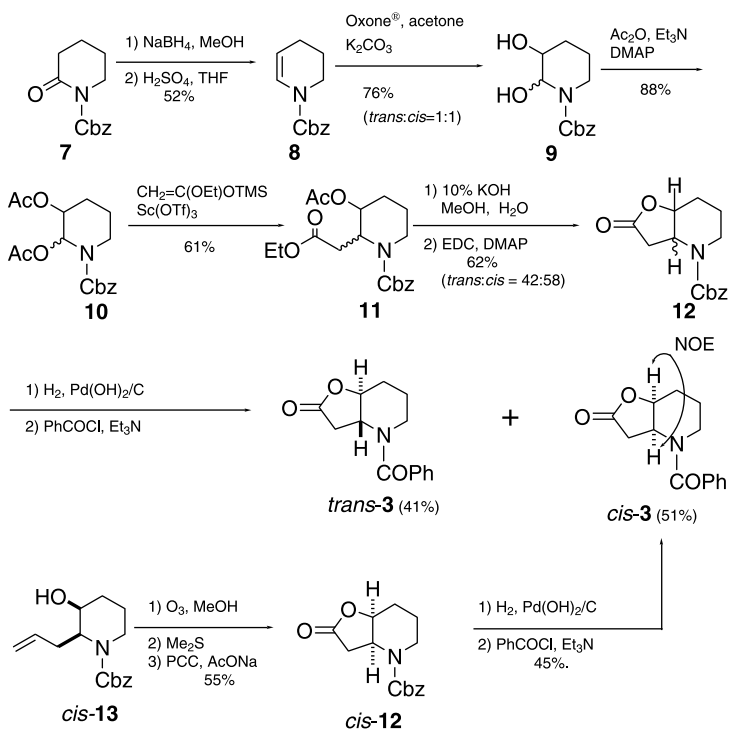
doi:10.1016/S0040-4020(03)00139-X



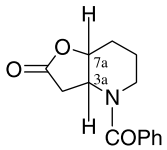
Scheme 1.

(**9**) was prepared via the Oxone® oxidation of 2,3-dehydropiperidine (**8**), which is prepared easily from piperidone (**7**). *N*-Cbz-protected piperidine lactone (**12**) was prepared from **9** according to Kobayashi's method.[11] As they discussed, the reaction of diacetate **10** with non-substituted ketene silylacetal has low diastereoselectivity to give acetate (**11**). Deprotection followed by benzoylation of **12** afforded a separable mixture (3:4) of *trans*-**3** and *cis*-**3**. In order to reliably determine the structure of *trans*-**3** and *cis*-**3**, *cis*-**3** was prepared from *cis*-2-allyl-3-hydroxypiperidine derivative (*cis*-**13**) using our previously reported method[9a,b] (Scheme 2). Ozonolysis of *cis*-**13**, followed by PCC oxidation afforded *cis*-piperidine lactone (*cis*-**12**) with a cbz group. Hydrogenolysis and benzoylation of *cis*-**12** gave *cis*-**3** in which NOE between H_{3a} and H_{7a} was observed in the NOESY spectrum.



Scheme 2.

Table 2. The melting point and ^{1}H NMR data of piperidine lactone (**3**)



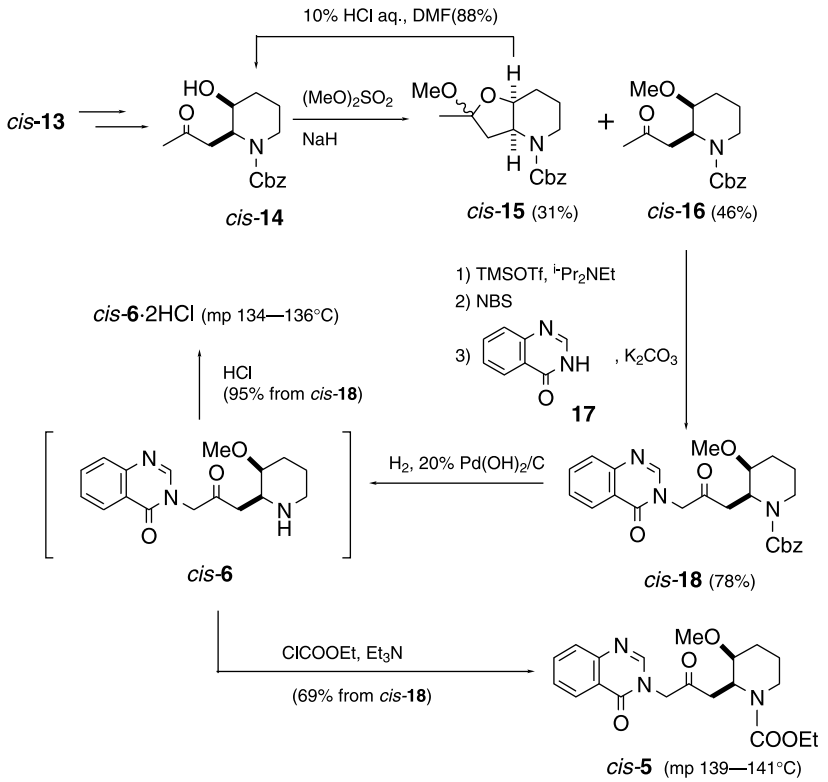
Compd	Mp (°C)	^{1}H NMR	
		H_{3a}	H_{7a}
3	99–101	5.15 (q, J=8.5 Hz)[a]	4.69 (m, J=8.5, 8.5, 5.0 Hz)[a]
cis-**3**[b]	85–86	5.15 (q, J=7.7 Hz)[a]; 5.09 (q, J=7.8 Hz)[c,d]	4.69 (dt, J=7.7, 4.9 Hz)[a]; 4.68 (dd, J=12.5, 7.5 Hz)[c,d]
trans-**3**[e]	133–134	3.24–3.65 (m)[a]; 3.30–3.39 (m)[c]	3.97–4.08 (m)[a]; 4.06 (ddd, J=110, 10.0, 4.0 Hz)[c]

[a] 60 MHz.
[b] NOE between H_{3a} and H_{7a} in NOESY spectrum was observed.
[c] 500 MHz
[d] 80°C.
[e] NOE between H_{3a} and H_{7a} in NOESy spectrum was not observed.

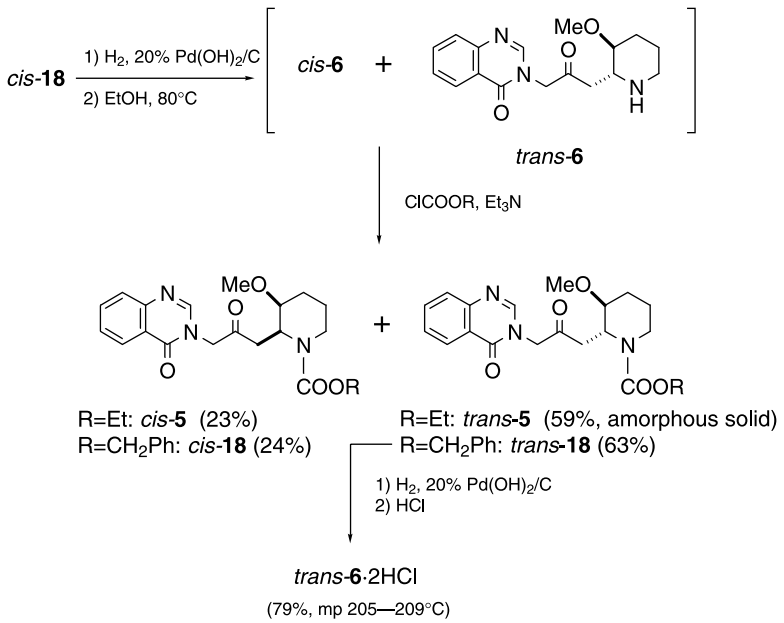
The melting points and ^{1}H NMR data for *cis*-**3**, *trans*-**3**, and reported **3** are summarized in Table 2. Although the melting point of **3** and *cis*-**3** differed, the ^{1}H NMR data for **3** and *cis*-**3** showed good agreement.

Burgess et al., who reported another method of synthesizing **1** in 1996, used Barringer's result to determine the *syn* or *anti* configuration of a derivative of **13** prepared by the reaction of piperidine oxide with allyl silane.[12] This result should also be corrected along with Barringer's proposal.

We think that Baker et al. definitely prepared *trans* form of **1**, because their racemic compound (**1**) exhibited half the antimalarial activity of (+)-**1** and recent work has shown that the activity of the *cis* form (isofebrifugine) of (+)-**1** is less than one-tenth that of the *trans* form. Additionally, the melting point of our synthesized **1** agreed with that of Baker's. Namely, isomerization at the 2 position in the piperidine ring must occur in the synthetic stage after *cis*-**3**. Our next attempt focused on the synthesis of other intermediates (**5** and **6**) in Baker's method of synthesizing **1** (Scheme 3). Methylation of the 2-acetonyl derivative (*cis*-**14**) from *cis*-**13** afforded an *O*-methylated compound (*cis*-**16**) and acetal (*cis*-**15**) in 46 and 31% yield, respectively. Acetal *cis*-**15** was transformed to *cis*-**14** by treatment with acid for reuse. Successive *O*-silylation, bromination, and coupling reaction with 4(3*H*)-quinazolinone (**17**) afforded the *cis*-5-methoxy derivative (*cis*-**18**) as a crystalline solid in 78% yield. Although the hydrogenolysis of *cis*-**18** afforded *cis*-**6**, we could not purify *cis*-**6**, since *cis*-**6** readily



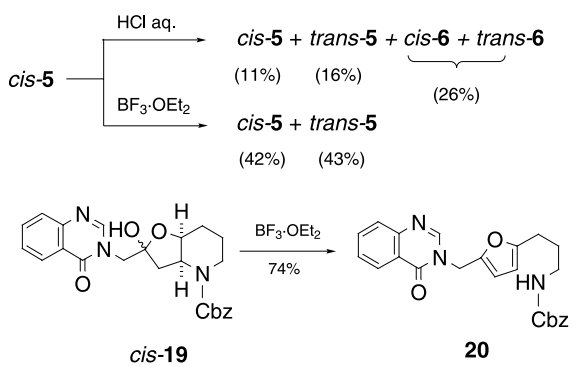
Scheme 3.



Scheme 4.

isomerized with heating to give a mixture of *cis*-**6** and *trans*-**6**. We purified the dihydrochloride (*cis*-**6**·2HCl) of *cis*-**6** and it decomposed at 134–136°C, which differed markedly from the 195–198°C[5b] of **6** prepared by Baker. By contrast, N-ethoxycarbonylation of *cis*-**6** afforded *cis*-**5** with a melting point of 139–141°C, which agreed with the value (138–140°C) for **5** prepared by Baker.

Comparing the melting points of **5** and *cis*-**5**, and **6** and *cis*-**6** indicated that compound **5** has the *cis*-form and **6** has the *trans*-form. To confirm these results, our final attempt focused on the synthesis of *trans*-**5** and *trans*-**6** (Scheme 4), utilizing the isomerization between *cis*-**6** and *trans*-**6**. Refluxing *cis*-**6** in EtOH obtained by the hydrogenolysis of *cis*-**18** gave an inseparable mixture (2:1) of *trans*-**6** and *cis*-**6**. N-ethoxycarbonylation of the mixture gave *trans*-**5** (59%) and *cis*-**5** (23%), which could be separated by column chromatography; *trans*-**5** was an amorphous solid. N-benzyloxycarbonylation of the mixture of *trans*-**6** and *cis*-**6** also afforded a separable mixture of *trans*-**18** and *cis*-**18** in 63 and 24% yield, respectively. Hydrogenolysis of *trans*-**18** gave pure *trans*-**6** and its dihydrochloride (*trans*-**6**·2HCl) decomposed at 205–209°C, which is similar to the value (195–198°C) for **6** obtained by Baker.



Scheme 5.

Isomerization to the *trans*-form from the *cis*-form certainly occurred at the stage of synthesizing **6** from **5** in Baker's synthesis. We re-investigated the deprotection of *cis*-**5** under reflux in 6N HCl for 4 h following the method of Baker's synthesis (Scheme 5). Although we could not obtain the pure dihydrochloride of **5**, we isolated *cis*-**5** (11%), *trans*-**5** (16%), and a mixture (26%) of *cis*-**6** and *trans*-**6**. Treatment of *cis*-**5** with excess $BF_3{\cdot}OEt_2$ under reflux in MeCN for 1 h gave a mixture of *cis*-**5** (42%) and *trans*-**5** (43%). These results strongly indicated that *cis*-**5** isomerizes to *trans*-**5** under acidic conditions. Considering our finding that the dihydrochloride (*cis*-**6**·2HCl) of *cis*-**6** did not isomerize even when heated in refluxing water for 8 h, unlike the free base *cis*-**6**, we think that *cis*-**5** isomerizes to afford a mixture of *cis*-**5** and *trans*-**5** under acidic conditions followed by hydrolysis, which results in a mixture of *cis*-**6** and *trans*-**6**, and that compound **6** obtained by Baker was the dihydrochloride (*trans*-**6**·2HCl) of *trans*-**6**. From our previous reaction of the demethoxy compound (*cis*-**19**) of *cis*-**18** with $BF_3{\cdot}OEt_2$ to afford furan derivatives (**20**),[13] the reaction of *N*-protected febrifugine derivatives with acid is of great interest to us.

We have almost solved the puzzle concerning Baker's synthesis and have proved that Baker's structural determination of every compound until **5** involving piperidine lactone (**3**) in their synthetic route was correct.

3. Experimental

3.1. General

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. Mass spectra (MS) were recorded on a VG-70SE spectrometer. ^1H and ^{13}C NMR spectra were run on a JASCO MY 60FT, a Varian VXR-200, a Varian Mercury (300 MHz) or a Varian

VXR-500 spectrometer. Analytical HPLC was performed with a Shimadzu SPD-6A or Waters 510 instrument on a silica gel column, Chemcosorb 5Si-U (Chemco). Merck silica gel 60 (230–400 mesh) and Wako activated alumina (300 mesh) were employed for column chromatography. Extracts were dried over anhydrous $MgSO_4$.

3.1.1. Benzyl 1,2,3,4-tetrahydro-1-pyridinecarboxylate (8). Sodium brohydride (1.79 g, 47.3 mmol) was added portionwise to a solution of benzyl 2-oxopiperidine-1-caroboxylate (**7**, 11.01 g, 47.2 mmol)[8c] in MeOH (200 ml) at 0°C. The solution was stirred at the same temperature for 15 min. The mixture was poured into ice water (400 ml) and extracted with AcOEt (200 ml×2). The AcOEt layer was washed with brine (400 ml), dried, and concentrated. To a solution of the residue (about 10 g) in THF (100 ml) was added H_2SO_4 (0.5 ml) and the solution was stirred at room temperature for 1 h. The mixture was poured into saturated aqueous $KHCO_3$ solution (300 ml) and extracted with AcOEt (300 ml×2). The AcOEt layer was washed with brine (300 ml), dried, and concentrated. The residue was subjected to column chromatography (SiO_2; hexane/AcOEt=3:1) to give **8** (5.34 g, 52%) as colorless oil, whose ^1H NMR data was agreed with reported one.[11] ^1H NMR (200 MHz, $CDCl_3$) δ: 1.78–1.89 (2H, t), 2.00–2.09 (2H, t), 3.63 (2H, t, J=5.6 Hz), 4.86 (0.5H, dt, J=8.4, 4.0 Hz), 4.97 (0.5H, dt, J=8.2, 4.0 Hz), 5.18 (2H, s), 6.80 (0.5H, d, J=8.6 Hz), 6.89 (0.5H, d, J=8.4 Hz), 7.36–7.39 (5H, m).

3.1.2. Benzyl 2,3-dihydroxy-1-piperidinecarboxylate (9). A solution of oxone® (10.6 g, 17.3 mmol) in water (70 ml) was added dropwise to a solution of **8** (1.88 g, 8.65 mmol) and K_2CO_3 (2.39 g, 17.3 mmol) in acetone (30 ml) and water (30 ml) at 0°C for 15 min. The solution was stirred at the room temperature for 2 h. The mixture was poured into ice water (100 ml) and extracted with AcOEt (100 ml×2). The AcOEt layer was washed with brine (100 ml), dried, and concentrated. The residue was subjected to column chromatography (SiO_2; hexane/AcOEt=1:1) to give **9**[11] (1.65 g, 76%) as colorless viscous oil. IR (neat): 3400, 1680, 1260 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$) δ:1.12–2.02 (4H, m), 2.99–4.17 (5H, m), 5.11 (2H, s), 5.58 (0.5H, d, J=2.5 Hz), 5.71 (0.5H, d, J=3.7 Hz), 7.33 (5H, s). HRMS (FAB) m/z Calcd for $C_{13}H_{16}NO_3$ (MH^+-H_2O): 234.1130. Found: 234.1143.

3.1.3. Benzyl 2,3-diacetoxy-1-piperidinecarboxylate (10). Acetic anhydride (0.29 ml, 3.07 mmol) was added dropwise to a solution of **9** (0.13 g, 0.52 mmol) and DMAP (6.3 mg, 0.05 mmol) in Et_3N (0.43 ml, 3.09 mmol). The solution was stirred at the room temperature for 2 h. To the mixture was added to saturated aqueous $KHCO_3$ solution (10 ml) in cooling and the mixture was extracted with AcOEt (20 ml×2). The AcOEt layer was washed with brine (10 ml×5), saturated aqueous $KHCO_3$ (10 ml), and brine (10 ml), dried, and concentrated. The residue was subjected to column chromatography (SiO_2; hexane/AcOEt=3:1) to give 10[11] (1.5 g, 88%) as colorless viscous oil. IR (neat): 1750, 1720 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.64–1.87 (4H, m), 1.99 (1.5H, s), 2.00 (1.5H, s), 2.93–3.13 (1H, m), 3.92–4.09 (1H, m), 4.83–4.93 (1H, m), 5.16 (2H, ABq, J=12.2, 16.6 Hz), 6.68 (0.5H, d, J=2.6 Hz), 6.99 (0.5H, d, J=3.4 Hz), 7.26–4.93 (5H, m). HRMS (FAB) m/z Calcd for $C_{15}H_{18}NO_3$ (MH^+-AcOH): 276.1237. Found: 276.1236.

3.1.4. Benzyl 3-acetoxy-2-ethoxycarbonylmethyl-1-piperidinecarboxylate (11). A solution of **10** (130 mg, 0.4 mmol) and 1-ethoxy-1-[(trimethylsilyl)oxy]ethane[11] (0.13 g, 0.8 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise to a solution of $Sc(OTf)_3$ (19 mg, 0.04 mmol) in CH_2Cl_2 (1 ml) in CH_2Cl_2 (1.5 ml) at 0°C. The solution was stirred at the room temperature for 4 h. The mixture was poured into saturated aqueous $KHCO_3$ solution (10 ml) and extracted with CH_2Cl_2 (20 ml×2). The CH_2Cl_2 layer was washed with water (10 ml) and brine (10 ml), dried, and concentrated. The residue was subjected to column chromatography (SiO_2; hexane/^{t}BuOMe=1:1) to give **11** (85.3 mg, 61%) as colorless oil. IR (neat): 1740, 1700, 1240 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$) δ:1.20 (3H, t, J=7.4 Hz), 1.73–2.40 (4H, m), 1.93 (1.5H, s), 2.04 (1.5H, s), 2.55–3.22 (3H, m), 3.93–4.24 (3H, m), 4.74–5.15 (2H, m), 5.15 (2H, s), 7.37 (5H, s). HRMS (FAB) m/z Calcd for $C_{19}H_{26}NO_6$ (MH^+): 364.1760. Found: 364.1750.

3.1.5. Benzyl 2-oxooctahydrohuro[3,2-*b*]pyridine-4-carboxylate (*trans*-12 and *cis*-12). A solution of **11** (0.11 g, 0.30 mmol) in 10% aqueous KOH (MeOH/H_2O=1:1) solution was stirred at the room temperature for 1.5 h. The mixture was acidified by 10% aqueous HCl solution and extracted with AcOEt (20 ml×2). The AcOEt layer was washed with brine (10 ml), dried, and concentrated. To a solution of the residue in CH_2Cl_2 (10 ml) was added EDC (58 mg, 0.30 mmol) and DMAP (7 mg, 0.06 mmol). The mixture was stirred at the room temperature for 3 h. To the mixture was added CH_2Cl_2 (10 ml) and the CH_2Cl_2 layer was washed with water (10 ml) and brine (10 ml), dried, and concentrated. The residue was subjected to column chromatography (SiO_2; AcOEt/$CHCl_3$=1:5) to give **12** (51.9 mg, 62%, *tarns*:*cis*=42:58) as colorless oil. HPLC: column, Chemcosorb 5Si-U; column temperature, room temperature; eluent, AcOEt/hexane=1:3; flow rate=1.0 ml/min; wavelength, 254 nm; t_R=10.5 and 16.3 min.

3.1.6. Benzyl (3a*RS*,7a*RS*)-2-oxooctahydrofuro[3,2-*b*]pyridine-4-carboxylate (*cis*-12). Ozone gas was passed through a solution of benzyl (2*RS*,3*RS*)-2-allyl-3-hydroxy-piperidine-1-carboxylate[9b] (2.20 g, 8.0 mmol) in MeOH (30 ml) at −78°C for 2 h and Ar gas passed through at the same temperature. To the mixture was added dropwise Me_2S (0.88 ml, 12.0 mmol). The mixture was stirred at the room temperature for 1 h. The solvent was removed and the residue was dissolved in Et_2O. The Et_2O layer was washed with brine (30 ml×3), dried, and concentrated. To a suspended solution of PCC (5.17 g, 24.0 mmol) and AcONa (0.39 g, 4.7 mmol) in CH_2Cl_2 (30 ml) added dropwise a solution of the residue in CH_2Cl_2 (5 ml). The mixture was stirred at the room temperature for 3 h. To the mixture added Et_2O (100 ml), which was combined with washing Et_2O (10 ml×3) of the precipitates. The Et_2O layer was dried and concentrated. The residue was subjected to column chromatography (SiO_2; AcOEt/$CHCl_3$=1:9) to give *cis*-**12** (1.22 g, 55%) as colorless oil. IR ($CHCl_3$): 1780, 1700, 1240, 1160 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 80°C) δ: 1.49–1.64 (2H, m), 1.76–1.78 (1H, m), 2.09 (1H, brs), 2.59 (1H, dd, J=17.0, 9.3 Hz), 2.71 (1H, brs), 2.97 (1H,

brs), 3.97 (1H, brs), 4.62 (1H, dd, J=13.5, 8.0 Hz), 4.92 (1H, dd, J=16.8, 8.3 Hz), 5.14 (2H, ABq, J=12.5, 12.2 Hz), 7.34–7.39 (5H, m). MS (FAB, positive ion mode) m/z: 276 (MH^+). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.12; H, 6.05; N, 4.98.

3.1.7. 4-Benzoyloctahydrofuro[3,2-*b*]pyridin-2-one (*trans*-3 and *cis*-3). A mixture of **12** (0.33 g, 1.2 mmol) and 20% $Pd(OH)_2$/C (0.03 g) in acetone (10 ml) was stirred at the room temperature for 18 h under H_2 atmosphere. The mixture was filtered off and the solvent was removed. To a solution of residue and Et_3N (0.18 ml, 1.29 mmol) in $CHCl_3$ (10 ml) was added dropwise benzoyl chloride (0.15 ml, 1.29 mmol) at 0°C. The mixture was stirred at the room temperature for 1 h. The mixture washed with 1N aqueous HCl solution (10 ml), saturated aqueous $KHCO_3$ solution (10 ml), dried, and concentrated. The residue was subjected to column chromatography (SiO_2; hexane/AcOEt=3:2) to give *trans*-**3** (0.12 g, 41%) as colorless needle, mp 133–134°C (AcOEt/hexane). IR (KBr) cm^{-1}: 1790, 1640. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.67–1.81 (2H, m), 1.87–1.91 (1H, m), 2.38–2.42 (1H, m), 2.97 (1H, ddd, J=13.5, 11.5, 3.0 Hz), 3.11 (1H, dd, J=16.5, 12.5 Hz), 3.30–3.39 (2H, m), 3.89 (1H, dt, J=14.0, 4.3 Hz), 4.06 (1H, ddd, J=11.0, 10.0, 4.0 Hz), 7.40–7.45 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.1, 27.9, 36.0, 49.0, 60.1, 80.7, 127.5, 128.5, 130.7, 135.1, 173.0, 173.9. MS (FAB, positive ion mode) m/z: 246 (MH^+). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.52; H, 5.95; N, 5.65. The next eluant gave *cis*-**3** (0.15 g, 51%) as colorless flakes, mp 85–86°C (AcOEt/cyclohexane). IR ($CHCl_3$) cm^{-1}: 1780, 1630. ^1H NMR (500 MHz, $CDCl_3$, 80°C) δ: 1.59–1.68 (1H, m), 1.76–1.86 (2H, m), 2.06–2.23 (1H, m), 2.68 (1H, dd, J=17.5, 8.0 Hz), 2.79 (1H, dd, J=17.8, 8.0 Hz), 4.08 (1H, ddd, J=13.7, 10.4, 3.9 Hz), 3.89 (1H, d, J=13.7 Hz),), 4.68 (1H, dd, J=12.5, 7.5 Hz), 5.09 (1H, d, J=7.8 Hz), 7.37–7.46 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.1, 26.0, 30.8, 75.3, 126.6, 128.6, 130.1, 135.2, 171.8, 174.1. MS (FAB, positive ion mode) m/z: 246 (MH^+). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.54; H, 6.07; N, 5.78.

3.1.8. (3a*RS*,7a*RS*)-4-Benzoyloctahydrofuro[3,2-*b*]pyridine-2-one (*cis*-3). A mixture of *cis*-**12** (0.50 g, 1.82 mmol) and 20% $Pd(OH)_2$/C (0.05 g) in acetone (20 ml) was stirred at the room temperature for 24 h under H_2 atmosphere. The mixture was filtered off and the solvent was removed. To a solution of residue and Et_3N (0.25 ml, 1.79 mmol) in $CHCl_3$ (25 ml) was added dropwise benzoyl chloride (0.23 ml, 1.98 mmol) at 0°C. The mixture was stirred at the room temperature for 1 h. To the mixture was added $CHCl_3$ (20 ml) and the mixture was washed with 1N aqueous HCl solution (20 ml), saturated aqueous $KHCO_3$ solution (20 ml), dried, and concentrated. To a solution of the residue was subjected to column chromatography (SiO_2; hexane/AcOEt=1:1) to give *cis*-**3** (0.20 g, 45%) as colorless flakes, mp 86–87°C (AcOEt/cyclohexane).

3.1.9. Benzyl (3a*RS*,7a*RS*)-2-methoxy-2-methyloctahydrofuro[3,2-*b*]pyridine-4-carboxylate (*cis*-15) and benzyl (2*RS*,3*RS*)-3-methoxy-2-(2-oxopropyl)piperidine-1-caroboxylate (*cis*-16). Sodium hydride (0.088 g, 60% dispersion in mineral oil, 2.2 mmol) was added portionwise to a solution of benzyl (2*RS*,3*RS*)-2-hydroxyl-3-(2-oxopropyl)piperidine-1-caroboxylate (*cis*-**14**)[9b] (0.58 g, 2.0 mmol) in dry DMF (10 ml) and $(MeO)_2SO_2$ (0.21 ml, 2.2 mmol) was added dropwised to the mixture. The mixture was stirred at the room temperature for 2.5 h. The mixture was poured into water (50 ml) and extracted with AcOEt (50 ml×2). The AcOEt layer was washed with water (50 ml) and brine (50 ml), dried, and concentrated. The residue was subjected to column chromatography (SiO_2; AcOEt/hexane=1:1) to give *cis*-**15** (0.18 g, 31%) as colorless oil. IR (neat) cm^{-1}: 1700. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.42 (3/3H, s), 1.46 (6/3H, s), 1.64–1.91 (4 H, m), 2.10 (2/3H, dd, J=13.0, 9.0 Hz), 2.35 (2/3H, dd, J=13.0, 8.2 Hz), 2.80–3.18 (1H, m), 3.21 (6/3H, s), 3.28 (3/3H, s), 3.74–4.08 (1 H, m), 4.17–4.28 (1H, m), 4.67–4.97 (1H, m), 5.14 (2H, s), 7.35 (5H, s). MS (FAB, positive ion mode) m/z: 305 (M^+), 306 $(M+1)^+$. HRMS (FAB) Calcd for $C_{17}H_{23}NO_4$ $(M)^+$: 305.1627. Found: 305.1664. The next eluant gave *cis*-**16** (0.28 g, 46%) as colorless oil. IR (neat) cm^{-1}: 1700. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.21–1.97 (4H, m), 2.17 (3H, brs), 2.38–2.57 (1H, m), 2.77 (2H, dd, J=14.8, 5.4 Hz), 3.20–3.30 (1H, m), 3.34 (3H, s), 3.83–4.18 (1H, m), 5.00–5.24 (1H, m), 5.13 (2H, s), 7.36 (5H, s). MS (FAB, positive ion mode) m/z: 306 (M^+). HRMS (FAB) Calcd for $C_{17}H_{24}NO_4$ (MH^+): 306.1705. Found: 306.1753.

3.1.10. Benzyl (2*RS*,3*RS*)-3-hydroxyl-2-(2-oxopropyl)-piperidine-1-caroboxylate (*cis*-14). A mixture of *cis*-**15** (46.0 mg, 0.15 mmol) in dry DMF (10 ml) and 10% aqueous HCl solution was stirred at the room temperature for 0.5 h. The mixture was poured into water (50 ml) and extracted with AcOEt (50 ml×2). The AcOEt layer was washed with saturated aqueous $KHCO_3$ solution (50 ml) and brine (50 ml), dried, and concentrated. The residue was subjected to column chromatography (SiO_2; AcOEt/hexane=1:1) to give *cis*-**14** (38.5 mg, 88%) as colorless oil.

3.1.11. 3-{3-[(2*RS*,3*RS*)-1-Benzyloxycarbonyl-3-methoxy-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone (*cis*-18). Diisopropylethylamine (0.63 ml, 3.6 mmol) and TMSOTf (0.65 ml, 4.0 mmol) was added to a solution of *cis*-**16** (0.92 g, 3.0 mmol) in dry CH_2Cl_2 (10 ml). The mixture was stirred at the room temperature for 20 min under Ar gas. To the mixture was added NBS (0.64 g, 3.6 mmol). The mixture was stirred at the room temperature for 1.5 h. The mixture was poured into 10% aqueous $Na_2S_2O_3$ solution (80 ml) and extracted with AcOEt (80 ml×2). The AcOEt layer was washed with saturated aqueous $KHCO_3$ solution (80 ml) and brine (80 ml), dried, and concentrated. To a solution of the residue in dry DMF (10 ml) added anhydrous K_2CO_3 (0.50 g, 3.6 mmol) and **17** (0.53 g, 3.6 mmol). The mixture was stirred at the room temperature for 1 h. The mixture was poured into water (80 ml) and extracted with AcOEt (80 ml×2). The AcOEt layer was washed with water (80 ml) and brine (80 ml), dried, and concentrated. The residue was subjected to column chromatography (Al_2O_2; AcOEt) to give *cis*-**18** (1.06 g, 78%) as colorless flakes, mp 120–122.5°C (AcOEt). IR (nujol) cm^{-1}: 1730, 1680. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.36–2.04 (4H, m), 2.56–2.75 (1H, m), 2.75–3.17 (2H, m), 3.23–3.48 (1H, m), 3.37 (3H, s), 3.89–4.08 (1H, m), 4.80–4.98 (1H, m), 5.00–5.23 (4H, m),

7.33 (5H, s), 7.50 (1H, td, *J*=7.3, 1.6 Hz), 7.69–7.81 (2H, m), 7.97 (1H, brs), 8.28 (1 H, ddd, *J*=8.1, 1.5, 0.6 Hz). MS (FAB, positive ion mode) *m/z*: 450 (MH^+). Anal. Calcd for $C_{25}H_{27}N_3O_5$: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.66; H, 6.02; N, 9.37.

3.1.12. 3-{3-[(2*RS*,3*RS*)-1-Benzyloxycarbonyl-3-methoxy-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone (*cis*-18) and 3-{3-[(2*RS*,3*SR*)-1-benzyloxycarbonyl-3-methoxy-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone (*trans*-18). A mixture of *cis*-**18** (0.60 g, 1.3 mmol) and 20% $Pd(OH)_2$/C (0.06 g) in MeOH and THF (1:1, 8 ml) was stirred at the room temperature for 3 h under H_2 gas. The mixture was filtered off and concentrated. A solution of the residure in EtOH was heated at 80°C for 1 h. The mixture was concentrated. To a solution of the residue in CH_2Cl_2 (7 ml) was added dropwise Et_3N (0.22 ml, 1.6 mmol) and $ClCOOCH_2Ph$ (0.23 ml, 1.6 mmol) at 0°C. The mixture was stirred at the room temperature for 0.5 h under Ar gas. The mixture was poured into water (50 ml) and extracted with AcOEt (50 ml×2). The AcOEt layer was washed with brine (50 ml), dried, and concentrated. The residue was subjected to column chromatography (Al_2O_3; AcOEt/hexane=1:1) to give *cis*-**18** (0.14 g, 24%) as colorless flakes. The next eluant gave *trans*-**18** (0.38 g, 63%) as amorphous solid. IR ($CHCl_3$) cm^{-1}: 1735, 1680. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.21–1.96 (4 H, m), 2.71–3.06 (3H, m), 3.23–3.46 (1H, m), 3.38 (3H, s), 3.94–4.17 (1 H, m), 4.77–5.03 (2H, m), 5.14 (2H, s), 7.34 (5H, s), 7.51 (1H, td, *J*=7.3, 1.7 Hz), 7.70–7.82 (2H, m), 7.90 (1H, brs), 8.26 (1H, d, *J*=7.5 Hz). MS (FAB, positive ion mode) *m/z*: 450 (MH^+). HRMS (FAB) Calcd for $C_{25}H_{28}N_3O_5$ (MH^+): 450.2029. Found: 450.2028.

3.1.13. 3-{3-[(2*RS*,3*RS*)-3-methoxy-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone dihydrochloride (*cis*-6·2HCl). A mixture of *cis*-**18** (0.20 g, 0.44 mmol) and 20% $Pd(OH)_2$/C (0.02 g) in MeOH and THF (1:1, 4 ml) was stirred at the room temperature for 2 h under H_2 gas. The mixture was filtered off and conc. HCl solution (0.50 ml) was added to the filterate. The mixture was concentrated to give *cis*-**6**·2HCl (0.17 g, 95%) as colorless sands, mp 134–136°C (dec.) (AcOEt/cyclohexane). IR (KBr) cm^{-1}: 3410, 2720, 1740, 1705, 1665. ^1H NMR (500 MHz, $CD_3COOD+D_2O$) δ: 1.67 (1H, t, *J*=13.8 Hz), 1.75 (1H, d, *J*=13.5 Hz), 1.90–2.15 (1H, m), 2.25 (1H, d, *J*=14.0 Hz), 3.19 (1H, t, *J*=11.5 Hz), 3.38 (2H, d, *J*=5.5 Hz), 3.44 (3H, s), 3.51 (1H, d, *J*=12.0 Hz), 3.71 (1H, brs), 3.92 (1H, brs), 5.41 (2H, dd, *J*=30.0, 18.0 Hz), 7.84 (1H, t, *J*=15.0 Hz), 7.98 (1H, d, *J*=8.5 Hz), 8.10 (1H, t, *J*=7.5 Hz), 8.24–8.58 (1 H, m), 9.41 (1H, s). MS (FAB, positive ion mode) *m/z*: 316 (MH^+-2HCl). Anal. Calcd for $C_{17}H_{21}N_3O_3$·2HCl 8/5H_2O: C, 48.95; H, 6.33; N, 10.07. Found: C, 48.65; H, 5.99; N, 10.11.

3.1.14. 3-{3-[(2*RS*,3*SR*)-3-methoxy-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone dihydrochloride (*trans*-6·2HCl). A mixture of *trans*-**18** (0.19 g, 0.42 mmol) and 20% $Pd(OH)_2$/C (0.019 g) in MeOH and THF (1:1, 4 ml) was stirred at the room temperature for 2 h under H_2 gas. The mixture was filtered off and conc. HCl solution (0.42 ml) was added to the filterate. The mixture was concentrated to give *trans*-**6**·2HCl (0.13 g, 79%) as colorless sands, mp. 205–209°C (dec.) (MeOH). IR (KBr) cm^{-1}: 3390, 2800–2400, 1740, 1705, 1665. ^1H NMR (500 MHz, $CD_3COOD+D_2O$) δ: 1.56–1.66 (1 H, m), 1.77–1.88 (1H, m), 2.01–2.11 (1H, m), 2.25–2.33 (1 H, m), 3.15 (1H, td, *J*=11.6, 3.5 Hz), 3.32 (1H, dd, *J*=18.8, 7.3 Hz), 3.41–3.57 (3H, m), 3.47 (3H, s), 3.78 (1H, dd, *J*=12.5, 7.0 Hz), 5.34 (2H, s,), 7.82 (1H, t, *J*=7.5 Hz), 7.91 (1H, d, *J*=8.0 Hz), 8.01 (1H, td, *J*=7.8, 1.5 Hz), 8.36 (1H, dd, *J*=8.0, 1.0 Hz), 9.03 (1H, s). MS (FAB, positive ion mode) *m/z*: 316 (MH^+-2HCl). Anal. Calcd for $C_{17}H_{21}N_3O_3$·2HCl·5/4H_2O: C, 49.70; H, 6.26; N, 10.23. Found: C, 49.94; H, 6.06; N, 10.27.

3.1.15. 3-{3-[(2*RS*,3*RS*)-1-Ethoxycarbonyl-3-methoxy-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone (*cis*-5). A mixture of *cis*-**18** (0.20 g, 0.44 mmol) and 20% $Pd(OH)_2$/C (0.02 g) in MeOH and THF (1:1, 10 ml) was stirred at the room temperature for 1 h under H_2 gas. The mixture was filtered off and concentrated under the room temperature. To a solution of the residue in CH_2Cl_2 (4 ml) was added dropwise Et_3N (0.076 ml, 0.55 mmol) and ClCOOEt (0.052 ml, 0.54 mmol) at 0°C. The mixture was stirred at the room temperature for 0.5 h under Ar gas. The mixture was poured into water (30 ml) and extracted with AcOEt (30 ml×2). The AcOEt layer was washed with brine (30 ml), dried, and concentrated. The residue was crystallized from hexane to give *cis*-**5** (0.12 g, 69%) as colorless needles, mp 139–141°C (AcOEt). IR (KBr) cm^{-1}: 1725, 1690, 1680. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25 (3H, t, *J*=6.9 Hz), 1.35–2.06 (4 H, m), 1.74 (1/2H), 2.38–3.15 (3H, m), 3.23–3.49 (1H, m), 3.37 (3H, s), 3.80–4.03 (1H, m), 4.13 (2H, dd, *J*=14.1, 6.9 Hz), 4.76–5.31 (3H, m), 7.50 (1H, td, *J*=7.3, 1.7 Hz), 7.69–7.82 (2H, m), 8.00 (1H, brs), 8.28 (1H, dd, *J*=7.7, 1.7 Hz, 5-H). MS (FAB, positive ion mode) *m/z*: 388 (MH^+). Anal. Calcd for $C_{20}H_{25}N_3O_5$·1/4H_2O: C, 61.29; H, 6.56; N, 10.72. Found: C, 61.39; H, 6.43; N, 10.92.

3.1.16. 3-{3-[(2*RS*,3*RS*)-1-Ethoxycarbonyl-3-methoxy-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone (*cis*-5) and 3-{3-[(2*RS*,3*SR*)-1-ethoxycarbonyl-3-methoxy-2-piperidinyl]-2-oxopropyl}-4(3*H*)-quinazolinone (*trans*-5). A mixture of *cis*-**18** (0.80 g, 1.8 mmol) and 20% $Pd(OH)_2$/C (0.08 g) in MeOH and THF (1:1, 10 ml) was stirred at the room temperature for 2 h under H_2 gas. The mixture was filtered off and concentrated. A solution of the residure in EtOH was heated at 80°C for 1 h. The mixture was concentrated. To a solution of the residue in CH_2Cl_2 (10 ml) was added dropwise Et_3N (0.297 ml, 2.1 mmol) and ClCOOEt (0.204 ml, 2.1 mmol) at 0°C. The mixture was stirred at the room temperature for 0.5 h under Ar gas. The mixture was poured into water (80 ml) and extracted with AcOEt (80 ml×2). The AcOEt layer was washed with brine (80 ml), dried, and concentrated. The residue was subjected to column chromatography (Al_2O_3; AcOEt/hexane=3:1) to give *cis*-**5** (0.16 g, 23%) as colorless needles. The next eluant gave *trans*-**5** (0.41 g, 59%) as amorphous solid. IR ($CHCl_3$) cm^{-1}: 1730, 1680. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25 (3H, t, *J*=7.2 Hz), 1.35–1.97 (4H, m), 2.72–3.01 (3H, m), 3.27–3.36 (1H, m), 3.39 (3H, s), 3.90–4.08 (1H, m), 4.13 (2H, dd, *J*=14.1, 7.2 Hz), 4.87–5.10 (3H, m), 7.51 (1H, td, *J*=7.5, 1.8 Hz), 7.68–7.81 (2H, m), 7.99 (1H, brs), 8.27 (1H, d, *J*=8.4 Hz, 5-H). MS (FAB, positive ion mode)

m/z: 388 (MH^+). HRMS (FAB) Calcd for $C_{20}H_{26}N_3O_5$ (MH^+): 388.1872. Found: 388.1887.

3.2. Reaction of *cis*-5 with 6N HCl

A solution of *cis*-**5** (116 mg, 0.30 mmol) in 6N aqueous HCl solution was heated at reflux for 4 h. The mixture was poured into saturated aqueous $KHCO_3$ solution (50 ml) and extracted with AcOEt (30 ml×2). The AcOEt layer was washed with brine (50 ml), dried, and concentrated. The residue was subjected to column chromatography (Al_2O_3; AcOEt/hexane=2:1) to give *cis*-**5** (12.2 mg, 11%) as colorless needles. The next eluant (AcOEt/hexane=2:1) gave *trans*-**5** (18.5 mg, 16%) as amorphous solid. The next eluant (EtOH) gave a mixture of *cis*-**6** and *trans*-**6** (24.7 mg, 26%).

3.3. Reaction of *cis*-5 with $BF_3{\cdot}OEt_2$

A mixture of *cis*-**5** (310 mg, 0.80 mmol) and $BF_3{\cdot}OEt_2$ (0.98 ml, 8.0 mmol) in MeCN (6 ml) was heated at reflux for 1 h. The mixture was poured into saturated aqueous $KHCO_3$ solution (50 ml) and extracted with AcOEt (50 ml×2). The AcOEt layer was washed with brine (50 ml), dried, and concentrated. The residue was subjected to column chromatography (Al_2O_3; AcOEt/hexane=2:1) to give *cis*-**5** (129 mg, 42%) as colorless needles and *trans*-**5** (133 mg, 43%) as amorphous solid.

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