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PREPARATION OF CHIRAL RIGHT-HALF MODELS OF ANTITUMOR BISTETRAHYDROISOQUINOLINEQUINONE NATURAL PRODUCTS

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This paper is dedicated to Professor Dr. Kiyoshi Tomioka on the occasion of his 70th birthday.

Abstract – The preparation of chiral right-half model compounds of bistetrahydroisoquinolinequinone natural products having a lactam carbonyl group **(-)-1** or an aminonitrile group **(+)-2** from **(-)-14** was presented. The crucial steps of this synthesis include the *N*-methylation of compound **(-)-12** and ring closure to generate **(-)-19a** without any epimerization at C-2.[1]

INTRODUCTION

Natural products belonging to the bistetrahydroisoquinolinequinone family,[2] including saframycins and renieramycins, have received considerable attention due to their potent biological activities and structural diversity. Although useful as seed compounds for drug discovery, these molecules are very difficult to obtain in large amounts from natural sources or by chemical synthesis. Given this background, our research group has been working on the preparation of simplified model compounds and conducting structure-activity relationship studies of their antitumor activities (**Figure 1**).[3,4]

We previously reported the preparation of right-half model compound **(*rac*)-1**, which possessed a methyl group at C-2 position, *via* key intermediate **(-)-14** (**Chart 1**).[5] Unfortunately, the low values of the optical rotation of some intermediates in the synthetic route for **(-)-14** suggested the possibility of epimerization at C-2 during this transformation. In particular, there were doubts that the *N*-methylation of **(-)-12** under strong basic condition occurred.[6] We report herein an improvement of the preparation of key intermediate **(-)-14** and its transformation into chiral right-half model **(-)-1**. In addition, we describe the synthesis of **(+)-2** having an aminonitrile group at C-21 position, which may be very important to produce strong

antitumor activity, as exemplified by saframycin A or renieramycin M.

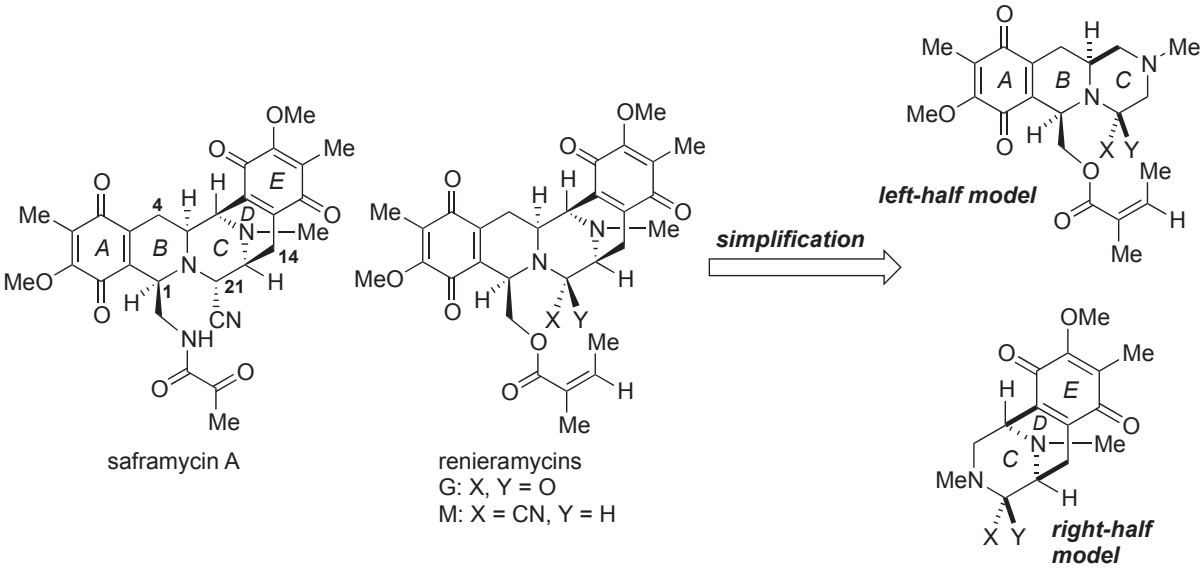


Figure 1. Structures of bistetrahydroisoquinolinequinone natural products along with simplified model

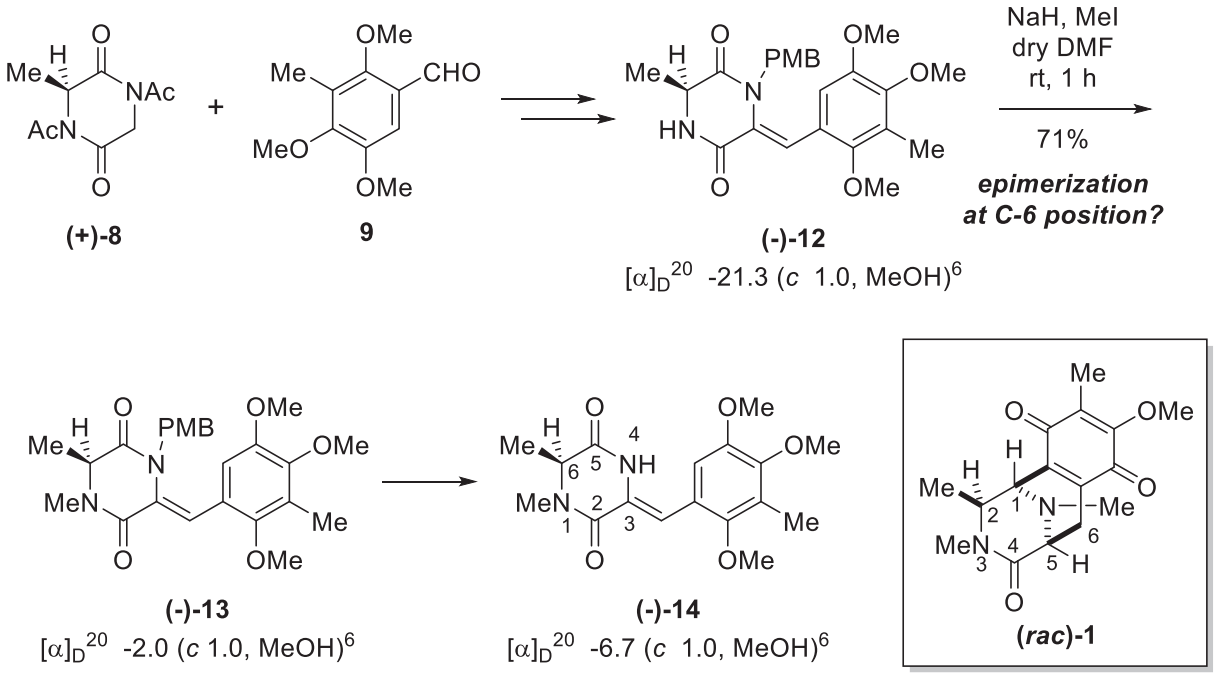
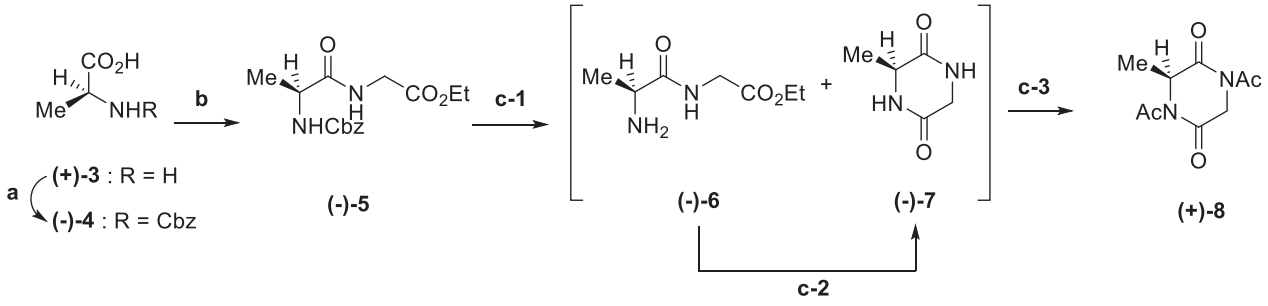


Chart 1. Synthesis of right-half model including preparation of key intermediate **(-)-14**

RESULTS AND DISCUSSION

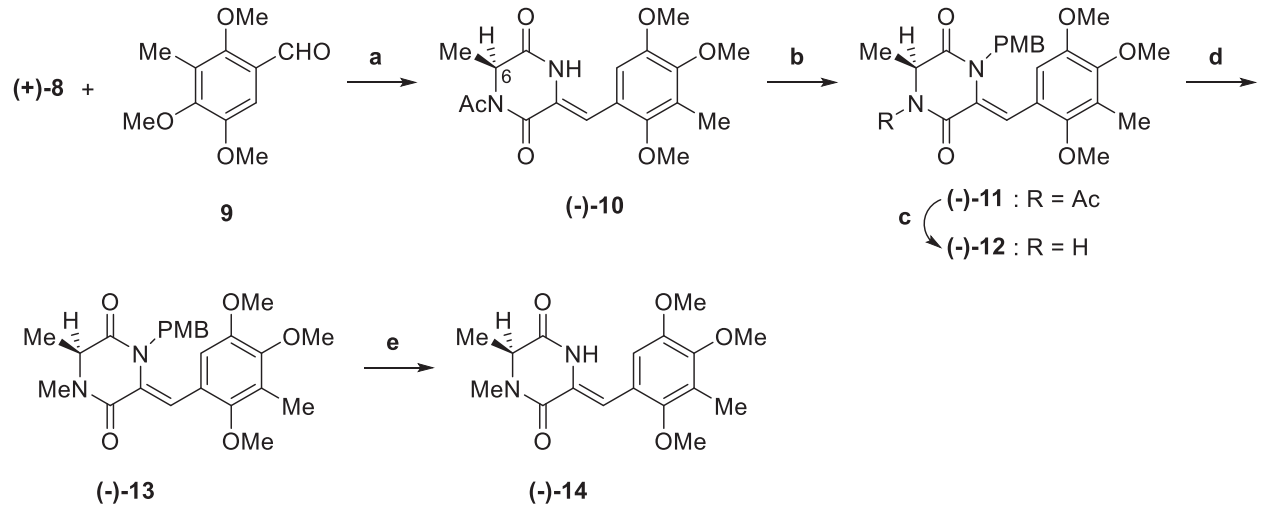
Our synthesis began with the elaboration of piperazine-2,5-dione **(+)-8**[5,7] (**Scheme 1**). Condensation of *N*-Cbz-L-alanine **(-)-4** with glycine afforded **(-)-5** in 87% yield. As removal of the Cbz group of **(-)-5** by catalytic hydrogenation in the presence of 10% Pd/C[8] in ethanol gave a mixture of **(-)-6** and **(-)-7**, this

mixture was refluxed with AcOH in ethanol to convert remaining intermediate **(-)-6** into **(-)-7**. Finally, **(-)-7** was acetylated with acetic anhydride to generate **(+)-8** in 78% from **5**.



Scheme 1. a) CbzCl, $NaOH/H_2O$, 0 °C, 5 h, 82%; b) $H_2NCH_2CO_2Et{\cdot}HCl$, TEA, DCC, CH_2Cl_2, 0 °C and 25 °C, 1 h, 87%; c-1) H_2, 10% Pd/C, EtOH, 25 °C, 4 h; c-2) AcOH, EtOH, reflux, 17 h; c-3) Ac_2O, 110 °C, 3 h, 78% (3 steps).

Next, we focused on the improvement of the synthetic pathway from **(+)-8** into **(-)-14** (**Scheme 2**).

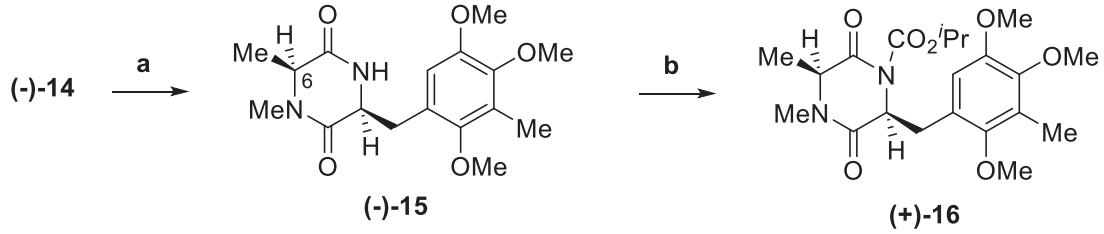


Scheme 2. a) ^{t}BuOK/^{t}BuOH, CH_2Cl_2, 25 °C, 1 h, 76%, 99% ee; b) NaH, PMBCl, DMF, 25 °C, 2 h, 75%, 99% ee; c) $NH_2NH_2{\cdot}H_2O$, DMF, 25 °C, 30 min, 99%, 99% ee; d) K_2CO_3, MeI, DMF, 25 °C, 18 h, 86%, 99% ee; e) H_2SO_4/TFA (1 : 16), 25 °C, 30 min, 96%, 99% ee.

Condensation of **(+)-8** with benzaldehyde **9**[9] afforded **(-)-10** in 76% yield, 99% ee.[10] Protecting the secondary amide of **(-)-10** with a PMB group,[11] followed by removal of the Ac group of **(-)-11** with $NH_2NH_2{\cdot}H_2O$ afforded **(-)-12** in 74% yield from **10**. In our previous work[5,6] where we used NaH as the strong base for the *N*-methylation step of **(-)-12**, the optical purity dramatically decreased. As a result of

examination of several bases, we found that although a bulky strong base, i.e., ^{t}BuOK, could not suppress the epimerization at C-6, a mild condition (such as K_2CO_3) generated **(-)-13** without any isomerization. In this heterogeneous condition (K_2CO_3 in DMF), it was revealed that vigorous stirring was also important to suppress the epimerization at C-6. Removal of the PMB group was then accomplished with H_2SO_4/TFA (1 : 16) to furnish key intermediate **(-)-14**. The enantiomeric excess of **(-)-14** was determined to be 99% by HPLC analysis.

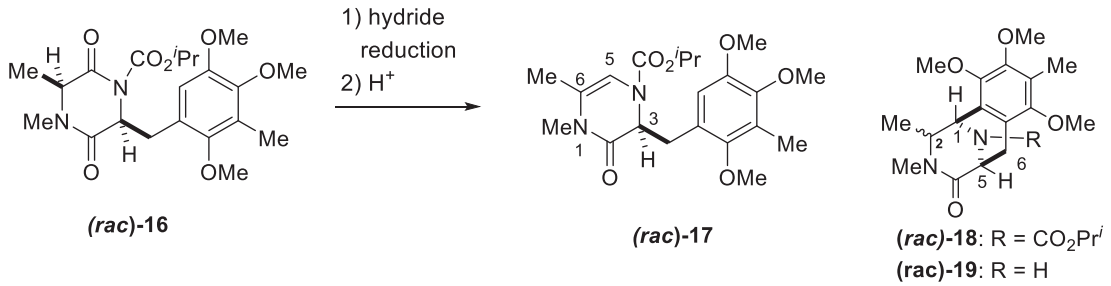
With key intermediate **(-)-14** in hand, reduction of the double bond of **(-)-14** by catalytic hydrogenation in the presence of 10% Pd/C in ethanol occurred from the opposite face against the methyl group at C-6 in 78% yield (**Scheme 3**). Treatment of **(-)-15** with isopropyl chloroformate and base gave cyclization precursor **(+)-16** in 86% yield.



Scheme 3. a) H_2, 10% Pd/C, EtOH, 25 ^{o}C, 3 h, 78%, 99% ee; b) $ClCO_2Pr^{i}$, TEA, DMAP, CH_2Cl_2, 25 ^{o}C, 10 h, 86%.

Then, we investigated the conditions for the cyclization reaction. We reported that chemoselective reduction of the carbonyl group at C-5 position with isopropyloxycarbonyl group in **(*rac*)-16** with Li(^{t}BuO)$_3$AlH, followed by treatment with several acids caused undesirable problems (**Table 1**).[5] Reduction of **(*rac*)-16** followed by dehydration with formic acid gave enamine **(*rac*)-17** in 79% yield without producing any cyclization products (Entry 1). Cyclization with TFA generated a diastereomeric mixture of cyclized product **(*rac*)-18** (ca. 1 : 1). It might be isomerized at C-2 in **18** during the cyclization reaction (Entry 2). Furthermore, treatment with *conc* H_2SO_4 and TFA led to not only the formation of cyclized product but also the removal of the isopropyloxycarbonyl group along with isomerization at C-2 (Entry 3). The ratio of diastereomers **(*rac*)-19** was confirmed by ^{1}H-NMR spectroscopy to be 1 : 1.

Table 1. Investigation of acidic conditions for cyclization step in our previous work[5]



Entry	Acid	Temp (°C)	Time (h)	Yield (%)		
				***(rac)*-17**	***(rac)*-18***	***(rac)*-19***
1	HCO_2H	70	0.5	79	—	—
2	TFA	60-70	24	—	51	—
3	*conc* H_2SO_4-TFA	25	overnight	—	—	98

*Yields of **(*rac*)-18** and **(*rac*)-19** ware calculated as 1 : 1 mixture of diastereomers

A proposed mechanism for this reaction is illustrated in **Chart 2**. Initially, the dehydration of aminoalcohol **20**, which was produced by treatment of **(*rac*)-16** with $Li(^tBuO)_3AlH$, afforded iminium ion **A**. This intermediate was easily transformed into enamine **(*rac*)-17**. In the weakly acidic condition, such as when HCO_2H was used, the reaction might be stopped at this stage. In the more strongly acidic condition, such as when TFA and *conc* H_2SO_4 were used, could receive enough acidity to afford **(*rac*)-19** together with epimerization at C-2 position. The removal of the isopropyloxycarbonyl group with isomerization at C-2 would depend on the acidity. Therefore, it might be important to find a suitable p*Ka* for the intramolecular electrophilic cyclization to maintain the stereochemistry at C-2 position.

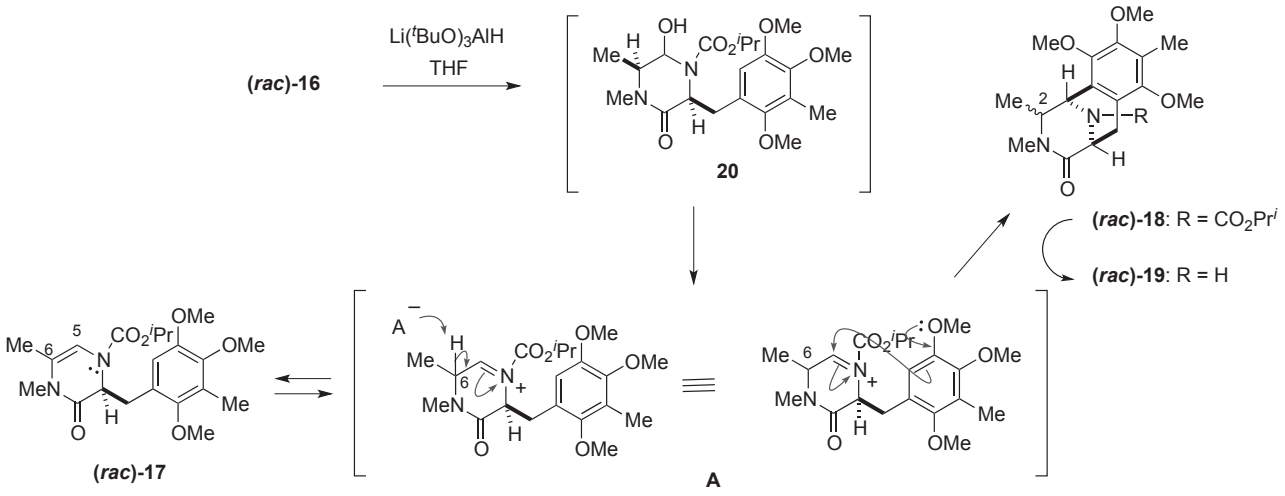
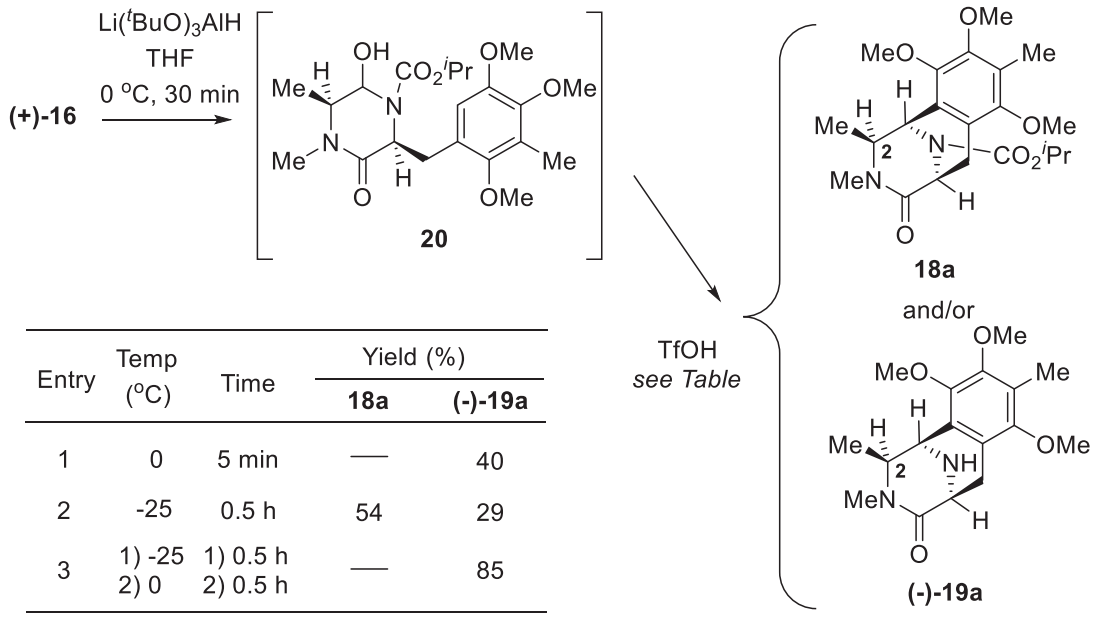


Chart 2. Plausible mechanism of the cyclization step to complete enamine generation

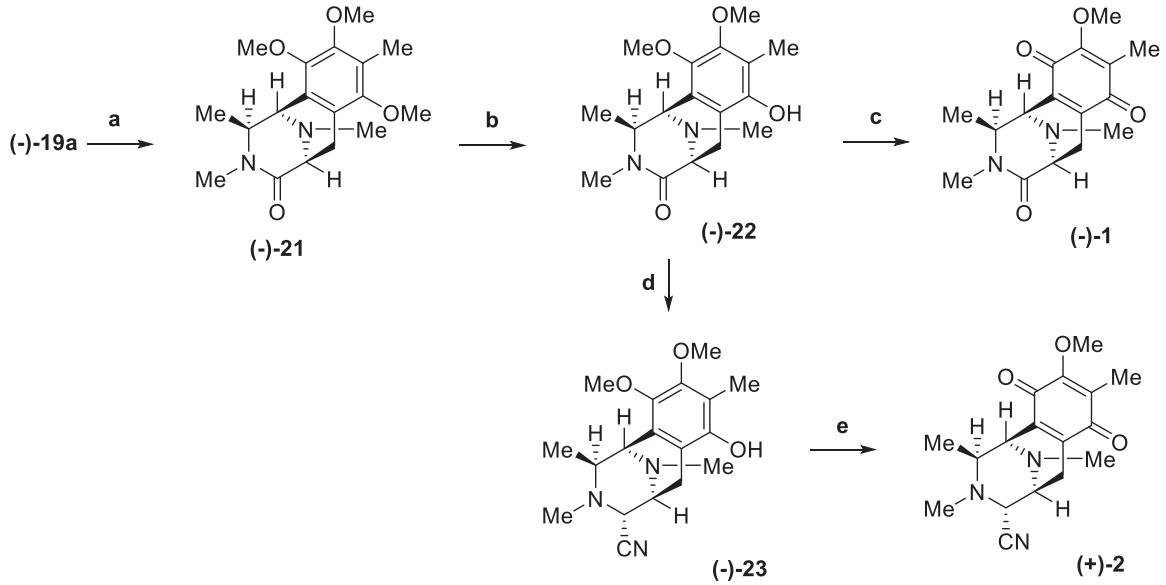
When **(+)-16** was treated with Li(^{t}BuO)$_3$AlH to afford aminoalcohol **20** and then with TfOH[12] at 0 °C, cyclization proceeded smoothly and **(-)-19a** was exclusively obtained in 40% yield together with several inseparable degradation products (**Table 2**, Entry 1). In order to prevent the formation of side products, we investigated the reaction conditions, specifically solvent[13] and reaction temperature. As shown in Entry 2, the yield of **18a** was 54% and that of **(-)-19a** was 29% without epimerization at -25 °C (freezing point of TfOH is -40 °C). These results suggest that aminoalcohol **20** was stable at -25 °C. However, the transformation of **18a** into **(-)-19a** might be intercepted to give the reaction potential energy. Thus, **20** was treated with TfOH at -25 °C to promote cyclization, and this was followed by the removal of isopropyloxycarbonyl group at 0 °C to generate only **(-)-19a** in 85% yield.



Entry	Temp (°C)	Time	Yield (%)	
			18a	**(-)-19a**
1	0	5 min	—	40
2	-25	0.5 h	54	29
3	1) -25 2) 0	1) 0.5 h 2) 0.5 h	—	85

Table 2. Investigation of cyclization reaction with TfOH, focusing on temperature condition

Finally, the synthesis of target molecules **(-)-1** and **(+)-2** from **(-)-19a** was achieved by the following transformations (**Scheme 4**). The reductive *N*-methylation of **(-)-19a** afforded **(-)-21** in 93% yield. Partial demethylation of **(-)-21** with BBr_3 gave **(-)-22** in 99% yield, and oxidation of the phenol group with 8 M HNO_3 produced *p*-quinone **(-)-1** in 88% yield. On the other hand, reduction of the lactam carbonyl group of **(-)-22** by $LiAlH_2(OEt)_2$, followed by the addition of aqueous KCN solution and AcOH generated desired compound **(-)-23** in 86% yield. Subsequent oxidative demethylation of **(-)-23** with CAN produced target compound **(+)-2** in 87% yield.



Scheme 4. a) 37% HCHO-H_2O, HCO_2H, 70 ºC, 1 h, 93%; b) BBr_3, CH_2Cl_2, -78 ºC, 20 min, -78 to 0 ºC, 3.5 h, and then 0 ºC, 1 h, 99%; c) 8 M HNO_3, 0 ºC, 45 min, 88%; d-1) $LiAlH_2(OEt)_2$, THF, 0 ºC, 1 h; d-2) aqueous KCN, AcOH, 25 ºC, 1 h, 86%; e) CAN, MeCN/H_2O, 0 ºC, 1 h, 87%.

In summary, we succeeded in the optimization of the synthetic route to key chiral intermediate **(-)-14** by determining the base and the stirring speed for the *N*-methylation of **(-)-12**. The transformation of **(-)-14** into chiral model molecules **(-)-1** and **(+)-2** was also accomplished, which involves cyclization using TfOH without epimerization at C-2 as the key step. Efforts are being made to apply this transformation to the synthesis of versatile right-hand half models in optically active forms, and medicinal chemistry research on them is under way.

EXPERIMENTAL

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured with Horiba SEPA-300 and 500 polarimeters. IR spectra were obtained with a Shimadzu Prestige-21/IR Affinity-1 Fourier Transform Infrared (FT-IR) spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL ECS-400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C, on a JEOL AL-400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C, and on a JEOL AL-300 spectrometer at 300 MHz for ^{1}H. NMR spectra were measured in $CDCl_3$ and chemical shifts were recorded in δ_H values relative to Me_4Si (TMS) as the internal standard. Mass spectra were recorded on a JMS-700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were conducted on a YANACO MT-6 CHN CORDER elemental analyzer. High performance liquid chromatography (HPLC): CHIRALPAK IC (Daicel).

(*S*)-2-{[(Benzyloxy)carbonyl]}amino}propanoic acid: **(-)-4**

Benzyl chloroformate (34.4 mL, 240 mmol) and 4 M aqueous NaOH solution (50.2 mL) were added dropwise into a solution of L-alanine (**(+)-3**) (17.8 g, 200 mmol) in 2 M aqueous NaOH solution (100 mL) over 45 min at 0 °C, and the mixture was stirred at the same temperature for 5 h. After the reaction mixture was washed with Et_2O (200 mL x 2), the aqueous layer was made acidified with concentrated HCl at 0 °C, and extracted with $CHCl_3$ (600 mL x 3). The combined extracts were washed with H_2O (180 mL), dried, and concentrated in vacuo to give **(-)-4** (36.6 g, 82%) as colorless needles, mp 80.0-81.0 °C (*lit*.,[14] mp 84-85 °C).

$[\alpha]_D^{25}$ -19.1 (*c* 1.0, EtOH). ν_{max} (KBr) 3335, 3032, 1695, 1537, 1464, 1454, 1336, 1292, 1277, 1253, 1076, 1037, 1028, 1020 cm^{-1}. δ_H (400 MHz) 1.45 (3H, d, *J* = 7.1 Hz, C*H*$_3$), 4.42 (1H, quint, *J* = 7.1 Hz, 2-H), 5.09 (1H, d, *J* = 12.5 Hz, C*H*), 5.13 (1H, d, *J* = 12.5 Hz, C*H*), 5.39 (1H, br d, *J* = 7.1 Hz, *N*H), 7.29-7.38 (5H, m, Ph). δ_C (100 MHz) 18.3 (CH_3), 49.4 (CH), 67.1 (CH_2), 128.1 (CH), 128.2 (CH), 128.5 (CH), 136.0 (C), 155.8 (NCO), 177.6 (CO_2H).

(*S*)-Ethyl 2-{2-([(benzyloxy)carbonyl]amino)propanamido)acetate: **(-)-5**

Et_3N (9.9 mL, 71.5 mmol), **(-)-4** (14.5 g, 65 mmol) and a suspension of DCC (14.8 g, 71.5 mmol) in CH_2Cl_2 (65 mL) were added successively to a suspension of glycine ethyl ester hydrochloride (10.0 g, 71.5 mmol) in CH_2Cl_2 (120 mL) at -8 °C, and the mixture was stirred at 0 °C for 1 h, and then 25 °C for 1 h. After the precipitate was removed by filtration, the filtrate was washed with 5% aqueous $NaHCO_3$ solution (250 mL x 3), H_2O (250 mL x 3), 1 M aqueous HCl solution (250 mL x 3) and H_2O (250 mL x 3), dried, and concentrated in vacuo. The residue (20.5 g) was subjected to column chromatography on SiO_2 (250 g) with hexane-EtOAc (1:1) to give **(-)-5** (17.5 g, 87%). An analytical sample was obtained by recrystallization from hexane- EtOAc as colorless needles, mp 99.0-101.0 °C (*lit*.,[15] mp 98-99 °C).

$[\alpha]_D^{25}$ -21.2 (*c* 1.2, MeOH). ν_{max} (KBr) 3292, 1764, 1697, 1654, 1557, 1539, 1375, 1354, 1321, 1263, 1246, 1192, 1171, 1130, 1074, 1055, 1022 cm^{-1}. δ_H (400 MHz) 1.28 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.41 (3H, d, *J* = 7.1 Hz, 2'-CH_3), 4.02 (2H, br d, *J* = 5.3 Hz, 2-CH_2), 4.21 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 4.30 (1H, m, 2'-H), 5.09 (1H, q, *J* = 12.3 Hz, C*H*Ph), 5.15 (1H, q, *J* = 12.3 Hz, C*H*Ph), 5.35 (1H, br s, *N*H), 6.61 (1H, br s, *N*H), 7.28-7.39 (5H, m, Ph). δ_C (100 MHz) 14.1 (CH_3), 18.5 (CH_3), 41.3 (NCH_2), 50.4 (CH), 61.5 (OCH_2CH_3), 67.0 (CH_2), 128.0 (CH), 128.2 (CH), 128.5 (CH), 136.1 (C), 156.0 (NCO), 169.7 (CO_2Et), 172.6 (CO_2CH_2).

(*S*)-1,4-Diacetyl-3-methylpiperazine-2,5-dione: **(+)-8**

A suspension of **(-)-5 (**3.08 g, 10.0 mmol) in EtOH (80 mL) was hydrogenated over 10% Pd on carbon (1.17 g) at 25 °C for 4 h. Acetic acid (1.7 mL, 30.0 mmol) was added to a solution of the residue (1.97 g)

in EtOH (80 mL) at 25 ºC, and the mixture was heated under reflux for 17 h. The reaction mixture was cooled to 0 ºC, and then it was concentrated in vacuo to give a residue.[16] A suspension of the residue (1.64 g) in Ac_2O (43 mL) was stirred at 110 ºC for 3 h. The reaction mixture was concentrated in vacuo, and the residue was diluted with H_2O (100 mL), and extracted with EtOAc (100 mL x 3). The combined extracts were washed with 5% aqueous $NaHCO_3$ solution (100 mL), dried, and concentrated in vacuo. The crude product (2.69 g) was subjected to column chromatography on SiO_2 (30 g) with hexane-EtOAc (2:1) to give **(+)-8** (1.65 g, 78%) as a colorless oil.

$[\alpha]_D^{25}$ +61.7 (*c* 1.0, MeOH). ν_{max} ($CHCl_3$) 3022, 1716, 1416, 1383, 1371, 1308, 1290, 1259, 1242, 1227, 1206, 1142, 1084, 986 cm^{-1}. δ_H (300 MHz) 1.54 (3H, d, *J* = 7.3 Hz, 3-CH_3) 2.57 (3H, s, COC*H*$_3$), 2.59 (3H, s, COC*H*$_3$), 4.03 (1H, d, *J* = 18.5 Hz, 6-H), 5.15 (1H, d, *J* = 18.5 Hz, 6-H), 5.26 (1H, q, *J* = 7.3 Hz, 3-H). δ_C (100 MHz) 17.7 (CH_3), 26.8 ($COCH_3$), 26.9 ($COCH_3$), 46.4 (6-CH_2), 53.9 (CH), 165.3 (C=O), 168.6 (C=O), 170.9 (C=O), 171.2 (C=O). EIMS *m/z* (%): 212 (M^+, 50), 170 (100), 169 (70), 43 (97). HREIMS calcd for $C_9H_{12}N_2O_4$: 212.0797. Found: 212.0794.

(6*S*,3*Z*)-1-Acetyl-6-methyl-3-(2,4,5-trimethoxy-3-methylbenzylidene)piperazine-2,5-dione: **(-)-10**

A solution of *tert*-BuOK in *tert*-BuOH (0.5 M, 4.6 mL, 2.30 mmol) was added to a solution of **(+)-8** (488 mg, 2.30 mmol) and 2,4,5-trimethoxy-3-methylbenzaldehyde (**9**)[9] (484 mg, 2.30 mmol) in CH_2Cl_2 (4.6 mL) over 10 min at 0 ºC, and then the mixture was stirred at 25 ºC for 1 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution (20 mL) at 0 ºC, and extracted with CH_2Cl_2 (30 mL x 3). The combined extracts were washed with brine (30 mL), dried, and concentrated in vacuo. The residue (847 mg) was subjected to column chromatography on SiO_2 (30 g) with hexane-EtOAc (5:1) to give **9** (92.6 mg, 19% recovery) and hexane-EtOAc (2:1) to give **(-)-10** (605 mg, 76%, 99%*ee*). An analytical sample was obtained by recrystallization from EtOAc as colorless needles, mp 136.5-137.5 ºC.

$[\alpha]_D^{26}$ -8.2 (*c* 1.0, $CHCl_3$). The *ee* value was determined by HPLC analysis using CHIRALPAK IC [hexane/EtOH = 50/50, flow 1.0 mL/min, t_r (minor) = 8.50 min, t_r (major) = 6.74 min]. ν_{max} (KBr) 1699, 1685, 1678, 1628, 1466, 1458, 1389, 1371, 1252, 1234, 1084 cm^{-1}. δ_H (400 MHz) 1.48 (3H, d, *J* = 7.1 Hz, 6-CH_3) 2.25 (3H, s, 3'-CH_3), 2.62 (3H, s, CO*C*H$_3$), 3.64 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.11 (1H, q, *J* = 7.1 Hz, 6-H), 6.68 (1H, s, 6'-H), 7.04 (1H, s, 3a-H), 9.25 (1H, br s, *N*H). δ_C (100 MHz) 9.5 (3'-CH_3) 19.7 (6-CH_3), 26.9 (CO*C*H$_3$), 52.9 (C-6), 55.9 (OCH_3), 60.4 (OCH_3), 61.4 (OCH_3), 111.9 (C-6'), 117.4 (C-3a), 121.2 (C-3), 125.6 (C-1'), 126.7 (C-3'), 149.3, 149.6, 149.7 (C-2', C-4', C-5'), 161.4 (C-2), 166.8 (C-5), 172.0 (*C*OCH$_3$). EIMS *m/z* (%): 363 (M^+ + 1, 16), 362 (M^+, 82), 290 (18), 289 (100), 206 (15). HREIMS *m/z* calcd for $C_{18}H_{22}N_2O_6$, 362.1478. Found: 362.1477.. Anal. Calcd for $C_{18}H_{22}N_2O_6$: C 59.66, H 6.12, N 7.73. Found: C 59.68, H 6.05, N 7.75.

(6*S,3Z*)-1-Acetyl-4-(4-methoxybenzyl)-6-methyl-3-(2,4,5-trimethoxy-3-methylbenzylidene)piperazine-2,5-dione: **(-)-11**

NaH (60% oil dispersion) (748 mg, 18.7 mmol) was added to a solution of **(-)-10** (6.16 g, 17.0 mmol) in dry DMF (180 mL) slowly at 0 °C, and the mixture was stirred at same temperature for 40 min. PMBCl (3.87 g, 24.7 mmol) was added into the reaction mixture, which was stirred at 25 °C for 2 h. The reaction mixture was concentrated in vacuum, and the residue was diluted with H_2O (200 mL), and extracted with hexane/EtOAc (1:2, 200 mL x 3). The combined extracts were washed with H_2O (200 mL), dried, and concentrated in vacuo to give a residue (10.2 g), recryatallization of which from Et_2O afforded **(-)-11** (6.13 g, 75%, 99%*ee*) as colorless prisms, mp 123.0-125.0 °C.

$[\alpha]_D^{24.5}$ -21.6 (*c* 1.0, MeOH). The *ee* value was determined by HPLC analysis using CHIRALPAK IC [hexane/EtOH = 80/20, flow 1.0 mL/min, t_r (minor) = 8.50 min, t_r (major) = 10.31 min]. ν_{max} (KBr) 2995, 2938, 2839, 1705, 1686, 1628, 1514, 1487, 1460, 1408, 1385, 1368, 1240, 1180, 1130, 1087 cm^{-1}. δ_H (400 MHz) 1.55 (3H, d, *J* = 7.1 Hz, 6-CH_3), 2.25 (3H, s, 3'-CH_3), 2.56 (3H, s, CO*C*H_3), 3.60 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.03 (1H, d, *J* = 14.7 Hz, C*H*), 5.26 (1H, q, *J* = 7.1 Hz, 6-H), 5.26 (1H, d, *J* = 14.7 Hz, C*H*), 6.66 (1H, s, 6'-H), 6.72 (2H, d, *J* = 8.7 Hz, 2 x ArH), 6.84 (2H, d, *J* = 8.7 Hz, 2 x ArH), 7.36 (1H, s, 3a-H). δ_C (100 MHz) 9.6 (3'-CH_3) 17.9 (6-CH_3), 27.0 (CO*C*H_3), 46.4 (*C*H_2), 52.7 (C-6), 55.2 (OCH_3), 56.0 (OCH_3), 60.5 (OCH_3), 61.8 (OCH_3), 109.7 (C-6'), 113.8 (CH), 121.2 (C-1'), 121.3 (C-3a), 126.2 (s, C-3'), 128.2 (C), 128.8 (C), 129.0 (CH), 149.2 (C), 149.9 (C), 152.5 (C), 159.1 (C), 163.9 (C-2), 167.9 (C-5), 171.6 (*C*OCH_3). EIMS *m/z* (%): 483 (20), 482 (M^+, 71), 451 (12), 121 (100). HREIMS *m/z* calcd for $C_{26}H_{30}N_2O_7$, 482.2051. Found: 482.2053. Anal. Calcd for $C_{26}H_{30}N_2O_7$: C 64.71, H 6.27, N 5.81. Found: C 64.73, H 6.28, N 5.78.

(6*S,*3*Z*)-4-(4-Methoxybenzyl)-6-methyl-3-(2,4,5-trimethoxy-3-methylbenzylidene)piperazine-2,5-dione: **(-)-12**

Hydrazine monohydrate (2.7 mL, 54.5 mmol) was added to a solution of **(-)-11** (5.03 g, 10.4 mmol) in DMF (143 mL) at 25 °C, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into H_2O (200 mL) at 0 °C and the mixture was extracted with $CHCl_3$ (200 mL x 3). The combined extracts were washed with H_2O (200 mL), dried, and concentrated in vacuo to give a residue (6.80 g), which was subjected to column chromatography on SiO_2 (70 g) with hexane-$CHCl_3$ (1:1-1:4) to furnish **(-)-12** (4.53 g, 99%, 99%*ee*) as a colorless amorphous powder.

$[\alpha]_D^{24.5}$ -20.4 (*c* 1.0, MeOH). The *ee* value was determined by HPLC analysis using CHIRALPAK IC [hexane/EtOH = 50/50, flow 1.0 mL/min, t_r (minor) = 5.52 min, t_r (major) = 5.86 min]. ν_{max} (KBr) 2938, 1690, 1628, 1514, 1485, 1456, 1445, 1408, 1371, 1306, 1248, 1227, 1177, 1128, 1088, 1009, 995 cm^{-1}. δ_H (400 MHz) 1.56 (3H, d, *J* = 7.0 Hz, 6-CH_3), 2.23 (3H, s, 3'-CH_3), 3.56 (3H, s, OCH_3), 3.73 (3H, s, OCH_3),

3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.20 (1H, dq, *J* = 7.0, 2.1 Hz, 6-H), 4.65 (2H, s, C*H*$_2$), 6.63 (1H, s, 6'-H), 6.70 (2H, d, *J* = 8.7 Hz, 2 x ArH), 6.84 (2H, d, *J* = 8.7 Hz, 2 x ArH), 7.15 (1H, br s, *N*H), 7.19 (1H, s, 3a-H). δ_C (100 MHz) 9.5 (3'-CH_3), 18.6 (6-CH_3), 46.6 (CH_2), 51.0 (C-6), 55.1 (O*C*H_3), 56.0 (OCH_3), 60.4 (OCH_3), 61.2 (OCH_3), 110.3 (C-6'), 113.7 (CH), 118.0 (C-3a), 121.9 (C-1'), 126.0 (C), 128.6 (C), 128.8 (CH), 129.5 (C), 149.0 (C), 149.1 (C), 151.9 (C), 158.8 (C), 165.5 (C-5), 168.3 (C-2). EIMS *m/z* (%): 441 (M^+ + 1, 18), 440 (M^+, 66), 410 (22), 409 (87), 319 (15), 304 (26), 288 (21), 217 (12), 121 (100). HREIMS *m/z* calcd for $C_{24}H_{28}N_2O_6$, 440.1946. Found: 440.1948.

(6*S*, 3*Z*)-4-(4-Methoxybenzyl)-1,6-dimethyl-3-(2,4,5-trimethoxy-3-methylbenzylidene)piperazine-2,5-dione: **(-)-13**

K_2CO_3 (8.85 g, 64.0 mmol) and MeI (2.20 mL, 35.2 mmol) was added successively into a solution of **(-)-12** (7.05 g, 16.0 mmol) in DMF (64 mL) at 0 °C, and the mixture was stirred vigorously at 25 °C for 18 h. The reaction mixture was diluted with H_2O (32 mL) and extracted with $CHCl_3$ (64 mL x 3). The combined extracts were washed with brine (64 mL), dried, and concentrated in vacuo to give a residue. The residue (8.52 g) was subjected to column chromatography on SiO_2 (300 g) with $CHCl_3$-benzene-EtOAc (5:1:1) to give **(-)-13** (6.29 g, 86%, 99%*ee*) as a pale yellow amorphous powder.

$[\alpha]_D^{24}$ -27.2 (*c* 1.0, MeOH). The *ee* value was determined by HPLC analysis using CHIRALPAK IC [hexane/EtOH = 50/50, flow 1.0 mL/min, t_r (minor) = 6.27 min, t_r (major) = 7.30 min]. ν_{max} (KBr) 2936, 1686, 1624, 1514, 1485, 1452, 1423, 1406, 1389, 1337, 1306, 1229, 1250, 1177, 1132, 1088, 1032, 1009 cm^{-1}. δ_H (400 MHz) 1.55 (3H, d, *J* = 6.9 Hz, 6-CH_3), 2.23 (3H, s, 3'-CH_3), 3.04 (3H, s, 4-CH_3), 3.55 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.04 (1H, q, *J* = 6.9 Hz, 6-H), 4.06 (1H, d, *J* = 14.9 Hz, C*H*), 5.14 (1H, d, *J* = 14.9 Hz, C*H*), 6.59 (1H, s, 6'-H), 6.70 (2H, d, *J* = 8.6 Hz, 2 x ArH), 6.82 (2H, d, *J* = 8.6 Hz, 2 x ArH), 7.19 (1H, s, 3a-H). δ_C (100 MHz) 9.5 (3'-CH_3), 17.4 (6-CH_3), 32.2, (4-CH_3), 46.3 (CH_2), 55.1 (O*C*H_3), 56.0 (OCH_3), 59.2 (C-6), 60.4 (OCH_3), 61.2 (OCH_3), 110.2 (C-6'), 113.7 (CH), 117.7 (C-3a), 122.3 (C-1'), 125.9 (C-3'), 128.5 (CH), 128.9 (CH), 129.4 (C), 148.9, 149.0 (C), 151.7 (C), 158.8 (C), 162.8 (C-5), 167.9 (C-2). EIMS *m/z* (%): 454 (M^+, 28), 424 (26), 423 (100), 318 (16), 302 (14), 121 (39). HREIMS *m/z* calcd for $C_{25}H_{30}N_2O_6$, 454.2102. Found: 454.2101.

(6*S*, 3*Z*)-1,6-Dimethyl-3-(2,4,5-trimethoxy-3-methylbenzylidene)piperazine-2,5-dione: **(-)-14**

Concentrated H_2SO_4 (2.9 mL) was added into a solution of **(-)-13** (2.05 g, 4.51 mmol) in TFA (47 mL) over 10 min at 0 °C, and the reaction mixture was stirred at 25 °C for 30 min. The mixture was poured into H_2O (350 mL) at 0 °C and extracted with $CHCl_3$ (350 mL x 3). The combined extracts were washed with 5% aqueous $NaHCO_3$ solution (350 mL), dried, and concentrated in vacuo to give a residue (2.15 g), which was subjected to column chromatography on SiO_2 (40 g) with benzene-EtOAc (1:1) to give **(-)-14**

(1.45 g, 96%, 99%*ee*) as a colorless amorphous powder. An analytical sample was obtained by recrystallization from hexane- EtOAc to give pure (-)-**14** as colorless needles, mp 140.5-142.0 °C. $[\alpha]_D^{25}$ -155.4 (*c* 1.0, MeOH). The *ee* value was determined by HPLC analysis using CHIRALPAK IC [hexane/EtOH = 80/20, flow 1.0 mL/min, t_r (minor) = 14.15 min, t_r (major) = 16.33 min]. ν_{max} (KBr) 3246. 2943, 1684, 1620, 1492, 1458, 1443, 1400, 1364, 1341, 1256, 1246, 1086 cm^{-1}. δ_H (400 MHz) 1.54 (3H, d, *J* = 7.1 Hz, 6-CH_3), 2.24 (3H, s, 3'-CH_3), 3.10 (3H, s, *N*CH_3), 3.62 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.05 (1H, q, *J* = 7.1 Hz, 6-H), 6.65 (1H, s, 3a-H), 6.89 (1H, s, 6'-H), 9.28 (1H, br s, *N*H). δ_C (100 MHz) 9.4 (3'-CH_3), 18.9 (6-CH_3), 32.9 (*N*CH_3), 55.8 (OCH_3), 58.7 (d, C-6), 60.3 (OCH_3), 61.0 (OCH_3), 111.7 (C-3a), 113.4 (C-6'), 121.7 (C-1'), 125.3 (C), 126.4 (C), 148.6 (C), 148.9 (C), 149.6 (C), 159.1 (C-2), 166.3 (s, C-5). EIMS *m/z* (%): 334 (M^+, 31), 304 (18), 303 (100). HREIMS *m/z* calcd for $C_{17}H_{22}N_2O_5$, 334.1527. Found: 334.1528. Anal. Calcd for $C_{17}H_{22}N_2O_5$: C 61.07, H 6.63, N 8.38. Found: C 61.41, H 6.43, N 8.23.

(3*S*,6*S*)-1,6-Dimethyl-3-(2,4,5-trimethoxy-3-methylbenzyl)piperazine-2,5-dione: **(-)-15**

A suspension of **(-)-14 (**3.21 g, 9.60 mmol) in EtOH (350 mL) was hydrogenated over 10% Pd on carbon (3.06 g) at 25 °C for 3 h. The catalyst was removed by filtration, then the filtrates were concentrated in vacuum, diluted with 5% aqueous $NaHCO_3$ solution (100 mL), and extracted with CH_2Cl_2 (100 mL x 3). The combined extracts were washed with H_2O (100 mL), dried, and concentrated in vacuo. The residue (3.48 g) was subjected to column chromatography on SiO_2 (50 g) with EtOAc-MeOH (20:1-10:1) to give **(-)-15** (3.15 g, 98%, 99%*ee*) as a colorless amorphous powder, recrystallization of which from EtOAc afforded **(-)-15** (2.52 g, 78%, >99%*ee*) as colorless needles, mp 148.0-150.0 °C.

$[\alpha]_D^{25.5}$ -72.2 (*c* 1.0, $CHCl_3$). The *ee* value was determined by HPLC analysis using CHIRALPAK IC [hexane/EtOH = 50/50, flow 1.0 mL/min, t_r (minor) = 8.00 min, t_r (major) = 10.77 min]. ν_{max} (KBr) 3183, 2940, 1682, 1643, 1489, 1466, 1449, 1412, 1337, 1238, 1119, 1086 cm^{-1}. δ_H (400 MHz) 1.26 (3H, d, *J* = 7.1 Hz, 6-CH_3), 2.21 (3H, s, 3'-CH_3), 2.96 (1H, dd, *J* = 13.5, 8.3 Hz, 3a-Hα), 2.96 (3H, s, *N*CH_3), 3.29 (1H, dd, *J* = 13.5, 3.7 Hz, 3a-Hβ), 3.67 (3H, s, OCH_3), 3.77 (3H, s, 4'-OCH_3), 3.81 (3H, s, OCH_3), 3.83 (1H, q, *J* = 7.1 Hz, 6-H), 4.29 (1H, m, *J* = 8.3, 3.7 Hz, 3-H), 6.00 (1H, br s, *N*H), 6.55 (1H, s, 6'-H). δ_C (100 MHz) 9.7 (3'-CH_3), 18.3 (6-CH_3), 32.3 (*N*CH_3), 35.7 (C-3a), 56.0 (OCH_3), 56.5 (C-3), 57.4 (C-6), 60.2 (OCH_3), 60.6 (OCH_3), 111.2 (C-6'), 123.3 (C-1'), 126.1 (C), 147.4 (C), 149.5 (C), 151.4 (C), 165.4 (C-2), 167.9 (C-5). EIMS *m/z* (%): 336 (M^+, 24), 196 (12), 195 (100), 165 (10). HREIMS *m/z* calcd for $C_{17}H_{24}N_2O_5$, 336.1684. Found: 336.1683. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C 60.70, H 7.19, N 8.33. Found: C 60.84, H 7.17, N 8.50.

(3*S*,6*S*)-Isopropyl 3,4-dimethyl-2,5-dioxo-6-(2,4,5-trimethoxy-3-methylbenzyl)piperazine-1-carboxylate: **(+)-16**

Isopropyl chloroformate (5.2 mL, 44.0 mmol) was added into a mixture of **(-)-15** (2.49 g, 7.40 mmol), Et_3N (2.9 mL, 22.2 mmol) and DMAP (2.49 g, 22.2 mmol) in CH_2Cl_2 (170 mL) at 0 ºC, and the mixture was stirred at 25 ºC for 10 h. The reaction mixture was diluted with 1 M aqueous HCl solution (120 mL) and extracted with $CHCl_3$ (60 x 3 mL). The combined extracts were washed with 1 M aqueous HCl solution (120 mL), and then 5% aqueous $NaHCO_3$ solution (120 mL), dried, and concentrated in vacuo. The residue (3.56 g) was subjected to column chromatography on SiO_2 (50 g) with hexane-EtOAc (1:1-1:2) to give **(+)-16** (2.68 g, 86%, >99%*ee*) as a pale yellow oil. An analytical sample was obtained by recrystallization from hexane-Et_2O gave pure (-)-**15** as colorless prisms, mp 45.0-46.0 ºC.

$[\alpha]_D^{25}$ +64.2 (*c* 1.0, $CHCl_3$). The *ee* value was determined by HPLC analysis using CHIRALPAK IC [hexane/EtOH = 50/50, flow 1.0 mL/min, t_r (minor) = 7.33 min, t_r (major) = 10.56 min]. ν_{max} (KBr) 3593, 3501, 2984, 2941, 2839, 2359, 1778, 1721, 1659, 1624, 1593 cm^{-1}. δ_H (400 MHz) 0.98 (3H, d, *J* = 7.1 Hz, 3-CH_3), 1.26 (3H, d, *J* = 6.3 Hz, CH(C*H*$_3$)$_2$), 1.30 (3H, d, *J* = 6.3 Hz, CH(C*H*$_3$)$_2$), 2.19 (3H, s, 3'-CH_3), 2.89 (3H, s, 4-CH_3), 3.10 (1H, dd, *J* = 13.9, 5.7 Hz, 6a-H), 3.42 (1H, dd, *J* = 13.9, 5.3 Hz, 6a-H), 3.62 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.94 (1H, q, *J* = 7.1 Hz, 6-H), 5.01 (1H, sept, *J* = 6.3 Hz, C*H*(CH$_3$)$_2$), 5.06 (1H, dd, *J* = 5.7, 5.3 Hz, 6-H), 6.52 (1H, s, 6'-H). δ_C (100 MHz) 9.7 (3'-CH_3), 17.3 (3-CH_3), 21.5 (CH(*C*H$_3$)$_2$), 21.6 (CH(*C*H$_3$)$_2$), 31.7 (4-CH_3), 34.0 (C-6a), 56.0 (OCH_3), 59.0 (C-3), 59.7 (C-6), 60.1 (OCH_3), 60.5 (OCH_3), 71.9 (*C*H(CH$_3$)$_2$), 111.9 (C-6'), 123.1 (C-1'), 125.9 (C), 147.4 (C), 149.2 (C), 151.4 (C-2'or *C*O$_2$^{i}Pr), 151.6 (C-2'or *C*O$_2$^{i}Pr), 165.1 (C-5), 167.0 (C-2). EIMS *m/z* (%): 422 (M^+, 35), 196 (12), 195 (100). HREIMS *m/z* calcd for $C_{21}H_{30}N_2O_7$, 422.2053. Found: 422.2058. Anal. Calcd for $C_{21}H_{30}N_2O_7 \cdot 1/2\ H_2O$: C 58.46, H 7.24, N 6.49. Found: C 58.69, H 7.05, N 6.52.

(1*R*,2*S*,5*S*)-7,9,10-Trimethoxy-2,3,8-trimethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[*d*]azocin-4(1*H*)-one: **(-)-19a**

Li(*tert*-BuO)$_3$AlH (719 mg, 2.82 mmol) was added to a solution of **(+)-16** (291 mg, 0.69 mmol) in THF (44 mL) at 0 ºC, and the mixture was stirred at the same temperature for 30 min. Anhydrous Na_2SO_4 was added into the reaction mixture, and the reaction was quenched by the addition of H_2O (40 mL). The rmixture was filtered through celite pad, and the residue was washed with $CHCl_3$ (300 mL). The combined filtrates were concentrated in vacuum and extracted with $CHCl_3$ (40 mL x 3). The combined extracts were washed with brine (40 mL), dried, and concentrated in vacuo to give a residue in the form of a pale yellow amorphous powder, and it was used in the next step without further purification. TfOH (11 mL) was added to the residue at -25 ºC, and the resulting reaction mixture was stirred at the same temperature for 30 min, and then 0 ºC for 30 min. The mixture was poured into ice-water (10 mL), and

then it was neutralized with saturated aqueous $NaHCO_3$ solution (160 mL). The mixture was extracted with $CHCl_3$ (40 mL x 3), and the combined extracts were washed with brine (40 mL), dried, and concentrated in vacuo to give a residue (156 mg). The aqueous layer was extracted with EtOAc (40 mL x 3). The combined extracts were washed with brine (40 mL), dried, and concentrated in vacuo to give a residue (95.1 mg). The combined residue was subjected to column chromatography on SiO_2 (40 g) with $CHCl_3$-MeOH (50:1-20:1) to afford **(-)-19a** (187 mg, 85%) as a pale yellow solid. An analytical sample was obtained by recrystallization from Et_2O to give a pure **(-)-19a** as pale yellow needles, mp 144-146 °C. $[\alpha]_D^{24}$ -98.0 (*c* 0.9, $CHCl_3$). ν_{max} (KBr) 3312, 2982, 2938, 2870, 2830, 1641, 1624, 1471, 1342, 1282, 1213, 1080 cm^{-1}. δ_H (400 MHz) 1.15 (3H, d, *J* = 6.5 Hz, 2-CH_3), 2.19 (3H, s, 8-CH_3), 2.86 (3H, s, 3-CH_3), 2.96 (1H, dd, *J* = 17.9, 7.3 Hz, 6-Hα), 3.09 (1H, dd, *J* = 17.9, 1.1 Hz, 6-Hβ), 3.68 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.93 (1H, dq, *J* = 6.5, 5.1 Hz, 2-H), 3.99 (1H, br d, *J* = 7.3 Hz, 5-H), 4.46 (1H, d, *J* = 5.1 Hz, 1-H). δ_C (100 MHz) 9.3 (8-CH_3), 15.9 (2-CH_3), 27.9 (C-6), 29.6 (*N*CH_3), 49.1 (C-1), 52.4 (C-5), 59.4 (C-2), 59.7 (OCH_3), 59.9 (OCH_3), 60.1, (OCH_3), 122.6 (C-6a), 124.6 (C), 124.8 (C), 146.4 (C), 149.5 (C), 152.5 (C), 171.2 (C-4). EIMS *m/z* (%): 320 (M^+, 14), 235 (26), 234 (100), 204 (13). HREIMS *m/z* calcd $C_{17}H_{24}N_2O_4$, 320.1736, Found: 320.1733. Anal. Calcd for $C_{17}H_{24}N_2O_4$: C 63.73, H 7.55, N 8.74. Found: C 63.73, H 7.61, N 8.70.

(1*R*,2*S*,5*S*)-7,9,10-Trimethoxy-2,3,8,11-tetramethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[*d*]azocin-4(1*H*)-one: **(-)-21**

37% Aqueous formaldehyde solution (30 mL) was added into a mixture of **(-)-18** (1.03 g, 3.20 mmol) in formic acid (34 mL) at 60 °C, the mixture was heated at 70 °C for 1 h. The reaction mixture was concentrated in vacuum, the residue was diluted with H_2O (60 mL), made pH 8 with saturated aqueous $NaHCO_3$ solution (150 mL), and extracted with $CHCl_3$ (180 mL x 3). The combined extracts were washed with H_2O (180 mL), dried, and concentrated in vacuo. The residue (1.18 g) was subjected to column chromatography on SiO_2 (40 g) with hexane-EtOAc-MeOH (76:19:5) to give **(-)-21** (991.8 mg, 93%) as a pale yellow oil. An analytical sample was obtained by recrystallization from hexane-EtOAc gave a pure **(-)-21** as colorless prisms, mp 109-110.5 °C.

$[\alpha]_D^{24}$ -155.2 (*c* 1.0, $CHCl_3$). ν_{max} (KBr) 2999, 2936, 2862, 2832, 1637, 1629, 1464, 1406, 1337, 1244, 1111, 1013 cm^{-1}. δ_H (400 MHz) 1.12 (3H, d, *J* = 6.6 Hz, 2-CH_3) , 2.19 (3H, s, 8-CH_3), 2.44 (3H, s, *N*CH_3), 2.86 (3H, s, 3-CH_3), 2.90 (1H, d, *J* = 18.1 Hz, 6-Hβ), 3.03 (1H, dd, *J* = 18.1, 6.6 Hz, 6-Hα), 3.68 (1H, br d, *J* = 6.6 Hz, 5-H), 3.69 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.00 (1H, dq, *J* = 6.6, 5.3 Hz, 2-H), 4.14 (1H, dd, *J* = 5.3, 1.4 Hz, 1-H). δ_C (100 MHz) 9.3 (8-CH_3), 15.5 (2-CH_3), 22.9 (C-6), 29.6 (3-CH_3), 40.0 (11-CH_3), 55.6 (C-1), 56.5 (C-2), 58.4 (C-5), 59.8 (OCH_3), 60.0 (OCH_3), 60.2 (OCH_3), 122.0 (C-6a), 122.7 (C-10a), 124.5 (C-8), 147.5 (C-10), 149.7 (C-9), 152.3 (C-7), 171.0 (C-4). EIMS *m/z*

(%): 334 (M^+, 11), 249 (24), 248 (100), 218 (14). HREIMS *m/z* calcd $C_{18}H_{26}N_2O_4$, 334.1893. Found: 334.1890. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C 64.65, H 7.84, N 8.38. Found: C 64.60, H 7.86, N 8.35.

(1*R*,2*S*,5*S*)-7-Hydroxy-9,10-dimethoxy-2,3,8,11-tetramethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[*d*]azocin-4(1*H*)-one: **(-)-22**

A solution of BBr_3 in CH_2Cl_2 solution (1.0 M, 15.6 mL, 15.6 mmol) was added into a solution of **(-)-21** (303.6 mg, 0.91 mmol) in CH_2Cl_2 (25 mL) at -78 °C, and the mixture was stirred at the same temperature for 20 min, warmed to 0 °C over 3.5 h, and then the stirring was continued for 1 h at 0 °C. After the reaction mixture was poured into ice-water (10 mL), it was neutralized with 5% aqueous $NaHCO_3$ solution (20 mL), and extracted with CH_2Cl_2 (30 mL x 3). The combined extracts were washed with H_2O (50 mL), dried, and concentrated in vacuo. The residue (301 mg) was subjected to column chromatography on SiO_2 (20 g) with $CHCl_3$-MeOH (30:1-20:1) to give **(-)-22** (288 mg, 99%) as a pale yellow amorphous powder.

$[\alpha]_D^{25}$ -133.5 (*c* 1.0, $CHCl_3$). ν_{max} (KBr) 3246, 2985, 2936, 1634, 1629, 1456, 1416, 1341, 1115, 1065 cm^{-1}. δ_H (400 MHz) 1.12 (3H, d, *J* = 6.6 Hz, 2-CH_3), 2.16 (3H, s, 8-CH_3), 2.43 (3H, s, 11-CH_3), 2.87 (3H, s, 3-CH_3), 2.93 (2H, d, *J* = 4.1 Hz, 6-H_2), 3.74 (3H, s, OCH_3), 3.74-3.79 (1H, overlapped, 5-H), 3.78 (3H, s, OCH_3), 4.00 (1H, dq, *J* = 6.6, 5.3 Hz, 2-H), 4.14 (1H, dd, *J* = 5.3, 1.6 Hz, 1-H), 6.58 (1H, br s, OH). δ_C (100 MHz) 9.0 (8-CH_3), 15.4 (2-CH_3), 22.3 (C-6), 30.0 (3-CH_3), 39.8 (11-CH_3), 55.6 (C-1), 57.2 (C-2), 58.4 (C-5), 60.2 (OCH_3), 60.4 (OCH_3), 115.1 (C-6a), 118.2 (C-8), 121.5 (C-10a), 144.7 (C-10), 148.4 (C-7), 149.6 (C-9), 171.4 (C-4). EIMS *m/z* (%): 320 (M^+, 12), 235 (23), 234 (100). HREIMS *m/z* calcd $C_{17}H_{24}N_2O_4$, 320.1736. Found: 320.1734.

(1*R*,2*S*,5*S*)-9-Methoxy-2,3,8,11-tetramethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[*d*]azocine-4,7,10(1*H*)-trione: **(-)-1**

8 M Aqueous HNO_3 solution (2.5 mL) was added into **(-)-22** (80.0 mg, 0.25 mmol) at 0 °C, and the mixture was stirred at same temperature for 45 min. The mixture was poured into H_2O (20 mL) at 0 °C, it was carefully neutralized with 5% aqueous $NaHCO_3$ solution (40 mL), and extracted with $CHCl_3$ (20 mL x 3). The combined extracts were washed with H_2O (20 mL), dried, and concentrated in vacuo. The residue (81.2 mg) was subjected to column chromatography on SiO_2 (20 g) with $CHCl_3$-MeOH (20:1) to give **(-)-1** (66.8 mg, 88%) as a yellow oil.

$[\alpha]_D^{24}$ -148.1 (*c* 1.0, $CHCl_3$). ν_{max} ($CHCl_3$) 3026, 3005, 2943, 1655, 1614, 1450, 1339, 1314, 1267, 1227, 1150, 1132 cm^{-1}. δ_H (400 MHz) 1.06 (3H, d, *J* = 6.7 Hz, 2-CH_3), 1.96 (3H, s, 8-CH_3), 2.37 (3H, s, 11-CH_3), 2.69 (1H, dd, *J* = 20.8, 1.3 Hz, 6-Hβ), 2.80 (1H, dd, *J* = 20.8, 6.6 Hz, 6-Hα), 2.89 (3H, s, 3-CH_3), 3.65 (1H, dt, *J* = 6.6, 1.3 Hz, 5-H), 3.97 (3H, s, OCH_3), 4.00 (1H, dq, *J* = 6.7, 5.2 Hz, 2-H), 4.12

(1H, br d, *J* = 5.2 Hz, 1-H). δ_C (100 MHz) 8.7 (8-CH_3), 17.2 (2-CH_3), 23.2 (C-6), 29.6 (*N*CH_3), 39.6 (*N*CH_3), 53.6 (C-1), 56.0 (C-2), 57.9 (C-5), 60.8 (OCH_3), 129.1 (C-8), 136.4 (C-10a), 141.5 (C-6a), 155.8 (C-9), 170.0 (C-4), 182.5 (C-10), 186.3 (C-7). EIMS *m/z* (%): 305 (M^+ + 1, 18), 304 (M^+, 100), 220 (16), 219 (38), 218 (61), 205 (10), 204 (69), 202 (13), 201 (26), 190 (20), 176 (20). HREIMS *m/z* calcd $C_{16}H_{20}N_2O_4$, 304.1423. Found: 304.1420.

(1*R*,2*S*,4*R*,5*S*)-7-Hydroxy-9,10-dimethoxy-2,3,8,11-tetramethyl-1,2,3,4,5,6-hexahydro-1,5-epiminobenzo-[*d*]azocine-4-carbonitrile: **(-)-23**

EtOAc (450 μL, 4.56 mmol) was added into a solution of $LiAlH_4$ in Et_2O (1.0 M, 4.56 mL, 4.56 mmol) at 0 °C slowly, and the mixture was stirred at same temperature for 1 h. A solution of **(-)-19** (364.0 mg, 1.14 mmol) in THF (18.5 mL) was added to the above solution at 0 °C carefully, and the reaction mixture was stirred at same temperature for 1 h. Acetic acid (1.44 mL, 25.8 mmol) and a solution of KCN (454.5 mg, 6.84 mmol) in H_2O (1.1 mL) were successively added, and stirring was continued at 25 °C for 1 h. After the reaction mixture was diluted with H_2O (100 mL) and extracted with $CHCl_3$/MeOH (9:1, 100 mL x 3). The combined extracts were washed with H_2O (100 mL), dried, and concentrated in vacuo to give a residue (378.9 mg), which was subjected to column chromatography on SiO_2 (40 g) with hexane-EtOAc (2:1) to furnish **(-)-23** (325.8 mg, 86%) as a pale yellow solid. An analytical sample was obtained by recrystallization from EtOAc as colorless needles, mp 188-190 °C.

$[\alpha]_D^{24}$ -7.7 (*c* 1.0, $CHCl_3$). ν_{max} (KBr) 3443, 2943, 2232, 1474, 1458, 1447, 1344, 1254, 1233, 1117, 1074, 1045 cm^{-1}. δ_H (400 MHz) 0.97 (3H, d, *J* = 6.8 Hz, 2-CH_3), 2.14 (3H, s, 8-CH_3), 2.25 (3H, s, 11-CH_3), 2.29 (3H, s, 3-CH_3), 2.35 (1H, d, *J* = 17.6 Hz, 6-Hβ), 2.90 (1H, dd, *J* = 17.6, 7.8 Hz, 6-Hα), 2.94 (1H, dq, *J* = 6.8, 2.8 Hz, 2-H), 3.38 (1H, br d, *J* = 7.8 Hz, 5-H), 3.72 (3H, s, OCH_3), 3.74 (1H, d, *J* = 2.4 Hz, 4-H), 3.79 (3H, s, OCH_3), 3.87 (1H, d, *J* = 2.8 Hz, 1-H), 4.48 (1H, s, OH). δ_C (100 MHz) 8.7 (8-CH_3), 15.7 (2-CH_3), 21.4 (C-6), 40.3 (3-CH_3), 41.6 (11-CH_3), 54.9 (C-5), 57.6 (C-1), 58.1 (C-2), 60.3 (OCH_3), 60.4 (OCH_3), 63.4 (C-4), 115.8 (C-8), 116.1 (C-6a), 116.7 (CN), 123.4 (C-10a), 145.1 (C-10), 146.5 (C-7), 149.1 (C-9). EIMS *m/z* (%): 331 (M^+, 6), 274 (26), 236 (8), 235 (50), 234 (100). HREIMS *m/z* calcd $C_{18}H_{25}N_3O_3$, 331.1896. Found: 331.1895. Anal. Calcd for $C_{18}H_{25}N_3O_3 \cdot 1/4H_2O$: C 64.36, H 7.65, N 12.51. Found: C 64.73, H 7.73, N 12.01, C 64.63, H 7.78, N 11.99.

(1*R*,2*S*,4*R*,5*S*)-9-Methoxy-2,3,8,11-tetramethyl-7,10-dioxo-1,2,3,4,5,6,7,10-octahydro-1,5-epiminobenzo-[*d*]azocine-4-carbonitrile: **(+)-2**

A solution of **(-)-23** (152.5 mg, 0.46 mmol) in MeCN (15 mL) was added into a solution of CAN (1.29 g, 2.3 mmol) in H_2O (15 mL) at 0 °C, and the mixture was stirred at same temperature for 1 h. The reaction mixture was poured into ice-water (40 mL) and extracted with EtOAc (40 mL x 3). The combined

extracts were washed with H_2O (40 mL), dried, and concentrated in vacuo. The residue (174.9 mg) was subjected to column chromatography on SiO_2 (15 g) with hexane-EtOAc (3:1) to give **(+)-2** (126.7 mg, 87%) as a deep orange amorphous powder.

$[\alpha]_D^{24}$ +36.6 (*c* 0.25, $CHCl_3$). ν_{max} (KBr) 2978, 2941, 1653, 1616, 1449, 1373, 1321, 1307, 1298, 1226, 1190, 1148 cm^{-1}. δ_H (400 MHz) 0.89 (3H, d, *J* = 6.7 Hz, 2-CH_3), 1.96 (3H, s, 8-CH_3), 2.21 (1H, d, *J* = 20.7 Hz, 6-Hβ), 2.26 (3H, s, 11-CH_3), 2.28 (3H, s, 3-CH_3), 2.75 (1H, dd, *J* = 20.7, 7.3 Hz, 6-Hα), 2.92 (1H, dq, *J* = 6.7, 2.5 Hz, 2-H), 3.31 (1H, br d, *J* = 7.3 Hz, 5-H), 3.66 (1H, d, *J* = 2.4 Hz, 4-H), 3.83 (1H, d, *J* = 2.5 Hz, 1-H), 3.98 (3H, s, OCH_3). δ_C (100 MHz) 8.7 (8-CH_3), 16.8 (2-CH_3), 21.6 (C-6), 39.9 (3-CH_3), 41.3 (11-CH_3), 54.7 (C-5), 55.7 (C-1), 56.8 (C-2), 60.8 (9-OCH_3), 62.3 (C-4), 116.2 (CN), 128.6 (C-8), 136.6 (C-10a), 141.6 (C-6a), 155.5 (C-9), 182.7 (C-10), 186.8 (C-7). EIMS *m/z* (%): 315 (M^+, 15), 221 (14), 220 (100), 219 (35), 218 (29), 204 (30), 201 (11), 176 (10). HREIMS *m/z* calcd $C_{17}H_{21}N_3O_3$, 315.1583. Found: 315.1582.

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REFERENCES AND NOTES

1. For simplicity, IUPAC names and numbering were used for all synthetic compounds except natural products.
2. (a) T. Arai and A. Kubo, *The Alkaloids*, ed. by A. Brossi, Academic Press: New York, 1983, **21**, 55; (b) J. D. Scott and R. M. Williams, *Chem. Rev*., 2002, **102**, 1669.
3. For the preparation of left-half model: (a) K. Nakai, M. Yokoya, and N. Saito, *Chem. Pharm. Bull*., 2013, **61**, 853; (b) K. Nakai, K. Kubo, M. Yokoya, and N. Saito, *Tetrahedron*, 2014, **70**, 6529.
4. For the preparation of right-half model: (a) N. Saito, Y. Obara, S. Harada, Y. Shida, and A. Kubo, *Tetrahedron*, 1994, **50**, 3915; (b) N. Saito, M. Tachi, R. Seki, H. Kamayachi, and A. Kubo, *Chem. Pharm. Bull.*, 2000, **48**, 1549; (c) Y. Koizumi, A. Kubo, K. Suwanborirux, and N. Saito, *Heterocycles*, 2002, **57**, 2345; (d) M. Yokoya, A. Fujino, A. Yaguchi, M. Yamazaki, and N. Saito, *Heterocycles*, 2016, **93**, 802.
5. N. Saito, M. Tanitsu, T. Betsui, R. Suzuki, and A. Kubo, *Chem. Pharm. Bull*., 1997, **45**, 1120.
6. N. Saito, T. Betsui, S. Ando, and S. Kimura, unpublished results.
7. T. Kanmera, S. Lee, H. Aoyagi, and N. Izumiya. *Tetrahedron Lett.*, 1979, **20**, 4483.
8. In our previous report,[4] we used hydrogenolysis with 20% Pd/C instead of 10% Pd/C, and only **(-)-7** was obtained. Currently, it is very difficult to purchase commercially available 20% Pd/C in Japan.

9. A. Kubo, N. Saito, H. Yamato, and Y. Kawakami, *Chem. Pharm. Bull.*, 1987, **53**, 2525; (b) K. Matsuo, M. Okumura, and K. Tanaka, *Chem. Pharm. Bull.*, 1982, **30**, 4170.
10. The crystalline forms of **(*rac*)-10** and **(-)-10** are quite different: **(*rac*)-10** exists as prisms, and **(-)-10**, as needles. These crystals could be easily separable and the optical purity of **(-)-10** could be increased with recrystallization.
11. In this reaction, although NaH was used as the strong base, epimerization did not occur. We speculate that the acidity of *N*-H proton might be higher than that of the proton at C-2, as the conjugated system of the *N*-H proton is longer than that of the C-H proton at C-2.
12. I. Ortín, J. F. González, E. de la Cuesta, and C. Avendaño, *Bioorg. Med. Chem.*, 2010, **18**, 6813.
13. The dehydration of **20** with TfOH (9 eq.) in a variety of solvents such as THF, DMSO, DMF, or CH_2Cl_2 at 0 °C for 30 min, **17** was only produced in 86%, 84%, 63%, 90% yields, respectively.
14. I. J. Galpin, K. A. Mohammed, A. Patel, and G. Proestley, *Tetrahedron*, 1988, **44**, 1763.
15. (a) R. Paul and G. W. Anderson, *J. Am. Chem. Soc*., 1958, **80**, 4432; (b) R. Paul and G. W. Anderson, *J. Am. Chem. Soc.*, 1960, **82**, 4596.
16. An analytical sample **(-)-7** ($[\alpha]_D^{27}$ -19.1 (*c* 1.0, DMF)) was obtained by recrystallization from EtOAc as colorless prisms, mp 223-223.5 °C (lit.,[7,17] mp 228-230 °C).
17. P. Cledera, C. Avendaño, and J. C. Menéndez, *Tetrahedron*, 1998, **54**, 12349.