A Short Path to the 1,3-*cis*-Substituted Core Skeleton of Tetrahydroisoquinolines

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The family of tetrahydroisoquinoline alkaloids has attracted considerable attention because of their biological activity and novel structures.[1] Natural alkaloids, such as saframycins,[2] renieramycins,[3] and ecteinascidin 743,[4] which are shown in Figure 1 possess potent antitumor, antibiotic, and antimicrobial activities. A number of methods to synthesize these alkaloids have been published recently.[1b,5]

Efforts to develop strategies to synthesize these alkaloids have encountered the key stereochemical issue of installing the common *cis* relationship at the C1 and C3 positions of the core structures. Several interesting approaches include radical cylization,[6] the addition of organometallic compounds followed by ionic hydrogenation,[7] and intermolecular[8] or intramolecular Pictet-Spengler reaction.[9]

We were interested in inducing a *cis* relationship for the related piperidine rings in the course of alkaloid synthesis under reductive cyclization,[10] and we wanted a new way that uses the existing C3 stereocenter of a natural product to induce the desired stereochemistry between C1 and C3 by stereoselective hydrogenation (Scheme 1). For this approach, we used *L*-dopa as the starting material and prepared an oxalate amide **3**. The oxalate amide moiety would provide a cyclic imine ester **2** *via* the Bischler-Napieralski reaction, which could be reduced stereoselectively to afford the required *cis* relationship, and then azide-ester cyclization would afford lactam **1** containing a [3.3.1] ring system.

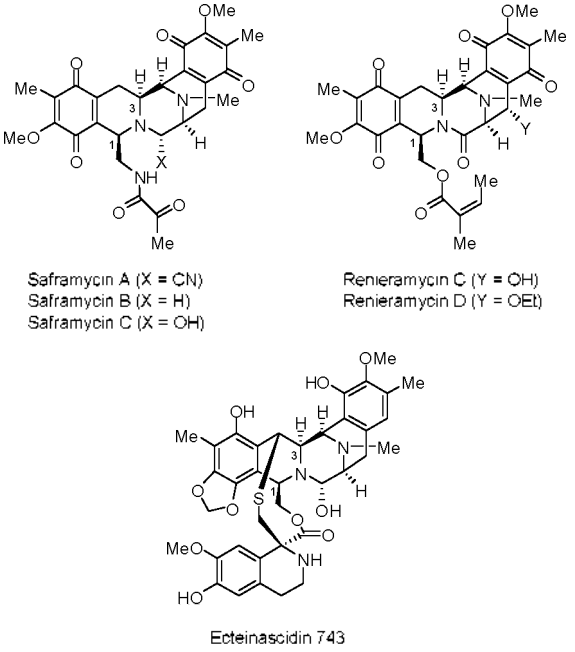
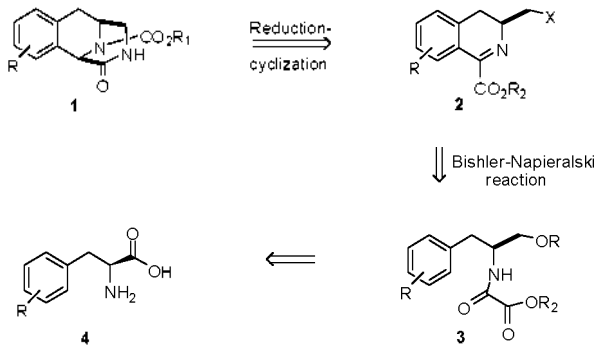


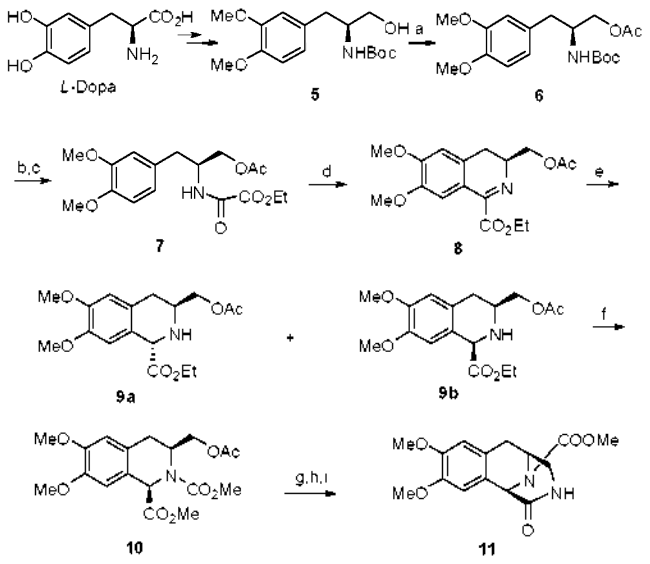
Figure 1. Structures of saframycins, renieramycins, and ecteinascidin 743.

Preparation of the substrate **5** was accomplished by the known procedures starting with *L*-dopa[11] and the product was converted to acetate **6** in quantitative yield (Scheme 2). Deprotection of the Boc group of **6** was carried out using $AlCl_3$, and the corresponding amine product was treated with ethyl oxalyl chloride to yield oxalate amide **7** in 81% yield. The Bischler-Napieralski reaction of **7** with P_2O_5 in $CHCl_3$ under refluxing condition afforded the cyclic imine ester **8** in 79% yield. However, use of $POCl_3$, the common reagent, under various solvents resulted in decomposition only. Reduction of **8** under hydrogen atmosphere with Pd/C provided a *ca.* 1:4 mixture of tetrahydroisoquinoline isomers **9a** and **9b** in 18% and 74% yields. The major product **9b** was converted to **10** by protection with methyl chloroformate (81%). Then hydrolysis of **10** to alcohol (60%), reaction with diphenylphosphoryl azide (DPPA) to give the corresponding azide (65%),[12] and Staudinger reaction with this azide provided the desired lactam **11** in 51% yield. The other azide isomer obtained by the identical method from **9a** did not afford any lactam moiety under the same reaction conditions.

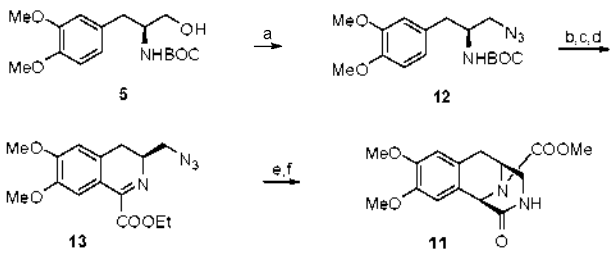
To find a more practical route toward the lactam **11**, we tried a sequential reductive process to obtain **11** from **13** (Scheme 3). Compound **5** was transformed to **12**, using DPPA to furnish the azide functional group. This was followed by a three-step sequence from **12**, deprotection of the Boc group



Scheme 1



Scheme 2. Reagents and conditions (a) Ac_2O, Et_3N, DMAP/CH_2Cl_2, 99%; (b) $AlCl_3$, CH_2Cl_2; (c) $ClCOCO_2Et$, $NaHCO_3$, 81% for 2 steps; (d) P_2O_5, $CHCl_3$, reflux, 79%; (e) H_2, Pd/C, 74%; (f) $ClCO_2Me$, pyridine/CH_2Cl_2, 81%; (g) K_2CO_3, MeOH, 60%; (h) DPPA, DEAD, PPh_3, 65%; (i) PPh_3, THF-H_2O, 51%.



Scheme 3. Reagents and conditions (a) DPPA, DEAD, PPh_3, 70%; (b) $AlCl_3$, CH_2Cl_2; (c) $ClCOCO_2Et$, $NaHCO_3$, 61% for 2 steps; (d) P_2O_5, $CHCl_3$, reflux, 79%; (e) H_2, MeOH, Pd/C, 54%; (f) $ClCO_2Me$, pyridine/CH_2Cl_2, quantitative yield.

with $AlCl_3$, oxalate formation with ethyl oxalyl chloride, and the Bischler-Napieralski reaction with P_2O_5 to provide cyclic imine ester **13** in 39% total yield.

Under hydrogen atmosphere with Pd/C (Scheme 3), a lactam product was obtained as a single isomer in 54% yield and the protection of the lactam-amine product with chloromethyl-formate yielded the lactam **11** in quantitative yield, confirming the desired reductive sequential cyclization from compound **13**. It seemed that the single isomer formation would be attributed to the formation of lactam followed by hydrogenation of double bond.

We have developed a short path to the 1,3-*cis*-substituted core skeleton of tetrahydroisoqunolines, using the Bischler-Napieralski reaction followed by reductive cyclization. We are applying this short approach to synthesize natural tetrahydroisoqunoline compounds.

Experimental Section

(*S*)-2-(*tert*-Butoxycarbonylamino)-3-(3,4-dimethoxyphenyl) propyl acetate (6). To a solution of (S)-2-(tert-butoxycarbonyl-amino)-3-(3,4-dimethoxyphenyl)propyl alcohol **5** (311 mg, 1 mmol) in anhydrous CH_2Cl_2 (10 mL) were added Ac_2O (0.95 mL, 10 mmol), Et_3N (1.4 mL, 20 mmol) and DMAP (10 mg). After stirred for 2 h at rt, the reaction solution was dissolved in water and extracted with CH_2Cl_2 (20 mL × 3), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (n-hexane/EtOAc 2 : 1) to give the product **6** (350 mg, 99%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.81 (1H, d, J = 8.8 Hz), 6.72-6.70 (2H, m), 4.78 (1H, b, NH), 4.07 (1H, m), 4.05 (2H, m), 3.87 (3H, s, OMe), 3.85 (3H, s, OMe), 2.81 (1H, m), 2.73 (1H, dd, J = 7.2, 14 Hz), 2.09 (3H, s), 1.42 (9H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 155.1, 148.8, 147.7, 129.6, 121.2, 112.2, 111.2, 79.4, 65.0, 55.8, 55.5, 50.5, 37.3, 28.2, 20.7. EI-HRMS calcd for $C_{18}H_{27}NO_6$ 353.1838, found: 353.1831.

(*S*)-2-(*tert*-Ethyloxalylamino)-3-(3,4-dimethoxyphenyl) propyl acetate (7). To a solution of **6** (2.83 g, 8.02 mmol) in anhydrous CH_2Cl_2 (40 mL) was added $AlCl_3$ (2.14 g, 16.04 mmol), followed by the addition of COClCOOEt (1.78 mL, 16.04 mmol) after 1 h. The reaction mixture was stirred for 30 min, and solid $NaHCO_3$ (2.02 g, 24.06 mmol) was added. After 1 h, the reaction mixture was then treated with aqueous saturated $NaHCO_3$ solution slowly and water and extracted with CH_2Cl_2 (70 mL × 3). The organic phases were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (n-hexane/EtOAc 1 : 1) to afford **7** (2.29 g, 81%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, d, J = 8.8 Hz, NH), 6.80 (1H, d, J = 8.8 Hz), 6.72 (1H, m), 4.43 (1H, m), 4.34 (2H, q, J = 7.2 Hz), 4.12 (2H, m), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 2.85 (2H, m), 2.11 (3H, s), 1.39 (3H, t, J = 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 160.4, 156.1, 149.0, 147.9, 128.6, 121.1, 112.0, 111.2, 64.1, 63.2, 55.8, 55.7, 50.1, 36.6, 20.7, 13.8. EI-HRMS calcd for $C_{17}H_{23}NO_7$ 353.1475, found: 353.1478.

(*S*)-Ethyl-3-(acetoxymethyl)-6,7-dimethoxy-3,4-dihydro-isoquinoline-1-carboxylate(8). A mixture of **7** (1.67 g, 4.73 mmol) and P_2O_5 (9.4 g, 33.12 mmol) in anhydrous $CHCl_3$ (50 mL) was refluxed at 80 °C for 12 h. Then, the reaction mixture was cooled by an ice-water bath, slowly treated with NaOH 2M solution until pH = 9 and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resultant residue was purified by silica gel column chromatography (n-hexane/EtOAc 1 : 1) to yield the product **8** (1.25 g, 79%) as a reddish liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, s), 6.72 (1H, s), 4.53-4.33 (4H, m), 3.93 (3H, s, OMe), 3.89 (3H, s, OMe), 3.83 (1H, m), 2.75 (1H, dd, J = 5.6, 16 Hz), 2.63 (1H, dd, J = 14, 28.4 Hz), 2.10 (3H, s), 1.43 (3H, t, J = 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.0, 165.0, 159.5, 151.9, 147.6, 130.7, 118.7, 110.4, 110.1, 66.9, 62.0, 56.4, 56.1, 56.0, 27.8, 21.0, 14.2. EI-HRMS calcd for $C_{17}H_{21}NO_6$ 335.1369, found: 335.1361.

Ethyl-3-(acetoxymethyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline-1-carboxylate isomers (9). Compound **8** (652 mg, 1.95 mmol) in MeOH (15 mL) was hydrogenated with catalytic amount of Pd/C 10% (105 mg) for 2 h under H_2 gas atmosphere in a balloon. After filtration through a Celite layer,

the filtrate was evaporated *in vacuo* and the resulting residue was purified by silica gel column chromatography (n-hexane/EtOAc 1 : 1 to 1 : 2) to give the product **9a** as a colerless liquid (131 mg, 18%) and the product **9b** (485 mg, 74%) as a yellowish liquid. Compound **9a**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, s), 6.58 (1H, s), 4.65 (1H, s), 4.32 (1H, m), 4.19 (2H, m), 4.00 (1H, m), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 3.57 (1H, m), 2.60 (1H, m), 2.13 (3H, s), 1.29 (3H, t, J = 7.2 Hz). Compound **9b**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, s), 6.59 (1H, s), 4.83 (1H, s), 4.35-4.16 (4H, m), 3.86 (3H, s, OMe), 3.84 (3H, s, OMe), 3.16 (1H, m), 2.65 (1H, m), 2.12 (3H, s), 1.34 (3H, t, J = 7.2 Hz).^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.3, 171.0, 148.2, 147.5, 126.9, 123.8, 112.0, 108.4, 67.6, 61.5, 60.1, 55.83, 55.82, 51.1, 31.2, 20.9, 14.3. EI-HRMS calcd for $C_{17}H_{23}NO_6$ 337.1525, found: 337.1521.

Cyclic lactam (11). To a solution of **9b** (72 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (10 mL) were added anhydrous pyridine (35 μL, 0.43 mmol) and ClCOOMe (33 μL, 0.43 mmol) successively. After 3 h, the solvent was removed under reduced pressure and the resultant residue was purified by silica gel column chromatography (n-hexane/EtOAc 1 : 1) to yield the protected amine (67 mg, 81%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.06 (1H, s), 6.23 (1H, s), 5.54 (0.55H, s), 5.45 (0.45H, s), 4.81 (0.45H, m), 4.60 (0.55H, m), 4.35-4.17 (3H, m), 4.05 (1H, m), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 3.79 (1.7H, s), 3.76 (1.3H, s), 3.00 (1H, dd, J = 6, 16 Hz), 2.80 (1H, m), 2.04 (1.7H, s), 2.00 (1.3H, s), 1.30 (3H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.8, 170.7, 170.4, 156.3, 155.8, 148.5, 147.7, 147.6, 123.7, 123.4, 120.8, 120.0, 111.5, 111.3, 109.1, 64.8, 64.2, 61.4, 61.3, 56.9, 56.7, 55.7, 55.6, 52.9, 52.8, 48.1, 47.7, 29.8, 29.6, 20.6, 13.9. EI-HRMS calcd for $C_{19}H_{25}NO_8$ 395.1580, found: 395.1585. Anhydrous K_2CO_3 (19 mg, 0.135 mmol) was added to the solution of the protected amine above (107 mg, 0.27 mmol) in anhydrous MeOH (10 mL). After stirred for 1 h at rt, the reaction mixture was treated with water and extracted with EtOAc (20 mL ×3), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (n-hexane/EtOAc 1 : 2) to yield the alcohol (55 mg, 60%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.07 (0.65H, s), 7.01 (0.35H, s), 6.63 (0.35H, s), 6.61 (0.65H, s), 5.65 (0.65H, s), 5.60 (0.35H, s), 4.64 (1H, m), 3.95-3.73 (12H, m), 3.75-3.44 (2H, m), 3.02-2.97 (1H, m), 2.80-2.60 (1H, m).To a solution of the resultant alcohol (22 mg, 0.065 mmol) in anhydrous THF (2 mL) at 0 °C were added PPh_3 (38 mg, 0.143 mmol), DEAD (23 μL, 0.143 mmol). After 5 min, DPPA (31 μL, 0.143 mmol) was added and the mixture was stirred at rt for 2 h. The reaction mixture was treated with H_2O (0.4 mL), then evaporated *in vacuo* and purified by silica gel column chromatography (n-hexane/EtOAc 1 : 1) to afford azide **10** (15.4 mg, 65%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.98 (0.6H, s), 6.96 (0.4H, s), 6.66 (1H, s), 5.58 (0.6H, s), 5.49 (0.4H, s), 4.60 (0.4H, m), 4.43 (0.4H, m), 3.88 (3H, s), 3.86 (3H, s), 3.8 (3H, s), 3.79 (1.6H, s), 3.77 (1.4H, s), 3.70-3.65 (1H, m), 3.35-3.29 (1H, m), 3.05-2.95 (1H, m), 2.87-2.79 (1H, m).The mixture of azide **10** (10 mg, 0.027 mmol), PPh_3 (15 mg, 0.055 mmol) in THF/H_2O (8 mL/0.2 mL) was stirred overnight at rt. After evaporation in reduced pressure, the resultant residue was purified by silica gel column chromatography (EtOAc/MeOH 20 : 1) to yield lactam **11** (4.2 mg, 51%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.86 (1H, s), 6.60 (1H, s), 6.50 (0.3H, s, NH), 6.36 (0.7H, s, NH), 5.42 (0.3H, s), 5.31 (0.7H, s), 4.98 (0.7H, bm), 4.85 (0.3H, bm), 3.88 (3H, s, OMe), 3.84 (3H, s, OMe), 3.74 (3H, s), 3.38 (1H, dd, J = 7.2, 16.4 Hz), 3.20 (1H, dd, J = 1.2, 12 Hz), 2.70 (1H, d, J = 17.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.8, 154.7, 149.0, 147.6, 124.7, 124.4, 111.4, 109.6, 56.5, 56.0, 55.9, 53.1, 47.1, 42.5, 32.6. EI-HRMS calcd for $C_{15}H_{18}N_2O_5$ 306.1216, found: 306.1217.

(*S*)-2-(*tert*-Ethyloxalylamino)-3-(3,4-dimethoxyphenyl)propyl azide (12). To a solution of **5** (623 mg, 2 mmol) in anhydrous THF (20 mL) at 0°C were added PPh_3 (577 mg, 4.4 mmol), DEAD (693 μL, 4.4 mmol), DPPA (950 uL, 4.4 mmol) consecutively. After stirred at rt for 2 h, the reaction mixture was treated with H_2O (1 mL), then evaporated *in vacuo* and purified by silica gel column chromatography (n-hexane/EtOAc 2 : 1) to afford the product **12** (470 mg, 70%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.81 (1H, d, J = 8 Hz), 6.75-6.72 (2H, m), 4.71 (1H, b, NH), 3.94 (1H, m), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 3.42-3.26 (2H, m), 2.86-2.67 (2H, m), 1.43 (9H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.0, 148.9, 147.7, 129.5, 121.2, 112.1, 111.3, 79.6, 55.8, 55.7, 53.0, 51.2, 37.5, 28.2. EI-HRMS calcd for $C_{16}H_{24}N_4O_4$ 336.1798, found: 336.1800.

(*S*)-Ethyl-3-(azidomethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-1-carboxylate(13). To a solution of **12** (350 mg, 1.04 mmol) in anhydrous CH_2Cl_2 (10 mL) was added $AlCl_3$ (278 mg, 2.08 mmol). After 1 h, COClCOOEt (173 μL, 1.56 mmol) was added. The reaction mixture was stirred at rt for 30 min and solid $NaHCO_3$ (263 mg, 3.12 mmol) was slowly added. Being stirred at rt for 1 h, the reaction mixture was then treated with saturated $NaHCO_3$ solution slowly, water and extracted with CH_2Cl_2 (20 mL ×3). The organic phases were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (n-hexane/EtOAc 1 : 1) to afford the oxalate amide product (213 mg, 61%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.83-6.70 (3H, m), 4.38-4.29 (3H, m), 3.88 (3H, s, OMe), 3.87 (3H, s, OMe), 3.52-3.38 (2H, m), 2.92-2.79 (2H, m), 1.40 (3H, t, J = 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.3, 156.1, 149.1, 148.0, 128.5, 121.2, 112.0, 111.3, 63.4, 55.8, 52.3, 50.5, 37.0, 13.9. EI-HRMS calcd for $C_{15}H_{20}N_4O_5$ 336.1434, found: 336.1429. A mixture of the oxalate amide (127 mg, 0.378 mmol) and P_2O_5 (751 mg, 2.65 mmo) in anhydrous $CHCl_3$ (10 mL) was refluxed at 80 °C for 12 h. Then, the reaction mixture was cooled by ice-water bath, slowly treated with NaOH 2 M solution until pH = 9 and extracted with CH_2Cl_2 (20 mL ×3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resultant residue was purified by silica gel column chromatography (n-hexane/EtOAc 1 : 1) to yield the product **13** (77 mg, 64%) as a liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, s), 6.73 (1H, s), 4.45 (2H, m), 3.93 (3H, s, OMe), 3.89 (3H, s, OMe), 3.75 (2H, m), 3.61 (1H, m), 2.79 (1H, dd, J = 5.6, 15.6 Hz), 2.70 (1H, m), 1.42 (3H, t, J = 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 64.7, 159.2, 151.9, 147.6,

130.5, 118.6, 110.4, 110.1, 62.0, 57.3, 56.0, 55.9, 54.9, 28.2, 14.1. EI-HRMS calcd for $C_{15}H_{18}N_4O_4$ 318.1328, found: 318.1329.

Cyclic lactam (11). Compound **13** (28 mg, 0.088 mmol) in MeOH (7 mL) was hydrogenated at rt for 6 h using Pd/C 10% (14 mg). After filtration through a Celite layer and evaporation in vacuum, the resultant residue was purified by silica gel column chromatography (EtOAc/MeOH 10 : 1) to give the lactam product (11.8 mg, 54%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.83 (1H, s), 6.60 (1H, s), 6.39 (1H, s, NH), 4.34 (1H, s), 3.86 (3H, s, OMe), 3.82 (3H, s, OMe), 3.80 (2H, m), 3.22 (2H, m), 2.77 (1H, bs, NH), 2.65 (1H, d, J = 17.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.1, 148.7, 147.4, 126.9, 124.6, 111.6, 109.8, 57.2, 56.0, 55.9, 48.3, 43.2, 33.4. EI-HRMS calcd for $C_{13}H_{16}N_2O_3$ 248.1161, found: 248.1161. To a solution of the above lactam (10 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (5 mL) were added anhydrous pyridine (4 μL, 0.048 mmol) and ClCOOMe (7 μL, 0.08 mmol) successively. After stirred overnight at rt, the reaction mixture was evaporated under reduced pressure and purified by silica gel column chromatography (EtOAc/MeOH 10 : 1) to yield the product **11** (11 mg, 99%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.86 (1H, s), 6.60 (1H, s), 6.50 (0.3H, s, NH), 6.36 (0.7H, s, NH), 5.42 (0.3H, s), 5.31 (0.7H, s), 4.98 (0.7H, bm), 4.85 (0.3H, bm), 3.88 (3H, s, OMe), 3.84 (3H, s, OMe), 3.74 (3H, s), 3.38 (1H, dd, J = 7.2, 16.4 Hz), 3.20 (1H, dd, J = 1.2, 12 Hz), 2.70 (1H, d, J = 17.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.8, 154.7, 149.0, 147.6, 124.7, 124.4, 111.4, 109.6, 56.5, 56.0, 55.9, 53.1, 47.1, 42.5, 32.6. EI-HRMS calcd for $C_{15}H_{18}N_2O_5$ 306.1216, found: 306.1217.

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