# 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. ${ }^{1 \mathrm{~b}, 5}$

Efforts to develop strategies to synthesize these alkaloids have encountered the key stereochemical issue of installing the common cis relationship at the C 1 and C 3 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 C 3 stereocenter of a natural product to induce the desired stereochemistry between C 1 and C 3 by stereoselective hydrogenation (Scheme 1). For this approach, we used $L$-dopa

Saframycin $A(X=C N)$
Saframycin $B(X=H)$ Saframycin C ( $\mathrm{X}=\mathrm{OH}$ )


Figure 1. Structures of saframycins, renieramycins, and ecteinascidin 743.
as the starting material and prepared an oxalate amide 3. The oxalate amide moiety would provide a cyclic imine ester $\mathbf{2}$ 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.

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 $\mathrm{AlCl}_{3}$, and the corresponding amine product was treated with ethyl oxalyl chloride to yield oxalate amide 7 in $81 \%$ yield. The BischlerNapieralski reaction of 7 with $\mathrm{P}_{2} \mathrm{O}_{5}$ in $\mathrm{CHCl}_{3}$ under refluxing condition afforded the cyclic imine ester 8 in $79 \%$ yield. However, use of $\mathrm{POCl}_{3}$, the common reagent, under various solvents resulted in decomposition only. Reduction of $\mathbf{8}$ under hydrogen atmosphere with $\mathrm{Pd} / \mathrm{C}$ provided a $c a$. 1:4 mixture of tetrahydroisoquinoline isomers 9 a and $9 b$ in $18 \%$ and $74 \%$ yields. The major product $\mathbf{9 b}$ was converted to $\mathbf{1 0}$ 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 $\mathbf{1 1}$ from $\mathbf{1 3}$ (Scheme 3). Compound $\mathbf{5}$ was transformed to $\mathbf{1 2}$, using DPPA to furnish the azide functional group. This was followed by a three-step sequence from 12, deprotection of the Boc group


1
$\xrightarrow[\text { cydization }]{\text { Reduction- }}$
cyclization

|| Bishler-Napieralski reaction


4



Scheme 1


Scheme 2. Reagents and conditions (a) $\mathrm{Ac}_{2} \mathrm{O}, \mathrm{Et} \mathrm{t}_{3} \mathrm{~N}, \mathrm{DMAP} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$, $99 \%$; (b) $\mathrm{AlCl}_{3}, \mathrm{CH}_{2} \mathrm{Cl}_{2}$; (c) $\mathrm{ClCOCO}_{2} \mathrm{Et}, \mathrm{NaHCO}_{3}, 81 \%$ for 2 steps; (d) $\mathrm{P}_{2} \mathrm{O}_{5}, \mathrm{CHCl}_{3}$, reflux, $79 \%$; (e) $\mathrm{H}_{2}, \mathrm{Pd} / \mathrm{C}, 74 \%$; (f) $\mathrm{ClCO}_{2} \mathrm{Me}$, pyridine $/ \mathrm{CH}_{2} \mathrm{Cl}_{2}, 81 \%$; (g) $\mathrm{K}_{2} \mathrm{CO}_{3}$, $\mathrm{MeOH}, 60 \%$; (h) DPPA, DEAD, $\mathrm{PPh}_{3}, 65 \%$; (i) $\mathrm{PPh}_{3}$, THF-H2O, $51 \%$.


5


13
$\xrightarrow{a}$


12
$\xrightarrow{\mathrm{e}, \mathrm{f}}$


Scheme 3. Reagents and conditions (a) DPPA, $\mathrm{DEAD}, \mathrm{PPh}_{3}, 70 \%$; (b) $\mathrm{AlCl}_{3}, \mathrm{CH}_{2} \mathrm{Cl}_{2}$; (c) $\mathrm{ClCOCO}_{2} \mathrm{Et}, \mathrm{NaHCO}_{3}, 61 \%$ for 2 steps; (d) $\mathrm{P}_{2} \mathrm{O}_{5}, \mathrm{CHCl}_{3}$, reflux, $79 \%$; (e) $\mathrm{H}_{2}, \mathrm{MeOH}, \mathrm{Pd} / \mathrm{C}, 54 \%$; (f) $\mathrm{ClCO}_{2} \mathrm{Me}$, pyridine $/ \mathrm{CH}_{2} \mathrm{Cl}_{2}$, quantitative yield.
with $\mathrm{AlCl}_{3}$, oxalate formation with ethyl oxalyl chloride, and the Bischler-Napieralski reaction with $\mathrm{P}_{2} \mathrm{O}_{5}$ 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 chloromethylformate 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 BischlerNapieralski 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 ( $311 \mathrm{mg}, 1$ $\mathrm{mmol})$ in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$ were added $\mathrm{Ac}_{2} \mathrm{O}(0.95$ $\mathrm{mL}, 10 \mathrm{mmol}), \mathrm{Et}_{3} \mathrm{~N}(1.4 \mathrm{~mL}, 20 \mathrm{mmol})$ and DMAP ( 10 mg ). After stirred for 2 h at rt , the reaction solution was dissolved in water and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20 \mathrm{~mL} \times 3)$, dried over anhydrous $\mathrm{MgSO}_{4}$ and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (n-hexane/EtOAc $2: 1$ ) to give the product $6(350 \mathrm{mg}, 99 \%)$ as a white solid. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.81(1 \mathrm{H}, \mathrm{d}, J=$ $8.8 \mathrm{~Hz}), 6.72-6.70(2 \mathrm{H}, \mathrm{m}), 4.78(1 \mathrm{H}, \mathrm{b}, \mathrm{NH}), 4.07(1 \mathrm{H}, \mathrm{m})$, $4.05(2 \mathrm{H}, \mathrm{m}), 3.87(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.85(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 2.81(1 \mathrm{H}$, $\mathrm{m}), 2.73(1 \mathrm{H}, \mathrm{dd}, J=7.2,14 \mathrm{~Hz}), 2.09(3 \mathrm{H}, \mathrm{s}), 1.42(9 \mathrm{H}, \mathrm{s})$. ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 170.7,155.1,148.8,147.7$, $129.6,121.2,112.2,111.2,79.4,65.0,55.8,55.5,50.5,37.3$, 28.2, 20.7. EI-HRMS calcd for $\mathrm{C}_{18} \mathrm{H}_{27} \mathrm{NO}_{6} 353.1838$, found: 353.1831.
(S)-2-(tert-Ethyloxalylamino)-3-(3,4-dimethoxyphenyl) propyl acetate (7). To a solution of $\mathbf{6}(2.83 \mathrm{~g}, 8.02 \mathrm{mmol})$ in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(40 \mathrm{~mL})$ was added $\mathrm{AlCl}_{3}(2.14 \mathrm{~g}, 16.04$ 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 $\mathrm{NaHCO}_{3}(2.02 \mathrm{~g}, 24.06 \mathrm{mmol})$ was added. After 1 h , the reaction mixture was then treated with aqueous saturated $\mathrm{NaHCO}_{3}$ solution slowly and water and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(70 \mathrm{~mL} \times 3)$. The organic phases were washed with brine, dried over anhydrous $\mathrm{MgSO}_{4}$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane/EtOAc 1: 1) to afford $7(2.29 \mathrm{~g}, 81 \%)$ as a white solid. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.31(1 \mathrm{H}, \mathrm{d}, J=8.8 \mathrm{~Hz}$, $\mathrm{NH}), 6.80(1 \mathrm{H}, \mathrm{d}, J=8.8 \mathrm{~Hz}), 6.72(1 \mathrm{H}, \mathrm{m}), 4.43(1 \mathrm{H}, \mathrm{m}), 4.34$ $(2 \mathrm{H}, \mathrm{q}, J=7.2 \mathrm{~Hz}), 4.12(2 \mathrm{H}, \mathrm{m}), 3.87(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.86(3 \mathrm{H}$, $\mathrm{s}, \mathrm{OMe}), 2.85(2 \mathrm{H}, \mathrm{m}), 2.11(3 \mathrm{H}, \mathrm{s}), 1.39(3 \mathrm{H}, \mathrm{t}, J=7.2 \mathrm{~Hz})$. ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 170.7,160.4,156.1,149.0$, $147.9,128.6,121.1,112.0,111.2,64.1,63.2,55.8,55.7,50.1$, 36.6, 20.7, 13.8. EI-HRMS calcd for $\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{NO}_{7}$ 353.1475, found: 353.1478 .
(S)-Ethyl-3-(acetoxymethyl)-6,7-dimethoxy-3,4-dihydro-isoquinoline-1-carboxylate(8). A mixture of $7(1.67 \mathrm{~g}, 4.73$ $\mathrm{mmol})$ and $\mathrm{P}_{2} \mathrm{O}_{5}(9.4 \mathrm{~g}, 33.12 \mathrm{mmol})$ in anhydrous $\mathrm{CHCl}_{3}(50$ mL ) was refluxed at $80^{\circ} \mathrm{C}$ for 12 h . Then, the reaction mixture was cooled by an ice-water bath, slowly treated with NaOH 2 M solution until $\mathrm{pH}=9$ and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(50 \mathrm{~mL} \times$ 3). The combined organic layer was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The resultant residue was purified by silica gel column chromatography ( n -hexane/EtOAc $1: 1)$ to yield the product $\mathbf{8}(1.25 \mathrm{~g}, 79 \%)$ as a reddish liquid. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.23(1 \mathrm{H}, \mathrm{s}), 6.72(1 \mathrm{H}, \mathrm{s})$, 4.53-4.33 ( $4 \mathrm{H}, \mathrm{m}$ ), $3.93(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.89(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe})$, $3.83(1 \mathrm{H}, \mathrm{m}), 2.75(1 \mathrm{H}, \mathrm{dd}, J=5.6,16 \mathrm{~Hz}), 2.63(1 \mathrm{H}, \mathrm{dd}, J=$ $14,28.4 \mathrm{~Hz}), 2.10(3 \mathrm{H}, \mathrm{s}), 1.43(3 \mathrm{H}, \mathrm{t}, J=7.2 \mathrm{~Hz}) .{ }^{13} \mathrm{C}-\mathrm{NMR}$ $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 171.0,165.0,159.5,151.9,147.6,130.7$, 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 $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO}_{6} 335.1369$, found: 335.1361 .

Ethyl-3-(acetoxymethyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline-1-carboxylate isomers (9). Compound 8 (652 $\mathrm{mg}, 1.95 \mathrm{mmol})$ in $\mathrm{MeOH}(15 \mathrm{~mL})$ was hydrogenated with catalytic amount of $\mathrm{Pd} / \mathrm{C} 10 \%(105 \mathrm{mg})$ for 2 h under $\mathrm{H}_{2}$ 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 9 a as a colerless liquid ( $131 \mathrm{mg}, 18 \%$ ) and the product $\mathbf{9 b}(485 \mathrm{mg}, 74 \%)$ as a yellowish liquid. Compound 9a: ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.94$ $(1 \mathrm{H}, \mathrm{s}), 6.58(1 \mathrm{H}, \mathrm{s}), 4.65(1 \mathrm{H}, \mathrm{s}), 4.32(1 \mathrm{H}, \mathrm{m}), 4.19(2 \mathrm{H}, \mathrm{m})$, $4.00(1 \mathrm{H}, \mathrm{m}), 3.86(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.85(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.57(1 \mathrm{H}$, $\mathrm{m}), 2.60(1 \mathrm{H}, \mathrm{m}), 2.13(3 \mathrm{H}, \mathrm{s}), 1.29(3 \mathrm{H}, \mathrm{t}, J=7.2 \mathrm{~Hz})$. Compound 9b: ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.89(1 \mathrm{H}, \mathrm{s})$, $6.59(1 \mathrm{H}, \mathrm{s}), 4.83(1 \mathrm{H}, \mathrm{s}), 4.35-4.16(4 \mathrm{H}, \mathrm{m}), 3.86(3 \mathrm{H}, \mathrm{s}$, $\mathrm{OMe}), 3.84(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.16(1 \mathrm{H}, \mathrm{m}), 2.65(1 \mathrm{H}, \mathrm{m}), 2.12$ $(3 \mathrm{H}, \mathrm{s}), 1.34(3 \mathrm{H}, \mathrm{t}, J=7.2 \mathrm{~Hz}) .{ }^{13} \mathrm{C}-\mathrm{NMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ $\delta 172.3,171.0,148.2,147.5,126.9,123.8,112.0,108.4,67.6$, 61.5, 60.1, 55.83, 55.82, 51.1, 31.2, 20.9, 14.3. EI-HRMS calcd for $\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{NO}_{6} 337.1525$, found: 337.1521 .

Cyclic lactam (11). To a solution of $\mathbf{9 b}$ ( $72 \mathrm{mg}, 0.21 \mathrm{mmol}$ ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$ were added anhydrous pyridine ( $35 \mu \mathrm{~L}, 0.43 \mathrm{mmol}$ ) and ClCOOMe ( $33 \mu \mathrm{~L}, 0.43 \mathrm{mmol}$ ) 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 ( $67 \mathrm{mg}, 81 \%$ ) as a colorless liquid. ${ }^{1} \mathrm{H}-\mathrm{NMR}$ $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.06(1 \mathrm{H}, \mathrm{s}), 6.23(1 \mathrm{H}, \mathrm{s}), 5.54(0.55 \mathrm{H}$, s), $5.45(0.45 \mathrm{H}, \mathrm{s}), 4.81(0.45 \mathrm{H}, \mathrm{m}), 4.60(0.55 \mathrm{H}, \mathrm{m}), 4.35-$ $4.17(3 \mathrm{H}, \mathrm{m}), 4.05(1 \mathrm{H}, \mathrm{m}), 3.87(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.86(3 \mathrm{H}, \mathrm{s}$, OMe), $3.79(1.7 \mathrm{H}, \mathrm{s}), 3.76(1.3 \mathrm{H}, \mathrm{s}), 3.00(1 \mathrm{H}, \mathrm{dd}, J=6,16$ $\mathrm{Hz}), 2.80(1 \mathrm{H}, \mathrm{m}), 2.04(1.7 \mathrm{H}, \mathrm{s}), 2.00(1.3 \mathrm{H}, \mathrm{s}), 1.30(3 \mathrm{H}, \mathrm{m})$. ${ }^{13}$ C-NMR (100 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 170.8,170.7,170.4,156.3$, 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 $\mathrm{C}_{19} \mathrm{H}_{25} \mathrm{NO}_{8} 395.1580$, found: 395.1585. Anhydrous $\mathrm{K}_{2} \mathrm{CO}_{3}$ ( $19 \mathrm{mg}, 0.135 \mathrm{mmol}$ ) was added to the solution of the protected amine above ( $107 \mathrm{mg}, 0.27 \mathrm{mmol}$ ) in anhydrous MeOH $(10 \mathrm{~mL})$. After stirred for 1 h at rt , the reaction mixture was treated with water and extracted with EtOAc ( $20 \mathrm{~mL} \times 3$ ), dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ 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. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.07$ $(0.65 \mathrm{H}, \mathrm{s}), 7.01(0.35 \mathrm{H}, \mathrm{s}), 6.63(0.35 \mathrm{H}, \mathrm{s}), 6.61(0.65 \mathrm{H}, \mathrm{s})$, $5.65(0.65 \mathrm{H}, \mathrm{s}), 5.60(0.35 \mathrm{H}, \mathrm{s}), 4.64(1 \mathrm{H}, \mathrm{m}), 3.95-3.73$ $(12 \mathrm{H}, \mathrm{m}), 3.75-3.44(2 \mathrm{H}, \mathrm{m}), 3.02-2.97(1 \mathrm{H}, \mathrm{m}), 2.80-2.60$ $(1 \mathrm{H}, \mathrm{m})$.To a solution of the resultant alcohol ( $22 \mathrm{mg}, 0.065$ mmol ) in anhydrous THF ( 2 mL ) at $0{ }^{\circ} \mathrm{C}$ were added $\mathrm{PPh}_{3}$ ( 38 $\mathrm{mg}, 0.143 \mathrm{mmol})$, DEAD ( $23 \mu \mathrm{~L}, 0.143 \mathrm{mmol}$ ). After 5 min , DPPA ( $31 \mu \mathrm{~L}, 0.143 \mathrm{mmol}$ ) was added and the mixture was stirred at rt for 2 h . The reaction mixture was treated with $\mathrm{H}_{2} \mathrm{O}$ $(0.4 \mathrm{~mL})$, then evaporated in vacuo and purified by silica gel column chromatography ( n -hexane/EtOAc $1: 1$ ) to afford azide 10 ( $15.4 \mathrm{mg}, 65 \%$ ) as a colorless liquid. ${ }^{1} \mathrm{H}$-NMR ( 400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.98(0.6 \mathrm{H}, \mathrm{s}), 6.96(0.4 \mathrm{H}, \mathrm{s}), 6.66(1 \mathrm{H}, \mathrm{s})$, $5.58(0.6 \mathrm{H}, \mathrm{s}), 5.49(0.4 \mathrm{H}, \mathrm{s}), 4.60(0.4 \mathrm{H}, \mathrm{m}), 4.43(0.4 \mathrm{H}, \mathrm{m})$, $3.88(3 \mathrm{H}, \mathrm{s}), 3.86(3 \mathrm{H}, \mathrm{s}), 3.8(3 \mathrm{H}, \mathrm{s}), 3.79(1.6 \mathrm{H}, \mathrm{s}), 3.77$ $(1.4 \mathrm{H}, \mathrm{s}), 3.70-3.65(1 \mathrm{H}, \mathrm{m}), 3.35-3.29(1 \mathrm{H}, \mathrm{m}), 3.05-2.95$ $(1 \mathrm{H}, \mathrm{m}), 2.87-2.79(1 \mathrm{H}, \mathrm{m})$. The mixture of azide $\mathbf{1 0}(10 \mathrm{mg}$, 0.027 mmol ), $\mathrm{PPh}_{3}(15 \mathrm{mg}, 0.055 \mathrm{mmol})$ in $\mathrm{THF} / \mathrm{H}_{2} \mathrm{O}$ ( 8 $\mathrm{mL} / 0.2 \mathrm{~mL}$ ) was stirred overnight at rt . After evaporation in
reduced pressure, the resultant residue was purified by silica gel column chromatography ( $\mathrm{EtOAc} / \mathrm{MeOH} 20: 1$ ) to yield lactam 11 ( $4.2 \mathrm{mg}, 51 \%$ ) as a white solid. ${ }^{1} \mathrm{H}-\mathrm{NMR}(400 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \delta 6.86(1 \mathrm{H}, \mathrm{s}), 6.60(1 \mathrm{H}, \mathrm{s}), 6.50(0.3 \mathrm{H}, \mathrm{s}, \mathrm{NH}), 6.36$ ( $0.7 \mathrm{H}, \mathrm{s}, \mathrm{NH}$ ), 5.42 ( $0.3 \mathrm{H}, \mathrm{s}$ ), 5.31 ( $0.7 \mathrm{H}, \mathrm{s}), 4.98(0.7 \mathrm{H}, \mathrm{bm})$, $4.85(0.3 \mathrm{H}, \mathrm{bm}), 3.88$ (3H, s, OMe), 3.84 ( $3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}$ ), 3.74 $(3 \mathrm{H}, \mathrm{s}), 3.38(1 \mathrm{H}, \mathrm{dd}, J=7.2,16.4 \mathrm{~Hz}), 3.20(1 \mathrm{H}, \mathrm{dd}, J=1.2$, $12 \mathrm{~Hz}), 2.70(1 \mathrm{H}, \mathrm{d}, J=17.6 \mathrm{~Hz}) .{ }^{13} \mathrm{C}-\mathrm{NMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ $\delta 169.8,154.7,149.0,147.6,124.7,124.4,111.4,109.6,56.5$, 56.0, 55.9, 53.1, 47.1, 42.5, 32.6. EI-HRMS calcd for $\mathrm{C}_{15} \mathrm{H}_{18}$ $\mathrm{N}_{2} \mathrm{O}_{5} 306.1216$, found: 306.1217.
(S)-2-(tert-Ethyloxalylamino)-3-(3,4-dimethoxyphenyl)propyl azide (12). To a solution of $5(623 \mathrm{mg}, 2 \mathrm{mmol})$ in anhydrous THF ( 20 mL ) at $0^{\circ} \mathrm{C}$ were added $\mathrm{PPh}_{3}(577 \mathrm{mg}, 4.4$ mmol ), DEAD ( $693 \mu \mathrm{~L}, 4.4 \mathrm{mmol}$ ), DPPA ( $950 \mathrm{uL}, 4.4 \mathrm{mmol}$ ) consecutively. After stirred at rt for 2 h , the reaction mixture was treated with $\mathrm{H}_{2} \mathrm{O}(1 \mathrm{~mL})$, then evaporated in vacuo and purified by silica gel column chromatography (n-hexane/ EtOAc $2: 1)$ to afford the product $12(470 \mathrm{mg}, 70 \%)$ as a colorless liquid. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.81(1 \mathrm{H}, \mathrm{d}, J=$ $8 \mathrm{~Hz}), 6.75-6.72(2 \mathrm{H}, \mathrm{m}), 4.71(1 \mathrm{H}, \mathrm{b}, \mathrm{NH}), 3.94(1 \mathrm{H}, \mathrm{m})$, $3.87(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.86(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe})$, 3.42-3.26 ( $2 \mathrm{H}, \mathrm{m}$ ), 2.86-2.67 (2H, m), $1.43(9 \mathrm{H}, \mathrm{s}) .{ }^{13} \mathrm{C}-\mathrm{NMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ $\delta 155.0,148.9,147.7,129.5,121.2,112.1,111.3,79.6,55.8$, 55.7, 53.0, 51.2, 37.5, 28.2. EI-HRMS calcd for $\mathrm{C}_{16} \mathrm{H}_{24} \mathrm{~N}_{4} \mathrm{O}_{4}$ 336.1798, found: 336.1800.
(S)-Ethyl-3-(azidomethyl)-6,7-dimethoxy-3,4-dihydroiso-quinoline-1-carboxylate(13). To a solution of $\mathbf{1 2}$ ( 350 mg , 1.04 mmol ) in anhydrous $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$ was added $\mathrm{AlCl}_{3}$ ( $278 \mathrm{mg}, 2.08 \mathrm{mmol}$ ). After $1 \mathrm{~h}, \mathrm{COClCOOEt}(173 \mu \mathrm{~L}, 1.56$ mmol ) was added. The reaction mixture was stirred at rt for 30 min and solid $\mathrm{NaHCO}_{3}(263 \mathrm{mg}, 3.12 \mathrm{mmol})$ was slowly added. Being stirred at rt for 1 h , the reaction mixture was then treated with saturated $\mathrm{NaHCO}_{3}$ solution slowly, water and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20 \mathrm{~mL} \times 3)$. The organic phases were washed with brine, dried over anhydrous $\mathrm{MgSO}_{4}$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane/EtOAc 1:1) to afford the oxalate amide product ( $213 \mathrm{mg}, 61 \%$ ) as a colorless liquid. ${ }^{1} \mathrm{H}-\mathrm{NMR}$ ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 6.83-6.70 ( $3 \mathrm{H}, \mathrm{m}$ ), 4.38-4.29 ( $3 \mathrm{H}, \mathrm{m}$ ), $3.88(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.87(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.52-3.38(2 \mathrm{H}, \mathrm{m})$, 2.92-2.79 (2H, m), $1.40(3 \mathrm{H}, \mathrm{t}, J=7.2 \mathrm{~Hz}) .{ }^{13} \mathrm{C}-\mathrm{NMR}(100$ $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 160.3,156.1,149.1,148.0,128.5,121.2,112.0$, 111.3, 63.4, 55.8, 52.3, 50.5, 37.0, 13.9. EI-HRMS calcd for $\mathrm{C}_{15} \mathrm{H}_{20} \mathrm{~N}_{4} \mathrm{O}_{5}$ 336.1434, found: 336.1429. A mixture of the oxalate amide ( $127 \mathrm{mg}, 0.378 \mathrm{mmol}$ ) and $\mathrm{P}_{2} \mathrm{O}_{5}(751 \mathrm{mg}, 2.65$ mmo ) in anhydrous $\mathrm{CHCl}_{3}(10 \mathrm{~mL})$ was refluxed at $80^{\circ} \mathrm{C}$ for 12 h . Then, the reaction mixture was cooled by ice-water bath, slowly treated with NaOH 2 M solution until $\mathrm{pH}=9$ and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20 \mathrm{~mL} \times 3)$. The combined organic layer was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The resultant residue was purified by silica gel column chromatography ( n -hexane/EtOAc $1: 1$ ) to yield the product 13 ( $77 \mathrm{mg}, 64 \%$ ) as a liquid. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ $7.28(1 \mathrm{H}, \mathrm{s}), 6.73(1 \mathrm{H}, \mathrm{s}), 4.45(2 \mathrm{H}, \mathrm{m}), 3.93(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe})$, $3.89(3 \mathrm{H}, \mathrm{s}, \mathrm{OMe}), 3.75(2 \mathrm{H}, \mathrm{m}), 3.61(1 \mathrm{H}, \mathrm{m}), 2.79(1 \mathrm{H}, \mathrm{dd}$, $J=5.6,15.6 \mathrm{~Hz}), 2.70(1 \mathrm{H}, \mathrm{m}), 1.42(3 \mathrm{H}, \mathrm{t}, J=7.2 \mathrm{~Hz})$. ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 64.7,159.2,151.9,147.6$,
$130.5,118.6,110.4,110.1,62.0,57.3,56.0,55.9,54.9,28.2$, 14.1. EI-HRMS calcd for $\mathrm{C}_{15} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{4}$ 318.1328, found: 318.1329 .

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

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