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# Synthesis of a New Conformation-Constrained L-Tyrosine Analogue as a Potential Scaffold for SH2 Domain Ligands

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The enantioselective synthesis of a new tricyclic tyrosine analogue is reported. This conformation-contrained SH2 domain ligand scaffold **2** was designed on the basis of the natural ligand, whose structure contains the elements of a tyrosine moiety having $\chi_1$ and $\chi_2$ angles constrained to values observed for a phosphotyrosyl (pTyr) residue bound to the $p56^{lck}$ SH2 domain. It represents a unique, highly constrained amino acid, which may be of value in signal transduction studies. Three key steps, an asymmetric tandem Michael addition, an intramolecular Friedel−Crafts reaction, and an intramolecular Mannich reaction, were successfully applied in the presented synthetic route.

## Introduction

Various SH2 domains are associated with different human diseases, most commonly cancer. In recent years, the SH2 domains have been commonly selected as targets for drug design, which continues to draw more and more attention in the biomedical community. For example, inhibition of specific Src homology 2 (SH2) domain-binding interactions could potentially afford new therapeutics for a variety of diseases, including cancer.[1] To date, many SH2 domain ligands have been designed[2] which appear to bind along the surface of the SH2 domain with specific recognition features protruding into the protein. Because of the central role played by the pTyr residue, its analogues have become important tools for developing SH2 domain-binding antagonists.[3] To enhance binding affinities of flexible ligands, one useful approach is to reduce entropy penalties by constraining ligands to conformations approximating those required for binding. Many conformationally restricted amino acids, such as analogues of phenylalanine[4] and tyrosine,[1,5] have been devised for these purposes. The X-ray and solution structures of liganded SH2 domains[7] have provided a clear definition of relevant binding geometries that would be required for the conformationally constrained pTyr analogues. In 1997, Burke and colleagues first reported the synthetic route of racemic **1**[6] based on this idea, in which a methyl group was added on the $\beta$-position of the amino acid to block the side reactions during the synthesis. According to the structural information of the SH2−ligand complex, we think this methyl group is not necessary to constrain the conformation. Also, only the L-form of this amino acid analogue will be able to bind properly with the SH2 domain. Herein, we wish to report our recent work on the enantioselective synthesis of tricyclic analogue **2**, which was designed according to the previously reported X-ray structures of a pTyr-containing peptide bound to the $p56^{lck}$ SH2 domain,[7] whose $\chi_1$ and $\chi_2$ torsion angles were very closely

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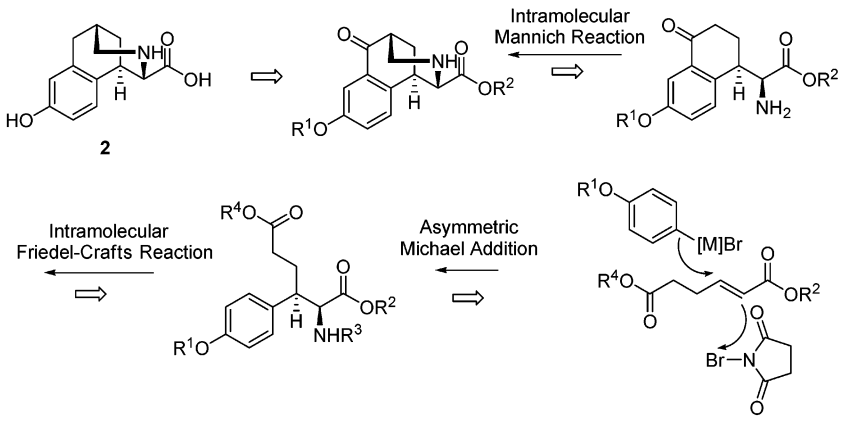
**SCHEME 1**



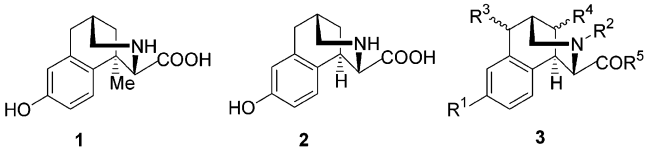




**FIGURE 1.** Structures of conformation-constrained tyrosine analogues.

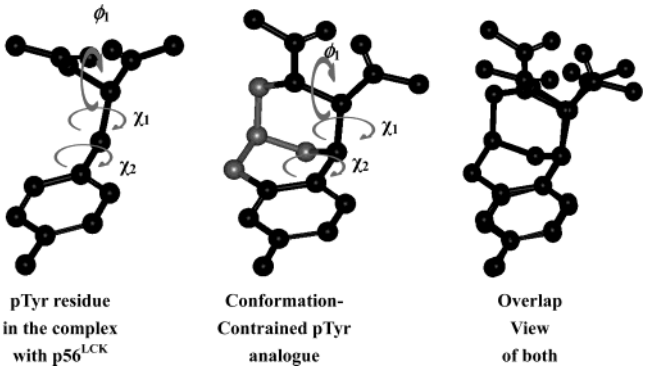



**FIGURE 2.** Conformation of the pTyr residue and its analogue.

approximated to those of the SH2 domain-bound pTyr residue (Figures 1 and 2). The presented synthesis has the advantages of future diversity development on such a SH2 domain ligand scaffold, which could be generally represented by **3**.

## Synthesis

Our synthetic strategy of L-tyrosine analogue **2** is based on a tandem asymmetric Michael addition with the assistance of Evans' auxiliary,[8] followed by an intramolecular Friedel−Crafts reaction to furnish the second six-membered ring and an intramolecular Mannich reaction to construct the aza-six-membered ring (Scheme 1).

Refluxing succinic anhydride with *tert*-butyl alcohol for 24 h gave **4**[9] as a colorless crystal, which was then reduced with borane[10] to afford the alcohol **5** (Scheme 2). Swern oxidation of **5** gave the aldehyde, which was immediately reacted with phosphonate **6**[11] with the aid of diisopropylethylamine and LiCl to give unsaturated amide **7** in 51% yield[12] ($E/Z$ = 6.8/1, the two isomeric olefins could be easily separated by chromatography). The use of NaHMDS (sodium bis(trimethylsilyl) amide)[13] lowered the $E/Z$ ratio to 2.5/1.

Both of the α and $\beta$ stereogenic centers of **8** were constructed by a tandem reaction sequence of asymmetric Michael addition and subsequent electrophilic α-bromination[8a,8b] from ***E*-7** (Scheme 2). Thus, the crude bromide could be converted to the corresponding azide **8** with $NaN_3$. The resultant azide **8** was purified by recrystallization (de > 99.8%, HPLC). Cleavage of the auxiliary with LiOH and hydrogen peroxide followed by esterification with diazomethane gave the ester **9** in 95% yield. Reduction of azide **9** by hydrogenation and subsequent protection of the resultant amine with methyl chloroformate afforded ester **10**. Treatment of **10** with trifluroacetic acid[14] provided the Friedel−Crafts reaction precursor **11**.

The intramolecular Friedel−Crafts reaction of **11** proved to be difficult. No product could be detected when freshly prepared acid chloride (from **11**) was treated with various Lewis acids (e.g., $AlCl_3$, $FeCl_3$, $SnCl_4$, $ZnCl_2$, $BF_3$·$Et_2O$) in dichoromethane. It was determined that the solvent played a key role for the efficient formation of acid chloride and subsequent intramolecular Friedel−Crafts reaction. After optimization of the solvent, acid chloride was efficiently formed in a mixed solvent system ($CH_2Cl_2/CS_2$ = 1/6). The following cationic cyclization was then accomplished in the presence of $AlCl_3$ affording the ketone **12** in 81% yield (two steps from acid **11**, Scheme 2). It is noteworthy that the rates of Friedel−Crafts reaction and N-deprotection were approximately equal when a benzyloxycarbonyl served as the amine protecting group.

Cleavage of the methylcarbomate group of **12** with TMSI[15] followed by direct intramolecular Mannich reac-

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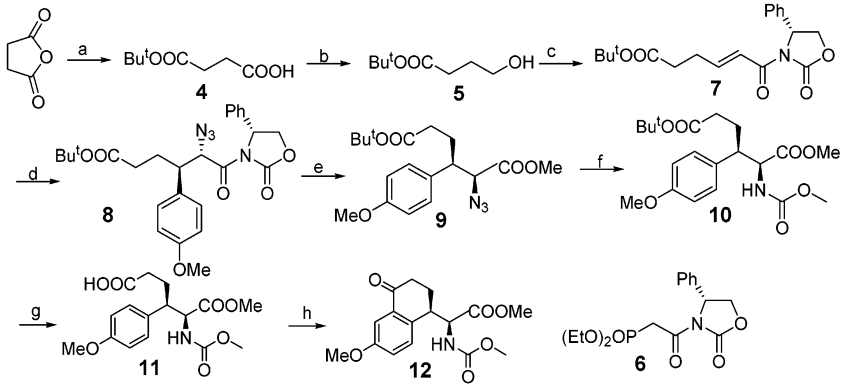
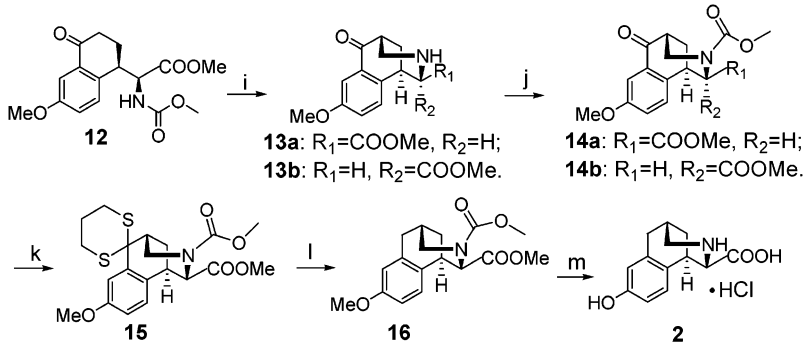
**SCHEME 2**[a]



[a] Reagents and conditions: (a) *N*-hydroxysuccinimide, DMAP, *tert*-butyl alcohol, toluene, reflux, 24 h, 78%; (b) $BH_3$·DMS, THF, rt, 24 h, 74%; (c) (1) $(COCl)_2$, DMSO, $NEt_3$, $CH_2Cl_2$, (2) **6**, LiCl, $(i\text{-}Pr)_2NEt$, $CH_3CN$, 51%, $E/Z$ = 6.8/1 based on isolated yields; (d) (1) CuBr·$Me_2S$, 4-methoxybenzylMgBr, NBS, THF, (2) $NaN_3$, DMF, 60% for two steps; (e) (1) LiOH·$H_2O$, $H_2O_2$, THF and $H_2O$, (2) $CH_2N_2$, $Et_2O$, 95%; (f) (1) Pd/C, $H_2$, methanol; (2) ClCOOMe, $KHCO_3$, dioxane and $H_2O$, 91% for two steps; (g) TFA, $Et_3SiH$, $CH_2Cl_2$, rt, 2 h, 93%; (h) (1) $(COCl)_2$, DMF (cat), $CS_2$ and $CH_2Cl_2$, (2) $AlCl_3$, $CH_2Cl_2$, 81%.

**SCHEME 3**[a]



[a] Reagents and Conditions: (i) (1) TMSI, $CH_3CN$, reflux, 40 min; (2) HCHO (aq), ethanol, reflux, 12 h, 43% for two steps, **13a**/**13b** = 4/1; (j) **13a**, ClCOOMe, 83%; (k) **14a**, 1,3-propanedithiol, $BF_3$ etherate, 100%; (l) Raney Nickel, EtOH, 73%; (m) 6 N HCl, reflux, 100%.

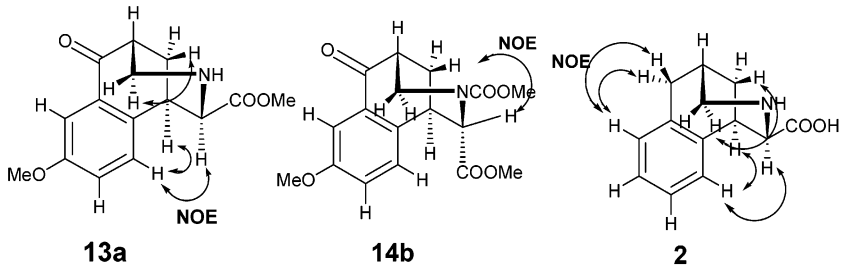


**FIGURE 3.** NOE of compounds **13a**, **14b**, and **2**.

tion (refluxing with formaldehyde in ethanol for 12 h) afforded the tricyclic amines **13** in 43% yield as a 4:1 mixture of **13a** and **13b** (the two isomers could be separated easily by chromatograghy) (Scheme 3 and Figure 3). Interestingly, if the free amine intermediate was purified by chromatography, the following Mannich reaction with formaldehyde in EtOH with a catalytic amount of acetic acid gave **13b** as the only product. On the other hand, if the free amine was protected with methyl chloroformate again, **12** was formed as the only product. This means that the nature of the acid catalyst (HI or HOAc) used in this Mannich reaction might make a big difference in stereoselectivity, although the details of the mechanism are still unclear at this stage.

Protection of amide **13a** with methyl chloroformate gave ketone **14a**. Hydrogenolysis of ketone **14a** in acetic acid with a catalytic amount of perchloric acid gave amide **16**.[16] It is also noteworthy that use of excess perchloric acid resulted in full reduction of the phenyl ring, while with too less amount of perchloric acid the reaction gave only the corresponding alcohol (produced by partially reduction of ketone) in high yield. To improve the procedure, we protected **14a** as the dithio ketal **15**, and

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**15** was then smoothly reduced with Raney nickel in ethanol at room temperature to afford **16**. The amino acid analogue **2** was finally obtained from **16** in high yield by refluxing in 6 N HCl for 4 days. The stereochemistries of final product **2** and key intermediates **13a** and **14b** were confirmed by NOESY spectra, which are shown in Figure 3.

## Summary

In conclusion, an enantioselective synthetic route to the tricyclic amino acid analogue **2** was developed, utilizing a tandem asymmetric Michael addition/substitution reaction, intramolecular Friedel−Crafts reaction, and intramolecular Mannich reaction as key steps. All the stereochemistries in the synthesis were well controlled, and the key reactions were optimized. This work is a good starting point to develop new SH2 domain ligands based on the conformation-constrained tyrosine analogue **2** as scaffold. The chemical diversity study toward **3** and further development of new SH2 domain ligands on the basis of this scaffold are in progress.

## Experimental Section

**General Methods.** All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gastight syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use; optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. $^1$H NMR spectra were recorded at 300 MHz and are reported in parts per million ($\delta$) downfield relative to TMS as internal standard, and $^{13}$C NMR spectra were recorded at 75 MHz and assigned in parts per million ($\delta$). Flash column chromatography was performed on silica gel (10−40 $\mu$m) using a mixture of petroleum ether and ethyl acetate as the eluent.

**Succinic Acid Mono-*tert*-butyl Ester (4).** To a mixture of succinic anhydride (30 g, 0.30 mol), *N*-hydroxysuccinimide (0.30 equiv, 10 g, 0.09 mol), and DMAP (0.10 equiv, 3.5 g, 0.03 mol) in toluene (150 mL) were added *tert*-butyl alcohol (1.3 equiv, 35 mL, 0.37 mol) and $Et_3N$ (0.3 equiv, 0.09 mol, 12.5 mL). The suspension was refluxed for 24 h. The solution was cooled and diluted with EtOAc (150 mL). The reaction mixture was washed with 10% citric acid and brine, dried over $Na_2SO_4$, and concentrated to give a brown oil. The oil was recrystallized with ether and petroleum ether at −20 °C to give **4** as a white crystal (41 g, 78%). Mp: 44−45 °C (lit.[9] mp 49−50 °C, lit.[17] mp 50−51.5 °C). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.65−2.50 (m, 4 H), 1.45 (s, 9 H) ppm.

**4-Hydroxybutanoic Acid *tert*-Butyl Ester (5).** To a solution of acid **4** (21.2 g, 0.122 mol) in dry THF (183 mL) at 0 °C was added $BH_3$·$Me_2S$ (2.0 M, 65.5 mL, 0.131 mol) dropwise. After being stirred at room temperature for 24 h, the mixture was cooled to 0 °C. Water (100 mL) and solid $K_2CO_3$ were added to the reaction mixture. The reaction mixture was extracted with $Et_2O$ (200 mL × 3), and the combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was distilled to give a colorless liquid (14.5 g, 74%). Bp: 73−74 °C/2.0−3.0 mmHg (lit.[18] bp 62−63 °C/0.1 Torr). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.70 (t, $J$ = 6.0 Hz, 2 H), 2.40−2.30 (m, 3 H), 1.85 (m, 2 H), 1.45 (s, 9 H) ppm. EIMS (*m*/*z*): 105 (5.03), 87 (45.60), 57 (100).

**(*E*)- and (*Z*)-6-Oxo-6-[(4*S*)-(2-oxo-4-phenyl-oxazolidin-3-yl)]hex-4-enoic Acid *tert*-Butyl Ester (7).** To a solution of oxalyl chloride (5.0 mL, 57.1 mmol) in dry $CH_2Cl_2$ (120 mL) at −75 °C was added DMSO (8.0 mL, 116 mmol) in dry $CH_2Cl_2$ (40 mL). After the solution was stirred at −75 °C for an additional 15 min, alcohol **5** (6.0 g, 37.5 mmol) in dry $CH_2Cl_2$ (40 mL) was added over 5 min. After the resulting solution was stirred at −75 °C for 2 h, dry $Et_3N$ (42.0 mL, 0.30 mol) was added, and the mixture was slowly warmed to room temperature. Saturated $NH_4Cl$ was added, and the mixture was extracted with $Et_2O$. The combined $Et_2O$ extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was redissolved in $Et_2O$ (50 mL) and filtered to remove the $Et_3N$·HCl, and the filtrate was concentrated to give a yellow oil which was used directly in the next step.

To a suspension of LiCl (2.23 g, 52.5 mmol) in dry $CH_3CN$ (150 mL) at 0 °C were added (*i*-Pr)$_2$NEt (16.4 mL, 93.9 mmol) and phosphonate **6** (15.5 g, 45.6 mmol), and then freshly prepared aldehyde in dry $CH_3CN$ (10 mL) was added. After the mixture was stirred at room temperature for 24 h, water (100 mL) was added. $CH_3CN$ was removed in vacuo, and the resulting mixture was extracted with $Et_2O$ (200 mL × 3). The combined $Et_2O$ extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography to give **7** as a white solid (*E*-isomer, 5.7 g) and a yellow oil (*Z*-isomer, 0.84 g) in 51% total yield. Date for (*E*)-**7**. Mp: 93.0−94.0 °C. $[\alpha]^{20}_D$: −80.4 (c 1.09, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.40−7.20 (m, 6 H), 7.10 (dt, $J$ = 15.3, 6.6 Hz, 1 H), 5.50 (dd, $J$ = 8.7, 3.9 Hz, 1 H), 4.70 (t, $J$ = 8.7 Hz, 1 H), 4.25 (m, 1 H), 2.55 (m, 2 H), 2.40 (m, 2 H), 1.45 (s, 9 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 171.4, 164.3, 153.6, 151.9, 149.7, 139.0, 129.2, 128.6, 125.9, 120.7, 120.3, 80.7, 70.0, 57.7, 33.5, 28.0, 27.9 ppm. EIMS (*m*/*z*): 346 ($MH^+$, 1.82), 291 (17.65), 290 (100). IR (KBr): 2976, 1767, 1687, 1195, 1032, 768, 697 cm$^{-1}$. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.04; H, 6.70; N, 3.97. Date for (*Z*)-**7**. $[\alpha]^{20}_D$: −74.2 (c 0.85, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.40−7.00 (m, 7 H), 5.45 (dd, $J$ = 9.0, 3.9 Hz, 1 H), 4.65 (t, $J$ = 9.0 Hz, 1 H), 4.25 (m, 1 H), 3.35 (m, 1 H), 2.55−2.30 (m, 2 H), 1.65 (m, 1 H), 1.40 (s, 3 H), 1.15 (s, 6 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 171.4, 164.5, 153.6, 151.7, 149.7, 139.0, 129.1, 128.6, 125.8, 120.7, 120.2, 80.7, 72.6, 69.8, 72.6, 69.8, 60.4, 57.6, 33.5, 29.5, 28.8, 28.0, 27.6 ppm. EIMS (*m*/*z*): 289 [$(MH - C_4H_9)^+$, 54.8]. ESI (*m*/*z*): 346.2 ($MH^+$, 25.0), 363.2 [$(M + NH_4)^+$, 57.0]. IR (film): 2976, 1782, 1689, 1386, 1363, 1082, 711, 530 cm$^{-1}$. HR-ESI: calcd for ($C_{19}H_{23}NO_5$ + Na) 368.1474, found 368.1468.

**(4*R*,5*S*)-5-Azido-4-(4-methoxylphenyl)-6-oxo-6-[(4*S*)-(2-oxo-4-phenyloxazolidin-3-yl)]hexanoic Acid *tert*-Butyl Ester (8).** To a solution of CuBr·$Me_2S$ (900 mg, 4.38 mmol) in dry THF (9.0 mL) and dry $Me_2S$ (9.0 mL) at −45 °C was added freshly prepared 4-methoxyphenylmagnesium bromide (0.50 M, 8.8 mL, 4.4 mmol) dropwise. The mixture was warmed to −15 to −10 °C over 30 min. The unsaturated amide (*E*)-**7** (1.0 g, 2.90 mmol) in dry THF (5.0 mL) was added slowly at −15 to −10 °C. After being sitrred at the same temperature for 20 min, the reaction mixture was cooled to −78 °C, and NBS (0.78 g, 4.38 mmol) in dry THF (10 mL) was added. After an additional 1 h, saturated $NaHSO_3$ (10 mL) was added at −78 °C and the reaction mixture was warmed to room temperature and extracted with $Et_2O$ (50 mL × 3). The combined organic extracts were washed with water (50 mL × 3) and brine (50 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography to give the crude product as a yellow oil (1.26 g).

To a solution of above crude product in DMF (20 mL) was added $NaN_3$ (461 mg, 7.10 mmol) in one portion at room temperature. After being stirred for 4 h, the reaction mixture was diluted with EtOAc (100 mL) and water (100 mL), and the aqueous phase was extracted with EtOAc (50 mL × 2). The combined organic extracts were washed by brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was recrystallized with $CH_2Cl_2$ and petroleum ether to give the first

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crop (**8**, 700 mg) as a white solid followed by the second crop (**8**, 150 mg), in a total yield of 60% for two steps. Mp: 185.0−186.0 °C. $[\alpha]^{20}_D$: −27.1 (*c* 1.63, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.30−7.10 (m, 3 H), 7.05 (d, $J$ = 8.7 Hz, 2 H), 6.75−6.65 (m, 4 H), 5.40 (d, $J$ = 9.9 Hz, 1 H), 5.35 (dd, $J$ = 8.7, 3.9 Hz, 1 H), 4.65 (t, $J$ = 8.7 Hz, 1 H), 4.10 (dd, $J$ = 8.7, 3.9 Hz, 1H), 3.80 (s, 3 H), 3.10 (m, 1 H), 2.20 (m, 1 H), 2.00−1.80 (m, 3 H), 1.40 (s, 9H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 172.1, 169.1, 158.8, 152.9, 137.5, 129.6, 129.5, 128.9, 128.2, 125.2, 114.1, 80.2, 69.9, 62.2, 57.5, 55.1, 45.6, 32.6, 28.0, 27.4 ppm. EIMS (*m*/*z*): 467 (1.07), 466 (1.05), 411 (7.65), 410 (7.29), 193 (100). IR (KBr): 3060, 2082, 1772, 1217, 760, 557 $cm^{-1}$. Anal. Calcd for $C_{26}H_{30}N_4O_6$: C, 63.15; H, 6.11; N, 11.33. Found: C, 63.08; H, 6.15; N, 11.40. de > 99.80% by HPLC (a Kromasil $C_{18}$ cloumn, UV detector 220 nm, eluent $CH_3CN/H_2O$ (1:1 to 100:0), flow rate 1.0 mL/min).

**(2*S*,3*R*)-2-Azido-3-(4-methoxyphenyl)hexanedioic Acid 6-*tert*-Butyl Ester 1-Methyl Ester (9).** To a solution of azide **8** (1.86 g, 3.76 mmol) in THF (57 mL) and water (19 mL) at −5 to 0 °C was added $H_2O_2$ (30% aq, 1.82 mL, 16.1 mmol) over 5 min. $LiOH\cdot H_2O$ (253 mg, 6.03 mmol) was added in three portions. After the mixture was stirred for 30 min, saturated $Na_2SO_3$ (15 mL) was added to the reaction mixture, and the THF was removed in vacuo. The resulting mixture was extracted with $Et_2O$. The aqueous phase was then acidified to pH 3−4 and extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo to give a white solid. To a solution of this white solid in $Et_2O$ (20 mL) at 0 °C was added $CH_2N_2$ in $Et_2O$ until the solution turned yellow. After the mixture was stirred for another 20 min, excess $CH_2N_2$ was destroyed with glacial acetic acid. The reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography to give **9** as a colorless oil (1.30 g, 95%). $[\alpha]^{20}_D$: +17.8 (*c* 2.40, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.10 (m, 2 H), 6.85 (m, 2 H), 3.90 (d, $J$ = 7.8 Hz, 1 H), 3.80 (s, 3 H), 3.60 (s, 3 H), 3.10 (m, 1 H), 2.20−1.90 (m, 4 H), 1.40 (s, 9 H) ppm. EIMS (*m*/*z*): 321 [$(M - N_3)^+$, 1.23], 264 (9.39), 193 (100), 147 (55.78). IR (film): 2979, 2109, 1743, 1728, 1252, 1150, 832 $cm^{-1}$. Anal. Calcd for $C_{18}H_{25}N_3O_5$: C, 59.49; H, 6.93; N, 11.56. Found: C, 59.32; H, 6.92; N, 11.41. (The auxiliary was recycled in 80% yield.)

**(2*S*,3*R*)-2-Methoxycarbonylamino-3-(4-methoxyphenyl)-hexanedioic Acid 6-*tert*-Butyl Ester 1-Methyl Ester (10).** To a solution of ester **9** (1.30 g, 3.58 mmol) in methanol (30 mL) was added Pd/C (10%, 260 mg). After the mixture was stirred at room temperature for 5 h under 1 atm of $H_2$, Pd/C was filtered off and the filtrate was concentrated in vacuo. To a solution of the above residue in dioxane (20 mL) and water (20 mL) were added $K_2CO_3$ (720 mg, 7.20 mmol) and ClCOOMe (0.34 mL, 4.40 mmol). After the mixture was stirred for 2 h at room temperature, dioxane was removed in vacuo, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography to give **10** as a colorless oil (1.29 g, 91%). $[\alpha]^{20}_D$: +3.0 (*c* 1.93, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.05 (m, 2 H), 6.85 (m, 2 H), 5.30 (d, $J$ = 9.0 Hz, 1 H), 4.50 (m, 1 H), 3.80 (s, 3 H), 3.65 (s, 3 H), 3.55 (s, 3 H), 2.90 (m, 1 H), 2.20−1.90 (m, 4 H), 1.40 (s, 9 H) ppm. EIMS (*m*/*e*): 396 ($MH^+$, 0.41), 395 ($M^+$, 0.88), 394 (1.45), 340 (16.16), 193 (100). ESIMS (*m*/*z*): 396.1 ($MH^+$). IR (film): 3352, 2978, 1728, 1514, 834 $cm^{-1}$. HR-EIMS: calcd for $C_{20}H_{29}NO_7$ 395.1944, found 395.1976.

**(2*S*,3*R*)-2-Methoxycarbonylamino-3-(4-methoxyphenyl)-hexanedioic Acid 1-Methyl Ester (11).** To a solution of ester **10** (1.29 g, 3.26 mmol) in $CH_2Cl_2$ (6.8 mL) was added $Et_3SiH$ (1.40 mL, 8.67 mmol), followed by TFA (3.30 mL, 44.6 mmol). After being stirred at room temperature for 1 h, the reaction mixture was concentrated in vacuo to give a colorless oil, which was purified by flash column chromatography to give acid **11** as a white wax (1.03 g, 93%). $[\alpha]^{20}_D$: +12.0 (*c* 1.00, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.05 (m, 2 H), 6.85 (m, 2 H), 5.50 (d, $J$ = 9.6 Hz, 1H), 4.50 (m, 1 H), 3.80 (s, 3 H), 3.70 (s, 3 H), 3.50 (s, 3 H), 2.95 (m, 1 H), 2.30−2.00 (m, 4 H) ppm. EIMS (*m*/*e*): 340 ($MH^+$, 0.40), 323 (0.69), 280 (2.22), 262 (3.28), 193 (100). ESI-MS (*m*/*z*): 341 [$(M + 2H)^+$, 15], 340 ($MH^+$, 100). IR (film): 3330, 2955, 1716, 1249, 833 $cm^{-1}$. HR-EIMS: calcd for $C_{16}H_{21}NO_7$ 339.1318, found 339.1346.

**(*S*)-Methoxycarbonylamino-[(1*R*)-6-methoxy-4-oxo-2,3-dihydronaphthalen-1-yl]acetic Acid Methyl Ester (12).** To a solution of acid **11** (1.03 g, 3.04 mmol) in dry $CH_2Cl_2$ (4 mL) and $CS_2$ (24 mL) at 0 °C was added $(COCl)_2$ (0.80 mL, 9.33 mmol), followed by the slow addition of dry DMF (70 uL, 0.91 mmol). The mixture was warmed to room temperature and stirred for 2 h. The solvent was removed to give a yellow oil. To the solution of this oil in dry $CH_2Cl_2$ (50 mL) at 0 °C was added $AlCl_3$ (1.30 g, 9.74 mmol) in one portion. The reaction mixture was warmed to room temperature and stirred for 5 h. Ice was added, and the reaction mixture was extracted with $CH_2Cl_2$ (50 mL × 3). The $CH_2Cl_2$ extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography to give ketone **12** as a white solid (795 mg, 81%). Mp: 132.0−133.0 °C. $[\alpha]^{20}_D$: +124.3 (*c* 1.11, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.55 (d, $J$ = 3.0 Hz, 1 H), 7.15 (d, $J$ = 8.7 Hz, 1 H), 7.05 (dd, $J$ = 8.7, 3.0 Hz, 1 H), 5.25 (d, $J$ = 8.7 Hz, 1 H), 4.95 (m, 1 H), 3.85 (s, 3 H), 3.65 (s, 3H), 3.60 (s, 3 H), 3.30 (m, 1 H), 2.90 (m, 1 H), 2.60 (m, 1 H), 2.15 (m, 2 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 196.9, 172.4, 158.9, 156.6, 134.2, 133.5, 129.2, 121.3, 109.8, 56.0, 55.3, 52.4, 52.1, 40.9, 35.2, 24.3 ppm. EIMS (*m*/*z*): 290 [$(M - MeO)^+$, 0.88], 246 (4.08), 187 (5.23), 175 (100). IR (KBr) 3405, 2954, 1723, 1682, 1288, 1049, 828 $cm^{-1}$. Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.71; H 5.99; N, 4.30.

**(1*R*,9*R*,12*S*)-5-Methoxy-8-oxo-11-azatricyclo[7.3.1.$0^{2,7}$]-trideca-2(7),3,5-triene-12-carboxylic Acid Methyl Ester (13).** To a solution of ketone **12** (220 mg, 0.68 mmol) in dry $CH_3CN$ (10 mL) was added TMSI (0.50 mL, 3.50 mmol). After being refluxed for 40 min, the mixture was cooled to 0 °C and methanol (5.0 mL) was added slowly. The solvent was removed, the residue was redissolved in ethanol (10 mL), and HCHO (36% aq, 110 $\mu$L, 1.32 mmol) was added. After being refluxed for 12 h, the reaction mixture was cooled to room temperature. Ethanol was removed in vacuo, and the residue was extracted with $Et_2O$. The aqueous phase was basified with saturated $NaHCO_3$, saturated with solid NaCl, and extracted with $CH_2Cl_2$ again. The combined $CH_2Cl_2$ extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography to give **13a** as a white solid (64 mg) and **13b** as a colorless oil (16 mg) in 43% total yield). Data for **13a**. Mp: 133.0−134.0 °C. $[\alpha]^{20}_D$: +114.4 (c 0.56, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.50 (d, $J$ = 2.8 Hz, 1 H), 7.25 (d, $J$ = 8.4 Hz, 1 H), 7.10 (dd, $J$ = 8.4, 2.8 Hz, 1 H), 3.90−3.80 (m, 6 H), 3.55 (s, 1 H), 3.45 (s, 1 H), 3.20 (dd, $J$ = 11.7, 3.0 Hz, 1 H), 3.10 (d, $J$ = 11.7 Hz, 1 H), 2.55 (s, 1 H), 2.30 (m, 1 H), 2.05 (m, 1 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 201.1, 173.4, 159.0, 138.5, 135.2, 128.8, 121.8, 108.7, 60.0, 55.5, 52.2, 46.8, 42.4, 35.7, 29.3 ppm. EIMS (*m*/*z*): 277 [$(M + 2H)^+$, 1.63], 276 ($MH^+$, 7.34), 275 ($M^+$, 1.68), 274 (12.19), 216 (100). IR (KBr): 3383, 2951, 2932, 1731, 1679, 1232, 1029, 844, 548 $cm^{-1}$. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.02; H, 6.31; N, 4.90. Data for **13b**. $[\alpha]^{20}_D$: +137.8 (*c* 0.90, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.50 (d, $J$ = 2.7 Hz, 1 H), 7.05 (dd, $J$ = 8.1, 2.7 Hz, 1 H), 6.85 (d, $J$ = 8.1 Hz, 1 H), 3.90 (s, 3 H), 3.60 (s, 3 H), 3.25 (s, 1 H), 3.15−3.05 (m, 2 H), 2.70 (d, $J$ = 2.4 Hz, 1 H), 2.45 (d, $J$ = 11.4 Hz, 1 H), 2.40 (m, 1 H), 2.10 (d, $J$ = 13.2 Hz, 1 H), 1.80 (m, 1 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 200.4, 172.3, 158.5, 137.9, 134.6, 128.8, 121.4, 108.4, 61.5, 55.6, 51.3, 49.3, 42.4, 36.5, 28.6 ppm. EIMS (*m*/*z*): 260 [$(M - CH_3)^+$, 15.0]. IR (film): 3002, 2950, 1733, 1687, 1496, 1281, 1172, 1023, 786, 541 $cm^{-1}$. HR-ESI: calcd for ($C_{15}H_{17}NO_4$ + H) 276.1236, found 276.1230.

**(1*R*,9*R*,12*S*)-5-Methoxy-8-oxo-11-azatricyclo[7.3.1.0$^{2,7}$]-trideca-2(7),3,5-triene-11,12-dicarboxylic Acid Dimethyl Ester (14a).** To a solution of amide **13a** (50 mg, 0.182 mmol) in water (4 mL) and dioxane (4 mL) were added $KHCO_3$ (40 mg, 0.40 mmol) and ClCOOMe (16 uL, 0.21 mmol) at room temperature. After the mixture was stirred at room temperature overnight, dioxane was removed in vacuo and the aqueous phase was extracted with EtOAc (20 mL × 3). The combined EtOAc extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography to give **14a** as a colorless oil (45 mg, 83%) and recovered **13a** (5 mg). $[\alpha]^{20}_D$: +89.0 (c 1.31, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.50 (m, 1 H), 7.30 (m, 1 H), 7.10 (m, 1 H), 4.80 (s, 0.6 H), 4.65 (s, 0.40 H), 4.40−4.20 (m, 1 H), 3.80 (m, 6 H), 3.70−3.40 (m, 5 H), 2.70 (m, 1 H), 2.40 (m, 1 H), 2.00 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 199.1/198.5$_{(conformer)}$, 170.7, 159.1, 157.0/156.4, 137.0, 133.8/133.5, 129.3/128.9, 122.3, 109.0, 60.2/59.9, 59.2, 55.4, 52.9/52.5, 45.2/44.7, 41.3, 35.3, 28.1 ppm. EIMS (*m*/*z*): 334 ($MH^+$, 0.58), 333 ($M^+$, 3.38), 275 (18.11), 274 (100), 43 (43.76). IR (film): 2955, 1743, 1709, 1686, 1447, 1229, 1022, 792, 525 cm$^{-1}$. HR-EIMS: calcd for $C_{17}H_{29}NO_6$ 333.1212, found 333.1252. ee > 99% by HPLC (a chiracel AS column, UV detector 254 nm, eluent *i*-PrOH/hexane (3:7), flow rate 0.7 mL/min).

**(1*R*,9*R*,12*S*)-5-Methoxy-11-azatricyclo[7.3.1.0$^{2,7}$]trideca-2(7),3,5-triene-11,12-dicarboxylic Acid Dimethyl Ester (16).** To a solution of **14a** (36 mg, 0.11 mmol) in dry $CH_2Cl_2$ (5.0 mL) at 0 °C were added $BF_3{\cdot}Et_2O$ (20 uL, 0.16 mmol) and 1,3-propanedithiol (40 $\mu$L, 0.40 mmol). After the mixture was stirred at room temperature for 48 h, the reaction was quenched with saturated $NaHCO_3$ and the mixture was extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography to give **15** as a colorless oil (45 mg, 100%).

To a solution of compound **15** (45 mg, 0.11 mmol) in EtOH (10 mL) was added Raney-Nickel (about 0.5 g). After 40 min, Raney-Nickel was filtered through a pad of Celite and the filtrate was concentrated. The residue was redissoved in EtOAc and washed with water and brine. The organic extracts were dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography to give **16** as a white solid (25 mg, 73%). Mp: 140.0−141.0 °C. $[\alpha]^{20}_D$: +8.6 (*c* 0.39, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.10 (m, 1 H), 6.70 (m, 1 H), 6.60 (m, 1 H), 4.70 (d, $J$ = 2.4 Hz, 0.5 H), 4.50 (d, $J$ = 2.4 Hz, 0.5 H), 4.10 (d, $J$ = 13.2 Hz, 0.5 H), 3.90 (d, $J$ = 13.2 Hz, 0.5 H), 3.80−3.70 (m, 6 H), 3.60−3.30 (m, 5 H), 3.10 (m, 1 H), 2.80 (m, 1 H), 2.20 (m, 1 H), 1.80 (m, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 171.3, 158.3, 157.3/156.9$_{(conformer)}$, 137.9/137.5, 130.0, 129.1/128.9, 113.0/112.7, 112.2/111.7, 61.5/61.1, 55.0, 52.7/52.3, 48.7/48.5, 35.0, 34.8, 34.2, 26.3, 25.9 ppm. EIMS (*m*/*z*): 320 ($MH^+$, 3), 319 ($M^+$, 15), 261 (20), 260 (100). IR (KBr): 2997, 1738, 1207, 854, 618 cm$^{-1}$. HR-EIMS: calcd for $C_{17}H_{21}NO_5$ 319.1420, found 319.1415.

**(1*R*,9*R*,12*S*)-5-Hydroxy-11-azatricyclo[7.3.1.0$^{2,7}$]trideca-2(7),3,5-triene-12-carboxylic Acid Hydrochloride Salt (2).** Compound **16** (44 mg, 0.14 mmol) was refluxed with HCl (6 N, 10 mL) for 4 days. The mixture was concentrated in vacuo to give **2** as a white solid (38 mg, 100%). $[\alpha]^{20}_D$: +33.2 (*c* 1.20, $H_2O$). $^1$H NMR (500 MHz, $D_2O$): $\delta$ 7.20 (d, $J$ = 8.3 Hz, 1 H), 6.80 (d, $J$ = 8.3 Hz, 1H), 6.75 (s, 1 H), 4.15 (s, 1 H), 3.70 (dd, $J$ = 13.0, 3.0 Hz, 1 H), 3.60 (s, 1 H), 3.30 (d, $J$ = 13.0 Hz, 1 H), 3.20 (dd, $J$ = 18.4, 6.8 Hz, 1 H), 2.90 (d, $J$ = 18.4 Hz, 1 H), 2.50 (s, 1 H), 2.00 (d, $J$ = 13.6 Hz, 1 H), 1.85 (d, $J$ = 13.6 Hz, 1 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 172.5, 157.3, 140.3, 132.7, 129.6, 117.6, 116.9, 62.9, 50.0, 35.2, 35.0, 26.7, 26.1 ppm. EIMS (*m*/*z*): 234 ($MH^+$, 1.91), 233 ($M^+$, 16.03), 189 (16.03), 188 (100), 145 (45.69), 88 (85.05). ESIMS (*m*/*z*): 274 [$(M + K + 2H)^+$, 5], 235 [$(M + 2H)^+$, 4], 234 ($MH^+$, 100). IR (KBr): 3220, 2413, 1704, 1449, 1230, 1167, 807, 657, 545 cm$^{-1}$. HR-EIMS: calcd for $C_{13}H_{15}NO_3$ 233.1052, found 233.1021.

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**Supporting Information Available:** The $^1$H NMR spectra of key intermediates **8**, **12**, **13a**, **14a**, **16**, and **2**, $^{13}$C NMR spectra of **13a**, **14a**, **16**, and **2**, and NOESYs of **13a**, **14b**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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