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Modular Access to N-Substituted *cis*-3,5-Diaminopiperidines

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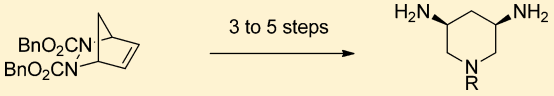
Supporting Information

ABSTRACT: A sequence of oxidative cleavage/reductive amination/hydrogenolysis enables the preparation of N-substituted *cis*-3,5-diaminopiperidines from a readily available bicyclic hydrazine. This new synthetic route provides a simple and general access to RNA-friendly fragments with a good chemical diversity.



The design of small molecular RNA ligands is a growing field[1] since the recent understanding of the key role of RNA in many cellular regulation processes.[2] Among the different strategies used to design such ligands, one of the most successful is to build libraries from a "RNA friendly" small molecular scaffold.[3] This approach has been recently illustrated by the group of Hermann, who showed that the *cis*-3,5-diaminopiperidine moiety **1** can lead either to antibacterial compounds **2** targeting the 16S bacterial rRNA[4] or binders of hepatitis C virus internal ribosome entry site (IRES) **3** with antiviral properties (Figure 1).[5]

As a structural mimetic of 2-deoxystreptamine (DOS), the central core of aminoglycosides, the *meso cis*-3,5-diaminopiperidine scaffold is indeed a very simple and cleverly designed building block, which enables the preparation of libraries by functionalization of the piperidine nitrogen atom. However, as recognized by the authors themselves,[5] the access to the protected building block **4**, obtained in 3 steps from 2-chloro-3,5-dinitropyridine in 38% yield, is hampered by a problematic high-pressure hydrogenation step. Furthermore, the selective functionalization of the piperidine nitrogen in the presence of the two NHBoc functional groups can also be expected to be problematic under certain experimental conditions. Herein, we describe a general approach for the preparation of diversely N-substituted *cis*-3,5-diaminopiperidines that can overcome these synthetic limitations.

In our ongoing work on the fragment-based design of small molecular RNA binders, we have shown that bicyclic hydrazine **5** is a powerful building block for the preparation of substituted *cis*-1,3-diaminocyclopentanes.[6] As a Diels–Alder adduct, this heterocycle is routinely prepared on a large scale (30–40g) and obtained in a quantitative yield by a simple precipitation.[7] The large availability of this starting material prompted us to investigate the access to *cis*-3,5-diaminopiperidines by an oxidative cleavage-reductive amination sequence[8] that would deliver a direct precursor of compounds **1** after hydrogenolysis (Scheme 1).

The preparation of triazabicyclo[3,2,1]octane **7a** (Scheme 1) was first investigated using a two-step approach. Dihydroxylation of compound **5** led to bicyclic hydrazine **6** in 86% yield. Oxidative cleavage followed by a double reductive amination with 4-methoxybenzylamine led to the expected product **7a** in 82% yield. An alternative strategy is to conduct an ozonolysis of compound **5**, followed by the reductive amination. Using this procedure, compound **7a** was obtained in 76% overall yield. Beside a better yield, this pathway avoids the use of osmium salts and aqueous conditions for the oxidative cleavage. In both cases, all attempts to isolate in good yield the bis-aldehyde intermediate failed. The scope of this double amination reaction is rather large, as exemplified in Scheme 1. Aliphatic (**7a–e**) or aromatic (**7f–j**) amines but also diamines (**7m**) provide moderate to good yields for this transformation. Interestingly, this method enables the introduction of a stereogenic center α to the piperidine nitrogen without racemization (compounds **7k,l**).[9]

As the double reductive amination cannot be conducted with amides, access to acylated triazabicyclo[3,2,1]octanes was investigated. Compound **7n**, prepared in 54% yield from **5** using pathway B, was deprotected to provide compound **8**. This bicyclic heterocycle can be functionalized by acylation, peptidic coupling, or carbamoylation (Scheme 2).

The reductive cleavage and deprotection of bicyclic compounds was conducted under hydrogen atmosphere using Pd or Pt. Experimental conditions had to be tuned in order to avoid catalyst poisoning by some final polyamines or the over-reduction of heteroaromatic rings. In most of the cases, the final diamines could be obtained in good to quantitative yields (Scheme 3).

Finally, our strategy can also provide a simple access to the building block **4** in 58% from compound **13a** (Scheme 4). This synthetic route allows the preparation of Hermann's intermediate **4** from cyclopentadiene in six steps and 44% overall yield with only two column purification steps. Although this route is longer than the three-step synthesis of Hermann, the overall yield is in the same range and this method avoids the high-pressure hydrogenation step.

In summary, we have established a simple and general access to N-substituted *cis*-3,5-diaminopiperidines in 3–5 steps starting from a readily available precursor. The functional

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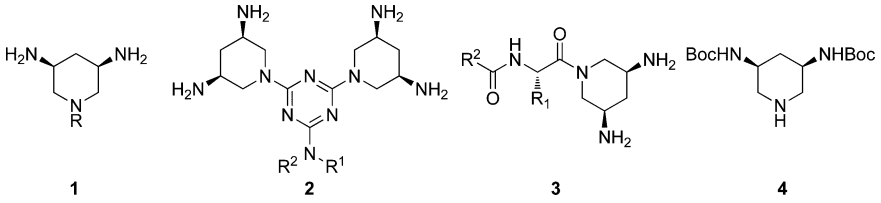
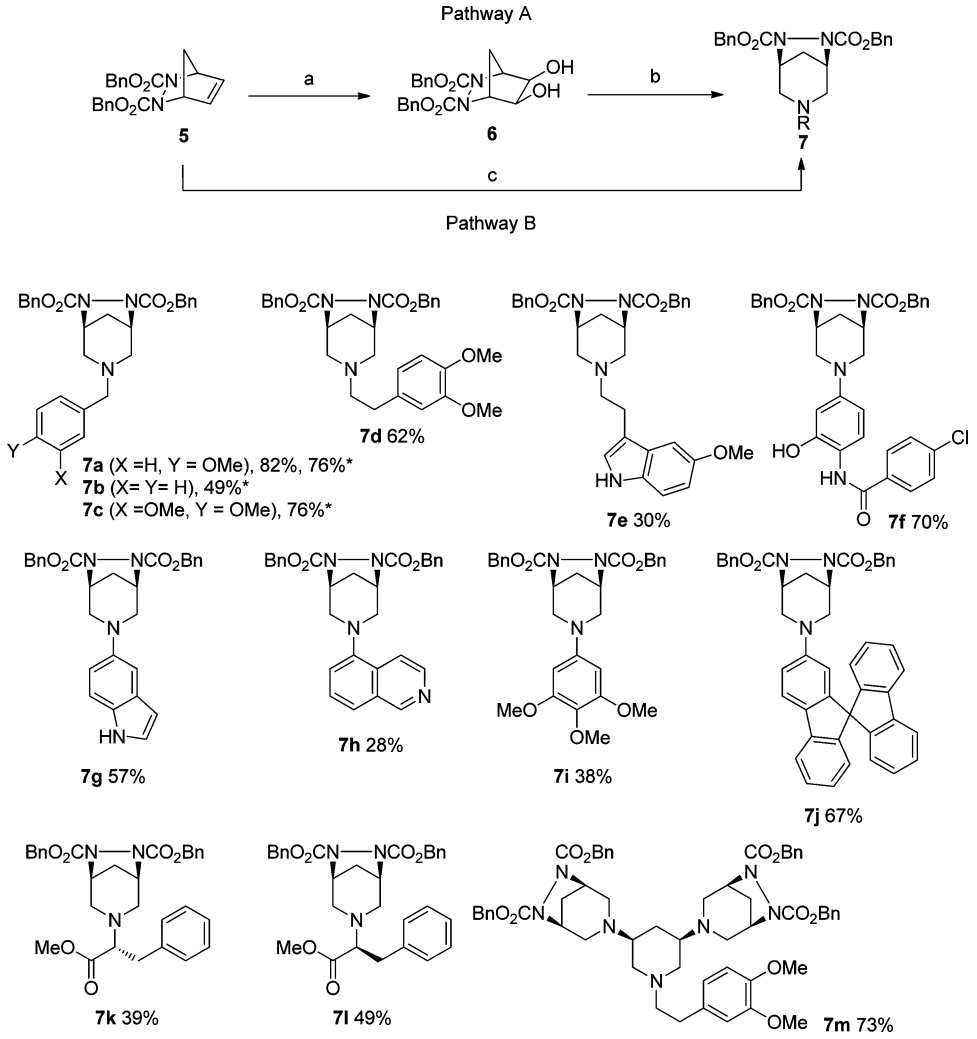


Figure 1. Selected examples of diaminopiperidines.

Scheme 1. Synthetic Pathways for the Preparation of Compounds 7[a]



[a]Reagents and conditions: (a) $K_2OsO_4{\cdot}2H_2O$ (0.8%), NMO (1.2 equiv), THF/H_2O 90:10, 18 h, 86%. (b) (i) $NaIO_4$ (2.3 equiv), MeOH/H_2O or $NaIO_4$ (1.4 equiv), SiO_2/H_2O/CH_2Cl_2; (ii) RNH_2, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, 3−22 h. (c) (i) O_3, Me_2S, CH_2Cl_2, −78 °C; (ii) RNH_2, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, 3−22 h. *Obtained with pathway B.

group tolerance of the key reductive amination step enables the introduction of a broad chemical diversity. We have also shown that Hermann's key intermediate can be obtained using this strategy, without any high pressure reduction step. The access to the polypiperidine skeleton such as **13i** through an iterative synthesis is also noteworthy.

EXPERIMENTAL SECTION

Representative Preparation of 7a (Pathway A, Using $NaIO_4$ on Silica). To a vigorously stirred suspension of silica (3.1 g) in CH_2Cl_2 (49 mL) was added a 0.65 M aqueous solution of $NaIO_4$ (3 mL, 1.95 mmol) dropwise. Diol **6**[6d,f] (574 mg, 1.44 mmol) in CH_2Cl_2 (47 mL) was then added, and the reaction was monitored by TLC until disappearance of the initial product. The reaction mixture was filtered on a sintered glass packed with Na_2SO_4, concentrated, and dissolved in CH_2Cl_2 (7 mL). 4-Methoxybenzylamine (217 mg, 1.58 mmol) was added, followed by $NaBH(OAc)_3$ (915 mg, 4.32 mmol) and acetic acid (0.15 mL). After stirring for 16 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (CH_2Cl_2/ethyl acetate 95:5) afforded **7a** (592 mg, 1.18 mmol, 82%).

Dibenzyl 3-(4-Methoxybenzyl)-3,6,7-triazabicyclo[3.2.1]-octane-6,7-dicarboxylate 7a. Colorless oil; ^1H NMR (300 MHz, $(CD_3)_2SO$, 72 °C) δ 1.85 (s, 2H), 2.15 (d, J = 10.9 Hz, 2H), 3.06 (br s, 2H), 3.41 (s, 2H), 3.72 (s, 3H), 4.35 (br s, 2H), 5.11 (AB system, $\Delta\delta$ = 0.07, J = 12.6 Hz, 4H), 6.81 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 8.2

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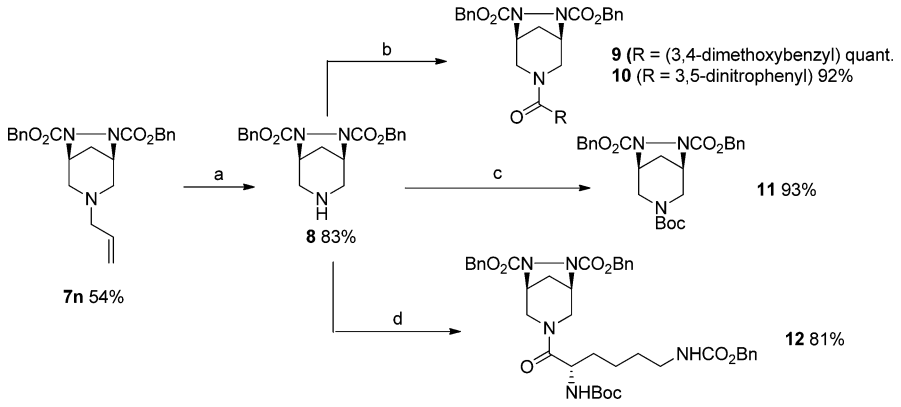
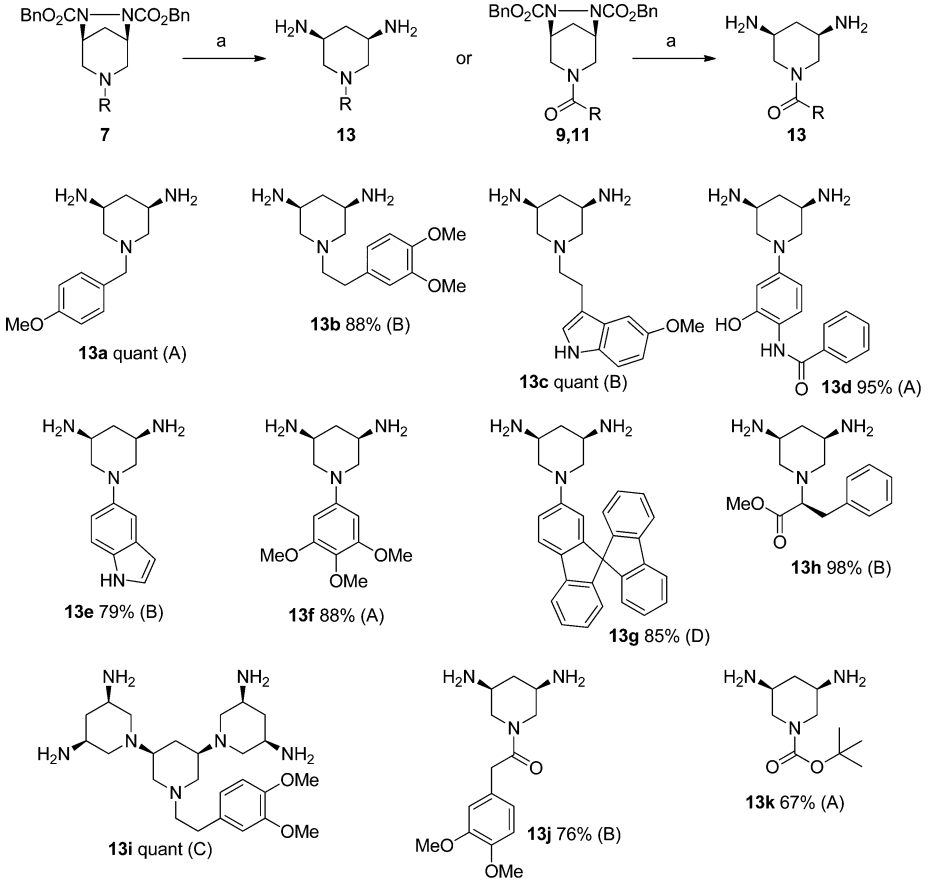
Scheme 2. Synthetic Pathways for the Preparation of Acylated Triazabicyclo[3,2,1]octanes[a]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$ (1%), 1,3-dimethylbarbituric acid (3 equiv), CH_2Cl_2, reflux, 5 h. (b) RCOCl (1.5 equiv), Et_3N (3 equiv), 1,2-dichloroethane, reflux. (c) Boc_2O (1.1 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 2 h. (d) Boc-Lys(Z)-OH (1.1 equiv), EDC (1.5 equiv), Et_3N (7 equiv), CH_2Cl_2, 5 h.

Scheme 3. Preparation of N-Substituted Diaminopiperidines[a]



[a]Reagents and conditions: (a) **Method A**, H_2, Pd/C 10%, MeOH. **Method B**, H_2, Pd/C 10%, Pd black, MeOH. **Method C**, H_2, Pd/C 10%, Pd black, MeOH/HCl. **Method D**, H_2, PtO_2, AcOH.

Hz, 2H), 7.32 (s, 10H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 75 °C) δ 36.1, 54.9, 55.6, 56.4, 60.2, 67.4, 114.1, 127.9, 128.2, 128.7, 130.1, 136.8, 157.0, 159.0; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{29}H_{32}N_3O_5$ 502.2342, found 502.2331.

Dibenzyl 3-(3,4-Dimethoxyphenethyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7d. Yield 84 mg, 62%, pale yellow oil; ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 72 °C) δ 1.86 (s, 2H), 2.24 (d, J = 10.4 Hz, 2H), 2.47–2.61 (m, 4H), 3.17 (br s, 2H), 3.72 (s, 3H), 3.75 (s, 3H), 4.38 (br s, 2H), 5.12 (s, 4H), 6.68 (d, J = 8.1 Hz, 1H), 6.76 (s, 1H), 6.82 (d, J = 8.1 Hz, 1H), 7.29–7.34 (m, 10H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 70 °C) δ 32.7, 36.2, 55.2, 56.3, 56.5, 58.4, 67.3, 113.4, 113.9, 121.0, 127.9, 128.2, 128.5, 133.6, 137.0, 148.0, 149.6, 157.2; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{31}H_{36}N_3O_6$ 546.2604, found 546.2588.

Dibenzyl 3-(4-(4-Chlorobenzamido)-3-hydroxyphenyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7f. Yield 80 mg, 70%, pale yellow oil; ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 70 °C) δ 2.00–2.16 (m, 2H), 2.96 (s, 2H), 3.91 (br s, 2H), 4.66 (s, 2H), 5.10–

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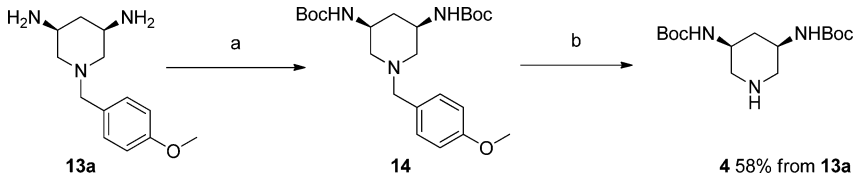
Scheme 4. Preparation Hermann's Building Block 4[a]



[a]Reagents and conditions: (a) Boc_2O (4.5 equiv), THF/$NaOH_{aq}$, 1 h. (b) CAN (2.6 equiv), $SiO_2/H_2O/CH_2Cl_2$, 1 h.

5.25 (m, 4H), 6.33 (d, J = 8.5 Hz, 1H), 6.43 (s, 1H), 7.20−7.50 (m, 11H), 7.60 (d, J = 8.6 Hz, 2H), 8.05 (d, J = 8.6 Hz, 2H), 9.28 (s, 1H), 9.48 (s, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 70 °C) δ 36.0, 52.1, 57.4, 69.0, 104.1, 106.8, 119.1, 127.0, 129.2, 129.5, 130.2, 130.3, 131.3, 135.4, 138.2, 138.2, 150.5, 152.4, 158.3, 166.3; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{34}H_{31}N_4O_6ClNa$ 649.1830, found 649.1827.

Dibenzyl 3-(Isoquinolin-5-yl)-3,6,7-triazabicyclo[3.2.1]-octane-6,7-dicarboxylate 7h. Yield 247 mg, 28%, pale yellow oil; ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 70 °C) δ 2.00−2.12 (m, 1H), 2.16 (d, J = 11.5 Hz, 1H), 3.04 (br d, J = 9.7 Hz, 2H), 3.51 (br d, J = 9.7 Hz, 2H), 4.60 (s, 2H), 4.97−5.29 (m, 4H), 7.05−7.47 (m, 11H), 7.56 (t, J = 7.8 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 8.04 (d, J = 5.5 Hz, 1H), 8.30 (br s, 1H), 9.24 (s, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 70 °C) δ 36.1, 55.6, 56.7, 67.6, 116.6, 121.7, 123.6, 127.8, 128.2, 128.6, 130.0, 131.8, 136.6, 142.9, 147.3, 153.0, 157.3; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{30}H_{28}N_4O_4Na$ 531.2008, found 531.2003.

Dibenzyl 3-(9,9′-Spirobi[fluoren]-2-yl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7j. Yield 192 mg, 67%, white amorphous solid; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 70 °C) δ 1.88−1.94 (m, 1H), 1.99 (d, J = 11.1 Hz, 1H), 2.80 (br s, 2H), 3.64 (br s, 2H), 4.48 (br s, 2H), 4.76−5.15 (m, 4H), 6.01 (s, 1H), 6.49 (d, J = 7.5 Hz, 1H), 6.61 (d, J = 7.5 Hz, 2H), 6.81 (d, J = 7.2 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 7.10 (t, J = 7.4 Hz, 2H), 7.26 (br s, 10H), 7.32 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.81 (t, J = 8.6 Hz, 2H), 7.96 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 70 °C) δ 35.7, 52.1, 57.2, 67.8, 68.9, 109.9, 115.4, 120.9, 122.1, 122.2, 122.8, 124.9, 125.0, 125.3, 125.4, 127.9, 129.2, 129.6, 129.8, 130.2, 133.8, 138.1, 143.1, 143.2, 143.8, 149.8, 150.8, 151.7, 152.2, 158.1; HRMS (ESI-Orbitrap) [M + H]$^+$ calcd for $C_{46}H_{38}N_3O_4$ 696.2857, found 696.2820.

Tetrabenzyl 3,3′-((3*S*,5*R*)-1-(3,4-Dimethoxyphenethyl)-piperidine-3,5-diyl)bis(3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate) 7m. Yield 136 mg, 73%, colorless oil; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 75 °C) δ 1.01 (q, J = 11.1 Hz, 1H), 1.63−1.72 (m, 3H), 1.85 (s, 4H), 2.30−2.53 (m, 8H), 2.55−2.62 (m, 2H), 2.75−2.81 (br d, J = 9.5 Hz, 2H), 2.84−3.15 (m, 4H), 3.73 (s, 6H), 4.34 (br s, 4H), 5.13 (AB system, $\Delta\delta$ = 0.06, J = 12.6 Hz, 8H), 6.68 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 7.33 (s, 20H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 75 °C) δ 31.2, 34.3, 37.7, 53.3, 57.2, 57.8, 57.9, 58.0, 60.4, 61.5, 68.7, 114.9, 115.5, 122.5, 129.3, 129.6, 130.2, 135.2, 138.4, 149.4, 151.0, 158.8; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{57}H_{66}N_7O_{10}$ 1008.4871, found 1008.4862.

Representative Preparation of 7e (Pathway A, Using $NaIO_4$ in MeOH/H_2O). To a solution of **6** (233 mg, 0.58 mmol) in MeOH/H_2O (70:30, 7.7 mL) was added $NaIO_4$ (288 mg, 1.35 mmol). The solution was stirred for 1 h at room temperature, diluted with CH_2Cl_2 (5 mL), and filtered through a Celite pad. The filtrate was concentrated and dissolved in CH_2Cl_2 (4 mL). 5-Methoxytryptamine (111 mg, 0.58 mmol) was added, and the reductive amination was conducted according to the preparation of **7a**. Flash chromatography (cyclohexane/ethyl acetate 65:35) afforded **7e** (96 mg, 0.17 mmol, 30%).

Dibenzyl 3-(2-(5-Methoxy-1*H*-indol-3-yl)ethyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7e. Colorless oil; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 75 °C) δ 1.88 (s, 2H), 2.28 (br s, 2H), 2.61−2.74 (m, 4H), 3.11 (br s, 2H), 3.76 (s, 3H), 4.40 (br s, 2H), 5.13 (s, 4H), 6.72 (d, J = 8.8 Hz, 1H), 6.94 (s, 1H), 7.06 (s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.25−7.40 (m, 10H), 10.4 (br s, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 75 °C) δ 22.8, 36.2, 55.1, 56.2, 56.6, 57.3, 67.3, 101.3, 111.4, 112.3, 112.8, 123.6, 127.9, 128.2, 128.7, 132.2, 137.0, 153.7, 157.1; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{32}H_{35}N_4O_5$ 555.2608, found 555.2594.

Dibenzyl 3-(1*H*-Indol-5-yl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7g. Yield 102 mg, 57%, colorless oil; ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 75 °C) δ 1.92−2.11 (m, 2H), 2.89 (d, J = 10.7 Hz, 2H), 3.80 (br s, 2H), 4.58 (s, 2H), 5.14 (s, 4H), 6.29 (s, 1H), 6.70 (d, J = 9.3 Hz, 1H), 6.92 (s, 1H), 7.17−7.38 (m, 12H), 10.53 (br s, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 75 °C) δ 35.3, 52.6, 56.4, 67.4, 101.2, 106.3, 112.0, 113.1, 125.7, 127.8, 128.1, 128.7, 128.8, 131.7, 136.8, 144.1, 157.1; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{29}H_{29}N_4O_4$ 497.2189, found 497.2185.

Dibenzyl 3-(3,4,5-Trimethoxyphenyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7i. Yield 135 mg, 38%, colorless oil; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 75 °C) δ 2.03−2.10 (m, 2H), 2.90 (br s, 2H), 3.61 (s, 3H), 3.72 (s, 6H), 3.83 (br s, 2H), 4.61 (s, 2H), 5.17 (s, 4H), 6.02 (s, 2H), 7.32 (br s, 10H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 70 °C) δ 34.6, 50.9, 55.9, 56.5, 60.6, 67.5, 93.5, 127.7, 128.2, 128.7, 131.7, 136.7, 146.9, 153.8, 157.0 ; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{30}H_{33}N_3O_7Na$ 570.2216, found 570.2218.

Dibenzyl 3-((*R*)-1-Methoxy-1-oxo-3-phenylpropan-2-yl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7k. Yield 106 mg, 39%, colorless oil; ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 70 °C) δ 1.86 (s, 2H) ; 2.45−2.63 (m, 2H), 2.67 (dd, J = 4.9 Hz, 1H), 2.94 (dd, J = 13.5 Hz, J = 10.0 Hz, 1H), 3.10−3.28 (m, 2H), 3.43 (dd, J = 10.0 Hz, J = 4.9 Hz, 1H), 3.51 (s, 3H), 4.40 (br s, 2H), 5.12 (s, 4H), 7.08−7.40 (m, 15H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 70 °C) δ 35.4, 35.9, 49.8, 51.2, 54.0, 56.3, 56.6, 67.3, 67.4, 67.7, 126.7, 127.9, 128.3, 128.7, 128.7, 129.2, 136.9, 138.4, 157.1, 171.4; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{31}H_{33}N_3O_6Na$ 566.2267, found 566.2267; $[\alpha]^{20}_D$ +21.1 (c 1.0, $CHCl_3$).

Dibenzyl 3-((*S*)-1-Methoxy-1-oxo-3-phenylpropan-2-yl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7l. Yield 147 mg, 49%, colorless oil. NMR and MS data are similar to enantiomer **7k**; $[\alpha]^{20}_D$ −19.5 (c 1.0, $CHCl_3$).

Representative Preparation of 7b (Pathway B). Ozone was bubbled into a solution of **5**[7] (753 mg, 2.07 mmol) in dry CH_2Cl_2 (10 mL) at −78 C until it became light blue, at which point argon was bubbled to remove excess ozone. The ozonide was quenched by Me_2S (1.5 mL), and the reaction mixture was warmed to room temperature, concentrated, and dissolved in CH_2Cl_2 (9 mL). Benzylamine (244 mg, 2.28 mmol) was added, and the reductive amination was conducted according to the preparation of **7a**. Flash chromatography (CH_2Cl_2/ethyl acetate 98:2 up to 95:5) afforded **7b** (481 mg, 1.02 mmol, 49%).

Dibenzyl 3-Benzyl-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7b. Colorless oil; ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 70 °C) δ 1.87 (s, 2H), 2.20 (br s, 2H), 3.06 (br s, 2H), 3.50 (s, 2H), 4.37 (br s, 2H), 5.05−5.18 (m, 4H), 7.20−7.35 (m, 15H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 70 °C) δ 36.2, 55.1, 56.4, 60.8, 67.4, 127.3, 127.9, 128.2, 128.5, 128.7, 128.9, 136.8, 138.5, 157.0; HRMS (ESI-Orbitrap) [M + H]$^+$ calcd for $C_{28}H_{30}N_3O_4$ 472.2236, found 472.2221.

Dibenzyl 3-(3,4-Dimethoxybenzyl)-3,6,7-triazabicyclo-[3.2.1]octane-6,7-dicarboxylate 7c. Yield 218 mg, 76%, colorless oil; ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 70 °C) δ 1.80−1.95 (m, 2H), 2.17 (d, J = 10.2 Hz), 3.05 (br s, 2H), 3.41 (br s, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 4.37 (br s, 2H), 4.99−5.18 (m, 4H), 6.75 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.89 (s, 1H), 7.32 (s, 10H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 70 °C) δ 37.7, 56.6, 57.7, 57.8, 57.9, 61.9, 68.8, 114.3, 115.3, 122.7, 129.4, 129.7, 130.2, 132.8, 138.3, 150.2, 151.1,

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158.4; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{30}H_{34}N_3O_6$ 532.2447, found 532.2419.

Dibenzyl 3-Allyl-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7n. Yield 955 mg, 54%, colorless oil; ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 70 °C) δ 1.80−1.89 (m, 2H), 2.17 (br s, 2H), 2.96 (br d, J = 6.1 Hz, 2H), 3.09 (br s, 2H), 4.38 (br s, 2H), 5.06 (d, J = 10.2 Hz, 1H), 5.10−5.19 (m, 5H), 5.62 (ddt, J = 6.1 Hz, J = 10.2 Hz, J = 16.3 Hz, 1H), 7.30−7.37 (m, 10H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 70 °C) δ 37.6, 56.6, 57.9, 60.6, 68.7, 118.8, 129.4, 129.7, 130.1, 136.9, 138.4, 158.6; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{24}H_{27}N_3O_4$ 422.2079, found 422.2073.

Dibenzyl 3,6,7-Triazabicyclo[3.2.1]octane-6,7-dicarboxylate 8. Compound **7n** (900 mg, 2.13 mmol), *N*,*N*-dimethylbarbituric acid (998 mg, 6.39 mmol), and $Pd(PPh_3)_4$ (25 mg, 21 μmol) were dissolved in CH_2Cl_2 (6.3 mL) under an argon atmosphere. The solution was refluxed for 5 h, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (CH_2Cl_2/MeOH 97:3) afforded **8** (673 mg, 1.76 mmol, 83%). Yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.91 (d, J = 11.3 Hz, 1H), 1.99−2.12 (m, 1H), 2.43 (br s, 1H), 2.70 (br d, J = 11.8 Hz, 2H), 3.06 (br s, 2H), 4.34 (br s, 2H), 5.22 (s, 4H), 7.34 (s, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.5, 50.4, 58.5, 69.5, 129.5, 129.7, 130.0, 137.3, 158.0; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{21}H_{24}N_3O_4$ 382.1767, found 382.1779.

Dibenzyl 3-(2-(3,4-Dimethoxyphenyl)acetyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 9. To a solution of **8** (41 mg, 0.11 mmol) in dry 1,2-dichloroethane (1.2 mL) were added triethylamine (44 μL, 0.32 mmol) and 3,4-dimethoxyphenylacetylchloride (28 μL, 0.16 mmol). The solution was stirred for 1.5 h at room temperature and then at 45 °C, quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (CH_2Cl_2/MeOH 98:2) afforded **9** (60 mg, quantitative). Colorless oil; ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 70 °C) δ 2.02−2.08 (m, 1H), 2.21 (d, J = 11.7 Hz, 1H), 2.98 (s, 2H), 3.30 (br s, 2H), 4.54 (s, 2H), 5.14 (AB system, $\Delta\delta$ = 0.10, J = 12.5 Hz, 4H), 7.32 (s, 10H), 8.51 (s, 2H), 8.83 (s, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 70 °C) δ 36.6, 57.2, 69.3, 121.0, 129.1, 129.3, 129.8, 130.2, 137.8, 140.8, 150.2, 157.9, 168.4; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{28}H_{26}N_5O_9$ 576.1731, found 576.1731.

Dibenzyl 3-(3,5-Dinitrobenzoyl)-3,6,7-triazabicyclo[3.2.1]-octane-6,7-dicarboxylate 10. To a solution of **8** (200 mg, 0.52 mmol) in dry 1,2-dichloroethane (5 mL) were added triethylamine (216 μL, 1.57 mmol) and 3,5-dinitrobenzoylchloride (183 mg, 0.79 mmol). The solution was stirred for 6 h at 80 °C, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (CH_2Cl_2/Ethyl acetate 90:10) afforded **10** (280 mg, 0.49 mmol, 92%). Pale yellow oil; ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 70 °C) δ 1.93−2.00 (m, 1H), 2.10 (d, J = 11.7 Hz, 1H) ; 2.87 (br s, 1H), 3.23 (br s, 1H), 3.46 (s, 1H), 3.52 (s, 1H), 3.73 (s, 6H), 4.12 (br s, 1H), 4.45 (br s, 2H), 4.51 (s, 2H), 5.10 (AB system, $\Delta\delta$ = 0.04, J = 12.3 Hz, 4H), 6.67 (d, J = 8.2 Hz, 1H), 6.77 (s, 1H), 6.84 (d, J = 8.2 Hz, 1H), 7.34 (s, 10H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 70 °C) δ 36.0, 41.1, 56.8, 57.7, 57.8, 69.1, 114.6, 115.8, 123.1, 129.4, 129.8, 129.9, 130.2, 138.0, 149.8, 150., 157.9, 172.8; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{31}H_{34}N_3O_7$ 560.2397, found 560.2403.

6,7-Dibenzyl 3-*tert*-Butyl 3,6,7-Triazabicyclo[3.2.1]octane-3,6,7-tricarboxylate 11. To a solution of **8** (81 mg, 0.21 mmol) in CH_2Cl_2 (0.6 mL) were added Et_3N (32 μL, 233 μmol) and Boc_2O (51 mg, 0.23 mmol), and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (CH_2Cl_2/MeOH 99:1) afforded **11** (95 mg, 0.2 mmol, 93%). Colorless oil; ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 70 °C) δ 1.38 (s, 9H), 1.95 (s, 1H), 2.03 (d, J = 11.5 Hz, 1H), 2.98 (br s, 2H), 4.10 (br s, 2H), 4.45 (s, 2H), 5.09−5.17 (m, 4H), 7.34 (s, 10H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 70 °C) δ 29.9, 35.9, 48.5, 56.7, 69.1, 81.0, 129.3, 129.7, 130.2, 138.0, 156.4; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{26}H_{32}N_3O_6$ 482.2291, found 482.2300.

Dibenzyl 3-(6-(((Benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)hexanoyl)-3,6,7-triazabicyclo[3.2.1]-octane-6,7-dicarboxylate 12. To a solution of **8** (68 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (1.75 mL) were added Boc-Lys(Z)-OH (75 mg, 0.20 mmol), Et_3N (173 mL, 1.25 μmol), and EDC (51 mg, 0.27 mmol). The solution was stirred for 5 h, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (CH_2Cl_2/MeOH 97:3) afforded **12** (107 mg, 0.14 mmol, 81%). Colorless oil; ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 70 °C) δ 1.17−1.62 (m, 15H), 1.92−2.01 (m, 1H), 2.12 (d, J = 11.7 Hz, 1H), 2.87 (br s, 1H), 2.93−3.02 (m, 2H), 3.33 (br s, 1H), 4.03 (br s, 1H), 4.23 (br s, 1H), 4.34 (br s, 1H), 4.49 (s, 1H), 4.54 (s, 1H), 5.03 (s, 2H), 5.12 (br s, 4H), 6.05−6.50 (m, 1H), 6.86 (br s, 1H), 7.07−7.55 (m, 15H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 70 °C) δ 23.1, 28.7, 29.6, 31.7, 34.6, 41.0, 51.1, 55.4, 65.7, 67.8, 78.6, 127.8, 128.0, 128.1, 128.3, 128.7, 128.8, 136.6, 137.9, 155.6, 156.5, 173.2; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{40}H_{50}N_5O_9$ 744.3608, found 744.3596; $[\alpha]^{20}_D$ −7.6 (*c* 1.0, $CHCl_3$).

General Procedures for Hydrogenolysis. A solution of bicyclic hydrazine in solvent (**Methods A** and **B**: MeOH; **Method C**: MeOH/HCl pH 3; **Method D**: distilled acetic acid) was stirred in the presence of catalyst (**A**: 10% palladium on activated charcoal (0.2 equiv); **B** and **C**: 10% palladium on activated charcoal (0.2 equiv) and palladium black (0.01 equiv); **D**: PtO_2 (0.15 equiv)) under hydrogen atmosphere (1 atm). If needed, 0.1 equiv of catalyst can be added after 24 h to reach completion. The reaction mixture was filtered through a Celite pad and concentrated to afford the final diamine.

(3*S*,5*R*)-1-(4-Methoxybenzyl)piperidine-3,5-diamine 13a (Method A). Yield 40 mg, quantitative, colorless oil; ^{1}H NMR (250 MHz, CD_3OD) δ 0.84 (q, J = 11.6 Hz, 1H), 1.62 (t, J = 10.4 Hz, 2H), 2.09 (d, J = 11.6 Hz, 1H), 2.75−2.87 (m, 2H), 2.94 (dd, J = 10.4 Hz, J = 4.4 Hz, 2H), 3.50 (s, 2H), 3.77 (s, 3H), 6.86 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 43.3, 48.1, 55.8, 61.5, 63.0, 114.8, 130.4, 131.9, 160.6; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{13}H_{22}N_3O$ 236.1762, found 236.1756.

(3*S*,5*R*)-1-(3,4-Dimethoxyphenethyl)piperidine-3,5-diamine 13b (Method B). Yield 62 mg, 88%, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (q, J = 11.7 Hz, 1H), 1.25 (br s, 4H), 1.71 (t, J = 10.1 Hz, 2H), 2.17 (d, J = 11.7 Hz, 1H), 2.60−2.71 (m, 2H), 2.75−2.85 (m, 2H), 2.92−3.03 (m, 2H), 3.06 (d, J = 10.1 Hz, 2H), 3.90 (s, 3H), 3.91 (s, 3H), 6.77−6.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 44.9, 47.6, 55.8, 55.9, 60.3, 62.3, 111.1, 111.9, 120.5, 132.8, 147.2, 148.7; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{15}H_{26}N_3O_2$ 280.2025, found 280.2029.

(3*S*,5*R*)-1-(2-(5-Methoxy-1*H*-indol-3-yl)ethyl)piperidine-3,5-diamine 13c (Method B). Yield 29 mg, quantitative, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (q, J = 11.4 Hz, 1H), 1.30 (br s, 4H), 1.75 (t, J = 10.3 Hz, 2H), 2.19 (d, J = 11.4 Hz, 1H), 2.74−2.81 (m, 2H), 2.95−3.07 (m, 4H), 3.13 (dd, J = 10.3 Hz, J = 3.2 Hz, 2H), 3.90 (s, 3H), 6.90 (d, J = 8.8 Hz, 1H), 7.04 (s, 1H), 7.08 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 45.0, 47.7, 56.0, 58.9, 62.4, 100.6, 111.9, 112.1, 113.9, 122.4, 127.8, 131.4, 153.9; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{16}H_{25}N_4O$ 289.2028, found 289.2021.

***N*-(4-((3*S*,5*R*)-3,5-Diaminopiperidin-1-yl)-2-hydroxyphenyl)-benzamide 13d (Method A).** Yield 21 mg, 95%, orange oil; ^{1}H NMR (300 MHz, CD_3OD) δ 1.45 (q, J = 11.0 Hz, 1H), 2.26 (d, J = 11.0 Hz, 1H), 2.74 (dd, J = 11.9 Hz, J = 9.2 Hz, 2H), 3.22 (m, 2H), 3.66 (dd, J = 11.9 Hz, J = 2.9 Hz, 2H), 6.57 (dd, J = 8.8 Hz, J = 2.3 Hz, 1H), 6.62 (d, J = 2.3 Hz, 1H), 7.52−7.60 (m, 4H), 7.97 (d, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 36.4, 46.3, 54.6, 105.1, 108.4, 118.8, 124.3, 127.2, 128.4, 131.6, 134.2, 149.5, 150.2, 167.3; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{18}H_{23}N_4O_2$ 327.1821, found 327.1821.

(3*S*,5*R*)-1-(1*H*-Indol-5-yl)piperidine-3,5-diamine 13e (Method B). Yield 22 mg, 79%, colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ

0.96 (q, J = 11.6 Hz, 1H), 1.39 (br s, 4H), 2.24 (d, J = 11.6 Hz, 1H), 2.33 (dd, J = 11.1 Hz, J = 10.3 Hz, 2H), 3.12 (m, 2H), 3.60 (dd, J = 11.1 Hz, J = 4.4 Hz, 2H), 6.48 (br s, 1H), 6.97 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.17 (t, J = 2.7 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 8.34 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.7, 47.8, 61.3, 102.3, 108.5, 111.5, 116.4, 124.7, 128.3, 131.4, 145.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{13}H_{19}N_4$ 231.1610, found 231.1606.

(3*S*,5*R*)-1-(3,4,5-Trimethoxyphenyl)piperidine-3,5-diamine 13f (Method A). Yield 45 mg, 88%, colorless oil; ^{1}H NMR (300 MHz, CD_3OD) δ 1.06 (q, J = 11.4 Hz, 1H), 2.20 (br d, J = 11.4 Hz, 1H), 2.35 (dd, J = 11.6 Hz, J = 10.4 Hz, 2H), 2.95 (m, 2H), 3.65 (dd, J = 11.6 Hz, J = 4.3 Hz, 2H), 3.71 (s, 3H), 3.84 (s, 6H), 6.27 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 41.9, 46.8, 55.1, 57.5, 59.9, 95.0, 131.5, 148.2, 153.4; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{14}H_{24}N_3O_3$ 282.1818, found 282.1815.

(3*S*,5*R*)-1-(9,9′-Spirobi[fluoren]-2-yl)piperidine-3,5-diamine 13g (Method D). Yield 78 mg, 85%, yellow amorphous solid; ^{1}H NMR (300 MHz, CD_3OD) δ 1.58 (q, J = 11.0 Hz, 1H), 2.44 (d, J = 10.0 Hz, 1H), 2.62 (t, J = 11.0 Hz, 2H), 3.28−3.34 (m, 2H), 3.69 (d, J = 10.0 Hz, 2H), 6.31 (s, 1H), 6.54 (d, J = 7.6 Hz, 1H), 6.62 (d, J = 7.6 Hz, 2H), 7.02 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.6 Hz, 3H), 7.28−7.40 (m, 3H), 7.83 (t, J = 8.5 Hz, 2H), 7.90 (d, J = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 22.4, 34.0, 46.1, 53.4, 65.9, 112.6, 117.1, 119.1, 119.8, 120.6, 123.3, 123.6, 126.5, 127.6, 135.1, 141.1, 141.6, 148.3, 148.9, 150.2, 150.6; HRMS (APCI-Orbitrap) $[M + H]^+$ calcd for $C_{30}H_{28}N_3$ 430.2283, found 430.2276.

(*S*)-Methyl 2-((3*S*,5*R*)-3,5-Diaminopiperidin-1-yl)-3-phenylpropanoate 13h (Method B). Yield 39 mg, 98%, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (q, J = 11.4 Hz, 1H), 1.47 (br s, 4H), 1.89 (t, J = 10.3 Hz, 1H), 2.05 (t, J = 10.3 Hz, 1H), 2.12 (d, J = 11.4 Hz, 1H), 2.80−2.99 (m, 4H), 3.04−3.15 (m, 2H), 3.50 (dd, J = 7.9 Hz, J = 7.0 Hz, 1H), 3.64 (s, 3H), 7.15−7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.6, 44.8, 47.7, 47.9, 51.1, 56.3, 61.2, 69.1, 126.4, 128.3, 129.1, 138.1, 171.7; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{15}H_{24}N_3O_2$ 278.1869, found 278.1864; $[\alpha]^{20}_D$ −19.0 (*c* 1.0, CH_3OH).

(3*S*,3′*R*,3″*S*,5*R*,5′*S*,5″*R*)-1′-(3,4-Dimethoxyphenethyl)-[1,3′:5′,1″-terpiperidine]-3,3″,5,5″-tetraamine 13i (Method C). Yield 44 mg, quantitative, colorless oil; ^{1}H NMR (500 MHz, CD_3OD) δ 1.55−1.70 (m, 3H), 2.12 (d, J = 10.9 Hz, 1H), 2.45−2.56 (m, 6H), 2.60−2.69 (m, 2H), 2.95−3.11 (m, 6H), 3.15−3.26 (m, 4H), 3.30−3.37 (m, 6H), 3.82 (s, 3H), 3.86 (s, 3H), 6.84 (d, J = 8.5 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.94 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 28.7, 32.3, 34.5, 48.0, 48.1, 52.8, 53.5, 55.2, 56.7, 60.0, 60.8, 113.5, 114.0, 122.2, 132.4, 149.4, 150.6; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{25}H_{45}N_7O_2Na$ 498.3532, found 498.3526.

1-((3*S*,5*R*)-3,5-Diaminopiperidin-1-yl)-2-(3,4-dimethoxyphenyl)ethanone 13j (Method B). Yield 16 mg, 76%, colorless oil; ^{1}H NMR (500 MHz, CD_3OD) δ 1.43 (q, J = 11.8 Hz, 1H), 2.21 (d, J = 11.8 Hz, 1H), 2.80−2.87 (m, 2H), 2.95−3.10 (m, 2H), 3.76 (d, J = 4.9 Hz, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 3.99 (d, J = 13.5 Hz, 1H), 4.41 (d, J = 13.5 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.84 (s, 1H), 6.86 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 38.2, 41.0, 47.0, 47.5, 48.0, 52.4, 56.7, 113.4, 114.0, 122.5, 128.9, 149.8, 150.9, 173.2; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{15}H_{24}N_3O_3$ 294.1817, found 294.1815.

(3*S*,5*R*)-*tert*-Butyl 3,5-diaminopiperidine-1-carboxylate 13k (Method A,. Flash chromatography (CH_2Cl_2/MeOH 97:3 then CH_2Cl_2/(MeOH/NH_4OH 30% aq 90:10) 90:10): 17 mg, 67%, colorless oil; ^{1}H NMR (500 MHz, CD_3OD) δ 0.93 (q, J = 11.5 Hz, 1H), 1.36 (s, 9H), 2.03−2.06 (m, 1H), 2.23 (br s, 2H), 2.55−2.62 (m, 2H), 4.00 (dd, J = 11.5 Hz, J = 4.5 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 27.3, 42.6, 46.8, 50.0, 50.6, 79.9, 154.9; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{10}H_{22}N_3O_2$ 216.1712, found 216.1713.

Di-*tert*-butyl ((3*S*,5*R*)-1-(4-Methoxybenzyl)piperidine-3,5-diyl)dicarbamate 14. Compound **13a** (58 mg, 0.25 mmol) was dissolved in THF/H_2O (50:50, 5.2 mL). Boc_2O (242 mg, 1.11 mmol) was added. The solution was stirred for 1 h at room temperature and extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford **14** (115 mg, quantitative). White amorphous solid; ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 70 °C) δ 1.12 (q, J = 11.8 Hz, 1H), 1.37 (s, 18H), 1.69 (br s, 2H), 1.91 (d, J = 11.8 Hz, 1H), 2.81 (d, J = 9.7 Hz, 2H, H′$_2$ and H′$_6$), 3.37−3.48 (m, 4H), 3.76 (s, 3H), 6.44 (broad s, 2H), 6.88 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H);^{13}C NMR (125 MHz, $(CD_3)_2SO$, 70 °C) δ 30.2, 39.0, 48.6, 57.0, 59.3, 62.8, 79.6, 115.6, 131.6, 131.8, 156.8, 160.4; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{23}H_{38}N_3O_5$ 436.2812, found 436.2809.

Di-*tert*-butyl (3*S*,5*R*)-Piperidine-3,5-diyldicarbamate 4. A solution of CAN (351 mg, 0.64 mmol) in water (0.32 mL) was added dropwise to a flask charged with silica (753 mg). CH_2Cl_2 (3.1 mL) was added, and **14** (0.25 mmol) dissolved in CH_2Cl_2 (1.5 mL) was added to the stirred reaction mixture. The suspension was stirred for 1 h at room temperature and filtered. Flash chromatography (CH_2Cl_2/(MeOH/NH_4OH 30% aq 90:10) 95:5) of the residual afforded **4** (45 mg, 0.14 mmol, 58%). White amorphous solid; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 1.12 (q, J = 11.9 Hz, 1H), 1.38 (s, 18H), 1.90 (d, J = 11.9 Hz, 1H), 2.02 (t, J = 10.8 Hz, 2H), 2.82 (d, J = 10.8 Hz, 2H), 3.15−3.20 (m, 2H), 6.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 30.1, 39.8, 49.6, 52.3, 79.4, 156.8; HRMS (ESI-Orbitrap) $[M + H]^+$ calcd for $C_{15}H_{30}N_3O_4$ 316.2236, found 316.2239.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H, ^{13}C NMR spectra. Copies of chiral HPLC of compounds **7k,l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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