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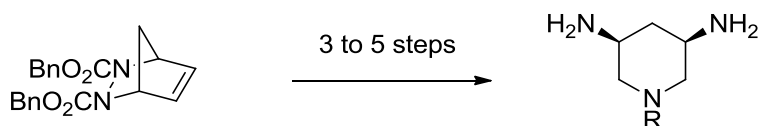
Modular access to N-substituted *cis*-3,5-diaminopiperidines

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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 field¹ 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 ribosomal RNA⁴ or binders of Hepatitis C Virus internal ribosome entry site (IRES) **3** with anti-viral properties (Figure 1).⁵

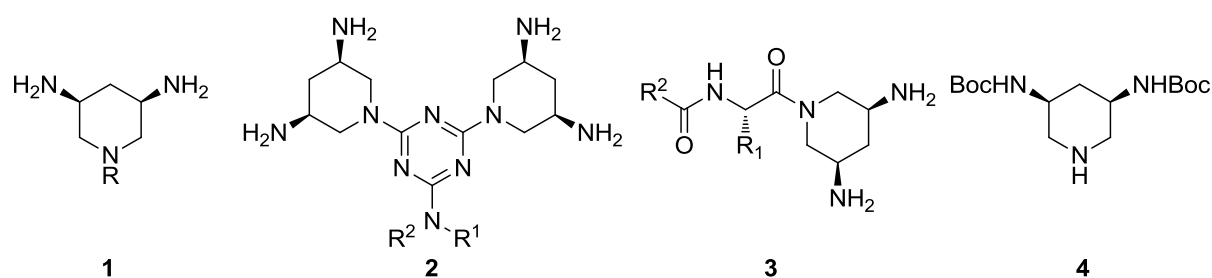
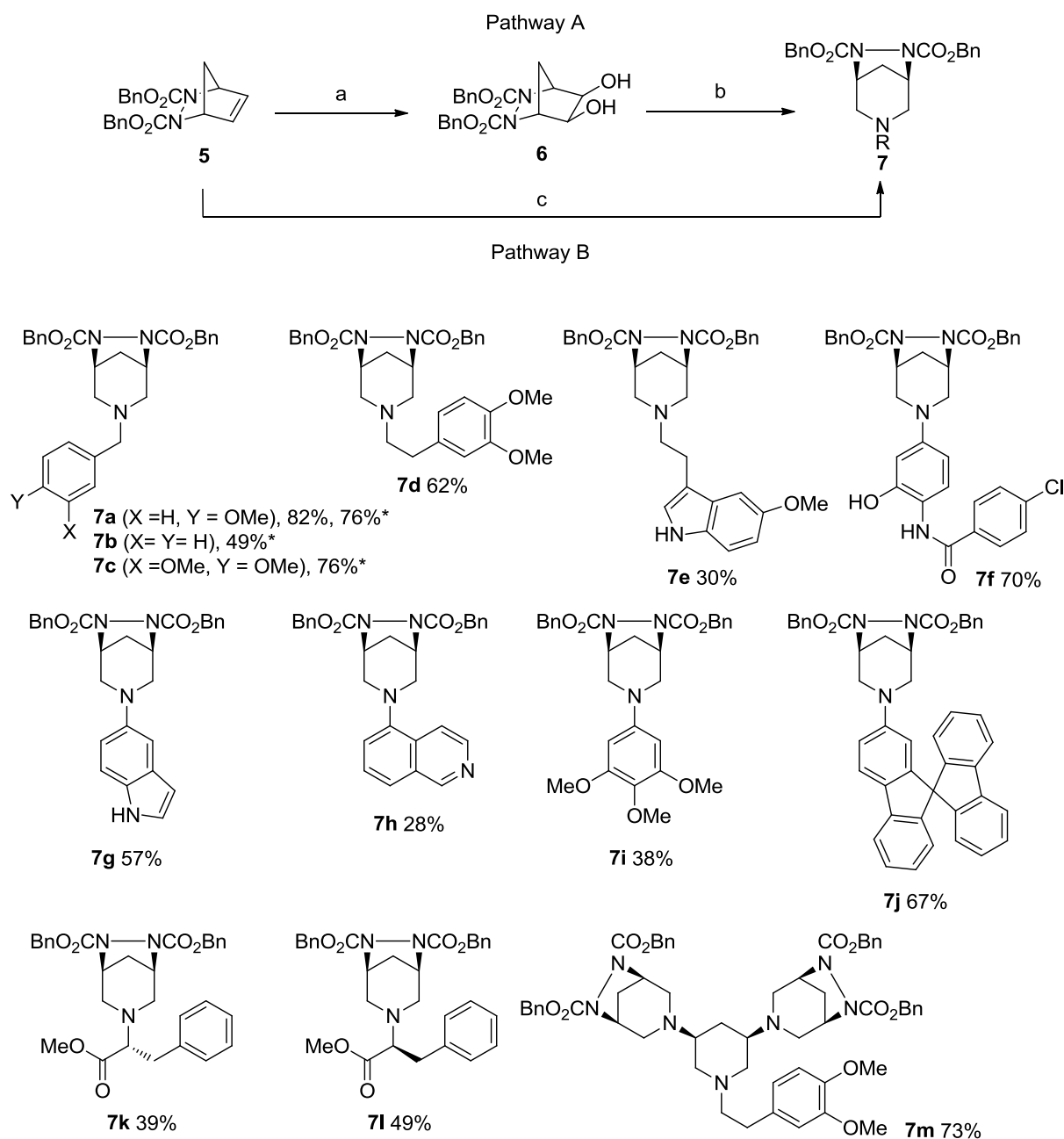


FIGURE 1. Selected examples of diaminopiperidines

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 sequence⁸ that would deliver a direct precursor of compounds **1** after hydrogenolysis (Scheme 1).

SCHEME 1. Synthetic pathways for the preparation of compounds 7^a



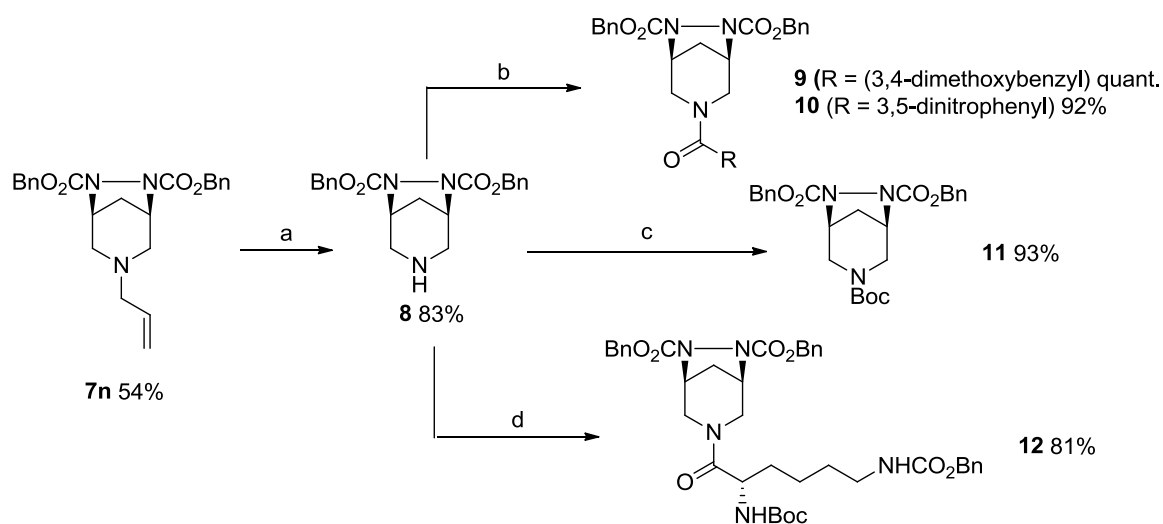
^a Reagents and conditions: (a) $K_2OsO_4 \cdot 2H_2O$ (0.8%), NMO (1.2 equiv), THF/H₂O 90:10, 18 h, 86%. (b) (i) $NaIO_4$ (2.3 equiv), MeOH/H₂O or $NaIO_4$ (1.4 equiv), SiO₂/H₂O/CH₂Cl₂, (ii) RNH₂, $NaBH(OAc)_3$, AcOH, CH₂Cl₂, 3-22 h. (c) (i) O₃, Me₂S, CH₂Cl₂, -78 °C. (ii) RNH₂, $NaBH(OAc)_3$, AcOH, CH₂Cl₂, 3-22 h. * Obtained with pathway B.

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).

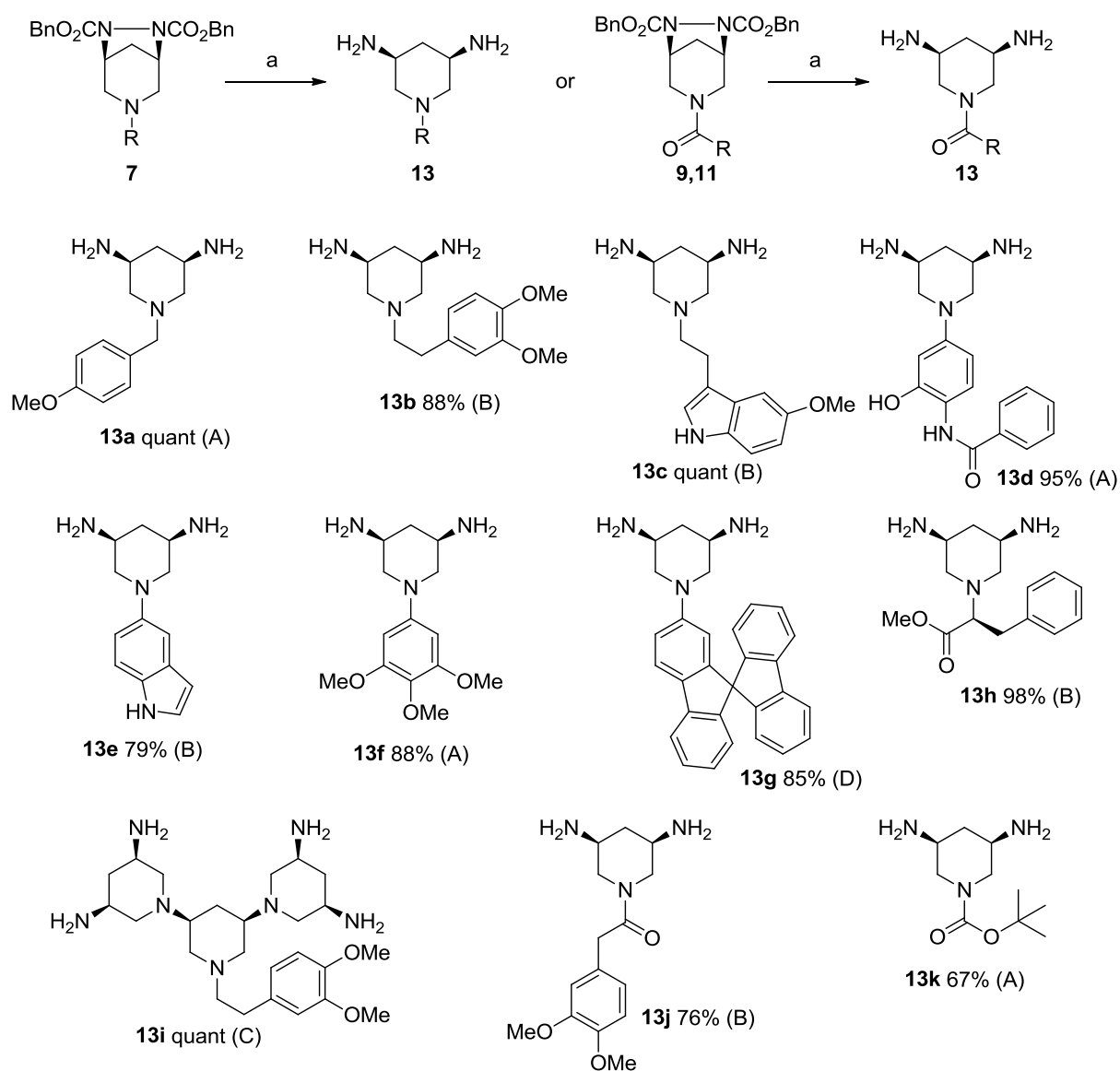
SCHEME 2. Synthetic pathways for the preparation of acylated triazabicyclo[3,2,1]octanes^a



^a Reagents and conditions: (a) Pd(PPh₃)₄ (1%), 1,3-dimethylbarbituric acid (3 equiv), CH₂Cl₂, reflux, 5 h. (b) RCOCl (1.5 equiv), Et₃N (3 equiv), 1,2-dichloroethane, reflux. (c) Boc₂O (1.1 equiv), Et₃N (1.1 equiv), CH₂Cl₂, 2 h. (d) Boc-Lys(Z)-OH (1.1 equiv), EDC (1.5 equiv), Et₃N (7 equiv), CH₂Cl₂, 5 h.

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).

SCHEME 3. Preparation of N-substituted diaminopiperidines^a

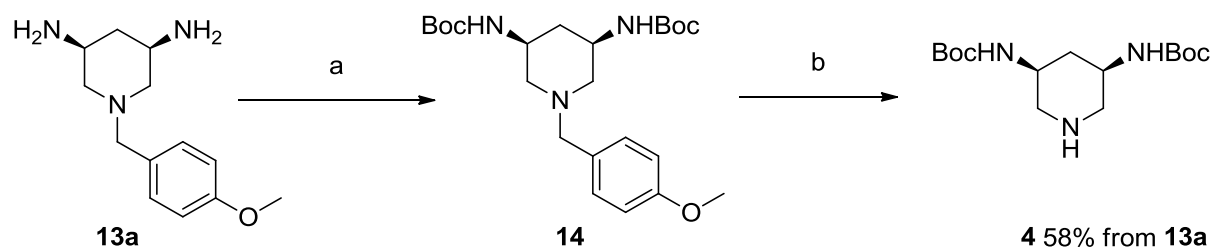


^a Reagents and conditions: (a) Method **A** H₂, Pd/C 10%, MeOH. Method **B** H₂, Pd/C 10%, Pd black, MeOH. Method **C** H₂, Pd/C 10%, Pd black, MeOH.HCl. Method **D** H₂, PtO₂, AcOH.

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 it avoids the high-pressure hydrogenation step.

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), $\text{SiO}_2/\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$, 1 h.

In summary, we have established a simple and general access to N-substituted *cis*-3,5-diaminopiperidines in 3 to 5 steps starting from a readily available precursor. The functional 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 polypiperidine skeleton such as **13i** through an iterative synthesis is also noteworthy.

Experimental section

The preparation of 7a is representative (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 molar 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

Na₂SO₄, concentrated and dissolved in CH₂Cl₂ (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 hours at room temperature, the reaction was quenched with saturated aqueous NaHCO₃, extracted with CH₂Cl₂, the combined organic layers were dried over MgSO₄, filtered, and concentrated. Flash chromatography (CH₂Cl₂/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, (CD₃)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, Δδ = 0.07, *J* = 12.6 Hz, 4H), 6.81 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.32 (s, 10H); ¹³C NMR (75 MHz, (CD₃)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 C₂₉H₃₂N₃O₅ 502.2342, found 502.2331

Dibenzyl 3-(3,4-dimethoxyphenethyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7d: 84 mg, 62%, pale yellow oil; ¹H NMR (300 MHz, (CD₃)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); ¹³C NMR (75 MHz, (CD₃)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 C₃₁H₃₆N₃O₆ 546.2604, found 546.2588

Dibenzyl 3-(4-(4-chlorobenzamido)-3-hydroxyphenyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7f: 80 mg, 70%, pale yellow oil; ¹H NMR (500 MHz, (CD₃)₂SO, 70 °C, δ) 2.00-2.16 (m, 2H), 2.96 (s, 2H), 3.91 (br s, 2H), 4.66 (s, 2H), 5.10-5.25 (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); ¹³C NMR (125 MHz, (CD₃)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 C₃₄H₃₁N₄O₆ClNa 649.1830, found 649.1827

Dibenzyl 3-(isoquinolin-5-yl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7h: 247 mg, 28%, pale yellow oil; ¹H NMR (300 MHz, (CD₃)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); ¹³C NMR (75 MHz, (CD₃)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 C₃₀H₂₈N₄O₄Na 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: 192 mg, 67%, white amorphous solid; ¹H NMR (400 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 C₄₆H₃₈N₃O₄ 696.2857, found 696.2820

Tetrabenzyl 3,3'-((3S,5R)-1-(3,4-dimethoxyphenethyl)piperidine-3,5-diyl)bis(3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate) 7m: 136 mg, 73%, colorless oil; ¹H NMR (400 MHz, (CD₃)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, $(\text{CD}_3)_2\text{SO}$, 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 $\text{C}_{57}\text{H}_{66}\text{N}_7\text{O}_{10}$ 1008.4871, found 1008.4862

The preparation of 7e is representative (Pathway A, using NaIO₄ in MeOH/H₂O)

To a solution of **6** (233 mg, 0.58 mmol) in MeOH/H₂O (70:30, 7.7 mL) was added NaIO₄ (288 mg, 1.35 mmol). The solution was stirred for one hour at room temperature, diluted with CH₂Cl₂ (5 mL) and filtered through a celite pad. The filtrate was concentrated and dissolved in CH₂Cl₂ (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-1H-indol-3-yl)ethyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7e: colorless oil; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$, 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, $(\text{CD}_3)_2\text{SO}$, 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 $\text{C}_{32}\text{H}_{35}\text{N}_4\text{O}_5$ 555.2608, found 555.2594

Dibenzyl 3-(1H-indol-5-yl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7g: 102 mg, 57%, colorless oil; ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$, 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, $(\text{CD}_3)_2\text{SO}$, 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 C₂₉H₂₉N₄O₄ 497.2189, found 497.2185

Dibenzyl 3-(3,4,5-trimethoxyphenyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate

7i: 135 mg, 38%, colorless oil; ¹H NMR (400 MHz, (CD₃)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); ¹³C NMR (75 MHz, (CD₃)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 C₃₀H₃₃N₃O₇Na 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: 106 mg, 39%, colorless oil; ¹H NMR (300 MHz, (CD₃)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); ¹³C NMR (75 MHz, (CD₃)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 C₃₁H₃₃N₃O₆Na 566.2267, found 566.2267; [α]_D²⁰ +21.1 (*c* 1.0, CHCl₃)

Dibenzyl 3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)-3,6,7-triazabicyclo[3.2.1]octane-

6,7-dicarboxylate 7l: 147 mg, 49%, colorless oil. NMR and MS data are similar to enantiomer **7k**

[α]_D²⁰ -19.5 (*c* 1.0, CHCl₃)

The preparation of 7b is representative (Pathway B)

Ozone was bubbled into a solution of **5**⁷ (753 mg, 2.07 mmol) in dry CH₂Cl₂ (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 Me₂S (1.5 mL), and the reaction was warmed to room temperature, concentrated and dissolved in CH₂Cl₂ (9 mL). Benzylamine (244 mg, 2.28

mmol) was added and the reductive amination was conducted according to the preparation of **7a**. Flash chromatography (CH₂Cl₂/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;

¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 C₂₈H₃₀N₃O₄ 472.2236, found 472.2221

Dibenzyl 3-(3,4-dimethoxybenzyl)-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7c:

218 mg, 76%, colorless oil; ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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, 158.4; HRMS (ESI-Orbitrap)[M+H]⁺ calcd for C₃₀H₃₄N₃O₆ 532.2447, found 532.2419

Dibenzyl 3-allyl-3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 7n: 955 mg, 54%,

colorless oil; ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 C₂₄H₂₇N₃O₄ 422.2079, found 422.2073

Dibenzyl 3,6,7-triazabicyclo[3.2.1]octane-6,7-dicarboxylate 8:

7n (900 mg, 2.13 mmol), N,N-dimethylbarbituric acid (998 mg, 6.39 mmol) and Pd(PPh₃)₄ (25 mg, 21 μmol) were dissolved in CH₂Cl₂ (6.3 mL) under argon atmosphere. The solution was refluxed for 5 hours, quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated. Flash chromatography (CH₂Cl₂/MeOH 97:3) afforded **8** (673 mg, 1.76 mmol, 83 %).

yellow oil; ¹H NMR (250 MHz, CDCl₃, 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); ¹³C NMR (125 MHz, CDCl₃, 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 C₂₁H₂₄N₃O₄ 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) was added triethylamine (44 μL, 0.32 mmol) and 3,4-dimethoxyphenylacetylchloride (28 μL, 0.16 mmol). The solution was stirred for 1.5 hour at room temperature and then at 45 °C, quenched with saturated aqueous NH₄Cl, extracted with CH₂Cl₂ and the combined organic layers were dried over MgSO₄, filtered and concentrated. Flash chromatography (CH₂Cl₂/MeOH 98:2) afforded **9** (60 mg, quantitative).

colorless oil; ¹H NMR (500 MHz, (CD₃)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, Δδ = 0.10, *J* = 12.5 Hz, 4H), 7.32 (s, 10H), 8.51 (s, 2H), 8.83 (s, 1H); ¹³C NMR (125 MHz, (CD₃)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 C₂₈H₂₆N₅O₉ 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) was added triethylamine (216 μL, 1.57 mmol) and 3,5-dinitrobenzoylchloride (183 mg, 0.79 mmol). The

solution was stirred for six hours at 80°C, quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated. Flash chromatography (CH₂Cl₂/Ethyl acetate 90:10) afforded **10** (280 mg, 0.49 mmol, 92 %).

pale yellow oil; ¹H NMR (500 MHz, (CD₃)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, Δδ = 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); ¹³C NMR (125 MHz, (CD₃)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 C₃₁H₃₄N₃O₇ 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 CH₂Cl₂ (0.6 mL) was added Et₃N (32 μL, 233 μmol) and Boc₂O (51 mg, 0.23 mmol), and the mixture was stirred for 2 hours. The reaction was quenched with saturated aqueous NaHCO₃, extracted with CH₂Cl₂ and the combined organic layers were dried over MgSO₄, filtered and concentrated. Flash chromatography (CH₂Cl₂/MeOH 99:1) afforded **11** (95 mg, 0.2 mmol, 93%).

colorless oil; ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 C₂₆H₃₂N₃O₆ 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 CH₂Cl₂ (1.75 mL) was added Boc-Lys(Z)-OH (75 mg, 0.20 mmol), Et₃N (173 mL, 1.25 μmol) and EDC (51 mg, 0.27 mmol). The solution was stirred for 5 hours, quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and concentrated. Flash chromatography (CH₂Cl₂/MeOH 97:3) afforded **12** (107 mg, 0.14 mmol, 81%).

colorless oil; ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (75 MHz, (CD₃)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 C₄₀H₅₀N₅O₉ 744.3608, found 744.3596; [α]_D²⁰ -7.6 (*c* 1.0, CHCl₃)

General procedures for hydrogenolysis

A solution of bicyclic hydrazine in solvent (**Methods A and B**: MeOH, **Method C**: MeOH.HCl pH3, **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**: PtO₂ (0.15 equiv)) under hydrogen atmosphere (1 atm). If needed, 0.1 equiv of catalyst can be added after 24 hours 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): 40 mg, quantitative, colorless oil; ¹H NMR (250 MHz, CD₃OD, 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); ¹³C

NMR (125 MHz, CD₃OD, 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 C₁₃H₂₂N₃O 236.1762, found 236.1756

(3*S*,5*R*)-1-(3,4-dimethoxyphenethyl)piperidine-3,5-diamine 13b (Method B): 62 mg, 88%, colorless oil; ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₁₅H₂₆N₃O₂ 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): 29 mg, quantitative, colorless oil; ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₁₆H₂₅N₄O 289.2028, found 289.2021

N-(4-((3*S*,5*R*)-3,5-diaminopiperidin-1-yl)-2-hydroxyphenyl)benzamide 13d (Method A): 21 mg, 95%, orange oil; ¹H NMR (300 MHz, CD₃OD, 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); ¹³C NMR (75 MHz, CD₃OD, 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 C₁₈H₂₃N₄O₂ 327.1821, found 327.1821

(3*S*,5*R*)-1-(1*H*-indol-5-yl)piperidine-3,5-diamine 13e (Method B): 22 mg, 79%, colorless oil; ¹H NMR (300 MHz, CDCl₃, 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)[$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{13}\text{H}_{19}\text{N}_4$ 231.1610, found 231.1606

(3*S*,5*R*)-1-(3,4,5-trimethoxyphenyl)piperidine-3,5-diamine 13f (Method A): 45 mg, 88%, colorless oil; ^1H 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)[$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{24}\text{N}_3\text{O}_3$ 282.1818, found 282.1815

(3*S*,5*R*)-1-(9,9'-spirobi[fluoren]-2-yl)piperidine-3,5-diamine 13g (Method D): 78 mg, 85%, yellow amorphous solid; ^1H 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)[$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{30}\text{H}_{28}\text{N}_3$ 430.2283, found 430.2276

(*S*)-methyl 2-((3*S*,5*R*)-3,5-diaminopiperidin-1-yl)-3-phenylpropanoate 13h (Method B): 39 mg, 98%, colorless oil; ^1H 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)[$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{N}_3\text{O}_2$ 278.1869, found 278.1864; $[\alpha]_{\text{D}}^{20}$ -19.0 (c 1.0, CH_3OH)

(3S,3'R,3''S,5R,5'S,5''R)-1'-(3,4-dimethoxyphenethyl)-[1,3':5',1''-terpiperidine]-

3,3'',5,5''-tetraamine 13i (Method C): 44 mg, quantitative, colorless oil; ¹H NMR (500 MHz, CD₃OD, 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); ¹³C NMR (125 MHz, CD₃OD, 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 C₂₅H₄₅N₇O₂Na 498.3532, found 498.3526

1-((3S,5R)-3,5-diaminopiperidin-1-yl)-2-(3,4-dimethoxyphenyl)ethanone 13j (Method B):

16 mg, 76%, colorless oil; ¹H NMR (500 MHz, CD₃OD, 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); ¹³C NMR (125 MHz, CD₃OD, 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 C₁₅H₂₄N₃O₃ 294.1817, found 294.1815

(3S,5R)-tert-butyl 3,5-diaminopiperidine-1-carboxylate 13k (Method A, Flash

chromatography (CH₂Cl₂/MeOH 97:3 then CH₂Cl₂/(MeOH/NH₄OH30%aq 90:10) 90:10): 17 mg, 67%, colorless oil; ¹H NMR (500 MHz, CD₃OD, 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); ¹³C NMR (125 MHz, CD₃OD, δ) 27.3, 42.6, 46.8, 50.0, 50.6, 79.9, 154.9; HRMS (ESI-Orbitrap)[M+H]⁺ calcd for C₁₀H₂₂N₃O₂ 216.1712, found 216.1713

Di-tert-butyl ((3S,5R)-1-(4-methoxybenzyl)piperidine-3,5-diyl)dicarbamate 14:

13a (58 mg, 0.25 mmol) was dissolved in THF/H₂O (50:50, 5.2 mL). Boc₂O (242 mg, 1.11 mmol) was added. The solution was stirred for 1 hour at room temperature, extracted with ethyl acetate and the combined organic layers were dried over MgSO₄, filtered, and concentrated to afford **14** (115 mg, quantitative).

white amorphous solid; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, 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, $(\text{CD}_3)_2\text{SO}$, 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)[$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{23}\text{H}_{38}\text{N}_3\text{O}_5$ 436.2812, found 436.2809

Di-tert-butyl (3S,5R)-piperidine-3,5-diylldicarbamate 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 hour at room temperature and filtered. Flash chromatography ($\text{CH}_2\text{Cl}_2/(\text{MeOH}/\text{NH}_4\text{OH}30\%\text{aq}$ 90:10) 95:5) of the residual afforded **4** (45 mg, 0.14 mmol, 58 %).

white amorphous solid; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, 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, $(\text{CD}_3)_2\text{SO}$, δ) 30.1, 39.8, 49.6, 52.3, 79.4, 156.8; HRMS (ESI-Orbitrap)[$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{30}\text{N}_3\text{O}_4$ 316.2236, found 316.2239

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

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