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Aurélie Blond, Serge Turcaud, Thomas Lecourt, Laurent Micouin. Diastereoselective Ring Homologation of Bicyclic Hydrazines: Access to cis -1,3-Diaminocyclohexitols. ACS Omega, 2018, 3 (11), pp.15302-15307. 10.1021/acsomega.8b02910 . hal-02186751

HAL Id: hal-02186751

https://hal.science/hal-02186751v1

Submitted on 17 Jul 2019

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Cite This: ACS Omega 2018, 3, 15302−15307

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Diastereoselective Ring Homologation of Bicyclic Hydrazines: Access to *cis*-1,3-Diaminocyclohexitols

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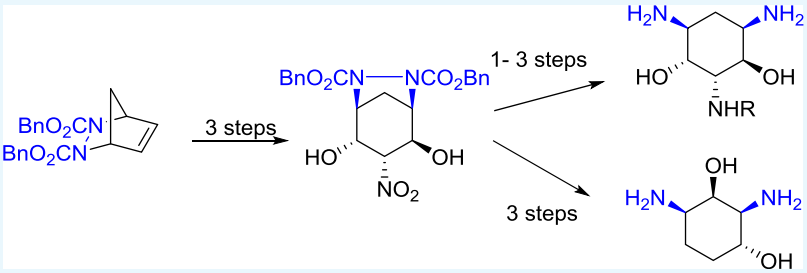
Supporting Information



ABSTRACT: A sequence of oxidative cleavage/double nitroaldol condensation followed by a few simple synthetic transformations can lead to polyhydroxylated di- and triaminocyclohexanes from a readily available bicyclic hydrazine. This new synthetic route provides a simple and general access to densely substituted privileged scaffolds or fragments with a perfect control of their relative configuration.

INTRODUCTION

Aminocyclohexitols are a group of natural or synthetic compounds with numerous biological activities.[1] Among them, *cis*-1,3-diaminocyclitols such as streptamine **1** or 2-deoxystreptamine **2** are known to play a crucial role in the biological activity of aminoglycosides, a major class of antibiotics (Figure 1).[2] Furthermore, substituted *cis*-1,3-diaminocycloalkanes have been reported to be valuable fragments or scaffolds for the design of RNA binders.[3] In this context, our group has been involved in the synthesis of polysubstituted 1,3-diamino cyclopentanes **3**[4] or piperidines **4**[5] starting from bicyclic hydrazine **5**.[6] Herein, we wish to report a straightforward and fully stereoselective approach toward hydroxylated 1,3-di- and 1,3,5-triaminocyclohexanes from a single precursor.

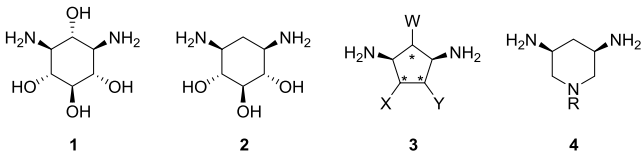


Figure 1. Examples of *cis*-1,3-diaminocyclitols and structural mimetics.

In our previous work, we have shown that aldehyde **6** could be obtained from hydrazine **5** using either ozonolysis or a two-step dihydroxylation−oxidative cleavage sequence.[5] This aldehyde was then engaged in a reductive amination to deliver precursors of piperidines **4**. We envisaged the possibility of conducting a double nitroaldol reaction, from the same precursor **6**, to prepare a bicyclic adduct **7** that would deliver polyhydroxylated 1,3,5-triaminocyclohexanes **8** after reductive cleavage of the hydrazine moiety (Scheme 1).

Cyclization of bis-aldehydes with nitromethane was indeed intensively investigated by Lichtenthaler and Ogawa on various substrates, including 1,5-dialdehydes derived from mono- or polysaccharides ("Sugar dialdehydes"), leading to diastereomeric mixtures of nitroinositols.[7]

Such a strategy was also reported by Hasegawa and Sable for the preparation of triaminocyclohexanediols.[8] From compound **9**, obtained in seven steps from *cis*-3,5-dibromocyclopentene, reaction with nitromethane under basic conditions gave an equimolar amount of diastereoisomers **10** and **11** in 80% overall yield (Scheme 2).

RESULTS AND DISCUSSION

The nitroaldol condensation was investigated using compound **12**, prepared from **5** in 86% yield, as the starting material (Table 1). The transient bis-aldehyde was generated by an oxidative cleavage and engaged in the next step without any other treatment than a filtration of the reaction mixture. No reaction was observed using sodium hydroxide[9] as a base (entries 1−3). The use of sodium alkoxide[10] led to the desired compound, albeit with a large amount of degradation product

Received: October 23, 2018
Accepted: November 1, 2018
Published: November 12, 2018

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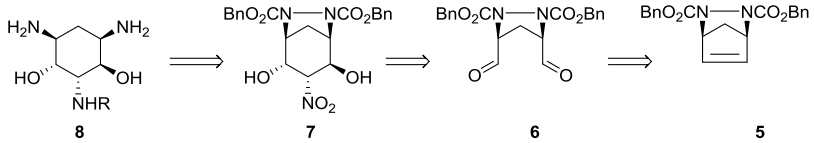
Scheme 1. Retrosynthetic Route



Scheme 2. Nitroaldol Condensation from 1,3-Diaminocyclopentanediol 9

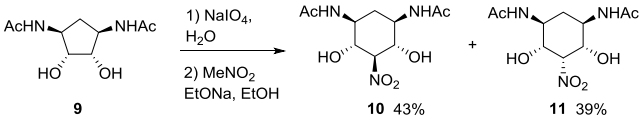
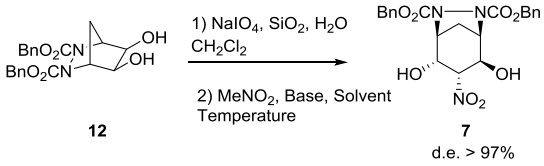


Table 1. Nitroaldol Reaction Optimization



	$MeNO_2$ (equiv)	base	solvent	temp. (°C)	yield (%)
1	50	2 M NaOH (0.04 equiv)	$MeOH/H_2O$	10	
2	30	2 M NaOH (0.04 equiv)	$MeOH/H_2O$	r.t	
3	1.6	2 M NaOH (0.04 equiv)	$MeOH/H_2O$	r.t	
4	3	MeONa	MeOH	r.t	6
5	30	MeONa	MeOH	r.t	16
6	30	EtONa	EtOH	r.t	<16
7	30	MeONa (0.1 equiv)	MeOH	r.t	26
8	50	Et_3N (0.15 equiv)		r.t	78

(entries 4–6). The presence of benzyl alcohol in the crude reaction mixture indicated that benzylcarbamates were cleaved under these basic conditions. A slight yield improvement could be obtained by lowering the base concentration (entry 7). Finally, best conditions were obtained using triethylamine[11] as a base and running the reaction in nitromethane as a solvent (entry 8), leading to compound **7** in 78% yield on a multigram scale.

Although six possible diastereomers can theoretically be obtained with this condensation (Figure 2), compound **7** was formed as a single diastereomer, as determined by the NMR analysis of the crude reaction product. Its configuration could be determined by the NMR analysis of the purified compound. ^1H and ^{13}C NMR experiments revealed the absence of any plane of symmetry, discarding the formation of meso compounds. The equatorial orientation of the nitro group was furthermore established using correlation spectroscopy and nuclear Overhauser effect spectroscopy experiments. The stereoselective formation of **7** can be explained by the reaction of the transient bis-aldehyde keeping a C_s symmetrical conformation, followed by ring closure and equilibration toward the thermodynamically favored bicyclic equatorial diastereomer. This thermodynamic control is much more efficient in the case of the formation of the rigid diazabicyclo[3.2.1]octane skeleton than with the synthesis of polysubstituted cyclohexanes reported by Hasegawa and Sable.

The reactivity of adduct **7** was then explored (Scheme 3). Hydrogenolysis under acidic conditions led to the triamino-cyclohexitol **8a** in a quantitative yield. The selective reduction of the nitro group was performed in the presence of zinc in acetic acid, leading to compound **13** in a quantitative yield. This compound could be functionalized by reductive amination with aldehyde or ketone, leading to compounds **14** and **15**. N-substituted triaminocyclohexitols **8b** and **8c** were obtained after hydrogenolysis.

On the basis of our previous experience in acid-catalyzed stereoselective skeletal rearrangements of bicyclic hydrazines, we investigated the behavior of compound **13** under nitrous acid deamination conditions.[12] Despite many experimental efforts, we were not able to obtain the corresponding alcohol from the diazonium intermediate. However, we were pleased to obtain compound **16** by adding a bromide source in the reaction mixture. The formation of **16**, established by NMR analysis, can be explained by the formation of a transient azetidinium followed by a selective ring opening, leading to rearranged compound **16** (Scheme 4).[13]

Compound **16** was quantitatively converted into diamine **17** by hydrogenolysis (Scheme 5).[14]

■ CONCLUSIONS

In conclusion, we have reported a ring-homologation reaction of bicyclic hydrazines based on a sequential oxidative cleavage/

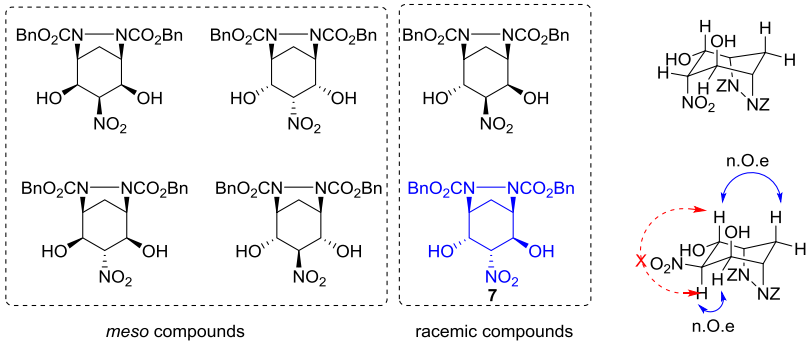


Figure 2. Possible stereoisomers and relative configuration of compound **7**.

DOI: 10.1021/acsomega.8b02910
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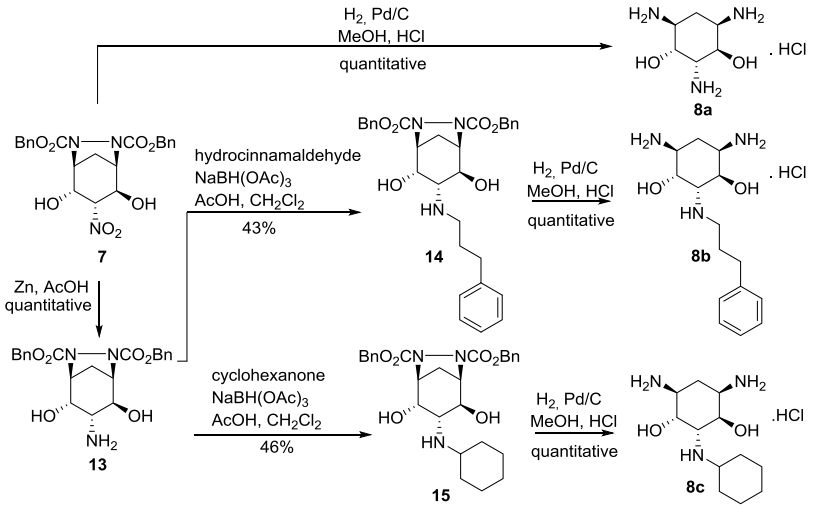
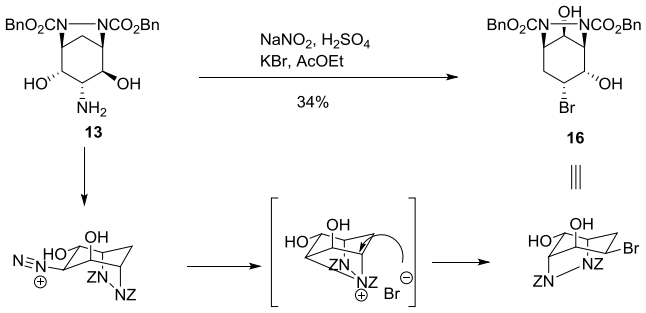
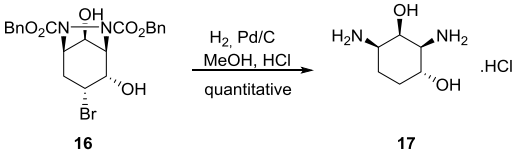
Scheme 3. Synthesis of *cis*-1,3-Diamino 5-Amino Cyclohexitols 8a−c



Scheme 4. Synthesis of Compound 16



Scheme 5. Synthesis of *cis*-1,3-Diamino Cyclohexitol 17



double nitroaldol condensation. This fully diastereoselective reaction enables the control of the relative configuration of five contiguous stereogenic centers in a single operation. The polyfunctionalized bicyclic hydrazine **7**, prepared on a gram scale from readily available bicyclic hydrazine **5**, furthermore provides a straightforward access to a large diversity of 1,3-di- and 1,3,5-triaminocyclohexitols in 1−3 steps using simple synthetic transformations.

■ EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial suppliers and used as received without further purification. Compounds **5** and **12** were prepared according to reported procedures.[5] Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.20 mm silica gel (60-F254) with visualization by UV light or staining with phosphomolybdic acid, ninhydrin, or Dragendorff's reagent. Column chromatography was performed on silica gel 60 Å (40−63 μm). All ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker NMR spectrometers operating at 300, 400, or 500 MHz (^{1}H value) and at 75 or 125 MHz (^{13}C value), respectively. HRMS spectra were recorded on an Orbitrap mass spectrometer or on an ESI-QTOF II instrument Shimadzu.

Dibenzyl 2,4-Dihydroxy-3-nitro-6,7-diazabicyclo[3.2.1]octane-6,7-dicarboxylate 7. To a vigorously stirred suspension of chromatographic grade silica gel (9.90 g) in CH_2Cl_2 (156 mL) was added a 0.65 M aqueous solution of $NaIO_4$ (9.95 mL, 6.47 mmol, 1.4 equiv) dropwise while stirring, whence a flaky suspension was formed. Diol **12** (1.84 g, 4.62 mmol, 1 equiv) in CH_2Cl_2 (150 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 nitromethane (12.5 mL, 231 mmol, 50 equiv). Triethylamine (96 μL, 0.69 mmol, 0.15 equiv) was added. The solution was stirred for 3 h at room temperature and was then concentrated. Flash chromatography (CH_2Cl_2/MeOH 98:2) afforded **7** (1.64 g, 3.59 mmol, 78%) as a colorless oil.

^{1}H NMR (300 MHz, $(CD_3)_2SO$, 70 °C): δ (ppm) 1.80 (dt, J = 5.5, 12.4 Hz, 1H), 2.38 (d, J = 12.4 Hz, 1H), 4.18 (dd, J = 4.9, 9.5 Hz, 1H), 4.30−4.42 (m, 2H), 4.50 (dd, J = 2.5, 5.5 Hz, 1H), 4.63 (br s, 1H), 5.00−5.27 (m, 4H), 5.64 (br s, 1H), 5.95 (d, J = 5.2 Hz, 1H), 7.30−7.38 (m, 10H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 70 °C): δ 27.3, 59.5, 62.9, 66.1, 66.8, 67.0, 67.3, 89.1, 127.1, 127.3, 127.6, 128.0, 135.6, 135.7, 153.8, 156.9; IR (CH_2Cl_2) ν: 3429, 1701, 1557, 1498, 1455, 1388, 1301, 1190, 1150, 1113, 1068, 1018, 955, 755, 698 cm^{-1}; HRMS (ESI +-TOF) m/z: calcd for $C_{22}H_{23}N_3O_8Na$ $[M + Na]^+$, 480.1377; found, 480.1380.

2,4,6-Triaminocyclohexane-1,3-diol 8a. To a solution of **7** (47 mg, 103 μmol, 1 equiv) in MeOH·HCl pH 3 (1.8 mL) was added 10% palladium on activated charcoal (23 mg, 0.2 equiv). The resulting black suspension was stirred at room temperature under hydrogen (1 atm) for 17 h and then hydrogen was bubbled in the reaction mixture few seconds. After stirring for 4 additional hours, the reaction mixture was filtered through a fritted glass funnel packed with Celite. Celite was washed with a CH_2Cl_2/MeOH mixture (50:50). The filtrate was concentrated to afford the final triamine **8a** hydrochloride (18 mg, 103 μmol, quantitative yield) as a colorless oil.

^{1}H NMR (400 MHz, CD_3OD, hydrochloride): δ (ppm) 1.65 (ddd, J = 11.7, 5.7, 4.6 Hz, 1H), 2.30 (d, J = 11.7 Hz,

DOI: 10.1021/acsomega.8b02910
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1H), 2.70 (dd, J = 9.2, 4.6 Hz, 1H), 3.32 (dd, J = 5.7, 1.6 Hz, 1H), 3.40 (dd, J = 9.2, 1.6 Hz, 1H), 3.48 (t, J = 4.6 Hz, 1H), 3.78 (t, J = 4.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD, hydrochloride): δ (ppm) 31.4, 55.0, 60.1, 60.6, 71.2, 75.9; HRMS (ESI+-TOF) m/z: calcd for $C_6H_{16}N_3O_2$ [M + H]$^+$, 162.1237; found, 162.1244.

4,6-Diamino-2-((3-phenylpropyl)amino)cyclohexane-1,3-diol 8b. Compound **8b** hydrochloride was obtained from **14** in a quantitative yield (19 mg, colorless oil) using the same procedure as for compound **8a**.

^{1}H NMR (500 MHz, CD_3OD, hydrochloride): δ (ppm) 1.80−1.96 (m, 2H), 1.96−2.08 (m, 1H), 2.20 (br s, 1H); 2.52−2.89 (m, 2H), 3.24 (br s, 1H), 3.49 (t, J = 9.3 Hz, 1H), 3.77 (d, J = 10.1 Hz, 1H), 4.14 (d, J = 9.3 Hz, 1H), 4.21 (br s, 1H), 7.03−7.36 (m, 5H); ^{13}C NMR (125 MHz, CD_3OD, hydrochloride): δ (ppm) 28.0, 31.8, 34.4, 48.4, 59.6, 62.5, 63.7, 63.5, 71.1, 127.1, 129.6, 129.8, 143.0; IR (MeOH) ν: 3366, 3230, 2939, 2866, 1599, 1513, 1455, 1212, 1103, 1042 cm^{-1}; MS (ES+) m/z: 280 [M + H]$^+$.

4,6-Diamino-2-(cyclohexylamino)cyclohexane-1,3-diol 8c. Compound **8c** hydrochloride was obtained from **15** in a quantitative yield (18 mg, colorless oil) using the same procedure as for compound **8a**.

^{1}H NMR (400 MHz, CD_3OD, hydrochloride): δ (ppm) 1.22−1.47 (m, 3H), 1.47−1.67 (m, 2H), 1.72 (d, J = 13.0 Hz, 1H), 1.92 (d, J = 13.0 Hz, 2H), 2.11 (q, J = 12.4 Hz, 1H), 2.22−2.39 (m, 3H), 3.35−3.42 (m, 1H), 3.72 (ddd, J = 12.4, 11.1, 4.1 Hz, 1H), 3.81 (dd, J = 5.0, 3.1 Hz, 1H), 4.07 (dt, J = 12.4, 3.3 Hz, 1H), 4.31 (dd, J = 11.1, 5.0 Hz, 1H), 4.44 (t, J = 3.1 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD, hydrochloride): δ (ppm) 24.3, 24.6, 26.0, 28.5, 46.6, 48.4, 59.0, 59.6, 64.5, 64.6; IR (MeOH) ν: 3366, 3230, 2938, 2866, 1599, 1514, 1456, 1212, 1103, 1083, 1042 cm^{-1}; HRMS (ESI+-Orbitrap) m/z: calcd for $C_{12}H_{26}N_3O_2$ [M + H]$^+$, 244.2020; found, 244.2014.

Dibenzyl 3-Amino-2,4-dihydroxy-6,7-diazabicyclo[3.2.1]octane-6,7-dicarboxylate 13. To a solution of **7** (304 mg, 664 μmol, 1 equiv) in distilled acetic acid (5.2 mL) was added activated zinc dust (869 mg, 13.3 mmol, 20 equiv). After stirring for 2 h at 60 °C, the reaction was filtered through a fritted glass funnel packed with Clarcel and then through a nylon syringe filter 0.45 μm. The filtrate was concentrated to afford **13** (404 mg, triacetate, quantitative yield) as a yellow oil. Compound **13** was systematically accompanied by 3 equiv of acetic acid and was characterized and further used as such.

^{1}H NMR (300 MHz, CD_3OD, 50 °C, triacetate): δ (ppm) 1.72−1.88 (m, 1H), 1.97 (br s, 9H, 3 CH_3CO), 2.40 (d, J = 12.0 Hz, 1H), 2.82−2.97 (m, 1H), 3.69−3.82 (d, J = 9.8 Hz, 1H), 4.34 (br s, 1H); 4.45 (br s, 1H), 4.54 (br s, 1H), 5.03−5.29 (m, 4H), 7.33 (br s, 10H); ^{13}C NMR (75 MHz, CD_3OD, 50 °C, triacetate): δ (ppm) 22.2 ($COCH_3$), 29.6, 55.6, 61.8, 64.4, 67.1, 69.7, 69.5, 72.3, 129.1, 129.2, 129.4, 129.4, 129.6, 129.7, 137.3, 156.8, 159.5, 179.2; IR (MeOD) ν: 3425, 1714, 1559, 1455, 1421, 1348, 1154, 750, 699 cm^{-1}; HRMS (ESI+-TOF) m/z: calcd for $C_{22}H_{25}N_3O_6Na$ [M + Na]$^+$, 450.1636; found, 450.1645.

Dibenzyl 2,4-Dihydroxy-3-((3-phenylpropyl)amino)-6,7-diazabicyclo[3.2.1]octane-6,7-dicarboxylate 14. To a solution of **13** (160 mg, triacetate, 263 μmol, 1 equiv) in CH_2Cl_2 (0.9 mL) and MeOH (0.1 mL) was added hydrocinnamaldehyde (34 μL, 263 μmol, 1 equiv), followed by $NaBH(OAc)_3$ (223 mg, 1.05 mmol, 4 equiv) and acetic acid (0.05 mL). After stirring for 20 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/MeOH 93:7 then CH_2Cl_2/(MeOH/NH_4OH 30% aq 90:10) 93:7) afforded **14** (61 mg, 111 μmol, 43%) as a colorless oil.

^{1}H NMR (400 MHz, $(CD_3)_2SO$, 70 °C): δ (ppm) 1.59−1.73 (m, 3H), 2.16−2.28 (m, 2H), 2.34 (br s, 1H), 2.52 (br s, 1H), 2.54−2.67 (m, 2H), 3.35 (dd, J = 9.3, 1.5 Hz, 1H), 4.03 (br s, 1H), 4.32 (t, J = 4.7 Hz, 1H); 4.35 (dd, J = 5.3, 1.5 Hz, 1H), 5.01−5.21 (m, 4H), 7.09−7.43 (m, 15H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 70 °C): δ (ppm) 28.7, 31.9, 33.3, 46.8, 60.5, 61.0, 63.4, 64.3, 67.4, 67.8, 72.0, 126.0, 127.9, 128.2, 128.3, 128.4, 136.7, 142.6, 155.1, 158.0; HRMS (ESI+-TOF) m/z: calcd for $C_{31}H_{36}N_3O_6$ [M + H]$^+$, 546.2599; found, 546.2601.

Dibenzyl 3-(Cyclohexylamino)-2,4-dihydroxy-6,7-diazabicyclo[3.2.1]octane-6,7-dicarboxylate 15. To a solution of **13** (134 mg, triacetate, 220 μmol, 1 equiv) in CH_2Cl_2 (1.3 mL) was added cyclohexanone (23 μL, 220 μmol, 1 equiv), followed by $NaBH(OAc)_3$ (186 mg, 880 μmol, 4 equiv) and acetic acid (0.05 mL). The solution was stirred for 4 h at room temperature, and additional $NaBH(OAc)_3$ (93 mg, 440 μmol, 2 equiv) was added. After stirring for 3 additional hours, 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 95:5 then CH_2Cl_2/(MeOH/NH_4OH 30% aq 90:10) 93:7] afforded **15** (52 mg, 102 μmol, 46%) as a yellow oil.

^{1}H NMR (400 MHz, $(CD_3)_2SO$, 70 °C): δ (ppm) 0.86−1.08 (m, 2H), 1.08−1.32 (m, 3H), 1.53 (br s, 1H), 1.58−1.78 (m, 5H), 2.21 (d, J = 11.9 Hz, 1H), 2.33−2.47 (m, 2H), 3.31 (d, J = 9.1 Hz, 1H), 3.99 (br s, 1H), 4.32 (t, J = 4.3 Hz, 1H), 4.35 (d, J = 4.9 Hz, 1H), 5.00−5.25 (m, 4H), 7.24−7.44 (m, 10H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 70 °C): δ = 24.6, 24.8, 26.2, 28.7, 33.0, 34.5, 53.9, 57.8, 60.6, 63.3, 65.1, 67.4, 67.8, 72.1, 127.9, 128.1, 128.3, 128.4, 128.7, 128.8, 136.6, 136.7, 155.1, 157.9; IR (CH_2Cl_2) ν: 3413, 2928, 2854, 1706, 1498, 1451, 1392, 1306, 1220, 1185, 1147, 1092, 1054, 1022, 753, 698 cm^{-1}; HRMS (ESI+-Orbitrap) m/z: calcd for $C_{28}H_{36}N_3O_6$ [M + H]$^+$, 510.2599; found, 510.2584.

Dibenzyl 3-Bromo-2,8-dihydroxy-6,7-diazabicyclo[3.2.1]octane-6,7-dicarboxylate 16. To a solution of **13** (148 mg, triacetate, 244 μmol, 1 equiv) in 2.5 M solution of H_2SO_4 (2.5 mL) and ethyl acetate (1 mL) were added KBr (102 mg, 854 μmol, 3.5 equiv) and then $NaNO_2$ (120 mg, 1.73 mmol, 7.1 equiv) dissolved in water (1.36 mL) dropwise at 0 °C. The reaction mixture was stirred for 1 h, and a half and additional KBr (102 mg, 854 μmol, 3.5 equiv) and then $NaNO_2$ (120 mg, 1.73 mmol, 7.1 equiv) dissolved in water (1.36 mL) were added. After stirring 16 h at room temperature, the reaction mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (CH_2Cl_2/MeOH 98:2) afforded **16** (41 mg, 83 μmol, 34%) as an orange oil.

^{1}H NMR (300 MHz, $(CD_3)_2SO$, 70 °C): δ (ppm) 2.04 (t, J = 12.7, 1H), 2.24−2.43 (m, 1H), 3.85 (ddd, J = 12.7, 6.3, 3.9 Hz, 1H), 4.02−4.09 (m, 1H), 4.11 (d, J = 4.5 Hz, 1H), 4.26 (d, J = 5.1 Hz, 1H), 4.46 (br s, 1H), 5.09−5.22 (m, 4H), 7.28−7.40 (m, 10H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 70 °C): δ (ppm) 35.7, 48.8, 64.5, 67.7, 67.9, 68.7, 69.7, 127.9, 128.0, 128.3, 128.8, 128.1, 136.6, 136.7, 156.8; IR (CH_2Cl_2) ν: 3443,

DOI: 10.1021/acsomega.8b02910
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2927, 1704, 1498, 1456, 1391, 1328, 1296, 1213, 1149, 1102, 1062, 1022, 902, 755, 698 cm^{-1}; HRMS (ESI+-TOF) m/z: calcd for $C_{22}H_{24}BrN_2O_6Na$ $[M + Na]^+$, 513.0632; found, 513.0634.

2,4-Diaminocyclohexane-1,3-diol 17. To a solution of **16** (18 mg, 37 μmol, 1 equiv) in MeOH·HCl (1 mL) was added 10% palladium on activated charcoal (10 mg, 0.2 equiv) under argon. The resulting black suspension was stirred at room temperature under hydrogen (1 atm) for 25 h. MeOH·HCl 1.25 M (0.5 mL) and 10% palladium on activated charcoal (2 mg) were added under argon. The resulting black suspension was stirred at room temperature under hydrogen (1 atm) for 21 h and filtered through a nylon syringe filter 0.45 μm. The filtrate was concentrated to afford the final diamine **17** hydrochloride (7 mg, quantitative yield) as an orange oil.

^{1}H NMR (400 MHz, hydrochloride, CD_3OD): δ (ppm) 1.45−1.53 (m, 1H), 1.78−1.90 (m, 2H), 2.01−2.12 (m, 1H), 3.09 (dd, J = 10.4, 2.7, 1H), 3.36−3.42 (m, 1H); 3.81 (td, J = 11.0, 4.9, 1H), 4.29 (t, J = 2.7, 1H); ^{13}C NMR (75 MHz, hydrochloride, CD_3OD): δ (ppm) 22.2, 30.2, 51.0, 57.3, 65.3, 66.1; IR (MeOH) ν: 3351, 1697, 1642, 1422, 1370, 1238, 1100 cm^{-1}; HRMS (ESI+-Orbitrap) m/z: calcd for $C_6H_{15}N_2O_2$ $[M + H]^+$, 147.1128; found, 147.1127.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02910.

Copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from CNRS, MRT (grant to A.B.), is acknowledged.

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ACS Omega 2018, 3, 15302−15307