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.⁷ Among them, cis-1,3-diaminocyclohexitols 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).⁸ Furthermore, substituted cis-1,3-

diaminocycloalkanes have been reported to be valuable fragments or scaffolds for the design of RNA binders.⁹ In this context, our group has been involved in the synthesis of polysubstituted 1,3-diamino cyclopentanes ³ or piperidines ⁴ starting from bicyclic hydrazine ⁴. 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.

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.

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Figure 1. Examples of cis-1,3-diaminocyclohexitols and structural mimetics.
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 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. $^1$H 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 $C_2$ 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. 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).

Compound 16 was quantitatively converted into diamine 17 by hydrogenolysis (Scheme 5).

■ CONCLUSIONS

In conclusion, we have reported a ring-homologation reaction of bicyclic hydrazines based on a sequential oxidative cleavage/
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-diaminocyclohexitol 8a−c.

**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. 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 1H NMR and 13C NMR spectra were recorded on Bruker NMR spectrometers operating at 300, 400, or 500 MHz (1H value) and at 75 or 125 MHz (13C value), respectively. HRMS spectra were recorded on an Orbitrap mass spectrometer or on an ESI-QTOF II instrument Shimadzu.

**Scheme 3. Synthesis of cis-1,3-Diamino 5-Amino Cyclohexitol 8a−c**

**Scheme 4. Synthesis of Compound 16**

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

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 CH2Cl2 (156 mL) was added a 0.65 M aqueous solution of NaIO4 (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 CH2Cl2 (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 2SO4, 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 (CH2Cl2/MeOH 98:2) afforded 7 (1.64 g, 3.59 mmol, 78%) as a colorless oil.

1H NMR (300 MHz, (CD3)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); 13C NMR (75 MHz, (CD3)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, 135.8, 156.9; IR (CH2Cl2) ν: 3429, 1701, 1557, 1498, 1455, 1388, 1301, 1190, 1150, 1113, 1068, 1018, 755 cm⁻¹; HRMS (ESI + TOF) m/z: calc for C22H23N3O8Na [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 CH2Cl2/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.

1H NMR (400 MHz, CD3OD, hydrochloride): δ (ppm) 1.65 (ddd, J = 11.7, 5.7, 4.6 Hz, 1H), 2.30 (d, J = 11.7 Hz,
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); 13C NMR (100 MHz, CD3OD, hydrochloride): δ (ppm) 31.4, 55.0, 60.1, 60.6, 71.2, 75.9; HRMS (ESI+TOF) m/z: calcd for C6H16N2O2 [M + H]+, 162.1237; found, 162.1244.

4.6-Diamo-2-((3-phenylpropylamino)cyclohexane-1,3-diol 8b. Compound 8b hydrochloride was obtained from 4 in a quantitative yield (19 mg, colorless oil) using the same procedure as for compound 8a.

1H NMR (500 MHz, CD3OD, 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); 13C NMR (125 MHz, CD3OD, 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-Diamo-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.

1H NMR (400 MHz, CD3OD, 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 (g, J = 12.4 Hz, 1H), 2.22–2.39 (m, 3H), 3.36–3.42 (m, 1H), 3.72 (d, 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); 13C NMR (75 MHz, CD3OD, 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 C12H14N2O2 [M + H]+, 224.2020; found, 224.24.

**Dibenzy 3-Amino-2,4-dihydroxy-6,7-diazabicyclo[3.2.1]octane-6,7-dicarboxylic acid 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 quenched with filtered and concentrated. Flash chromatography (CH3Cl2/MeOH 98:2) afforded 13 (52 mg, 102 μmol, 46%) as a yellow oil.

**Dibenzy 3-Bromo-2,8-dihydroxy-6,7-diazabicyclo[3.2.1]octane-6,7-dicarboxylic acid 16.** To a solution of 13 (148 mg, triacetate, 244 μmol, 1 equiv) in CH3Cl2 (1.3 mL) was added cyclohexanone (23 μL, 220 μmol, 1 equiv), followed by NaBH(OAc)2 (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)2 (93 mg, 440 μmol, 2 equiv) was added. After stirring for 3 additional hours, the reaction was quenched with saturated aqueous NaHCO3 and extracted with CH2Cl2, and the combined organic layers were dried over MgSO4, filtered, and concentrated. Flash chromatography (CH3Cl2/MeOH 98:2) was afforded 16 (41 mg, 83 μmol, 34%) as an orange oil.

**Dibenzy 3-Bromo-2,8-dihydroxy-6,7-diazabicyclo[3.2.1]octane-6,7-dicarboxylic acid 16.** To a solution of 13 (148 mg, triacetate, 244 μmol, 1 equiv) in CH3Cl2 (0.9 mL) and MeOH (0.1 mL) was added hydrocinnamaldehyde (34 μL, 263 μmol, 1 equiv), followed by NaBH(OAc)2 (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 NaHCO3 and extracted with CH2Cl2, and the combined organic layers were dried over MgSO4, filtered, and concentrated. Flash chromatography (CH3Cl2/MeOH 98:2) afforded 16 (41 mg, 83 μmol, 34%) as an orange oil.
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 was 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 diamin 17 hydrochloride (7 mg, quantifiable yield) as an orange oil.

1H NMR (400 MHz, hydrochloride, CD3OD): 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); 1.81 (td, J = 11.0, 4.9, 1H), 4.29 (t, J = 2.7, 1H); 13C NMR (75 MHz, hydrochloride, CD3OD): 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 C12H18BrN2O2Na [M + Na]+, 315.0632; found, 315.0634.

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The authors declare no competing financial interest.

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