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Synthesis of Hydroxy- and Polyhydroxy-Substituted 1,3-Diaminocyclohexanes

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Abstract: The synthesis of hydroxy-*trans*-1,3-diaminocyclohexanes based on nitroso-Diels-Alder cycloaddition of (cyclohexadienyl) phthalimide is reported.

Key words: cycloaddition - regioselectivity - amino alcohols - enantiomeric resolution

Trihydroxy-1,3-diaminocyclohexanes [also known as 2-de-oxy-streptamine (**1**), Figure 1] are present as key structural features in aminoglucoside antibiotics, such as kanamycin A (**2**), which bind to the bacterial 16S ribosomal RNA.[1] While the majority of aminoglucoside antibiotics possess a *cis*-1,3-diaminocyclohexane subunit, certain 'designer' analogues, containing a *trans*-1,3-diaminocyclohexane subunit exhibit interesting differential binding to bacterial and human rRNA. For example, **3** binds ca. one order of magnitude more tightly to *E. coli* 16S rRNA (K_d = 6 ± 0.5 μM) compared to human 18S rRNA (K_d = 68 ± 6.9 μM).[2] Additionally, 2,3,4-trihydroxycyclohexane-*trans*-1,5-diamines (e.g., **4**) have been prepared as sugar mimics,[3] and 2-hydroxycyclohexane-*trans*-1,5-diamines (e.g., **5**) have been utilized as intermediates in the synthesis of CC chemokine receptor 2 antagonists.[4] We herein report the synthesis of a series of hydroxydiaminocyclohexanes from the readily available[5] tricarbonyl(cyclohexadienyl)iron(1+) cation.

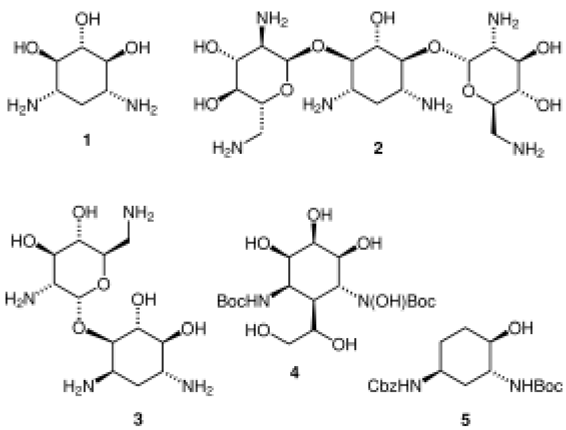
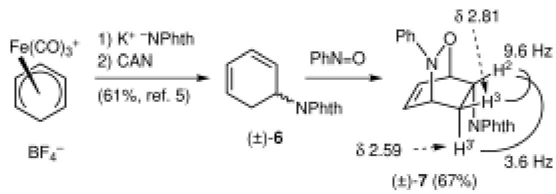


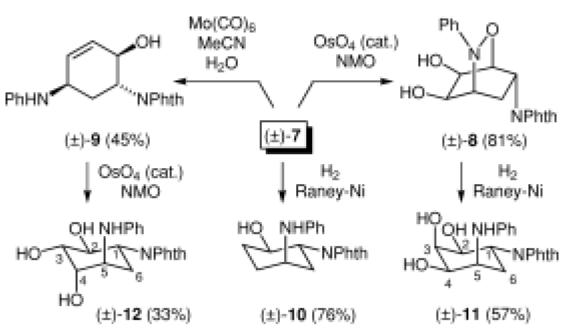
Figure 1

We have recently reported the synthesis of racemic *N*-(cyclohexa-2,4-dienyl)phthalimide [(±)-**6**] (Scheme 1) from the (cyclohexadienyl)$Fe(CO)_3^+$ cation.[6] Cycloaddition of *6* with nitrosobenzene[7] gave the 2-oxa-3-azaoxabicyclo[2.2.2]oct-5-ene (±)-**7**. The structure of **7** was tentatively assigned on the basis of its ^{1}H NMR spectral data. Assignment of the signals for the diastereotopic methylene protons (H3 and H3′) was facilitated by the magnitude of their vicinal couplings to H2; the *syn*-coupling (ca. 0° dihedral angle) is larger than the *anti*-coupling (ca. 120° dihedral angle). The signal for H3′ appears upfield of the signal for H3. These relative chemical shifts are due to the anisotropic effect of the olefin functionality. This tentative assignment was eventually corroborated on the basis of single crystal X-ray diffraction analysis.[8]



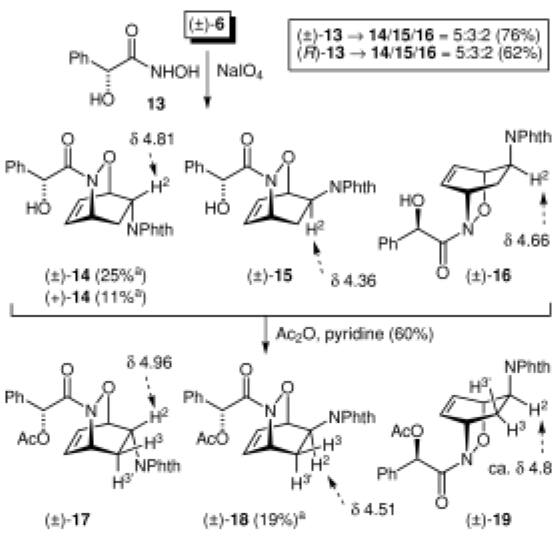
Scheme 1

Dihydroxylation of **7** gave a single diol (±)-**8**. The relative stereochemistry of **8** was tentatively based on the perception that reaction would occur on the face of the olefin opposite to the sterically bulky phthalimide group. This tentative assignment was eventually corroborated by further derivatization of **8** (*vide infra*). Reductive N-O bond cleavage of **8** with molybdenum hexacarbonyl[9] gave a single allylic alcohol, (±)-**9**. Hydrogenation of **7** or **8** over Raney nickel gave (±)-**10** or (±)-**11**, respectively, while dihydroxylation of **9** gave the triol (±)-**12** (Scheme 2). The structural assignment for **10** was tentatively assigned based on the structure of **7**; this tentative assignment was eventually corroborated by single crystal X-ray diffraction analysis.[8] The structures for **11** and **12** were assigned on the basis of their ^{1}H NMR spectral data. In particular, the signal for $H6_{ax}$ of each appears as a doublet (J ~ 3-4 Hz) of triplets (J ~ 13 Hz), indicative that the C1 phthalimide and the C5 phenylamino substituents are *trans*. Similarly, the signal for H1 of each appears as a doublet of doublet of doublets (J ~ 4.5, 10.8, and 13 Hz) indicative that the C1 phthalimide and the C2 hydroxy groups are *trans*. The relative stereochemistry of the C2 and C3 hydroxy groups was assigned on the basis of the H2/H3 coupling (**11**, J = 2.6 Hz; **12**, J = 9.6 Hz).



Scheme 2

The preparation of optically active bicyclooxazines has been accomplished by the addition of optically active nitroso acyls to achiral dienes[10] and by the copper-catalyzed addition of achiral nitroso acyls to achiral dienes in the presence of a chiral ligand.[11] More recently, Jana and Studer have demonstrated a catalytic, enantioselective, and regiodivergent addition of 2-nitrosopyridine to racemic cyclohexadienes.[12] To explore the possibility of generating optically active oxazines, the reaction of (±)-**6** with the nitroso acyl generated from (±)-mandelohydroxamic acid [(±)-***13***] was examined (Scheme 3). This gave a mixture of three diastereomeric cycloadducts ***14***, ***15***, and ***16*** in a ratio of ca. 5:3:2 (76%). Fractional crystallization of the mixture from acetonitrile gave the racemic diastereomer (±)-***14*** (25% isolated yield), whose structure was unambiguously assigned on the basis of single crystal X-ray diffraction analysis (Figure 3). Similarly, reaction of (±)-***6*** with the nitroso acyl generated from (*R*)-***13*** gave an optically active mixture of diastereomers ***14***-***16***; fractional crystallization of this mixture gave pure (+)-***14*** (11%).



Scheme 3 [a] Isolated yield of pure compound

The mother liquors from the recrystallization of **14**, **15**, and **16** could not be further purified by recrystallization or chromatography. In this case, acylation of the racemic mixture of **14**-**16** gave a mixture of racemic **17**, **18**, and **19**; separation of this mixture by preparative TLC gave pure (±)-**18**, and a mixture of **17** and **19**. The structures of **14**-**19** were tentatively assigned as indicated on the basis of their ^{1}H NMR spectral data. Notably, the chemical shifts for signals of the 2-oxa-3-azabicyclo[2.2.2]octane core of acetate **17** are relatively similar to those for **14**. Similarly, the chemical shifts for **15** or **16** are relatively similar to those of **18** or **19** respectively. The upfield chemical shift for H2 of **15** (δ = 4.36), relative to that for H2 of **14** or **16** (δ = 4.81 or 4.68, respectively) is due to the anisotropic effect of the olefin functionality.

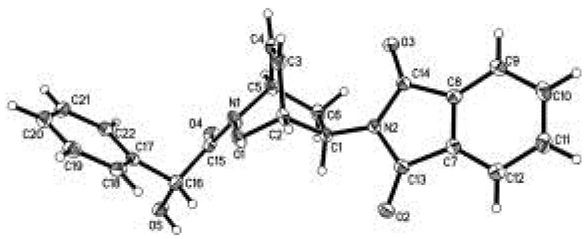
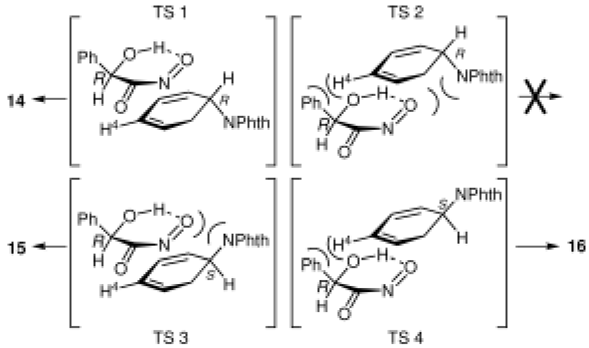


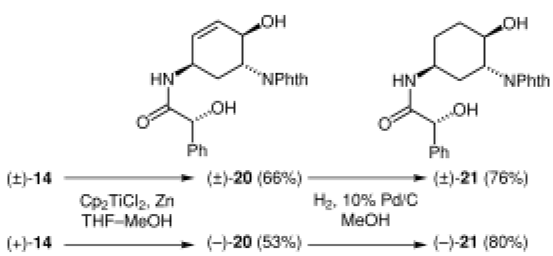
Figure 2 ORTEP drawing of (±)-**14** with crystallographic numbering. $C_{22}H_{18}N_2O_5$; orthorhombic, *ABa*2, $Z = 8$, $a = 21.9065(4)$ Å, $b = 28.3819(6)$ Å, $c = 5.80740(10)$Å, $V = 3610.74(12)$ Å³; 30401 reflections measured, 3175 unique ($R_{\text{int}} = 0.0252$). The final wR^2 was 0.0701 (all data). CCDC 778912.

The diastereoselectivity may be rationalized by consideration of the possible transition states leading to the products (Scheme 4). It has been proposed that the nitroso dienophile derived from mandelohydroxamic acid reacts primarily in a six-membered ring hydrogen-bonded conformer.[10a] Approach of the (*R*)-nitroso dienophile to the *exo*-face of (*R*)-**6** (i.e., TS 1) does not involve any steric hindrance, while approach of the (*R*)-nitroso dienophile to the *endo*-face of (*R*)-**6** (i.e., TS 2) involves steric repulsion between H4 and the phenyl substituent and between the nitroso oxygen and the phthalimide substituent. Thus, TS 1 (leading to **14**) should be greatly favored over TS 2. In comparison, approach of the (*R*)-nitroso dienophile to the *exo*-face of (*S*)-**6** (i.e., *TS 3*) involves repulsion between the nitroso oxygen and the phthalimide substituent, while approach of the (*R*)-nitroso dienophile to the *endo*-face of (*S*)-**6** (i.e., TS 4) involves steric repulsion between H4 and the phenyl substituent. Thus, the energies of *TS 3* (leading to **15**) and TS 4 (leading to **16**) are more equally matched in energy.



Scheme 4

Attempted reduction of bicyclic oxazine (±)-**14** with hydrogen over Raney nickel gave an intractable mixture of unidentified products. In comparison, reduction using titanocene(III) chloride[13] proceeded to afford (±)-**20**, which upon further catalytic hydrogenation gave the saturated diaminocyclohexane (±)-**21** (Scheme 5). Similar processing of (+)-**14** gave (-)-**20** and (-)-**21**, respectively. The structural assignments for **20** and **21** are based on comparison of their ^{1}H NMR spectral data with that for the previously prepared **9** and **10**, respectively.



Scheme 5

In summary, the cycloaddition of (cyclohexadienyl)phthalimide (±)-**6** with nitrosobenzene proceeds in a diastereofacial- and regioselective fashion to afford bicyclic oxazine (±)-**7**. In contrast, reaction of (±)-**6** with the optically active nitroso acyl derived from mandelohydroxamic acid gave a mixture of three cycloadducts; the structure of the major product **14** was confirmed by X-ray crystal structure. The oxazine **7** could be rapidly transformed into hydroxy-*trans*-1,3-diaminocyclohexanes **10**-**12**, while oxazines (+)-**14** was transformed into the optically active hydroxy-*trans*-1,3-

diaminocyclohexane (-)-**21**. The structural assignments are based on their NMR spectral data and confirmed by X-ray diffraction for **10**.

Elemental analyses were obtained from Midwest Microlabs, Ltd., Indianapolis, IN, and HRMS were obtained from the University of Nebraska Center for mass spectrometry. Anhyd CH_2Cl_2 and anhyd DMF were purchased from Aldrich Chemical Company. Reactions were performed in flame-dried glassware under an atmosphere of N_2 unless otherwise noted. Compounds **6**,[6] (±)-**13**, and (*R*)-**13**[10a] were prepared by literature procedures.

3-Phenyl-7-phthalimido-2-oxa-3-azabicyclo[2.2.2]oct-5-ene [(±)-7]

To a solution of nitrosobenzene (220 mg, 2.04 mmol) in anhyd CH_2Cl_2 (8 mL), at r.t. under N_2, was added in one portion solid **6** (230 mg, 1.02 mmol). The mixture was stirred for 2 h and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane-EtOAc, 4:1) to afford (±)-**7** (224 mg, 67%) as a colorless solid; mp 148-151°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59 (td, *J* = 3.6, 13.6 Hz, 1 H), 2.81 (ddd, *J* = 3.2, 9.6, 13.2 Hz, 1 H), 4.63-4.67 (m, 1 H), 4.90 (td, *J* = 4.0, 9.6 Hz, 1 H), 5.01 (dt, *J* = 1.6, 5.2 Hz, 1 H), 6.38 (ddd, *J* = 1.8, 6.4, 8.2 Hz, 1 H), 6.53 (ddd, *J* = 1.6, 5.6, 8.4, 1 H), 6.96 (t, *J* = 7.6 Hz, 1 H), 7.03 (d, *J* = 7.6 Hz, 2 H), 7.24 (t, *J* = 7.6 Hz, 2 H), 7.70-7.84 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6, 48.2, 57.1, 69.4, 117.7, 122.5, 123.3, 128.4, 128.7, 131.7, 132.6, 134.3, 151.8, 168.5.

Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.11; H, 4.89; N, 8.46.

3-Phenyl-7-phthalimido-2-oxa-3-zabicyclo[2.2.2]octane-5,6-diol [(±)-8]

A sample of **7** (70 mg, 0.21 mmol) in acetone was treated with catalytic OsO_4 (in toluene) and NMO for 10 h at r.t. in a fashion similar to the typical procedure to give (±)-**12**. After the standard workup, the residue was adsorbed onto silica gel using CH_2Cl_2. This purified by column chromatography (layered onto silica gel, hexane-EtOAc, 1:1) to give (±)-**8** (63 mg, 81%) as a colorless solid; mp 183-186°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (ddd, *J* = 4.8, 11.6, 14.4 Hz, 1 H), 2.72 (ddd, *J* = 1.2, 7.6, 14.4 Hz, 1 H), 3.44 (d, *J* = 7.6 Hz, OH, 1 H), 3.71 (d, *J* = 10.0 Hz, OH, 1 H), 3.98-4.13 (m, 2 H), 4.34 (t, *J* = 7.6 Hz, 1 H), 4.58 (dt, *J* = 3.2, 9.2 Hz, 1 H), 4.88 (ddd, *J* = 4.0, 8.0, 11.2 Hz, 1 H), 7.04 (t, *J* = 7.2 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.24 (dd, *J* = 7.2, 8.8 Hz, 2 H), 7.73-7.86 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 45.0, 59.5, 64.1, 66.0, 76.6, 116.1, 122.8, 123.8, 129.4, 131.5, 134.7, 149.8, 168.6.

Anal. Calcd for $C_{20}H_{18}N_2O_5 \cdot 0.6\ H_2O$: C, 63.69; H, 5.13. Found: C, 63.66; H, 4.93.

N -[(1 *S* *,2 *S* *,5 *S* *)-2-Hydroxy-5-(phenylamino)cyclohex-3-enyl]phthalimide [(±)-9]

To a solution of **7** (200 mg, 0.600 mmol) in MeCN (8 mL) and H_2O (0.7 mL) was added $Mo(CO)_6$ (158 mg, 0.600 mmol). The mixture was heated at reflux for 1 h, and then concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, hexane-EtOAc, 1:1) gave (±)-**9** (90 mg, 45%) as a pale yellow foamy solid; mp 73-75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.05 (br d, *J* = 13.2 Hz, 1 H), 2.77 (dt, *J* = 4.8, 13.2 Hz, 1 H), 4.23 (br s, 1 H), 4.39 (ddd, *J* = 3.4, 9.8, 13.2 Hz, 1 H), 4.84 (dd, *J* = 1.4, 9.8 Hz, 1 H), 5.82-5.95 (m, 2 H), 6.64 (d, *J* = 7.6 Hz, 2 H), 6.71 (d, *J* = 7.2 Hz, 1 H), 7.17 (dd, *J* = 7.0, 8.6 Hz, 2 H), 7.65-7.80 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9, 48.0, 51.2, 68.4, 113.3, 117.9, 123.4, 128.4, 129.6, 131.9, 133.8, 134.2, 146.7, 169.0.

HRMS (FAB): *m/z* [M^+] calcd for $C_{20}H_{18}N_2O_3$: 334.1317; found: 334.1321.

N -[(1 *S* *,2 *S* *,5 *R* *)-2-Hydroxy-5-(phenylamino)cyclohexyl]phthalimide [(±)-10]; Typical Procedure

In a small hydrogenation vessel, was placed a solution of **7** (0.3 g, 0.9 mmol) in MeOH (30 mL). A slurry of Raney Ni (0.5 mL, 50% in H_2O) was added and the mixture was stirred under H_2 (2.76 bar) for 4 h. After releasing the excess H_2 pressure, the mixture was filtered through Celite and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc, adsorbed onto silica gel and purified by column chromatography (silica gel, hexane-EtOAc, 1:1) to give (±)-**10** (225 mg, 74%) as a light yellow solid; mp 180-183°C.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.74-2.05 (m, 5 H), 2.51 (dt, *J* = 3.6, 13.1 Hz, 1 H), 3.80 (br s, 1 H), 4.27-4.40 (m, 2 H), 6.59 (t, *J* = 7.6 Hz, 1 H), 6.69 (d, *J* = 7.6 Hz, 2 H), 7.09 (t, *J* = 7.6 Hz, 2 H), 7.74-7.83 (m, 4 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 29.4, 30.3, 33.4, 54.1, 70.3, 114.6, 118.1, 124.1, 130.2, 133.5, 135.3, 149.2, 170.4; one signal obscured by solvent.

Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99. Found: C, 71.50; H, 6.04.

N -[(1 *S* *,2 *R* *,3 *S* *,4 *S* *,5 *S* *)-2,3,4-Trihydroxy-5-(phenylamino)cyclohexyl]phthalimide [(±)-11]

The reduction of **8** (0.160 g, 0.437 mmol) in MeOH (30 mL) with H_2 (2.76 bar) catalyzed by Raney Ni (0.3 mL, 50% in H_2O) was carried out in a fashion similar to the typical procedure for (±)-**10**. Purification of the crude product by column chromatography (silica gel, EtOAc) gave (±)-**11** (91 mg, 57%) as a colorless solid; mp 233-235°C.

^{1}H NMR (400 MHz, CD_3OD): δ = 2.03 (td, *J* = 3.8, 13.2 Hz, 1 H), 2.31 (dt, *J* = 3.2, 13.2 Hz, 1 H), 3.84 (dd, *J* = 3.0, 4.3 Hz, 1 H), 3.99-4.03 (m, 1 H), 4.21 (t, *J* = 2.6 Hz, 1 H), 4.34 (dd, *J* = 2.6, 10.8 Hz, 1 H), 4.64 (ddd, *J* = 3.8, 10.8, 13.2 Hz, 1 H), 6.57 (t, *J* = 7.6 Hz, 1 H), 6.62 (d, *J* = 8.0 Hz, 2 H), 7.08 (t, *J* = 7.6 Hz, 2 H), 7.75-7.83 (m, 4 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 30.1, 48.3, 54.9, 70.2, 70.7, 76.4, 114.2, 117.9, 124.1, 130.3, 133.4, 135.4, 149.4, 170.3.

HRMS (FAB): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_5$: 369.1450; found: 369.1448.

N -[(1 *S* *,2 *R* *,3 *R* *,4 *R* *,5 *S* *)-2,3,4-Trihydroxy-5-(phenylamino)cyclohexyl]phthalimide [(±)-12]; Typical Procedure

To a solution of **9** (50 mg, 0.15 mmol) in acetone (0.8 mL) was added a solution of NMO (30.0 mg, 0.230 mmol) in H_2O (0.3 mL) followed by a solution of OsO_4 in toluene (0.1 mL, 10 mol%). The mixture was stirred for 15 h at r.t. and then $Na_2S_2O_4$ (26 mg) was added and stirring was continued for a further 30 min. The mixture was concentrated and the residue purified by column chromatography (silica gel, hexane-EtOAc, 1:4) to give (±)-**12** (18 mg, 33%) as a colorless solid; mp 253-255˚C.

^1H NMR (300 MHz, CD_3OD): δ = 1.78 (br d, *J* = 13.3 Hz, 1 H), 3.00 (dt, *J* = 3.9, 13.3 Hz, 1 H), 3.70-3.78 (m and dd, *J* = 2.7, 9.3 Hz, 2 H total), 4.11 (narrow t, *J* = 2.6 Hz, 1 H), 4.43 (ddd, *J* = 4.2, 10.8, 13.2 Hz, 1 H), 4.55 (d, *J* = 9.6, 10.2 Hz, 1 H), 6.62 (t, *J* = 7.2 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 2 H), 7.11 (dd, *J* = 7.5, 8.4 Hz, 2 H), 7.76-7.83 (m, 4 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 28.1, 51.6, 53.3, 69.9, 71.9, 73.7, 113.6, 117.4, 123.7, 129.8, 132.7, 135.1, 148.6, 168.8.

HRMS (FAB): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_5$: 369.1450; found: 369.1447.

3-Mandeloyl-7-phthalimido-2-oxa-3-azabicyclo[2.2.2]oct-5-enes 14-16; Typical Procedure

To a rapidly stirring solution of (±)-**6** (0.600 g, 2.67 mmol) and $NaIO_4$ (0.683 g, 3.19 mmol) in CH_2Cl_2 (10 mL), DMF (10 mL), and H_2O (5 mL) was added, over a period of 45 min, a solution of (±)-mandelohydroxamic acid (0.441 g, 2.64 mmol) in DMF (10 mL). The mixture was stirred for an additional 3 h, then poured into H_2O and extracted several times with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel, hexanes-EtOAc, 1:1) to afford a colorless solid (0.795 g, 77%). Analysis of this product by ^{1}H NMR spectroscopy indicated it to be a mixture of **14**, **15**, and **16** (5:3:2). Recrystallization (MeCN) of two batches of the above size gave (±)-**14** (0.513 g, 25%).

(±)-*14*

Mp 160-162°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (ddd, *J* = 2.7, 4.5, 13.5 Hz, 1 H), 2.60 (ddd, *J* = 3.3, 9.0, 13.5 Hz, 1 H), 4.15 (d, *J* = 7.5 Hz, 1 H), 4.73 (t, *J* = 3.9 Hz, 1 H), 4.81 (td, *J* = 4.5, 9.0 Hz, 1 H), 5.25-5.36 (m and d, *J* = 6.6 Hz, 2 H total), 5.79 (t, *J* = 6.6 Hz, 1 H), 6.57 (t, *J* = 6.6 Hz, 1 H), 7.19-7.30 (m, 5 H), 7.65-7.80 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 47.6, 48.6, 71.6, 71.8, 123.5, 127.8, 128.08, 128.12, 128.2, 131.4, 134.47, 134.51, 137.5, 168.1, 173.1.

Anal. Calcd for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.64. Found: C, 67.48; H, 4.65.

(±)-*15*

^{1}H NMR (partial, $CDCl_3$): δ = 2.30-2.50 (m, 2 H), 4.36 (td, *J* = 4.0, 8.4 Hz, 1 H), 4.97-5.03 (m, 1 H), 5.21 (d, *J* = 7.2 Hz, 1 H), 6.53 (t, *J* = 6.8 Hz, 1 H), 6.88 (t, *J* = 6.8 Hz, 1 H).

(±)-*16*

^{1}H NMR (partial, $CDCl_3$): δ = 4.75-4.80 (m, 1 H), 5.50-5.55 (m, 1 H), 6.15 (t, *J* = 6.9 Hz, 1 H), 6.39 (t, *J* = 6.8 Hz, 1 H).

X-ray Structural Analysis of (±)-*14*

A crystal suitable for X-ray diffraction analysis was grown from MeCN. Formula: $C_{22}H_{18}N_2O_5$, orthorhombic, space group *Aba*2, *a* = 21.9065(4), *b* = 28.3819(6), *c* = 5.80740(10) Å, *V* = 3610.74(12) $Å^3$, *Z* = 8, d_{calcd} = 1.436 mg/m^3, *u* = 0.854 mm^{-1}, 3175 unique reflections, w*R*2 = 0.0701.

(7 *S*)-3-[(*R*)-Mandeloyl]-7-phthalimido-2-oxa-3-azabicyclo[2.2.2]oct-5-ene [(+)-14]

Reaction of (±)-**6** (0.300 g, 1.33 mmol) with the nitrosoacyl generated from (*R*)-mandelohydroxamic acid (0.212 g, 1.27 mmol) was carried out in a fashion similar to the typical procedure for **14**-**16** using (±)-mandelohydroxamic acid. Purification of the residue by column chromatography (silica gel, hexanes-EtOAc, 1:1) gave a colorless solid (0.316 g, 62%). Recrystallization (MeCN) gave (+)-**14** (57 mg, 11%); mp 180-183°C.

$[\alpha]_D^{20}$ +126.5 (*c* 0.429, CH_2Cl_2).

The ^{1}H NMR spectrum of this product was identical to that of the racemic compound.

Reaction of 3-Mandeloyl-7-phthalimido-2-oxa-3-azabicyclo[2.2.2]oct-5-ene with Acetic Anhydride

To a mixture of **14**, **15**, and **16** (80 mg, 0.20 mmol) in CH_2Cl_2 (1 mL), at r.t. was added dropwise pyridine (0.10 mL, 1.0 mmol) followed by Ac_2O (0.10 mL, 1.1 mmol). The mixture was stirred for 12 h, diluted with CH_2Cl_2 and quenched with 1 M HCl. The mixture was extracted several times with CH_2Cl_2 and the combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by preparative TLC (hexane-EtOAc = 7:3) gave (±)-**18** (17 mg, 19%) as a colorless oil, followed by a mixture of (±)-**17** and (±)-**19** (ca. 8:3 ratio, 39 mg, 41%) as a colorless oil.

(±)-*18*

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3 H), 2.38-2.43 (m, 2 H), 4.47-4.55 (m, 1 H), 5.00-5.05 (m, 1 H), 5.33-5.38 (br s, 1 H), 6.13 (s, 1 H), 6.55 (br t, *J* = 6.8 Hz, 1 H), 6.89 (br t, *J* = 7.2 Hz, 1 H), 7.39-7.55 (m, 5 H), 7.70-7.80 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 26.9, 47.3, 48.9, 72.2, 73.7, 123.5, 128.4, 128.5, 128.9, 129.2, 131.5, 134.3, 134.5, 135.0, 168.2, 170.7; one CO signal not observed.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{24}H_{20}N_2NaO_6$: 455.1219; found: 455.1216.

(±)-*17*

^1H NMR (partial, $CDCl_3$): δ = 2.45 (br d, *J* = 12.8 Hz, 1 H), 2.67 (ddd, *J* = 3.2, 9.8, 12.8 Hz, 1 H), 4.80-4.84 (br s, 1 H), 4.96 (dt, *J* = 4.2, 9.2 Hz, 1 H), 5.28-5.33 (br s, 1 H), 5.94 (br t, *J* = 6.8 Hz, 1 H), 6.24 (s, 1 H), 6.61 (br t, *J* = 6.8 Hz, 1 H).

(±)-*19*

^1H NMR (partial, $CDCl_3$): δ = 2.31 (dd, *J* = 2.8, 14.0 Hz, 1 H), 2.82 (ddd, *J* = 3.6, 9.6, 13.6 Hz, 1 H), 4.73-4.77 (br s, 1 H), 5.47-5.51 (br s, 1 H), 6.38 (br t, *J* = 7.2 Hz, 1 H).

(2 *R* *)-2-Hydroxy- *N* -[(1 *R* *,4 *R* *,5 *R* *)-4-hydroxy-5-phthalimidocyclohex-2-enyl)-2-phenylacetamide [(±)-20]; Typical Procedure

To titanocene dichloride (93 mg, 0.38 mmol) and activated zinc dust (50 mg, 0.75 mmol), under N_2 at r.t. was added freshly distilled THF (1.2 mL). The mixture was stirred for 45 min during which time the solution changed in color from red to olive green. The green mixture was cooled to -30°C and a solution of (±)-**14** (60 mg, 0.15 mmol) in MeOH (1.5 mL) was added. The mixture was stirred for 1 h with the temperature maintained between -15 to -30°C. The mixture was warmed to r.t. and quenched with sat. aq NH_4Cl (5 mL) and then filtered through filter-aid. The filtrate was extracted several times with EtOAc, and the combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (silica gel, EtOAc) gave (±)-**20** (40 mg, 66%) as a colorless solid; mp 223-225°C.

^1H NMR (400 MHz, CD_3OD): δ = 1.75 (tdd, *J* = 1.6, 3.2, 14.0 Hz, 1 H), 2.64 (dt, *J* = 4.8, 14.0 Hz, 1 H), 4.40 (ddd, *J* = 12.8, 9.4, 3.1 Hz, 1 H), 4.49-4.54 (m, 1 H), 4.98 (s, 1 H), 5.75-5.81 (m, 1 H), 5.94 (br d, *J* = 10.0 Hz, 1 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.31 (t, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.78-7.74 (m, 2 H), 7.84-7.81 (m, 2 H); one signal obscured by solvent.

^{13}C NMR (100 MHz, CD_3OD): δ = 32.4, 45.8, 52.1, 67.9, 75.8, 124.2, 127.4, 128.4, 129.4, 129.7, 133.4, 135.6, 136.5, 141.8, 170.1, 175.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{20}N_2NaO_5$: 415.1270; found: 415.1274.

(2 *R*)-2-Hydroxy- *N* -[(1 *R* ,4 *R* ,5 *R*)-4-hydroxy-5-phthalimidocyclohex-2-enyl]-2-phenylacetamide [(-)-20]

The titanium-mediated reduction of (+)-**14** (50 mg, 0.13 mmol) was carried out in a fashion similar to the typical procedure for (±)-**20**. Purification of the residue by column chromatography (silica gel, EtOAc) gave (-)-**20** as a colorless solid; mp 193-195 °C.

$[\alpha]_D^{20}$ -106 (*c* 0.270, MeOH).

The ^1H NMR spectrum of this product was identical to that of the racemic compound.

(2 *R* *)-2-Hydroxy- *N* -[(1 *S* *,4 *R* *,5 *R* *)-4-hydroxy-5-phthalimidocyclohexyl]-2-phenylacetamide [(±)-21]

The reduction of (±)-**20** (30 mg, 0.077 mmol) in MeOH (6 mL) with H_2 (2.76 bar) catalyzed by 10% Pd/C (2.5 mg) was carried out in a fashion similar that for the typical procedure for (±)-**10**. The mixture was filtered through filter-aid and concentrated. Purification of the residue by column chromatography (EtOAc) gave (±)-**21** (23 mg, 76%) as a colorless solid; mp 150-152°C.

^1H NMR (300 MHz, CD_3OD): δ = 2.05-1.50 (m, 6 H), 2.43 (dt, *J* = 3.0, 12.3 Hz, 1 H), 4.34-4.04 (m, 3 H), 5.03 (br s, 1 H), 7.51-7.23 (m, 5 H), 7.84-7.71 (m, 4 H); one signal obscured by solvent.

^{13}C NMR (75 MHz, CD_3OD): δ = 29.0, 30.7, 33.3, 46.4, 54.1, 69.7, 75.6, 124.1, 128.4, 129.4, 129.8, 133.4, 135.4, 141.8, 170.2, 175.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{22}N_2NaO_5$: 417.1426; found: 417.1422.

(2 *R*)-2-Hydroxy- *N* -[(1 *S* ,4 *R* ,5 *S*)-4-hydroxy-5-phthalimidocyclohex-1-yl)-2-phenylacetamide [(-)-21]

The reduction of (-)-**20** (25 mg, 0.064 mmol) was carried out in a fashion similar to that for (±)-**20**. Purification of the residue by column chromatography (silica gel, EtOAc) gave (-)-**21** as a colorless oil.

$[\alpha]_D^{20}$ -84 (*c* 0.20, MeOH).

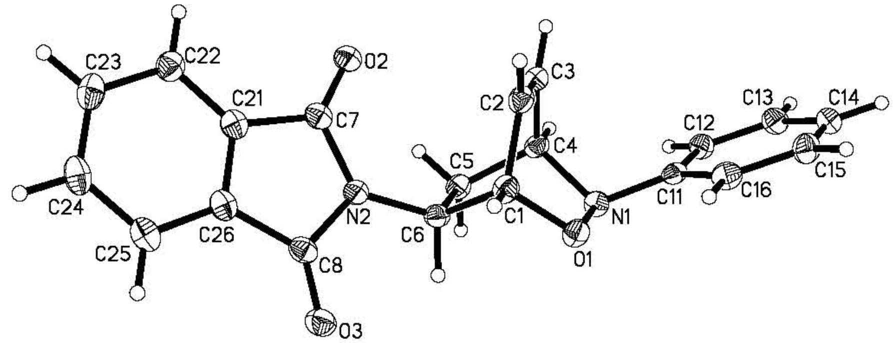
The ^1H NMR spectrum of this product was identical to that of the racemic compound.

Supporting Information for this article is available online: https://www.thieme-connect.de/media/synthesis/201106/supmat/sup_m07110ss-10-1055_s-0030-1258430.pdf

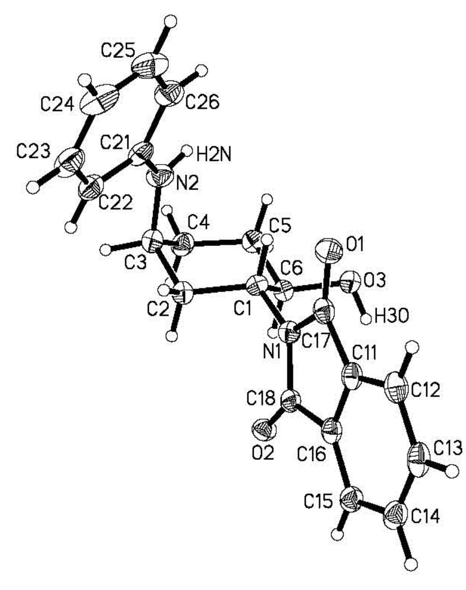
Synthesis of Hydroxy- and Polyhydroxy-Substituted 1,3-Diaminocyclohexanes

Anobick Sar, Sergey Lindeman, William A. Donaldson*

Supporting Information



ORTEP drawing of (±)-**7** with crystallographic numbering. $C_{20}H_{16}N_2O_3$; monoclinic, *C2/*c, *Z* = 8, *a* = 25.6400(13) Å, *b* = 5.4993(3) Å, *c* = 22.3486(12) Å, *β* = 99.259(3)°, *V* = 3110.1(3) Å^3; 21439 reflections measured, 2775 unique (R_{int} = 0.0603). The final wR^2 was 0.1064 (all data). CCDC 778910.



Synthesis, Vol. 6 (March 2011): pg. 924-928. DOI.

ORTEP drawing of (±)-**10** with crystallographic numbering. $C_{20}H_{20}N_2O_3$; monoclinic, *P21/*c, *Z* = 4, *a* = 14.9286(4) Å, *b* = 6.8883(2) Å, *c* = 16.4514(5) Å, *β*= 99.053(2)°, *V* = 1670.67(8) $Å^3$; 13354 reflections measured, 2920 unique (R_{int} = 0.0217). The final wR^2 was 0.0969 (all data). CCDC 778911.

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The crystallographic data has been deposited with the CCDC for compounds (±)-**7** (CCDC 778910), (±)-**10** (CCDC 778911), and (±)-**14** (CCDC 778912), respectively. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retreiving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB12 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.ccdc.cam.ac.uk. For the ORTEPs of (±)-**7** and (±)-**10** see Supporting Information.