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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 aminoglycoside antibiotics, such as kanamycin A (2), which bind to the bacterial 16S ribosomal RNA.1 While the majority of aminoglycoside antibiotics possess a cis-1,3-diaminocyclohexane subunit, certain ‘designer’ analogues, containing a trans-1,3-diaminocyclohexane

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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**ₐ = 6 ± 0.5 µM) compared to human 18S rRNA (**K**ₐ = 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 available⁵ 
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 Cycloadition of 6 with 
nitrosobenzene⁷ 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 ¹H 
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 (\(J \sim 3-4\) Hz) of triplets (\(J \sim 13\) 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 (\(J \sim 4.5, 10.8,\) 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 and by the copper-catalyzed addition of achiral nitroso acyls to achiral dienes in the presence of a chiral ligand. More recently, Jana and Studer have demonstrated a catalytic, enantioselective, and regiodivergent addition of 2-nitrosopyridine to racemic cyclohexadienes. 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 1H 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_{2}O_{5}; orthorhombic, A巴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_{int} = 0.0252). The final wR² 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.\textsuperscript{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.
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 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.

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 CH₂Cl₂ and anhyd DMF were purchased from Aldrich Chemical Company. Reactions were performed in flame-dried glassware under an atmosphere of N₂ unless otherwise noted. Compounds 6,6 (±)-13, and (R)-13¹⁰ 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 CH₂Cl₂ (8 mL), at r.t. under N₂, 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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100 MHz, CDCl₃): 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 C₂₀H₁₆N₂O₃: 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 OsO₄ (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 CH₂Cl₂. 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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100 MHz, CDCl₃): 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 C₂₀H₁₈N₂O₅·0.6 H₂O: 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 H₂O (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.

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100 MHz, CDCl₃): 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.

\[ N -[(1 \ S *, 2 \ S *, 5 \ R *)-2\text{-Hydroxy-5-(phenylamino)cyclohexyl}]phthalimide \ [(\pm)\text{-}10]; \text{Typical Procedure} \]

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\(_2\)O) 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 (\pm)-10 (225 mg, 74%) as a light yellow solid; mp 180-183\(^\circ\)C.

\[ ^1H \text{ NMR (300 MHz, CD}_3\text{OD):} \delta = 1.74-2.05 \text{ (m, 5 H)}, 2.51 \text{ (dt,} \ J = 3.6, 13.1 \text{ Hz, 1 H)}, 3.80 \text{ (br s, 1 H)}, 4.27-4.40 \text{ (m, 2 H)}, 6.59 \text{ (t,} \ J = 7.6 \text{ Hz, 1 H)}, 6.69 \text{ (d,} \ J = 7.6 \text{ Hz, 2 H)}, 7.09 \text{ (t,} \ J = 7.6 \text{ Hz, 2 H)}, 7.74-7.83 \text{ (m, 4 H)}. \]

\[ ^{13}C \text{ NMR (100 MHz, CD}_3\text{OD):} \delta = 29.4, 30.3, 33.4, 54.1, 70.3, 114.6, 118.1, 124.1, 130.2, 133.5, 135.3, 149.2, 170.4; \text{one signal obscured by solvent.} \]


\[ N -[(1 \ S *, 2 \ R *, 3 \ S *, 4 \ S *, 5 \ S *)-2,3,4\text{-Trihydroxy-5-(phenylamino)cyclohexyl}]phthalimide \ [(\pm)\text{-}11] \]

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\(_2\)O) was carried out in a fashion similar to the typical procedure for (\pm)-10. Purification of the crude product by column chromatography (silica gel, EtOAc) gave (\pm)-11 (91 mg, 57%) as a colorless solid; mp 233-235\(^\circ\)C.

\[ ^1H \text{ NMR (400 MHz, CD}_3\text{OD):} \delta = 2.03 \text{ (td,} \ J = 3.8, 13.2 \text{ Hz, 1 H)}, 2.31 \text{ (dt,} \ J = 3.2, 13.2 \text{ Hz, 1 H)}, 3.84 \text{ (dd,} \ J = 3.0, 4.3 \text{ Hz, 1 H)}, 3.99-4.03 \text{ (m, 1 H)}, 4.21 \text{ (t,} \ J = 2.6 \text{ Hz, 1 H)}, 4.34 \text{ (dd,} \ J = 2.6, 10.8 \text{ Hz, 1 H)}, 4.64 \text{ (ddd,} \ J = 3.8, 10.8, 13.2 \text{ Hz, 1 H)}, 6.57 \text{ (t,} \ J = 7.6 \text{ Hz, 1 H)}, 6.62 \text{ (d,} \ J = 8.0 \text{ Hz, 2 H)}, 7.08 \text{ (t,} \ J = 7.6 \text{ Hz, 2 H)}, 7.75-7.83 \text{ (m, 4 H)}. \]
$^{13}$C NMR (100 MHz, CD$_3$OD): $\delta = 30.1, 48.3, 54.9, 70.2, 70.7, 76.4, 114.2, 117.9, 124.1, 130.3, 133.4, 135.4, 149.4, 170.3.$

HRMS (FAB): $m/z [M + H]^+$ calcd for C$_{20}$H$_{21}$N$_2$O$_5$: 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$_2$O (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$_2$S$_2$O$_4$ (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.

$^1$H NMR (300 MHz, CD$_3$OD): $\delta = 1.78$ (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- $d_6$): $\delta = 28.1, 51.6, 53.3, 69.9, 71.9, 73.7, 113.6, 117.4, 123.7, 129.8, 132.7, 135.1, 148.6, 168.8.$

HRMS (FAB): $m/z [M + H]^+$ calcd for C$_{20}$H$_{21}$N$_2$O$_5$: 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$_2$Cl$_2$ (10 mL), DMF (10 mL), and H$_2$O (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$_2$O and
extracted several times with CH$_2$Cl$_2$. The combined extracts were washed with brine, dried (Na$_2$SO$_4$), 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$_2$O$_5$: 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$_2$O$_5$, orthorhombic, space group Aba2,
\[ a = 21.9065(4), \quad b = 28.3819(6), \quad c = 5.80740(10) \text{ Å}, \quad V = 3610.74(12) \text{ Å}^3, \quad Z = 8, \quad d_{\text{calcd}} = 1.436 \text{ mg/m}^3, \quad u = 0.854 \text{ mm}^{-1}, \quad 3175 \text{ unique reflections, } wR2 = 0.0701. \]

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

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.

\[[\alpha]_D^{20} +126.5 \ (c \ 0.429, \ \text{CH}_2\text{Cl}_2).\]

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

\section*{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 \text{CH}_2\text{Cl}_2 (1 mL), at r.t. was added dropwise pyridine (0.10 mL, 1.0 mmol) followed by \text{Ac}_2\text{O} (0.10 mL, 1.1 mmol). The mixture was stirred for 12 h, diluted with \text{CH}_2\text{Cl}_2 and quenched with 1 M HCl. The mixture was extracted several times with \text{CH}_2\text{Cl}_2 and the combined extracts were washed with brine, dried (Na\textsubscript{2}SO\textsubscript{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.

\section*{(±)-18}

\(^1\text{H} \text{NMR} (400 \text{ MHz, } \text{CDCl}_3): \delta = 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 \text{ Hz}, \ 1 \ H), \ 6.89 \ (br \ t, \ J = 7.2 \text{ Hz}, \ 1 \ H), \ 7.39-7.55 \ (m, \ 5 \ H), \ 7.70-7.80 \ (m, \ 4 \ H). \]
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 20.9, 26.9, 47.3, 48.9, 72.2, 73.7, 123.5, 128.4, 128.5, 128.9, 129.2, 131.5, 134.3, 134.5, 135.0, 168.2, 170.7\); one CO signal not observed.

HRMS (ESI): \(m/z [M + Na]^+\) calcd for C\(_{24}\)H\(_{20}\)N\(_2\)NaO\(_6\): 455.1219; found: 455.1216.

(±)-17

\(^1\)H NMR (partial, CDCl\(_3\)): \(\delta = 2.45\) (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

\(^1\)H NMR (partial, CDCl\(_3\)): \(\delta = 2.31\) (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 \(-30^\circ\)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\(_4\)Cl (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\(_2\)SO\(_4\)), 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.

\(^1\)H NMR (400 MHz, CD\(_3\)OD): \(\delta = 1.75\) (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, \(J = 12.8, 9.4, 2.8\) Hz, 1 H).
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$_3$OD): $\delta$ = 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$_2$NaO$_5$: 415.1270; found: 415.1274.

$(2\,R\,)-2$-Hydroxy-\,N-\,[$(1\,R,4\,R,5\,R\,)-4$-hydroxy-5-phthalimidocyclohexyl]-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 $^1$H 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.

$^1$H NMR (300 MHz, CD$_3$OD): $\delta$ = 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.
¹³C NMR (75 MHz, CD₃OD): 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.


(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.

[α]₀₂⁰ -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_{2}O_{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) Å³; 21439 reflections measured, 2775 unique (R_{int} = 0.0603). The final wR² was 0.1064 (all data). CCDC 778910.
ORTEP drawing of (±)-10 with crystallographic numbering. C_{20}H_{20}N_{2}O_{3}; monoclinic, \textit{P}2\textit{1}/c, \textit{Z} = 4, \textit{a} = 14.9286(4) Å, \textit{b} = 6.8883(2) Å, \textit{c} = 16.4514(5) Å, \beta = 99.053(2)^{\circ}, \textit{V} = 1670.67(8) Å^{3}; 13354 reflections measured, 2920 unique (\textit{R}_{\text{int}} = 0.0217). The final \textit{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/retrieving.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.