De novo synthesis of polyhydroxyl aminocyclohexanes†

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The syntheses of 12 stereochemically diverse polyhydroxyl aminocyclohexane ("aminocyclitols") derivatives are described. These short syntheses require 2–5 steps from *N*-(2,4-cyclohexadien-1-yl)phthalimide, which is prepared in two steps from tricarbonyl(cyclohexadienyl)iron(1+). The relative stereochemistries of the aminocyclitols were assigned by ^{1}H NMR spectroscopy as well as X-ray diffraction analysis.

Introduction

Polyhydroxyl aminocyclohexanes ("aminocyclitols", *cf.* Fig. 1) and derivatives are important biological entities. For example, 2-deoxy-*scyllo*-inosamine (**1**) is an intermediate in the biosynthesis of deoxystreptamine, a component of the aminoglycoside antibiotics,[1] while the isomeric 5-amino-1,2,3,4-cyclohexanetetraols **2**[2] and **3**[3] were found to be inhibitors of α-glucosidase and α-galactosidase (IC_{50} = 12.5 and 20 μM, respectively). Similarly, 1-amino-2,5-cyclohexanediols are structural components of potential antibiotics such as **5**.[4] A variety of synthetic routes to aminocyclitols have been reported starting from quercitols (deoxyinositols),[2,3] from inositols *via* deoxygenation,[5] from carbohydrates *via* Ferrier carbocyclic ring-closure,[4,6] *via* 6-*exo* radical cyclization of carbohydrate derived oximes,[7] and from chiral 1,7-octadienes *via* ring-closing metathesis.[8] We herein report the *de novo* synthesis of a series of aminocyclitols from the readily available[9] tricarbonyl(cyclohexadienyl)iron(1+) cation.

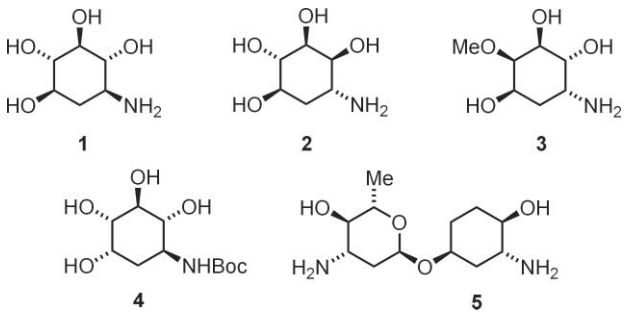
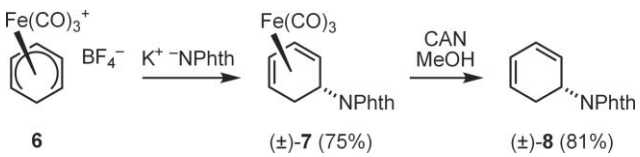


Fig. 1 Representative polyhydroxyl aminocyclohexanes.

Results and discussion

Reaction of tricarbonyl(cyclohexadienyl)iron(1+) **6** with potassium phthalimide proceeded *via* attack at the dienyl terminus to afford the complex (±)-**7** (Scheme 1). Decomplexation of **7** with Ce^{4+} gave the free ligand *N*-(2,4-cyclohexadien-1-yl)phthalimide, (±)-**8**. The structures of **7** and **8** were assigned on the basis of their NMR spectral data. In particular, the ^{1}H NMR signals for **7** at δ 2.77, 3.13, 5.53 and 5.67 ppm and the ^{13}C NMR signals at δ 57.1, 58.2, 86.0 and 86.7 ppm correspond to the hydrogens and carbons of an η^4-bound cyclohexadiene ligand.[10] Similarly, the ^{1}H NMR spectrum of **8** exhibits two signals for the diastereotopic methylene protons at δ 2.38 and 2.78 ppm while the ^{13}C NMR spectrum of **8** exhibits signals at δ 27.0 and 47.9 ppm corresponding to the two sp^3 hybridized carbons.



Scheme 1 Preparation of (cyclohexadienyl)phthalimide.

Cycloaddition of **8** with singlet oxygen gave a separable mixture of endoperoxides (±)-**9** and (±)-**10** (eqn (1)). The relative stereochemistry of **9** and **10** were tentatively assigned by comparison of their ^{1}H NMR spectral data. For each, assignment of the signals for the diastereotopic methylene protons (H^3 and $H^{3'}$) was facilitated by the magnitude of their vicinal couplings to H^2; the *syn*-coupling (*ca.* 0° dihedral angle) is larger than the *anti*-coupling (*ca.* 120° dihedral angle).[11] The signal for $H^{3'}$ of **9** appears upfield of that for **10**, while the signal for H^3 of **9** appears downfield of that for **10**. These relative chemical shifts are due to the anisotropic effect of the olefin functionality. These tentative stereochemical assignments were eventually corroborated by

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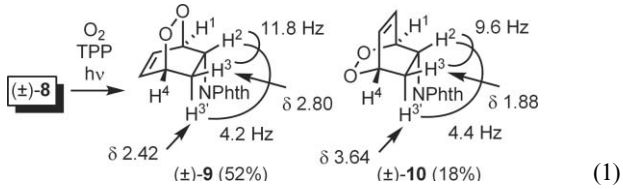
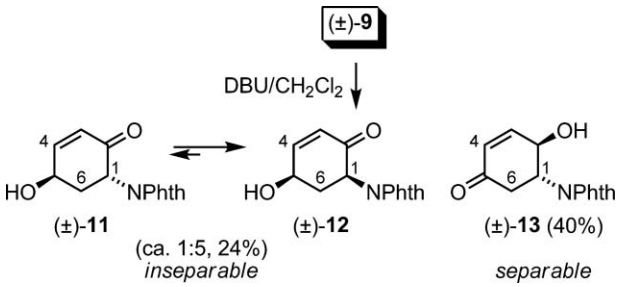
† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of new compounds and ORTEPs for **9**, **10**, **18**, **33**, **34**, and **35**. CCDC reference numbers 767841, 767844–767848. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c004730a

single crystal diffraction analysis of each.‡ The facial selectivity of this cycloaddition reaction (*i.e.* the major product arises *via* approach on the face opposite to the phthalimide substituent), is similar to that previously reported for the cycloaddition of nitrosobenzene and 3-methyl-5-phenyl-1,3-cyclohexadiene.[12]



(1)

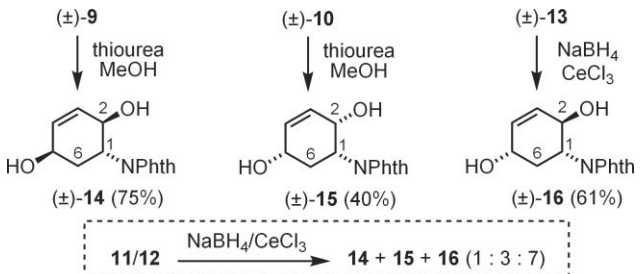
Kornblum–DeLaMare rearrangement[13] of **9** with DBU gave a mixture of **11**–**13** (eqn (2)). While cyclohexenone **13** could be obtained pure by chromatographic separation, the epimers **11** and **12** were only characterized as a mixture. The structure of **13** was assigned by comparison of its NMR spectral data with that of 5-azido-4-(triisopropylsilyloxy)-2-cyclohexen-1-one.[14] The structures of **11**/**12** were assigned on the basis of their ^{1}H NMR spectral data. In particular, the signals for the diastereotopic protons (H-6/H-6′) of **11** (δ 2.26 and 3.02 ppm) and **12** (δ 2.47 and 2.81 ppm) appear upfield of those for **13** (δ 2.67 and 3.43 ppm) while the signals for H-1 of **11** (δ 5.34 ppm) and **12** (δ 4.98 ppm) appear downfield of the signal for H-1 of **13** (δ 4.65 ppm). These relative chemical shifts are due to either the presence or absence of a neighboring carbonyl group. Furthermore, the relative stereochemistry of the substitutents at C-1/C-5 of **11** (*trans*-) and **12** (*cis*-) were assigned on the based on coupling patterns for H-6′; (**11**, dt, J = 3.6 and 13.2 Hz; **12**, td, J = 11.4 and 14.4 Hz). The smaller doublet coupling for **11** (compared to **12**) is consistent with an axial–equatorial relative stereochemistry of H-5/H-6′ in this structure.



(2)

The regioisomeric cyclohexenones arise due to deprotonation at either position adjacent to the endoperoxide; *i.e.* deprotonation of H-1 results in the formation of **11**/**12** while deprotonation of H-4 (see eqn (1)) results in formation of **13**. The stereoisomers **11** and **12** presumably are the result of base catalyzed epimerization α to the carbonyl; the diequatorial stereoisomer **12** being more stable than the axial–equatorial stereoisomer **11**.

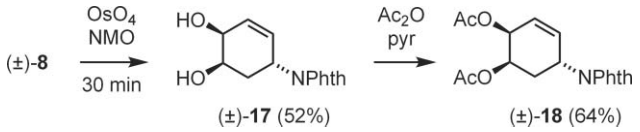
Thiourea reduction of **9** gave (±)-**14** in good yield (Scheme 2), similarly reduction of **10** with thiourea gave (±)-**15**, albeit in attenuated yield (40%). Alternative reduction conditions (Zn/HOAc,[15a] KI/HOAc/H_2O,[15b] or $NaBH_4$/MeOH[15c]) did not result in improved yield. Reduction of **13** under Luche conditions[16] gave (±)-**16**, while reduction of the mixture of **11**/**12** gave a mixture of (±)-**14**, (±)-**15** and (±)-**16** (*ca.* 1 : 3 : 7 by ^{1}H NMR integration). Separation of this mixture by preparative TLC gave additional **16** (20%). The structures of **14**–**16** were assigned on the basis of their ^{1}H NMR spectral data. In particular, each of these *N*-(3-cyclohexen-1-yl)phthalimides is anticipated to adopt a half-chair conformer in which the bulky phthalimide substituent occupies a pseudo-equatorial orientation. The signals for the H-6_{ax} proton of **15** and **16** appear as a doublet of doublet of doublets (**15**, J = 10.8, 12.8 and 14.4; **16**, J = 10.0, 12.0 and 13.2). These three large couplings are due to the diaxial relative orientations of H-6_{ax} with respect to H-1 and H-5 in both **15** and **16** as well as the geminal coupling to H-6_{eq}). In comparison, the signal for H-6_{ax} of **14** appears as a doublet of triplets (dt, J = 4.8 and 13.6); the smaller coupling corresponds to the axial–equatorial relative orientation of H-6_{ax} and H-5. The signals for H-1 of **14** and **16** appear as a doublet of doublet of doublets (**14**, J = 3.2, 10.0 and 13.6; **16**, J = 3.0, 9.2 and 13.6); the *ca.* 9–10 Hz coupling for each is indicative of a diaxial orientation of the H-1 and H-2 protons.



Scheme 2 Preparation of stereoisomeric (2,5-dihydroxy-3-cyclohexen-1-yl)phthalimides.

Brief exposure (30 min) of (±)-**8** to catalytic dihydroxylation conditions gave the diol (±)-**17** (Scheme 3), whose structure was

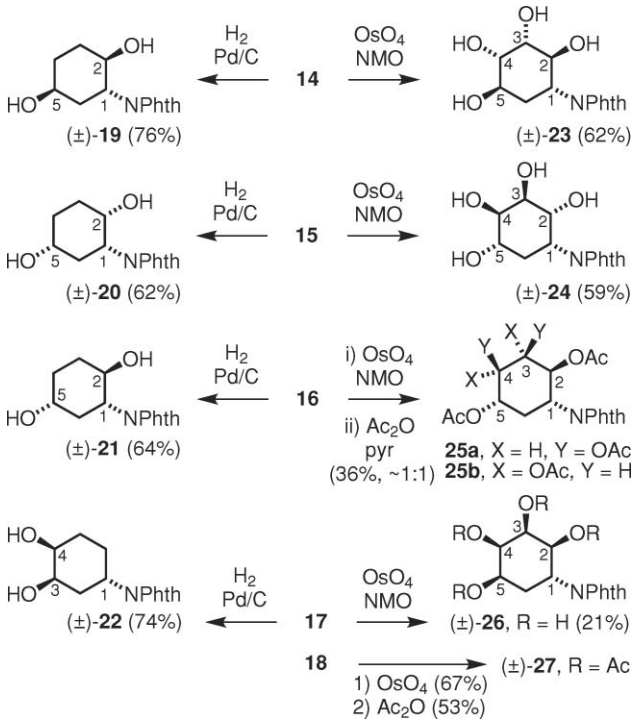
‡ The cif files for **9**, **10**, **18**, **33**, **34**, and **35** have been deposited with the CCDC.† **9**: CCDC # 767847; **10**: CCDC # 767848; **18**: CCDC # 767846; **25a**: CCDC # 767841; **33**: CCDC # 768802; **34**: CCDC # 767845; **35**: CCDC # 767844. The crystal structures for **26**, **33** and **34** are all heavily disordered. The nature of the disorder is that the H-bonding networks have a quasi-mirror symmetry and thus can accommodate both enantiomers. These three crystals are centrosymmetric, so they are racemates on the macro level; however, on the micro level, the two enantiomeric forms randomly substitute each other in H-bonded networks. Crystal structure data for compound (±)-**26**: $C_{14}H_{15}NO_6$; M = 293.27; monoclinic, P21/n; a = 12.0696(6), b = 6.9279(4), c = 15.8178(8) Å, β = 108.536(2)°; U = 1254.02(11) Å^3; T = 100(2) K; Z = 4; 10253 reflections measured, 2215 unique (R_{int} = 0.0278). The final wR^2 was 0.2512 (all data). CCDC # 768801. Crystal structure data for compound (±)-**25a**: $C_{22}H_{23}NO_{10}$; M = 461.41; monoclinic, $C2/c$; a = 27.7646(12), b = 11.6104(5), c = 16.3768(7) Å, β = 123.535(2)°; U = 4400.5(3) Å^3; T = 100(2) K; Z = 8; 17563 reflections measured, 3843 unique (R_{int} = 0.0431). The final wR^2 was 0.1035 (all data). CCDC # 767841. Crystal structure data for compound (±)-**37**: $C_{22}H_{23}NO_{10}$; M = 461.41; monoclinic, P21/n; a = 8.8800(3), b = 10.6102(3), c = 23.7595(8) Å, β = 91.799(2)°; U = 2237.48(12) Å^3; T = 100(2) K; Z = 4; 18364 reflections measured, 3972 unique (R_{int} = 0.0193). The final wR^2 was 0.0839 (all data). CCDC # 767842. Crystal structure data for compound (±)-**38**: $C_{22}H_{23}NO_{10}$; M = 461.41; monoclinic, P21/c; a = 7.3527(2), b = 21.4079(7), c = 14.1359(5) Å, β = 93.921(2)°; U = 2219.87(12) Å^3; T = 100(2) K; Z = 4; 17338 reflections measured, 3890 unique (R_{int} = 0.0265). The final wR^2 was 0.1019 (all data). CCDC # 767843.



Scheme 3 Dihydroxylation of (cyclohexadienyl)phthalimide **8**.

tentatively assigned on the basis of its ^{1}H NMR spectral data. In particular, the signal for the axial H-6′ proton of **17** appears at δ 2.35 ppm (ddd, J = 2.0, 10.2 and 13.6 Hz); the small coupling corresponds to the axial–equatorial relative orientation of H-6′ and H-5. Reaction of **17** with acetic anhydride gave the diacetate (±)-**18**. The relative configuration of **18** was assigned on the basis of single crystal X-ray diffraction,† which consequently corroborated the structural assignment of **17**. Dihydroxylation of **8** occurs more rapidly at the olefin remote to the electron withdrawing phthalimide substituent.

Catalytic reduction of **14**, **15**, **16** and **17** gave the saturated *N*-(dihydroxycyclohexyl)phthalimides (±)-**19**, (±)-**20**, (±)-**21**, and (±)-**22** (Scheme 4). The structures for diols **19–22** were assigned on the basis of the structures of each precursor; the ^{1}H NMR spectra for **19–22** are consistent with these assignments (*vide infra*).



Scheme 4 Hydrogenation and dihydroxylation of *N*-(dihydroxycyclohexenyl)phthalimides.

Osmium catalyzed dihydroxylation of **14** or **15** gave a single tetraol (±)-**23** or (±)-**24**, while dihydroxylation of (±)-**17** gave (±)-**26**, albeit in low yield (Scheme 4). We attribute this lower yield to the diminished solubility of the product under the reaction conditions. In comparison, dihydroxylation of the diacetate (±)-**18** proceeds in moderate yield; the product was characterized as the tetraacetate (±)-**27**. In contrast to these results, dihydroxylation of **16**, followed by peracetylation, gave a nearly equimolar mixture of tetraacetates (±)-**25a** and **b**. The structural assignment for **26** was determined by single crystal X-ray diffraction analysis (Fig. 2)†‡ which indicated that the C-1 phthalimide and the C-2 and C-5 hydroxyls are equatorial and the C-3 and C-5 hydroxyl groups are axial. Tetraol **23** was shown to be diastereomeric with **26** by NMR spectroscopy, and was thus assigned a structure which is consistent with this relationship and consistent with *syn*-dihydroxylation. The structures of **24**, **25a**, **25b** and **27** were assigned on the basis of their ^{1}H NMR spectral data and the stereochemistry of their presursors (*vide infra*), and the structure of **25a** was confirmed by single crystal X-ray diffraction analysis (Fig. 3). In accord with the selectivity noted by Kishi, *et al.*,[17] dihydroxylation of **14** and **15** occurred preferentially on the face of the olefin opposite to the adjacent hydroxyl groups. In the case of **16**, the stereodirection effect of the two resident hydroxyls is mismatched, and thus a mixture of two diastereomeric tetraacetates is isolated. For diol **17** and diacetate **18**, dihydroxylation occurs on the face opposite to phthalimide substitutent. It should be noted that the directing influence of the phthalimide group is greater than that for the C-4 hydroxyl group.

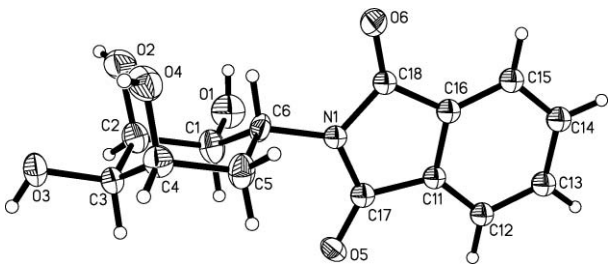


Fig. 2 ORTEP of (±)-**26** (arbitrary atomic numbering).

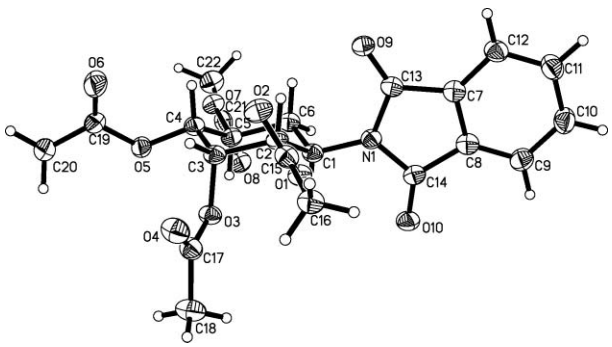
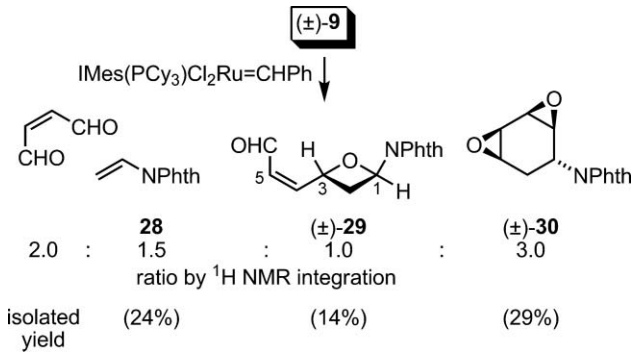


Fig. 3 ORTEP of (±)-**25a** (arbitrary atomic numbering).

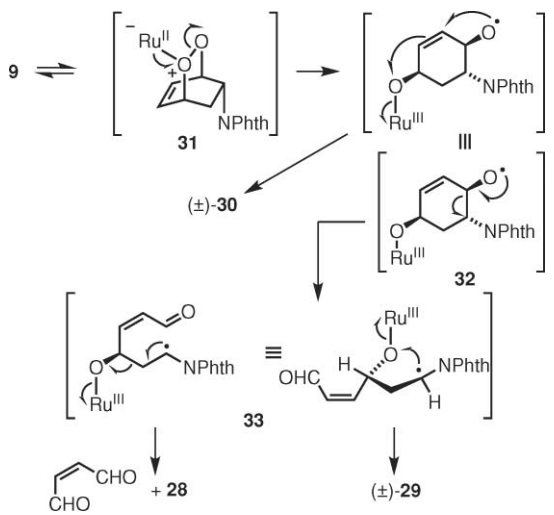
Treatment of the major endoperoxide **9** with Grubbs' 2nd generation catalyst,[18] in the absense of any additional olefin, proceeded rapidly with the complete disappearance of starting material (*ca.* 30 min). Analysis of the crude product mixture by ^{1}H NMR spectroscopy indicated this to be a mixture of *Z*-2-butendial, *N*-vinylphthalimide (**28**), oxetane (±)-**29** and bisepoxide (±)-**30** in a ratio of *ca.* 2 : 1.5 : 1 : 3 (Scheme 5). Purification of this mixture by column chromatography gave **28**, **29** and **30**. While 2-butendial was not recovered after chromatography, it was identified in the crude reaction mixture by comparison to its literature ^{1}H NMR spectral data.[19] *N*-Vinylphthalimide (**28**) was identified by comparison to its literature mp and NMR spectral data.[20] The structural assignment for **29** was based on its ^{1}H NMR



Scheme 5 Ru-catalyzed rearrangement of **9**.

spectral data. In particular, signals at δ 10.15 (d, $J = 7.2$ Hz), 6.88 (ddd, $J = 0.8$, 6.8 and 11.5 Hz) and 6.07 ppm (dd, $J = 7.2$ and 11.6 Hz) correspond to the 3-oxo-1-*Z*-butenyl sidechain. The signals at 6.33 (q, $J = 7.2$ Hz) and 6.40 ppm (ddd, $J = 1.2$, 5.0 and 8.3 Hz) correspond to H-3 and H-1 of the oxetane ring; similar chemical shifts have been reported for oxetane based nucleoside analogs.[21] The structural assignment for **30** was also based on its NMR spectral data. In particular, the four relatively narrow one proton signals in the ^{1}H NMR spectrum of **30** at δ 3.26, 3.30, 3.54–3.56 and 3.58–3.60 ppm correspond to the four epoxide methine protons. These chemical shifts are similar to other cyclohexane bisepoxides.[22]

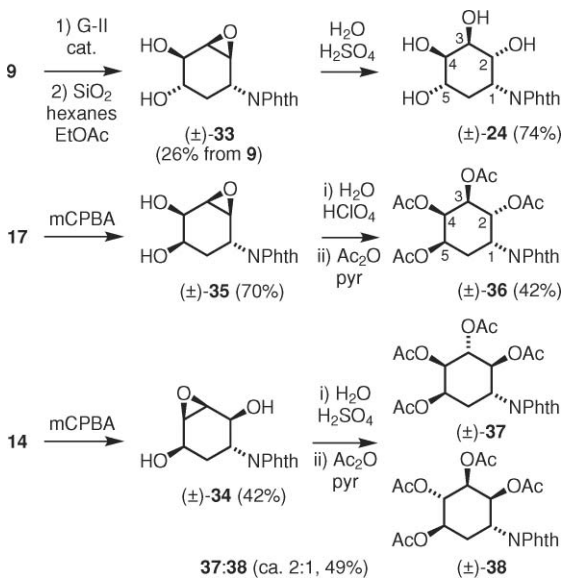
The metal-mediated rearrangement of 1,4-epiperoxides (endoperoxides), including the use of Ru(II) reagents, has previously been reported.[23] An inner-sphere radical mechanism may be proposed to account for formation of the products **27–30** (Scheme 6). Complexation of a coordinatively unsaturated Ru(II) species with **9**, at the less sterically hindered oxygen, generates **31**. One electron exchange effects opening of the weak O–O bond to give the oxyradical **32**. Interaction with the double bond serves to generate the bisepoxide **30**. Alternatively, C–C bond scission of **32** results in the nitrogen-stabilized radical species **33**. Radical **33** may undergo further C–C cleavage to generate **27** and **28**, or reaction of the carbon radical at oxygen generates the oxetane ring **29**. A similar mechanism has been proposed to account



Scheme 6 Proposed mechanism for Ru-catalyzed rearrangement of **9**.

for the formation of β-lactones from the keto endoperoxide of phenol.[24]

Allowing the crude product from the reaction of **9** with Grubbs' catalyst to stand on a column of silica gel overnight led to the isolation of the epoxydiol (±)-**33** (Scheme 7). This product presumably arises *via* selective hydrolysis of the bisepoxide **30**. Treatment of **14** or **17** with mCPBA gave a single epoxide in each case [(±)-**34** or (±)-**35**, respectively, Scheme 7]. The structural assignments for **33–35** are based on single crystal X-ray diffraction analysis of each.†‡ Notably, **34** and **35** arise *via* epoxidation on the same face of the olefin as the adjacent hydroxyl group.[25] Hydrolysis of **33** gave tetraol (±)-**24**, while hydrolysis/acetoxylation of **35** gave tetraacetate (±)-**36**. In contrast, hydrolysis/acetoxylation of **34** gave a mixture of diastereomeric tetraacetates (±)-**37** and (±)-**38** (*ca.* 2 : 1 ratio by ^{1}H NMR integration). Separation of the mixture of **37**/**38** was aided by slow recrystallization from ethyl acetate. The two distinct crystalline forms were manually separated by tweezers. Tetraol **24** was identified by comparison of its spectral data with the sample prepared by dihydroxylation of **15** (*vide supra*). The products **36–38** are based on their NMR spectral data (*vide infra*); and the assignments for **37** and **38** were corroborated by single crystal X-ray diffraction analysis of each (Fig. 4 and 5, respectively).†‡ The products **24**, **36** and **38** arise by a diaxial ring opening of the epoxide ring, while hydrolysis/acetoxylation of **34** *via* a diequatorial, boat-like transition state leads to **37**.



Scheme 7 Generation of aminocyclitol tetraacetates *via* epoxidation and hydrolysis.

The structural assignments for many of the polyhydroxyl cyclohexylphthalimides are based on their ^{1}H NMR spectral data. In particular, for those compounds in which the C-1 phthalimide and the C-5 hydroxyl/acetoxy are *cis* (*i.e.* diequatorial; **20**, **21**, **24** and **25a**/**b**) the signal for H-6$_{ax}$ appears as either a quartet (J ~ 12 Hz) or as a doublet of triplets ($J = 10.9$ and 12.9). Conversely, for those compounds in which the C-1 phthalimide and the C-5 hydroxyl/acetoxy are *trans* (**19**, **23**, **26**, **27**, **36**, **37** and **38**), the signal for H-6$_{ax}$ appears as a doublet (J ~ 2.4) of triplets (J ~ 13). For structures in which the C-1 phthalimide and the C-2

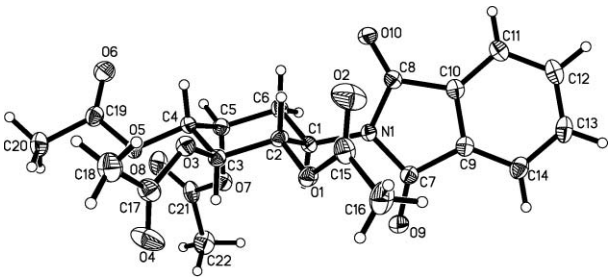


Fig. 4 ORTEP of (±)-**37** (arbitrary atomic numbering).

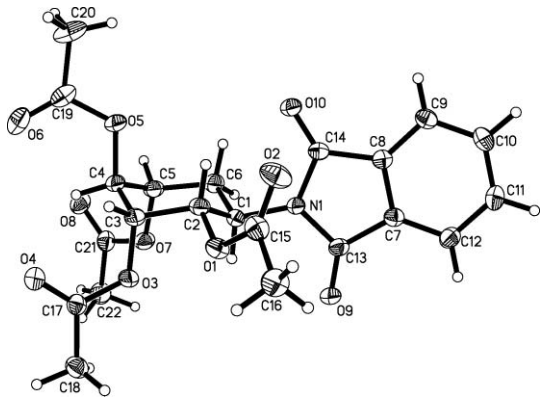


Fig. 5 ORTEP of (±)-**38** (arbitrary atomic numbering).

hydroxyl/acetoxy are *trans* (*i.e.* diequatorial; **19**, **21**, **25a/b**, **27**, **37** and **38**) the signal for H-1 appears as either a doublet of doublet of doublets (J ~ 4.5, 10.5 and 13 Hz) or as a doublet (J ~ 4.2) of triplets (J ~ 12). Conversely, for those compounds in which the C-1 phthalimide and the C-2 hydroxyl/acetoxy are *cis* the signal for H-1 appears as a broad doublet (**20**, $J = 14$) or a doublet of doublet of doublets (**24** or **36**; J ~ 3, 4 and 13 Hz). For the tetraacetates in which H-2 is axial (**25a**, **25b**, **37** or **38**), the magnitude of the coupling between H-2 and H-3 allows for assignment of their relative stereochemistry (diaxial, J_{H2-H3} ~ 10 Hz; axial–equatorial, J_{H2-H3} ~ 3–4 Hz). Similarly, for tetraols or tetraacetates in which H-5 is axial (**24**, **25a**, **25b**), the stereochemistry of the C-4 substitutent may be assigned axial or equatorial based on the magnitude of the coupling between H-4 and H-5.

Conclusions

By sequential oxidation ($^1O_2$, dihydroxylation and/or epoxidation), rearrangement, reduction, or hydrolysis reactions, a single (cyclohexadienyl)phthalimide can be used to prepare a series of stereochemically diverse polyhydroxy aminocyclohexanes. The structural assignments of these products are based on their NMR spectral data as well as X-ray diffraction in certain cases.

Experimental

General methods

All reactions involving moisture or air sensitive reagents were carried out under an nitrogen atmosphere in oven-dried glassware with anhydrous solvents. Purifications by chromatography were carried out using silica gel 60 (40–63 μm). NMR spectra were recorded on either a Varian Mercury+ 300 MHz or a Varian UnityInova 400 MHz instrument. $CDCl_3$, CD_3OD, d_6-acetone and d_6-DMSO were purchased from Cambridge Isotope Laboratories. ^1H NMR spectra were calibrated to 7.27 ppm for residual $CHCl_3$, 3.31 ppm for CD_2HOD, 2.05 ppm for d_5-acetone or 2.50 ppm for d_5-DMSO. ^{13}C NMR spectra were calibrated from the central peak at 77.23 ppm for $CDCl_3$, 49.15 ppm for CD_3OD, 29.92 ppm for d_6-acetone or 39.51 for d_6-DMSO. Coupling constants are reported in Hz. Elemental analyses were obtained from Midwest Microlabs, Ltd., Indianapolis, IN, and high-resolution mass spectra were obtained from the University of Nebraska Center for Mass Spectrometry.

Tricarbonyl-(5-phthalimido-1,3-cyclohexadiene)iron (±)-7

To a solution of **6** (920 mg, 2.95 mmol) in dry CH_2Cl_2 (40 mL), at room temperature under N_2, was added solid potassium phthalimide (820 mg, 4.43 mmol). The mixture was stirred for 5 h, and then quenched with water 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 (SiO_2, hexane–ethyl acetate = 6 : 1) to afford (±)-**7** (807 mg, 75%) as a light yellow solid (Found: C, 56.10; H, 3.18. Calcd for $C_{17}H_{11}O_5Fe$: C, 55.92; H, 3.04.); mp 166–169 °C; δ_H (400 MHz, $CDCl_3$) 2.00 (1H, br d, $J = 15.1$ Hz, H-6α), 2.31 (1H, ddd, $J = 4.2$, 11.4 and 15.1, H-6β), 2.77 (1H, ddd, $J = 1.0$, 3.2 and 6.3, H-4), 3.15–3.11 (1H, m, H-1), 4.80 (1H, td, $J = 3.7$ and 11.5, H-5), 5.53 (1H, t, $J = 5.6$, H-3), 5.67 (1H, t, $J = 5.7$, H-4) and 7.60–7.83 (4H, m, Phth); δ_C (100 MHz, $CDCl_3$) 27.3 (C-6), 48.1 (C-5), 57.1, 58.2 (C-1, C-4), 86.0, 86.7 (C-2, C-3), 123.3, 132.1, 134.2 (3 × Phth), 168.2 (N–C=O) and 211.4 (M–CO).

N-(2,4-Cyclohexadien-1-yl)phthalimide (±)-8

To a stirring solution of iron complex **7** (800 mg, 2.19 mmol) in methanol (110 mL) was added solid ceric ammonium nitrate (360 mg, 6.56 mmol). The mixture was stirred for 2 h and then quenched with water 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 (SiO_2, hexane–ethyl acetate = 4 : 1) to give (±)-**8** (400 mg, 81%) as a colorless solid (Found: C, 74.60; H, 4.94; N, 6.24. Calcd for $C_{14}H_{11}O_2$: C, 74.65; H, 4.92; N, 6.22); mp 138–140 °C; δ_H (400 MHz, $CDCl_3$) 2.38 (1H, ddd, $J = 5.6$, 10.0 and 17.2, H-6), 2.78 (1H, tdd, $J = 3.1$, 15.2 and 17.6, H-6′), 5.20 (1H, tdd, $J = 2.9$, 9.6 and 15.2, H-1), 5.68 (1H, dd, $J = 3.0$ and 9.6, CH=CH), 5.89–6.10 (3H, m, CH=CH) and 7.71–7.86 (4H, m, Phth); δ_C (100 MHz, $CDCl_3$) 27.5 (C-6), 45.9 (C-1), 123.2 (Phth), 123.7, 125.3, 125.5, 125.6 (C-2, C-3, C-4, C-5), 132.1, 133.9 (2 × Phth) and 176.2 (N–C=O).

Singlet oxygen cycloaddition

To a 100 mL two-necked round-bottomed flask, equipped with a condenser, was added a solution of (±)-**8** (1.00 g, 4.44 mmol) in $CHCl_3$ (16 mL) and tetraphenylporphine (138 mg, 5 mol%). The deep purple solution was stirred at 0 °C and irradiated with a 60 W tungsten-halogen lamp for 8 h while ultrapure O_2 was bubbled through the solution. The reaction mixture was concentrated under reduced pressure and the residue purified by

column chromatography (SiO_2, hexane–ethyl acetate = 4 : 1) to give (±)-**9** (593 mg, 52%) as a colorless solid. Further elution (hexane–ethyl acetate = 3 : 1) gave (±)-**10** (201 mg, 18%) as a colorless solid.

***N*-(8,9-Dioxobicyclo[2.2.2]oct-5-en-2-yl)phthalimide (±)-9.** (Found: C, 65.45; H, 4.39. Calcd for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31); mp 155–157 °C; δ_H (400 MHz, $CDCl_3$) 2.42 (1H, ddd, J = 2.0, 4.4 and 13.6, H-3), 2.80 (1H, ddd, J = 4.0, 9.6 and 13.6, H-3′), 4.84–4.98 (3H, m, H-1, H-2 and H-4), 6.65 (1H, ddd, J = 1.6, 6.0 and 8.0, C*H*=CH), 6.88 (1H, ddd, J = 1.6, 6.0 and 8.0, CH=C*H*), 7.71–7.74 and 7.79–7.83 (4H total, AA′BB′, Phth); δ_C (100 MHz, $CDCl_3$) 28.5 (C-3), 45.9 (C-2), 71.2 (C-1 or C-4), 123.5, 129.5, 131.6, 134.0, 134.5 (*C*H=*C*H and Phth), and 168.3 (N–C=O); one peak obscured by solvent.

***N*-(8,9-Dioxobicyclo[2.2.2]oct-5-en-2-yl)phthalimide (±)-10.** (Found: C, 65.46; H, 4.34. Calcd for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31); mp 235–240 °C; δ_H (300 MHz, $CDCl_3$) 1.88 (1H, ddd, J = 1.9, 11.8 and 13.8, H-3), 3.64 (1H, td, J = 4.2 and 13.8, H-3′), 4.41 (1H, ddd, J = 1.8, 4.5 and 12.0, H-2), 4.67 (1H, qd, J = 1.7 and 6.3, H-1), 4.89 (1H, qdd, J = 1.8, 3.6 and 5.7, H-4), 6.75–6.87 (2H, m, H-5 and H-6), 7.70–7.74 and 7.78–7.83 (4H total, AA′BB′, Phth); δ_C (75 MHz, $CDCl_3$) 21.0 (C-3), 47.2 (C-2), 70.9, 75.2 (C-1, C-4), 123.5, 130.8, 132.0, 134.0, 134.3 (C-5, C-6 and Phth) and 168.9 (N–C=O).

N-(5-Hydroxy-2-oxo-3-cyclohexen-1-yl)phthalimide 11/12 and *N*-(2*S**-hydroxy-5-oxo-3-cyclohexen-1*S**-yl)phthalimide (±)-13

To a solution of cyclic peroxide **9** (690 mg, 2.68 mmol) in dry CH_2Cl_2 (25 mL) at room temperature was added dropwise 1,8-diazabicyclo[5.4.0]undec-7-ene (0.70 mL, 4.0 mmol). The mixture was stirred for 15 min, diluted with additional CH_2Cl_2 (20 mL), neutralized with amberlite IRC–76, filtered and concentrated. Purification of the residue by column chromatography (SiO_2, hexane–ethyl acetate = 1 : 1) gave (±)-**13** (278 mg, 40%) as a colorless solid, followed by a mixture of **11**/**12** (164 mg, 24%, mp 192–195 °C) as a colorless solid.

(±)-**13**: (Found: C, 65.01; H, 4.31. Calcd for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31); mp 175–177 °C; δ_H (400 MHz, $CDCl_3$) 2.67 (1H, dd, J = 4.8 and 16.4, H-6_{eq}), 3.43 (1H, dd, J = 13.6 and 16.4, H-6_{ax}), 4.65 (1H, ddd, J = 4.8, 10.0 and 14.0, H-1), 5.33 (1H, br d, J = 10.4, H-2), 6.11 (1H, d, J = 10.0, H-4), 7.02 (1H, dd, J = 1.6 and 10.0, H-3) and 7.78–7.89 (4H, m, Phth); δ_C (75 MHz, $CDCl_3$) 40.2 (C-6), 53.6 (C-1), 67.7 (C-2), 123.8 (Phth), 129.6 (C-4), 131.8, 134.6 (2 × Phth), 152.3 (C-3), 168.5 (N–C=O) and 196.4 (C=O).

12: δ_H (400 MHz, CD_3OD) 2.43–2.51 (1H, m, H-6), 2.81 (1H, td, J = 11.4 and 14.4, H-6′), 4.75–4.84 (1H, m, H-5), 4.98 (1H, dd, J = 5.0 and 14.6, H-1), 6.09 (1H, dd, J = 2.4 and 10.8, H-3), 7.12 (1H, d, J = 10.4, H-4) and 7.78–7.96 (m, 4H, Phth).

11: δ_H (partial, 400 MHz, CD_3OD) 2.26 (1H, br d, J = 13.2, H-6), 3.02 (1H, dt, J = 3.6 and 13.2, H-6′), 4.58–4.60 (1H, m, H-5) and 5.35 (1H, dd, J = 4.8 and 13.2, H-1).

N-(2*R**,5*S**-Dihydroxy-3-cyclohexen-1*S**-yl)phthalimide (±)-14

To a solution of **9** (25 mg, 0.097 mmol) in methanol (1.5 mL) at room temperature under nitrogen was added solid thiourea (7.0 mg, 0.097 mmol). The mixture was stirred for 15 h, then concentrated under vacuum and the residue purified by column chromatography (SiO_2, hexane–ethyl acetate = 3 : 1) to afford (±)-**14** (19 mg, 75%) as a colorless solid (Found: C, 64.92; H, 5.11. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05); mp 180–183 °C; δ_C (400 MHz, $CDCl_3$) 1.97 (1H, br d, J = 14.0, H-6_{eq}), 2.28 (1H, br s, O*H*), 2.35 (1H, br s, O*H*), 2.82 (1H, dt, J = 4.8 and 13.6, H-6_{ax}), 4.42 (1H, br s, H-5), 4.58 (1H, ddd, J = 3.2, 10.0 and 13.6, H-1), 4.84 (1H, br d, J = 9.2, H-2), 5.92 (2H, narrow m, C*H*=C*H*), 7.70–7.74 and 7.81–7.85 (4H total, AA′BB′, Phth); δ_C (100 MHz, CD_3OD) 35.1 (C-6), 51.5, 65.2, 68.5 (C-1, C-2 and C-5), 124.1, 130.1, 133.5, 134.8, 135.4 (*C*H=CH and Phth) and 170.2 (N–C=O).

N-(2*S**,5*R**-Dihydroxy-3-cyclohexen-1*S**-yl)phthalimide (±)-15

Cyclic peroxide **10** (0.10 g, 0.40 mmol) was reduced with thiourea in a fashion similar to the preparation of **14**. The reaction mixture was concentrated under vacuum and the residue was purified by column chromatography (SiO_2, hexane–ethyl acetate = 1 : 4) to give (±)-**15** (40 mg, 40%) as a colorless solid (Found: C, 64.77; H, 5.08. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05); mp 167–174 °C; δ_H (400 MHz, $CDCl_3$) 2.21 (1H, br d, J = 12.8, H-6_{eq}), 2.26 (1H, d, J = 7.2, O*H*), 2.81 (1H, d, J = 8.8, O*H*), 2.85 (1H, ddd, J = 10.8, 12.8 and 14.4, H-6_{ax}), 4.17–4.23 (1H, m), 4.43–4.45 (2H, m), 5.96–5.97 (2H, narrow m, C*H*=C*H*), 7.70–7.74 and 7.81–7.85 (4H total, AA′BB′, Phth); δ_C (100 MHz, CD_3OD) δ 31.2 (C-6), 52.7, 65.8, 69.1 (C-1, C-2, C-5), 124.1, 128.2, 133.4, 135.4, 136.8 (*C*H=*C*H and Phth) and 170.4 (N–C=O).

N-(2*R**,5*R**-Dihydroxy-3-cyclohexen-1*S**-yl)phthalimide (±)-16

To a solution of **13** (270 mg, 1.05 mmol) in methanol (6 mL) was added $CeCl_3 \cdot 7H_2O$ (391 mg, 1.05 mmol) followed by $NaBH_4$ (80 mg, 2.1 mmol). The reaction mixture was stirred for 45 min and then quenched with water. The mixture was extracted several times with ethyl acetate and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (SiO_2, hexane–ethyl acetate = 1 : 1) gave (±)-**16** (167 mg, 61%) as a colorless solid (Found: C, 64.93; H, 5.27. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05); mp 187–190 °C; δ_H (400 MHz, CD_3OD) 2.09–2.15 (1H, m, H-6_{eq}), 2.46 (1H, ddd, J = 10.0, 12.0 and 13.2, H-6_{ax}), 4.19 (1H, ddd, J = 3.0, 9.2 and 13.6, H-1), 4.39–4.46 (1H, m), 4.85–4.95 (1H, m), 5.73 (1H, td, J = 1.6 and 10.4, CH=CH), 5.78 (1H, qd, J = 1.9 and 10.4, CH=CH) and 7.78–7.89 (4H, m, Phth); δ_C (75 MHz, d$_6$-acetone) 36.8 (C-6), 54.5 (C-1), 67.5, 67.7 (C-2 and C-5), 123.7, 131.8, 133.1, 134.0, 135.0 (*C*H=CH and Phth) and 169.0 (N–C=O).

N-(4*R**,5*S**-Dihydroxy-2-cyclohexen-1*S**-yl)phthalimide (±)-17

To a solution of diene **8** (750 mg, 3.33 mmol) in acetone (15 mL) was added a solution of *N*-methylmorpholine *N*-oxide (960 mg, 8.19 mmol) in water (4 mL) followed by a solution of OsO_4 in toluene (2 mL, 10 mol%). The reaction mixture was stirred for 30 min at room temperature and then solid $Na_2S_2O_4$ (0.6 g) was added and stirring continued for another 30 min. The crude reaction mixture was adsorbed on silica gel, applied to the top of a chromatography column and purified (hexane–ethyl acetate = 1 : 4) to give (±)-**17** (447 mg, 52%) as a colorless solid (Found: C, 64.87; H, 5.02. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05); mp

178–181 °C; δ_H (400 MHz, CD_3OD) 2.12 (1H, dtd, $J = 1.6$, 5.8 and 13.4, H-6_{eq}), 2.35 (1H, ddd, $J = 2.0$, 10.2 and 13.6, H-6_{ax}), 4.17–4.22 (1H, m), 4.30–4.34 (1H, m), 5.11–5.17 (1H, m), 5.63 (1H, dtd, $J = 1.6$, 2.4 and 10.2, CH=C*H*), 5.73 (1H, dt, $J = 1.6$, 2.0 and 10.4, CH=C*H*) and 7.78–7.85 (4H, m, Phth); δ_C (100 MHz, CD_3OD) δ 33.4 (C-6), 45.4 (C-1), 68.6, 69.5 (C-4, C-5), 124.2 (Phth), 129.1 (*C*H=CH), 131.9, 133.4 (2 × Phth), 135.5 (*C*H=CH), and 169.6 (N–C=O).

N-(4*R**,5*S**-Diacetoxy-2-cyclohexen-1*S**-yl)phthalimide (±)-18

To a suspension of diol **17** (30 mg, 0.12 mmol) in CH_2Cl_2 (0.8 mL), at room temperature, was added dropwise pyridine (0.10 mL, 1.2 mmol). Upon addition of pyridine the mixture became clear. Acetic anhydride (0.10 mL, 1.2 mmol) was added and the resultant mixture was stirred for 12 h. The reaction mixture was quenched with 1 M HCl (5 mL) 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 (SiO_2, hexane–ethyl acetate = 1 : 1) to afford (±)-**18** (27 mg, 68%) as a colorless solid (Found: C, 63.64; H, 5.12. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99); mp 151–154 °C; δ_H (300 MHz, $CDCl_3$) 2.07 (3H, s, OAc), 2.15 (3H, s, OAc), 2.19–2.28 (1H, m, H-6_{eq}), 2.54 (1H, ddd, $J = 2.1$, 9.3 and 13.8 Hz, H-6_{ax}), 5.17 (1H, ddd, $J = 2.9$, 6.3 and 9.3 Hz, H-1), 5.62–5.67 and 5.68–5.72 (2H, 2 × m, H-4 and H-5), 5.78 (2H, s, H-2 and H-3), 7.72–7.77 and 7.82–7.88 (4H total, AA′BB′, Phth); δ_C (75 MHz, $CDCl_3$) 21.1 and 21.3 (2 × *C*H_3CO_2), 30.0 (C-6), 44.1 (C-1), 67.9, 68.3 (C-4 and C-5), 123.6, 127.1 (2 × Phth), 129.9 (*C*H=CH), 132.0 (Phth), 134.4 (*C*H=CH), 168.0 (N–C=O), 170.4 and 170.7 (2 × CH_3CO_2).

N-(2*R**,5*R**-Dihydroxycyclohex-1*S**-yl)phthalimide (±)-19

A solution of **14** (0.20 g, 0.77 mmol) in methanol (20 mL), containing a suspension of 10% Pd/C (60 mg) was stirred under H_2 (40 psi) for 5 h. After releasing the excess H_2 pressure, the reaction mixture was filtered through Celite. The filtrate was concentrated, adsorbed to silica and applied to a column of silica. Elution (hexane–ethyl acetate = 1 : 4) gave (±)-**19** (143 mg, 76%) as a colorless solid (Found: C, 64.20; H, 5.73. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79); mp 198–200 °C; δ_H (400 MHz, CD_3OD) 1.60–1.72 (1H, m), 1.84–1.91 (4H, m), 2.42 (1H, dt, $J = 2.4$ and 13.2, H-6_{ax}), 4.14 (1H, pent, $J = 2.6$, H-5), 4.26 (1H, dt, $J = 6.4$ and 9.8, H-2), 4.47 (1H, ddd, $J = 4.0$, 10.0 and 12.8, H-1) and 7.75–7.88 (4H, m, Phth); δ_C (100 MHz, CD_3OD) δ 29.8, 31.9, 36.3 (C-3, C-4 and C-6), 53.5 (C-1), 66.7, 70.2 (C-2 and C-5), 124.0, 133.5, 135.3 (3 × Phth), 170.3 (N–C=O).

N-(2*S**,5*S**-Dihydroxycyclohex-1*S**-yl)phthalimide (±)-20

The reduction of **15** (40.0 mg, 0.154 mmol) in methanol (7 mL) with H_2 (40 psi) catalyzed by 10% Pd/C (*ca.* 5 mg) was carried out in a fashion similar to the reduction of **14**. Purification of the residue by column chromatography (hexane–ethyl acetate = 1 : 4) gave (±)-**20** (25 mg, 62%) as a colorless solid (Found: C, 62.03; H, 5.70. Calcd for $C_{14}H_{15}NO_4 \cdot \frac{1}{2}H_2O$: C, 62.21; H, 5.96); mp 175–177 °C; δ_H (300 MHz, CD_3OD) 1.60–1.95 (5H, m, H-3, H3′, H-4, H4′, H6_{eq}), 2.88 (1H, td, $J = 11.7$ and 13.5, H-6_{ax}), 3.60–3.72 (1H, m), 3.98 (1H, br s), 4.18 (1H, ddd, $J = 2.2$, 3.8, 13.5) and 7.75–7.90 (4H, m, Phth); δ_C (100 MHz, CD_3OD) δ_C 29.5, 30.4, 33.6 (C-3, C-4, C-6), 55.4 (C-1), 68.5, 70.8 (C-2 and C-5), 124.2, 133.3, 135.5 (Phth) and 170.6 (N–C=O).

N-(2*R**,5*S**-Dihydroxycyclohex-1*S**-yl)phthalimide (±)-21

The reduction of **16** (56.0 mg, 0.216 mmol) in methanol (10 mL) with H_2 (40 psi) catalyzed by 10% Pd/C (*ca.* 5 mg) was carried out in a fashion similar to the reduction of **14**. Filtration of the reaction mixture through Celite and concentration of the filtrate gave (±)-**21** (36 mg, 64%) as a colorless solid (Found: C, 64.01; H, 5.76. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.76); mp 243–245 °C; δ_H (300 MHz, CD_3OD) 1.38–1.55 (2H, m), 1.93–2.18 (3H, m), 2.25 (1H, q, $J = 12.0$, H-6_{ax}), 3.64–3.76 (1H, m), 4.02 (1H, ddd, $J = 4.4$, 9.3 and 13.5, H-1), 4.21–4.31 (1H, m), 7.78–7.90 (4H, m, Phth); δ_C (75 MHz, CD_3OD) δ 32.4, 34.3, 38.2 (C-3, C-4, C-6), 55.9 (C-1), 69.6, 70.0 (C-2 and C-5), 124.1, 133.4, 135.4 (Phth), 170.1 (N–C=O).

N-(3*S**,4*R**-Dihydroxycyclohex-1*R**-yl)phthalimide (±)-22

The reduction of **17** (0.10 g, 0.38 mmol) in methanol (10 mL) with H_2 (40 psi) catalyzed by 10% Pd/C (*ca.* 5 mg) was carried out in a fashion similar to the reduction of **14**. Purification by column chromatography (SiO_2, hexane–ethyl acetate = 1 : 4) gave (±)-**22** (75 mg, 74%) as a colorless solid; mp 243–245 °C; δ_H (300 MHz, CD_3OD) δ 1.60–1.80 (2H, m), 1.84–1.96 (2H, m), 2.28 (1H, dq, $J = 4.2$ and 13.0, H-2_{ax}), 2.52 (1H, dt, $J = 2.4$ and 12.8, H-2_{ax}), 3.67 (1H, ddd, $J = 2.9$, 4.5 and 11.5, H-4), 4.03–4.07 (1H, narrow m, H-3), 4.58 (1H, tt, $J = 4.1$ and 12.8, H-1) and 7.75–7.88 (4H, m, Phth); δ_C (100 MHz, d_6-DMSO) δ 27.3, 27.6, 34.3 (C-2, C-5, C-6), 44.3 (C-1), 68.6, 70.2 (C-3 and C-4), 122.9, 131.5, 134.3 (Phth), 168.0 (N–C=O); FAB-HRMS calcd for $C_{14}H_{15}NO_4Li$ ($M+Li^+$) 268.1161, found 268.1157.

N-(2*R**,3*S**,4*R**,5*S**-Tetrahydroxycyclohex-1*S**-yl)phthalimide (±)-23

To a stirring solution of **14** (60 mg, 0.23 mmol) in acetone (1 mL) was added a solution of *N*-methylmorpholine *N*-oxide (70 mg, 0.58 mmol) in water (0.3 mL) followed by a solution of OsO_4 in toluene (0.1 mL, 10 mol%). The reaction mixture was stirred for 20 h at room temperature and then $Na_2S_2O_4$ (35 mg) was added and stirred for another 30 min. The mixture was concentrated, adsorbed to silica using methanol and purified by column chromatography (SiO_2, CH_2Cl_2–methanol = 9 : 1) to give (±)-**23** (42 mg, 62%) as a colorless solid (Found: C, 57.29; H, 5.34. Calcd for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.15); mp 267–270 °C; δ_H (400 MHz, CD_3OD) 1.69 (1H, td, $J = 2.8$ and 13.2, H-6_{eq}), 2.82 (1H, dt, $J = 2.8$ and 13.2, H-6_{ax}), 3.73 (1H, dd, $J = 3.2$ and 9.6, H-3), 3.93–4.00 (2H, m, H-4 and H-5), 4.43–4.50 (2H, m, H-1 and H-2) and 7.78–7.87 (4H, m, Phth); δ_C (100 MHz, CD_3OD) 31.2 (C-6), 51.6 (C-1), 70.4, 70.7, 74.0, 74.4 (C-2, C-3, C-4 and C-5), 124.1, 133.5, 135.4 (3 × Phth) and 170.2 (N–C=O).

N-(2*S**,3*R**,4*S**,5*R**-Tetrahydroxycyclohex-1*S**-yl)phthalimide (±)-24

The dihydroxylation **15** (30.0 mg, 0.115 mmol) with catalytic OsO_4 and NMO was carried out in a fashion similar to the dihydroxylation of **14**. Purification of the residue by column

chromatography (SiO_2, ethyl acetate) gave (±)-**24** (20 mg, 59%) as a colorless solid (Found: C, 57.53; H, 5.11. Calcd for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.15); mp 253–255 °C; δ_H (400 MHz, CD_3OD) 1.89 (1H, td, J = 3.8 and 12.4, H-6_{eq}), 2.86 (1H, q, J = 12.4, H-6_{ax}), 3.71 (1H, dd, J = 2.8 and 9.6, H-4), 3.82 (1H, ddd, J = 4.8, 10.0 and 11.6, H-5), 3.94–3.99 (2H, m, H-2 and H3), 4.69 (1H, ddd, J = 2.0, 4.4 and 14.0, H-1) and 7.78–7.87 (4H, m, Phth); δ_C (100 MHz, CD_3OD) δ 31.3 (C-6), 50.1 (C-1), 70.5, 74.0, 74.1, 74.2 (C-2, C-3, C-4 and C-5), 124.2, 133.3, 135.5 (3 × Phth) and 170.7 (N–C=O).

N-(2*S**,3*S**,4*R**,5*S**-Tetraacetoxycyclohex-1*R**-yl)phthalimide (±)-25a and *N*-(2*S**,3*R**,4*S**,5*S**-tetraacetoxycyclohex-1*R**-yl) phthalimide (±)-25b

The dihydroxylation of **16** (160 mg, 0.620 mmol) with catalytic OsO_4 and NMO was carried out in a fashion similar to the dihydroxylation of **14**. Purification of the crude product (SiO_2, ethyl acetate–methanol = 9 : 1) gave a mixture of two tetraols (82 mg) as a colorless solid. The mixture (82 mg, 0.27 mmol) was suspended in acetic anhydride (0.6 mL) at room temperature and pyridine (0.4 mL) was added dropwise. After stirring overnight, the reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl (7 mL). The mixture was extracted several times with ethyl acetate and the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (SiO_2, hexane–ethyl acetate = 1 : 1) gave a mixture of (±)-**25a** and (±)-**25b** (*ca.* 9 : 11 by ^{1}H NMR integration) (104 mg, 36%) as a colorless solid (Found: C, 57.27; H, 5.03. Calcd for $C_{22}H_{23}NO_{10}$: C, 57.26; H, 5.02); mp 150–160 °C; δ_H (400 MHz, $CDCl_3$) (13H, 8×s and 2×m, H-6 and OAc for **a** and **b**), 2.56 (0.45H, dt, J = 10.9 and 12.9, H-6_{ax} **25a**), 3.14 (0.55H, q, J = 12.7, H-6_{ax} **25b**), 4.40 (0.55H, ddd, J = 4.8, 10.4 and 13.6, H-1 **25b**), 4.77 (0.45H, ddd, J = 4.8, 11.0 and 13.4, H-1 **25a**), 5.04 (0.55H, ddd, J = 2.0, 4.4 and 12.0, H-5 **25b**), 5.07 (0.55H, dd, J = 2.8 and 10.4, H-3 **25b**), 5.24-5.22 (0.45H, dd, J = 2.6 and 10.2, H-4 **25a**), 5.33 (0.45H, m, H-5 **25a**), 5.63 (0.55H, narrow m, H-4 **25b**), 5.71 (0.45H, t, J = 2.8, H-3 **25a**), 5.77 (0.45H, dd, J = 2.6 and 11.0, H-2 **25a**), 5.92 (0.55H, t, J = 10.4, H-2 **25b**), 7.70–7.88 (4H, m, Phth).

N-(2*S**,3*S**,4*R**,5*R**-Tetrahydroxycyclohex-1*R**-yl)phthalimide (±)-26

The dihydroxylation **17** (100 mg, 0.380 mmol) with catalytic OsO_4 and NMO was carried out in a fashion similar to the dihydroxylation of **14**. Purification of the residue by column chromatography (SiO_2, methanol–CH_2Cl_2 = 1 : 4, few drops of NH_4OH) gave (±)-**26** (22 mg, 21%) as a colorless solid. mp 243–245 °C; δ_H (d_6-DMSO, 300 MHz) δ 1.79 (1H, td, J = 3.6 and 13.2, H-6_{eq}), 2.19 (1H, dt, J = 1.8 and 13.2, H-6_{ax}), 3.46 (1H, td, J = 2.7 and 6.3, H-6), 3.86–3.96 (2H, br m), 4.02–4.10 (1H, br m), 4.55 (1H, dt, J = 4.2 and 12.0, H-1), 4.84–4.94 (3H, m, 3 × OH), 5.03 (1H, d, J = 5.7, OH) and 7.80–7.92 (4H, m, Phth); δ_C (75 MHz, d_6-DMSO) 32.4 (C-6), 46.5 (C-1), 68.3, 69.2, 70.4, 75.3 (C-2, C-3, C-4, C-5), 122.8, 131.6, 134.3 (3 × Phth) and 168.4 (N–C=O); FAB-HRMS calcd for $C_{14}H_{15}NO_6Li$ (M+Li^+) 300.1059, found 300.1067.

N-(2*S**,3*S**,4*R**,5*R**-Tetraacetoxycyclohex-1*R**-yl)phthalimide (±)-27

The dihydroxylation of diacetate **18** (60 mg, 0.17 mmol) with catalytic OsO_4 and NMO was carried out in a fashion similar to the dihydroxylation of **14**. Purification of the residue by column chromatography (SiO_2, hexanes–ethyl acetate = 1 : 4) gave a mixture of diol-diacetates as a colorless solid (44 mg, 67%). Acetoxylation of the crude product (40 mg, 0.11 mmol) with acetic anhydride and pyridine was carried out in a fashion similar to the acetoxylation of **17**. Purification of the residue by column chromatography (SiO_2, hexanes–ethyl acetate = 1 : 1) gave a (±)-**27** as a colorless solid (26 mg, 51%). (Found: C, 56.86; H, 5.10. Calcd for $C_{22}H_{23}NO_{10}$: C, 57.26; H, 5.04); mp 165–167 °C; δ_H ($CDCl_3$, 400 MHz) δ 1.79 (3H, s, OAc), 1.97 (3H, s, OAc), 1.96–2.05 (1H, m, H-6_{eq}), 2.12 (3H, s, OAc), 2.16 (3H, s, OAc), 2.76 (1H, br t, J = 14.0, H-6_{ax}), 4.90 (1H, dt, J = 4.2 and 12.2, H-1), 5.11 (1H, br s), 5.45 (1H, br s), 5.64–5.74 (2H, m) and 7.78–7.85 (4H, m, Phth); δ_C (100 MHz, $CDCl_3$) 20.6, 20.7, 21.0, 21.2 (4 × CH_3CO_2), 29.6 (C-6), 44.3 (C-1), 67.5, 68.3, 68.5, 69.3 (C-2, C-3, C-4 and C-5), 123.7, 131.6, 134.5 (3 × Phth), 168.1, 169.6, 169.7, 170.2, 170.4 (5 × C=O).

Reaction of endoperoxide with Grubbs' catalyst

To a solution of endoperoxide (±)-**9** (50 mg, 0.19 mmol) in dry CH_2Cl_2 (1.5 mL), at room temperature, was added Grubbs' II catalyst (1.6 mg, 10 mol%). The mixture was stirred for 30 min and then concentrated under reduced pressure. Analysis by ^{1}H NMR spectroscopy indicated this to be mixture of *Z*-2-butendial, **28**, (±)-**29** and (±)-**30** in a ratio of 2 : 1.5 : 1 : 3. *Z*-2-Butendial was identified by comparison to the literature spectral data.[15] The residue was purified by column chromatography (SiO_2, hexane–ethyl acetate gradient 10 : 1 to 1 : 4) to give **28** (8 mg, 24%) as a colorless solid, followed by (±)-**29** (7 mg, 14%) as a colorless oil, and finally (±)-**30** (14 mg, 29%) as a colorless solid.

***N*-Vinylphthalimide 28.** mp 84–86 °C (lit.[19] mp 83–86 °C); δ_H (300 MHz, $CDCl_3$) 5.06 (1H, d, J = 10.3, H-2_{trans}), 6.10 (1H, d, J = 16.3, H-2_{cis}), 6.89 (1H, dd, J = 9.9 and 16.5, H-1), 7.73–7.79 and 7.86–7.91 (4H total, AA′BB′, Phth); δ_C (75 MHz, $CDCl_3$) 104.8, 123.9, 124.0, 131.8, 134.7, 166.7.

Oxetane (±)-29. δ_H (400 MHz, $CDCl_3$) 3.04 (1H, td, J = 8.0 and 12.0, H-2), 3.82 (1H, ddd, J = 4.6, 7.6 and 12.0, H-2′), 6.07 (1H, dd, J = 7.2 and 11.6, H-5), 6.33 (1H, q, J = 7.2, H-3), 6.40 (1H, ddd, J = 1.2, 5.0 and 8.3, H-1), 6.88 (1H, ddd, J = 0.8, 6.8 and 11.5, H-4), 7.78–7.80 (2H, m, Phth), 7.92–7.94 (2H, m, Phth), 10.15 (1H, d, J = 7.2, CHO); δ_C (75 MHz, $CDCl_3$) 33.8 (C-2), 74.9, 77.8 (C-1 and C-3), 123.9 (Phth), 129.8 (C-5), 131.9, 134.9 (2 × Phth), 150.5 (C-4), 167.4 (N–C=O), 191.3 (CHO). FAB-HRMS calcd for $C_{14}H_{11}NO_4$ (M+H^+) 258.0766, found 258.0766.

***N*-(2,4-Cyclohexadien-1-yl)phthalimide bisepoxide (±)-30.** (Found: C, 65.15; H, 4.36. Calcd for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.36); mp 205–207 °C; δ_H (400 MHz, $CDCl_3$) 2.13 (1H, ddd, J = 2.6, 6.6 and 15.0, H-6), 2.40 (1H, ddd, J = 2.4, 9.2 and 14.8, H-6′), 3.26 (1H, dd, J = 2.6 and 3.8), 3.30 (1H, td, J = 2.4 and 4.0), 3.54–3.56 (1H, m), 3.58–3.60 (1H, m), 4.59 (1H, ddd, J = 2.4, 6.8 and 9.4, H-1), 7.75–7.77 (2H, AA′BB′, Phth), 7.86–7.88

(2H, AA′BB′, Phth); δ_C (75 MHz, $CDCl_3$) 26.0 (C-6), 43.5, 47.3, 49.3, 49.7, 50.7, 123.7, 131.9, 134.6 (3 × Phth), 168.0 (N–C=O).

N-(2,3-Epoxy-4*R**,5*S**-dihydroxycyclohex-1*R**-yl)phthalimide (±)-33

To a stirring solution of **9** (150 mg, 0.584 mmol) in dry CH_2Cl_2 (5 mL) at room temperature was added Grubbs' second generation catalyst (50 mg, 10 mol%). The mixture was stirred for 30 min and then concentrated under reduced pressure and applied to a column of silica (prepared with hexanes). The column was eluted (hexane–ethyl acetate = 4 : 1); however, before any material exited the column the solvent flow was stopped and left to stand overnight. After 12 h continued elution (ethyl acetate), gave (±)-**33** as a colorless solid (40 mg, 26%). mp 215–218 °C; δ_H (400 MHz, CD_3OD) 1.81–1.91 (1H, m, H-6_{eq}), 1.98 (1H, q, J = 12.0, H-6_{ax}), 3.38 (1H, dd, J = 1.5 and 3.6), 3.45 (1H, dd, J = 1.5 and 3.6), 3.64 (1H, ddd, J = 3.6, 8.4 and 12.0, H-5), 3.87 (1H, dd, J = 1.5 and 8.5, H-4), 4.58 (1H, dd, J = 6.9 and 11.4, H-1), 7.78–7.90 (4H, m, Phth); δ_C (75 MHz, CH_3OD) δ 35.3, 46.6, 58.8, 59.8, 68.3, 74.8, 124.4, 133.3, 135.8 (Phth), 169.1 (N–C=O); FAB-HRMS calcd for $C_{14}H_{14}NO_5$ ($M+H^+$) 276.0872, found 276.0875.

N-(3,4-Epoxy-2*S**,5*R**-dihydroxycyclohex-1*R**-yl)phthalimide (±)-34

To a stirring solution of (±)-**14** (50.0 mg, 0.193 mmol) in CH_2Cl_2 (1 mL) was added a solution of mCPBA (0.1 g, ~70 wt%, ~0.4 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 7 h and then quenched with 10% aqueous NEt_3 (10 mL). The resulting mixture was extracted several times with ethyl acetate and the combined extracts washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (SiO_2, ethyl acetate) to give (±)-**34** (22.0 mg, 42%) as a colorless solid. (Found: C, 60.58; H, 4.80. Calcd for $C_{14}H_{13}NO_5 \cdot 0.1H_2O$: C, 60.69; H, 4.80); mp 203–206 °C; δ_H (400 MHz, CD_3OD) 1.68 (1H, br d, J = 14.0, H-6_{eq}), 2.52 (1H, ddd, J = 6.0, 12.4 and 14.4, H-6_{ax}), 3.47–3.49 (2H, narrow m, H-3 & H-4), 4.25–4.29 (1H, m, H-5), 4.52 (1H, ddd, J = 3.2, 9.6 and 13.0, H-1), 4.66 (1H, d, J = 9.2, H-2), 7.78–7.89 (4H, m, Phth); δ_C (100 MHz, CD_3OD) 36.1 (C-6), 48.8 (C-1), 57.3, 59.0, 64.9, 68.6 (C-2, C-3, C-4, C-5), 124.1, 133.4, 135.5 (3 × Phth), 170.1 (N–C=O).

N-(2,3-Epoxy-4*R**,5*R**-dihydroxycyclohex-1*R**-yl)phthalimide (±)-35

The epoxidation of (±)-**17** (100 mg, 0.400 mmol) with mCPBA (0.2 g, 0.8 mmol) was carried out in a fashion similar to the epoxidation of **27**, except that the reaction was stirred for 12 h. The resulting mixture was extracted several times with CH_2Cl_2, and the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. The excess Et_3N was removed under high vacuum to give (±)-**35** (73 mg, 70%) as a colorless solid (Found: C, 59.95; H, 4.69. Calcd for $C_{14}H_{13}NO_5 \cdot \frac{1}{4}H_2O$: C, 60.10; H, 4.86); mp 167–170 °C; δ_H (400 MHz, $CDCl_3$) 2.03 (1H, ddd, J = 2.0, 10.7 and 13.7, H-6_{ax}), 2.25 (1H, dddd, J = 1.6, 4.2, 6.9 and 13.7, H-6_{eq}), 2.89 (1H, d, J = 11.6, OH), 3.05 (1H, d, J = 10.0, OH), 3.48 (1H, dd, J = 1.6 and 3.6), 3.65–3.68 (1H, narrow m), 3.97–4.25 (1H, m, H-4), 4.19 (1H, ddd, J = 1.6, 4.3 and 9.5, H-5), 4.88 (1H, dd, J = 6.9 and 10.6, H-1), 7.75–7.80 and 7.85–7.89 (4H total, AA′BB′, Phth); δ_C (100 MHz, $CDCl_3$) 32.3 (C-6), 41.7 (C-1), 58.7, 58.9, 67.2, 68.4 (C-2, C-3, C-4 and C-5), 123.8, 131.9, 134.7 (3 × Phth), 167.8 (N–C=O).

Hydrolysis of epoxydiol 33

To a solution of (±)-**33** (65 mg, 0.236 mmoL) in water (3 mL) was added concentrated H_2SO_4 (6 drops). The suspension was heated at reflux, after 30 min all of the material dissolved, and after an additional 20 min a colorless solid began to precipitate. The mixture was heated for a total of 70 min, cooled to room temperature and concentrated under reduced pressure. The concentrated syrup was adsorbed to a small amount of silica gel and this was applied to the top of a column of silica. Elution (ethyl acetate) gave (±)-**24** as a colorless solid (48 mg, 74%). The mp and ^{1}H NMR spectral data for this material was identical to that previously obtained.

N-(2*R**,3*S**,4*R**,5*R**-Tetraacetoxycyclohex-1*R**-yl)phthalimide (±)-36

To a suspension of epoxide **35** (137 mg, 0.498 mmol) in water (10 mL) was added 70% aqueous $HClO_4$ (6 drops) and the suspension was heated at reflux. After 20 min of heating the suspension turned clear and after a further 30 min a colorless solid compound began to separate from solution. The mixture was heated for an additional 20 min (total 70 min), cooled to room temperature, filtered, and the residue dried under high vacuum to afford a crude tetraol (86 mg); mp 265–267 °C. A sample of the crude tetraol (70 mg, 0.24 mmol) in acetic anhydride (0.20 mL) and pyridine (0.15 mL) was stirred for 18 h. During this time the undissolved material went into solution. The reaction mixture was diluted with ethyl acetate (5 mL) and quenched with 1 M aqueous HCl (10 mL) and the resulting mixture was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, hexane–ethyl acetate = 1 : 1) to afford (±)-**36** as a colorless solid (79 mg, 42% overall). (Found: C, 57.15; H, 5.04. Calcd for $C_{22}H_{23}NO_{10}$: C, 57.26; H, 5.04); mp 67–70 °C; δ_H (400 MHz, $CDCl_3$) 2.02, 2.06, 2.11, 2.17 (13H, 4xs and m, H-6_{eq} & OAc), 3.18 (1H, br t, J = 11.0, H-6_{ax}), 5.04 (1H, ddd, J = 3.3, 4.5 and 11.1, H-1), 5.31–5.36 (1H, narrow m), 5.38–5.43 (2H, narrow m), 5.64–5.70 (1H, m, H-5), 7.70–7.86 (4H, m, Phth); δ_C (75 MHz, $CDCl_3$) 20.95, 21.0, 21.2 (2 × CH_3CO_2), 27.4 (C-6), 44.8 (C-1), 67.9, 68.2, 69.3, 70.0 (C-2, C-3, C-4, C-5), 123.6, 131.7, 134.5 (3 × Phth), 168.7, 170.1, 170.2 (3 × C=O).

Hydrolysis/acetylation of epoxide (+)-34

The hydrolysis/acetylation of epoxide **34** (160 mg, 0.582 mmol) in water (7 mL) was carried out in a fashion similar to that for the hydrolysis of **35**, except that concentrated H_2SO_4 (14 drops) was used as acid instead of $HClO_4$. The crude tetraol mixture was peracetylated (Ac_2O/pyr) in a fashion similar to the preparation of **36**. Purification of the residue by column chromatography (SiO_2, hexane–ethyl acetate = 1 : 1) gave a colorless solid (137 mg, 51% overall). Analysis of the ^{1}H NMR of this product indicated that it consisted of a mixture of diastereomers (~2 : 1). Slow recrystallization of the mixture (ethyl acetate) gave (±)-**37** as long

rectangular crystals and (±)-**38** as more cubic crystals. These were manually separated (tweezers) to afford the pure diastereomers.

***N* - (2*S**,3*R**,4*R**,5*R** - Tetraacetoxycyclohex - 1*R** - yl)phthalimide (±)-37.** (Found: C, 57.18; H, 4.96. Calcd for $C_{22}H_{23}NO_{10}$: C, 57.26; H, 5.04); mp 215–217 °C; δ_H (300 MHz, $CDCl_3$) 1.85, 2.02, 2.21 (13H, 4×s and m, H-6_{eq} and OAc), 2.93 (1H, dt, $J = 2.1$ and 14.0, H-6_{ax}), 4.70 (1H, ddd, $J = 4.8$, 10.5 and 13.2, H-1), 5.11 (1H, dd, $J = 2.8$ and 10.7, H-4), 5.51–5.58 (2H, m, H-3 and H-5), 5.73 (1H, dd, $J = 9.6$ and 10.5, H-2), 7.70–7.88 (4H, m, Phth); δ_C (75 MHz, $CDCl_3$) 20.6, 20.8, 20.7, 21.3 ($4 \times CH_3CO_2$), 28.7 (C-6), 47.4 (C-1), 67.5, 70.4, 71.6, 71.7 (C-2, C-3, C-4, C-5), 123.8, 131.6, 134.6 (3 × Phth), 168.0, 170.0, 170.1, 170.15, 170.17 (5 × C=O).

***N* - (2*S**,3*S**,4*S**,5*R** - Tetraacetoxycyclohex - 1*R** - yl)phthalimide (±)-38.** (Found: C, 57.17; H, 4.98. Calcd for $C_{22}H_{23}NO_{10}$: C, 57.26; H, 5.04); mp 218-221 °C; δ_H (300 MHz, $CDCl_3$) 1.85 (3H, s, OAc), 2.00–2.13 (1H, br d, $J = 14.4$, H-6_{eq}), 2.15, 2.17, 2.21 (9H, 3×s, OAc), 2.99 (1H, ddd, $J = 3.6$, 12.5 and 14.4, H-6_{ax}), 4.92 (1H, ddd, $J = 4.2$, 10.9 and 12.2, H-1), 5.10–5.13 (1H, narrow m), 5.16 (1H, dt, $J = 1.5$ and 3.0), 5.48 (1H, dt, $J = 1.2$ and 3.5, H-5), 5.87 (1H, dd, $J = 3.6$ and 10.8, H-2), 7.73–7.90 (4H, m, Phth); δ_C (75 MHz, $CDCl_3$) 20.8, 21.0, 21.1, 21.2 ($4 \times CH_3CO_2$), 29.2 (C-6), 44.5 (C-1), 68.1, 68.6, 68.7, 69.0 (C-2, C-3, C-4, C-5), 123.7, 131.7, 134.5 (3 × Phth), 168.2, 169.0, 169.7, 169.74, 169.9 (5 × C=O).

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