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Generation of Molecular Complexity from Cyclooctatetraene: Preparation of Aminobicyclo[5.1.0]octitols

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Generation of Molecular Complexity from Cyclooctatetraene: Preparation of Aminobicyclo[5.1.0]octitols

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Abstract: A series of eight stereoisomeric *N*-(tetrahydroxy bicyclo-[5.1.0]oct-2*S**-yl)phthalimides were prepared in one to four steps from *N*-(bicyclo[5.1.0]octa-3,5-dien-2-yl)phthalimide (±)-**7**, which is readily available from cyclooctatetraene (62 % yield). The structural assignments of the stereoisomers were established by ^{1}H NMR spectral data as well as X-ray crystal structures for certain members. The outcomes of several epoxydiol hydrolyses, particularly ring contraction and enlargement, are of note. The isomeric phthalimides as well as the free amines did not exhibit β-glucosidase inhibitory activity at a concentration of less than 100 μM.

Introduction

Polyhydroxyl aminocyclohexanes (aminocyclitols) are present as aglycon units in numerous aminoglycoside antibiotics, and certain of these compounds possess glycosidase inhibitory activity.[1] A ring-expanded aminocycloheptitol **1** (Figure 1) has been isolated from the roots of *Physalis alkekengi* var. francheti;[2] similar structures (−)-**2** and (+)-**3** are α-D-glucosidase inhibitors in the low micromolar range.[3,4] There are relatively few bicyclic aminocyclitiols known. The aminobicyclo[4.1.0]heptitols **4 a** and (+)-**4 b** were designed to mimic the half-chair conformation of the oxacarbenium ion intermediate in glycolytic bond cleavage. Compound **4 a** inhibits yeast α-glycosidase (K_i=0.107±0.015 μM), whereas the corresponding acetamido **4 b** is relatively inactive against this enzyme.[5] Balci and co-workers have reported the preparation of an amino bicyclo[4.2.0]octitol (±)-**5**.[6] As part of our continued interest in the use of the simple hydrocarbon cyclooctatetraene for the synthesis of complex molecules,[7,8] we herein report on the preparation of a series of eight protected amino bicyclo[5.1.0]octitiols [6].

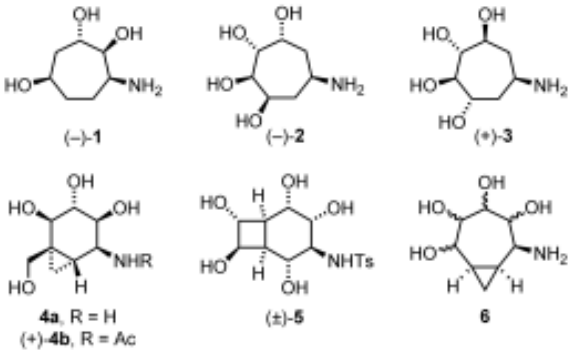

Figure 1. Representative polyhydroxy aminocycloheptanes and polyhydroxy aminobicyclo[n.m.0]alkanes.

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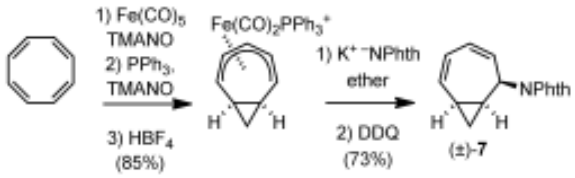
N-(Bicyclo[5.1.0]hepta-3,5-dien-1-yl)phthalimide (±)-**7** was prepared from cyclooctatetraene in five steps and in 62 % yield using a slight modification to the literature procedure (Scheme 1).[8b] The use of 2,3-dichloro-5,6-dicyanoquinone (DDQ) instead of ceric ammonium nitrate (CAN) in the oxidative decomplexation step was found to give superior yields.1



Scheme 1. Preparation of *N*-(bicyclo[5.1.0]octa-3,5-dien-2-yl)phthalimide **7** (TMANO=trimethylamine *N*-oxide).

Results and Discussion

The treatment of (±)-**7** with singlet oxygen gave (±)-**8** as a single diastereomer (Scheme 2). The relative stereochemistry of **8** was tentatively assigned on the basis of that previously observed for the products of **7** with arylnitroso dienophiles.[9] This tentative assignment was eventually corroborated on the basis of further reactions. Reduction of **8** with zinc in acetic acid gave the enediol (±)-**9**. Alternatively, the Kornblum–DeLaMare rearrangement[10,11] of **8** with triethylamine gave a separable mixture of two regioisomeric enones (the bicyclic enone (±)-**10** predominantly in 95 % yield). Reduction of **10** under Luche conditions gave a unique endiol (±)-**11**. The C2—C3 relative stereochemistry of **9**, **10**, and **11** were each assigned on the basis of their ^{1}H NMR spectral data; in particular, a large coupling between H-2 and H-3 ($J\approx$10 Hz) is indicative of a diaxial relationship of these protons.

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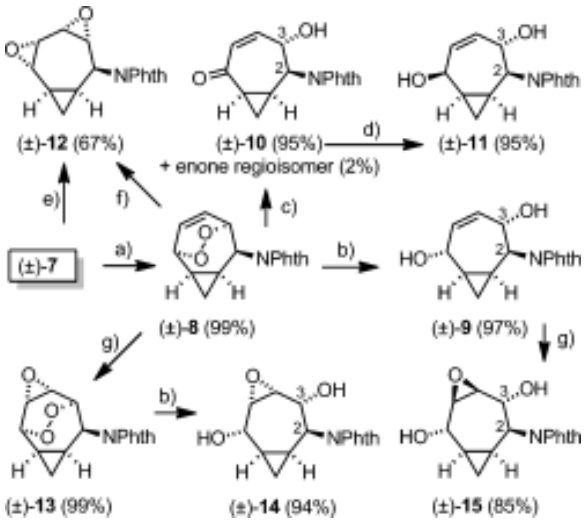

Scheme 2. Oxidation of *N*-(bicyclo[5.1.0]octa-3,5-dien-2-yl)phthalimide. Reagents: a) $^1O_2$, *hv* (sunlamp), TPP; b) Zn/HOAc; c) NEt_3; d) $NaBH_4$, $CeCl_3$, MeOH; e) *m*CPBA (2 equiv); f) *hv* (Hg vapor), C_6H_6; g) CF_3CO_3H.

The treatment of **7** with two equivalents of *m*-chloroperoxybenzoic acid gave bisepoxide (±)-**12**. This same compound was obtained, albeit in lower overall yield, by photolysis of **8** with a medium pressure Hg vapor lamp. Epoxidation of **8** with trifluoroperacetic acid (generated by reaction of trifluoroacetic anhydride with hydrogen peroxide) gave the epoxy endoperoxide (±)-**13**. The relative stereochemistry of **12** and **13** was established by using single-crystal X-ray diffraction analysis.[12] Reduction of **13** with zinc and acetic acid gave the epoxydiol (±)-**14**. The relative stereochemical assignment for **14** was based on the assigned structure of **13**, and the fact that endoperoxide reduction takes place with retention of configuration at the C—O bonds. Epoxidation of the enediol **9** with trifluoroperacetic acid gave epoxydiol (±)-**15**, whose structure was tentatively assigned because the stereochemical assignment indicated that it was unique from that of the diastereomeric epoxydiol **14**. This tentative stereochemical assignment was eventually corroborated by single-crystal X-ray diffraction analysis (Figure 2). Notably, for both **14** and **15**, a large coupling between H-2 and H-3 ($J \approx 11$–12 Hz) indicated that these two protons have a diaxial orientation.

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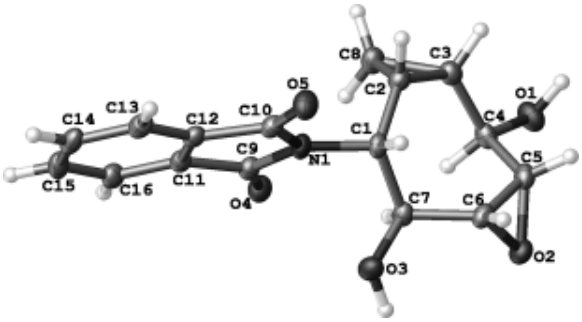
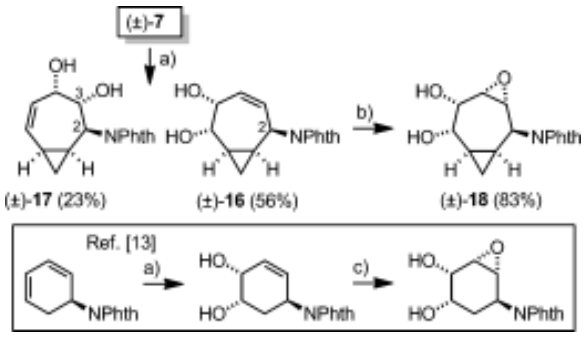


Figure 2. Structure of (±)-**15** (arbitrary atomic numbering).

Catalytic dihydroxylation of bicyclic diene (±)-**7** using one equivalent of *N*-methylmorpholine *N*-oxide (NMO) gave a separable mixture of two regioisomeric enediols (±)-**16** and (±)-**17** (Scheme 3). The major product arises from dihydroxylation on the olefin more remote to the electron-withdrawing phthalimide substituent at C-2. The structures of **16** and **17** were tentatively assigned on the basis of their ^{1}H NMR spectral data. In particular, the chemical shift for H-2 of **16** (δ=5.68 ppm) compared with that for H-2 of **17** (δ=5.25 ppm) is indicative of the proximity of the double bond to H-2 in **16**. Additionally, a large coupling between H-2 and H-3 of **17** (J=10.6 Hz) is indicative of a diaxial relationship of these protons. Epoxidation of **16** with trifluoroperacetic acid gave a single epoxydiol (±)-**18**. The relative stereochemistries of **16** and **18** were tentatively assigned on the basis of the stereochemistries we previously observed for the dihydroxylation of *N*-(2,4-cyclohexadien-1-yl)phthalimide and the epoxidation of this enediol (see inset Scheme 3), both of which were established by X-ray diffraction analysis.[13] The tentative stereochemical assignments of **16** and **17** were eventually corroborated by X-ray diffraction analysis of the tetraols derived from exhaustive hydroxylation of **7** (see below).[3]



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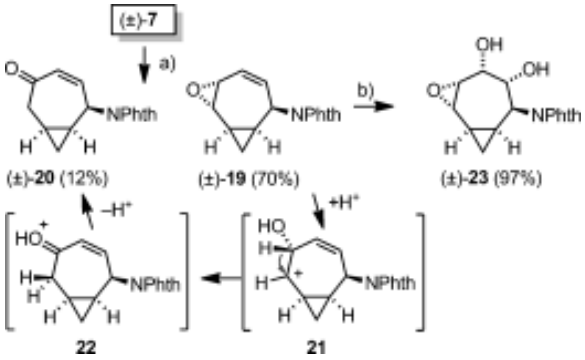
Scheme 3. Oxidative functionalization of *N*-(bicyclo[5.1.0]octa-3,5-dien-2-yl)phthalimide and precedent for stereochemical assignments.[13] Reagents: a) OsO_4 (cat.)/NMO (1 equiv); b) $(CF_3CO)_2O$, H_2O_2; c) *m*CPBA (1 equiv).

Epoxidation of **7** with one equivalent of *m*CPBA gave a separable mixture of monoepoxide (±)-**19** and enone (±)-**20** (Scheme 4). The structural assignment for **19** was established by single-crystal X-ray diffraction analysis,[12] whereas the structural assignment for **20** is based on its NMR spectral data. In particular, the presence of signals at δ=198.9, 141.9, and approximately 123.8 ppm in the ^{13}C NMR spectrum of **20** are consistent with a α,β-unsaturated ketone. Additionally, signals at δ=2.95 and 3.11 ppm (J_{gem}=15.2 Hz) in the ^{1}H NMR spectrum and a CH_2 signal at δ=41.5 ppm in the distortionless enhancement by polarization transfer (DEPT) NMR spectrum of **20** are indicative of a diastereotopic set of geminal protons adjacent to a carbonyl group and the carbon to which they are attached. Because the relative ratio of **19** to **20** depended on the quality of the *meta*-chloroperbenzoic acid (*m*CPBA) used as well as on reaction time and time of exposure of the reaction mixture to silica gel, we propose that enone **20** arises from **19** by acid-promoted rearrangement. Thus, protonation of the epoxide in **19** followed by regioselective cleavage of the C—O bond adjacent to the cyclopropane ring leads to carbocation **21**. Hydride migration affords the protonated enone **22**, which upon deprotonation affords **20**. This type of epoxide-to-ketone rearrangement is reminiscent of the "NIH-shift" for enzymatic hydroxylation of arenes.[14] Dihydroxylation of **19** gave a single epoxydiol (±)-**23**, whose structure was established by single-crystal X-ray diffraction analysis. 4[12]



Scheme 4. Oxidative functionalization of *N*-(bicyclo[5.1.0]octa-3,5-dien-2-yl)phthalimide. Reagents: a) *m*CPBA (1 equiv); b) OsO_4 (cat.)/NMO (1 equiv).

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As we have previously reported,[8b] osmium-catalyzed hydroxylation of **7** with excess NMO as a reoxidant gave a separable mixture of two tetraols (±)-**24** and (±)-**25** (Scheme 5). The structures of **24** and **25** were tentatively assigned on the basis of their ^{1}H NMR spectral data (see below); these tentative assignments were eventually corroborated by single-crystal X-ray diffraction analysis (Figure 3 and Figure 4). 3, 4 [12]

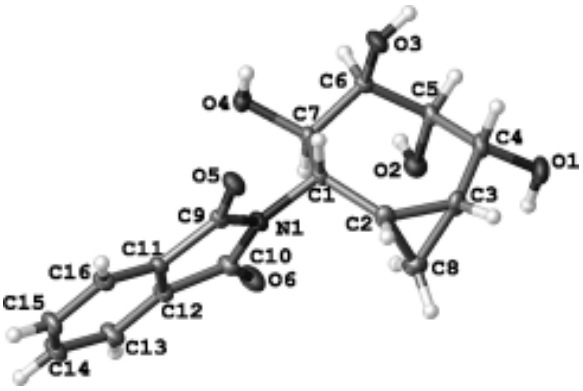

Figure 3. Structure of (±)-**24** (arbitrary atomic numbering).

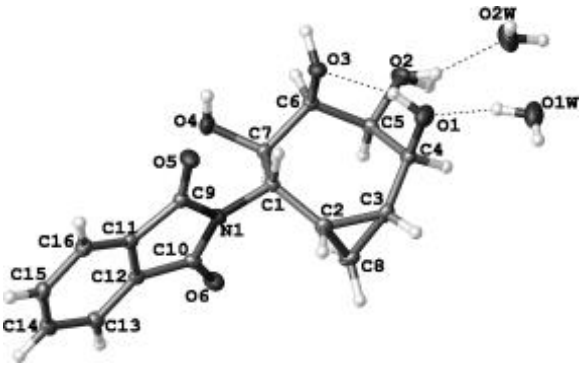

Figure 4. Structure of (±)-**25**·2 H_2O (arbitrary atomic numbering).

Furthermore, the unambiguous identification of the structures of **24** and **25** bolstered the stereochemical assignments for **17** and **16**. Presumably, the introduction of two pairs of hydroxyl groups to **7** occurs in a stepwise fashion, and thus tetraol **24** arises through dihydroxylation of **17** on face of the olefin opposite to the C-4 hydroxyl group, according to the Kishi model for stereoselectivity.[15] Alternatively, tetraol **25** arises from dihydroxylation of **16**; however, in this case the hydroxyl groups are introduced *anti* to the phthalimide

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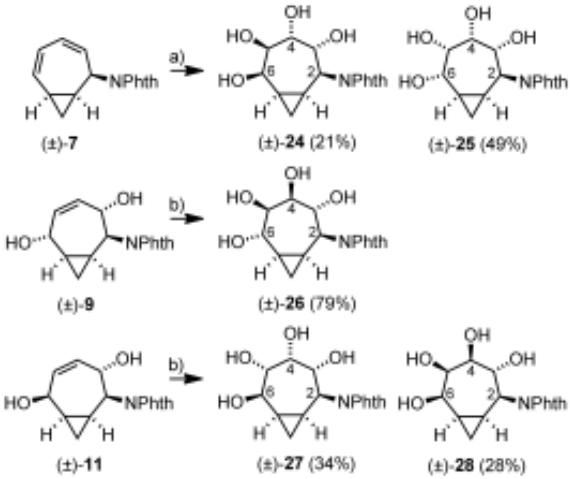
group at C-2. Notably, a separate experiment in which a mixture of **16**/**17** was subjected to dihydroxylation gave a mixture of **25**/**24** in the same ratio. Dihydroxylation of enediol **9** gave a single tetraol (±)-**26**, whereas a similar reaction of **11** gave a separable mixture of (±)-**27** and (±)-**28**. The structures of polyols **24**, **25**, **26**, **27**, and **28** were tentatively assigned on the basis of their ^{1}H NMR spectral data (see below) and the fact that dihydroxylation occurs in a *syn*-fashion; the spectral analysis of the bicyclic tetraols will be discussed separately.[5]



Scheme 5. Preparation of aminopolyols by dihydroxylation. Reagents: a) OsO_4 (cat.)/NMO (2 equiv); b) OsO_4 (cat.)/NMO (1 equiv).

Hydrolysis of epoxydiols **18** or **23** using CBr_4/THF/H_2O[16] gave a single tetraol (±)-**29** or (±)-**27**, respectively (Scheme 6).[6]

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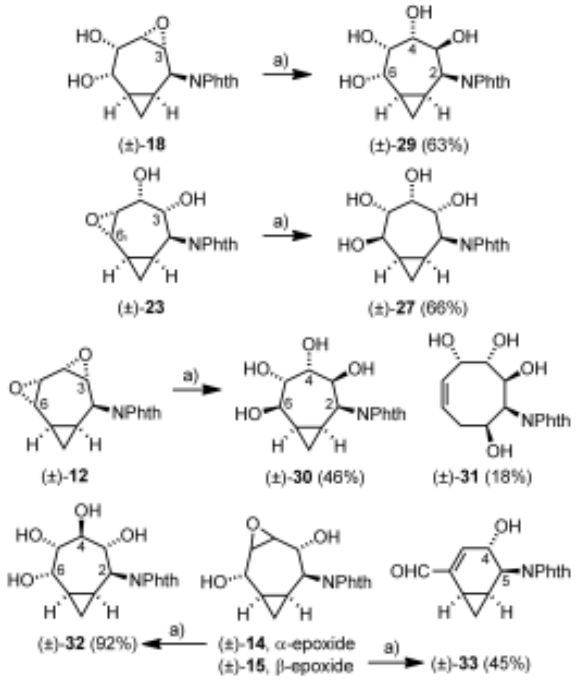

Scheme 6. Preparation of aminopolyols by epoxide hydrolysis. Reagents: a) $THF/H_2O/CBr_4$.

In contrast, hydrolysis of bisepoxide **12** gave a separable mixture of bicyclic tetraol (±)-**30** and the cyclooctene tetraol (±)-**31**. Hydrolysis of the epoxydiol **14** gave the tetraol (±)-**32**. In contrast, reaction of the diastereomeric epoxydiol **15** gave a unique aldehyde (±)-**33**. The structures of the epoxide hydrolysis products were tentatively assigned on the basis of their NMR spectral data; the spectral analysis of the bicyclic tetraols **29**, **30**, and **32** will be discussed in a separate paragraph. The tentative structural assignment for **32** was eventually corroborated by using single-crystal X-ray diffraction analysis (Figure 5). [5][12]

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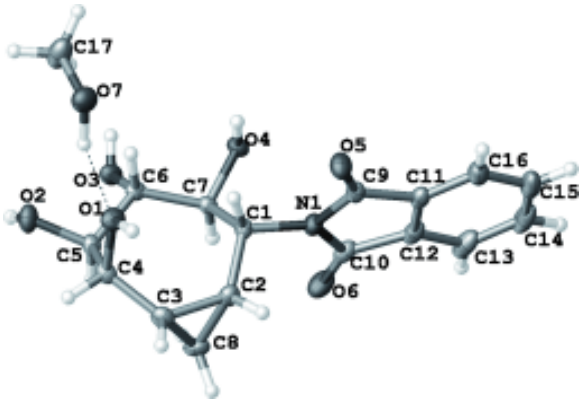

Figure 5. Structure of (±)-**32**·CH_3OH (arbitrary atomic numbering).

For cyclooctene **31**, vicinally coupled signals in its ^{1}H NMR spectrum at δ=5.74 and 5.81 ppm (J_{cis}=10.8 Hz) and geminally coupled signals at δ=2.31 and 2.89 ppm (J_{gem}=12.4 Hz) are consistent with the *cis* olefinic functionality and adjacent methylene group, respectively. The stereochemistry of the four hydroxyl substituents relative to the phthalimide group in (±)-**31** was eventually assigned on the basis of the single-crystal X-ray diffraction analysis (Figure 6). 6[12]

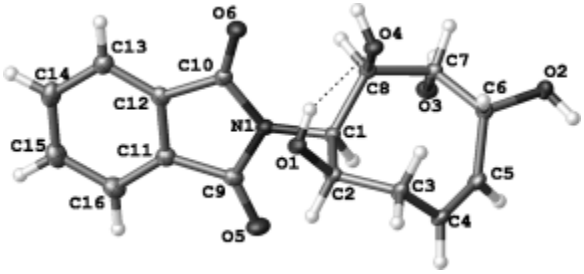

Figure 6. Structure of (±)-**31** (arbitrary atomic numbering).

For 2-formylbicyclo[4.1.0]hept-2-ene (**33**), a singlet and narrow doublet at δ=9.54 and 6.52 ppm, respectively, in its ^{1}H NMR spectrum, and signals at δ=194.0, 148.0, and 144.6 ppm in its ^{13}C NMR spectrum are indicative of the 2,3-disubstituted enal functionality present. In addition, the relatively large coupling between H-4 and H-5 (J=9.8 Hz) is consistent with these two protons having a *trans*-diaxial relationship. The tentative structure for **33** was eventually corroborated by using single-crystal X-ray diffraction analysis (Figure 7). 7[12]

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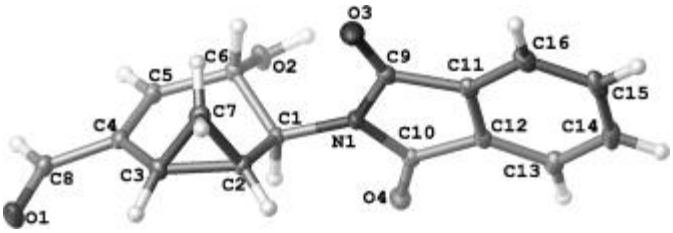

Figure 7. Structure of (±)-**33** (arbitrary atomic numbering).

The structural assignments for many of the diastereomeric polyhydroxyl bicyclo[5.1.0]octanes are based on their ^{1}H NMR spectral data. The carbon skeleton present in these compounds adopts an expanded chair-like conformer, with the cyclopropane ring acting similar to a methylene group in a cyclohexane ring and the phthalimide substituent at C-2 occupying an equatorial orientation; this can be observed in the crystal structures of **24**, **25**, and **32**. For this reason, it is possible to utilize the Karplus relationship between the coupling constant and dihedral angle of coupled protons.[17] In particular, for the six diastereomers in which the C-2 phthalimide and the C-3 hydroxyl are *trans* (i.e., diequatorial; **24**, **25**, **26**, **27**, **28**, and **32**), the coupling between H-2 and H-3 is relatively large (J≈11 Hz). Conversely, for the two diastereomers in which the C-2 phthalimide and C-3 hydroxyl are *cis* (**29** and **30**), the coupling between H-2 and H-3 is considerably smaller (2.2 Hz). In addition, for the diastereomers in which the C-3 and C-4 hydroxyl groups are diequatorial (**26**, **28**, and **32**), the coupling between H-3 and H-4 is relatively large (≈10 Hz), whereas for those diastereomers in which the C-3 hydroxyl is equatorial and the C-4 hydroxyl is axial (**24**, **25**, and **27**) the coupling between H-3 and H-4 is considerably smaller (≈0–2 Hz). For those diastereomers in which the C-5 and C-6 hydroxyl groups are diequatorial (**27** and **30**), or the C-4 and C-5 hydroxyls are diequatorial (**32**), the coupling between the protons on these carbons is relatively large (≈9 Hz). In addition, the relative stereochemistry of certain adjacent hydroxyl groups was assigned on the basis of the known *syn* relationship engendered by osmium-catalyzed dihydroxylation and the known *anti* relationship engendered by epoxide hydrolysis under these conditions.

The outcome of the epoxide hydrolyses deserves comment. The hydrolysis of epoxydiol **18** to give **29** proceeds through selective

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cleavage of the C3—O bond. The resulting *trans*- diaxial orientation of the C3 and C4 hydroxyl groups can be rationalized on the basis of the Furst–Plattner rule for ring opening through a chair-like transition state.[18] In contrast, hydrolysis of epoxydiol **23** proceeds through cleavage of the C6—O bond to generate a *trans*-diequatorial relationship. This selective cleavage is the result of a greater stabilization of the partial positive charge on the protonated form of the epoxydiol at C-6 because of the stabilizing influence of the adjacent cyclopropane ring.[19]

The hydrolysis of bisepoxide **12** yields two products. It is proposed that the bicyclo[5.1.0]octanetetraol **30** arises through initial opening of the C3-C4 oxirane ring in a diaxial fashion to generate the C3 diastereomer of **23**; subsequent epoxide opening of the C5-C6 oxirane occurs at the C6—O bond similar to **23**. We propose that the cyclooctene product **31** is the product of initial protonation at the C5—C6 oxirane (**34**, Scheme 7). A number of possible routes may be envisioned (Scheme 7): 1) a cyclopropyl to butenyl carbocation rearrangement to generate **35**, followed by a facially selective reaction with water to afford **36**; or 2) an S_N2'-type opening in which attack of a molecule of water at C1 of the protonated epoxide cleaves both the cyclopropane ring and the epoxide ring to directly generate **36**; or 3) an intramolecular attack of one of the phthalimide oxygens at C1 of the cyclopropane with concomitant opening of both three-membered rings to generate **38**, followed by addition of water to give the hydroxyisoindolinone **39**, which can collapse to **37**.[20] We favor the latter mechanism (3) for a number of reasons. It seems unlikely that a "free" carbocation such as **35** would lead to a stereoselective outcome. In fact, attempts to computationally model the protonated bisepoxide **34** using B3LYP/6-311+G(d,p) instead resulted in **38** as a minimized structure. Addition of explicit water to the optimization of protonated **34** did result in a minimized structure, in which the distance between the C1 cyclopropane carbon and the phthalimide oxygen was 3.2 Å. This structure also revealed that approach of an external water molecule (i.e., pathway 2) would be significantly hindered by the phthalimide substituent.

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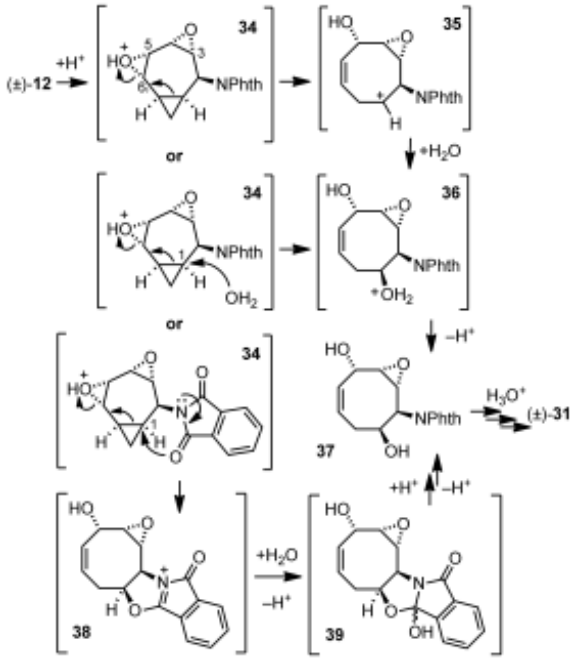

Scheme 7. Intramolecular participation of the phthalimide oxygen in ring opening of **12** to afford cyclooctene **31**.

Finally, the ring-contracted aldehyde **33**, formed from exposure of **15** to the standard hydrolysis conditions, arises because of a concerted 1,2-shift of C7 to C5 with concomitant opening of the protonated epoxide ring (Scheme 8).[21] Deprotonation of the resultant oxocarbenium ion **40**, followed by dehydration gives **33**. We rationalize the divergent reaction pathways for diastereomeric epoxydiols **14** and **15** on the basis of stereoelectronic control. As can be seen in the crystal structure for **15** (Figure 2), the bond that shifts is aligned nearly antiperiplanar with the C5—O bond. This alignment would not be present in diastereomer **14**, which undergoes a more classical epoxide ring opening.[8]

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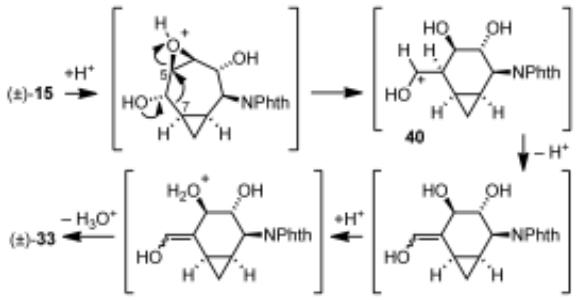
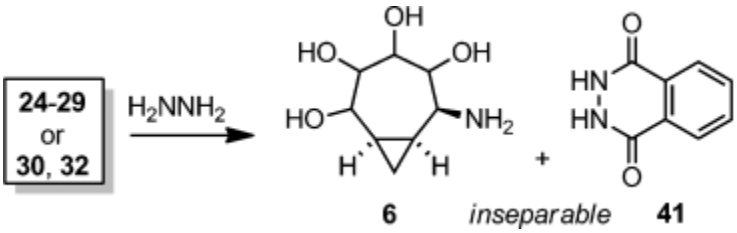


Scheme 8. Proposed mechanism for ring contraction of **15**.

Deprotection of the phthalimide group proved to be challenging. The attempted acid hydrolysis of the phthalimide group leads to products in which the cyclopropane ring is no longer intact, as evidenced by ^{1}H NMR spectroscopy. The exact nature of these ring-opened products was not established. Use of anion exchange resins,[22] partial reduction with $NaBH_4$ in acidic medium followed by heating at reflux,[23] or treatment with *n*-butylamine[24] or methylamine[25] similarly led to complex mixtures of unidentified products. Ultimately, cleavage of the phthalimide groups of **24**–**29**, **30**, and **32** with hydrazine [Eq. (1)] proceeded to give the corresponding amines **6**; however, separation of these compounds from the byproduct 2,3-dihydro-1,4-phthalazinedione **41** eluded attempts in our hands with normal and reversed-phase chromatography. Nonetheless, the inhibitory activity of **24**–**29**, **30**, **32**, and the mixtures of amine diastereomers **6** and **41** against β-glucosidase was evaluated.[26] In all cases we observed no inhibition at concentrations of less than 100 μM.



(1)

Conclusion

Eight racemic stereoisomeric *N*-(tetrahydroxybicyclo-[5.1.0]oct-2*S**-yl)phthalimides **24**–**29**, **30**, and **32**, have been prepared from *N*-(bicyclo[5.1.0]octa-3,5-dien-2-yl)phthalimide (±)-**7**, which is itself prepared from cyclooctatetraene. The structural assignments for these

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stereoisomers was established by using $^{3}J_{H-H}$ coupling values and corroborated for **24**, **25**, and **32** by using X-ray diffraction analysis. Certain epoxydiol hydrolyses resulted in ring-expanded or ring-contracted products. Hydrazinolysis of the phthalimide group led to the corresponding amines, which were inseparable from the 2,3-dihydro-1,4-phthalazinedione byproduct. Neither the phthalimides nor the free amines exhibited β-glucosidase inhibitory activity at concentrations of less than 100 μM.

Experimental Section

General methods

All reactions involving moisture or air-sensitive reagents were carried out under a nitrogen atmosphere in oven-dried glassware with anhydrous solvents. THF and diethyl ether were distilled from sodium/benzophenone. Purifications by flash chromatography were carried out using silica gel (32–63 μ). NMR spectra were recorded on either a Varian Mercury+ 300 MHz or a Varian UnityInova 400 MHz instrument. $CDCl_3$, CD_3OD, [D_6]DMSO, and [D_6]acetone were purchased from Cambridge Isotope Laboratories. ^{1}H NMR spectra were calibrated to δ=7.27 ppm for residual $CHCl_3$, 3.31 ppm for CD_2HOD, 2.50 ppm for [D_5]DMSO, or 2.05 ppm for [D_5]acetone. ^{13}C NMR spectra were calibrated from the central peak at δ=77.23 ppm for $CDCl_3$, 49.15 ppm for CD_3OD, 39.52 ppm for [D_5]DMSO, or 29.92 ppm for [D_6]acetone. Coupling constants are reported in Hz.

Syntheses

5-Phthalimido-7,8-dioxatricyclo[4.2.2.0^{2,4}]dec-9-ene (±)-8: Tetraphenylporphorine (TPP) (9 mg, 0.139 mmol) was added to a solution of diene (±)-**7** (350 mg, 1.394 mmol) in $CHCl_3$ (20 mL). The deep-purple solution was irradiated with a 100 W halogen lamp, while ultra-pure O_2 was bubbled through the solution and stirred in an ice bath for 6 h. The reaction mixture was concentrated, and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate=2:3) to give (±)-**8** (286 mg, 72 %) as a colorless solid. M.p.=159–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.70–7.90 (m, 4 H; Phth), 6.55 (dd, J=8.2, 8.6 Hz, 1 H; C=CH), 6.26 (dd, J=8.2, 9.0 Hz,

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1 H; C=CH), 5.33–5.26 (m, 2 H; H-2, H-6), 4.48–4.45 (br s, 1 H; H-5), 1.71–1.62 (m, 2 H; H-2, H-4), 1.44 (pent, *J*=8.4, 1 H; H-3'), 0.74–0.64 ppm (m, 1 H; H-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.4 (C=O), 134.4, 132.0, 128.7, 127.4, 123.6, 77.9, 77.4, 52.2 (C-5), 17.5, 15.4, 11.1 ppm; elemental analysis calcd (%) for $C_{16}H_{13}NO_4$: C 67.84; H 4.62; found: C 67.81; H 4.64.

10-Phthalimido-2,5-dioxatetracyclo[7.1.0^{1,3}.0^{4,6}]decane (±)-12: *m*-Chloroperoxybenzoic acid (319 mg, ≈70 % wt., ≈1.29 mmol) was added to a solution of diene (±)-**7** (130 mg, 0.516 mmol) in freshly distilled CH_2Cl_2 (5 mL). The reaction mixture was stirred under N_2 for 12 h, after which monitoring by TLC indicated the disappearance of starting material. The mixture was concentrated and the solid residue was treated with saturated aqueous bicarbonate (5 mL) with stirring for 30 min. The mixture was extracted several times with ethyl acetate, dried (Na_2SO_4), and concentrated. Recrystallization of the residue from benzene gave colorless crystals of (±)-**12** (137 mg, 93 %). M.p.>250 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.92–7.72 (m, 4 H; Phth), 5.16 (d, *J*=5.6 Hz, 1 H; H-8), 3.70 (dd, *J*=4.2, 5.4 Hz, 1 H), 3.51 (dd, *J*=4.4, 6.0 Hz, 1 H), 3.47 (dd, *J*=2.6, 4.2 Hz, 1 H), 3.31 (dd, *J*=2.4, 4.4 Hz, 1 H), 1.46 (tt, *J*=6.0, 9.6 Hz, 1 H; H-9), 1.29 (td, *J*=4.0, 6.0 Hz, 1 H; H-10'), 1.05–1.12 ppm (m, 2 H; H-1, H-10); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.1 (C=O), 134.4, 132.1, 123.6, 58.5, 53.7, 52.2, 51.2, 47.6, 19.9, 11.3, 11.1 ppm; elemental analysis calcd (%) for $C_{16}H_{13}NO_4$: C 67.84; H 4.62; found: C 67.44; H 4.68. The same bisepoxide could be generated by irradiation of a solution of (±)-**8** in benzene with a medium-pressure Hg lamp (67 %).

***N*-(3*R**,6*R**-Dihydroxybicyclo[5.1.0]oct-4-en-2*R**-yl)phthalimide (±)-9**: Activated zinc dust (250 mg) was added to a solution of endoperoxide (±)-**8** (250 mg, 0.880 mmol) in CH_2Cl_2 (20 mL), followed by dropwise addition of a solution of acetic acid (537 mg, 8.803 mmol) in CH_2Cl_2 (2 mL) over a 10 min period. The reaction mixture was stirred for 2 h at 0 °C, and then filtered through a Celite column. The column was then washed with methanol. The fractions collected were allowed to slowly evaporate under atmospheric pressure, and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate=1:4) to give (±)-**9** (249 mg, 98 %) as colorless crystals. M.p.=217–219 °C; ^{1}H NMR (600 MHz, CD_3OD): δ=7.90–7.79 (m, 4 H; Phth), 5.82 (ddd, *J*=2.1, 6.3, 12.0 Hz, 1 H; H-

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5), 5.62 (ddd, *J*=1.2, 3.6, 12.0 Hz, 1 H; H-4), 4.78 (td, *J*=3.0, 10.8 Hz, 1 H; H-3), 4.66 (dd, *J*=4.2, 10.8 Hz, 1 H; H-2), 4.47 (dt, *J*=1.5, 5.8 Hz, 1 H; H-6), 1.35 (tt, *J*=5.7, 9.0 Hz, 1 H; H-7), 1.21 (ddt, *J*=4.5, 6.3, 9.0 Hz, 1 H; H-1), 0.95 (q, *J*=5.8 Hz, 1 H; H-8*endo*), 0.81 ppm (dt, *J*=5.4, 9.0 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, CD_3OD): δ=170.3 (C=O), 135.4, 134.0, 133.5, 133.3, 124.1, 70.6, 67.2, 53.5, 23.2, 17.1, 9.2 ppm. HRMS (FAB): *m*/*z* calcd for $C_{16}H_{15}NO_4$+Na^+: 308.0893 [*M*+Na^+]; found: 308.0895.

***N*-(3*R**-Hydroxy-6-oxo-bicyclo[5.1.0]oct-4-en-2*R**-yl)phthalimide (±)-10 and *N*-(6*S**-Hydroxy-3-oxo-bicyclo[5.1.0]oct-4-en-2*R**-yl)phthalimide**: A solution of Et_3N (0.25 mL, 1.761 mmol) in CH_2Cl_2 (5 mL) was added to a solution of endoperoxide (±)-**8** (250 mg, 0.880 mmol) in freshly distilled CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, the solvent evaporated, and the residue was purified by column chromatography (SiO_2, CH_2Cl_2) to give (±)-**10** (238 mg, 95 %) followed by (±)-*N*-(6*S**-Hydroxy-3-oxo-bicyclo[5.1.0]oct-4-en-2*R**-yl)phthalimide (5 mg, 2 %), both as colorless solids. (±)**-10**: M.p. 227–228 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.85–7.83 (4 H, m, Phth), 6.40 (dd, *J*=2.4, 13.2 Hz, 1 H; H-4), 5.91 (ddd, *J*=1.6, 2.8, 13.6 Hz, 1 H; H-5), 4.97 (tdd, *J*=2.4, 9.6, 10.0 Hz, 1 H; H-2), 4.80 (d, *J*=10.0 Hz, 1 H; H-3), 2.23 (d, *J*=9.2 Hz, 1 H; OH), 2.14 (ddt, *J*=1.6, 5.4, 9.1 Hz, 1 H; H-7), 1.73 (q, *J*=8.7 Hz, 1 H; H-8*endo*), 1.62 (td, *J*=5.8, 7.2 Hz, 1 H; H-1), 1.45 ppm (dt, *J*=6.0, 8.7 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, [D_6]acetone): δ=199.0 (C-6), 168.7 (C=O Phth), 145.0, 135.1, 133.2, 127.0, 123.9, 68.0, 53.4, 28.2, 21.2, 13.5 ppm; elemental analysis calcd (%) for $C_{16}H_{13}NO_4$: C 67.84; H 4.62; found: C 67.92; H 4.65.

(±)-*N*-(6*S-Hydroxy-3-oxo-bicyclo[5.1.0]oct-4-en-2*R**-yl)phthalimide**: M.p. 182–183 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=7.92–7.82 (m, 4 H; Phth), 7.01 (dd, *J*=3.0, 12.0 Hz, 1 H; H-5), 6.07 (dd, *J*=2.8, 12.0 Hz, 1 H; H-4), 4.52 (d, *J*=10.8 Hz, 1 H), 4.48 (td, *J*=2.6, 9.2 Hz, 1 H), 2.08 (ddt, *J*=4.8, 7.0, 10.6, 1 H; H-1), 1.69–1.61 (m, 1 H; H-7), 1.25 (dt, *J*=5.6, 7.6 Hz, 1 H; H-8*exo*), 1.01 ppm (q, *J*=4.9 Hz, 1 H; H-8*endo*); ^{13}C NMR (100 MHz, CD_3OD): δ=194.7 (C-3), 169.5 (C=O Phth), 158.2, 135.8, 133.2, 129.5, 124.5, 74.1, 64.3, 27.5, 18.2, 13.6 ppm.

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***N*-(3*R**,6*S**-Dihydroxybicyclo[5.1.0]oct-4-en-2*R**-yl)phthalimide (±)-11**: $[CeCl_3]\cdot 7\,H_2O$ (604 mg, 1.620 mmol) was added to a solution of (±)-**10** (230 mg, 0.810 mmol) in THF (4 mL) and methanol (7 mL). The mixture was stirred at room temperature until all the material dissolved (≈30 min). The solution was cooled to −78 °C and $NaBH_4$ (62 mg, 1.620 mmol) was added portionwise. The reaction mixture was stirred at −78 °C for 5 h, the solvent concentrated, and the resultant residue was partitioned between water and ethyl acetate. Evaporation of the solvent gave (±)-**11** (220 mg, 94 %) as a colorless solid. M.p. 225–227 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=7.90–7.78 (m, 4 H; Phth), 5.55 (td, *J*=2.4, 13.2 Hz, 1 H; H-4), 5.47 (qd, *J*=1.7, 13.2 Hz, 1 H; H-5), 4.84–4.81 (m, 1 H; H-6), 4.60 (qd, *J*=2.4, 10.1 Hz, 1 H; H-3), 4.49 (d, *J*=10.4 Hz, 1 H; H-2), 1.42–1.34 (m, 1 H; H-7), 1.21 (dt, *J*=6.1, 9.3 Hz, 1 H; H-1), 0.96 (q, *J*=5.9 Hz, 1 H; H-8*endo*), 0.70 ppm (dt, *J*=5.9, 8.8 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, CD_3OD): δ=170.0, 135.4, 133.6, 132.0, 130.4, 124.2, 69.1, 68.4, 53.6, 19.9, 16.2, 2.5 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{15}NO_4$+Na^+: 308.0893 [*M*+Na^+]; found: 308.0895.

Epoxidation of (±)-8: H_2O_2 (0.25 mL, 3.5 mmol, 50 wt % solution) was added to an ice-cold solution of trifluoroacetic anhydride (0.50 mL, 3.5 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 5 min at 0 °C and then at room temperature for 1 h. The previously prepared trifluoroperacetic acid solution was then added dropwise to an ice-cold solution of endoperoxide (±)-**8** (130 mg, 0.458 mmol) in CH_2Cl_2 (2.5 mL) and THF (2.5 mL). After addition was complete, the mixture was warmed to room temperature and stirred for 4 h. The solvent was evaporated by blowing nitrogen gas over the solution to give (±)-**13** (136 mg, 99 %) as a colorless solid. M.p. 205–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.93–7.85 (m, 2 H; Phth), 7.82–7.73 (m, 2 H; Phth), 5.59 (dd, *J*=3.5, 7.0 Hz, 1 H), 5.08 (dt, *J*=3.6, 6.8 Hz, 1 H), 4.49 (q, *J*=3.5 Hz, 1 H; H-2), 3.85 (t, *J*=4.1 Hz, 1 H), 3.40 (t, *J*=4.5 Hz, 1 H), 1.91 (q, *J*=6.1 Hz, 1 H; H-8*endo*), 1.77 (ddt, *J*=2.0, 6.8, 8.7 Hz, 1 H; H-1), 1.49 (pent, *J*=7.9 Hz, 1 H; H-7), 0.96 ppm (td, *J*=6.3, 8.8 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.4, 134.7, 131.8, 123.8, 79.0, 74.7, 52.3, 47.9, 47.0, 16.5, 15.8, 9.7 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{13}NO_5$+Na^+: 322.0686 [*M*+Na^+]; found: 322.0688.

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***N*-(4*R**,5*S**-Epoxy-3*R**,6*S**-dihydroxybicyclo[5.1.0]oct-2*S**-yl)phthalimide (±)-14**: The reduction of epoxy endoperoxide (±)-**13** (110 mg, 0.367 mmol) in CH_2Cl_2 (5 mL) with activated zinc dust (110 mg) was carried out in a fashion similar to the preparation of (±)-**9**. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=19:1) to give (±)-**14** (63 mg, 63 %) as a colorless solid. M.p. 194–195 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=7.91–7.73 (m, 4 H; Phth), 4.80 (dd, *J*=3.5, 11.0 Hz, 1 H; H-2), 4.54 (dd, *J*=0.8, 11.0 Hz, 1 H; H-3), 4.43 (t, *J*=3.5 Hz, 1 H; H-6), 3.29 (d, *J*=1.2 Hz, 1 H), 3.28–3.20 (m, 1 H), 1.15 (ddt, *J*=3.5, 6.7, 9.3 Hz, 1 H; H-7), 1.07 (dddt, *J*=0.8, 4.0, 6.7, 9.3 Hz, 1 H; H-1), 0.78 (dt, *J*=5.5, 9.2 Hz, 1 H; H-8*exo*), 0.68 ppm (q, *J*=6.3 Hz, 1 H; H-8*endo*); ^{13}C NMR (100 MHz, CD_3OD): δ=170.2, 135.4, 133.5, 124.2, 70.1, 65.6, 61.0, 58.0, 51.6, 19.8, 18.5, 7.2 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{15}NO_5$+Na^+: 324.0842 [*M*+Na^+]; found: 324.0843.

***N*-(4*S**,5*R**-Epoxy-3*R**,6*S**-dihydroxybicyclo[5.1.0]oct-2*S**-yl)phthalimide (±)-15**: The epoxidation of enediol (±)-**9** (70 mg, 0.245 mmol) in CH_2Cl_2/THF (1:1, 5 mL) with trifluoroacetic acid was carried out in a fashion similar to the preparation of (±)-**13**. Purification of the crude residue column chromatography (SiO_2, hexanes/ethyl acetate gradient=2:3→3:7) to give recovered **9** (9 mg) followed by (±)-**15** (53 mg, 83 % based on recovered starting material (b.r.s.m.)) as a colorless solid. M.p. 205–206 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=7.85 (br s, 4 H; Phth), 4.78 (dd, *J*=7.6, 12.0 Hz, 1 H; H-2), 4.01 (dd, *J*=6.8, 12.0 Hz, 1 H; H-3), 3.32–3.19 (m, 2 H; H-5 and H-6), 3.03 (dd, *J*=4.7, 6.8 Hz, 1 H; H-4), 1.34 (tt, *J*=7.2, 9.2 Hz, 1 H), 1.29–1.20 (m, 1 H), 0.99 (td, *J*=5.2, 6.4 Hz, 1 H; H-8*endo*), 0.86 ppm (ddd, *J*=4.4, 8.8, 9.6 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, CD_3OD): δ=170.5, 170.2, 135.6, 135.4, 133.6, 133.0, 124.3, 124.1, 76.7, 68.6, 60.1, 58.5, 53.4, 23.5, 17.6, 13.1 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{15}NO_5$+Na^+: 324.0842 [*M*+Na^+]; found: 324.0844.

***N*-(5*S**,6*R**-Dihydroxybicyclo[5.1.0]oct-3-en-2*R**-yl)phthalimide (±)-16 and *N*-(3*R**,4*S**-dihydroxybicyclo[5.1.0]oct-5-en-2*S**-yl)phthalimide (±)-17**: A solution of *N*-methylmorpholine-*N*-oxide (0.32 mL, 1.2 mmol, 50 wt % in water) was added to a solution of diene (±)-7 (300 mg, 1.20 mmol) in acetone (10 mL), followed by a solution of OsO_4 (0.2 mL, 0.2 M in toluene). The mixture was stirred for 1 h at room temperature. The

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reaction was quenched with $NaHSO_3$ (100 mg) and stirred for 30 min then adsorbed onto silica gel for purification by column chromatography (SiO_2, hexanes/ethyl acetate=2:3) to give recovered **7** (81 mg), followed by (±)-**16** (138 mg, 56 % b.r.s.m.) followed by (±)-**17** (72 mg, 29 % b.r.s.m.), both as colorless solids. (±)-**16**: M.p. 218–221 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.90–7.70 (m, 4 H; Phth), 5.68 (pent, *J*=2.8 Hz, 1 H; H-2), 5.55 (ddd, *J*=2.0, 5.2, 12.8 Hz, 1 H; C=CH), 5.43 (ddd, *J*=2.0, 3.6, 12.8 Hz, 1 H; C=CH), 4.60–4.68 (m, 1 H; H-5), 4.10–4.20 (m, 1 H; H-6), 2.41 (d, *J*=8.4 Hz, 1 H; OH), 2.25 (d, *J*=3.6 Hz, 1 H; OH), 1.48 (tt, *J*=6.7, 9.1 Hz, 1 H; H-7), 1.22–1.14 (m, 1 H; H-1), 1.08 (q, *J*=5.9 Hz, 1 H; H-8*endo*), 0.83 ppm (dt, *J*=5.9, 8.7 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.0, 134.3, 132.2, 128.6, 127.2, 123.5, 73.0, 71.9, 48.7, 17.9, 16.5, 7.2 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{15}NO_4$+Na^+: 308.0893 [*M*+Na^+]; found: 308.0894. (±)-**17**: M.p.=219–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.88–7.81 (m, 2 H; Phth), 7.76–7.67 (m, 2 H; Phth), 6.16 (dd, *J*=5.8, 11.8 Hz, 1 H; H-5), 5.65 (dd, *J*=7.6, 12.0 Hz, 1 H; H-6), 5.25 (dd, *J*=4.0, 10.4 Hz, 1 H; H-2), 4.40–4.30 (m, 2 H; H-5 and H-6), 2.43 (d, *J*=8.0 Hz, 1 H; OH), 1.98 (d, *J*=5.5 Hz, 1 H; OH), 1.54–1.45 (m, 1 H; H-1), 1.41 (dq, *J*=4.0, 8.8 Hz, 1 H; H-7), 1.05 (dt, *J*=4.6, 9.2 Hz, 1 H; H-8*exo*), 0.90 ppm (q, *J*=5.9 Hz, 1 H; H-8*endo*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.2, 134.7, 134.1, 132.3, 123.4, 123.3, 71.1, 68.7, 50.1, 19.6, 15.9, 13.4 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{15}NO_4$+Na^+: 308.0893 [*M*+Na^+]; found: 308.0894.

***N*-(3*R**,4*R**-Epoxy-5*S**,6*S**-dihydroxybicyclo[5.1.0]oct-2*S**-yl)phthalimide** (±)-**18**: The epoxidation of enediol (±)-**16** (138 mg, 0.484 mmol) in CH_2Cl_2 (5 mL) with trifluoroacetic acid was carried out in a fashion similar to the preparation of **15**. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate=30:70) to give (±)-**18** (121 mg, 83 %) as a colorless solid. M.p.>250 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ=7.93–7.81 (m, 4 H; Phth), 4.94 (d, *J*=5.9 Hz, 1 H; H-2), 4.82 (t, *J*=6.5 Hz, 1 H), 4.59 (d, *J*=5.1 Hz, 1 H), 4.49 (d, *J*=8.2 Hz, 1 H), 4.36 (t, *J*=5.9 Hz, 1 H), 3.98 (t, *J*=5.5 Hz, 1 H), 3.73 (d, *J*=5.9 Hz, 1 H), 1.61 (dq, *J*=5.1, 8.6 Hz, 1 H; H-7), 1.20 (q, *J*=5.7 Hz, 1 H; H-8*endo*), 1.04 (tt, *J*=5.9, 8.6 Hz, 1 H; H-1), 0.84 ppm (dt, *J*=6.7, 8.6 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, [D_6]DMSO): δ=168.5, 134.7, 131.3, 123.1, 82.0, 80.6, 72.9,

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70.3, 50.7, 15.5, 14.2, 7.7 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{15}NO_5$+Na^+: 324.0842 [*M*+Na^+]; found: 324.0846.

***N*-(5*R**,6*S**-Epoxybicyclo[5.1.0]oct-3-en-2*S**-yl)phthalimide (±)-19 and *N*-(5-oxobicyclo[5.1.0]oct-3-en-2*S**-yl)phthalimide (±)-20**: A solution of *meta*-chloroperoxybenzoic acid (196 mg, ≈0.794 mmol, ≈70 wt %) in freshly distilled CH_2Cl_2 (2 mL) was added dropwise to a solution of diene (±)-**7** (200 mg, 0.794 mmol) in freshly distilled CH_2Cl_2 (4 mL). The solution was stirred under N_2 for 5 h, at which time monitoring by TLC showed complete disappearance of starting material. The solvent was evaporated and the residue was treated with saturated bicarbonate solution (5 mL) with stirring for 30 min. The mixture was extracted several times with CH_2Cl_2, concentrated, and purified by column chromatography (SiO_2, hexanes/ethyl acetate=7:3) to give (±)-**19** (153 mg, 70 %) followed by (±)-**20** (28 mg, 12 %), both as colorless solids. (±)-**19**: M.p. 196–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=0.90–0.97 (1 H, m, H-8*exo*), 1.07 (1 H, br q, *J*=7.6 Hz, H-8*endo*), 1.58 (2 H, m, H-1 and H-7), 3.19 (1 H, t, *J*=4.8 Hz, H-5 or H-6), 3.57 (1 H, t, *J*=4.8 Hz, H-5 or H-6), 5.63 (1 H, br d, *J*=12.0 Hz, H-3), 5.78 (1 H, *J*=2.9, 5.5, 12.0 Hz, H-4), 5.91 (1 H, d, *J*=2.4 Hz, H-2), 7.70–7.93 ppm (4 H, m, Phth); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=8.3, 13.8, 18.8, 47.6, 52.8, 54.9, 123.4, 123.5, 132.2, 132.8, 134.2, 167.9 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{13}NO_3$+Na^+: 290.0788 [*M*+Na^+]; found: 290.0789. (±)-**20**: M.p. 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=0.74 (1 H, dt, *J*=6.4 and 9.0 Hz, H-8*exo*), 1.03 (1 H, q, *J*=5.7 Hz, H-8*endo*), 1.20–1.28 (2 H, m, H-1 and H-7), 2.95 (1 H, d, *J*=15.2 Hz, H-6), 3.11 (1 H, br d, *J*=15.2 Hz, H-6′), 5.61–5.64 (1 H, br s, H-2), 6.12 (1 H, ddd, *J*=1.8, 3.1, 12.9 Hz, H-4), 6.24 (1 H, dd, *J*=2.6, 13.0 Hz, H-3), 7.75–7.93 ppm (4 H, m, Phth); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=4.7, 8.4, 17.9, 41.6, 49.4, 123.78, 123.84, 132.0, 132.6, 134.6, 141.9, 167.7, 198.9 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{13}NO_3$+Na^+: 290.0788 [*M*+Na^+]; found: 290.0789.

***N*-(5*S**,6*S**-Epoxy-3*R**,4*R**-dihydroxybicyclo[5.1.0]oct-2*S**-yl)phthalimide (±)-23**: The dihydroxylation of (±)-**19** (100 mg, 0.373 mmol) in acetone (5 mL) with catalytic OsO_4 (0.14 mL, 0.2 M in toluene) and *N*-methylmorpholine-*N*-oxide (100 mg, 0.857 mmol) in water (1 mL) was carried out in a fashion similar to the dihydroxylation of (±)-**7**. Purification of the residue by column chromatography (SiO_2, hexanes/ethyl acetate gradient 1:1→1:4) gave (±)-**23** (109 mg, 97 %)

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as a colorless solid. M.p.>220 °C; ^{1}H NMR (400 MHz, [D$_6$]acetone): *δ*=7.84 (s, 4 H; Phth), 5.19 (dd, *J*=5.8, 11.4 Hz, 1 H; H-2), 4.36–4.41 (m, 2 H; H-3 and H-4), 4.16 (d, *J*=6.8 Hz, 1 H; OH), 3.58 (br d, *J*=4.8 Hz, 1 H), 3.35 (ddd, *J*=0.6, 4.2, 6.8 Hz, 1 H), 3.19 (d, *J*=5.2 Hz, 1 H; OH), 1.56 (br q, *J*=8.3 Hz, 1 H; H-7), 1.23 (tt, *J*=6.8, 8.8 Hz, 1 H; H-1), 0.96 (dt, *J*=4.9, 6.7 Hz, 1 H; H-8*endo*), 0.84 ppm (dt, *J*=4.8, 9.2 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, [D$_6$]acetone): *δ*=169.8, 135.4, 133.6, 124.1, 70.7, 67.9, 58.4, 56.5, 53.0, 20.8, 16.8, 7.2 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{15}NO_5$+Na$^+$: 324.0842 [*M*+Na$^+$]; found: 324.0843.

***N*-(3*R**,4*R**,5*S**,6*S**-Tetrahydroxybicyclo[5.1.0]oct-2*S**-yl)phthalimide (±)-25** and ****N*-(3*R**,4*R**,5*R**,6*R**-tetrahydroxybicyclo[5.1.0]oct-2S*-yl)phthalimide (±)-24**: The exhaustive hydroxylation of (±)-**7** (300 mg, 1.20 mmol) in acetone with catalytic OsO_4 was carried out in a similar fashion to the dihydroxylation of **7** except that an excess of NMO (419 mg, 3.59 mmol) was used. Purification of the residue by column chromatography (SiO_2, CH_2Cl_2/MeOH=10:1) gave (±)-**25** (187 mg, 49 %) followed by (±)-**24** (79 mg, 21 %) both as a colorless solids. (±)-**25**: M.p. 229–230 °C; ^{1}H NMR (400 MHz, CD_3OD): *δ*=7.89–7.76 (m, 4 H; Phth), 5.16 (dd, *J*=2.6, 10.6 Hz, 1 H; H-2), 4.50–4.44 (m, 1 H; H-6), 4.27 (dd, *J*=1.8, 11.0 Hz, 1 H; H-3), 4.14–4.10 (m, 1 H; H-4), 3.54 (t, *J*=2.2 Hz, 1 H; H-5), 1.39 (ddt, *J*=4.8, 7.0, 9.2 Hz, 1 H; H-7), 1.19 (ddt, *J*=2.6, 6.6, 9.2 Hz, 1 H; H-1), 0.89–0.74 ppm (m, 2 H; H-8*exo* and H-8*endo*); ^{13}C NMR (100 MHz, CD_3OD): *δ*=169.9, 135.3, 135.2, 133.7, 133.3, 124.2, 123.8, 81.0, 76.1, 69.7, 68.8, 50.8, 20.8, 18.7, 6.8 ppm; elemental analysis calcd (%) for $C_{16}H_{17}NO_6 \cdot 0.2\,H_2O$: C 59.51, H 5.43, N 4.34; found: C 59.56, H 5.49, N 4.35. (±)-**24**: M.p. 241–244 °C; ^{1}H NMR (400 MHz, CD_3OD): *δ*=7.87–7.75 (m, 4 H; Phth), 5.05 (dd, *J*=2.9, 11.2 Hz, 1 H; H-2), 4.59 (d, *J*=10.6 Hz, 1 H; H-3), 4.34 (d, *J*=3.5 Hz, 1 H; H-6), 4.00 (s, 2 H; H-4 and H-5), 1.63–1.53 (m, 1 H), 1.23–1.02 (m, 2 H), 0.63 ppm (dt, *J*=5.3, 9.0 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, CD_3OD): *δ*=170.2, 135.3, 135.1, 124.1, 123.8, 76.4, 75.9, 68.7, 66.3, 51.7, 19.8, 18.1, 7.3 ppm; elemental analysis calcd (%) for $C_{16}H_{17}NO_6$: C 60.18, H 5.37; found: C 60.18, H 5.32.

***N*-(3*R**,4*S**,5*R**,6*S**-Tetrahydroxybicyclo[5.1.0]oct-2*S**-yl)phthalimide (±)-26**: Dihydroxylation of (±)-**9** (140 mg, 0.489

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mmol) in acetone with catalytic OsO_4 and NMO (85 mg, 0.73 mmol) was carried out in a similar fashion to the dihydroxylation of **7**. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate=1:4) to give (±)-**26** (133 mg, 85 %) as a colorless solid. M.p. 254–255 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=7.90–7.78 (m, 4 H; Phth), 4.71 (dd, *J*=3.8, 10.2 Hz, 1 H; H-2), 4.37 (t, *J*=10.0 Hz, 1 H; H-3), 4.30 (t, *J*=5.4 Hz, 1 H; H-6), 4.05 (dd, *J*=2.8, 6.0 Hz, 1 H; H-5), 3.64 (dd, *J*=2.6, 9.4 Hz, 1 H; H-4), 1.50 (q, *J*=6.1 Hz, 1 H; H-8*endo*), 1.26–1.18 (m, 1 H; H-7), 1.11 (ddt, *J*=3.6, 6.4, 9.4 Hz, 1 H; H-1), 0.71 ppm (1 H, dt, *J*=5.6, 9.2 Hz, H-8*exo*); ^{13}C NMR (100 MHz, CD_3OD): δ=170.2, 135.5, 135.3, 133.9, 133.4, 124.2, 124.0, 76.3, 73.6, 71.9, 66.4, 55.3, 20.5, 17.8, 7.6 ppm; elemental analysis calcd (%) for $C_{16}H_{17}NO_6$: C 60.18, H 5.36; found: C 60.01, H 5.36.

***N*-(3*R**,4*S**,5*R**,6*R**-Tetrahydroxybicyclo[5.1.0]oct-2*S**-yl)phthalimide (±)-28** and ***N*-(3*R**,4*R**,5*S**,6*R**-tetrahydroxybicyclo[5.1.0]oct-4-en-2*S**-yl)phthalimide (±)-27**: The dihydroxylation of (±)-**11** (300 mg, 1.049 mmol) in acetone with catalytic OsO_4 and NMO (184 mg, 1.573 mmol) was carried out in a fashion similar to the preparation of (±)-**26**. Purification of the residue by column chromatography (SiO_2, CH_2Cl_2/MeOH=2:3) to give (±)-**28** (93 mg, 28 %) followed by (±)-**27** (117 mg, 34 %), both as colorless solids. (±)-**28**: M.p. 201–203 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=7.91–7.72 (m, 4 H; Phth), 4.56 (dd, *J*=2.7, 11.0 Hz, 1 H; H-2), 4.45 (t, *J*=10.2 Hz, 1 H; H-3), 4.17–4.10 (m, 2 H; H-5 and H-6), 3.27 (dd, *J*=1.6, 9.4 Hz, 1 H; H-4), 1.70 (q, *J*=6.3 Hz, 1 H; H-8*endo*), 1.24–1.14 (m, 1 H; H-7), 1.09 (ddt, *J*=2.7, 6.3, 9.4 Hz, 1 H; H-1), 0.69 ppm (dt, *J*=5.5, 9.0 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, CD_3OD): δ=170.1, 170.0, 135.5, 135.2, 133.8, 133.3, 124.2, 124.0, 77.0, 76.0, 70.1, 66.4, 55.5, 20.2, 17.8, 8.4 ppm; elemental analysis calcd (%) for $C_{16}H_{17}NO_6$: C 60.18, H 5.36; found: C 59.93, H 5.29. (±)-**27**: M.p.>230 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=7.90–7.76 (m, 4 H; Phth), 5.50 (dd, *J*=3.0, 11.0 Hz, 1 H; H-2), 4.30 (d, *J*=10.4 Hz, 1 H; H-3), 4.26 (dd, *J*=3.6, 9.6 Hz, 1 H; H-6), 4.06 (s, 1 H; H-4), 3.34 (d, *J*=8.4 Hz, 1 H; H-5), 1.31 (ddt, *J*=3.6, 6.8, 9.6 Hz, 1 H; H-7), 1.16 (ddt, *J*=3.0, 6.6, 9.6 Hz, 1 H; H-1), 0.90 (q, *J*=6.4 Hz, 1 H; H-8*endo*), 0.67 ppm (dt, *J*=6.0, 9.0 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, CD_3OD): δ=170.5, 170.2, 135.4, 135.3, 133.8, 133.4, 124.2, 123.9, 78.1,

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74.1, 69.3, 68.6, 50.9, 20.0, 18.1, 4.9 ppm; elemental analysis calcd (%) for $C_{16}H_{17}NO_6$: C 60.18, H 5.36; found: C 59.65, H 5.38.

***N*-(3*R**,4*R**,5*S**,6*R**-Tetrahydroxybicyclo[5.1.0]oct-4-en-2*S**-yl)phthalimide (±)-27**: Carbon tetrabromide (20 mg, 0.058 mmol) was added as a catalyst to a solution of epoxydiol (±)-**23** (87 mg, 0.29 mmol) in water (3 mL). The mixture was heated at reflux with stirring for 8 h, the solvent was evaporated and the residue was recrystallized from methanol to give (±)-**27** as colorless crystals (61 mg, 66 %). The spectral date for this product was consistent with that previously obtained.

***N*-(3*S**,4*S**,5*S**,6*R**-Tetrahydroxybicyclo[5.1.0]oct-2*S**-yl)phthalimide (±)-30 and *N*-(1*R**,3*R**,4*R**,5?*-tetrahydroxy-6-cycloocten-2*R**-yl)phthalimide (±)-31**: The hydrolysis of bisepoxide (±)-**12** (90 mg, 0.32 mmol) in THF (5 mL), dionized water (7 mL), and a catalytic amount of CBr_4 (42 mg, 0.13 mmol) was carried out in a fashion similar to the hydrolysis of (±)-**23**. Purification of the residue by column chromatography (SiO_2, CH_2Cl_2/MeOH=19:1) gave (±)-**30** (46 mg, 46 %) followed by (±)-**31** (17 mg, 18 %), both as colorless solids. (±)-**30**: M.p. 218–220 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=7.92–7.80 (m, 4 H; Phth), 5.16 (t, *J*=2.2 Hz, 1 H; H-2), 4.28 (dd, *J*=3.8, 9.6 Hz, 1 H; H-6), 4.03 (td, *J*=1.7, 6.0 Hz, 1 H; H-3), 3.98 (dd, *J*=2.0, 6.0 Hz, 1 H; H-4), 3.64 (dd, *J*=1.6, 9.6 Hz, 1 H; H-5), 1.56 (q, *J*=6.0 Hz, 1 H; H-8*endo*), 1.32 (ddt, *J*=3.2, 6.4, 9.6 Hz, 1 H), 1.03 (br q, *J*=8.6 Hz, 1 H), 0.70 ppm (dt, *J*=5.6, 8.8 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, CD_3OD): δ=171.1, 135.7, 133.4, 124.4, 75.9, 74.6, 72.1, 70.1, 50.4, 19.7, 16.7, 7.6 ppm; elemental analysis calcd (%) for $C_{16}H_{17}NO_6$: C 60.18, H 5.36; found: C 59.84, H 5.29. (±)-**31**: ^{1}H NMR (400 MHz, CD_3OD): δ=7.90–7.78 (m, 4 H; Phth), 5.81 (dd, *J*=6.0, 10.8 Hz, 1 H; H-2), 5.74 (ddt, *J*=1.6, 6.8, 10.8 Hz, 1 H; H-1), 4.93 (br d, *J*=6.0 Hz, 1 H), 4.88 (d, *J*=4.0 Hz, 1 H), 4.30 (d, *J*=6.0 Hz, 1 H; H-4), 4.08 (dd, *J*=1.0, 5.8 Hz, 1 H; H-3), 3.93–3.86 (m, 1 H; H-7), 2.89 (dt, *J*=9.2, 12.4 Hz, 1 H; H-8), 2.31 ppm (td, *J*=6.6, 12.4 Hz, 1 H; H-8'); ^{13}C NMR (100 MHz, CD_3OD): δ=170.6, 138.3, 135.5, 133.4, 126.1, 124.2, 77.6, 77.1, 76.3, 69.0, 52.5, 34.7 ppm; HRMS (FAB): *m/z* calcd for $C_{16}H_{17}NO_6$+Na: 342.0948 [*M*+Na^+]; found: 342.0949.

***N*-(3*S**,4*R**,5*S**,6*S**-Tetrahydroxybicyclo[5.1.0]oct-2*S**-yl)phthalimide (±)-29**: Hydrolysis of epoxydiol (±)-**18** (120 mg,

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0.399 mmol) in THF (5 mL) with a catalytic amount of CBr_4 (26 mg, 0.079 mmol) was carried out in a fashion similar to the hydrolysis of (±)-**23**. Purification of the residue by column chromatography (SiO_2, CH_2Cl_2/MeOH gradient=19:1→9:1) gave recovered (±)-**18** (26 mg) followed by (±)-**29** (81 mg, 81 %) as a colorless solid. M.p. 202–204 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=7.92–7.86 (m, 2 H; Phth), 7.86–7.81 (m, 2 H; Phth), 5.33 (t, *J*=2.2 Hz, 1 H; H-2), 4.63 (d, *J*=4.4 Hz, 1 H; H-6), 4.07 (td, *J*=1.6, 6.0 Hz, 1 H; H-4), 4.04 (td, *J*=1.6, 6.0 Hz, 1 H; H-3), 3.83 (br s, 1 H; H-5), 1.54–1.46 (m, 1 H), 1.41–1.28 (m, 1 H), 1.11 (q, *J*=8.0 Hz, 1 H; H-8*endo*), 0.81 ppm (dt, *J*=5.5, 9.4 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, CD_3OD): δ=171.0, 135.7, 133.4, 124.4, 78.2 (br), 76.6, 68.6 (br), 50.4, 20.2, 18.5, 9.2 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{17}NO_6$+Na^+: 324.0948 [*M*+Na^+]; found: 324.0950.

***N*-(3*R**,4*S**,5*S**,6*S**-Tetrahydroxybicyclo[5.1.0]oct-2S*-yl)phthalimide (±)-32**: The hydrolysis of epoxydiol (±)-**14** (40 mg, 0.13 mmol) in THF (1 mL) and deionized water (5 mL) with a catalytic amount of CBr_4 (9 mg, 0.03 mmol) was carried out in a fashion similar to the hydrolysis of (±)-**23**. Purification of the residue by column chromatography (SiO_2, CH_2Cl_2/MeOH=9:1) gave (±)-**32** (39 mg, 92 %) as a colorless solid. M.p.=126–128 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=7.91–7.67 (m, 4 H; Phth), 4.79 (dd, *J*=2.8, 10.8 Hz, 1 H; H-2), 4.44–4.30 (br m, 1 H; H-6), 4.00 (dd, *J*=9.0, 10.2 Hz, 1 H; H-3), 3.53 (t, *J*=8.8 Hz, 1 H; H-4), 3.45 (br d, *J*=8.8 Hz, 1 H; H-5), 1.33 (tt, *J*=6.2, 9.3 Hz, 1 H; H-7), 1.17 (ddt, *J*=3.1, 6.3, 9.2 Hz, 1 H; H-1), 0.90 (q, *J*=6.3 Hz, 1 H; H-8*endo*), 0.80 ppm (td, *J*=6.1, 9.1 Hz, 1 H; H-8*exo*); ^{13}C NMR (100 MHz, CD_3OD): δ=168.5, 133.8, 132.0, 122.6, 73.2, 71.5, 68.1, 65.7, 51.9, 17.7, 16.7, 6.3 ppm; elemental analysis calcd (%) for $C_{16}H_{17}NO_6$: C 60.18, H 5.36; found: C 59.97, H 5.36.

Formylcyclohexene (±)-33: The hydrolysis of epoxydiol (±)-**15** (150 mg, 0.497 mmol) in THF (2 mL) and deionized water (10 mL) with a catalytic amount of CBr_4 (33 mg, 0.099 mmol) was carried out in a fashion similar to the hydrolysis of (±)-**23**. Purification of the residue by column chromatography (SiO_2, hexanes/ethyl acetate gradient=11:9 to 3:7) gave (±)-**33** as a colorless solid (53 mg, 45 %) followed by recovered starting material (±)-**15** (41 mg). (±)-**33**: M.p. 215–216 °C; ^{1}H NMR (400 MHz, CD_3OD): δ=9.54 (s, 1 H; CHO), 7.96–7.76 (m, 4 H; Phth), 6.52 (1 H, d, *J*=1.2 Hz, C=CH), 5.09 (d, *J*=9.8

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Hz, 1 H; H-4), 4.49 (dd, *J*=3.9, 9.8 Hz, 1 H; H-5), 2.09 (dt, *J*=4.7, 8.2 Hz, 1 H; H-1), 1.52 (ddt, *J*=3.9, 6.3, 8.4 Hz, 1 H; H-6), 1.13 (dt, *J*=5.1, 8.4 Hz, 1 H; H-7*exo*), 1.03 ppm (q, *J*=5.1 Hz, 1 H; H-7*endo*); ^{13}C NMR (100 MHz, CD_3OD): δ=194.0, 170.3, 148.0, 144.6, 135.5, 133.5, 124.2, 64.9, 54.7, 14.9, 14.4, 10.0 ppm; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{13}NO_4$+Na^+: 306.0737 [*M*+Na^+]; found: 306.0739.

β-Glucosidase inhibitions[22]

Activities against β-glucosidase were determined at 25 °C at pH in 100 mM sodium acetate buffer with *p*-nitrophenyl β-D-glucoside as substrate against β-D-glucosidase (Aldrich). The release of *p*-nitrophenolate was measured continuously at 405 nm.

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