Asymmetric Synthesis of *cis*-1,3-Diamino-1,3-dideoxycyclitols

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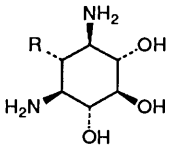
Starting with the hetero-Diels–Alder reaction of the *O*-isopropylidene-protected *cis*-cyclohexa-3,5-diene-1,2-diol with (−)-2,3:5,6-di-*O*-isopropylidene-1-nitroso-α-D-*manno*-furanosyl chloride the optically pure (+)-*endo*-adduct was exclusively formed. After reduction of the NO bond and protection of the amino group, the second nitrogen function was introduced by participation of the neighbouring trichloroacetimidate group in the addition of iodine to the C=C bond or in the epoxide opening of the corresponding tri-*O*-trichloroacetimidato-*trans*-epoxide derivative. Hydrolysis of the bicyclic dihydro-1,3-oxazoles, complete acetylation, deiodonation if necessary, and final simultaneous removal of all protective groups yielded (−)-1L-2,4-diamino-2,3,4-trideoxy-*allo*-inositol and (−)-1L-2,4-diamino-2,4-dideoxy-*chiro*-inositol in good overall yields.

The absolute configuration of the hetero-Diels–Alder *endo*-adduct was determined by chemical transformation.

The great majority of amino glycoside antibiotics contain 2-deoxystreptamine (2-DOS) **1** and streptamine **2** as aminocyclitol subunits.[1] Isomers of aminocyclitols **1** and **2** with



R = H **1**
R = OH **2**

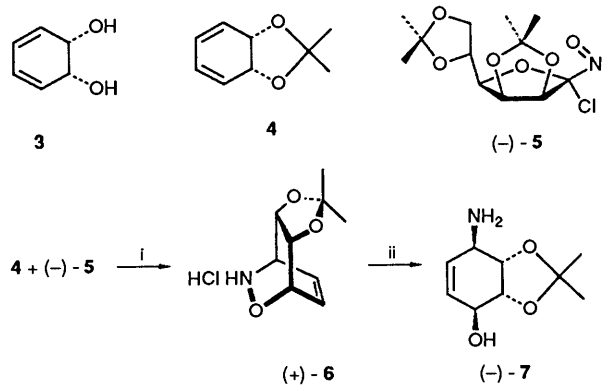
conserved configuration of the amino groups are attractive targets for selective syntheses considering their application for, *e.g.* mutasynthesis of new antibiotics [2] or as ligands in cytostatic Pt^{II} complexes.[3]

We have recently presented a stereoselective route to racemic *cis*-1,3-diamino-1,3-dideoxycyclitols based on the hetero-Diels–Alder reaction of an activated achiral nitroso dienophile with racemic *trans*-1,2-disubstituted cyclohexa-3,5-dienes.[4] Consequently, it was important to establish an analogous asymmetric synthesis of new 2-DOS and streptamine isomers. For this purpose we chose the chiral dienophile (−)-2,3:5.6-di-*O*-isopropylidene-1-nitroso-α-D-*manno*-furanosyl chloride **5**[5,6] and the biotechnologically produced achiral *cis*-cyclohexa-3,5-diene-1,2-diol **3** [6,7] as starting materials.

Results and Discussion

cis-Cyclohexa-3,5-diene-1,2-diol **3**[7] was protected as its stable 1,2-*O*-isopropylidene derivative **4**.[8] The isopropylidene protective group was chosen because of the significant advantages of compound **4** compared with the corresponding diacetoxy derivative.[6] Besides the higher reactivity (4 days at −40 °C instead of 14 days at −8 °C) in the racemic hetero-Diels–Alder reaction, the yield in the formation of compound (±)-**6** is considerably higher than the yield reported for the analogous reaction with the diacetoxy derivative.[6] Moreover (see below), the reductive cleavage of the N–O bond of the dihydrooxazines resulting from the hetero-Diels–Alder reaction with nitroso dienophiles could not be achieved without simultaneous deacetylations in the latter case. The ketal compound **6**, instead, could be selectively reduced under basic conditions to afford the preparatively useful mono alcohol **7** (Scheme 1).

The *meso*-diene **4** was subjected to the hetero-Diels–Alder reaction with (−)-2,3:5,6-di-*O*-isopropylidene-1-nitroso-α-D-*manno*-furanosyl chloride **5** to yield the *endo*-adduct stereoselectively while enantioselectively generating four chiral centres in the resulting dihydrooxazine (+)-**6**.[6]



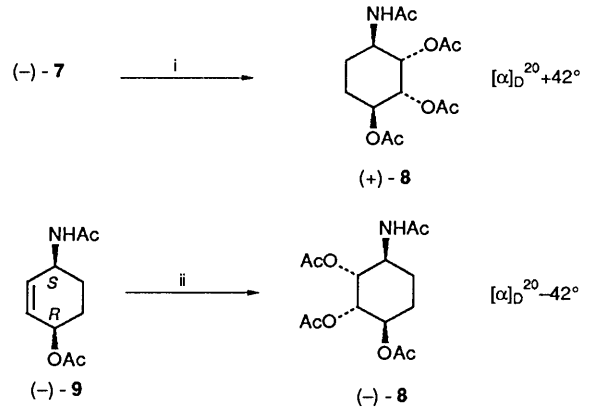
Scheme 1 *Reagents and conditions:* i, Et_2O–EtOH, −30 °C, 7 days; ii, Al/Hg, aq. THF (20:1), 0 °C, 2 days

The optical purity of isomer (+)-**6** could be determined by ^1H NMR spectroscopy using the Eu(tfc)$_3$ shift reagent and separation of the acetoxy signal of acetylated compound (−)-**10**. Acetylated (−)-**10** was used because attempts to achieve separation of the signals from the isopropylidene groups or the acetyl signal from the *N*-acetylated derivative of compound (+)-**6** failed. No trace of the other enantiomer was found, thus showing that the enantiomeric excess of (+)-**6** was > 97%. To determine the absolute configuration of (+)-**6** as described by Werbitzky,[6] the corresponding conduramine A1 derivative (−)-**7** was transformed to give the cyclohexane derivative (+)-**8** by de-*O*-isopropylidenation, catalytic hydrogenation, and complete acetylation (Scheme 2).

The opposite sense of the optical rotation of the enantiomer (−)-**8**,[6] which was prepared by *syn*-hydroxylation of the known cyclohexene derivative (1*R*,4*S*)-**9**,[5] confirmed the (1*S*,4*R*,5*S*,6*R*)-configuration of (−)-**7** and hence the (1*S*,4*R*,7*S*,8*S*)-configuration of (+)-**6**.

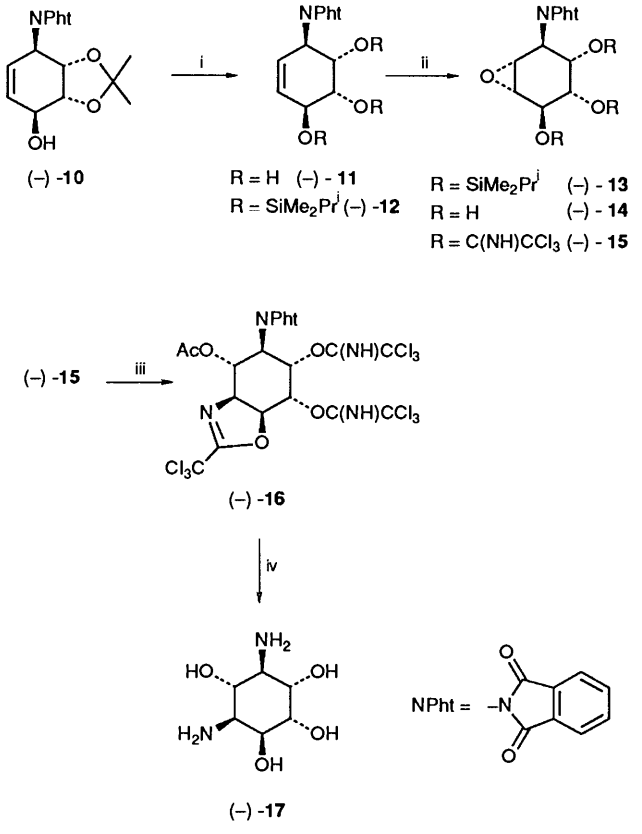
Al/Hg in tetrahydrofuran (THF)[9] served to reduce the dihydrooxazine (+)-**6** to the allylic aminocycohexenol (−)-**7** which was protected by phthaloylation[4] to yield compound (−)-**10** before hydrolysis to the triol (−)-**11** or formation of the corresponding trichloroacetimidate (−)-**18** with NaH and trichloroacetonitrile.

After protection of the hydroxy groups in compound (−)-



Scheme 2 *Reagents and conditions:* i, 0.01 mol dm^{-3} HCl, H_2, Pd/C (10%); then Ac_2O–pyr; ii, $KMnO_4$; then Ac_2O–pyr

11 as isopropyldimethylsilyl ethers (−)-**12**, epoxidation with *p*-nitroperbenzoic acid led to the *trans*-epoxide **13** exclusively. *trans*-Epoxidation of the silyl ether derivative of compound (−)-**10** failed since one methyl residue of the ketal function effectively shielded the ring from *anti*-attack. The silyl protective groups were removed by hydrolysis with 75% acetic acid and were replaced by trichloroacetimidato functions to give the tris-trichloroacetimidate (−)-**15** (see Scheme 3).

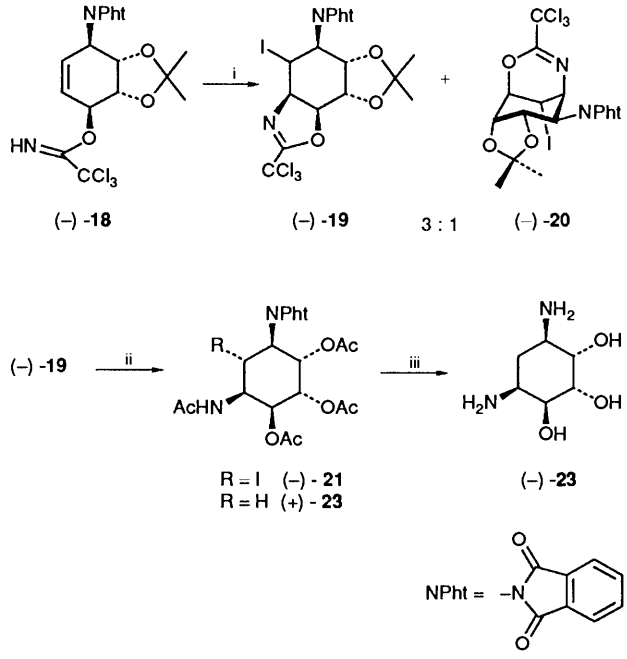


Scheme 3 *Reagents and conditions:* i, 80% HOAc; then Pr^iMe_2SiCl, imidazole, ii, *p*-$O_2NC_6H_4CO_3H$; then 75% HOAc; then Cl_3CCN–DBU; iii, Et_3Al, DME; then EtOH; then Ac_2O–pyr, iv, 0.1 mol dm^{-3} HCl; then N_2H_4

Stereoselective intramolecular epoxide opening by the vicinal trichloroacetimidato residue in the presence of triethylaluminium[10] yielded the 2-trichloromethyl-4,5-dihydro-1,3-oxazole (−)-**16** exclusively. Hydrolytic cleavage of the heterocycle with dil. HCl preceded the complete, simultaneous removal of all protective groups as shown below.

Neighbouring-group participation of the imidate residue of compound (−)-**18** in the addition of iodine from *N*-iodosuccinimide (NIS)[11] gave the 2-trichloromethyldihydro-1,3-oxazole (−)-**19** and the 2-trichloromethyl-1,3-oxazine (−)-**20** quantitatively in a 3:1 ratio. The unselective cyclisation resulting in the formation of both heterocycles was obviously due to the steric requirements of the 7,8-*O*-isopropylidene ring. This explanation is supported by the observation that analogous cyclisation reactions of monocyclic 5*c*,6*t*-disubstituted 4*c*-phthalimidocyclohex-2-enyl trichloroacetimidates occurred stereoselectively to form bicyclic 2-trichloromethyldihydro-1,3-oxazoles.[4] Fortunately, compounds (−)-**19** and (−)-**20** could be easily separated in one crystallisation step from ethyl acetate–hexane since, in contrast to the oxazole (−)-**19**, the oxazine (−)-**20** was very reluctant to crystallise.

Treatment of (−)-**19** with dil. HCl opened the heterocycle to give the *N*-protected iodoinosdiamine which had to be completely acetylated to compound (−)-**21** to ensure a good yield in the following dehalogenation step (see Scheme 4).



Scheme 4 *Reagents and conditions:* i, NIS–CH_2Cl_2, ii, HCl; then Ac_2O–pyr; then Bu_3SnH, AIBN; iii, N_2H_4, $CHCl_3$–EtOH, 80 °C

Reduction of iodide (−)-**21** with Bu_3SnH–azoisobutyronitrile (AIBN) in refluxing toluene[11] removed the iodo residue to afford the protected 2-deoxyinosdiamine (+)-**22**. Refluxing in chloroform–ethanol with excess of hydrazine simultaneously removed all protective groups from hydrolysed compounds (−)-**16** and (+)-**22**. Ion-exchange resin Amberlite IRA-400 (Cl^-) served to remove the formed phthalohydrazide from the mixture. Following chromatography on a Dowex 50W (H^+) ion-exchange column with water the diamino cyclitols were retained, which were eluted from the column with 1.5 mol dm^{-3} HCl.

The bishydrochlorides of (−)-1L-2,4-diamino-2,4-dideoxy-*chiro*-inositol (−)-**17** and (−)-1L-2,4-diamino-2,3,4-trideoxy-*allo*-inositol (−)-**23** were obtained by lyophilisation of the eluates and subsequent recrystallisation from methanol–acetone.

The enantiomers (+)-**17** and (+)-**23** are accessible in the same way by using (+)-2,3:5,6-di-*O*-isopropylidene-1-nitroso-α-L-*manno*-furanosyl chloride (+)-**5** in the initial hetero-Diels–Alder reaction. Dienophile **5** was prepared from the now commercially available L-mannono-1,4-lactone.[12]

Starting with the achiral 1-chloro-1-nitrosocyclohexane as

dienophile the analogous preparation of racemic compounds **17**[13] and **23** was carried out, differing only in the separation of the racemic hetero-Diels–Alder adduct (±)-**6** from the resulting cyclohexanone ketal by simple crystallisation from the reaction mixture instead of chromatography (see Experimental section).

Experimental

General.—M.p.s were determined (uncorrected) on a Büchi SMP-20 melting point apparatus. IR spectra were measured with a Perkin-Elmer IR 397 spectrometer for KBr pills. A Bruker WM 250 (250 MHz/63 MHz) spectrometer was used for ^1H and ^{13}C NMR spectra. Microanalyses were carried out with a Perkin-Elmer 240 B analyser. *J*-Values are given in Hz. Mass spectroscopy was performed using a Varian MAT 311 spectrometer. Optical rotation data were recorded with a Perkin-Elmer PE 141 polarimeter. TLC was carried out on Merck silica gel 60 F_{254} on aluminium sheets with mixtures of ethyl acetate–hexane as eluant. For column chromatography Merck silica gel 60 (particle size 0.063–0.2 mm/70–230 mesh) derived as stationary phase. All solvents were distilled, and then dried over appropriate molecular sieves before use.

Generally, the stereoselectivity of pivotal steps was determined by ^1H NMR spectroscopy of the crude products. The stereochemistry of all compounds was elucidated by decoupling ^1H NMR and, if necessary, by $^1H/^1H$- and $^1H/^{13}C$-COSY studies.

cis-Cyclohexa-3,5-diene-1,2-diol **3**, see ref. 7.

cis-5,6-*O*-Isopropylidenecyclohexa-1,3-diene **4**, see ref. 8.

(−)-2,3:5,6-Di-*O*-isopropylidene-1-nitroso-α-D-*manno*-furanosyl chloride (−)-**5**, see ref. 5.

(1S,4R,7S,8S)-(+)-7,8-O-*Isopropylidenedioxy*-2-*oxa*-3-*azabicyclo*[2.2.2]*oct*-5-*ene Hydrochloride* (+)-**6**.—A solution of diene **4** (6.9 g, 45.33 mmol) in diethyl ether (100 cm^3), dichloromethane (50 cm^3) and ethanol (4.5 cm^3) was cooled to −30 °C before the chiral dienophile (−)-**5** (13.95 g, 45.33 mmol) was added. After *ca.* 1 week the blue colour had vanished and a white precipitate had formed. After removal of the solvent the residue was purified by column chromatography with ethyl acetate–hexane (2:3) as eluent to remove the mannose derivative. The *oxazine* (+)-**6** was completely retained and finally eluted from the column with ethyl acetate–methanol (5:2) to afford crystals (8.17 g, 82%) after evaporation, m.p. 180–182 °C (decomp.); $[\alpha]_D^{20}$ +0.452° [*c* 1.0, THF/0.01 mol dm^{-3} NaOH (20:1)] (Found: C, 49.1; H, 6.5; N, 6.3. $C_9H_{14}ClNO_3$ requires C, 49.21; H, 6.42; N, 6.38%); ν_{max}/cm^{-1} 2980w, 2950w, 2600br s, 2500br s, 2410br s, 1625m, 1390m and 1380m; δ_H(250 MHz; $CDCl_3$) 6.67 (1 H,t, *J* 7.0 and 7.0, 6-H), 6.54 (1 H, t, *J* 7.0 and 7.0, 5-H), 5.07 (1 H, m, 1-H), 4.97 (1 H, dd, *J* 7.0 and 3.6, 4-H), 4.82 (1 H, m, 8-H), 4.66 (1 H, dd, *J* 4.4 and 6.8, 7-H) and 1.31 (6 H, s, Me); δ_C(63 MHz; CD_3OD) 135.17 and 128.38 (C-7 or -8), 122.71 (CMe_2), 73.36 and 73.06 (C-5 or -6), 70.51 (C-4), 52.23 (C-1), 25.64 and 25.42 (Me); *m/z* (field desorption) 184 ($M^{\cdot+}$ − HCl, 100%).

(1RS,4SR,7RS,8RS)-(±)-7,8-O-*Isopropylidenedioxy*-2-*oxa*-3-*azabicyclo*[2.2.2]*oct*-5-*ene* (±)-**6**.—A solution of diene **4** (6.6 g, 43.3 mmol) in diethyl ether (100 cm^3), dichloromethane (50 cm^3) and ethanol (4.5 cm^3) was cooled to −30 °C before addition of 1-chloro-1-nitrosocyclohexane (6 g, 43.3 mmol). After 4–5 days the blue colour had disappeared and a white solid had formed. Filtration and washing with diethyl ether (200 cm^3) gave pure racemate (±)-**6** (7.61 g, 80%), m.p. 178–181 °C (decomp.).

(1S,4R,5S,6R)-(−)-4-*Amino*-5,6,O-*isopropylidenedioxycyclohex*-2-*en*-1-*ol* (−)-**7**.—The oxazine (+)-**6** (7.7 g, 0.035 mmol) was dissolved in a mixture (100 cm^3) of THF–water (20:1) and kept under nitrogen. Following Keck's procedure[9] amalgamated aluminium sheets (1.9 g, 0.07 mol) were added to the solution within 2 days at 0 °C. After filtration and washing with propan-2-ol–acetone–THF (1:1:1) (*ca.* 200 cm^3) the combined organic phase was evaporated to leave *compound* (−)-**7** as an oil, which was dried to constant weight (6.14 g, 94%) under high vacuum; $[\alpha]_D^{20}$ −14.2° (*c* 1.0, THF) (Found: C, 58.1; H, 8.3; N, 7.5. $C_9H_{15}NO_3$ requires C, 58.36; H, 8.16; N, 7.56%); δ_H(250 MHz; $CDCl_3$) 6.12 (1 H, dd, *J* 9.6 and 4.3, 2-H), 5.92 (1 H, dd, *J* 9.6 and 4.3, 3-H), 5.39 (1 H, dd, *J* 7.5 and 3.9, 6-H), 4.16 (2 H, m, 1- and 5-H), 3.55 (1 H, t, *J* 4.3 and 4.3, 4-H), 1.40 (3 H, s, Me) and 1.33 (3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 132.83 and 131.29 (C-2 and -3), 108.66 (CMe_2), 79.82 and 79.75 (C-5 and -6), 68.63 (C-1), 50.81 (C-4), 26.58 (Me) and 24.33 (Me).

(1S,2R,3S,4R)-(+)-4-*Acetamidocyclohexane*-1,2,3-*triyl Triacetate* (+)-**8**.—Compound (−)-**7** (150 mg, 0.8 mmol) was stirred for 1 day in 0.1 mol dm^{-3} HCl (3 cm^3). The solution was evaporated, the residue was redissolved in methanol, and the solution was saturated with hydrogen. The hydrogenation was carried out with a prehydrogenated catalyst (10% Pd/C) (15 mg). The catalyst was removed, the solution was evaporated to dryness, and the residue was acetylated with acetic anhydride–pyridine. After recrystallisation from ethyl acetate–hexane triacetate (+)-**8** was obtained as a solid (214 mg, 84%), m.p. 99–101 °C; $[\alpha]_D^{20}$ +42.0° (*c* 5.0, $CHCl_3$) (lit.,[8] $[\alpha]_D^{20}$ +42.4°).

(1*R*,2*S*,3*R*,4*S*)-(−)-4-Acetamidocyclohexane-1,2,3-triyl triacetate (−)-**8**. See ref. 6; $[\alpha]_D^{20}$ −42.2° (*c* 5.0, $CHCl_3$).

(1R,4*S*)-(−)-4-Acetamidocyclohex-2-enyl acetate (−)-**9**, see ref. 5,6.

(1S,4R,5S,6R)-(−)-5,6-O-*Isopropylidenedioxy*-4-*phthalimidocyclohex*-2-*enol* (−)-**10**.—Compound (−)-**7** (4.867 g, 26.3 mmol), *N*-ethoxycarbonylphthalimide (5.760 g, 26.5 mmol) and sodium carbonate (3 g, 28 mmol) were carefully dried under high vacuum before being suspended in dry acetone (250 cm^3) with anhydrous calcium sulphate (sikkon, Fluka) (~2 g). The reaction mixture was kept at 30 °C and the reaction had finished after 1 day, as indicated by TLC. Column chromatography on silica gel [350 mm, 30 mm; ethyl acetate–hexane (2:3)] was necessary in order to isolate the *pure product* (7.66 g, 90%), $[\alpha]_D^{20}$ −45.5° (*c* 1.0, $CHCl_3$); m.p. 191 °C (Found: C, 64.6; H, 5.6; N, 4.3. $C_{17}H_{17}NO_5$ requires C, 64.75; H, 5.43; N, 4.44%); ν_{max}/cm^{-1} 3480s, 1765m, 1700s, 1380s and 1370m; δ_H(250 MHz; $CDCl_3$) 7.86 (2 H, m, ArH), 7.75 (2 H, m, ArH), 5.99 (1 H, dt, *J* 9.8, 3 and 3, 2-H), 5.67 (1 H, dt, *J* 9.8, 2.6 and 2.6, 3-H), 4.81 (1 H, m, 4-H), 4.64 (1 H, t, *J* 6 and 6, 5-H), 4.33 (2 H, m, 6- and 1-H), 2.74 (1 H, d, *J* 5.7, OH), 1.52 (3 H, s, Me) and 1.34 (3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 167.86, 134.22, 131.78 (C-2 or -3), 131.34, 125.92 (C-3 or -2), 123.49, 109.55 (CMe_2), 79.96 , 74.24 (C-5 or -6), 69.93 (C-1), 50.77 (C-4) and 27.28 and 25.11 (2 × Me); *m/z* (FD) 315 ($M^{\cdot+}$, 100%) and 300 ($M^{\cdot+}$ − CH_3, 18).

(1R,2R,3S,6R)-(−)-6-*Phthalimidocyclohex*-4-*ene*-1,2,3-*triol* (−)-**11**.—A suspension of the protected triol (−)-**10** (0.56 g, 1.78 mmol) in acetic acid (80%) (10 cm^3) was stirred at 65 °C. After 2 h the reaction had finished, indicated by TLC [ethyl acetate–hexane (1:1)]. After evaporation of the solution to dryness, the crude product was recrystallised from ethanol–hexane to give *compound* (−)-**11** (0.45 g, 92%) as a solid, $[\alpha]_D^{20}$ 112.0° (*c* 1.0, MeOH); m.p. 188 °C (decomp.) (Found: C, 61.0; H, 4.75; N, 4.9. $C_{14}H_{13}NO_5$ requires C, 61.09; H, 4.76; N, 5.09%); ν_{max}/cm^{-1} 3500vs, 3470vs, 3410vs, 1760s and 1700s; δ_H(250 MHz; $[^2H_6]$acetone) 7.85 (4 H, s, ArH), 5.80 (1 H, dddd, *J* 10, 4.0, 2.7 and 1.3, 4-H), 5.69 (1 H, dd, *J* 10 and 1.8, 5-H), 5.07 (1 H, m, 6-H), 4.55 (1 H, m, 1-H), 4.19 (1 H, m, 2- or 3-H) and 4.06 (1 H, m, 3- or 2-H); δ_C(63 MHz; CD_3OD) 169.88, 135.28, 133.34,

130.30 and 128.48 (C-4/5) 124.01, 75.32, 71.02 and 67.28 (C-1/2/3) and 51.71 (C-6); *m/z* (FD) 275 ($M^{\cdot+}$, 91%) and 257 ($M^{\cdot+} - H_2O$, 100).

(3S,4R,5S,6R)-(−)-3,4,5-*Tris*[*isopropyl(dimethyl)siloxy*]-6-*phthalimidocyclohexene* (−)-**12**.—To a solution of compound (−)-**11** (0.30 g, 1.10 mmol) and imidazole (0.56 g, 8.18 mmol) in dry dichloromethane (12 cm^3) under nitrogen was added chloro(isopropyl)dimethylsilane (0.63 cm^3, 3.92 mmol). After the mixture had been stirred at room temperature overnight TLC [ethyl acetate–hexane (1:1)] indicated the end of the reaction. The solution was then diluted with dichloromethane, washed twice with water, and dried over $MgSO_4$. Filtration and evaporation to dryness gave the *siloxane* (−)-**12** (0.62 g, 98%) as a yellowish, waxy solid clean enough for epoxidation, $[\alpha]_D^{20}$ −55.3° (*c* 1.0, $CHCl_3$) (Found: C, 60.2; H, 8.6. N, 2.45. $C_{29}H_{49}NO_5Si_3$ requires C, 60.48; H, 8.58; N, 2.43%); δ_H(250 MHz; $CDCl_3$) 7.83 (2 H, m, ArH), 7.70 (2 H, m, ArH), 5.70 (1 H, m, 2-H), 5.59 (1 H, dd, *J* 10 and 1.8, 1-H), 5.14 (1 H, br d, *J* 9.2, 6-H), 4.60 (1 H, dd, *J* 9.2 and 1.8, 5-H), 4.06 (1 H, t, *J* 3.7 and 3.7, 3-H), 3.85 (1 H, m, 4-H), 1.01–0.71 (21 H, m, Pr^i) and 0.16, 0.12, 0.11, 0.10, −0.09 and −0.28 (each 3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 168.22, 133.84, 132.16, 129.04 and 127.45 (C-1/2), 123.00, 76.50 (C-4), 71.14 (C-3), 67.84 (C-5), 50.53 (C-6), 16.87, 16.78 and 16.65 ($CHMe_2$), 14.99, 14.76 and 14.48 (*C*HMe) and −3.38, −3.45, −3.58, −3.77, −3.85 and −4.58 (Me); *m/z* (FD) 576 ($M^{\cdot+}$, 5.2%) and 532 ($M^{\cdot+} - Pr^i$, 100).

(1S,2S,4S,5R,6S)-(−)-4,5-*Epoxy*-6-*phthalimidocyclohexane*-1,2,3-*triol* (−)-**14**.—Compound (−)-**12** (0.40 g, 0.69 mmol) and *p*-nitroperbenzoic acid (85%) (0.26 g, 1.20 mmol) were stirred in abs. chloroform (10 cm^3) at room temperature with exclusion of moisture. After 2 days the reaction mixture was diluted with chloroform and extracted twice with saturated aq. sodium carbonate and once with water. After being dried over $MgSO_4$ the organic layer was evaporated to dryness.

For desilylation the residue **13** was then stirred in 75% acetic acid (5 cm^3) for 2 h. After removal of the solvent, recrystallisation from acetone–hexane yielded the *title epoxide* (−)-**14** (0.17 g, 87%), $[\alpha]_D^{20}$ −46.7° (*c* 1.0, acetone); m.p. 199 °C (Found: C, 57.5; H, 4.5, N, 4.6. $C_{14}H_{13}NO_6$ requires C, 57.73; H, 4.50; N, 4.81%); ν_{max}/cm^{-1} 3380br s, 1770s, 1700vs, 1270s, 910s and 790 s; δ_H(250 MHz; [$^2H_6$]acetone) 7.88 (4 H, s, ArH), 4.68 (1 H, d, *J* 10.1, 6-H), 4.42 (1 H, dd, *J* 10.1 and 2.5, 1-H), 4.33 (1 H, m, 3-H), 3.86 (1 H, m, 2-H), 3.47 (1 H, d, *J* 3.4, 5-H) and 3.28 (1 H, m, 4-H); δ_C(63 MHz; [$^2H_6$]acetone) 169.40, 135.73, 133.75, 124.47, 75.42, 69.49 and 67.01 (C-3/2/1), 57.04 and 56.37 (C-5/4) and 50.89 (C-6); *m/z* (FD) 291 ($M^{\cdot+}$, 100%).

(1S,2S,3S,4R,5R,6R)-(−)-4,5-*Epoxy*-6-*phthalimidocyclohexane*-1,2,3-*triyl Tristrichloroacetimidate* (−)-**15**. Epoxy triol (−)-**14** (0.22 g, 0.74 mmol) was suspended in dry dichloromethane (2.2 cm^3) with exclusion of moisture. After being cooled to −30 °C the suspension was treated first with trichloroacetonitrile (0.27 cm^3, 2.66 mmol) and then with diazabicycloundecene (DBU) (0.01 cm^3 0.07 mmol). The reaction mixture was stirred at −30 °C. After 1 day further DBU (0.005 cm^3, 0.003 mmol) was added and the mixture was stirred at −30 °C; after 3 days a clear, brown solution had been formed. After removal of the solvent under reduced pressure the crude product was purified by column chromatography through silica gel [ethyl acetate–hexane (1:4)], which gave *compound* (−)-**15** (0.50 g, 94%) as a non-crystalline solid, $[\alpha]_D^{20}$ −10.2° (*c* 1.0, $CHCl_3$) (Found: C, 33.2; H, 1.75; N, 7.7. $C_{20}H_{13}Cl_9N_4O_6$ requires C, 33.16; H, 1.81; N, 7.73%); ν_{max}/cm^{-1} 3180br s, 1775s, 1710vs, 1670s, 1390vs, 1340s, 1230m, and 830s; δ_H(250 MHz; $CDCl_3$) 8.73, 8.51 and 8.38 (each 1 H, s, NH), 7.87 (2 H, m, ArH), 7.74 (2 H, m, ArH), 6.02 (1 H, t, *J* 2.7 and 2.7, 2-H), 5.93 (1 H, dd, *J* 9.6 and 2.7, 1-H), 5.80 (1 H, d, *J* 3.4, 3-H), 5.23 (1 H, d, *J* 9.6, 6-H), 3.60 (1 H, m, 4-H) and 3.50 (1 H, d, *J* 3.2, 5-H); δ_C(63 MHz; $CDCl_3$) 167.31, 161.50, 161.26 and 161.20 (C=N), 134.39, 131.48, 123.60, 90.71, 90.52 and 90.36 (CCl_3), 71.74, 70.84 and 70.31 (C-1/2/3), 54.77 and 51.20 (C-4/5) and 45.83 (C-6); *m/z* (FD) [$M^{\cdot+}$] 729 (39%), 728 (51), 727 (92), 726 (25), 725 (100), 724 (36), 723 (53), 722 (17) and 721 (31).

(1S,2S,3R,4S,5S,6S)-(−)-2-*Acetoxy*-3-*phthalimido*-4,5-*bis*-(*trichloroacetimidato*)-8-*trichloromethyl*-7-*oxa*-9-*azabicyclo*-[4.3.0]*non*-8-*ene* (−)-**16**.—To an ice-cooled solution of compound (−)-**15** (0.40 g, 0.55 mmol) in dry 1,2-dimethoxyethane (DME) (17 cm^3) under nitrogen was added triethylaluminium (93%) (0.16 cm^3, 1.10 mmol). The solution was then stirred at 0 °C. After 3 h, TLC [ethyl acetate–hexane (1:2)] indicated the end of the reaction. After addition of ethanol (10 cm^3) to hydrolyse both the alcohol–triethyl aluminium complex and the remaining triethylaluminium the solution was stirred for an addition 30 min. Then the solution was diluted with diethyl ether, washed twice with saturated aq. sodium hydrogen carbonate and once with water, dried over $MgSO_4$, filtered, and evaporated to dryness. Because the product crystallised with difficulty, the crude product was purified chromatographically [ethyl acetate–hexane (1:3)] which yielded the bicyclic alcohol.

This was acetylated in acetic anhydride–pyridine overnight. After evaporation to dryness the residue was dissolved in dichloromethane. The solution was washed twice with water, dried over $MgSO_4$, and filtered. Concentration under reduced pressure gave *bicyclic compound* (−)-**16** (0.34 g, 80%), $[\alpha]_D^{20}$ −26.1° (*c* 1.0, $CHCl_3$) (Found: C, 34.3; H, 1.8; N, 7.3. $C_{22}H_{15}Cl_9N_4O_7$ requires C, 34.65; H, 1.98; N, 7.35%); ν_{max}/cm^{-1} 3350v, 1780s, 1755s, 1720vs, 1675s, 1385s, 1300m, 1220s, 1065s and 795s; δ_H(250 MHz; $CDCl_3$) 8.75 and 8.52 (each 1 H, s, NH), 7.87 (2 H, m, ArH), 7.74 (2 H, m, ArH), 6.42 (1 H, dd, *J* 2.9 and 7.6, 5-H), 5.89 (1 H, t, *J* 3.3 and 3.3, 4-H), 5.67 (1 H, t, *J* 9.9 and 9.9, 2-H), 5.49 (1 H, dd, *J* 7.6 and 9.9, 6-H), 4.76 (1 H, t, *J* 9.9 and 9.9, 1-H) and 4.61 (1 H, dd, *J* 3.3 and 9.9, 3-H); δ_C(63 MHz; $CDCl_3$) 171.11 (acetyl C=O), 169.91, 164.25, 161.23 and 160.68 (C=N), 134.41, 131.42, 123.74, 90.54, 90.30 and 88.32 (CCl_3), 81.57 (C-4), 74.45, 73.03, 70.12 and 68.06 (C-2/3/5/6), 52.73 (C-1) and 21.01 (Me); *m/z* (FD) [$M^{\cdot+}$] 772. (31%), 771 (67), 769 (47), 768 (64), 766 (100), 765 (13), 764 (61) and 762 (31).

(−)-1L-2,4-*Diamino*-2,4-*dideoxychiroinositol Dihydrochloride* (−)-**17**.—The acetylated bicycle (−)-**16**) (0.44 g, 0.58 mmol) was dissolved in a mixture of acetone (2.8 cm^3), methanol (4.3 cm^3) and 1 mol dm^{-3} HCl (2.8 cm^3) and the solution was stirred at room temperature for 3 h. Then the solution was evaporated to dryness and the residue was dried in high vacuum for several hours.

The residue, which consisted of differently protected phthalimido compounds, was dissolved in a mixture of ethanol (4.6 cm^3) and chloroform (2 cm^3). After saturation with nitrogen, anhydrous hydrazine (0.37 cm^3, 11.60 mmol) was added and the mixture was stirred at 80 °C under nitrogen for 12 h. During this time a white precipitate was formed. After evaporation of both the solvent and the remaining hydrazine the residue was treated with the anion-exchange resin Amberlite IRA 400 (Cl^- form). After filtration and washing of the ion-exchange resin with water the filtrate was treated on a cation-exchange column Dowex 50W (H^+-form) (24 cm/1.3 cm). The column was washed successively with 200 cm^3 portions of water, 0.5 mol dm^{-3} HCl, 1 mol dm^{-3} HCl, 1.5 mol dm^{-3} HCl, 2 mol dm^{-3} HCl, 2.5 mol dm^{-3} HCl and 5 mol dm^{-3} HCl. The fraction with 1.5 mol dm^{-3} HCl contained product (−)-**17**. After

evaporation to dryness the crude product was recrystallised from methanol–acetone to give pure compound (−)-**17** (0.12 g, 79%), $[\alpha]_D^{20}$ −26.71° (*c* 1.0, water); m.p. 155 °C (decomp.) (Found: C, 28.6; H, 6.35; N, 11.0. $C_6H_{16}Cl_2N_2O_4$ requires C, 28.70; H, 6.42; N, 11.16%); ν_{max}/cm^{-1} 3400br, 2900br and 2550br; δ_H(250 MHz; D_2O) 3.99 (1 H, t, *J* 3.3 and 3.3, 4-H), 3.87 (1 H, t, *J* 3.3 and 3.3, 5-H), 3.83 (1 H, dd, *J* 10.5 and 3.3, 6-H), 3.76 (1 H, t, *J* 10.5 and 10.5, 2-H), 3.32 (1 H, dd, *J* 10.5 and 3.3, 3-H) and 3.16 (1 H, t, *J* 10.5 and 10.5, 1-H); δ_C(63 MHz; D_2O, 1,4-dioxane) 71.98, 69.77, 68.52 and 68.38 (C-2/4/5/6) and 55.89 and 53.98 (C-1 and -3); m/z (FD) [$M^{\bullet+}$] 251 (0.6%), [$M^{\bullet+}$ − 2Cl] 180 (17), [$M^{\bullet+}$ − 2Cl] 179 (100) and [$M^{\bullet+}$ − 2HCl] 178 (1).

(1S,4R,5S,6R)-(−)-5,6-O-*Isopropylidenedioxy*-4-*phthalimido*-*cyclohex*-2-*enyl Trichloroacetimidate* (−)-**18**.—The allylic alcohol (−)-**10** (3.66 g, 11.6 mmol) was dissolved in dry dichloromethane (100 cm^3) and cooled on ice. After addition of sodium hydride (56 mg, 2.32 mmol) an ice-cooled solution of trichloroacetonitrile (1.675 g, 11.6 mmol) in dry dichloromethane (50 cm^3) was slowly poured into the alcoholate solution. TLC [ethyl acetate–hexane (1:2)] soon indicated the completion of the imidate formation. Acetic acid (139 mg, 2.32 mmol) was necessary to neutralise the imidate salt. Filtration through silica gel (1.5 g) and subsequent evaporation of the solvent gave the crude *product*, which was recrystallised from dichloromethane–hexane (4.85 g, 91%), $[\alpha]_D^{20}$ −12.4° (*c* 1.0, $CHCl_3$); m.p. 122 °C (Found: C, 49.5; H, 3.85; N, 6.0. $C_{19}H_{17}Cl_3N_2O_5$ requires C, 49.64; H, 3.73; N, 6.09%); ν_{max}/cm^{-1} 3320s, 2990s, 2970s, 2955s, 1780s, 1720s, 1660s, 1460m, 1380s, 1340m, 1280s and 1210s; δ_H(250 MHz; $CDCl_3$) 8.50 (1 H, s, NH), 7.83 (2 H, m, ArH), 7.72 (2 H, m, ArH), 5.92 (1 H, dt, *J* 10.1, 2.7 and 2.1, 2-H), 5.81 (1 H, dt, *J* 10.1, 2.5 and 2.5, 3-H), 5.58 (1 H, m, 4-H), 4.86 (1 H, m, 1-H), 4.68 (1 H, t, *J* 7 and 7, 6-H), 4.54 (1 H, dd, *J* 7 and 4.2, 5-H), 1.55 (3 H, s, Me) and 1.36 (3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 167.76, 161.93 (C=N), 134.15, 134.12, 131.81, 128.03 (C-2 and -3), 126.99 (C-3 and -2), 123.45, 109.74 (CMe_2), 91.10 (CCl_3), 76.44 (C-1), 73.18 (C-5 or -6), 61.00 (C-6 or -5), 50.35 (C-4) and 27.33 and 25.51 (2 × Me); *m/z* (FD) [$M^{\bullet+}$] 464 (3%), 463 (21), 462 (37), 461 (27), 460 (74), 459 (34), 458 (100) and 457 (6).

(1R,2S,3S,4S,5R,6S)-(−)-2-*Iodo*-4,5-*isopropylidenedioxy*-3-*phthalimido*-8-*trichloromethyl*-7-*oxa*-9-*azabicyclo*[4.3.0]*non*-8-*ene* (−)-**19**.—A solution of the imidate (−)-**18** (1.2 g, 2.61 mmol) in dry dichloromethane (100 cm^3) was cooled on ice before NIS (587 mg, 2.61 mmol) was added and the mixture was stirred overnight at the same temperature and then at least for 12 h at room temperature. The mixture was diluted to *ca.* 400 cm^3 volume and washed with an alkaline (pH 8) solution of sodium thiosulphate (0.5%; 200 cm^3). The organic phase was dried with sodium sulphate and evaporated to leave a crude mixture of compounds (−)-**19** and (−)-**20**. Stored at 5 °C, *compound* (−)-**19** recrystallised immediately from ethyl acetate (40 cm^3) after addition of a small quantity (*ca.* 5 cm^3) of hexane (1001 mg, 69% and 963 mg, 66% after second recrystallisation); $[\alpha]_D^{20}$ −67.5° (*c* 1.0, $CHCl_3$); m.p. 177–180 °C (decomp.) (Found: C, 38.8; H, 2.8; N, 4.7. $C_{19}H_{16}Cl_3IN_2O_5$ requires C, 38.97; H, 2.75; N, 4.78%); ν_{max}/cm^{-1} 2980m, 1780m, 1720s, 1660m, 1380s, 1230s, 1170m and 1060s; δ_H(250 MHz; $CDCl_3$) 7.89 (2 H, m, ArH), 7.77 (2 H, m, ArH), 4.96 (2 H, dt, *J* 3.3, 9.5 and 9, 1- and 3-H), 4.88 (1 H, t, *J* 9.5 and 9.5, 4-H), 4.70 (1 H, dd, *J* 6.1 and 3.3, 2′-H), 4.42 (2 H, dd, *J* 9.2 and 9, 5- and 6-H), 1.55 (3 H, s, Me) and 1.33 (3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 168.07, 166.86, 162.96 (C=N), 134.37, 131.51, 131.36, 123.95, 123.50, 110.16 (CMe_2), 85.91 (CCl_3), 83.84 (C-2), 74.65 and 73.92 (C-1 and -3), 71.98 (C-6), 54.53 (C-4), 27.38 (C-5) and 25.46 and 25.18 (2 × Me); *m/z* (FD) [$M^{\bullet+}$] 589 (3%), 588 (1), 587 (27), 586 (4) and 585 (9), [$M^{\bullet+}$ − 15] 573 (19), 572 (5), 571 (17), 570 (5) and 569 (24); [$M^{\bullet+}$ − 127] 463 (9), 462 (26), 461 (18), 460 (31), 459 (75), 458 (45) and 457 (100).

(1R,5S,6R,7S,8S,9R)-(−)-9-*Iodo*-7,8-*isopropylidenedioxy*-6-*phthalimido*-3-*trichloromethyl*-2-*oxa*-4-*azabicyclo*[3.3.1]*oct*-3-*ene* (−)-**20**.—*Compound* (−)-**20** was obtained from the mother liquor left from the preparation of (−)-**19** on further addition of hexane and recrystallisation at ~0 °C (304 mg, 21%), $[\alpha]_D^{20}$ −32.9° (*c* 1.0, $CHCl_3$); m.p. 220–224 °C (decomp.) (Found: C, 38.8; H, 2.85; N, 4.7. $C_{19}H_{16}Cl_3IN_2O_5$ requires C, 38.97; H, 2.75; N, 4.78%); ν_{max}/cm^{-1} 2960m, 2940m, 2920m, 1760s, 1710s, 1660s, 1460m, 1380s, 1350s, 1330s, 1250s, 1240s, 1220s, 1170s and 1060s; δ_H(250 MHz; $CDCl_3$) 7.88 (2 H, m, ArH), 7.76 (2 H, m, ArH), 6.10 (1 H, dd, *J* 8.5 and 7, 7-H), 5.04 (2 H, m, 1- and 8-H), 4.73 (2 H, m, 5- and 9-H), 4.08 (9 H, dd, 8.5 and 1.5-H), 1.46 (3 H, s, Me) and 1.43 (3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 168.04, 163.33 (C=N), 134.43, 131.38, 123.66, 109.73 (CMe_2), 85.98 (C-1), 83.94 (CCl_3), 75.13 and 71.97 (C-7 and -8), 66.79 (C-5), 56.44 (C-6), 30.76 (C-9) and 27.15 and 24.66 (2 × Me); *m/z* (FD) [$M^{\bullet+}$] 589 (19%), 588 (33), 587 (24) and 586 (83); [$M^{\bullet+}$ − 15] 574 (10), 573 (18), 572 (13), 571 (100), 570 (6) and 569 (87); [$M^{\bullet+}$ − 127] 460 (54) and 459 (33).

(1S,2R,3S,4R,5S,6S)-(−)-4-*Acetamido*-5-*iodo*-6-*phthalimido*-*cyclohexane*-1,2,3-*triyl* (−)-*Triacetate* **21**.—A solution of compound (−)-**19** (640 mg, 1.1 mmol) in dichloromethane–methanol–0.1 mol dm^{-3} (3:1:1) (20 cm^3) was stirred at room temp. for 5 h. The volume was reduced to *ca.* 40% under reduced pressure and the pH of the solution was adjusted to pH 7–8 with sodium hydrogen carbonate. Evaporation and drying left a solid, which was suspended in acetic anhydride–pyridine (10 cm^3–0.5 cm^3) and the mixture was stirred overnight. The reagents were removed as far as possible under reduced pressure, the residue was dissolved in dichloromethane (50 cm^3), and the solution was washed with 0.1 mol dm^{-3} HCl (20 cm^3), saturated aq. sodium hydrogen carbonate (20 cm^3) and water (20 cm^3). The organic phase was dried over magnesium sulphate to give triacetate (−)-**21** as a slightly yellowish solid after filtration and evaporation of the solvent. Recrystallisation from ethyl acetate–hexane afforded *compound* **21** as crystals (612 mg, 95%), $[\alpha]_D^{20}$ −0.32° (*c* 1.0, $CHCl_3$); m.p. 153–156 °C (Found: C, 44.8; H, 4.1; N, 4.8. $C_{22}H_{23}IN_2O_9$ requires C, 45.07; H, 3.95; N, 4.78%); ν_{max}/cm^{-1} 3070m, 1760m, 1730s, 1660m, 1540m, 1370s, 1240s, 1210s, 1140m and 1050s; δ_H(250 MHz; $CDCl_3$) 7.84 (2 H, m, ArH), 7.75 (2 H, m, ArH), 5.92 (1 H, d, *J* 9.3, NH), 5.69 (1 H, dd, *J* 11 and 3.4, 1-H), 5.50 (1 H, t, *J* 3.4 and 3.4, 2-H), 5.16 (1 H, t, *J* 11 and 12, 6-H), 5.13 (1 H, t, *J* 3.4 and 3.5, 3-H), 4.86 (1 H, t, *J* 12 and 12, 4-H), 4.86 (1 H, ddd, *J* 12 and 9.3 and 3.5, 5-H), 2.24 (6 H, s, 2 × Me), 2.16 (3 H, s, Me) and 2.02 (3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 169.47, 169.42, 169.21, 169.04, 167.88 and 166.72 (6 × C=O), 134.52, 134.44, 131.32, 130.88, 123.87 and 123.61 (6 × C-ar), 69.77 (C-1), 66.90 (C-3), 66.27 (C-2), 54.53 (C-6), 51.90 (C-4), 27.04 (C-5) and 23.17, 20.86, 20.85 and 20.41 (4 × Me); *m/z* (FD) [$M^{\bullet+}$] 587 (28%) and 586 (100).

(1S,2R,3S,4S,6R)-(+)-4-*Acetamido*-6-*phthalimidocyclo*-*hexane*-1,2,3-*triyl Triacetate* (+)-**22**.—Compound (−)-**21** (1.26 g, 2.15 mmol) was dissolved in dry, oxygen-free benzene (50 cm^3) before tributylstannane (2.50 g, 4 mol equiv.) and AIBN (35 mg, 0.1 mol equiv.) were added. The mixture was kept at 80 °C for 6 h. The solvent was then evaporated off under reduced pressure and the residue was dried under high vacuum. Purification of the product was achieved by chromatography on silica gel with ethyl acetate–hexane (1:1) as eluent. Recrystallisation from ethyl acetate–hexane yielded pure *compound* (+)-**22** (909 mg, 92%), $[\alpha]_D^{20}$ +1.85° (*c* 1.0, $CHCl_3$); m.p. 127–

131 °C (Found: C, 57.2; H, 5.4; N, 6.1. $C_{22}H_{24}N_2O_9$ requires C, 57.39; H, 5.25; N, 6.08%); ν_{max}/cm^{-1} 3050m, 1750m, 1660m, 1550m, 1380s, 1240s, 1220s, 1150m and 1050s; δ_H(250 MHz; $CDCl_3$) 7.81 (2 H, m, ArH), 7.71 (2 H, m, ArH), 5.79 (1 H, dd, *J* 3.3 and 12, 1-H), 5.78 (1 H, d, *J* 9.1, NH), 5.49 (1 H, dd, *J* 3.3 and 3.0, 2-H), 5.07 (1 H, t, *J* 3 and 3, 3-H), 4.72 (1 H, td, *J* 12, 12 and 4.4, 6-H), 4.58 (1 H, dddd, *J* 12, 9.1, 7 and 3, 4-H), 2.71 (1 H, q, *J* 12, 12 and 12, 5^a-H), 2.26 (3 H, s, Me), 2.18 (3 H, s, Me), 1.94 (3 H, s, Me), 1.81 (3 H, s, Me) and 1.68 (1 H, ddd, *J* 12, 7 and 4.4, 5^e-H); δ_C(63 MHz; $CDCl_3$) 170.09, 169.92, 169.78, 169.52, 169.35 and 169.25 (6 × C=O), 134.21, 134.03, 131.75, 131.11, 123.35 and 123.22 (6 × C-ar), 70.85, 70.38 and 67.45 (C-2, -1 and -3), 46.42 (C-6), 44.87 (C-4), 23.16 (C-5) and 21.03, 20.95, 20.81 and 20.50 (4 × Me); *m/z* (FD) [$M^{\bullet+}$] 461 (29%) and 460 (100).

(−)-L-2,4-*Diamino*-2,3,4-*trideoxyalloinositol Dihydrochloride* (−)-**23**.—To a solution of compound (+)-**22** (800 mg, 1.74 mmol) in chloroform–ethanol [20 cm^3 (5:3)] was added hydrazine (0.55 cm^3, 10 mol equiv.) After the mixture had been stirred at 80 °C for 12 h a white precipitate had been formed. After a further 24 h the mixture was evaporated to dryness. The crude product was purified by anion exchange and subsequent cation exchange. At first the residue was dissolved in a small amount of water and rinsed through a short Amberlite IRA 400 column (5 cm × 0.7 cm); after washing of the column with water the filtrate was eluted on a Dowex 50W (H^+)/200 column (24 cm × 1.3 cm). The column was eluted with increasing concentrations of HCl (200 cm^3 of: 0.5 mol dm^{-3}, 1.5 mol dm^{-3}, 2.5 mol dm^{-3}). The fraction from 1.5 mol dm^{-3} HCl contained *compound* (−)-**23** (337 mg, 72%), $[\alpha]_D^{20}$ −52.4° (*c* 1.0, water); m.p. 189–192 °C (Found: C, 30.5; H, 6.9; N, 1.20. $C_6H_{16}Cl_2N_2O_3$ requires C, 30.65; H, 6.86; N, 11.91%); ν_{max}/cm^{-1} 3600br, 2900br and 2100br; δ_H(250 MHz; D_2O), 3.82 (1 H, dt, *J* 12.4, 4 and 2.7, 2-H), 3.68 (1 H, t, *J* 3.3 and 3.0, 6-H), 3.60 (1 H, t, *J* 3.0 and 2.7, 1-H), 3.55 (1 H, dd, *J* 11 and 3.3, 5-H), 3.09 (1 H, td, *J* 12, 11 and 4.2, 4-H), 1.68 (1 H, dt, *J* 12, 4.2 and 4, 3e-H) and 1.49 (1 H, q, *J* 12, 12 and 12.4, 3a-H); δ_C(63 MHz; D_2O, 1,4-dioxane) 71.89 (C-6), 69.07 (C-1), 68.35 (C-5), 49.18 (C-4), 47.64 (C-2) and 27.68 (C-3); *m/z* (FD) [$M^{\bullet+}$] 163 (100%) and 162 (83).

Acknowledgements

We thank Dr. C. M. Weißhuhn and Mrs. B. Bubl for their help with the NMR experiments as well as Dr. C. Wünsche and Mr. H. Späth of the Analytical Research Dept. of Bayer AG Wuppertal who kindly recorded optical-rotation data. The co-operation of Mr. M. Fischer and Dr. J. Veith of the mass spectroscopy laboratory of the Technische Hochschule Darmstadt is gratefully acknowledged. We owe special thanks to Dr. F. M. T. Wynne of ICI Billingham, UK who generously supplied us with *cis*-cyclohexa-3,5-diene-1,2-diol **3**.

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Paper 1/02027G
Received 30*th April* 1991
Accepted 20*th May* 1991