Stereoselective Synthesis of (±)-*cis*-Inos-1,3-diamines

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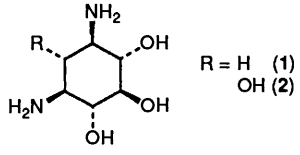
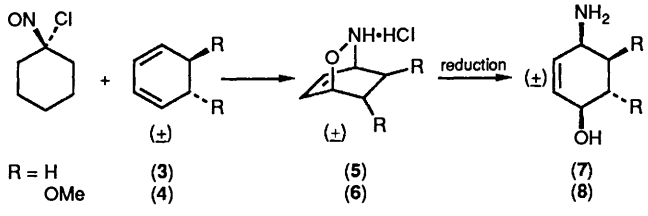
This contribution presents stereoselective routes to various *cis*-inos-1,3-diamines starting from readily available *cis*-4-aminocyclohexenols (**7**) and (**8**). The second nitrogen function is introduced into the ring by use of intramolecular cyclisations of neighbouring trichloroacetimidate groups. Hydrolytic cleavage of the resulting oxazolines (**15**), (**16**), (**27**), (**28**) and complete deprotection gave new *cis*-inos-1,3-diamines (**31**)–(**34**) in good overall yields.

A further example of stereoselective introduction of the second nitrogen function is the S_N2-type azide substitution of bromide from *O*-silylated 1*r*-amino-3*t*-bromo-2*c*,4*c*-dihydroxycyclohexane (**36**) and subsequent reduction of the azido function yielding 1*r*,3*c*-diamino-2*c*,4*c*-dihydroxycyclohexane (**38**).

Inosdiamines play an important role as essential moieties of numerous aminoglycoside and aminocyclitol antibiotics (AGAC); the most frequently occurring inosdiamines are 2-deoxystreptamine (**1**) and streptamine (**2**).[1] Moreover, there are applications of these compounds as substrates for mutasynthesis of new antibiotics[2] and as ligands in cytostatically active Pt^{II}-complexes.[3]



A promising strategy for the directed synthesis of streptamine-like (*i.e.*, with conserved *c*-1,3-diamino stereochemistry) inosdiamines starts with the known formation of bicyclic dihydro-1,2-oxazines (**5**) and (**6**) from cyclohexa-1,3-diene (**3**) or racemic 5,6-dimethoxycyclohexadiene (**4**) with 1-chloro-1-nitrosocyclohexane in a hetero-Diels–Alder reaction.[4] Reductive cleavage of the N–O bond leads to (4,5-disubstituted)-3*r*-amino-6*c*-hydroxycyclohexenes (**7**) and (**8**) (Scheme 1) which serve as key compounds in the synthesis.[5]

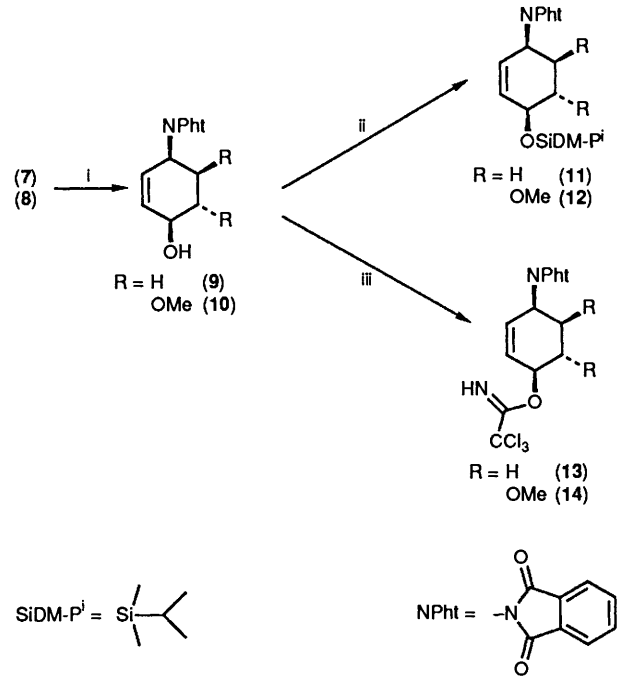


Scheme 1.

Results and Discussion

Amino alcohols (**7**) and (**8**) were protected by phthaloylation, resulting in allylic alcohols (**9**) and (**10**) ready for transformation to trichloroimidates (**13**) and (**14**) by Overman's method,[6] or for *O*-silylation with isopropyldimethylsilyl chloride to give compounds (**11**) and (**12**) (Scheme 2).

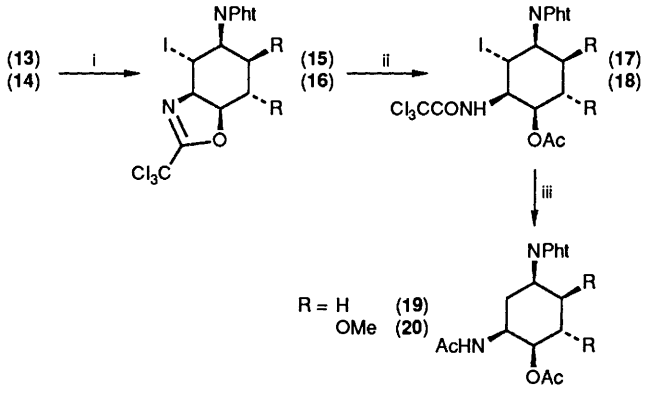
Intramolecular cyclisation of the imidates with *N*-iodosuccinimide (NIS) formed oxazolines (**15**) and (**16**) exclusively,[7] and this was confirmed by decoupling NMR studies. The cyclisation was followed by acidic hydrolysis and complete acetylation to afford compounds (**17**) and (**18**); excellent results



Scheme 2. *Reagents*: i, *N*-Ethoxycarbonylphthalimide–Na_2CO_3–acetone; ii, Pr^iMe_2SiCl–imidazole; iii, NaH; then Cl_3CCN.

in the exhaustive dehalogenation step with Bu_3SnH[7] (4 mol equiv.) then gave the acetamides (**19**) and (**20**) (Scheme 3). The phthalimido protective group was found to be most appropriate with respect to its non-participation in the halogenocyclisation step and its ability to be detected under UV light on TLC sheets.

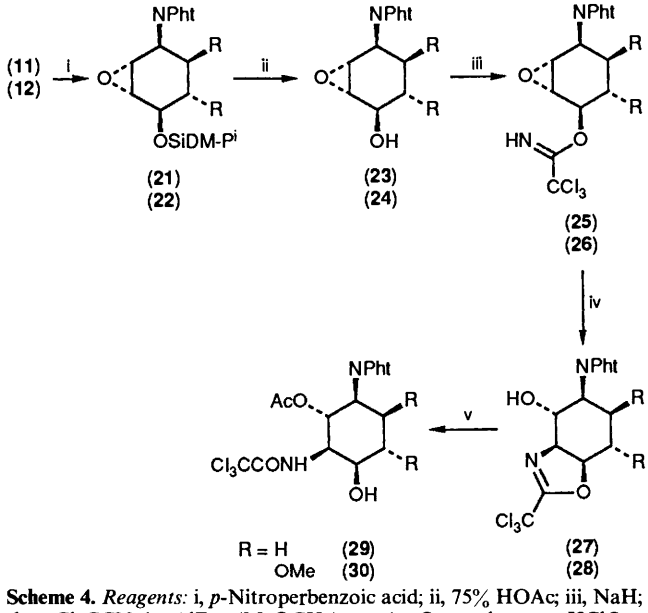
Allylic functional groups with acidic protons can trigger epoxidation reactions with peracids.[8] In cyclic systems the directing effect of such protons leads to the preferential formation of *cis*-epoxides.[9] To avoid this effect, all acidic protons of compounds (**7**) and (**8**) had to be displaced by protective groups, assuring that the epoxidising agent could react under steric control. The amino groups of compounds (**7**) and (**8**) were therefore transformed into the corresponding phthalimides while the hydroxy groups were protected as isopropyldimethylsilyl ethers. The epoxidation of compounds (**11**) and (**12**) occurred stereoselectively *anti* to the substituents



Scheme 3. *Reagents:* i, NIS; ii, $HClO_4$–MeOH; then Ac_2O–py; iii, Bu_3SnH–AIBN.

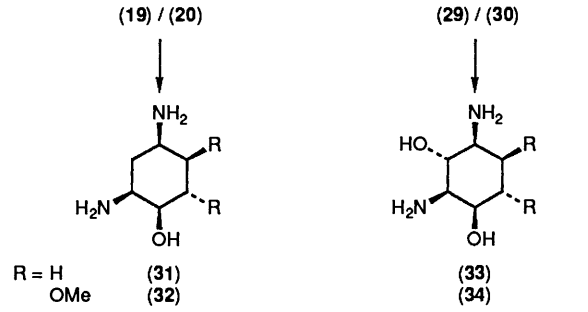
at C-1 and C-4. ^1H NMR spectroscopy of the crude products confirmed exclusive formation of the *trans*-epoxides (**21**) and (**22**).

Desilylation with 75% acetic acid afforded epoxy alcohols (**23**) and (**24**), which underwent quantitative trichloroimidate formation to afford products (**25**) and (**26**). Only triethylaluminium[10] catalysed the completely stereoselective intramolecular opening of the epoxide by the neighbouring trichloroimidate to the bicyclic oxazolines (**27**) and (**28**). After acetylation of the alcohol function in compounds (**27**) and (**28**), a catalytic quantity of $HClO_4$ in methanol was sufficient to open the oxazolines to afford the trichloroacetamides (**29**) and (**30**) (Scheme 4). We found that without prior acetylation the hydrolysis of the oxazolines gave low yields due to considerable attack of the acid at the phthalimido group.



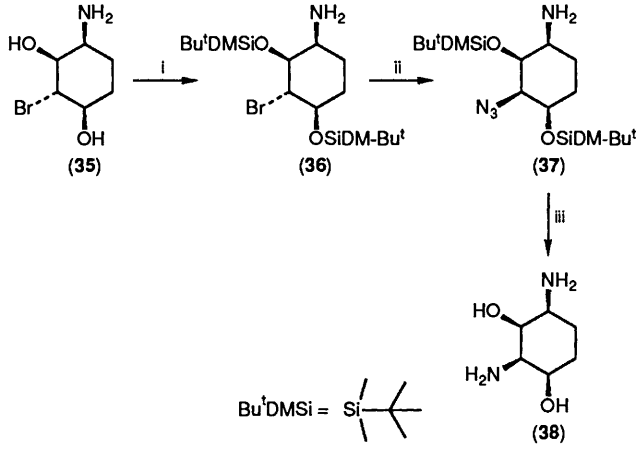
Scheme 4. *Reagents:* i, *p*-Nitroperbenzoic acid; ii, 75% HOAc; iii, NaH; then Cl_3CCN; iv, $AlEt_3$–$(MeOCH_2)_2$; v, Ac_2O–py; then cat. $HClO_4$–MeOH.

Treatment of the amide phthalimides (**19**), (**20**), (**29**), and (**30**) with anhydrous hydrazine (10 mol equiv.) quantitatively released the completely deprotected inosdiamines (**31**), (**32**), (**33**), and (**34**), which were isolated after removal of the resulting phthalohydrazide by use of an Amberlite IRA-400 (Cl^-) ion exchanger (Scheme 5). Purification could be achieved by crystallisation of the dihydrochlorides from methanol–acetone or alternatively by ion-exchange chromatography on a Dowex 50 W/200 (H^+) column.



Scheme 5. *Reagents and conditions:* H_2NNH_2–EtOH–chloroform, 80 °C, 20 h.

Starting with the readily available 1*r*-amino-3*t*-bromo-3*c*,4*c*-bis(t-butyldimethylsiloxy)cyclohexane (**36**) from previously described 1*r*-amino-3*t*-bromo-2*c*,4*c*-dihydroxycyclohexane (**35**)[11] the introduction of a nitrogen function in the 3*c*-position was successfully achieved in satisfying yield by nucleophilic substitution with azide ion to give compound (**37**) in dimethylformide (DMF) at temperatures between 110 and 130 °C. We found that temperatures exceeding 130 °C led to substantial substitution of the already introduced azido group by azide ion. Catalytic reduction (H_2/Pd–C) of the azido group followed by desilylation of compound (**37**) with dil. hydrochloric acid concluded the synthesis of 1*r*,3*c*-diamino-2*c*,4*c*-dihydroxycyclohexane dihydrochloride (**38**)·2HCl (Scheme 6).



Scheme 6. *Reagents and conditions:* i, $Bu^tMe_2SiOSO_2CF_3$–2,6-lutidine; ii, NaN_3–DMF, 130 °C; iii, Pd/C, H_2; then 0.1M-HCl.

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 (COSY) and $^1H/^{13}C$-correlated NMR studies.

Experimental

General.—M.p.s were determined (uncorrected) on a Büchi SMP-20 or a Gallenkamp melting point apparatus. IR spectra were measured with a Perkin-Elmer IR 397 spectrometer. Bruker WM 250 (250 MHz/63 MHz) and WM 300 (300 MHz/75.5 MHz) equipment delivered $^1H/^{13}C$ NMR data. Microanalyses were carried out with a Perkin-Elmer 240 B analyser at the Department of Analytical Chemistry at the Bergische Universität Wuppertal. Mass spectroscopy was kindly performed by Mr. M. Fischer at the mass spectroscopy laboratory of the Technische Hochschule Darmstadt, using a Varian MAT 311 equipment.

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)] served as stationary phase. All solvents were distilled and dried over appropriate molecular sieves before use.

Preparation of Compounds (**3**)–(**8**).—See ref. 5.

(±)-4c-*Phthalimidocyclohex*-2-*en*-1r-*ol* (**9**).—Compound (**7**) (1 g, 8.84 mmol), *N*-ethoxycarbonylphthalimide (1.94 g, 8.84 mmol), and sodium carbonate (0.1 g) were stirred under reflux in dry acetone (50 ml) for 5 h. After filtration the filtrate was concentrated under reduced pressure and the urethane formed during the reaction was removed by sublimation *in vacuo*. Crystallisation from ethanol yielded compound (**9**) (1.74 g, 81%) as white crystals, m.p. 169 °C (Found: C, 69.0; H, 5.25; N, 5.9. $C_{14}H_{13}NO_3$ requires C, 69.13; H, 5.39; N, 5.76%); ν_{max} 3 500, 1 770, 1 700, and 1 385 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 7.82 (2 H, m, ArH), 7.74 (2 H, m, ArH), 6.06 (1 H, m, *J* 10 and 2.5 Hz, 2-H), 5.67 (1 H, m, *J* 10, 2.5, and 1.3 Hz, 3-H), 4.78 (1 H, m, *J* 2.5 and 1.3 Hz, 4-H), 4.17 (1 H, m, *J* 3.5, 2, and 1.3 Hz, 1-H), 2.28, 2.00, and 1.83 (4 H, m, 5- and 6-H_2); δ_C(75.5 MHz; $CDCl_3$) 167.98 (C=O), 133.98, 131.89, 131.11, and 129.99 (C-2, -3, and ArC), 123.19 (aryl C), 62.45 (C-1), 46.79 (C-4), 29.98 (C-6), and 21.74 (C-5); *m*/*z* (field desorption) 243 (M^+, 100%).

(±)-5c,6t-*Dimethoxy*-4c-*phthalimidocyclohex*-2-*en*-1r-*ol* (**10**).—Compound (**8**) (1.27 g, 7.33 mmol), *N*-ethoxycarbonylphthalimide (1.61 g, 7.33 mmol), and sodium carbonate (80 mg) were dissolved in dry acetone (23 ml) and the solution was stirred at room temperature with exclusion of moisture. After 2 h, formation of the intermediate was complete (TLC, ethyl acetate). The reaction mixture was then diluted with dry acetone to 80 ml. After being further stirred at room temperature for 2 days the reaction mixture was filtered to remove sodium carbonate, and the filtrate was evaporated to dryness. The urethane which was formed during the reaction was removed by sublimation *in vacuo*. The crude product was then recrystallised from ethanol–diethyl ether–hexane to give *title compound* (**10**) (1.92, 86%) as white crystals, m.p. 133 °C (Found: C, 63.3; H, 5.7; N, 4.5. $C_{16}H_{17}NO_5$ requires C, 63.37; H, 5.65; N, 4.62%); ν_{max} 3 520, 1 760, 1 700, and 1 390 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 7.86 (2 H, m, ArH), 7.74 (2 H, m, ArH), 6.06 (1 H, ddd, *J* 10, 3.1, and 1.8 Hz, 2-H), 5.70 (1 H, ddd, *J* 10, 4.5, and 1.6 Hz, 3-H), 5.22 (1 H, m, 4-H), 4.19 (1 H, m, 1-H), 3.85 (1 H, dd, *J* 9 and 5.6 Hz, 6-H), 3.64 (3 H, s, OMe), 3.62 (1 H, dd, *J* 9 and 5.8 Hz, 5-H), 3.48 (3 H, s, OMe), 2.66 (1 H, d, *J* 8 Hz, OH); δ_C(75.5 MHz; $CDCl_3$) 168.47 (CO), 133.99 (aryl C), 132.85 and 121.78 (Aryl C and C-2 and -3), 131.72 and 123.20 (aryl C), 82.85 and 79.97 (C-5 and -6), 71.43 (C-1), 60.02 and 59.10 (OMe), and 46.95 (C-4); *m*/*z* (field desorption) 303 (M^+, 100%).

(±)-3r-*Isopropyldimethylsiloxy*-6c-*phthalimidocyclohexene* (**11**).—Compound (**9**) (500 mg, 2.06 mmol) and imidazole (350 mg, 5.14 mmol) were dissolved in absolute methylene dichloride (12.5 ml). After addition of isopropyldimethylsilyl chloride (0.39 ml, 2.52 mmol) the reaction mixture was stirred under nitrogen at room temperature for 2 h, then diluted with methylene dichloride, washed twice with water, dried (magnesium sulphate), and concentrated under reduced pressure. Drying of the residue under high vacuum yielded *title compound* (**11**) (672 mg, 95%) as a white, waxy solid which was used for epoxidation without further purification (Found: C, 66.0; H, 7.3; N, 3.9. $C_{19}H_{25}NO_3Si$ requires C, 66.44; H, 7.34; N, 4.08%); δ_H(250 MHz; $CDCl_3$) 7.82 (2 H, m, ArH), 7.69 (2 H, m, ArH), 5.90 (1 H, m, 1-H), 5.67 (1 H, dt, 2-H), 4.73 (1 H, m, 6-H), 4.21 (1 H, m, 3-H), 2.49–2.33 and 2.01–1.65 (4 H, m, 4- and 5-H_2), 1.00 (3 H, d, *J* 1.8 Hz, CHMe*Me*), 0.97 (3 H, d, *J* 1.7 Hz, CH*Me*Me), 0.93–0.79 (1 H, m, C*H*Me_2), 0.1 (3 H, s, Me), and 0.09 (3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 167.92 (CO), 133.82, and 132.02 (aryl C), 131.77, and 128.78 (C-1 and -2), 123.09 (aryl C), 63.28 (C-3), 47.33 (C-6), 30.86 and 22.64 (C-4 and -5), 16.94 (CH*Me*$_2$), 14.87 (*C*HMe_2), and −3.62 and −3.76 (Me); *m*/*z* (field desorption) 343 (M^+, 5%) and 300 (M^+ − $CHMe_2$, 100).

(±)-3r-*Isopropyldimethylsiloxy*-4t,5c-*dimethoxy*-6c-*phthalimidocyclohexene* (**12**).—To a solution of compound (**10**) (500 mg, 1.65 mmol) and imidazole (284 mg, 4.13 mmol) in absolute methylene dichloride (10 ml) was added isopropyldimethylsilyl chloride (0.315 ml, 1.98 mmol). After being stirred for 4 h at room temperature the mixture was diluted with methylene dichloride and extracted twice with water. Drying of the organic phase over magnesium sulphate, and then concentration under reduced pressure, gave *compound* (**12**) (633 mg, 95%) as a waxy, yellowish substance, pure enough for epoxidation (Found: C, 62.5; H, 7.3; N, 3.7. $C_{21}H_{29}NO_5Si$ requires C, 62.50; H, 7.24; N, 3.47%); δ_H(300 MHz; $CDCl_3$) 7.82 (2 H, m, ArH), 7.69 (2 H, m, ArH), 5.82 (1 H, dt, *J* 10, 1.9, and 1.9 Hz, 1-H), 5.48 (1 H, ddd, *J* 10, 4.5, and 2.1 Hz, 2-H), 5.19 (1 H, m, 6-H), 4.17 (1 H, ddd, *J* 7.3, 10.5, and 4.5 Hz, 3-H), 3.84 (1 H, dd, *J* 10.5 and 7.3 Hz, 4-H), 3.55 (3 H, s, OMe), 3.46 (1 H, dd, *J* 10.5 and 7 Hz, 5-H), 3.42 (3-H, s, OMe), 1.00 (3 H, s, CHMe*Me*), 0.98 (3 H, s, CH*Me*Me), 0.95–0.84 (1 H, m, C*H*Me_2), 0.13 (3 H, s, Me), and 0.12 (3 H, s, Me); δ_C(75.5 MHz; $CDCl_3$) 168.28 (CO), 135.04, 133.70, and 123.01 (aryl C), 131.66 and 120.48 (C-1 and -2), 83.41 and 80.27 (C-4 and -5) 72.94 (C-3), 60.94 and 59.24 (OMe), 46.95 (C-6), 16.76 and 16.72 (CH*Me*$_2$), 14.56 (*C*HMe_2), and −3.84 and −3.98 (Me); *m*/*z* (field desorption) 361 (M^+ − $CHMe_2$, 100%).

(±)-4c-*Phthalimidocyclohex*-2-*enyl* *Trichloroacetimidate* (**13**).—A solution of the allylic alcohol (**9**) (1.5 g, 6.16 mmol) in dry methylene dichloride (20 ml) was treated with sodium hydride (60 mg, 2.5 mmol) and trichloroacetonitrile (618 μl, 6.16 mmol) while at 0 °C. After 1 h TLC [EtOAc–hexane (1:1)] indicated completion of reaction. Addition of glacial acetic acid (144 μl, 2.5 mmol) gave the title imidate (**13**), which was isolated after filtration on Celite (2 g) and removal of the solvent under reduced pressure. Recrystallisation of the solid from ethyl acetate–hexane yielded *title compound* (**13**) as white crystals (2.29 g, 96%), m.p. 109 °C (Found: C, 49.4; H, 3.3; N, 7.2. $C_{16}H_{13}Cl_3N_2O_3$ requires C, 49.57; H, 3.38; N, 7.22%); ν_{max} 3 290, 1 770, 1 710, and 1 670 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 8.30 (1 H, br s, NH), 7.81 (4 H, m, ArH), 6.19 (1 H, m, 2-H), 5.97 (1 H, dt, *J* 1.5, 1.6, and 10 Hz, 3-H), 5.36 (1 H, m, 1-H), 4.85 (1 H, m, 4-H), 2.48 (1 H, dt, *J* 12, 11.5, and 10.2 Hz, 5a-H), 2.30 (1 H, m, 5e-H), 2.02 (1 H, m, 6a-H); and 1.81 (1 H, m, *J* 9.2 and 2.1 Hz, 6e-H); δ_C(63 MHz; $CDCl_3$) 167.77 (CO), 162.10 (C=N), 135.81 (C-2), 134.00 and 131.92 (aryl C), 125.68 (C-3), 123.23 (aryl C), 91.72 (CCl_3), 69.73 (C-1), 47.27 (C-4), and 26.84 and 22.62 (C-5 and -6); *m*/*z* (field desorption) 386 (100%), 387 (19), 388 (93), 389 (34), 390 (28), and 391 (7).

(±)-5c,6t-*Dimethoxy*-4c-*phthalimidocyclohex*-2-*enyl* *Trichloroacetimidate* (**14**).—A solution of the allylic alcohol (**10**) (1.0 g, 3.30 mmol) in dry methylene dichloride (10 ml) was treated with sodium hydride (30 mg, 1.25 mmol) and trichloroacetonitrile (346 μl, 3.46 mmol) while at 0 °C. After 1 h TLC [EtOAc–hexane (1:1)] indicated completion of reaction. Addition of glacial acetic acid (72 μl, 1.25 mmol) gave compound (**14**), which was isolated after filtration on Celite (2 g) and removal of the solvent under reduced pressure.

Recrystallisation of the solid from ethyl acetate–hexane yielded *title compound* (**14**) as white crystals (1.446 g, 98%), m.p. 167 °C (Found: C, 48.2; H, 3.8; N, 6.3. $C_{18}H_{17}Cl_3N_2O_5$ requires C, 48.29; H, 3.83; N, 6.26%); ν_{max} 3 340, 2 940, 2 830, 1 770, 1 720, 1 510, and 1 370 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 8.42 (1 H, br s, NH), 7.80 (4 H, m, ArH), 6.03 (1 H, dt, *J* 10 and 1.9 Hz, 2-H), 5.70 (1 H, ddd, *J* 10, 4.5, and 2 Hz, 3-H), 5.53 (1 H, ddt, *J* 7.7, 1.9, and 2 Hz, 1-H), 5.28 (1 H, m, 4-H), 4.21 (1 H, dd, *J* 10.3 and 7.7 Hz, 6-H), 3.62 (1 H, dd, *J* 10.3 and 8.5 Hz, 5-H), 3.59 (3 H, s, Me), and 3.46 (3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 168.51 (CO), 162.57 (C=N), 134.06, and 131.80 (aryl C), 128.75 (C-2), 123.96 (aryl C), 123.29 (C-3), 91.42 (CCl_3), 80.45 (C-1), 79.55 and 79.14 (C-5 and -6), 60.90 and 59.86 (2 × OMe), and 47.02 (C-4); *m/z* (field desorption) 446 (100%), 447 (71), 448 (90), 449 (54), 450 (33), and 451 (10).

(1R*,2R*,3S*,6R*)-2-*Iodo*-3-*phthalimido*-8-*trichloromethyl*-7-*oxa*-9-*azabicyclo*[4.3.0]*non*-8-*ene* (**15**).—To a solution of the imidate (**13**) (500 mg, 1.29 mmol) in chloroform (1 ml) at 0 °C was added NIS (290 mg, 1.29 mmol). After 24 h at 4 °C the cyclisation mixture was diluted with chloroform (50 ml) and washed with water (30 ml) containing 5% aq. sodium thiosulphate (2 ml). The organic phase was dried over sodium sulphate and filtered over silica gel (2 g). After removal of the solvent under reduced pressure the dihydro-oxazole (**15**) was obtained as a crude product. Crystallisation from ethyl acetate–hexane afforded the *title compound* as white crystals (609 mg, 92%), m.p. 233 °C (decomp.) (Found: C, 37.2; H, 2.4; N, 5.2. $C_{16}H_{12}Cl_3N_2O_3$ requires C, 37.42; H, 2.35; N, 5.45%); ν_{max} 2 960, 2 920, 1 770, 1 710, and 1 640 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.76–7.86 (4 H, m, ArH), 4.67 (1 H, dt, *J* 13, 7.3, and 3.5 Hz, 6-H), 4.63 (1 H, dd, *J* 9.1 and 7.3 Hz, 1-H), 4.49 (1 H, dd, *J* 12 and 9 Hz, 2-H), 4.37 (1 H, dt *J* 12, 10, and 4 Hz, 3-H), 2.58 (2 H, m, 4- and 5-H), 2.10 (1 H, m, 4- or 5-H), and 1.92 (1 H, m, 5- or 4-H); δ_C(63 MHz; $CDCl_3$) 167.50 (CO), 164.55 (C=N), 134.37, 131.46, and 123.60 (aryl C), 86.61 (CCl_3), 74.05 (C-1), 52.76 (C-3), 29.67 (C-2), and 25.09 and 24.51 (C-4 and -5); *m/z* (field desorption 511 (23%), 512 (89), 513 (76), 514 (100), 515 (31), 516 (44), 517 (7), and 518 (11).

(1R*,2S*,3S*,4R*,5S*,6S*)-2-*Iodo*-4,5-*dimethoxy*-3-*phthalimido*-8-*trichloromethyl*-7-*oxa*-9-*azabicyclo*[4.3.0]*non*-8-*ene* (**16**).—To a solution of the imidate (**14**) (500 mg, 1.117 mmol) in chloroform (1 ml) at 0 °C was added NIS (251 mg, 1.117 mmol). The cyclisation was complete after 24 h at 4 °C. The mixture was diluted with chloroform (50 ml) and washed with water (30 ml) containing 5% aq. sodium thiosulphate (2 ml). The organic phase was dried over sodium sulphate and filtered over silica gel (2 g). After removal of the solvent under reduced pressure the dihydro-oxazole (**16**) was obtained as a crude product. Crystallisation from ethyl acetate–hexane delivered the *title compound* (**16**) as white crystals (608 mg, 95%), m.p. 171 °C (decomp.) (Found: C, 37.7; H, 2.9; N, 4.8. $C_{18}H_{16}Cl_3IN_2O_5$ requires C, 37.69; H, 2.81; N, 4.88%); ν_{max} 2 940, 2 840, 1 780, 1 720, 1 650, 1 370, 1 130, 1 100, and 1 080 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.78–7.90 (4 H, m, ArH), 5.04 (1 H, dd, *J* 12 and 10 Hz, 2-H), 4.92 (1 H, dd, *J* 12 and 6.7 Hz, 3-H), 4.78 (1 H, t, *J* 10 and 9.8 Hz, 1-H), 4.69 (1 H, dd, *J* 9.8 and 6.2 Hz, 6-H), 4.17 (1 H, dd, *J* 8.5 and 6.2 Hz, 5-H), 3.60 (3 H, s, Me), 3.54 (1 H, dd, *J* 8.5 and 6.7 Hz, 4-H), and 3.33 (3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 167.94 and 167.90 (CO), 164.29 (C=N), 134.29, 134.15, 131.83, 131.06, and 123.67 (C-8 and aryl C), 86.15 (CCl_3), 85.12 (C-6), 78.55 and 77.85 (C-4 and -5), 72.58 (C-1), 60.20 and 59.88 (2 × OMe), 54.75 (C-3), and 23.71 (C-2); *m/z* (field desorption) 571 (18%), 572 (100), 573 (42), 574 (89), 575 (37), 576 (44), and 577 (6).

(±)-3t-*Iodo*-4c-*phthalimide*-2c-*trichloracetamidocyclohexyl Acetate* (**17**).—Compound (**15**) (200 mg, 0.389 mmol) was dissolved in a mixture of methylene dichloride, methanol, and 7% $HClO_4$ (5 ml–5 ml–0.5 ml) at room temperature. TLC showed completion of reaction after 1–2 h. The solvents were removed under reduced pressure and were replaced by water. The pH was adjusted to 8 with sodium hydrogen carbonate and the mixture was stirred for 1 h then extracted with methylene dichloride; the extract was dried and evaporated to give a white solid, which was acetylated with acetic anhydride–pyridine (20:1) for 12 h. The reagents were removed as far as possible under reduced pressure and the residue was redissolved in methylene dichloride (50 ml) and washed successively with 1M-HCl (20 ml), saturated aq. sodium hydrogen carbonate (20 ml), and water (20 ml). The organic phase was dried over magnesium sulphate to give compound (**17**) (216 mg, 97%) as a yellowish solid after filtration and evaporation of the solvent. Recrystallisation from ethyl acetate–hexane gave the *title acetate* as white crystals (207 mg, 93%), m.p. 254 °C (decomp.) (Found: C, 37.5; H, 2.9; N, 4.75. $C_{18}H_{16}Cl_3IN_2O_5$ requires C, 37.69; H, 2.81; N, 4.88%); ν_{max} 3 350, 1 770, 1 740, 1 700, 1 510, and 1 380 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.82 (4 H, m, ArH), 6.80 (1 H, d, *J* 9 Hz, NH), 5.21 (1 H, t, *J* 11.8 Hz, 3-H), 5.19 (1 H, dt, *J* 3 and 5.1 Hz, 1-H), 4.52 (1 H, dt, *J* 11.8, 12, and 4.2 Hz, 4-H), 4.37 (1 H, ddd, 2-H), 2.45 (1 H, m, 5- or 6-H), 2.26 (1 H, m, 6- or 5-H), 2.20 (3 H, s, Me), and 1.80 (2 H, m, 5- and 6-H); δ_C(63 MHz; $CDCl_3$) 169.56 (Ac), 167.57 (CO), 160.65 ($COCCl_3$), 134.39, 132.40, and 124.00 (aryl C), 92.31 (CCl_3), 69.85 (C-1), 58.15 and 55.75 (C-2 and -4), 29.94 (C-3), 27.07 and 23.87 (C-5 and -6), and 20.94 (Ac); *m/z* (field desorption) 573 (18%), 574 (100), 575 (44), 576 (74), 577 (41), 578 (40), and 579 (23).

(±)-3t-*Iodo*-5c,6t-*dimethoxy*-4c-*phthalimido*-2c-*trichloracetamidocyclohexyl Acetate* (**18**).—Compound (**16**) (200 mg, 0.348 mmol) was dissolved in a mixture of methylene dichloride, methanol, and 7% $HClO_4$ (5 ml–5 ml–0.5 ml) at room temperature. TLC showed completion of reaction after 1–2 h. The solvents were removed under reduced pressure and were replaced by water. The pH was adjusted to 8 with sodium hydrogen carbonate and the mixture was stirred for 1 h, and then extracted with methylene dichloride. The extract was dried and evaporated to give a white solid, which was acetylated with acetic anhydride–pyridine (20:1) for 12 h. The reagents were removed under reduced pressure and the residue was redissolved in methylene dichloride (50 ml) and washed successively with 1M-HCl (20 ml), saturated aq. sodium hydrogen carbonate (20 ml), and water (20 ml). The organic phase was dried over magnesium sulphate to give compound (**18**) (217 mg, 98%) as a slightly yellowish solid after filtration and evaporation of the solvent. Recrystallisation from ethyl acetate–hexane gave the *title acetate* as white crystals (208 mg, 94%), m.p. 236 °C (Found: C, 38.2; H, 3.3; N, 4.5. $C_{20}H_2OCl_3IN_2O_7$ requires C, 37.91; H, 3.18; N, 4.42%); ν_{max} 3 340, 1 770, 1 720, 1 515, and 1 370 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.81 (4 H, m, ArH), 6.88 (1 H, d, *J* 9.3 Hz, NH), 5.68 (1 H, t, *J* 12.1 Hz, 3-H), 5.10 (1 H, dd, *J* 3.5 and 1.5 Hz, 1-H), 4.83 (1 H, dd, *J* 12.1 and 3 Hz, 4-H), 4.72 (1 H, ddd, *J* 12.2, 9.3, and 3.5 Hz, 2-H), 3.95 (1 H, t, *J* 3.0 Hz, 5-H), 3.56 (3 H, s, Me), 3.49 (1 H, dd, *J* 2.9 and 1.5 Hz, 6-H), 3.22 (3 H, s, Me), and 2.13 (3 H, s, Ac); δ_C(63 MHz; $CDCl_3$) 170.11 (Ac), 167.60 (CO), 160.64 ($COCCl_3$), 134.22, 134.05, and 123.57 (aryl C), 92.41 (CCl_3), 79.51 and 72.45 (C-5 and -6), 69.56 (C-1), 58.65 (OMe), 58.50 (OMe), 57.18 and 54.82 (C-2 and -4), 25.92 (C-3), and 20.75 (Ac); *m/z* (field desorption) 633 (16%), 634 (100), 635 (40), 636 (81), 637 (36), 638 (44), and 639 (18).

(±)-2c-*Acetamido*-4c-*phthalimidocyclohexyl Acetate* (**19**).—To a solution of compound (**17**) (565 mg, 0.985 mmol) in dry, oxygen-free benzene (10 ml) were added Bu_3SnH (1.06 ml,

3.94 mmol) and azoisobutyronitrile (AIBN) (32 mg, 0.197 mmol). The reduction was run at 80 °C for 6 h; then all the solvent was evaporated off under reduced pressure. Column chromatography (silica gel; eluant ethyl acetate–hexane, 1:2) was necessary in order to isolate pure *compound* (**19**) (298 mg, 91%), m.p. 129 °C (Found: C, 63.0; H, 5.9; N, 8.1. $C_{18}H_{20}N_2O_5$ requires C, 62.78; H, 5.85; N, 8.13%); ν_{max} 3 380, 1 740, 1 700, 1 680, 1 510, and 1 360 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.84 (4 H, m, ArH), 5.77 (1 H, d, *J* 8.7 Hz, NH), 5.02 (1 H, dt, *J* 2.2, 1, and 1 Hz, 1-H), 4.28 (1 H, tt, *J* 12.3 and 4 Hz, 4-H), 4.20 (1 H, m, *J* 12.35, 8.7, 1.4, and 1 Hz, 2-H), 2.62 (1 H, q, *J* 12.35, 12.3, and 12.3 Hz, 3-H), 2.41 (1 H, ddd, *J* 13.3, 12.4, 12.3, and 3 Hz, 5a-H), 2.18 (3 H, s, Ac), 1.94 (3 H, s, Ac), 1.82 (1 H, dm, *J* 11.2 and 3 Hz, 6e-H), and 1.60 (3 H, m, 3e-, 5e-, and 6a-H); δ_C(63 MHz; $CDCl_3$) 170.32 (Ac), 169.18 (Ac), 167.72 (CO), 133.77, 131.48, and 122.84 (aryl C), 69.91 (C-1), 48.58 and 47.82 (C-2 and -4), 29.81 and 27.35 (C-5 and -6), 22.78 (Ac), and 21.01 (Ac); *m/z* (field desorption) 344 (100%).

(±)-6c-*Acetamido*-2t,3c-*dimethoxy*-4c-*phthalimidocyclohexyl Acetate* (**20**).—To a solution of compound (**18**) (1.6 g, 2.52 mmol) in dry, oxygen-free benzene (20 ml) were added Bu_3SnH (2.72 ml, 1.04 mmol) and AIBN (80 mg, 0.5 mmol). The reduction was run at 80 °C for 6 h; then all the solvent was evaporated off under reduced pressure. Column chromatography (silica gel; eluant ethyl acetate–hexane 1:2) was necessary to isolate pure *compound* (**20**) (939 mg, 92%), m.p. 238 °C (from ethyl acetate–hexane) (Found: C, 59.3; H, 5.9; N, 6.65. $C_{20}H_{24}N_2O_7$ requires C, 59.40; H, 5.98; N, 6.93%); ν_{max} 3 250m, 2 920m, 1 770, 1 700, 1 640, 1 550m, 1 370, 1 240, and 1 070 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.76 (4 H, m, ArH), 5.85 (1 H, d, *J* 8.4 Hz, NH), 4.98 (1 H, t, *J* 3 Hz, 1-H), 4.59 (1 H, dt, *J* 13, 3.5, and 3.5 Hz, 4-H), 4.46 (1 H, m, *J* 12.6, 8.4, and 3.8 Hz, 6-H), 3.87 (1 H, t, *J* 3 Hz, 2-H), 3.53 (1 H, dd, *J* 3.5 and 3 Hz, 3-H), 3.51 (3 H, s, OMe), 3.30 (1 H, ddd, *J* 12.6, 12.3, and 13 Hz, 5a-H), 3.22 (3 H, s, OMe), 2.13 (3 H, s, Ac), 1.96 (3 H, s, Ac), and 1.85 (1 H, dt, *J* 12.3, 3.5, and 3.5 Hz, 5e-H); δ_C(63 MHz; $CDCl_3$) 170.78 (Ac), 169.17 (Ac), 168.48 (CO), 133.91, 131.65, and 123.10 (aryl C), 78.15 (C-1), 73.31 and 70.36 (C-2 and -3), 58.44 (OMe), 49.68 and 45.35 (C-4 and -6), 24.93 (C-5), 23.28 (Ac), and 20.75 (Ac); *m/z* (field desorption) 404 (100%).

(±)-2t,3t-*Epoxy*-4c-*phthalimidocyclohexan*-1r-*ol* (**23**).—Compound (**11**) (707 mg, 2.06 mmol) and *p*-nitroperbenzoic acid (660 mg, 3.60 mmol) were dissolved in absolute chloroform (14 ml) and the solution was stirred for 4 days under nitrogen at room temperature, then concentrated to dryness under reduced pressure. The residue was then suspended in 75% acetic acid (10 ml) and the mixture was stirred for 2 h at room temperature. After addition of chloroform the solution was neutralised with sodium carbonate and extracted twice with saturated aq. sodium carbonate. The organic layer was then dried (magnesium sulphate), and concentrated under reduced pressure. The crude product was recrystallised from chloroform–hexane to give the *title epoxide* (**23**) (486 mg, 91%), m.p. 156 °C (Found: C, 64.6; H, 5.2; N, 5.2. $C_{14}H_{13}NO_4$ requires C, 64.86; H, 5.05; N, 5.40%); ν_{max} 3 540, 1 770, 1 700, 1 390, and 1 250 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 7.86 (2 H, m, ArH), 7.75 (2 H, m, ArH), 4.67 (1 H, t, *J* 8.6 Hz, 4-H), 4.34 (1 H, m, *J* 2.8 and 10.3 Hz, 1-H), 3.40 (1 H, dd, *J* 3.6 and 2.8 Hz, 2-H), 3.13 (1 H, d, *J* 3.6 Hz, 3-H), 3.07 (1 H, d, *J* 10.3 Hz, OH), and 2.0–1.57 (4 H, m, 5- and 6-H_2); δ_C(75.5 MHz; $CDCl_3$) 167.99 (CO), 134.34, 131.78, and 123.52 (aryl C), 64.31 (C-1), 54.36 and 53.91 (C-2 and -3), 43.15 (C-4), and 23.59 and 18.98 (C-5 and -6); *m/z* (field desorption) 259 (M^+, 100%).

(±)-2t,3t-*Epoxy*-5c,6t-*dimethoxy*-4c-*phthalimidocyclohexan*-1r-*ol* (**24**).—A solution of compound (**12**) (399 mg, 0.99 mmol) and *p*-nitroperbenzoic acid (362 mg, 1.98 mmol) in absolute chloroform (7 ml) was stirred for 4 days with exclusion of moisture at room temperature. After concentration under reduced pressure, the residue was suspended in 75% acetic acid (5 ml) and the mixture was stirred for 2 h at room temperature. Then chloroform was added and the mixture was neutralised with sodium carbonate and twice extracted with saturated aq. sodium carbonate. The organic layer was separated, dried (magnesium sulphate), and concentrated under reduced pressure. Crystallisation from chloroform–diethyl ether–hexane gave the *title epoxide* (**24**) (284 mg, 90%), m.p. 167–168 °C (Found: C, 60.3; H, 5.5; N, 4.3. $C_{16}H_{17}NO_6$ requires C, 60.19; H, 5.37; N, 4.39%); ν_{max} 3 540, 1 765, 1 700, 1 390, and 1 260 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 7.86 (2 H, m, ArH), 7.77 (2 H, m, ArH), 5.24 (1 H, m, 4-H), 4.06 (1 H, dd, *J* 10.3 and 5.5 Hz, 1-H), 3.48 (1 H, dd, *J* 10.3 and 5.2 Hz, 5-H), 3.38 (2 H, m, 2- and 3-H), 3.26 (1 H, dd, *J* 10.3 and 5.5 Hz, 6-H), 3.52 (3 H, s, OMe), 3.42 (3 H, s, OMe), and 3.08 (1 H, d, *J* 10.3 Hz, OH); δ_C(75.5 MHz; $CDCl_3$) 168.85 (CO), 134.43, 131.62, and 123.59 (aryl C), 83.88 and 78.11 (C-5 and -6), 72.10 (C-1), 59.93 and 59.06 (Me), 56.94 and 53.38 (C-2 and -3), and 46.48 (C-4); *m/z* (field desorption) 320 (M^+, 100%) and 319 (50).

(±)-2t,3t-*Epoxy*-4c-*phthalimidocyclohexyl Trichloroacetimidate* (**25**).—To a solution of compound (**23**) (400 mg, 1.54 mmol) in absolute methylene dichloride (12.3 ml) at 0 °C was added sodium hydride (37 mg, 1.54 mmol). After being stirred at 0 °C for 30 min this mixture was added to a solution of trichloroacetonitrile (0.310 ml, 3.08 mmol) in dry methylene dichloride (4.10 ml) at 0 °C. The mixture was kept at that temperature for 3 h and then was warmed to room temperature and kept overnight. Glacial acetic acid (0.09 ml) was added for protonation of the sodium salt of the title compound (**25**) which had been formed. Sodium acetate was removed by filtration through silica gel. After concentration of the filtrate under reduced pressure the crude product was recrystallised from ethyl acetate–hexane to give *title compound* (**25**) (588 mg, 94%) as a white solid, m.p. 134 °C (Found: C, 47.8; H, 3.2; N, 7.1. $C_{16}H_{13}Cl_3N_2O_4$ requires C, 47.61; H, 3.25; N, 6.94%); ν_{max} 3 310, 1 770, 1 710, 1 670, and 1 280 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 8.48 (1 H, s, NH), 7.88 (2 H, m, ArH), 7.76 (2 H, m, ArH), 5.50 (1 H, m, *J* 3.5, 3.5, and 1.3 Hz, 1-H), 4.56 (1 H, dd, *J* 11 and 6.5 Hz, 4-H), 3.59 (1 H, m, *J* 3.5 and 1.3 Hz, 2-H), 3.41 (1 H, d, *J* 3.5 Hz, 3-H), and 2.25–2.08, 2.02–1.91, 1.86–1.72, and 1.67–1.55 (4 H, m, 5- and 6-H_2); δ_C(75.5 MHz; $CDCl_3$) 167.49 (CO), 162.04 (C=N), 134.09, 131.85, and 123.37 (aryl C), 91.35 (CCl_3), 71.07 (C-1), 55.67 and 51.95 (C-2 and -3), 44.97 (C-4), and 21.64 and 20.44 (C-5 and -6); *m/z* (field desorption) 401 (26%), 402 (11), 403 (48), 404 (19), 405 (100), 406 (42), 407 (61), and 408 (23).

(±)-2t,3t-*Epoxy*-5c,6t-*dimethoxy*-4c-*phthalimidocyclohexyl Trichloroacetimidate* (**26**).—To a solution of compound (**24**) (300 mg, 0.94 mmol) in dry methylene dichloride (7.5 ml) at 0 °C was added sodium hydride (23 mg, 0.94 mmol). After being stirred at 0 °C for 30 min this mixture was added to a solution of trichloroacetonitrile (0.189 ml, 1.88 mmol) in dry methylene dichloride (2.5 ml) at 0 °C. The mixture was kept at that temperature for 3 h then was warmed to room temperature and kept overnight, when TLC indicated that the reaction was complete (ethyl acetate–hexane, 1:1). The thus formed sodium salt of the trichloroimidate was protonated by addition of glacial acetic acid (0.055 ml). Sodium acetate was removed by filtration through silica gel with ethyl acetate as eluant. The filtrate was concentrated under reduced pressure, and recrystallisation from chloroform–diethyl ether

gave *title compound* (**26**) (401 mg, 92%), m.p. 185–186 °C (Found: C, 46.3; H, 3.7; N, 5.9. $C_{18}H_{17}Cl_3N_2O_6$ requires C, 46.63; H, 3.70; N, 6.04%); ν_{max} 3 320, 1 770, 1 710, 1 665, 1 390, and 1 280 cm^{-1}; δ_H(300 MHz; [$^2H_6$]acetone) 8.59 (1 H, s, NH), 7.89 (2 H, m, ArH), 7.76 (2 H, m, ArH), 5.26 (1 H, dd, *J* 5.8 and 1.5 Hz, 4-H), 5.21 (1 H, d, *J* 8 Hz, 1-H), 3.75 (1 H, dd, *J* 10.8 and 8 Hz, 6-H), 3.52–3.42 (1 H, dd, *J* 10.8 and 5.8 Hz, 5-H), 3.46 (3 H, s, OMe), 3.44 (3 H, s, OMe), and 3.40 (2 H, m, 2- and 3-H); δ_C(75.5 MHz; $CDCl_3$) 168.42 (CO), 162.09 (C=N), 134.17, 131.73, and 123.52 (aryl C), 91.16 (CCl_3), 79.55, 78.04, and 77.60 (C-1, -5, and -6), 60.73 and 59.81 (OMe), 54.82 and 54.49 (C-2 and -3), and 46.66 (C-4); *m/z* (field desorption) 461 (21%), 462 (64), 463 (79), 464 (100), 465 (65), 466 (55), 467 (40), 468 (21), and 469 (34).

(±)-(1R*,2S*,3R*,6S*)-3-*Phthalimido*-8-*trichloromethyl*-7-*oxa*-9-*azabicyclo*[4.3.0]*non*-8-*en*-2-*ol* (**27**).—A solution of the imidate (**25**) (0.21 g, 0.52 mmol) in absolute 1,2-dimethoxyethane (DME) (25 ml) was cooled to 0 °C and treated with triethyl aluminium (0.137 ml, 1.04 mmol). The solution was kept at 0 °C overnight. Ethanol (10 ml) was then added and the mixture was stirred for 1 h at 0 °C, and was then diluted with diethyl ether, washed with water (×3), dried over sodium sulphate, and concentrated under reduced pressure. Crystallisation from chloroform–hexane gave the *title compound* (**27**) (0.189 g, 91%) as white crystals, m.p. 150–151 °C (decomp.) (Found: C, 47.8; H, 3.3; N, 7.05. $C_{16}H_{13}Cl_3N_2O_4$ requires C, 47.61; H, 3.25; N, 6.94%); ν_{max} 3 300, 1 765, 1 700, 1 640, and 1 390 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 7.81 (2 H, m, ArH), 7.71 (2 H, m, ArH), 4.95 (1 H, m, 6-H), 4.27 (1 H, m, *J* 10.9 and 8.1 Hz, 2-H), 4.14 (2 H, m, 1- and 3-H), 3.45 (1 H, d, *J* 3.8 Hz, OH), and 2.57–2.40, 2.10–1.94, and 1.94–1.80 (4 H, m, 4- and 5-H_2); δ_C(75.5 MHz; $CDCl_3$) 168.37 (CO), 164.53 (C=N), 134.04, 131.85, and 123.28 (C-8 and aryl C), 86.62 (CCl_3), 84.31 (C-6), 72.39 and 71.76 (C-1 and -2), 51.09 (C-3), and 25.07 and 23.11 (C-4 and -5); *m/z* (field desorption) 401 (26%), 402 (30), 403 (98), 404 (38), 405 (100), 406 (36), 407 (48), and 408 (18).

(±)-(1R*,2R*,3S*,4S*,5R*,6R*)-4,5-*Dimethoxy*-3-*phthalimido*-8-*trichloromethyl*-7-*oxa*-9-*azabicyclo*[4.3.0]*non*-8-*en*-2-*ol* (**28**).—A solution of the trichloroimidate (**26**) (500 mg, 1.1 mmol) in dry DME (90 ml) was cooled to 0 °C. After addition of triethylaluminium (0.295 ml, 2.16 mmol) the solution was stirred for 30 min at 0 °C and then at room temperature. After 2 h, TLC (ethyl acetate–hexane, 1:2) indicated completion of reaction. Ethanol (10 ml) was added to the ice-cooled mixture to decompose both any remaining triethylaluminium and the complex of triethylaluminium with the alcohol (**28**). After 1 h the solution was diluted with diethyl ether, washed with water (×3), dried over sodium sulphate, and concentrated under reduced pressure. Crystallisation from ethyl acetate–hexane afforded the *title compound* (**28**) (463 mg, 92.5%) as white crystals, m.p. 205 °C (Found: C, 46.5; H, 3.6; N, 5.9. $C_{18}H_{17}Cl_3N_2O_6$ requires C, 46.63; H, 3.70; N, 6.04%); ν_{max} 3 520, 1 780, 1 705, 1 660, and 1 385 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 7.86 (2 H, m, ArH), 7.74 (2 H, m, ArH), 4.88 (2 H, m, 2- and 6-H), 4.52 (1 H, dd, *J* 11 and 7 Hz, 3-H), 4.37 (1 H, t, *J* 10 Hz, 1-H), 4.05 (1 H, t, *J* 7 Hz, 5-H), 3.6 (3 H, s, OMe), 3.32 (3 H, s, OMe), and 3.59 (1 H, t, *J* 7 Hz, 4-H); δ_C(75.5 MHz; $CDCl_3$) 168.81 (CO), 163.60 (C=N), 134.09, 131.67, and 123.34 (C-8 and aryl C), 86.26 (CCl_3), 85.18 (C-6), 79.34 and 77.81 (C-4 and -5), 71.27 (C-1), 66.51 (C-2), 60.04 and 59.66 (OMe), and 52.95 (C-3); *m/z* (field desorption) 461 (16%), 462 (37), 463 (100), 464 (45), 465 (84), 466 (39), 467 (37), 468 (11), and 469 (10).

(±)-3t-*Hydroxy*-6t-*phthalimido*-2t-*trichloroacetamidocyclohexyl Acetate* (**29**).—The dihydro-oxazole (**27**) (185 mg, 0.46 mmol) was acetylated overnight in stirred acetic anhydride–pyridine at room temperature, the solution was then evaporated to dryness. To the residue were added methanol (17 ml) and perchloric acid (0.30 ml) and the mixture was stirred at room temperature. After 30 min, TLC indicated that the reaction was complete (ethyl acetate–hexane, 1:1). The solution was then diluted with methylene dichloride, washed with aq. sodium hydrogen carbonate, dried over magnesium sulphate, and evaporated to dryness. The crude product was recrystallised from ethyl acetate–hexane to give *title ester* (**29**) (190 mg, 89.9%) as a white solid, m.p. 204 °C (Found: C, 46.6; H, 3.6; N, 6.2. $C_{18}H_{17}Cl_3N_2O_6$ requires C, 46.63; H, 3.70; N, 6.04%); ν_{max} 3 550, 1 765, 1 730, 1 700, and 1 370 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 7.84 (2 H, m, ArH), 7.74 (2 H, m, ArH), 7.36 (1 H, d, *J* 8.5 Hz, NH), 5.97 (1 H, t, *J* 10.5 Hz, 1-H), 4.37 (1 H, m, 2-H), 4.29 (1 H, m, 3-H), 4.09 (1 H, m, 6-H), 2.96–2.80, 2.1–1.98, and 1.82–1.7 (4 H, m, 4- and 5-H_2), and 1.84 (3 H, s, Me); δ_C(75.5 MHz; $CDCl_3$) 171.02 (Ac), 167.83 (CO), 161.88 (*C*OCCl$_3$), 134.20, 131.47, and 123.47 (aryl C), 92.35 (CCl_3), 69.75 and 68.23 (C-1 and -3), 57.28 (C-2), 51.94 (C-6), 29.92 and 21.86 (C-4 and -5), and 20.56 (Me); *m/z* (field desorption) 461 (27%), 462 (24), 463 (75), 464 (48), 465 (100), 466 (37), 467 (48), and 468 (19).

(±)-3t-*Hydroxy*-4c,5t-*dimethoxy*-6t-*phthalimido*-2t-*trichloroacetamidocyclohexyl Acetate* (**30**).—The dihydro-oxazole (**28**) (225 mg, 0.49 mmol) was acetylated overnight in stirred acetic anhydride–pyridine at room temperature, and the solution was then evaporated to dryness. To the residue were added methanol (19 ml) and perchloric acid (0.40 ml) and the mixture was then stirred at room temperature. After 30 min, TLC indicated that the reaction was complete (ethyl acetate–hexane, 1:1). The solution was then diluted with methylene dichloride, washed with aq. sodium hydrogen carbonate, dried over magnesium sulphate, and evaporated to dryness. The crude product was recrystallised from ethyl acetate–hexane to yield the *title ester* (**30**) (203 mg, 79.9%) as a white solid, m.p. 208 °C (Found: C, 46.0; H, 4.0; N, 5.3. $C_{20}H_{21}Cl_3N_2O_8$ requires C, 45.87; H, 4.04; N, 5.35%); ν_{max} 3 420, 1 770, 1 730, 1 700, 1 520, 1 370, and 1 230 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 7.88 (2 H, m, ArH), 7.76 (2 H, m, ArH), 7.56 (1 H, d, *J* 8.9 Hz NH), 6.55 (1 H, t, *J* 11.2 Hz, 1-H), 4.80 (1 H, dd, *J* 11.7 and 2.8 Hz, 6-H), 4.33 (1 H, m, 2-H), 4.19 (1 H, m, 3-H), 3.86 (1 H, m, 5-H), 3.80 (1 H, t, *J* 3.2 Hz, 4-H), 3.72 (1 H, d, *J* 10.9 Hz, OH), 3.53 (3 H, s, OMe), 3.41 (3 H, s, OMe), and 1.88 (3 H, s, Ac); δ_C(75.5 MHz; $CDCl_3$) 170.43 (Ac), 167.85 (CO), 161.69 (*C*OCCl$_3$), 134.27, 131.29, and 123.49 (aryl C), 92.28 (CCl_3), 82.04 and 74.52 (C-4 and -5), 70.58 and 64.98 (C-1 and -3), 60.11 and 58.02 (OMe), 55.28 and 52.59 (C-2 and -6), and 20.63 (Ac); *m/z* (field desorption) 522 (47%), 523 (26), 524 (83), 525 (18), 526 (100), and 527 (29).

(±)-2c,4c-*Diaminocyclohexan*-1r-*ol Dihydrochloride* (**31**)·2HCl.—Compound (**19**) (326 mg, 0.946 mmol) was kept at 80 °C in a mixture of ethanol (5 ml) and chloroform (2 ml) containing hydrazine (320 µl; 10 mol equiv.). After 20 h all the solvent was removed under reduced pressure and the residue was dissolved in water. Chromatography through Amberlite IRA 400 ion-exchange resin (column size 5 cm × 1 cm) retained all the phthalohydrazide. After lyophilisation, *compound* (**31**)·2HCl was purified by recrystallisation from methanol–acetone or by ion-exchange chromatography through Dowex 50 W/200 ion-exchange resin with 0.5M-HCl (173 mg, 90%), m.p. 252 °C (decomp.) (Found: C, 35.1; H, 8.0; N, 13.55. $C_6H_{16}Cl_2N_2O$ requires C, 35.48; H, 7.93; N, 13.79%); ν_{max} 3 350br, 2 900br and 1 600–1 500br cm^{-1}; δ_H(250 MHz; D_2O) 4.09 (1 H, m, *J ca.* 0.02 Hz, 1-H), 3.41 (1 H, dt, *J* 13 and 2 Hz,

2-H), 3.30 (1 H, m, 4-H), and 1.6–2.05 (6 H, m, 3-, 5-, and 6-Hz); δ_C(63 MHz; D_2O–1,4-dioxane) 64.20 (C-1), 51.55, 48.54 (C-2 and -4), 29.27, 28.95, and 23.55 (C-3, -5, and -6); *m/z* (field desorption 130 (100%, M^+) and 112 (8, $M^+ - 17$).

(±)-(4c,6c-*Diamino*-2t,3c-*dimethoxycyclohexane*-1r-*ol Dihydrochloride* (**32**)·2HCl.—Compound (**20**) (200 mg, 0.49 mmol) was kept at 80 °C in a mixture of ethanol (5 ml) and chloroform (2 ml) containing hydrazine (156 μl; 10 mol equiv.). After 20 h all the solvent was removed under reduced pressure, and the residue was dissolved in water. Chromatography through Amberlite IRA 400 ion-exchange resin (column size 5cm × 1 cm) retained all the phthalohydrazide. After lyophilisation, *title compound* (**32**)·2HCl was purified by recrystallisation from methanol–acetone or by ion-exchange chromatography through Dowex 50 W/200 ion-exchange resin with 0.5M-HCl (114 mg, 88%), m.p. 178 °C (Found: C, 36.5; H, 7.8; N, 10.4. $C_8H_{20}Cl_2N_2O_3$ requires C, 36.51; H, 7.66; N, 10.64%); ν_{max} 3 350br, 2 900br, 1 600–1 500br, and 1 080 cm^{-1}; δ_H(250 MHz; $CDCl_3$; as triacetate) 5.90 (1 H, d, *J* 8.7 Hz, 6-NH), 5.57 (1 H, d, *J* 7.6 Hz, 4-NH), 4.96 (1 H, dd, *J* 3 and 2.8 Hz, 1-H), 4.44 (1 H, ddt, *J* 15.2, 7.6, and 4.3 Hz, 4-H), 4.28 (1 H, ddd, *J* 15.3, 8.7, 3.3, and 2.8 Hz, 6-H), 3.85 (1 H, t, *J* 3.0 Hz, 2-H), 3.46 (1 H, dd, *J* 4.2 and 3.0 Hz, 3-H), 3.44 (3 H, s, OMe), 3.35 (3 H, s, OMe), 2.08 (3 H, s, Ac), 1.96 (3 H, s, Ac), 1.94 (3 H, s, Ac), and 1.77 (2 H, m, 5-H_2); δ_C(63 MHz; D_2O–14-dioxane) 76.26 and 76.06 (C-2 and -3), 67.59 (C-1), 59.03 and 58.93 (2 × Me), 48.92 and 46.89 (C-4 and -6), and 25.08 (C-5); *m/z* (field desorption) 191 (100%, $M^+ + 1$).

(±)-2c,4c-*Diaminocyclohexane*-1r,3t-*diol Dihydrochloride* (**33**)·2HCl.—To a solution of compound (**29**) (300 mg, 0.65 mmol) in ethanol–chloroform (5:2) (7.4 ml) was added anhydrous hydrazine (0.12 ml, 3.9 mmol). After being stirred at 80 °C for 12 h the solution was evaporated to dryness. The crude product was purified by anion exchange and subsequent cation exchange: First the residue was dissolved in a small amount of water and rinsed through a short Amberlite IRA 400 column (5 cm × 7 cm); after the column had been washed with water the filtrate was chromatographed on a Dowex 50W(H^+)/200 column (24 cm × 1.3 cm). This column was eluted with increasing concentrations of HCl (200 ml each of: 0.5M, 1M, 1.5M, 2M, 2.5M, and 5M. The fraction run with 2M-HCl contained the required product (**33**). The *product* was crystallised from methanol–ethanol as a white solid (100 mg, 70%), m.p. 273 °C (decomp.) (Found: C, 32.7; H, 7.1; N, 12.75. $C_6H_{16}Cl_2N_2O_2$ requires C, 32.89; H, 7.36; N, 12.79%); ν_{max} 3 360, 2 960, 1 590, and 1 500 cm^{-1}; δ_H(300 MHz; CD_3OD) 4.18 (1 H, m, 1-H), 3.85 (1 H, t, *J* 10.3 and 10.3 Hz, 3-H), 3.17–3.04 (2 H, m, 2- and 4-H), and 2.02–1.86 and 1.79–1.66 (4 H, m, 5- and 6-H_2); δ_C(75.5 MHz; D_2O–dioxane as internal standard) 68.29 and 65.78 (C-1 and -3), 56.79 and 53.95 (C-2 and -4), and 28.07 and 22.41 (C-5 and -6); *m/z* (field desorption) 147 (M^+, 100%).

(±)-2c,4c-*Diamino*-5c,6t-*dimethoxycyclohexane*-1r,3t-*diol Dihydrochloride* (**34**)·2HCl.—To a solution of compound (**30**) (300 mg, 0.57 mmol' in ethanol–chloroform (5:2) (7.5 ml) was added anhydrous hydrazine (0.11 ml, 3.4 mmol). After the mixture had been stirred at 80 °C for 12 h a white precipitate had formed. The mixture was evaporated to dryness. The crude product was purified by anion exchange and subsequent cation exchange: First the residue was dissolved in a small amount of water and rinsed through a short Amberlite IRA 400 column of (5 cm × 0.7 cm); after the column had been washed with water the filtrate was eluted through a Dowex 50W(H^+)/200 column (24 cm × 1.3 cm). This column was eluted with increasing concentrations of HCl (200 ml each of: 0.5M, 1M, 1.5M, 2M, 2.5M, and 5M). The fraction run with 2M-HCl contained the required product (**34**) (120.6 mg, 76%). For characterisation, compound (**34**) was completely acetylated with acetic anhydride–pyridine; the product had m.p. 210 °C (Found: C, 51.0; H, 6.95; N, 7.2. $C_{16}H_{26}N_2O_8$ requires C, 51.33; H, 7.00; N, 7.28%); ν_{max} 3 260, 1 725, 1 640, 1 520, 1 360, and 1 220 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 5.81 (1 H, d, *J* 9.0, NH), 5.54 (1 H, d, *J* 9.7 Hz, NH), 5.12 (1 H, t, *J* 10.7 and 10.7, 3-H), 5.10 (1 H, m, 1-H), 4.64 and 4.54 (2 H, m, 2- and 4-H), 3.86 (1 H, t, *J* 3.0 Hz, 5- or 6-H), 3.53 (1 H, m, 6- or 5-H), 3.48 (3 H, s, OMe), 3.34 (3 H, s, OMe), 2.10 (3 H, s, Ac), 2.04 (3 H, s, Ac), 1.96 (3 H, s, Ac), and 1.93 (3 H, s, Ac); δ_C(75.5 MHz; $CDCl_3$) 172.11, 170.01, 169.22, and 169.16 (4 × Ac), 79.43 and 71.49 (C-5 and -6), 71.27 and 69.80 (C-1 and -3), 58.26 and 57.88 (OMe), 49.51 and 48.31 (C-2 and -4), and 23.04, 22.91, 20.64, and 20.56 (Ac); *m/z* (field desorption) 374 (M^+, 100%).

(±)-4c-*Amino*-2t-*bromocyclohexane*-1r,3c-*diol* (**35**)—see ref. 9.

(±)-3t-*Bromo*-2c,4c-*bis*(*t-butyldimethylsiloxy*)*cyclohexan*-1r-*amine* (**36**).—To a suspension of compound (**35**) (880 mg, 3.57 mmol) in dry methylene dichloride (5 ml) at 0 °C was added 2,6-lutidine (1.662 ml, 14.3 mmol). Within 30 min t-butyldimethylsilyl triflate (2.46 ml, 10.71 mmol) was added dropwise into the mixture to give a clear solution. Further treatment to provide complete silylation was found to be of benefit only if carried out at least 6 h later. All methylene dichloride was replaced by diethyl ether before the mixture was washed with water (×3). The organic phase was dried over sodium sulphate, separated by filtration, and evaporated to leave needles of bromide (**36**) (1.456 g, 93%), m.p. 116 °C (Found: C, 49.1; H, 9.4; N, 3.3. $C_{18}H_{40}BrNO_2Si_2$ requires C, 49.29; H, 9.19; N, 3.19%); ν_{max} 3 100, 2 950, 2 880, 1 620, 1 500, 1 460, 1 350, and 1 250 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 4.00 (1 H, t, *J* 9.7 Hz, 3-H), 3.66 (2 H, m, 2- and 4-H), 3.18 (1 H, ddd, *J* 3.3, 3.1, and 3 Hz, 1-H), 1.76 (1 H, m, 6-H), 1.73 (2 H, m, 5e- and 6-H), 1.62 (2 H, br, NH_2), 1.58 (1 H, dm, *J* 13.8 and 3.8 Hz, 5a-H), 0.92 (9 H, s, Bu^t), 0.89 (9 H, s, Bu^t), 0.18 (3 H, s, Me), 0.14 (3 H, s, Me), 0.10 (3 H, s, Me), and 0.07 (3 H, s, Me); δ_C(63 MHz; $CDCl_3$) 76.83 and 74.93 (C-2 and -4), 62.86 (C-1), 51.92 (C-3), 29.11 and 26.35 (C-5 and -6), 25.86 and 25.81 (Bu^t), 18.15 and 18.08 (CMe_3) and −4.26, −4.42, −4.46, and −4.50 (4 × Me); *m/z* 438 (M^+, 100%), 440 (M^+, 87), 383 ($M^+ - 57$, 91), and 380 ($M^+ - 57$, 73).

(±)-3c-*Azido*-2c,4c,*bis*(*t-butyldimethylsiloxy*)*cyclohexan*-1r-*amine* (**37**).—Sodium azide (400 mg, 3.07 mmol) and compound (**36**) (200 mg, 0.456 mmol) were dried for at least 1 h in high vacuum before they were suspended in carefully dried DMF (3 ml) under oxygen-free conditions. The mixture was vigorously stirred for 5 h at 120 °C, then cooled to room temperature, and diethyl ether (at least 200 ml) was added and the mixture was washed with water (2 × 100 ml). The organic phase was dried over sodium sulphate, separated by filtration, and evaporated to leave crude compound (**37**) (148 mg, 81%) as a slightly yellowish oil. Crystallisation from hexane at −30 °C gave the *title azide*, m.p. 53 °C (Found: C, 53.9; H, 9.9; N, 14.1. $C_{18}H_{40}N_4O_2Si_2$ requires C, 53.95; H, 10.06; N, 13.98%); ν_{max} 3 400, 2 930, 2 860, 2 100, 1 450, 1 360, and 1 260 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 3.78 (1 H, ddd, *J* 13.5, 8.7, and 5 Hz, 4-H), 3.60 (1 H, ddd, *J* 11.3, 4.7, and 3.2 Hz, 1-H), 3.35 (1 H, dd, *J* 11.3 and 3.3 Hz, 2-H), 3.32 (1 H, dd, *J* 5 and 3.3 Hz, 3-H), 1.92 (2 H, m, 5- and 6-H), 1.46 (2 H, m, 5- and 6-H), 0.92 (9 H, s, Bu^t), 0.88 (9 H, s, Bu^t), 0.12 (3 H, s, Me), 0.10 (3 H, s, Me), and 0.05 (6 H, s, 2 × Me); δ_C(63 MHz; $CDCl_3$) 76.05 and 71.56 (C-2 and -4), 61.25 (C-1), 57.44 (C-3), 29.68 and 26.52 (C-5 and -6), 25.78 and 25.75 (Bu^t), 18.03 and

17.98 (CMe_3) and −4.68, −4.80, −4.91, and −4.97 (4 × Me); *m/z* 401 (M^+, 18%) and 343 ($M^+ - 57$, 100).

(±)-2c,4c-*Diaminocyclohexane*-1r,3c-*diol Dihydrochloride* (**38**)·2HCl.—A solution of compound (**37**) (100 mg, 0.25 mmol) containing a catalytic amount of Pd/C (10%) in ethyl acetate–methanol (5:1 ml) was stirred under hydrogen (1 bar) for at least 1 day at room temperature. The catalyst was filtered off and the solvents were replaced by a mixture of hydrochloric acid (5 ml; 0.1M) and methanol (5 ml) which was kept at 40 °C for 2 days. All solvent was removed under reduced pressure and the residue was dried exhaustively under high-vacuum conditions. Recrystallisation from methanol–acetone afforded the *title hydrochloride of compound* (**38**) (46 mg, 84%), m.p. 269 °C (Found: C, 32.9; H, 7.5; N, 12.6. $C_6H_{16}Cl_2N_2O_2$ requires C, 32.89; H, 7.36; N, 12.78%); ν_{max} 3 350br, 2 900br, and 1 600–1 500br cm^{-1}; δ_H(250 MHz; D_2O) 3.95 (1 H, ddd, *J* 10.7, 5.2, and 1 Hz, 1-H), 3.89 (1 H, dd, *J* 10.8 and 4.5 Hz, 3-H), 3.70 (1 H, t, *J* 5.2 and 4.5 Hz, 2-H), 3.14 (1 H, dt, *J* 11, 11, and 4.3 Hz, 4-H), 2.05 (1 H, m, 5- or 6-H), 1.90 (1 H, m, 5- or 6-H), and 1.45 (2 H, m, any 2 H of 5-H_2 and 6-H_2); δ_C(63 MHz; D_2O–1,4-dioxane) 67.97 and 66.25 (C-1 and -3), 57.59 and 50.64 (C-2 and -4), and 26.05 and 24.47 (C-5 and -6); *m/z* (EI) 146 (M^+, 100%) and 128 ($M^+ - 18$, 44).

Acknowledgements

We thank our late colleague, Prof. G. Kresze, for his valuable support and encouragement. The assistance of Dr. M. Weißhuhn, Ms. B. Bubl, and Mr. M. Zientz is gratefully acknowledged.

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Paper 0/00611D
Received 10*th February* 1990
Accepted 14*th March* 1990