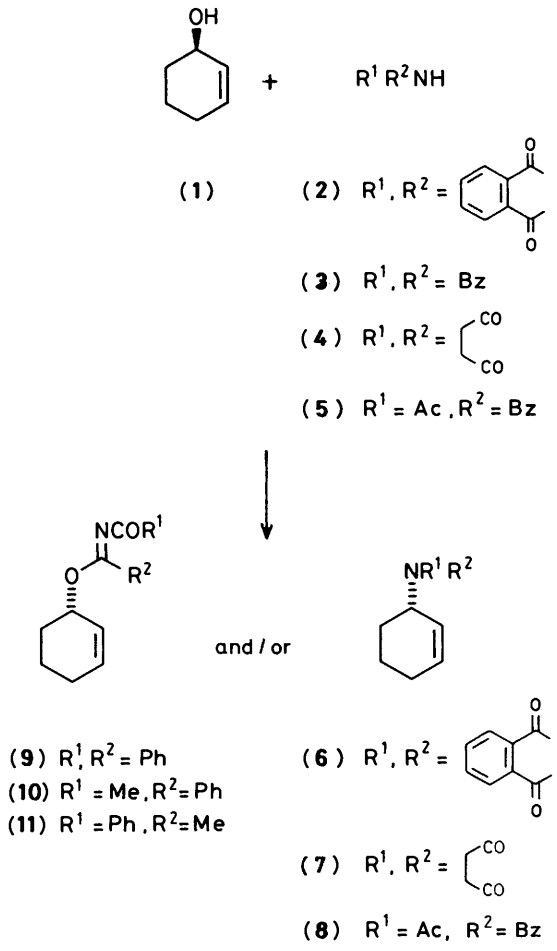
Stereocontrolled Preparation of Cyclohexane Amino Alcohols Utilising a Modified Mitsunobu Reaction

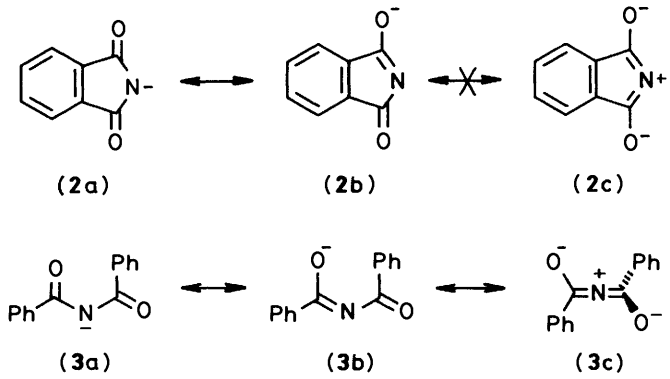
Peter G. Sammes * and Dean Thetford
Department of Chemistry, Brunel University, Uxbridge, Middlesex, UB8 3PH

A method for the introduction of amino groups into aliphatic systems is described. Cyclohex-2-enol reacts with aromatic diacylamines under Mitsunobu reaction conditions to give either *N*-alkylated or *O*-alkylated products in a controlled, predictable manner. The product cyclohexenes, with *N*-bromosuccinimide, give either 1,2- or 1,3-neighbouring group participation leading to 1,2,3-trisubstituted cyclohexanes. The adducts may be used to give a range of 1,2- and 1,3-amino alcohols in a stereocontrolled process.

In a recent paper[1] we described the synthesis of (L)-daunosamine and related sugars using a modified Mitsunobu reaction. Herein we describe further studies on this reaction using cyclohex-2-enol (**1**) as substrate.



The Mitsunobu reaction has previously been used for the introduction of nitrogen into aliphatic systems, principally by using triphenylphosphine and diethyl azodicarboxylate as activator and an azide salt as the nucleophile. In his review[2] Mitsunobu gave brief mention of the use of diacylamines but with few details.[3,4] In exploiting the latter observations we confirmed that phthalimide (**2**) reacts with the cyclohexenol (**1**) under these conditions to give the *N*-alkylated phthalimide (**6**) and found that *N*-benzoylbenzamide ('dibenzamide') (**3**) reacts completely by *O*-alkylation, to produce the imino ether (**9**). Both reactions proceed in high yield under ambient conditions. The disparity between the two systems may be rationalised by considering the localisation of negative charge about nitrogen. In the case of the phthalimide anion, represented by (**2a**) and (**2b**), resonance forms such as (**2c**) (Scheme 1) are not allowed



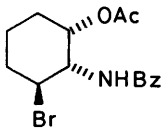
Scheme 1.

because of the steric constraints imposed by the five-membered imide ring; in the case of dibenzamide this constraint is absent and more charge resides about the oxygen atoms (**3a**), (**3b**), and (**3c**).

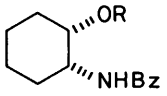
The usefulness of phthalimide as a masked amino group has been known for over a hundred years in its use in the Gabriel synthesis of primary amines,[5] though this method has its limitations.[6] The advantage of this modified Mitsunobu reaction is that a primary or secondary alcohol group may be activated *in situ* and treated with phthalimide under aprotic conditions at room temperature or below in minutes. The mildness of the conditions, involving the formation of a powerful leaving group, helps to suppress unwanted side reactions such as eliminations, except where these are favoured, as in the dehydration of malic to fumaric acid.[3] One other point on the mechanism of the reaction should be mentioned; because of the symmetry of our model substrate (**1**), we were not able to discern the degree of S_N2' reaction co-occurring with direct displacement of the alcohol group. There are some literature precedents that suggest allylic rearrangements during the Mitsunobu reaction tend to be minor[7] and we do not believe that this process is occurring in the reactions we are reporting.

The reactions of other diacylamines were also explored. With succinimide (**4**) nitrogen attack was observed,[2] leading to the imide (**7**); presumably the five-membered ring again constrains

electron density about the nitrogen atom, which is the preferred site of reaction. With *N*-acetylbenzamide (**5**) a mixture of two products was formed, the *N*-substituted imide (**8**) (34% yield) and the *O*-alkylated product (**10**) (35% yield). None of the isomeric imino ether (**11**) was isolated. The structure of the imino ether (**10**) was ascertained by reaction with *N*-bromosuccinimide in ethanolic chloroform to give the bromoacetate (**12**), the i.r. spectrum indicating $\nu_{max.}$(CO) at 1 740 (acetate) and 1 650 cm^{-1} (benzamide); the isomeric imino ether (**11**) would have been expected to form the corresponding acetylamino benzoate. The adduct (**12**) was converted into the known[8] benzamide (**14**) by reductive removal of the bromine, to give compound (**13**), followed by base hydrolysis.

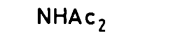


(**12**)

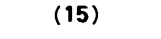


(**13**) R = Ac
(**14**) R = H

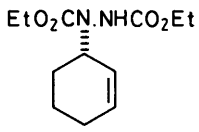
N-Acetylacetamide (**15**) and di-t-butyl iminodicarboxylate (**16**) did not react with the cyclohexenol (**1**) under the standard Mitsunobu reaction conditions. For these, preferential attack by the diethyl hydrazodicarboxylate anion, co-produced in the reaction, was observed to form the hydrazine dicarboxylate (**17**). In an attempt to suppress reaction of the hydrazodicarboxylate anion the reaction was buffered with boron trifluoride–diethyl ether. However, suppression of the reaction with both the diacylamine and the hydrazodicarboxylate occurred, and the alcohol self-condensed to produce the dicyclohexene ether (**18**) in modest yield (20%). Presumably, with the diacylamines (**15**) and (**16**), either the anion is not formed under the reaction conditions or else they react slowly compared to the other diacylamines studied.



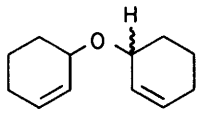
(**15**)



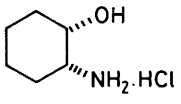
(**16**)



(**17**)



(**18**)



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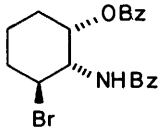

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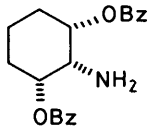
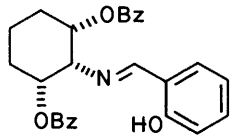
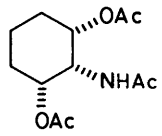


(**21**)

The conversion of the *O*-alkylated imino ether (**9**) to the *cis*-1,2-hydroxy amine (**19**) was described in the previous paper[1] (see also Scheme 2); further reactions of (**9**) have also been examined. Treatment with *N*-bromosuccinimide gave the intermediate (**20**). On heating this in 6M hydrochloric acid further neighbouring group participation occurred to give the all-*cis* 2-amino 1,3-dibenzoate (**21**). Transformation of the latter to the known triacetyl derivative (**23**)[9] proved troublesome, acid-catalysed hydrolysis being remarkably slow and base-catalysed hydrolysis resulting in the unwanted migration of the benzoyl group to the nitrogen atom.[10] In order to expedite removal of the ester groups, without concomitant acyl migration, the amine function was protected by conversion to its salicylaldimine derivative (**22**),[11] the esters removed by treatment with base, the product treated with dilute acid to remove the imine group and the resulting dihydroxyamine acetylated to give the product (**23**). The overall yield for the five



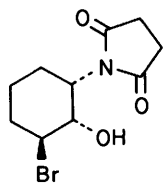
(**22**)



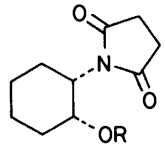
(**23**)

steps from cyclohexenol to the triacetyl derivative was 32%; the literature yield for a four-step process from cyclohexanone was 2%.[12]

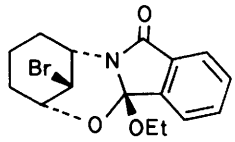
Treatment of the succinimide derivative (**7**) with *N*-bromosuccinimide in ethanolic chloroform also exhibited neighbouring group participation, the product being the bromohydrin (**24**), which could be reduced to the alcohol (**25**) and acetylated (**26**). Comparison of the ^1H n.m.r. signals with those from the previously described 1,2-amino alcohol confirmed the 1,2-*cis*-orientation.[1] With the phthalimido derivative (**6**), however, a different reaction course was observed; treatment with *N*-bromosuccinimide gave only the 1,3-adduct (**27**). Proof of the structure of this adduct was as follows; treatment with dilute acid furnished the alcohol (**28**), which was



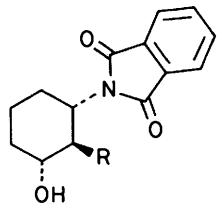
(**24**)



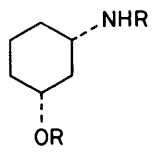
(**25**) R = H
(**26**) R = Ac



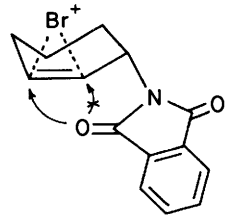
(**27**)



(**28**) R = Br
(**29**) R = H



(**30**) R = H
(**31**) R = Ac

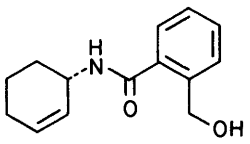


(**32**)

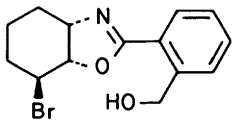
readily reduced with tributyltin hydride to give the desbromo compound (**29**). Release of the amine group by hydrazinolysis afforded the *cis*-1,3-amino alcohol (**30**), again characterized as the known diacetyl derivative (**31**).[13]

For the bromination of the conformationally mobile cyclohexene (**6**) the phthalimide group prefers to react *via* a six-membered transition state (**32**), the constraints imposed on the imide ring by the fused benzene ring preventing participation *via* a five-membered transition state. When this constraint is removed, as for the saturated succinimide derivative, the five-membered transition state is accommodated. It remains to be seen if this preference for 1,3-addition in the phthalimide series is maintained in more conformationally restricted ring systems.

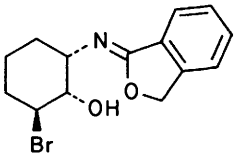
The phthalimide adduct (**6**) was used in one further sequence of reactions. Initial reduction of the phthalimide ring with sodium borohydride in isopropyl alcohol gave the amido alcohol (**33**). Reaction of this with *N*-bromosuccinimide in chloroform, in the absence of ethanol, proceeded smoothly to give the bromohydrin imino ether (**35**). Neighbouring group participation must occur, initially to give the intermediate (**34**), the adjacent hydroxy group then displacing the cyclohexanol group to produce the more stable imino ether. Reduction of the bromine group, to give the alcohol (**36**), followed by hydrolysis



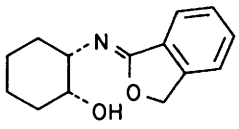
(**33**)



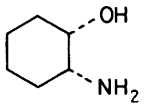
(**34**)



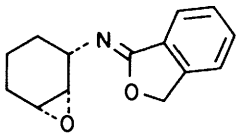
(**35**)



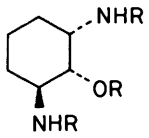
(**36**)



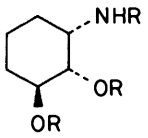
(**37**)



(**38**)



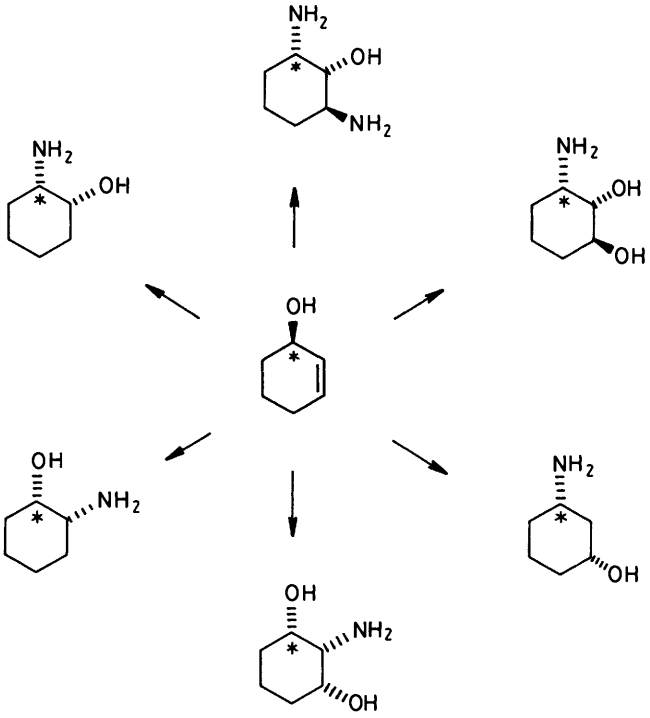
(**39**) R = H
(**40**) R = Ac



(**41**) R = H
(**42**) R = Ac

with dilute hydrochloric acid in methanol at room temperature gave the required amino alcohol (**37**) as it's hydrochloride (**19**). Alternatively the bromohydrin (**35**) could be transformed to its epoxide (**38**) by treatment with base. The epoxide ring could be opened up by nucleophilic attack at the 3-position; thus treatment with ammonia followed by hydrolysis gave the diamino alcohol (**39**), characterised as its triacetyl derivative (**40**). Treatment of the epoxide with perchloric acid gave the dihydroxy amine (**41**), also characterised as its triacetyl derivative (**42**).

The network of transformations described herein are summarised in Scheme 2. They represent a useful set of reactions for generating various amino alcohol derivatives.



Scheme 2.

Experimental

General Techniques.—M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 1420 Ratio Recording spectrophotometer, either for films or, for solids, in chloroform solution. ^{1}H N.m.r. spectra were recorded on a Varian EM 360A (60 MHz), a Perkin-Elmer R32 (90 MHz), a JEOL FX 90Q (90 MHz), a Bruker AM 250 (250 MHz), or a Bruker AM 400 (400 MHz) spectrometer and are quoted in p.p.m. relative to tetramethylsilane (TMS) (internal reference) for solutions in deuteriochloroform or as stated. Mass spectra were obtained with a Kratos MS 25 instrument. Accurate mass determinations were obtained with an AEI-Kratos MS 9/50 machine. For compounds containing bromine, accurate masses are given for the ^{79}Br isotope only. Microanalytical determinations were performed at the Universty of Leeds, by the Microanalytical Laboratory. T.l.c. was carried out on glass plates precoated with Merck Kieselgel 60 GF_{254}. Column chromatography was carried out either on MN-Kieselgel 60 (CAMLAB) or on Kieselgel 60G (Merck) and columns were generally packed and run under pressure. Solvents used for chromatography were distilled before use and solvent ratios are described in ratios of volumes before mixing. Light petroleum refers to that fraction with boiling range 60—80 °C, and ether refers to diethyl ether throughout.

Solvents were dried using the methods described by Perrin.[14] Chloroform was made ethanol-free by passing the solvent through an activated alumina column (basic) immediately before use. NBS was freshly recrystallised from hot water and dried over phosphorus pentaoxide, *in vacuo*, before use. AIBN was recrystallised from ether and stored at −10 °C in the dark. Unless otherwise stated, extracts of organic compounds were dried over anhydrous sodium sulphate. Solvents and volatile reagents were removed from extracts or reaction mixtures by

evaporation under reduced pressure, generally using a rotatory evaporator.

N-(*Cyclohex-2-enyl*)*phthalimide* (**6**).—Diethyl azodicarboxylate (DEAD) (3.9 g, 22.4 mmol) in dry THF (2 ml) was added dropwise to a stirred solution of cyclohex-2-enol (2.0 g, 20 mmol), PPh_3 (5.88 g, 22 mmol) and phthalimide (3.2 g, 21 mmol) in dry THF (30 ml) at 0 °C before the mixture was warmed to room temperature and stirred for a further 15 min. Silica gel (10 g) was added to the solution which was then evaporated to provide a residue. Chromatography of the latter on silica, using ethyl acetate–light petroleum (1:4) as eluant, yielded the title phthalimide (**6**) (2.66 g, 57%), m.p. 113—114 °C (lit.,[15] m.p. 113—114 °C); $\nu_{max.}$ 1 770, 1 710, 1 387, 1 360, 1 342, and 1 115 cm^{-1}; δ_H 1.6—2.5 (6 H, m), 4.9 (1 H, m), 5.53 (1 H, m), 5.92 m), and 7.6—7.9 (4 H, m, ArH). (Found: C, 73.9; H, 5.8; N, 6.1. Calc. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.8; N, 6.1%).

N-(*Cyclohex-2-enyl*)*succinimide* (**7**).—DEAD (3.9 g, 22.4 mmol) in dry THF (2 ml) was added to a stirred solution of cyclohex-2-enol (2 g, 20.4 mmol), PPh_3 (5.9 g, 22.4 mmol), and succinimide (2.3 g, 20.4 mmol) in THF (60 ml) at room temperature. After 15 min the solvent was removed and the residue chromatographed through silica gel, using ethyl acetate–light petroleum (1:4) as eluant to give an oil. This was dissolved in ether (25 ml) and the solution cooled to −25 °C; the precipitated solid was filtered off and the filtrate evaporated. The residual oil was distilled under reduced pressure to give the *title succinimide* (**7**) (1.93 g, 53%), b.p. 100—105 °C, 5 mmHg; $\nu_{max.}$ 1 775, 1 720, 1 390, 1 365, 1 182 cm^{-1}; δ_H 1.6—2.2 (6 H, m), 2.67 (4 H, s, 2 × CH_2CO), 4.73. (1 H, m), 5.4 (1 H, m), and 5.90 (1 H, m); *m/z* 179 (M^+, 5%), 15 (15), 150 (3), 123 (13), 100 (72), and 80 (100). (Found: C, 66.8; H, 7.4; N, 7.8. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%).

Cyclohex-2-enyl N-*Acetylbenzimidate* (**10**) *and* N-(*Cyclohex-2-enyl*)-N-*benzoylacetamide* (**8**).—DEAD (0.98 g, 5.6 mmol) in dry THF (1 ml) was added to a stirred solution of cyclohex-2-enol (0.5 g, 5.1 mmol), PPh_3 (1.47 g, 5.6 mmol) and N-acetylbenzamide (0.91 g, 5.6 mmol) in THF (20 ml) at room temperature. After 30 min the solvent was removed and the residue was chromatographed through silica gel, using ethyl acetate–light petroleum (1:4) as eluant, to give the *imidate* (**10**) (0.44 g, 35%) as a colourless oil, $\nu_{max.}$ 1 700, 1 660, 1 375, and 1 325 cm^{-1}; δ_H 1.5—2.2 (6 H, m), 2.07 (3 H, s, Me), 5.5 (1 H, m), 5.8.6.2 (2 H, m), and 7.2—8.1 (5 H, m, ArH); *m/z* 243 (M^+, 0.6%), 163 (19), 105 (100), 81 (11), and 77 (62). (Found: C, 74.1; H, 7.2; N, 5.8. $C_{15}H_{17}NO_2$ requires C, 74.1; H, 7.1; N, 5.8%).

Further elution gave the *imide* (**8**) (0.42 g, 34%) also as a colourless oil, b.p. 150—153 °C; $\nu_{max.}$ 1 670, 1 645, and 1 380 cm^{-1}; δ_H 1.7—2.2 (6 H, m), 1.95 (3 H, s, Me), 5.1 (1 H, m), 5.45—6.0 (2 H, m), 7.4—7.9 (5 H, m, aromatic H); *m/z* 243 (M^+, 0.8%), 200 (11), 138 (49), 105 (100), and 96 (50) (Found: C, 73.8; H, 7.1; N, 5.9. $C_{15}H_{17}NO_2$ requires C, 74.1; H, 7.1; N, 5.8%).

Further elution gave the *imide* (**8**) (0.42 g, 34%) also as a colourless oil, b.p. 150—153 °C; $\nu_{max.}$ 1 670, 1 645, and 1 380 cm^{-1}; δ_H 1.7—2.2 (6 H, m), 1.95 (3 H, s, Me), 5.1 (1 H, m), 5.45—6.0 (2 H, m), 7.4—7.9 (5 H, m, aromatic H); *m/z* 243 (M^+, 0.8%), 200 (11), 138 (49), 105 (100), and 96 (50) (Found: C, 73.8; H, 7.1; N, 5.9. $C_{15}H_{17}NO_2$ requires C, 74.1; H, 7.1; N, 5.8%).

1,2-cis-2,3-trans-2-*Benzamido*-3-*bromocyclohexyl Acetate* (**12**).—NBS (0.3 g, 1.7 mmol) was added to a stirred solution of the imidate (**10**) (0.35 g, 1.4 mmol) in chloroform (20 ml) and ethanol (1 ml). The solution was stirred for 30 min at room temperature and then washed with 1M aqueous sodium thiosulphate (10 ml). The organic layer was dried and evaporated under reduced pressure to give a yellow oil which was chromatographed through silica gel, using ethyl acetate–light petroleum (1:4) as eluant, to give the *title amide* (**12**) (0.384 g, 81%) as colourless needles, m.p. 153—154 °C; $\nu_{max.}$ 3 450, 1 740, 1 665, 1 510, and 1 485 cm^{-1}; δ_H 1.6—2.6 (6 H, m), 2.08 (3 H, s, Me), 4.1—4.6 (2 H, m), 5.32 (1 H, m), 6.2 (1 H, br d, *J* 7.7 Hz, exch. with D_2O NH), and 7.4—7.85 (5 H, m, ArH); *m/z* 339 (M^+, 0.4%), 296 (0.3), 260 (2), 216 (18), 199 (79), 171 (9), 122 (21), and 105 (100). (Found: C, 52.7; H, 5.2; Br, 23.6; N, 4.1. $C_{15}H_{18}BrNO_3$ requires C, 52.9; H, 5.3; Br, 23.5; N, 4.1%).

cis-2-*Benzamidocyclohexyl Acetate* (**13**).—Tributyltin hydride (0.15 g, 0.5 mmol) was added to a stirred solution of the bromoamide (**12**) (0.17 g, 0.5 mmol) and AIBN (3 mg) in toluene (2 ml) and methanol (0.5 ml) and the solution heated to reflux for 1 h. It was then evaporated and the residue was chromatographed through silica gel, using ethyl acetate–light petroleum (1:1) as eluant, to give a solid, which was recrystallised from ethyl acetate–hexane to aford the *amido ester* (**13**) (0.11 g, 84%), m.p. 126—128 °C; $\nu_{max.}$ 3 450, 1 735, 1 655, 1 510, and 1 485 cm^{-1}; δ_H 1.4—2.05 (8 H, m), 2.1 (3 H, s, Me), 4.23 (1 H, m), 5.13 (1 H, m), 6.3 (1 H, br d, *J* 8 Hz, exch. with D_2O, NH), and 7.35—7.8 (5 H, m, ArH); *m/z* 261 (M^+, 4%), 201 (28), 122 (35), and 105 (100) (Found: C, 68.8; H, 7.4; N, 5.1. $C_{15}H_{19}NO_3$ requires C, 68.9; H, 7.3; N, 5.3%).

A sample of the acetate (**13**) was hydrolysed with sodium methoxide in methanol at room temperature for 30 min. The mixture was then quenched with water and extracted with chloroform and the extract worked up to provide a solid. This was recrystallised from ethyl acetate–benzene to give the known *cis*-2-benzamidocyclohexanol (**14**), m.p. 185—186 °C (lit.,[6] m.p. 186 °C) (Found: C, 71.1; H, 7.8; N, 6.3. Calc. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4%).

Attempted Reaction of Cyclohex-2-enol with the Imides (**15**) *and* (**16**).—The following method was employed. DEAD (1.8 g, 10 mmol) in dry THF (1 ml) was added dropwise to a stirred solution of cyclohex-2-enol (1 g, 10 mmol), PPh_3 (2.6 g, 10 mmol) and the imide (10 mmol) in THF (20 ml) at 0 °C. The solution was stirred for 15 min at room temperature and then concentrated to provide a residue. This was chromatographed through silica gel, using ethyl acetate–light petroleum (1:1) as eluant to give recovered imide (85%) and *N*-(cyclohex-2-enyl)-*N*,*N*′-diethoxycarbonylhydrazine (**17**)[16] (2.1 g, 80%) as a colourless oil, b.p. 130—132 °C, 1 mm Hg; $\nu_{max.}$ 3 410, 1 755, 1 710, 1 415, 1 385, and 1 310 cm^{-1}; δ_H 1.25 (6 H, t, *J* 7 Hz, CH_3CH_2), 1.5—2.2 (6 H, m), 4.2 (4 H, q, *J* 7 Hz, CH_3CH_2), 1.5—2.2 (6 H, m), 4.2 (4 H, q, *J* 7 Hz, CH_3CH_2), 4.8 (1 H, m), 5.7 (2 H, m, vinylic H), and 6.45 (1 H, br s, NH); *m/z* 257 (MH^+, 3.3%), 177 (49), 168 (14), 138 (13), 130 (10), 105 (25), and 81 (100). (Found: C, 56.3; H, 7.8; N, 10.9. Calc. for $C_{12}H_{20}N_2O_4C$, 56.2; H, 7.9; N, 10.9%).

Dicyclohex-2-enyl Ether (**18**).—DEAD (3.8 g, 21.2 mmol) in dry THF (1 ml) was added dropwise to a stirred solution of PPh_3 (5.8 g, 21.3 mmol) in dry THF (5 ml) at 0 °C. The solution was stirred for 5 min at 0 °C and then added to a stirred solution of cyclohex-2-enol (1 g, 10.2 mmol) and boron trifluoride–diethyl ether (1.58 g, 11.2 mmol) in dry THF (15 ml) at 0 °C. The solution was allowed to warm to room temperature over 15 min and then evaporated and the residue chromatographed directly through silica gel, using ethyl acetate–light petroleum (1:4) as eluant to yield the title ether (**18**) (0.18 g, 20%) as a colourless oil; $\nu_{max.}$ 1 450, 1 430, 1 310, 1 080, and 725 cm^{-1}; δ_H 1.5—2.2 (12 H, m), 4.05 (2 H, br s, R_2CHO), and 5.6—6.0 (4 H, m, olefinic H) (Found: M^+, 178.136 11. Calc. for $C_{12}H_{18}O$: *M*, 178.135 82).

1,2-cis-2,3-cis-2-*Aminocyclohexane*-1,3-*diyl Dibenzoate Hydrochloride* (**21**).—6M Hydrochloric acid solution (6 ml)

was added to a stirred solution of the bromo amide ester (**20**)[1] (2.35 g, 5.8 mmol) in methanol (30 ml) and the solution stirred at reflux for 8 h. It was then evaporated to yield a pale yellow solid which was chromatographed through silica gel, using methanol–ethyl acetate (1:9) as eluant. This provided a colourless solid, which was recrystallised from ethyl acetate–light petroleum to give the *title diester* (**21**) (1.54 g, 70%), m.p. 183—185 °C; $\nu_{max.}$(Nujol) 3 275, 3 200—2 500, 1 740, 1 720, 1 602, 1 505, 1 255, and 710 cm^{-1}; δ_H 1.4—2.3 (9 H, m), 3.63 (1 H, br s, 2-H), 5.2 (2 H, m, 1-H and 3-H), and 5.3—8.15 (10 H, m, ArH). The salt was analysed as its tetraphenylborate monohydrate (Found: C, 78.0; H, 6.3; N, 2.1. $C_{44}H_{42}BNO_4 \cdot H_2O$ requires C, 78.0; H, 6.5; N, 2.1%).

1,2-cis-2,3-cis-2-(o(*Hydroxybenzylideneamino*)*cyclohexane*-1,3-*diyl Dibenzoate* (**22**).—Triethylamine (0.29 g, 2.9 mmol) in dry THF (3 ml) was added to a stirred solution of the amine hydrochloride (**21**) (1.1 g, 2.9 mmol) and salicylaldehyde (0.36 g, 2.9 mmol) in dry THF (40 ml). The solution was stirred for 2 h at room temperature and then evaporated and the residue chromatographed through silica gel, using ethyl acetate–light petroleum (1:1) as eluant, to afford, after crystallisation from ethyl acetate–chloroform, the *title compound* (**22**) (1.05 g, 82%), m.p. 159—161 °C; $\nu_{max.}$ 3 200—2 600, 1 718, 1 632, 1 270, and 1 113 cm^{-1}; δ_H 1.6—2.2 (6 H, m), 4.15 (1 H, t, *J* 3.3 Hz, 2-H), 5.2—4.54 (2 H, m, 1-H and 3-H), 6.8—7.95 (14 H, m, ArH), 8.34 (1 H, s, HC=N), and 13.38 (1 H, s, exch. with D_2O, OH) (Found: C, 73.0; H, 5.6; N, 3.2. $C_{27}H_{25}NO_5$ requires C, 73.1; H, 5.7; N, 3.2%).

1,2-cis-2,3-cis-2-*Acetamidocyclohexane*-1,3-*diyl Diacetate* (**23**).—The amine (**21**) (0.25 g, 0.56 mmol) in chloroform (5 ml) and methanol (5 ml) was added to a solution of freshly prepared sodium methoxide [from sodium (26 mg, 1.12 mmol) and methanol (10 ml)] and the solution left at room temperature for 10 min. 1M Hydrochloric acid (2 ml) was added to the solution which was stirred for a further 10 min and then evaporated. The residue was treated with methanol (5 ml) and the white salts were filtered off and the filtrate dried. Pyridine (1.5 ml) and acetic anhydride (2 ml) were added to the latter and the solution was stirred for 30 min at room temperature before it was evaporated under reduced pressure. The residual yellow solid was chromatographed through silica gel, using ethyl acetate–light petroleum (1:1) as eluant, to give the title acetate (**23**),[9] which was recrystallised from ethyl acetate–light petroleum to give colourless needles (0.101 g, 70%), m.p. 180—182 °C; $\nu_{max.}$ 3 460, 1 735, 1 680, 1 505, 1 437, and 1 120 cm^{-1}; δ_H 1.6—1.85 (6 H, m), 2.01 (3 H, s, CH_3CONH), 2.07 (6 H, s, $MeCO_2$), 4.43 (1 H, dt, *J* 9.1, 3.6 Hz, 2-H), 4.97 (2 H, m, 1-H and 3-H), and 5.7 (1 H, br d, *J* 9.1 Hz, exch. with D_2O, NH); *m/z* 257 (M^+, 1%), 214 (6), 198 (3), 155 (11), 154 (10), 137 (33), 112 (19), 111 (18), 96 (30), 69 (13), 60 (38), 56 (23), and 43 (100) (Found: C, 56.2; H, 7.2; N, 5.4. Calc. for $C_{12}H_{19}NO_5$: C, 56.0; H, 7.4; N, 5.4%).

1,2-trans-1,6-cis-2-*Bromo*-6-*succinimidocyclohexanol* (**24**).—NBS (1.9 g, 10.7 mmol) was added to a stirred solution of the succinimide (**7**) (1.6 g, 8.9 mmol) in chloroform (20 ml) and ethanol (1 ml) and the mixture was stirred at room temperature for 8 h. It was then washed with 1M aqueous sodium thiosulphate and the aqueous phase was back-extracted with chloroform (20 ml). The combined chloroform extracts were dried, and evaporated to give an oil. This was stirred in dilute hydrochloric acid (5 ml) and methanol (10 ml) for 12 h after which the solution was extracted with chloroform (2 × 20 ml) and the extract was dried. Evaporation of the latter under reduced pressure gave, as a colourless oil, the *succinimide* (**24**) (1.77 g, 72%), $\nu_{max.}$ 3 500—3 200, 1 770, 1 690, 1 395, 1 365, and 1 180 cm^{-1}; δ_H 1.25—2.2 (7 H, m), 1.75 (4 H, s, CH_2CO), 4.1 (1 H, m, 6-H), 4.38 (1 H, m, 1-H), and 4.95 (1 H, m, 2-H); *m/z* 275 (M^+, 2%), 256 (2), 196 (87), 178 (17), 124 (20), and 100 (100). (Found: M^+ 275.014 67. $C_{10}H_{14}BrNO_3$ requires *M*, 275.015 75).

cis-2-*Succinimidocyclohexanol* (**25**).—Tributyltin hydride (1.90 g, 6.5 mmol) was added to a stirred solution of the bromo-amide (**24**) (1.5 g, 5.4 mmol) and AIBN (4 mg, catalyst) in toluene (10 ml) and the mixture was heated to reflux for 1 h. It was then evaporated and the residue chromatographed through silica gel, using ethyl acetate–light petroleum (1:1) as eluant (1:1), to give a solid, which was recrystallised from ether–light petroleum to give colourless needles of the *alcohol* (**25**) (0.765 g, 72%), m.p. 89—91 °C, $\nu_{max.}$ 3 550—3 300, 1 770, 1 690, 1 400, 1 375, 1 365, 1 180, and 1 130 cm^{-1}; δ_H 1.2—2.65 (8 H, m), 2.74 (4 H, s, CH_2CO), 4.0—4.3 (2 H, m, 1-H and 2-H), and 4.45 (1 H, br s, exch. with D_2O OH); *m/z* 197 (M^+, 1%), 179 (2), 154 (4), 151 (3), 126 (13), 100 (31), and 98 (100) (Found: C, 61.1; H, 7.7; N, 7.0. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.7; N, 7.1%).

cis-2-*Succinimidocyclohexyl Acetate* (**26**).—The alcohol (**25**) (0.1 g) was stirred with acetic anhydride (1 ml) and pyridine (2 ml) at room temperature for 18 h after which the solvent was removed and the product oil chromatographed through silica gel, using ethyl acetate–light petroleum (1:1) as eluant, to give the *title acetate* (**26**) (0.16 g, 88%), m.p. 61—63 °C; $\nu_{max.}$ 1 775, 1 725, 1 700, 1 370, 1 175, and 1 020 cm^{-1}; δ_H 1.1—2.0 (6 H, m), 2.02 (3 H, s, $MeCO_2$), 2.59 (4 H, s, CH_2CO), 2.93 (1 H, dt, *J* 3.5, 13.5 Hz, 6-H), 4.10 (1 H, ddd, *J* 2.4, 3, 13.5 Hz, 2-H), and 5.2 (1 H, m, 1-H) (Found: M^+, 239.116 06. $C_{12}H_{17}NO_4$ requires *M*, 239.115 75).

(2RS,6SR,12bSR,13RS) 13-*Bromo*-12b-*ethoxy*-2,6-*methanol*[1,3]*oxazocino*[2,3-a]*iso-indol*-8-*one* (**27**).—NBS (1.0 g, 5.6 mmol) was added to a stirred solution of the phthalimide (**6**) (1.0 g, 4.4 mmol) in chloroform (30 ml) and ethanol (1 ml) and the mixture was stirred for 8 h at room temperature. It was then washed with 1M aqueous sodium thiosulphate (30 ml) and the aqueous phase was back extracted with chloroform (30 ml). The combined organic extracts were dried and evaporated and the resulting oil was chromatographed through silica gel, using ethyl acetate–light petroleum (1:1) as eluant, to give the *orthoamide* (**27**) (1.48 g, 96%) as an oil, $\nu_{max.}$ 1 710, 1 470, 1 385, 1 365, 1 328, 1 148, 1 080, 1 058, and 980 cm^{-1}; δ_H 1.14 (3 H, t, *J* 7 Hz, Me), 1.25—1.38 (2 H, m), 2.55 (1 H, dm, *J* 14.5 Hz, 10-H), 3.03 (1 H, dq, *J* 9, 7 Hz, OC*H*HMe), 3.39 (1 H, dq, *J* 9, 7 Hz, OCH*H*Me), 4.36 (1 H, tt, *J* 1.75, 3.5 Hz, 8-H), 4.55 (1 H, tt, *J* 1.75, 3.9 Hz, 12-H), 5.56 (1 H, tt, *J* 1.6, 3.9 Hz, 1-H), and 7.5—7.75 (4 H, m, ArH). (Found: M^+, 351.0476. $C_{16}H_{18}BrNO_3$ requires *M*, 351.0471).

1,2-trans-2,3-trans-2-*Bromo*-3-N-*phthalimidocyclohexanol* (**28**).—2M HCl (5 ml) was added to a stirred solution of the orthoamide (**27**) (1.0 g, 2.8 mmol) in methanol (20 ml) and the solution stirred at room temperature for 30 min. Most of the solvent was removed and chloroform (50 ml) was added to the residue. This solution was then washed with water (2 × 10 ml), dried and evaporated and the crystalline residue was recrystallised from ethyl acetate–light petroleum to give the *title amide* (**28**) (0.9 g, 98%), m.p. 171—173 °C; $\nu_{max.}$ 3 580, 1 775, 1 712, 1 375, 1 135, and 1 060 cm^{-1}; δ_H 1.4—2.35 (6 H, m), 2.53 (1 H, d, *J* 2.3 Hz, exch. with D_2O, OH), 3.75 (1 H, m, 1-H), 4.55 (1 H, td, *J* 11.4, 4.3 Hz, 3-H), 4.82 (1 H, dd, *J* 11.4, 9.3 Hz, 2-H), and 7.68—7.96 (4 H, m, ArH); *m/z* 323 (M^+, 1%), 305 (1), 252 (2), 226 (100), 202 (4), 186 (16), 173 (17), 160 (21), 148 (94), and 130 (42) (Found: C, 51.6; H, 4.3; Br, 24.5; N, 4.1. $C_{14}H_{14}BrNO_3$ requires C, 51.8; H, 4.3; Br, 24.6; N, 4.3%).

cis-3-*Phthalimidocyclohexanol* (**29**).—Tributyltin hydride (0.54 g, 1.85 mmol) was added to a stirred solution of the

bromoalcohol (**28**) (0.5 g, 1.54 mmol) and AIBN (2 mg, catalyst) in toluene (10 ml) and methanol (1 ml) and the solution was stirred at reflux for 1 h. It was then evaporated and the residue was chromatographed through silica gel, using ethyl acetate–light petroleum (1:1) as eluant, to give a white solid, which was recrystallised from ethyl acetate to give the *phthalimide* (**29**) (0.3 g, 80%), m.p. 205—207 °C; $\nu_{max.}$ 3 610, 1 770, 1 710, 1 375, and 1 100 cm^{-1}; δ_H 1.2—2.5 (9 H, m), 3.69 (1 H, br m, 1-H), 4.17 (1 H, tt, *J* 11.8, 4.3 Hz, 3-H), and 7.6—7.9 (4 H, m, ArH); *m/z* 245 (M^+, 20%), 227 (25), 202 (31), 186 (16), 174 (43), 173 (17), 160 (14), 148 (100), 130 (44), 105 (14), and 104 (24) (Found: C, 68.3; H, 5.9; N, 5.6. $C_{14}H_{15}NO_3$ requires C, 68.5; H, 6.1; N, 5.7%).

cis-3-*Acetamidocyclohexyl Acetate* (**31**).[13]—Hydrazine hydrate (42 mg, 0.8 mmol) was added to the stirred solution of the phthalimido alcohol (**29**) (0.2 g, 0.8 mmol) in 95% ethanol (10 ml) and the solution was heated to reflux for 2 h. It was then cooled to room temperature and concentrated HCl was added to it until it gave an acid reaction to Congo Red indicator paper. The white precipitate was filtered off and washed with ethanol (4 ml) and the combined filtrate was reduced in volume to *ca.* 5 ml. Water (5 ml) added and the further precipitate was filtered off. The filtrate was evaporated to leave the amino alcohol (**30**), as its hydrochloride salt, as a pale yellow oil. This material was characterised by acetylation; the oil was stirred in a mixture of acetic anhydride (2 ml) and pyridine (1 ml) for 8 h at room temperature. The reagents were evaporated and the residue chromatographed through silica gel, using ethyl acetate as eluant, to give a white solid. Recrystallisation of this from ethyl acetate gave the amido acetate (**31**) (0.146 g, 90%), m.p. 116—118 °C; $\nu_{max.}$ 3 445, 1 730, 1 665, 1 500, 1 365, 1 250, and 1 033 cm^{-1}; δ_H 1.0—2.3 (8 H, m), 1.95 (3 H, s, NH*Ac*), 2.03 (3 H, s, OAc), 3.9 (1 H, m, 3-H), 4.8 (1 H, tt, *J* 9.6 Hz, 4.3 Hz, 1-H), and 5.5 (1 H, br s, exch. with D_2O, NH); *m/z* 199 (M^+, 5%), 156 (4), 139 (100), 114 (28), 111 (12), and 97 (73), (Found: C, 60.3; H, 8.6; N, 7.2. Calc. for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.6; N, 7.0%).

o-*Cyclohex-2-enylcarbamoylbenzyl Alcohol* (**33**).—Sodium borohydride (1.76 g, 47 mmol) was added to a stirred solution of the phthalimide (**6**) (2.55 g, 11 mmol) in isopropyl alcohol (30 ml) and water (5 ml) at 0 °C. The solution was stirred whilst warming to room temperature over 1 h and then neutralised by careful addition of acetic acid. The solution was filtered and then extracted with ether (3 × 100 ml). The ether extract was dried and evaporated to give a white solid which was crystallised from ether–hexane to give colourless needles of the *amide* (**33**) (2.56 g, 99%), m.p. 114—116 °C; $\nu_{max.}$ 3 550—3 200, 3 440, 1 645, 1 510, 1 480, and 1 020 cm^{-1}; δ_H 1.6—2.1 (6 H, m), 4.5 (1 H, br s, exch. with D_2O, OH), 4.59 (2 H, s, CH_2OH), 4.67 (1 H, m, 1-H), 5.68 (1 H, m, 3-H), 5.93 (1 H, m, 2-H), and 7.3—7.55 (4 H, m, ArH); *m/z* 231 (M^+, 5%), 213 (64), 185 (35), 150 (26), 133 (92), and 118 (100) (Found: C, 72.7; H, 7.4; N, 5.9. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.0%).

1,2-trans-1,6-cis-2-*bromo*-6-(1,3-*dihydroisobenzofuran*-1-*ylideneamino*)-*cyclohexanol* (**35**).—NBS (1.2 g, 6.7 mmol) was added to a stirred solution of the amide (**33**) (1.3 g, 5.6 mmol) in chloroform (25 ml) and the solution was stirred for 1 h at room temperature. It was then washed with 1M aqueous sodium thiosulphate (10 ml) and the aqueous phase was back extracted with chloroform (25 ml). The combined organic extracts were dried and evaporated and the residue was chromatographed through silica gel, using ethyl acetate–light petroleum (1:4) as eluant, to give a white solid which was crystallised from ethyl acetate–hexane to give the *title compound* (**35**) (1.51 g, 87%), m.p. 166—168 °C; $\nu_{max.}$ 3 600—3 000, 1 695, 1 365, and 1 295 cm^{-1}; δ_H 1.5—2.1 (6 H, m), 3.08 (1 H, br s, exch. with D_2O, OH), 3.8 (1 H, br m, 1-H), 4.27—4.68 (2 H, m, 2-H and 6-H), 5.33 (2 H, CH_2Ph), and 7.28—7.86 (4 H, m, ArH) (Found: C, 53.9; H, 5.2; Br, 25.6; N, 4.4%; *m/z* 309.036 49. $C_{14}H_{16}BrNO_2$ requires C, 54.2; H, 5.2; Br, 25.7; N, 4.4%; M^+, 309.036 49).

1,2-cis-(1,3-*dihydroisobenzofuran*-1-*ylideneamino*)*cyclohexanol* (**36**).—Tributyltin hydride (0.34 g, 1.2 mmol) was added to a stirred solution of the imino ether (**35**) (0.26 g, 0.9 mmol) and AIBN (4 mg, catalyst) in toluene (20 ml) and methanol (1 ml). The solution was heated to reflux for 1 h after which the solvents were removed under reduced pressure. The residue was chromatographed through silica gel, using ethyl acetate–light petroleum (1:1) as eluant, to give a crystalline solid; recrystallisation of this from ether–hexane afforded the *title alcohol* (**36**) (0.18 g, 60%), m.p. 97—99 °C; $\nu_{max.}$ 3 600, 3 300, 1 700, 1 470, 1 085, and 1 030 cm^{-1}; δ_H 1.3—2.2 (8 H, m), 3.15 (1 H, br s, exch. with D_2O, OH), 3.9 (2 H, m, 1-H and 2-H), 5.32 (2 H, d, CH_2Ph), and 7.3—8.0 (4 H, m, ArH). (Found: C, 72.5; H, 7.3; N, 5.8. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.0%).

cis-2-*Aminocyclohexanol Hydrochloride* (**19**).[8]—6M HCl (2 ml) was added to a stirred solution of the imino ether (**36**) (0.1 g, 0.4 mmol) in methanol (4 ml) and the solution heated to reflux for 30 min. It was then evaporated under reduced pressure and the residue was dissolved in chloroform (10 ml) and extracted with water (2 × 10 ml). The aqueous phase was evaporated to dryness and the crystalline residue recrystallised from acetone to give the title compound (**19**) (45 mg, 73%), m.p. 180—182 °C, identical with the material described previously.[1,8]

1-(1,2-cis-2,3-cis-2,3-*Epoxycyclohexylimino*)-1,3-*dihydroisobenzofuran* (**38**).—Silver oxide (1.1 g, 4.8 mmol) was added to a vigorously stirred solution of the imino ether (**35**) (0.5 g, 1.6 mmol) in THF (15 ml) in the dark. The mixture was stirred for 8 h at room temperature before being filtered through Celite and evaporated. Trituration of the oil with hexane gave a solid which crystallised from ethyl acetate–hexane to give colourless crystals of the *epoxide* (**38**) (0.352 g, 92%), m.p. 85—87 °C; $\nu_{max.}$ 1 690, 1 470, 1 292, 1 083, 1 020, and 860 cm^{-1}; δ_H 1.3—2.0 (6 H, m), 3.25 (2 H, m, 2-H and 3-H), 4.2 (1 H, m, 1-H), 5.33 (2 H, s, CH_2Ph), and 7.3—8.0 (4 H, m, ArH); *m/z* 229 (M^+, 11%), 200 (10), 188 (55), 172 (47), 160 (100), 146 (17), 134 (67), and 118 (75) (Found: C, 73.4; H, 6.6; N, 6.0. $C_{14}H_{15}NO_2$ requires C, 73.4; H, 6.6; N, 6.1%).

1,2-cis-1,6-trans-2,6-*Diacetamidocyclohexyl Acetate* (**40**).—The epoxide (**38**) (0.25 g, 1.1 mmol) in ethanol (5 ml) and 35% (w/v) aqueous ammonia (8 ml) was heated to 100 °C for 1 h in a sealed steel tube. Water (5 ml) was added to the cooled solution which was then washed with chloroform (2 × 5 ml). The aqueous layer was freeze dried and the brown residual gum stirred in acetic anhydride (2 ml) and pyridine (2 ml) for 1 h at room temperature. The solvents were removed and the residue chromatographed through silica gel, using ethyl acetate–methanol (9:1) as eluant, to give a solid which was crystallised to give the *title acetate* (**40**) (0.25 g, 90%), m.p. 203—205 °C; $\nu_{max.}$ 3 450, 3 310, 1 730, 1 670, 1 510, 1 375, and 1 055 cm^{-1}; δ_H 1.2—1.9 (6 H, m), 1.95 (3 H, s, NH*Ac*), 2.01 (3 H, s, NH*Ac*), 2.06 (3 H, s, Ac), 4.15 (1 H, m, 6-H), 4.4 (1 H, m, 2-H), 4.82 (1 H, dd, *J* 9.2, 4.0 Hz, 1-H), 5.95 (1 H, br d, *J* 8 Hz, NH), and 6.17 (1 H, br d, NH); *m/z* 257 (MH^+, 4%), 196 (28), 154 (11), 37 (93), 112 (44), 86 (42), 84 (11), 70 (12), 60 (28), 56 (40), and 43 (100) (Found: C, 56.0; H, 7.6; N, 10.8. $C_{12}H_{20}N_2O_4$ requires C, 56.2; H, 7.8; N, 10.9%).

1,2-trans-2,3-cis-3-*Acetamidocyclohexane*-1,2-*diyl Diacetate* (**42**).—The epoxide (**38**) (0.5 g, 2.2 mmol) and perchloric acid (0.22 g, 2.2 mmol) in THF (10 ml) and water (5 ml) was heated to reflux for 2 h. Pyridine (2 ml) was added to the solution to

neutralise the acid and the bulk of the solvent was removed. The residual gum was dissolved in acetic anhydride (2 ml) and pyridine (3 ml) and the solution stirred at room temperature for 1 h. The excess of the reagents were removed and the residue chromatographed through silica gel, using methanol–ethyl acetate (1:9) as eluant, to give a white solid, which was recrystallised from ethyl acetate–light petroleum to give the *amido ester* (**42**) (0.48 g, 85%), m.p. 147—149 °C; $\nu_{max.}$ 3 450, 1 735, 1 670, 1 507, 1 370, 1 050, and 1 025 cm^{-1}; δ_H 1.5—1.8 (6 H, m), 1.98 (3 H, s, NH*Ac*), 2.07 (3 H, s, Ac), 2.10 (3 H, s, Ac), 4.4 (1 H, m, 3-H), 4.85—5.05 (2 H, m, 1-H and 2-H), and 5.85 (1 H, br d, *J* 8.3 Hz, NH); *m/z* 257 (M^+, 1%), 214 (6), 155 (12), 137 (36), 111 (22), 96 (38), 60 (48), and 43 (100) (Found: C, 56.0; H, 7.6; N, 5.6. $C_{12}H_{19}NO_5$ requires C, 56.0; H, 7.4; N, 5.4%).

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