Syntheses of derivatives of L-daunosamine and its C-3 epimer employing as the key step the asymmetric conjugate addition of a homochiral lithium amide to *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate

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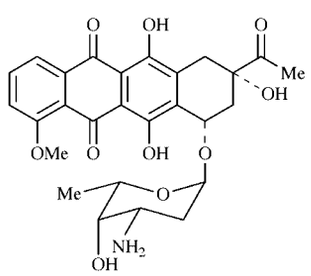
Received (in Cambridge, UK) 31st August 1999, Accepted 16th September 1999

The highly diastereoselective asymmetric conjugate addition of lithium (*R*)-*N*-benzyl-α-methylbenzylamide to methyl or *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate, followed by osmium tetroxide-catalysed dihydroxylation of the resulting adducts, provides a concise route to methyl L-daunosaminide hydrochloride and methyl 3-*epi*-D-daunosaminide hydrochloride, a strategy which is applicable to the synthesis of either enantiomer of these compounds. The selectivity of the key dihydroxylation reaction can be significantly improved by employing the Sharpless asymmetric dihydroxylation protocol. Possible alternative strategies using iodolactonisation or iodocyclocarbamation reactions as the key step were found to be much less satisfactory, due to either low selectivity, or the excessive number of steps that would be required.

Introduction

Since the discovery of the anthracycline[1] antibiotic daunorubicin **1**,[2] with its potent anticancer activity, and the subsequent development of the closely related compound adriamycin **2**[3] as a clinical drug, there has been great interest in



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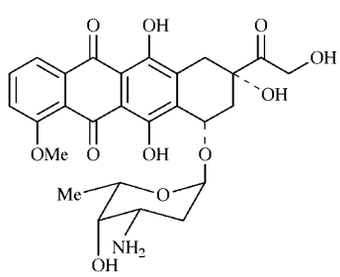

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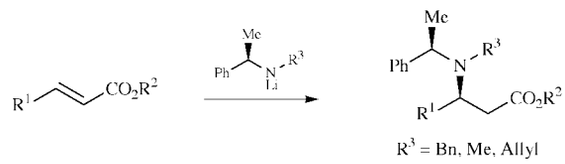
the synthesis of the glycoside constituent of these compounds, daunosamine,[4–10] and other related amino sugars. A number of asymmetric syntheses of daunosamine have been reported,[4] employing a wide variety of approaches that range from classical sugar chemistry,[5] through resolution[6] and synthesis from other chiral pool molecules,[7] to catalytic asymmetric synthesis,[8] reagent control,[9] and the use of chiral auxiliaries.[10]

The highly diastereoselective asymmetric conjugate addition of secondary lithium amides derived from α-methylbenzylamine has emerged from our laboratories as a powerful technique for the asymmetric synthesis of β-amino acids,[11] β-lactams,[12] and natural products containing this functionality.[13] It has been demonstrated that *N*-benzyl, *N*-methyl, and *N*-allyl lithium amides add to a variety of α,β-unsaturated esters and amides to give the conjugate adduct, in most cases, in excellent yield and with high diastereoselectivity (Scheme 1).



Scheme 1

Since daunosamine and the other 3-deoxy-3-amino sugars are essentially masked β-amino aldehydes, it was of interest to see whether these compounds could be synthesised using this conjugate 1,4-addition reaction to (*E*,*E*)-hexadienoate esters as the starting point. In particular, we wished to investigate the extent to which the stereochemistry of the subsequent introduction of the hydroxy groups onto a γ,δ-double bond could be controlled by the β-amino stereogenic centre. Three strategies were examined, in which the key steps after the conjugate addition reaction were, respectively, an iodolactonisation, an iodocyclocarbamation, and an osmium tetroxide-catalysed dihydroxylation. Only the last route was ultimately successful. Part of this work has been previously communicated.[14]

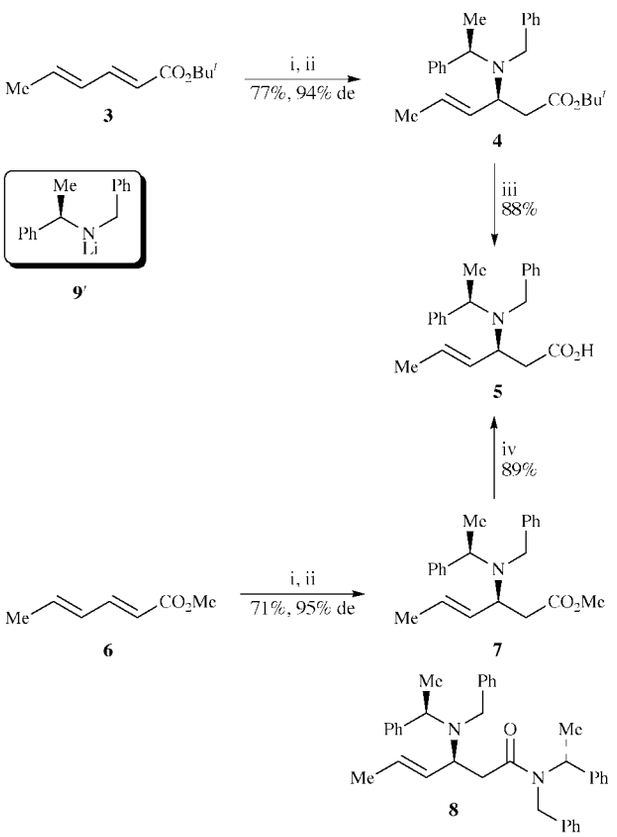
Results and discussion

Iodolactonisation strategy

The first approach examined was an iodolactonisation[15] strategy. Previous studies, notably those of Snider and Johnston[16] and Chamberlin and co-workers[17] into the bromo- and iodolactonisation reactions of substituted alk-4-enoic acids have revealed that high regio- and stereoselectivites can often be obtained. Predominant or exclusive γ-lactone formation has almost always been observed, the major exceptions being 3-substituted acids, which often give large quantities of the δ-lactone. These precedents suggested that iodocyclisation

of a 3-substituted hex-4-enoic acid might lead predominantly to a *cis*-substituted γ-lactone, although δ-lactone formation might be a problem. Starting from the Michael adduct of lithium (*R*)-*N*-benzyl-α-methylbenzylamide **9′** with a hexa-2,4-dienoate acceptor, this would establish the correct stereochemistries for the three contiguous stereocentres of daunosamine (assuming that the iodide would be substituted with inversion by an oxygen nucleophile in a later step).

As we have previously reported,[18] the addition of lithium (*R*)-*N*-benzyl-α-methylbenzylamide **9′** to *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate **3** proceeds in good yield and with high diastereoselectivity (Scheme 2). The resulting ester **4** is readily converted



Scheme 2 *Reagents and conditions*: i, **9′**, THF, −78 °C; ii, NH_4Cl(aq), −78 to 20 °C; iii, CF_3CO_2H, CH_2Cl_2, 20 °C; iv, LiOH, THF(aq), reflux.

to the corresponding acid **5** by treatment with trifluoroacetic acid. Addition to methyl (*E*,*E*)-hexa-2,4-dienoate **6**, also proceeds with high diastereoselectivity to afford the adduct **7**,[14] but the yield is somewhat lower, owing to the formation of the amide **8**, resulting from sequential 1,2- and 1,4-attack on the acceptor. The adduct **7** is also readily converted to the acid **5**, by treatment with lithium hydroxide in aqueous tetrahydrofuran.

Treatment of the acid **5** either with *N*-iodosuccinimide (NIS) or with iodine and sodium bicarbonate led to similar mixtures of reaction products, from which three iodolactones were isolated by chromatography (Scheme 3). Two of the iodolactones, **9** and **11**, were highly crystalline, and were purified further by recrystallisation. The iodolactone of intermediate polarity **10** remained an oil, and was purified by repeated chromatography, resulting in a greatly reduced yield, as it proved to be rather unstable on silica. Upon standing, the purified compound eventually solidified. Inspection of the ^{1}H NMR spectrum of the crude product mixture showed the three compounds to have been formed in approximately equal proportions.

IR spectroscopy revealed the two less polar products **9** and **10** to be γ-lactones (ν_{max} 1774 and 1785 cm^{-1} respectively) and the most polar product **11** to be a δ-lactone (ν_{max} 1736 cm^{-1}). The

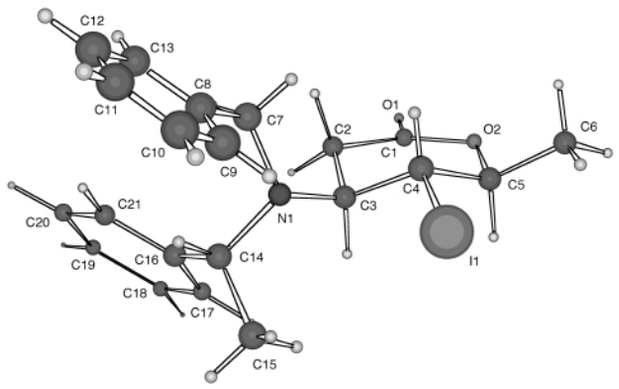
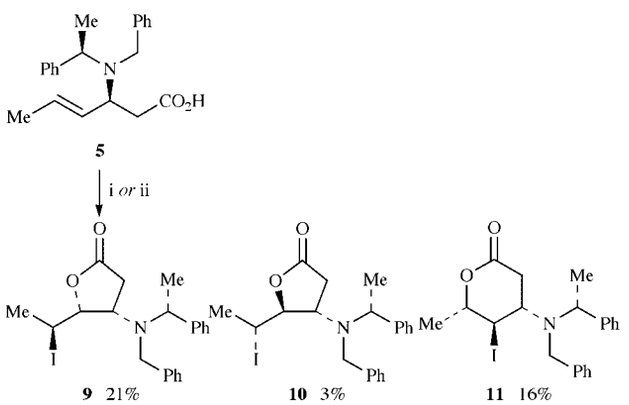


Fig. 1 X-Ray molecular structure of δ-lactone **11**.



Scheme 3 *Reagents and conditions*: i, NIS, THF(aq), 20 °C; ii, I_2, Et_2O, $NaHCO_3$(aq), 20 °C.

stereochemistry of δ-lactone **11** was unambiguously assigned by single-crystal X-ray analysis (Fig. 1). The absolute stereochemistry was assigned from the known (*R*)-configuration of the starting α-methylbenzylamine. The stereochemistries of γ-lactones **9** and **10** were determined by NOE studies, which allowed assignment of the relative stereochemistry of the ring junction. (Particularly diagnostic was the observation of an NOE between the β- and γ-protons of **9** (11.4% and 6.8% on irradiation of the β- and γ-proton respectively), but not of **10**, placing the former protons *cis*, and the latter *trans*). Since iodolactonisation proceeds with *anti* addition across the double bond,[15] and the β-stereochemistry was already known, this allowed assignment of all the stereogenic centres.

The low stereo- and regioselectivities were disappointing; although the formation of both γ- and δ-lactones was unsurprising in the light of studies on 3-substituted hex-4-enoic acids discussed above, the low stereoselectivity was not anticipated.

While both esters[17,19] and amides[20] have been reported to undergo iodolactonisation reactions under similar conditions to acids, neither the *tert*-butyl ester **4**, nor the methyl ester **7**, nor the corresponding dimethylamide proved to be reactive. Furthermore, in a brief investigation of bromolactonisation, the acid **5** and both esters (**4** and **7**) gave intractable products upon treatment with *N*-bromosuccinimide (NBS), presumably because the more strongly oxidising NBS was not compatible with the presence of an unprotected tertiary amine.

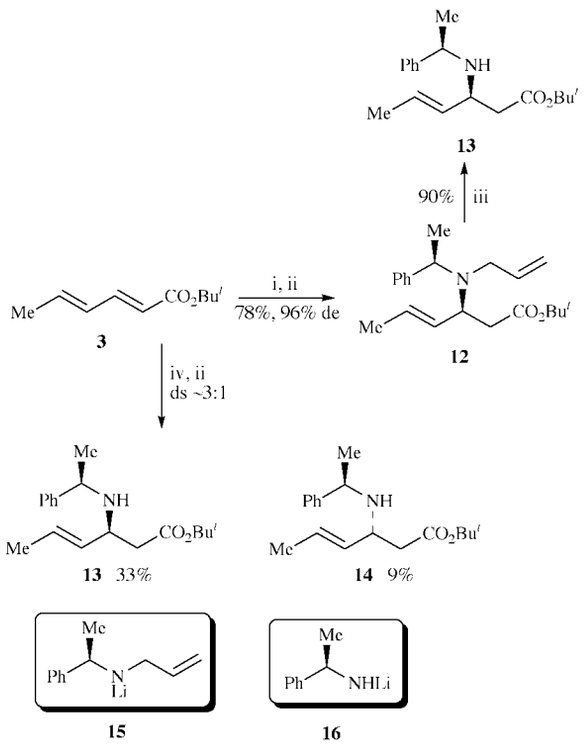
Iodocyclocarbamation strategy

The low selectivity of the iodolactonisation, and lack of success of the attempted bromolactonisation, prompted investigation into an iodocyclocarbamation reaction. Like iodolactonisation, this reaction has often been shown to offer good asymmetric induction from existing stereogenic centres.[15b,21]

To introduce onto the nitrogen of the Michael adduct a group suitable for halogenocyclisation requires removal of at

least one of the existing substituents. This is not possible with Michael adducts derived from (*R*)-*N*-benzyl-α-methylbenzylamine, since no conditions for debenzylation have been discovered which would not also hydrogenate a double bond. However, use of lithium (*R*)-*N*-allyl-α-methylbenzylamide **15**[12] provided an ideal solution.

As this laboratory has reported, addition of the lithium amide **15** to *tert*-butyl ester **3** proceeds in 96% de to give **12**, which can readily be deallylated by treatment with Wilkinson's catalyst to give **13** (Scheme 4).[12] After deallylation (but not



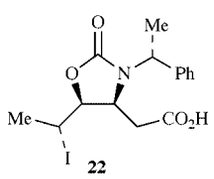
Scheme 4 *Reagents and conditions*: i, **15**, THF, −78 °C; ii, NH_4Cl(aq), −78 to 20 °C; iii, $(Ph_3P)_3RhCl$, reflux; iv, **16**, THF, −78 °C.

before), it was found to be possible to remove the small quantity of the minor diastereomer **14** by column chromatography on silica gel. To prove that the minor diastereomer isolated was indeed the C3-epimer (and not, for example, an isomer with a *Z* double bond), the less selective addition of lithium (*R*)-α-methylbenzylamide **16** to *tert*-butyl ester **3** was employed. This gave **13** and **14** in the ratio of ≈3 : 1, which were separated by chromatography.

The adduct **13**, obtained diastereomerically pure, was thus ready to be functionalised on nitrogen with a group suitable for iodocyclocarbamation. Both benzyloxycarbonyl and *tert*-butoxycarbonyl derivatives were prepared. However, the amine **13** proved highly resistant to standard methods of carbamate formation. This was apparently due to steric hindrance, since analogous compounds without the α-methyl substituent were known to react readily.[22] Eventually it was discovered that treating the amine **13** with neat dibenzyl dicarbonate or di-*tert*-butyl dicarbonate gave slow but very clean conversion to the corresponding carbamate (Scheme 5). Formation of the benzyl carbamate **17** was complete after 60 h, while *tert*-butyl carbamate **18** formation had gone to only 60% completion after 40 days, reflecting the greater reactivity of the former reagent.

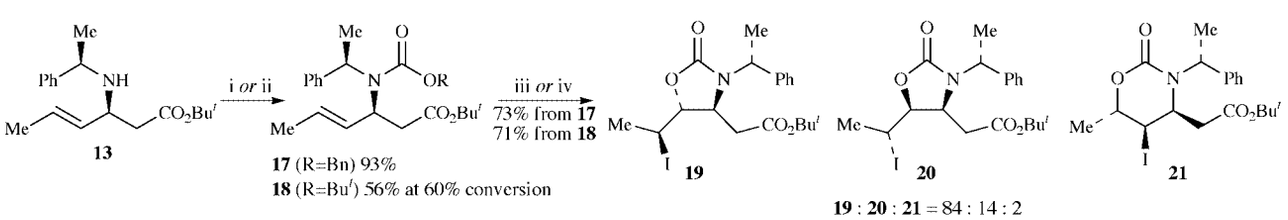
Both compounds readily underwent iodocyclocarbamation (Scheme 5). The benzyl carbamate **17** was most conveniently treated with iodine in dichloromethane. These conditions were not, however, suitable for the *tert*-butyl carbamate **18**, since the build-up of HI during the reaction caused substantial hydrolysis of the *tert*-butyl ester of the product cyclic carbamates. Therefore the *tert*-butyl carbamate **18** was treated either with NIS, or with iodine in the presence of saturated aq. sodium bicarbonate. These conditions were equally effective for the benzyl carbamate **17**, but, being slightly more experimentally involved, were not the preferred protocols. From each starting material, the same three iodocarbamate products were isolated, in a ratio (**19** : **20** : **21** 84 : 14 : 2) independent of the conditions employed. Thus none of the products was an iodolactone, consistent with cyclisation of the more nucleophilic carbamate being faster than cyclisation of the ester. The three products were readily separated by column chromatography on silica gel.

Only the major product **19** was crystalline, and stable once isolated; the two minor products were unstable oils. The oxazolidinone **20** decomposed to the corresponding carboxylic acid **22**, and so was fully characterised as the acid, the ester being

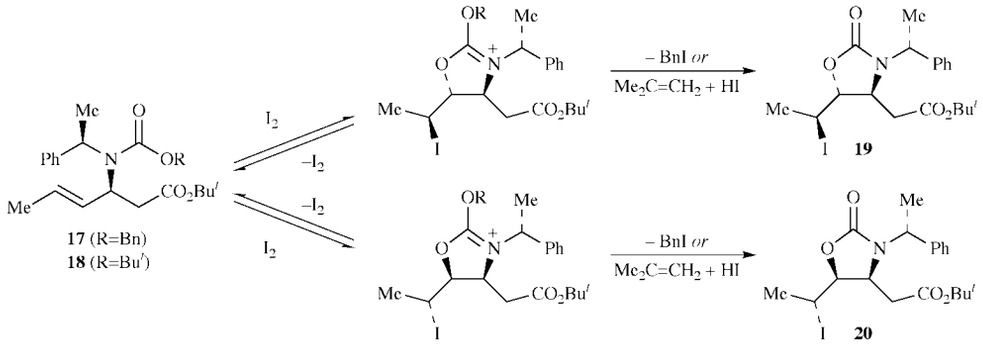


characterised only by ^{1}H NMR spectroscopy. It was conveniently compared with the acid **25** derived from hydrolysis of the ester of the major product **19** (*vide infra*). Both compounds exhibited a band in the infra-red spectrum attributable to the cyclic carbamate, whose high frequency compared with that for the acyclic carbamates **17** and **18** confirmed that the ring was 5- rather than 6-membered (ν_{max} 1751 cm^{-1} for **22** and 1747 cm^{-1} for **25**; *cf.* 1688 cm^{-1} for **18** and 1694 cm^{-1} for **17**). The stereochemistry of the ring junction, and, assuming *trans* addition across the double bond as required by the mechanism of iodocyclisation, the stereochemistry of the whole molecule was assigned for the two acids by analysis of the coupling constant in the ^{1}H NMR spectrum between the ring protons C(4)H and C(5)H. The major product **25** shows $J_{4,5}$ 3.2 Hz, and the minor product **22** $J_{4,5}$ 6.8 Hz. It is well known that *cis*-substituted oxazolidinones exhibit larger coupling constants than the analogous *trans*-substituted compounds,[23] and, furthermore, these values are close to those quoted for the similar oxazolidinones prepared by Ohno and co-workers.[21f] This leads to the stereochemical assignments as depicted for **19** and **20**.

The oxazinanone **21** decomposed rapidly into an intractable mixture of compounds, and so was only characterised by ^{1}H NMR spectroscopy; thus its assignment must be regarded as extremely tentative. It was considered to be a 6-membered



Scheme 5 *Reagents and conditions*: i, (R = Bn) $(BnOCO)_2O$, neat, 20 °C; ii, (R = Bu^t) $(Bu^tOCO)_2O$, neat, 20 °C; iii, (R = Bn) I_2, CH_2Cl_2, 20 °C; iv, (R = Bu^t) NIS, THF(aq), 20 °C; *or* I_2, Et_2O, $NaHCO_3$(aq), 20 °C.

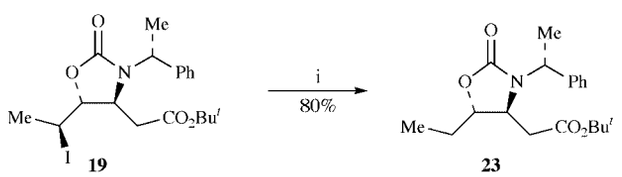


Scheme 6

carbamate partly because both the expected 5-membered products were already accounted for, and partly because of the observation of a large ($J_{5,6}$ 11.0 Hz) coupling constant, which suggested a *trans*-diaxial disposition of C(5)H and C(6)H. This in turn requires that the methyl and iodine substituents be equatorial. The small value ($J_{4,5}$ 4.4 Hz) for the other coupling constant in the ring places C(4)H equatorial and thus the C4 substituent axial.

The rationalisation of Ohno for the selectivity of his iodocyclocarbamation reaction[21f] seems equally applicable here. According to this model (Scheme 6; the 6-membered possibilities are omitted for clarity), both the attack of the iodine on the double bond, and the cyclisation, are reversible, and the irreversible step is the loss of benzyl iodide (or 2-methylpropene and hydrogen iodide). Thus equilibration between the *cis* and *trans* intermediates is possible, so that a thermodynamic mixture of intermediates results, and the *trans* product predominates, with the product ratio being independent of the reaction conditions or the substituent on the carbamate (benzyl or *tert*-butyl).

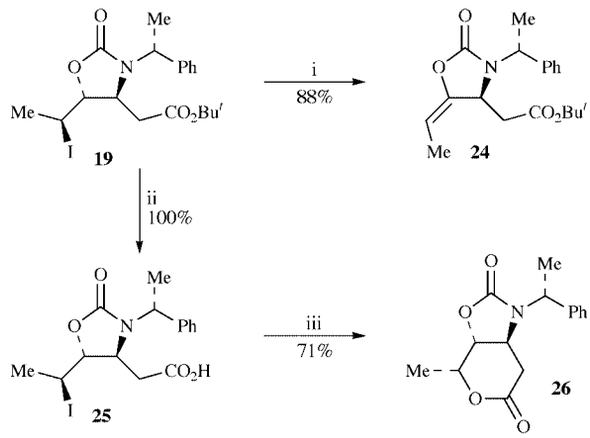
The major product **19** was deiodinated by tributyltin hydride (Scheme 7). Inspection of the ^{1}H NMR spectrum of the



Scheme 7 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhMe, reflux.

product **23** showed the disappearance of the methyl doublet at δ 1.91 and appearance of a methyl triplet at δ 0.98, providing further confirmation that a 5-membered carbamate had formed: a 6-membered carbamate would have retained the methyl doublet upon deiodination.

It remained to find a means to achieve substitution with inversion of the secondary iodide by an oxygen nucleophile. While primary iodides of iodolactones and iodocarbamates have been successfully subjected to such a nucleophilic substitution[21f,24] (although often with difficulty), no examples in the literature were found for a secondary iodide. Indeed, treatment of **19** with caesium acetate in DMF led to clean elimination to **24** (as the sole product isolated), with no substitution being observed (Scheme 8). The stereochemistry of the double bond in the product **24** was initially assigned as *E* by assuming that the single product obtained arose from elimination *via* a stereospecific *anti* E2 mechanism. NOE measurements confirmed the assignment. The proton on the double bond showed an NOE only to the adjacent methyl group (10% and 7.6% on irradiation of the methyl and olefinic proton respectively), while the methyl protons showed NOEs to the allylic and homoallylic protons (4.4% and 3% respectively on irradiation of the methyl), as expected.

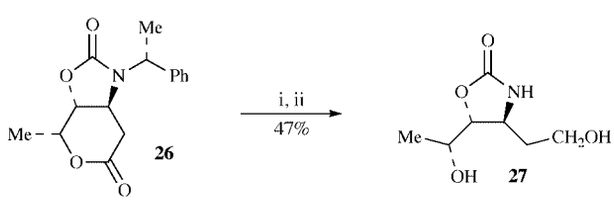


Scheme 8 *Reagents and conditions*: i, CsOAc, DMF, 20 °C; ii, CF_3CO_2H, CH_2Cl_2, 20 °C; iii, $AgOCOCF_3$, CH_2Cl_2, 20 °C.

Attention therefore turned to the possibility of an intramolecular displacement of the iodide. Accordingly, the *tert*-butyl ester **19** was cleaved to the acid **25** using trifluoroacetic acid in dichloromethane, and the acid was subsequently treated with one equivalent of silver trifluoroacetate in dichloromethane, giving the bicyclic product **26** with complete stereospecificity (Scheme 8). The structure shown for **26** was confirmed by NOE measurements and by analysis of the coupling constants around the 6-membered ring. The ring-junction protons display the large coupling constant (J 11.7) expected for their *trans*-diaxial disposition. Conversely, the proton next to the methyl group displays a much smaller coupling (J 6.2) to the adjacent ring proton, consistent with an axial–equatorial arrangement.

To convert compound **26** into the 3-*epi*-daunosamine system **29** requires reduction of the lactone, hydrolysis of the oxazolidinone, and debenzylation. Such oxazolidinones are hard to hydrolyse when a bulky substituent exists on the nitrogen.[22] It was also felt that diisobutylaluminium hydride (DIBAL) reduction of the lactone would be extremely problematic due to the high polarity of the molecule. Therefore the debenzylation was explored first.

As expected, a variety of hydrogenolysis conditions proved ineffective. Treatment with sodium in liquid ammonia achieved the required debenzylation, but also reduced the lactone (Scheme 9). The highly polar diol product **27** was hard to



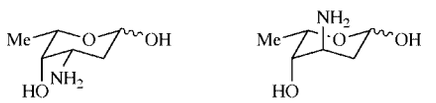
Scheme 9 *Reagents and conditions*: i, Na, NH_3(l), EtOH, THF, −78 °C; ii, NH_4Cl(s), −78 to 20 °C.

separate from the inorganic by-products of the reaction, but was finally isolated pure by means of repeated chromatography.

This route was not, however, pursued further. There seemed no concise strategy to accomplish the final two steps (selective oxidation of the primary alcohol and hydrolysis of the oxazolidinone), and the synthesis was already rather lengthy.

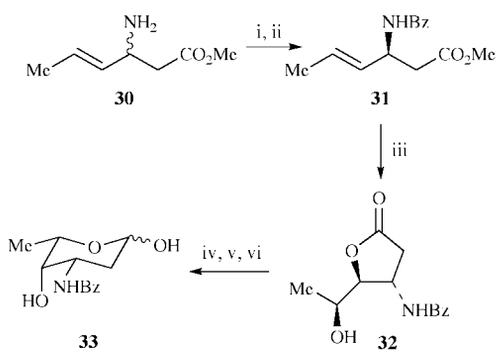
Dihydroxylation strategy

The disappointing results of the iodocyclisations prompted a study of the direct dihydroxylation of the double bond of the Michael adducts **4** and **7** using osmium tetroxide,[25] since this would provide routes to 3-*epi*-daunosamine **29** and daunosamine **28**, dependent upon the facial selectivity obtained in the dihydroxylation.



28 **29**

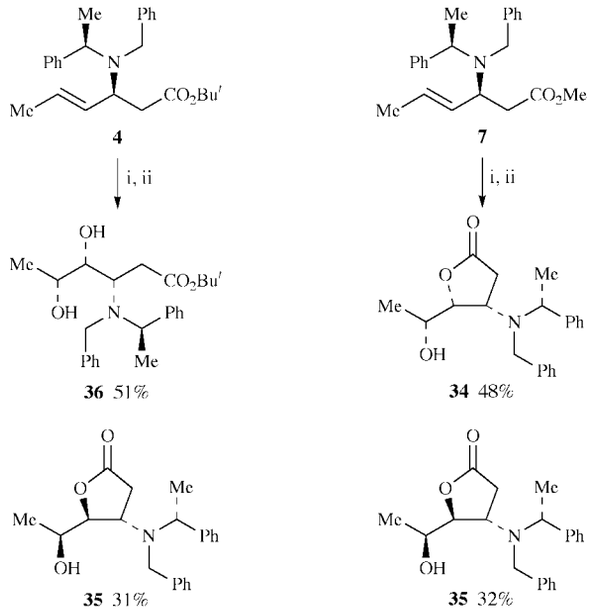
Two precedents existed for the synthesis of daunosamine using a substrate-controlled osmium tetroxide-catalysed dihydroxylation. The approach by Hauser and co-workers[6d] (Scheme 10) is most closely related to the current situation, but



Scheme 10 *Reagents and conditions*: i, Resolve with (2*R*,3*R*)-dibenzoyltartaric acid; ii, PhCOCl, py, Et_2O; iii, OsO_4, Me_3NO, Me_2CO(aq); iv, Ac_2O, py; v, DIBAL, THF; vi, NH_3, MeOH.

employs a different strategy for the introduction of the chirality. In this route, β-amino ester **30** was resolved with (2*R*,3*R*)-dibenzoyltartaric acid, and, after *N*-benzoylation, **31** was subjected to osmium tetroxide-catalysed dihydroxylation. The products cyclised *in situ*, if trimethylamine *N*-oxide was used as the co-oxidant, to give the required lactone **32** and its diastereomer in the ratio 62 : 38. After acetylation of the free hydroxy group (which considerably aided the subsequent reduction), reaction of the lactone with DIBAL followed by hydrolysis of the acetate gave *N*-benzoyl-L-daunosamine **33**.

The synthesis of methyl D-daunosaminide by Po and Uang[10b] also employed osmium tetroxide-catalysed dihydroxylation, which was completely stereospecific for their substrate. Treatment of the methyl ester **7** with osmium tetroxide (5 mol%), using potassium hexacyanoferrate(III) as the co-oxidant,[26] led to two lactones **34** and **35**, the two diol products undergoing cyclisation under the basic reaction conditions (Scheme 11). Use of *N*-methylmorpholine *N*-oxide[27] or trimethylamine *N*-oxide[6d] as the co-oxidant (with no potassium carbonate) gave more complex reaction mixtures, which appeared to be mixtures of cyclised and uncyclised products. This contrasts with the observations of Hauser and co-workers[6d] (Scheme 10), who found in their system that employing *N*-methylmorpholine *N*-oxide led to mixtures of cyclised and uncyclised products, while with trimethylamine *N*-oxide complete lactonisation was observed. The two lactone products **34** and **35** were separable by chromatography.



Scheme 11 *Reagents and conditions*: i, OsO_4 (cat.), $K_3Fe(CN)_6$, K_2CO_3, Bu^{t}OH(aq), 20 °C; ii, Na_2SO_3(s).

In contrast, under the same reaction conditions, the *tert*-butyl ester **4** gave one lactone product **35** identical to that obtained from the methyl ester, and one ester product **36** (Scheme 11). Again, the two products **35** and **36** were separable by chromatography.

The two lactones **34** and **35** displayed bands in the IR spectrum at ν_{max} 1775 and 1774 cm^{-1} respectively, clearly indicating a γ- not a δ-lactone. The stereochemistries of the products were assigned from the following considerations. First, it seemed likely that the isomer of the *tert*-butyl ester that had not cyclised would be the one that would lead to the more sterically demanding *cis*-substituted lactone. Secondly, the coupling constants in such disubstituted γ-lactones have been found to be indicative of stereochemistry:[6d] *cis*-substitution typically gives a coupling constant of around 7 Hz, while *trans*-substitution gives *J*-values around 3 Hz. The major lactone product **34** has $J_{3,4}$ 6.5 Hz, consistent with *cis*-substitution. In the ^{1}H NMR spectrum of the minor lactone product **35**, the signals for C(3)H and C(5)H are superimposed, and thus the pertinent coupling constant cannot be determined with certainty. Nevertheless, C(4)H appears as a doublet of doublets, *J* 5.6 Hz and 2.3 Hz, which is consistent with $J_{3,4}$ 2.3 Hz, consistent with *trans*-substitution. Finally, these stereochemistries were confirmed unambiguously by conversion of the lactones into the corresponding amino sugars (*vide infra*).

Both the reactions exhibit similar and disappointingly low facial selectivity. While it was disappointing that the allylic substituent exerted so little control over the facial selectivity of attack on the double bond, it was not unexpected in the light of the low selectivity encountered by Hauser and co-workers on a similar system (Scheme 10).[6d]

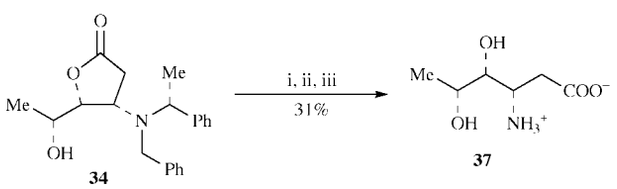
In an attempt to improve the selectivity, the Sharpless[28] asymmetric dihydroxylation[29] of **7** was investigated, exploiting the principles of double asymmetric induction.[30] This Sharpless methodology has previously been used by Wade and co-workers[8] to prepare methyl *N*,*O*-diacetyldaunosaminide and related amino sugars from *achiral* 3-(alk-1-enyl)-4,5-dihydrooxazole precursors. Treatment of **7** with AD-mix-α (which contains 0.1 mol% potassium osmate and 0.5 mol% of the chiral ligand) and one equivalent of methanesulfonamide[28] led almost entirely to recovered starting material, even after 1 week at room temperature. This is in accord with Sharpless's observation that allylic amines are poor substrates for catalytic dihydroxylation,[31] and the fact that, in the standard dihydroxylation

already described, it was found necessary to use 5 mol% osmium tetroxide. In the present case by increasing the osmium loading to 2 mol%, and correspondingly increasing the ligand loading to 10 mol%, still with one equivalent of methanesulfonamide, it was possible to make the reaction go to completion after 20 h at room temperature—this essentially corresponds to the Sharpless 'Modified-AD' conditions.[31] In the mismatched pairing when the 'α' ligand hydroquinine phthalazine-1,4-diyl diether [$(DHQ)_2PHAL$] was added, the ratio of **34** to **35** was 1:3. In the matched pairing when the 'β' ligand hydroquinidine phthalazine-1,4-diyl diether [$(DHQD)_2$-PHAL] was added, the ratio of **34** to **35** was 4.5:1. In the absence of any chiral ligand, the ratio was 3:2. Thus, a significant improvement towards whichever diastereoselectivity was desired was possible by employing the Sharpless methodology.

For conversion to the corresponding amino sugar, the lactones **34** and **35** required some combination of reduction to the lactol, and debenzylation of the nitrogen. Since the isomer **34** was in more plentiful supply, it was used as the model substrate.

First, DIBAL reduction of **34** was investigated. Upon treatment with 2 equiv. of DIBAL in dichloromethane between −45 and −35 °C for 1 h, complete disappearance of the starting material was observed. At lower temperatures (−78 °C) or with only 1 equiv. of DIBAL, incomplete reaction resulted. In the ^{1}H NMR spectrum of the crude reaction mixture, peaks at δ 4.93 (dd), 5.10 (t), and 5.40 (t) were observed, consistent with formation of a mixture of 5- and 6-membered lactols, each with up to two anomers. However, upon attempting to purify this material by chromatography, the only identifiable compound isolated from the column was *N*-benzyl-α-methylbenzylamine, suggesting that the lactols had undergone a retro-Michael reaction.

This was clearly undesirable, and so a strategy involving debenzylation before reduction was investigated. Under the usual conditions for debenzylation of the Michael adducts, ring opening of the lactone occurred, giving amino acid **37** as the product (Scheme 12). Its identity was clear from its mass



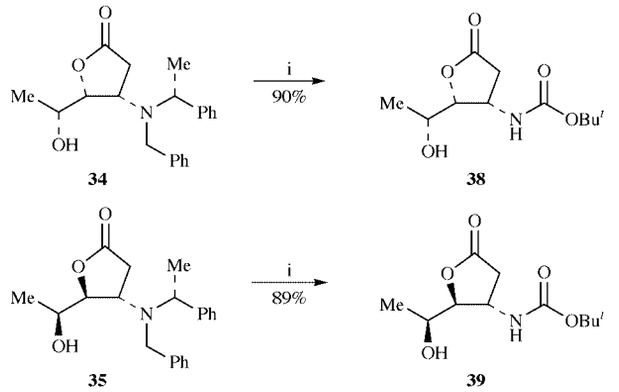
34 **37**

Scheme 12 *Reagents and conditions*: i, H_2, Pd/C, AcOH, 20 °C; ii, HCl, MeOH, 20 °C; iii, DOWEX 50X8-200 column.

spectrum (giving a strong peak for the protonated molecular ion), the characteristic appearance of its IR spectrum, and its low solubility in non-aqueous solvents.

Much more satisfactory was a procedure involving debenzylation with *in situ* Boc protection, developed by analogy with known methods for converting an azide[32] or an *N*-Z group[33] into the corresponding *N*-Boc group. This protection made the materials much easier to handle at this stage of the synthesis, and added no extra synthetic steps, as a debenzylation step would always be required, while it was planned to prepare the methyl glycoside at the end of the synthesis, under which conditions (methanolic hydrogen chloride) the Boc group would be cleaved. Both isomers of the lactone **34** and **35** were readily converted to the corresponding Boc derivatives **38** and **39** respectively in high yield (Scheme 13).

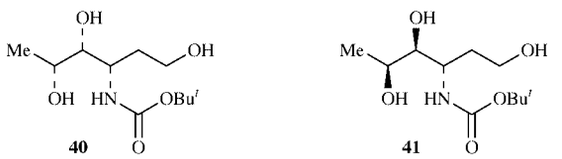
Attention was then turned to the DIBAL reduction of **38**. Of the solvents in which such reductions are commonly performed, all but THF and dichloromethane were ruled out by the insolubility of the substrate. Stoicheiometry turned out to be critical: with up to two equivalents of DIBAL, mostly starting material was recovered; three to four equivalents were found to be necessary for substantial conversion; however, over-reduction to the triol **40** began to be a problem. In THF, significant over-reduction was observed even when conversion was far from complete. In dichloromethane on the other hand, using 3.5 equivalents of DIBAL, it was possible to obtain complete conversion, with only minimal over-reduction. The conditions optimised for **38** were also applied to the lactone **39**, again with formation of only a small amount of the over-reduction product **41**.



34 **38**

35 **39**

Scheme 13 *Reagents and conditions*: i, H_2, $Pd(OH)_2$/C, $(Bu^tOCO)_2O$, EtOAc, 20 °C.

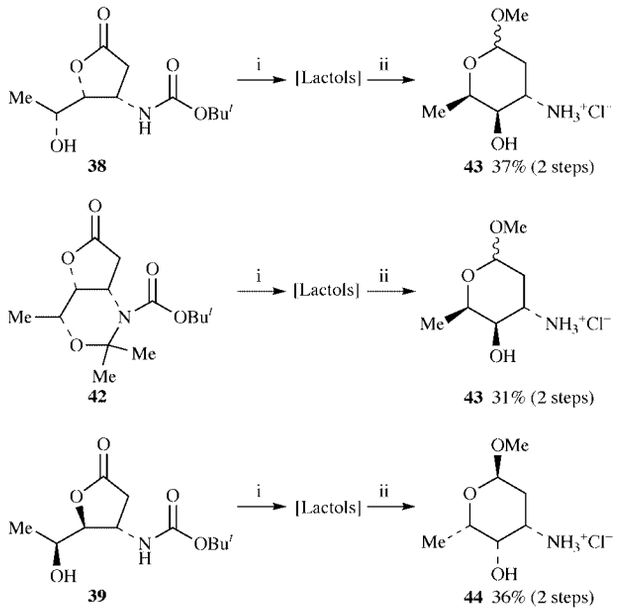


40 **41**

In both cases, the ^{1}H NMR spectra of the products were extremely complex; this was assumed to be due to equilibration between the two anomers of both 5- and 6-membered lactols. Therefore, after chromatographic separation from the over-reduction products **40** and **41** respectively, the lactols were converted directly into the corresponding amino sugars (*vide infra*).

Some reductions of lactones using DIBAL have been reported to proceed more readily if the molecule is made more lipophilic,[6d] and therefore, in an attempt to overcome the over-reduction problem altogether, this strategy was also investigated. Accordingly, the hydroxy and the NH groups of lactone **38** were protected as the isopropylidene derivative **42**, by treatment with 2-methoxypropene and pyridinium toluene-*p*-sulfonate (PPTS) in refluxing toluene. By contrast, lactone **39** could not be converted into the corresponding isopropylidene derivative under any conditions investigated, even after protracted reaction times. Furthermore, DIBAL reduction of **42** proved to be no more satisfactory than that of the unprotected compound. With 1.5–2 equivalents, incomplete conversion was found, while with 3 equivalents, complete conversion was achieved, but a new compound was observed in the ^{1}H NMR spectrum of the crude product, which presumably corresponded to the over-reduced compound. Again, the mixture of lactols (in this case only two, since the isopropylidene protection allows production of only the pair of anomeric 5-membered lactols) was isolated by chromatography and converted directly into methyl 3-*epi*-D-daunosaminide hydrochloride **43** (Scheme 14).

The mixture of lactols arising from DIBAL reduction of **38**, or that arising from the reduction of **42**, could be converted into methyl 3-*epi*-D-daunosaminide hydrochloride **43** by treatment with methanolic hydrogen chloride (Scheme 14). The crude product could be purified by chromatography,[9] and the salt was obtained, as a mixture of anomers, as a viscous oil that was hygroscopic and prone to darken rapidly in air.



Scheme 14 *Reagents and conditions*: i, DIBAL, CH_2Cl_2, −78 °C; ii, HCl, MeOH, 20 °C.

Both anomers of this compound have been reported only as the free base, and so it was necessary for comparison purposes to liberate the amine, which was achieved by means of ion-exchange. The β-anomer is the better characterised in the literature, and peaks in the ^{1}H NMR spectrum of the anomeric mixture corresponding to the minor component clearly correlated with the reported data for the β-anomer.[34] The major component was therefore the α-anomer.

The α-anomer of **43** has only been reported once in the literature (as the opposite enantiomer), and with rather incomplete NMR data given.[35] A pure sample of the α-anomer was obtained by chromatography (insufficient material was available to isolate the minor β-anomer in the same manner). The specific rotation $[\alpha]_D^{21}$ +126 (*c* 0.61 in $CHCl_3$) of this sample was in good agreement with the literature value for the enantiomer[35] $[\alpha]_D^{20}$ −132 (*c* 2.4 in $CHCl_3$). Furthermore the ^{1}H NMR spectrum (recorded at 300 MHz) matched the spectrum of the literature sample recorded at 80 MHz.†

The mixture of lactols from the reduction of lactone **39** was likewise treated with methanolic hydrogen chloride, to give, after column chromatography on silica gel, methyl α-L-daunosaminide hydrochloride **44** as a single anomer (Scheme 14).

An authentic sample of methyl α-L-daunosaminide hydrochloride **44** was prepared from commercially available methyl β-L-daunosaminide hydrochloride by treatment with methanolic hydrogen chloride, followed by recrystallisation (methanol–diethyl ether). The synthetic material was found to match the authentic material by ^{1}H NMR and mixed NMR spectroscopy. Some impurities were evident in the synthetic sample, but, after further purification by recrystallisation (methanol–diethyl ether), a sample was obtained that gave data {mp 184 °C (decomp.); [*a*] −146 (*c* 0.64 in MeOH)} in good agreement with those reported for the material derived from natural daunorubicin[2g] {mp 188–190 °C, (decomp.); $[\alpha]_D$ −140 (*c* 1 in MeOH)}.

Conclusions

Attempts at the synthesis of daunosamine or 3-*epi*-daunosamine using halogenocyclisation reactions have not been successful. The approach employing an iodolactonisation reaction was not pursued owing to the low selectivity exhibited by the reaction. Use of an iodocyclocarbamation reaction led to greater selectivity, but in favour of the isomer leading to the less desirable 3-*epi*-product, which in any case is accessible in a much more concise manner by direct dihydroxylation. Using an osmium tetroxide-catalysed dihydroxylation reaction, a short route to the daunosamine and 3-*epi*-daunosamine systems from (*E*,*E*)-hexa-2,4-dienoic acid has been developed. The strategy is applicable to the synthesis of either enantiomer of the products. The low intrinsic selectivity of the key dihydroxylation step can be significantly improved by employing the Sharpless Modified AD protocol.

Experimental

General

Specific optical rotations were determined using a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell, and are given in units of 10^{-1} deg cm^2 g^{-1}. Mps were recorded using either a Gallenkamp capillary apparatus or a Leica Galen III heated-stage apparatus, and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1750 FT spectrometer. Solution spectra were recorded using 1.0 mm sodium chloride cells. Selected diagnostic peaks only are quoted. Elemental analyses were performed by the Dyson Perrins analytical department. ^{1}H NMR spectra were recorded on a Bruker AM250 instrument (high-temperature spectra), and on Bruker WH300, AM500 or AMX500 instruments. ^{13}C NMR spectra were recorded on Bruker AC200, Varian Gemini 200, Bruker AM500 or AMX500 instruments. All spectra were referenced internally using the solvent signal (^{13}C spectra; or added 1,4-dioxane for spectra recorded in D_2O) or the residual protonated solvent signal (^{1}H spectra). Chemical shifts (δ) are quoted in ppm downfield from tetramethylsilane. Coupling constants (*J*) are quoted in Hz. First-order approximations are employed throughout. The multiplicities of the ^{13}C signals were determined by DEPT editing. The ^{13}C NMR spectra of non-cyclic carbamates contained peaks that were very broad. These are identified by an asterisk (*). Mass spectra were obtained using chemical ionisation (CI, NH_3) on a V.G. TRIO-1 GCMS instrument; using chemical ionisation (CI, NH_3) or desorption chemical ionisation (DCI) on a V.G. Masslab 20–250 instrument; using electrospray on a V.G. BIO-Q instrument, and using atmospheric pressure chemical ionisation (APCI) on a Platform instrument. Column chromatography was performed on silica gel (Kieselgel 60). THF and diethyl ether were distilled from sodium benzophenone ketyl under an atmosphere of dry nitrogen. Dichloromethane was distilled from calcium hydride under an atmosphere of dry nitrogen. Petrol refers to the fraction of light petroleum boiling in the range 40–60 °C, and was re-distilled before use. All reaction diastereoselectivities were estimated by peak integration in the ^{1}H NMR spectrum of the crude reaction products.

Preparation of methyl (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 7

Butyllithium (1.49 M; 8.0 cm^3, 11.9 mmol) was added to a solution of (*R*)-*N*-benzyl-(α-methylbenzyl)amine (2.7 g, 12.7 mmol) in anhydrous THF (10 cm^3) under nitrogen at 0 °C. The resultant deep claret solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of methyl (*E*,*E*)-hexa-2,4-dienoate **6** (1.0 g, 7.9 mmol) in anhydrous THF (5 cm^3) was added by cannula over 1 min, whereupon the reaction mixture turned rapidly brown. After being stirred at −78 °C for 2 h (during which time the solution turned a purple/brown colour) the reaction mixture was quenched by the dropwise addition of saturated aq. ammonium chloride (10 cm^3), and warmed to 20 °C, giving a yellow organic layer. Water (10 cm^3) and diethyl ether (20 cm^3) were added, the layers separated, and the

† We are very grateful to Professor C. Monneret for providing us with this spectrum.

aqueous layer extracted with diethyl ether (3 × 20 cm^3). The combined organic layers were dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel [petrol–diethyl ether (20:1)] to give *methyl (3S,αR)-(E)-3-N-[benzyl-N-(α-methylbenzyl)-amino]hex-4-enoate* **7** as a clear yellow oil in variable yield (0.90–1.90 g, 34–71%) (Found: C, 78.40; H, 8.08; N, 4.26. Calc. for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15%); $[\alpha]_D^{24}$ −25.4 (*c* 3.38 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1739 (s, ester C=O); *m/z* (electrospray) 338 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.38 [3H, d, *J* 6.8, C(α)*Me*], 1.71 [3H, d, *J* 4.7, C(6)H_3], 2.31 [1H, dd, $J_{2A,2B}$ 14.1, $J_{2A,3}$ 7.9, C(2)H_A], 2.49 [1H, dd, $J_{2A,2B}$ 14.1, $J_{2B,3}$ 6.8, C(2)H_B], 3.51 [3H, s, O*Me*], 3.65 [1H, d, *J* 14.2, NCH_AH$_B$Ph], 3.73 [1H, d, *J* 14.2, NCH$_A$$H_B$Ph], 3.78 [1H, app. q, *J* 7, C(3)*H*], 4.01 [1H, q, *J* 6.8, C(α)*H*], 5.47–5.64 [2H, m, C(4)*H* and C(5)*H*], 7.18–7.37 [10H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 16.5 and 18.1 [*C*(6) and C(α)*Me*], 38.6 [*C*(2)], 50.3 [N*C*H$_2$Ph], 51.4 [O*Me*], 56.6 [*C*(3) and *C*(α)], 126.6 [*C*(5) and *p-Ph*], 127.1 [*p-Ph*], 127.9, 128.0, 128.1 and 128.5 [*o*- and *m-Ph*], 131.2 [*C*(4)], 141.3 and 144.4 [*i-Ph*], 172.3 [*C*(1)].

Elution of the column with a more polar solvent mixture [petrol–diethyl ether (5:1)] afforded a second fraction, which was recrystallised twice from petrol–diethyl ether to give *(3S,αR,α′R)-(E)-N-benzyl-N-(α-methylbenzyl)-3-[N′-benzyl-N′-(α′-methylbenzyl)amino]hex-4-enamide* **8** as white needles (0.45 g, 11%), mp 113–114 °C (Found: C, 83.87; H, 8.08; N, 5.33. $C_{36}H_{40}N_2O$ requires C, 83.68; H, 7.80; N, 5.42%); $[\alpha]_D^{26}$ +44.9 (*c* 2.11 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1624 (s, amide C=O); *m/z* (electrospray) 517 (MH^+); δ_H(250 MHz; $C_6D_5CD_3$; 90 °C) 1.14 [3H, d, *J* 7.0, C(α)*Me*], 1.35 [3H, d, *J* 6.8, C(α′)*Me*], 1.62 [3H, d, *J* 4.2, C(6)H_3], 2.40 [2H, br m, C(2)H_2], 3.64 [2H, s, N′CH_2Ph], 3.81 [1H, d, *J* 16.7, NCH_AH$_B$Ph], 3.98 [1H, q, *J* 6.8, C(α′)*H*], 4.22–4.29 [1H, m, C(3)*H*], 5.47–5.64 [2H, m, C(4)*H* and C(5)*H*], 6.97–7.32 [20H, m, *Ph*] [signals for NCH$_A$$H_B$Ph and C(α)*H* were absent]; δ_C(50.3 MHz; $CDCl_3$) 16.9, 17.0, 17.5, 18.1 and 19.2 [*C*(6), C(α)*Me* and C(α′)*Me*], 38.9 and 39.3 [*C*(2)], 45.9, 46.8 and 50.5 [N*C*H$_2$Ph and N′*C*H$_2$Ph], 51.2, 55.8, 56.8, 57.0, 57.1 and 57.5 [*C*(3), *C*(α) and *C*(α′)], 126.2, 126.7, 126.9, 127.0, 127.2, 127.6, 127.7, 127.8, 128.0, 128.3, 128.5, 128.6, 128.7, 128.9 [*C*(5) and *o*-, *m*- and *p-Ph*], 131.3 and 131.6 [*C*(4)], 138.9, 139.9, 141.1, 141.7, 142.0, 144.9 and 145.1 [*i-Ph*], 172.4 and 172.8 [*C*(1)] (most signals are doubled owing to the presence of two amide rotamers).

Preparation of (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]hex-4-enoic acid 5

tert-Butyl (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-hex-4-enoate **4**[18] (2.0 g, 5.3 mmol) was dissolved in dichloromethane (20 cm^3), and trifluoroacetic acid (20 cm^3) was added. After stirring at 20 °C for 9 h, the solvents were removed *in vacuo* and the resulting viscous oil was dissolved in diethyl ether (50 cm^3). This solution was washed with saturated aq. sodium bicarbonate (50 + 30 + 20 cm^3), and the combined washings back-extracted with diethyl ether (2 × 30 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered, and the solvents removed *in vacuo*. Purification of the residue by column chromatography on silica gel [petrol–diethyl ether (1:2)] gave *(3S,αR)-(E)-3-[N-benzyl-N-(α-methylbenzyl)-amino]hex-4-enoic acid* **5** as a rather unstable, highly viscous clear colourless oil (1.5 g, 88%) (Found: C, 77.91; H, 7.71; N, 4.03. $C_{21}H_{25}NO_2$ requires C, 77.99; H, 7.79; N, 4.33%); $[\alpha]_D^{25}$ −49.5 (*c* 2.03 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1718 (s, C=O); *m/z* (CI, NH_3) 324 (MH^+, 100%); δ_H(300 MHz; $CDCl_3$) 1.55 [3H, d, *J* 6.9, C(α)*Me*], 1.79 [3H, dd, $J_{5,6}$ 6.2, $J_{4,6}$ 1.1, C(6)H_3], 2.27 [1H, dd, $J_{2A,2B}$ 17.2, $J_{2B,3}$ 4.4, C(2)H_B], 2.44 [1H, dd, $J_{2A,2B}$ 17.2, $J_{2A,3}$ 11.3, C(2)H_A], 3.74 [1H, d, *J* 13.5, NCH_AH$_B$Ph], 3.78 [1H, ddd, $J_{2A,3}$ 11.3, $J_{3,4}$ 8.0, $J_{2B,3}$ 4.4, C(3)*H*], 3.98 [1H, d, *J* 13.5, NCH$_A$$H_B$Ph], 4.16 [1H, q, *J* 6.9, C(α)*H*], 5.57 [1H, ddq, $J_{4,5}$ 15.3, $J_{3,4}$ 8.0, $J_{4,6}$ 1.1, C(4)*H*], 5.72 [1H, dq, $J_{4,5}$ 15.3, $J_{5,6}$ 6.2, C(5)*H*], 7.23–7.38 [10H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 16.0 and 18.2 [*C*(6) and C(α)*Me*], 36.2 [*C*(2)], 50.0 [N*C*H$_2$Ph], 57.2 and 58.5 [*C*(3) and *C*(α)], 127.2 [*C*(5)], 127.9 and 128.1 [*p-Ph*], 128.4, 128.6, 128.7 and 129.2 [*o*- and *m-Ph*], 131.0 [*C*(4)], 136.2 and 140.0 [*i-Ph*], 173.6 [*C*(1)].

Alternative preparation of (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoic acid 5

Methyl (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-hex-4-enoate **7** (1.0 g, 3.0 mmol) was dissolved in THF–water (5:2; 70 cm^3) and lithium hydroxide (0.23 g, 6.0 mmol) was added in one portion. The resulting solution was heated at reflux for 5 h and then concentrated *in vacuo*. The residue was taken up in water (100 cm^3), washed with diethyl ether (50 cm^3), and acidified with 1 M aq. hydrochloric acid (pH 4) before being extracted with ethyl acetate (3 × 50 cm^3). The combined ethyl acetate extracts were dried (magnesium sulfate), filtered, and concentrated *in vacuo* to give the crude acid **5** as a viscous clear yellow oil (0.85 g, 89%); data as in previous section.

Iodolactonisation of (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoic acid 5

(3*S*,α*R*)-(*E*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoic acid **5** (1.1 g, 3.4 mmol) was dissolved in THF–water (2:1; 75 cm^3) and NIS (1.53 g, 6.8 mmol) was added in one portion. The resulting pale yellow solution was stirred at 20 °C for 2 h, turning gradually dark brown. Aq. sodium thiosulfate (1 M; 25 cm^3) was added, causing the mixture to decolourise, and the mixture was extracted with diethyl ether (100 + 2 × 50 cm^3). The combined organic extracts were washed with brine (50 cm^3), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was found to consist of a mixture of iodolactones, which were separated by column chromatography on silica gel [petrol–diethyl ether (5:1)].

The least polar fraction gave *(3S,4R,5S,αR)-3-[N-benzyl-N-(α-methylbenzyl)amino]-5-iodohexano-4-lactone* **9** as a white solid (0.32 g, 21%). An analytical sample was prepared by recrystallisation from diethyl ether–hexane to give white needles, mp 148–151 °C (decomp.) (Found: C, 56.38; H, 5.17; N, 3.31. $C_{21}H_{24}INO_2$ requires C, 56.13; H, 5.38; N, 3.12%); $[\alpha]_D^{26}$ +191.6 (*c* 1.86 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1774 (s, γ-lactone C=O); *m/z* (CI, NH_3) 450 (MH^+, 1%), 232 (70, $MH^+ - I - PhCH_2$), 218 (100, $MH^+ - I - PhCHMe$); δ_H(500 MHz; $CDCl_3$) 1.61 [1H, d, $J_{2A,2B}$ 18.6, C(2)H_B], 1.63 [3H, d, *J* 7.2, C(α)*Me*], 2.08 [3H, d, *J* 6.9, C(6)H_3], 2.23 [1H, dd, $J_{2A,2B}$ 18.6, $J_{2A,3}$ 8.0, C(2)H_A], 3.68 [1H, d, *J* 14.9, NCH_AH$_B$Ph], 3.79 [1H, d, *J* 14.9, NCH$_A$$H_B$Ph], 3.88 [1H, q, *J* 7.2, C(α)*H*], 4.31 [1H, partially obscured dd, $J_{2A,3}$ 8.0, $J_{3,4}$ 5.7, C(3)*H*], 4.33 [1H, partially obscured dq, $J_{4,5}$ 11.0, $J_{5,6}$ 6.9, C(5)*H*], 4.70 [1H, dd, $J_{4,5}$ 11.0, $J_{3,4}$ 5.7, C(4)*H*], 7.16–7.51 [10H, m, *Ph*]; δ_H(500 MHz; d_6-acetone) 1.49 [1H, d, $J_{2A,2B}$ 18.3, C(2)H_B], 1.63 [3H, d, *J* 7.2, C(α)*Me*], 2.03 [3H, d, *J* 6.9, C(6)H_3], 2.48 [1H, dd, $J_{2A,2B}$ 18.3, $J_{2A,3}$ 8.0, C(2)H_A], 3.67 [1H, d, *J* 14.8, NCH_AH$_B$Ph], 3.80 [1H, d, *J* 14.8, NCH$_A$$H_B$Ph], 3.86 [1H, q, *J* 7.2, C(α)*H*], 4.39 [1H, dq, $J_{4,5}$ 10.9, $J_{5,6}$ 6.9, C(5)*H*], 4.45 [1H, dd, $J_{2A,3}$ 8.0, $J_{3,4}$ 5.7, C(3)*H*], 4.81 [1H, dd, $J_{4,5}$ 10.9, $J_{3,4}$ 5.7, C(4)*H*], 7.30–7.58 [10H, m, *Ph*]; δ_C(125.7 MHz; $CDCl_3$) 19.4 and 20.4 [C(6) and C(α)*Me*], 25.7 [*C*(5)], 32.8 [*C*(2)], 51.2 [N*C*H$_2$Ph], 54.1 and 56.9 [*C*(3) and *C*(α)], 88.6 [*C*(4)], 127.3 [*p-Ph*], 127.6 [*o*- or *m-Ph*], 127.9 [*p-Ph*], 127.9, 128.5 and 129.0 [*o*- and *m-Ph*], 138.4 and 139.4 [*i-Ph*], 176.1 [*C*(1)].

The middle fraction gave a clear colourless oil, which required repeated chromatography on silica gel for complete purification (accounting for the rather low isolated yield, since the compound is somewhat unstable on silica), to finally afford *(3S,4S,5R,αR)-3-[N-benzyl-N-(α-methylbenzyl)amino]-5-iodohexano-4-lactone* **10** as a clear colourless oil which solidified upon standing (0.045 g, 3%), mp 95–101 °C (Found: C, 56.29; H, 5.29; N, 2.93. $C_{21}H_{24}INO_2$ requires C, 56.13; H, 5.38; N,

3.12%); $[\alpha]_D^{26}$ +95.7 (*c* 0.82 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1785 (s, γ-lactone C=O); *m/z* (electrospray) 450 (MH^+); δ_H(500 MHz; $CDCl_3$) 1.46 [3H, d, *J* 7.1, C(α)*Me*], 1.99 [3H, d, *J* 7.2, C(6)H_3], 2.00 [1H, dd, $J_{2A,2B}$ 19.1, $J_{2B,3}$ 4.8, C(2)H_B], 2.21 [1H, dd, $J_{2A,2B}$ 19.1, $J_{2A,3}$ 9.6, C(2)H_A], 3.69 [2H, s, NCH_2Ph], 3.81 [1H, q, *J* 7.1, C(α)*H*], 3.95 [1H, apparent dt, *J* 9.6 and 4.6, C(3)*H*], 4.03 [1H, apparent t, *J* 4.1, C(4)*H*], 4.42 [1H, qd, $J_{5,6}$ 7.2, $J_{4,5}$ 4.1, C(5)*H*], 7.26–7.45 [10H, m, *Ph*]; δ_C(125.7 MHz; $CDCl_3$) 19.7 and 23.1 [C(6) and C(α)*Me*], 29.2 [*C*(5)], 29.8 [*C*(2)], 50.9 [N*C*H_2Ph], 57.8 and 58.6 [*C*(3) and *C*(α)], 87.5 [*C*(4)], 127.3 [*p-Ph*], 127.7 and 127.8 [*o-* and *m-Ph*], 127.9 [*p-Ph*], 128.7 [*o-* and *m-Ph*], 139.4 and 140.7 [*i-Ph*], 175.0 [*C*(1)].

The most polar fraction gave *(3S,4R,5S,αR)-3-[N-benzyl-N-(α-methylbenzyl)amino]-4-iodohexano-5-lactone* **11** as a white solid (0.24 g, 16%). An analytical sample was prepared by recrystallisation from diethyl ether–hexane to give white plates, mp 152–155 °C (decomp.) (Found: C, 55.98; H, 5.55; N, 3.00. $C_{21}H_{24}INO_2$ requires C, 56.13; H, 5.38; N, 3.12%); $[\alpha]_D^{26}$ +120.9 (*c* 1.80 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1736 (s, δ-lactone C=O); *m/z* (CI, NH_3) 450 (MH^+, 10%), 322 (60, $MH^+ - HI$), 232 (90, $MH^+ - I - PhCH_2$), 218 (100, $MH^+ - I - PhCHMe$); δ_H(500 MHz; $CDCl_3$) 1.45 [3H, d, *J* 7.0, C(α)*Me*], 1.63 [3H, d, *J* 6.2, C(6)H_3], 2.09 [1H, dd, $J_{2A,2B}$ 17.0, $J_{2B,3}$ 3.7, C(2)H_B], 2.31 [1H, dd, $J_{2A,2B}$ 17.0, $J_{2A,3}$ 7.9, C(2)H_A], 3.71 [1H, d, *J* 15.1, NCH_A-H_BPh], 3.77 [1H, d, *J* 15.1, NC$H_A H_B$Ph], 3.83–3.89 [3H, m, C(α)*H*, C(3)*H* and C(4)*H*], 4.47 [1H, dq, $J_{4,5}$ 10.6, $J_{5,6}$ 6.1, C(5)*H*], 7.29–7.56 [10H, m, *Ph*]; δ_C(125.7 MHz; $CDCl_3$) 20.1 and 22.5 [C(6) and C(α)*Me*], 31.8 [*C*(2)], 34.6 [*C*(4)], 50.5 [N*C*H_2Ph], 58.1 and 59.5 [*C*(3) and *C*(α)], 77.7 [*C*(5)], 127.2 [*p-Ph*], 127.7 [*o-* or *m-Ph*], 127.7 [*p-Ph*], 128.2, 128.5 and 128.6 [*o-* and *m-Ph*], 139.6 and 141.3 [*i-Ph*], 171.2 [*C*(1)].

A similar product mixture was obtained using iodine (3 equiv.) in diethyl ether in the presence of saturated aq. sodium bicarbonate.

Crystal structure of 11

Crystal data. $C_{21}H_{24}INO_2$, $M = 449.33$. Monoclinic, $a = 11.639(4)$, $b = 6.617(4)$, $c = 13.031(9)$ Å, $\beta = 92.3(4)°$, $V = 1002.66$ Å^3 (lattice parameters determined by least-squares refinement of the setting angles for 25 automatically centred reflections, $\lambda = 0.710\,69$ Å), space group $P2_1$, $Z = 2$, $D_c = 1.488$ g cm^{-3}. Pale yellow plates. Crystal dimensions $0.08 \times 0.05 \times 0.23$ mm, μ(Mo-Kα) = 15.9 cm^{-1}. Data collection temperature 293 K: 5214 reflections measured ($0 \le \theta \le 25°$, $-1 \le h \le 13$, $-1 \le k \le 7$, $-15 \le l \le 15$), 3515 unique (merging $R = 0.019$), giving 2756 with $I > 3\sigma(I)$. Patterson methods were used to locate I, N, O and some C atoms, with remaining C atoms located in difference Fourier maps. Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogens placed geometrically after each cycle of refinement. Each hydrogen was assigned the same Uiso value as the carbon to which it was attached. A total of 226 parameters were refined. A 3-term Chebyshev polynomial[36] was used as the weighting scheme. Final R and R_w values are 0.0265, 0.029. All crystallographic calculations were carried out using the CRYSTALS[37] program package on Micro VAX 3800 computer. Additional material available from the Cambridge Crystallographic Data Centre comprises fractional atomic coordinates, bond lengths and angles, and thermal parameters. CCDC reference number 207/357. See http://www.rsc.org/suppdata/p1/1999/3089 for crystallographic files in .cif format.

Preparation of *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 12

Butyllithium (1.60 M; 24.1 cm^3, 38.6 mmol) was added to a solution of (*R*)-*N*-allyl-(α-methylbenzyl)amine (7.19 g, 44.6 mmol) in anhydrous THF (40 cm^3) under nitrogen at 0 °C. The resultant yellow solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate **3** (5.0 g, 29.7 mmol) in anhydrous THF (15 cm^3) was added *via* cannula over 5 min, whereupon the reaction mixture turned rapidly orange/yellow. After being stirred at −78 °C for 1.5 h the reaction mixture was quenched by the dropwise addition of saturated aq. ammonium chloride (20 cm^3), and the mixture warmed to 20 °C, giving a pale yellow organic layer. Water (20 cm^3) and diethyl ether (100 cm^3) were added, the layers separated, and the aq. layer extracted with diethyl ether (2 × 20 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel [petrol–diethyl ether (20 : 1)] to give *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]hex-4-enoate **12** as a clear pale yellow oil (7.6 g, 78%) (Found: C, 76.43; H, 9.67; N, 3.94. Calc. for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N 4.25%); $[\alpha]_D^{26}$ −1.7 (*c* 3.35 in $CHCl_3$) {lit.,[12] $[\alpha]_D^{21}$ +2.7 (*c* 1.67 in $CHCl_3$) for enantiomer}; ν_{max}(thin film)/cm^{-1} 1729 (s, ester C=O); *m/z* (electrospray) 330 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.36 [3H, d, *J* 6.8, C(α)*Me*], 1.40 [9H, s, OCMe_3], 1.69 [3H, d, *J* 5.1, C(6)H_3], 2.26 [1H, dd, $J_{2A,2B}$ 14.2, $J_{2A,3}$ 8.4, C(2)H_A], 2.41 [1H, dd, $J_{2A,2B}$ 14.2, $J_{2B,3}$ 6.5, C(2)H_B], 3.12 [2H, app dt, *J* 6.1 and 1.5, NCH_2CH=CH_2], 3.82 [1H, app q, *J* 7, C(3)*H*], 4.00 [1H, q, *J* 6.8, C(α)*H*], 4.99 [1H, app dq, *J* 10.2 and 1.5, *cis*-CH=C(H)*H*], 5.07 [1H, app dq, *J* 17.1 and 1.7, *trans*-CH=C(H)*H*], 5.43–5.59 [2H, m, C(4)*H* and C(5)*H*], 5.78 [1H, ddt, *J* 17.1, 10.2 and 6.1, C*H*=CH_2], 7.17–7.38 [5H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 17.8 and 18.3 [*C*(6) and C(α)*Me*], 28.0 [OCMe_3], 39.8 [*C*(2)], 49.6 [N*C*H_2CH=CH_2], 57.1 and 57.2 [*C*(3) and *C*(α)], 80.0 [O*C*Me$_3$], 115.5 [CH=*C*H_2], 126.7 and 127.0 [*C*(5) and *p-Ph*], 127.8 and 128.1 [*o-* and *m-Ph*], 130.9 [*C*(4)], 139.2 [*C*H=CH$_2$], 145.5 [*i-Ph*], 171.7 [*C*(1)].

The diastereoselectivity of this reaction has previously been demonstrated to be 96% de.[12]

Preparation of *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-(α-methylbenzyl)-amino]hex-4-enoate 13

Tris(triphenylphosphine)rhodium(I) chloride (0.414 g, 0.447 mmol) was added to a solution of *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]hex-4-enoate **12** (2.94 g, 8.92 mmol) in acetonitrile–water (84 : 16; 50 cm^3), and the mixture was heated in a nitrogen stream, so that solvent was distilled out of the reaction vessel at a steady rate of ≈1 cm^3 min^{-1}. Fresh solvent mixture was continuously added from a dropping funnel to maintain the reaction mixture at constant volume. After 2.5 h, the reaction mixture was concentrated *in vacuo*, and loaded onto a column of basic alumina (10% deactivated; 50 g) which was then eluted with diethyl ether, to remove most of the catalyst residues. The resulting ethereal solution was concentrated *in vacuo*, and the residue purified by column chromatography on silica gel [petrol–diethyl ether (7 : 2)] to give *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-(α-methylbenzyl)amino]hex-4-enoate **13** as a clear pale yellow oil (2.32 g, 90%) (Found: C, 74.82; H, 9.60; N, 5.14. Calc. for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N 4.84%); $[\alpha]_D^{26}$ +44.0 (*c* 2.60 in $CHCl_3$) {lit.,[12] $[\alpha]_D^{21}$ −45.1 (*c* 1.69 in $CHCl_3$) for enantiomer}; ν_{max}(thin film)/cm^{-1} 3339 (m, br NH), 1728 (s, ester C=O); *m/z* (electrospray) 290 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.32 [3H, d, *J* 6.6, C(α)*Me*], 1.43 [9H, s, OCMe_3], 1.64 [3H, dd, $J_{5,6}$ 6.4, $J_{4,6}$ 1.6, C(6)H_3], 2.34 [1H, dd, $J_{2A,2B}$ 14.5, $J_{2A,3}$ 6.6, C(2)H_A], 2.40 [1H, dd, $J_{2A,2B}$ 14.5, $J_{2B,3}$ 6.5, C(2)H_B], 3.44 [1H, app q, *J* 7, C(3)*H*], 3.83 [1H, q, *J* 6.6, C(α)*H*], 5.24 [1H, ddq, $J_{4,5}$ 15.3, $J_{3,4}$ 8.0, $J_{4,6}$ 1.6, C(4)*H*], 5.54 [1H, dq, $J_{4,5}$ 15.3, $J_{5,6}$ 6.4, C(5)*H*], 7.20–7.31 [5H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 17.6 and 23.1 [*C*(6) and C(α)*Me*], 28.1 [OCMe_3], 41.8 [*C*(2)], 54.5 and 55.1 [*C*(3) and *C*(α)], 80.2 [O*C*Me$_3$], 126.6, 126.7 and 126.8 [*C*(5), *p-Ph* and *o-* or *m-Ph*], 128.3 [*m-* or *o-Ph*], 132.7 [*C*(4)], 146.2 [*i-Ph*], 171.2 [*C*(1)].

A second, slightly more polar fraction was also isolated from the column, arising from deallylation of the inseparable minor diastereomer of the lithium amide addition. Further purification by column chromatography on silica gel [petrol–

diethyl ether (3:1)] gave *tert-butyl (3R,αR)-(E)-3-[N-(α-methylbenzyl)amino]hex-4-enoate* **14** as a clear pale yellow oil (0.030 g, 1.2%) (Found: C, 74.72; H, 9.19; N, 5.80. $C_{18}H_{27}NO_2$ requires C, 74.70; H, 9.40; N 4.84%); $[\alpha]_D^{24}$ +52.1 (*c* 2.00 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3333 (m, br, NH), 1726 (s, ester C=O); *m/z* (CI, NH_3) 290 (MH^+, 100%); δ_H(300 MHz; $CDCl_3$) 1.31 [3H, d, *J* 6.7, C(α)*Me*], 1.41 [9H, s, OCMe_3], 1.68 [3H, dd, $J_{5,6}$ 6.1, $J_{4,6}$ 0.8, C(6)H_3], 1.74 [1H, br s, N*H*], 2.26 [1H, dd, $J_{2A,2B}$ 14.6, $J_{2B,3}$ 5.8, C(2)H_B], 2.33 [1H, dd, $J_{2A,2B}$ 14.6, $J_{2A,3}$ 7.5, C(2)H_A], 3.11 [1H, app q, *J* 7, C(3)*H*], 3.82 [1H, q, *J* 6.7, C(α)*H*], 5.24 [1H, ddq, $J_{4,5}$ 15.2, $J_{3,4}$ 8.0, $J_{4,6}$ 0.8, C(4)*H*], 5.36 [1H, dq, $J_{4,5}$ 15.2, $J_{5,6}$ 6.1, C(5)*H*], 7.19–7.34 [5H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 17.6 and 25.1 [*C*(6) and C(α)*Me*], 28.1 [OCMe_3], 42.5 [*C*(2)], 54.6 and 54.8 [*C*(3) and *C*(α)], 80.4 [O*C*Me$_3$], 126.7 and 127.6 [*C*(5), *p-Ph* and *o-* or *m-Ph*], 128.3 [*o-* or *m-Ph*], 132.2 [*C*(4)], 145.5 [*i-Ph*], 171.3 [*C*(1)].

Preparation of *tert*-butyl (3*S*,α*R*)- and (3*R*,α*R*)-(*E*)-3-[*N*-(α-methylbenzyl)amino]hex-4-enoate 13 and 14

Butyllithium (1.60 M; 2.79 cm^3, 4.46 mmol) was added by syringe over 2 min to a solution of (*R*)-α-methylbenzylamine (0.576 g, 4.75 mmol) in anhydrous THF (20 cm^3) under nitrogen at 0 °C. The resulting pale pink solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate **3** (0.500 g, 2.97 mmol) in anhydrous THF (8 cm^3) was added by cannula over 1 min, whereupon the pink solution turned orange, and the mixture was stirred at −78 °C for 15 min. The reaction was then quenched by the dropwise addition of saturated aq. ammonium chloride (2 cm^3), and the mixture was warmed to room temperature, giving a yellow organic layer. Water (2 cm^3) and diethyl ether (30 cm^3) were added, the layers separated, and the aqueous layer extracted with diethyl ether (2 × 5 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel [petrol–diethyl ether (7:2)] to give, as the less polar fraction, *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-(α-methylbenzyl)amino]hex-4-enoate **13** (0.285 g, 33%) and, as the more polar fraction, *tert*-butyl (3*R*,α*R*)-(*E*)-3-[*N*-(α-methylbenzyl)-amino]hex-4-enoate **14** (0.078 g, 9%); data as in the preceding paragraph.

Inspection of the ^{1}H NMR spectrum of the crude reaction mixture showed the two products **13** and **14** to have been formed in the ratio of approximately 3:1.

Preparation of *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-(benzyloxycarbonyl)-*N*-(α-methylbenzyl)amino]hex-4-enoate 17

A solution of dibenzyl dicarbonate (2.77 g, 9.68 mmol) and *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-(α-methylbenzyl)amino]hex-4-enoate **13** (0.700 g, 2.42 mmol) in dichloromethane (15 cm^3) was concentrated *in vacuo*, and the resulting oil kept at 20 °C *in vacuo* for 60 h. The residue was subjected to column chromatography on silica gel [petrol–diethyl ether (9:1)] to give *tert-butyl (3S,αR)-(E)-3-[N-(benzyloxycarbonyl)-N-(α-methylbenzyl)amino]hex-4-enoate* **17** as a clear, colourless oil (0.950 g, 93%) (Found: C, 74.05; H, 7.84; N, 3.41. $C_{26}H_{33}NO_4$ requires C, 73.73; H, 7.85; N 3.31%); $[\alpha]_D^{28}$ +22.1 (*c* 2.33 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1729 (s, ester C=O), 1694 (s, carbamate C=O); *m/z* (electrospray) 424 (MH^+); δ_H(250 MHz; $C_5D_5CD_3$; 70 °C) 1.23 [9H, s, OCMe_3], 1.46 [3H, d, *J* 7.1, C(α)*Me*], 1.51 [3H, dd, $J_{5,6}$ 6.4, $J_{4,6}$ 0.6, C(6)H_3], 2.16 [1H, dd, $J_{2A,2B}$ 15.4, $J_{2B,3}$ 3.9, C(2)H_B], 2.95 [1H, dd, $J_{2A,2B}$ 15.4, $J_{2A,3}$ 9.8, C(2)H_A], 4.31–4.39 [1H, m, C(3)*H*], 5.00 [1H, d, *J* 12.4, OCH_AH$_B$Ph], 5.14 [1H, d, *J* 12.4, OCH$_A$$H_B$Ph], 5.34 [1H, q, *J* 7.1, C(α)*H*], 5.54 [1H, dq, $J_{4,5}$ 15.4, $J_{5,6}$ 6.4, C(5)*H*], 5.87 [1H, dd, $J_{4,5}$ 15.4, $J_{3,4}$ 6.9, C(4)*H*], 6.96–7.29 [10H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 17.4* and 17.8 [*C*(6) and C(α)*Me*], 27.9 [OCMe_3], 40.5* [*C*(2)], 53.4* and 54.7 [*C*(3) and *C*(α)], 67.0 [O*C*H$_2$Ph], 80.1 [O*C*Me$_3$], 127.4, 128.0, 128.4 and 128.5 [*C*(5), *o-*, *m-* and *p-Ph*], 130.1* [*C*(4)], 136.7 and 140.9 [*i-Ph*], 155.6* [N*C*O], 170.3 [*C*(1)].

Preparation of *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-(*tert*-butoxycarbonyl)-*N*-(α-methylbenzyl)amino]hex-4-enoate 18

A solution of di-*tert*-butyl dicarbonate (1.13 g, 5.2 mmol) and *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-(α-methylbenzyl)amino]hex-4-enoate **13** (0.500 g, 1.73 mmol) in dichloromethane (10 cm^3) was concentrated *in vacuo*, and the resulting oil kept at 20 °C *in vacuo* for 40 days. The residue was subjected to column chromatography on silica gel [petrol–diethyl ether (7:1, then 2:1)] giving, as the more polar fraction, unchanged starting material (0.200 g, 40% recovery), and, as the less polar fraction, *tert-butyl (3S,αR)-(E)-3-[N-(tert-butoxycarbonyl)-N-(α-methylbenzyl)amino]hex-4-enoate* **18** as a clear, colourless oil [0.375 g, 56% (93% based on consumed starting material)] (Found: C, 71.16; H, 9.08; N, 3.48. $C_{23}H_{35}NO_4$ requires C, 70.92; H, 9.06; N, 3.60%); $[\alpha]_D^{28}$ +10.7 (*c* 2.54 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1731 (s, ester C=O), 1688 (s, carbamate C=O); *m/z* (electrospray) 390 (MH^+); δ_H(500 MHz; CD_3SOCD_3; 90 °C) 1.33 [9H, s, ester OCMe_3], 1.39 [9H, s, carbamate OCMe_3], 1.54 [3H, d, *J* 7.0, C(α)*Me*], 1.66 [3H, dd, $J_{5,6}$ 6.4, $J_{4,6}$ 1.6, C(6)H_3], 2.12 [1H, dd, $J_{2A,2B}$ 15.1, $J_{2B,3}$ 4.5, C(2)H_B], 2.66 [1H, dd, $J_{2A,2B}$ 15.1, $J_{2A,3}$ 9.4, C(2)H_A], 4.23–4.27 [1H, m, C(3)*H*], 5.06 [1H, q, *J* 7.0, C(α)*H*], 5.56 [1H, dqd, $J_{4,5}$ 15.5, $J_{5,6}$ 6.4, $J_{3,5}$ 1.0, C(5)*H*], 5.69 [1H, ddq, $J_{4,5}$ 15.5, $J_{3,4}$ 6.9, $J_{4,6}$ 1.6, C(4)*H*], 7.22–7.37 [5H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 17.2* and 17.7 [*C*(6) and C(α)*Me*], 27.9 and 28.5 [ester and carbamate OCMe_3], 40.7* [*C*(2)], 53.0* and 53.9 [*C*(3) and *C*(α)], 79.8 and 80.0 [ester and carbamate O*C*Me$_3$], 126.8, 127.0, 127.2 and 128.2 [*C*(5), *o-*, *m-* and *p-Ph*], 130.5* [*C*(4)], 141.6* [*i-Ph*], 155.0* [N*C*O], 171.2 [*C*(1)].

Iodocyclocarbamation of *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-(benzyloxycarbonyl)-*N*-(α-methylbenzyl)amino]hex-4-enoate 17

tert-Butyl (3*S*,α*R*)-(*E*)-3-[*N*-(benzyloxycarbonyl)-*N*-(α-methylbenzyl)amino]hex-4-enoate **17** (0.850 g, 2.00 mmol) was dissolved in dichloromethane (100 cm^3) and iodine (2.04 g, 8.00 mmol) was added in one portion. The resulting dark brown mixture was stirred for 2 h at 20 °C, protected from light. The solution was then washed with aq. sodium thiosulfate (1 M; 50 cm^3) (causing decolourisation), dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The crude product contained a mixture of iodocarbamates, which were separated by column chromatography on silica gel [petrol–diethyl ether (2:1)].

A very non-polar fraction contained benzyl iodide, δ_H(300 MHz; $CDCl_3$) 5.18 [2H, s, PhCH_2I], 7.35–7.39 [5H, m, *Ph*CH$_2$I].

The next fraction gave the least polar iodocarbamate, identified as (4*S*,5*S*,1′*R*,α*R*)-4-[(*tert*-butoxycarbonyl)methyl]-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin-2-one **20**, which was obtained as a yellow oil (0.078 g, 8.5%); δ_H(300 MHz; $CDCl_3$) 1.44 [9H, s, OCMe_3], 1.76 [3H, d, *J* 7.1, C(α)*Me*], 2.03 [3H, d, *J* 6.6, C(2′)H_3], 2.30 [2H, d, *J* 4.8, C(4)CH_2], 4.11–4.21 [2H, m, C(1′)*H* and C(4)*H*], 4.58 [1H, dd, $J_{5,1'}$ 10.5, $J_{4,5}$ 6.8, C(5)*H*], 4.91 [1H, q, *J* 7.1, C(α)*H*], 7.28–7.44 [5H, m, *Ph*].

This material decomposed upon standing to the corresponding carboxylic acid, which was purified by column chromatography on silica gel [petrol–diethyl ether (1:1)], to give *(4S,5S,1′R,αR)-4-(carboxymethyl)-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin-2-one* **22** as a yellow glass (0.068 g, 99%) (Found: C, 44.55; H, 4.24; N, 3.24. $C_{15}H_{18}INO_4$ requires C, 44.68; H, 4.50; N 3.47%); $[\alpha]_D^{22}$ −41.8 (*c* 1.99 in $CHCl_3$); ν_{max}-($CHCl_3$ solution)/cm^{-1} 1751 (s, oxazolidinone C=O), 1714 (s, acid C=O); *m/z* [electrospray (negative)] 403 ($M - H^-$); δ_H(300 MHz; $CDCl_3$) 1.75 [3H, d, *J* 7.1, C(α)*Me*], 2.06 [3H, d, *J* 6.6, C(2′)H_3], 2.33 [1H, dd, $J_{A,B}$ 17.0, $J_{A,4}$ 5.4, C(4)CH_AH$_B$], 2.41

[1H, dd, $J_{A,B}$ 17.0, $J_{B,4}$ 4.7, C(4)CH_AH_B], 4.03 [1H, dq, $J_{5,1'}$ 10.7, $J_{1',2'}$ 6.6, C(1′)*H*], 4.29 [1H, app q, *J* 5.5, C(4)*H*], 4.62 [1H, dd, $J_{5,1'}$ 10.7, $J_{4,5}$ 6.8, C(5)*H*], 5.09 [1H, q, *J* 7.1, C(α)*H*], 6.1 [1H, br s, O*H*], 7.29–7.42 [5H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 17.6 [C(α)*Me*], 19.9 [*C*(1′)], 25.1 [*C*(2′)], 32.4 [C(4)*C*H_2], 52.7 and 54.9 [*C*(4) and *C*(α)], 82.0 [*C*(5)], 127.3 [*o*- or *m*-*Ph*], 128.1 [*p*-*Ph*], 128.8 [*m*- or *o*-*Ph*], 140.2 [*i*-*Ph*], 157.0 [*C*(2)], 174.7 [*C*O_2H].

The next fraction gave *(4S,5R,1′S,αR)-4-[(tert-butoxycarbonyl)methyl]-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin-2-one* **19** as a yellow solid (0.580 g, 63%). An analytical sample was prepared by recrystallisation from diethyl ether–petrol to give off-white plates, mp 98–98 °C (Found: C, 49.42; H, 5.72; N, 3.04. $C_{19}H_{26}INO_4$ requires C, 49.68; H, 5.71; N 3.05%); $[\alpha]_D^{24}$ +35.0 (*c* 1.79 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1736 (s, oxazolidinone C=O), 1719 (s, ester C=O); *m*/*z* (CI, NH_3) 460 (MH^+, 40%), 404 (60, $MH^+ - C_4H_8$), 232 (70, $MH^+ - C_4H_8 - CO_2 - HI$), 105 (100, $PhCHMe^+$); δ_H(300 MHz; $CDCl_3$) 1.41 [9H, s, OC*Me*$_3$], 1.74 [3H, d, *J* 7.2, C(α)*Me*], 1.91 [3H, d, *J* 6.8, C(2′)*H*$_3$], 2.18 [2H, d, *J* 5.1, C(4)C*H*$_2$], 3.89 [1H, td, *J* 5.1 and 3.2, C(4)*H*], 4.07 [1H, app qn, *J* 6.8, C(1′)*H*], 4.19 [1H, dd, $J_{5,1'}$ 6.8, $J_{4,5}$ 3.2, C(5)*H*], 5.02 [1H, q, *J* 7.2, C(α)*H*], 7.30–7.43 [5H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 16.7 [C(α)*Me*], 22.7 [*C*(2′)], 27.1 [*C*(1′)], 27.9 [OC*Me*$_3$], 39.4 [C(4)*C*H_2], 52.3 and 56.1 [*C*(4) and *C*(α)], 82.1 [*C*(5) and OCMe_3], 127.4 [*o*- or *m*-*Ph*], 128.2 [*p*-*Ph*], 129.0 [*m*- or *o*-*Ph*], 140.7 [*i*-*Ph*], 156.6 [*C*(2)], 169.0 [*C*O_2CMe_3].

The most polar fraction gave an iodocarbamate (0.014 g, 1.5%) that decomposed rapidly upon standing, whose structure was, therefore, not determined unambiguously. However, the ^{1}H NMR data are consistent with the proposed structure (4*S*,5*R*,6*S*,α*R*)-4-[(*tert*-butoxycarbonyl)methyl]-5-iodo-6-methyl-3-(α-methylbenzyl)-1,3-oxazinan-2-one **21**; δ_H(300 MHz; $CDCl_3$) 1.38 [9H, s, OC*Me*$_3$], 1.59 [3H, d, *J* 6.1, C(6)*Me*], 1.67 [3H, d, *J* 7.2, C(α)*Me*], 2.03 [1H, dd, $J_{A,B}$ 17.7, $J_{B,4}$ 3.2, C(4)CH_AH_B], 2.57 [1H, dd, $J_{A,B}$ 17.7, $J_{A,4}$ 6.9, C(4)CH_AH_B], 4.02 [1H, dd, $J_{5,6}$ 11.0, $J_{4,5}$ 4.4, C(5)*H*], 4.27 [1H, app dt, *J* 7 and 4, C(4)*H*], 4.57 [1H, dq, $J_{5,6}$ 11.0, $J_{6,6\text{-Me}}$ 6.1, C(6)*H*], 5.52 [1H, q, *J* 7.2, C(α)*H*], 7.28–7.46 [5H, m, *Ph*].

Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed the proportions of the three iodocarbamates **19**:**20**:**21** to be ≈84:14:2.

Similar results were obtained using either of the reaction conditions described in the next paragraph.

Iodocyclocarbamation of *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-(*tert*-butoxycarbonyl)-*N*-(α-methylbenzyl)amino]hex-4-enoate 18

N-Iodosuccinimide (0.115 g, 0.513 mmol) was added in one portion to a stirred solution of *tert*-butyl (3*S*,α*R*)-(*E*)-3-[*N*-(*tert*-butoxycarbonyl)-*N*-(α-methylbenzyl)amino]hex-4-enoate **18** in THF–water (8:1; 9 cm^3) at 0 °C. The resulting pale yellow solution was stirred for 6 h, turning gradually dark brown. Aq. sodium thiosulfate (1 M; 15 cm^3) was added, causing the mixture to decolourise, and the mixture was extracted with diethyl ether (3 × 20 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried (magnesium sulfate), and concentrated *in vacuo*. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed the formation of the same three iodocarbamates in similar proportions to those obtained above. The products were isolated in the same manner, to give (4*S*,5*R*,1′*S*,α*R*)-4-[(*tert*-butoxycarbonyl)methyl]-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin-2-one **19** (0.063 g, 58%), (4*S*,5*S*,1′*R*,α*R*)-4-[(*tert*-butoxycarbonyl)methyl]-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin-2-one **20** (0.013 g, 11%) and (4*S*,5*R*,6*S*,α*R*)-4-[(*tert*-butoxycarbonyl)methyl]-5-iodo-6-methyl-3-(α-methylbenzyl)-1,3-oxazinan-2-one **21** (0.002 g, 1.7%).

The same product mixture was obtained when iodine (0.195 g, 0.770 mmol) in diethyl ether (5 cm^3) was employed, if the reaction was carried out in the presence of saturated aq. sodium bicarbonate (5 cm^3). In the absence of base, using iodine (0.195 g, 0.770 mmol) in dichloromethane (20 cm^3) resulted in a substantial degree of hydrolysis of the *tert*-butyl ester group of the product iodocarbamates, and hence reduced yields of the desired products.

Preparation of (4*S*,5*S*,α*R*)-4-[(*tert*-butoxycarbonyl)methyl]-5-ethyl-3-(α-methylbenzyl)oxazolidin-2-one 23

Tributyltin hydride (freshly distilled; 0.400 cm^3, 0.433 g, 1.49 mmol) was added to a solution of (4*S*,5*R*,1′*S*,α*R*)-4-[(*tert*-butoxycarbonyl)methyl]-5-(1′-iodoethyl)-3-(α-methylbenzyl)-oxazolidin-2-one **19** (0.200 g, 0.435 mmol) and 2,2′-azoisobutyronitrile (0.010 g, 0.061 mmol) in anhydrous toluene (40 cm^3), and the mixture was heated at reflux protected from moisture (calcium chloride drying tube) for 6 h. The solution was then concentrated *in vacuo*, and loaded onto a silica gel column. Elution with petrol–diethyl ether (10:1) removed the tin residues, then the crude product was obtained by elution with petrol–diethyl ether (2:1). Purification by further column chromatography on silica gel [petrol–diethyl ether (2:1)] gave *(4S,5S,αR)-4-[(tert-butoxycarbonyl)methyl]-5-ethyl-3-(α-methylbenzyl)oxazolidin-2-one* **23** as a clear, colourless oil (0.116 g, 80%) (Found: C, 68.39; H, 7.78; N, 4.43. $C_{19}H_{27}NO_4$ requires C, 68.44; H, 8.16; N, 4.20%); $[\alpha]_D^{21}$ +48.3 (*c* 2.06 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1747 (s, oxazolidinone C=O), 1732 (s, ester C=O); *m*/*z* (CI, NH_3) 334 (MH^+, 70%), 278 (100, $MH^+ - C_4H_8$); δ_H(300 MHz; $CDCl_3$) 0.98 [3H, t, *J* 7.4, C(5)-CH_2*Me*], 1.39 [9H, s, OC*Me*$_3$], 1.59–1.69 [2H, m, C(5)CH_2], 1.68 [3H, d, *J* 7.2, C(α)*Me*], 1.98 [1H, dd, $J_{A,B}$ 16.0, $J_{B,4}$ 4.4, C(4)CH_AH_B], 2.06 [1H, dd, $J_{A,B}$ 16.0, $J_{A,4}$ 8.9, C(4)CH_AH_B], 3.89 [1H, app dt, *J* 8.5 and 4, C(4)*H*], 4.05–4.11 [1H, m, C(5)*H*], 5.08 [1H, q, *J* 7.2, C(α)*H*], 7.28–7.42 [5H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 8.7 [*C*(5)CH_2*Me*], 16.6 [C(α)*Me*], 27.9 [C(5)*C*H_2 and OC*Me*$_3$], 39.5 [C(4)*C*H_2], 51.6 and 55.3 [*C*(4) and *C*(α)], 80.7 [*C*(5)], 81.6 [OCMe_3], 127.1 [*o*- or *m*-*Ph*], 127.9 [*p*-*Ph*], 128.6 [*m*- or *o*-*Ph*], 140.8 [*i*-*Ph*], 157.3 [*C*(2)], 169.3 [*C*O_2CMe_3].

Elimination reaction of (4*S*,5*R*,1′*S*,α*R*)-4-[(*tert*-butoxycarbonyl)methyl]-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin-2-one 19

Caesium acetate (0.025 g, 0.130 mmol) was added in one portion to a solution of (4*S*,5*R*,1′*S*,α*R*)-4-[(*tert*-butoxycarbonyl)methyl]-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin-2-one **19** (0.055 g, 0.120 mmol) in dimethylformamide (1 cm^3). The mixture was stirred at 20 °C for 48 h, then diethyl ether (20 cm^3) was added. After being washed successively with water (3 × 5 cm^3) and brine (5 cm^3), the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel [petrol–diethyl ether (2:1)] to give *(4S,αR)-(E)-4-[(tert-butoxycarbonyl)-methyl]-5-ethylidene-3-(α-methylbenzyl)oxazolidin-2-one* **24** as a white solid (0.035 g, 88%). An analytical sample was prepared by recrystallisation from diethyl ether–petrol to give white needles, mp 84–85 °C (Found: C, 68.58; H, 7.38; N, 4.39. $C_{19}H_{25}NO_4$ requires C, 68.86; H, 7.60; N 4.23%); $[\alpha]_D^{21}$ −24.2 (*c* 1.34 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1767 (s, oxazolidinone C=O), 1716 (s, ester C=O); *m*/*z* (CI, NH_3) 349 (MNH_4^+, 40%), 332 (30, MH^+), 293 (30, $MNH_4^+ - C_4H_8$), 276 (50, $MH^+ - C_4H_8$), 105 (100, $PhCHMe^+$); δ_H(300 MHz; $CDCl_3$) 1.41 [9H, s, OC*Me*$_3$], 1.54 [3H, dd, *J* 7.4 and 1.2, =CH*Me*], 1.77 [3H, d, *J* 7.2, C(α)*Me*], 2.36 [2H, d, *J* 3.9, C(4)CH_2], 4.72–4.73 [1H, m, C(4)*H*], 5.00 [1H, q, *J* 7.2, C(α)*H*], 5.15 [1H, dq, *J* 7.4 and 2.3, =C*H*Me], 7.30–7.45 [5H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 10.4 [=CH*Me*], 17.2 [C(α)*Me*], 27.8 [OC*Me*$_3$], 38.6 [C(4)*C*H_2], 52.3 and 52.7 [*C*(4) and *C*(α)], 81.7 [OCMe_3], 97.1 [=*C*HMe], 127.1 [*o*- or *m*-*Ph*], 127.9 [*p*-*Ph*], 128.7 [*m*- or *o*-*Ph*], 140.5 [*i*-*Ph*], 146.7 [*C*(5)], 155.2 [*C*(2)], 168.6 [*C*O_2CMe_3].

Preparation of (4*S*,5*R*,1′*S*,α*R*)-4-carboxymethyl-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin-2-one 25

(4*S*,5*R*,1′*S*,α*R*)-4-[(*tert*-Butoxycarbonyl)methyl]-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin-2-one **19** (0.300 g, 0.653 mmol) was dissolved in anhydrous dichloromethane (20 cm^3), and trifluoroacetic acid (5 cm^3) was added. After stirring of the solution for 1 h at 20 °C, the solvents were removed *in vacuo*, and the residue purified by column chromatography on silica gel (diethyl ether) to give *(4S,5R,1′S,α*R)-4-*carboxymethyl-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin*-2-*one* **25** as a yellow glass (0.265 g, 100%) (Found: C, 44.39; H, 4.70; N, 3.41. $C_{15}H_{18}INO_4$ requires C, 44.68; H, 4.50; N, 3.47%); $[\alpha]_D^{22}$ +37.8 (*c* 2.10 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 1747 (s, oxazolidinone C=O), 1714 (s, acid C=O); *m/z* [electrospray (negative)] 403 ($M - H^-$); δ_H(300 MHz; $CDCl_3$) 1.72 [3H, d, *J* 7.1, C(α)-*Me*], 1.91 [3H, d, *J* 6.8, C(2′)H_3], 2.25 [2H, d, *J* 5.2, C(4)CH_2], 3.95 [1H, app q, *J* 4, C(4)*H*], 4.11 [1H, app qn, *J* 6.8, C(1′)*H*], 4.19 [1H, dd, $J_{5,1'}$ 6.7, $J_{4,5}$ 3.2, C(5)*H*], 5.15 [1H, q, *J* 7.1, C(α)*H*], 7.31–7.41 [5H, m, *Ph*], 8.1 [1H, br s, O*H*]; δ_C(50.3 MHz; $CDCl_3$) 16.2 [C(α)*Me*], 22.6 [*C*(2′)], 26.9 [*C*(1′)], 37.9 [C(4)*C*H_2], 51.9 and 55.4 [*C*(4) and *C*(α)], 82.2 [*C*(5)], 127.4 [*o*- or *m*-*Ph*], 128.4 [*p*-*Ph*], 129.0 [*m*- or *o*-*Ph*], 140.3 [*i*-*Ph*], 157.2 [*C*(2)], 174.1 [*C*O_2H].

Preparation of (3a*R*,4*R*,7a*S*,α*R*)-4-methyl-1-(α-methylbenzyl)-3a,4,7,7a,-tetrahydropyrano[4,3-*d*]oxazol-2,6(1*H*)-dione 26

Silver trifluoroacetate (0.143 g, 0.647 mmol) was added in one portion to a solution of (4*S*,5*R*,1′*S*,α*R*)-4-carboxymethyl-5-(1′-iodoethyl)-3-(α-methylbenzyl)oxazolidin-2-one **25** (0.260 g, 0.645 mmol) in anhydrous dichloromethane (50 cm^3). The mixture was stirred for 2 h at 20 °C, during which time a yellow precipitate (silver iodide) formed. The mixture was washed with saturated aq. sodium bicarbonate (10 cm^3), filtered through Celite, dried (magnesium sulfate), filtered, and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel [dichloromethane–diethyl ether (1 : 1)] to give *(3aR,4R,7aS,α*R*)-4-methyl-1-(α-methylbenzyl)-3a,4,7,7a-tetrahydropyrano[4,3-d]oxazole-2,6(1H)-dione* **26** as a white solid (0.126 g, 71%). An analytical sample was prepared by recrystallisation from dichloromethane–diethyl ether to give fine white needles, mp 174.5–175.5 °C (Found: C, 65.25; H, 6.14; N, 5.20. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09%); $[\alpha]_D^{24}$ +96.2 (*c* 2.35 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 1741 (s, oxazolidinone C=O), 1729 (s, δ-lactone C=O); *m/z* (CI, NH_3) 293 (MNH_4^+, 100%), 278 (70, MH^+); δ_H(500 MHz; $CDCl_3$) 1.44 [3H, d, *J* 6.7, C(4)*Me*], 1.66 [3H, d, *J* 7.1, C(α)*Me*], 2.04 [1H, dd, $J_{7A,7B}$ 17.2, $J_{7A,7a}$ 12.4, C(7)H_A], 2.45 [1H, dd, $J_{7A,7B}$ 17.2, $J_{7B,7a}$ 4.8, C(7)H_B], 3.90 [1H, app td, *J* 12.1 and 4.8, C(7a)*H*], 4.27 [1H, dd, $J_{3a,7a}$ 11.7, $J_{3a,4}$ 6.2, C(3a)*H*], 4.98 [1H, app qn, *J* 6.5, C(4)*H*], 5.14 [1H, q, *J* 7.1, C(α)*H*], 7.30–7.40 [5H, m, *Ph*]; δ_C(125.7 MHz; $CDCl_3$) 15.1 [C(α)*Me*], 16.1 [C(4)*Me*], 37.8 [*C*(7)], 49.2 [*C*(7a)], 52.8 [*C*(α)], 74.9 [*C*(4)], 75.0 [*C*(3a)], 127.5 [*o*- or *m*-*Ph*], 128.8 [*p*-*Ph*], 129.2 [*m*- or *o*-*Ph*], 139.9 [*i*-*Ph*], 158.3 [*C*(2)], 166.0 [*C*(6)].

Reduction of (3a*R*,4*R*,7a*S*,α*R*)-4-methyl-1-(α-methylbenzyl)-3a,4,7,7a-tetrahydropyrano[4,3-*d*]oxazole-2,6(1*H*)-dione 26

Liquid ammonia (30 cm^3) was dried with sodium (until the blue colour persisted), recondensed, and stirred at −78 °C under nitrogen. Freshly cut sodium (0.0167 g, 0.726 mmol) was added in small pieces, causing a blue colour to appear. After stirring of this solution for 20 min, anhydrous ethanol (0.5 cm^3) was added, followed by a solution of (3a*R*,4*R*,7a*S*,α*R*)-4-methyl-1-(α-methylbenzyl)-3a,4,7,7a-tetrahydropyrano[4,3-*d*]oxazole-2,6(1*H*)-dione **26** (0.050 g, 0.182 mmol) in anhydrous THF (5 cm^3). The blue colour faded as the substrate was added, returned again, and finally disappeared after 10 min. After another 30 min, solid ammonium chloride (0.20 g, 3.74 mmol) was added in one portion. The flask was opened to air through a calcium chloride drying tube and left for 24 h at 20 °C for the ammonia to evaporate, before removal of the solvents *in vacuo*. The residue was subjected to repeated column chromatography on silica gel [ethyl acetate–methanol (7 : 3)] in order to separate the product from the inorganic residues, to finally afford *(4S,5R,1′R)-5-(1′-hydroxyethyl)-4-(2″-hydroxyethyl)oxazolidin-2-one* **27** as a clear, colourless, viscous oil (0.015 g, 47%) (Found: C, 47.98; H, 7.49; N, 7.96. $C_7H_{13}NO_4$ requires C, 47.99; H, 7.48; N, 8.00%); $[\alpha]_D^{21}$ −96.1 (*c* 1.52 in MeOH); ν_{max}(thin film)/cm^{-1} 1739 (s, oxazolidinone C=O); *m/z* (APCI) 176 (MH^+); δ_H(500 MHz; CD_3OD) 1.23 [3H, d, *J* 6.5, C(2′)H_3], 1.76–1.80 [2H, m, C(1″)H_2], 3.62–3.71 [2H, m, C(2″)H_2], 3.82 [1H, qd, $J_{1',2'}$ 6.5, $J_{5,1'}$ 3.8, C(1′)*H*], 3.87 [1H, app q, *J* 6, C(4)*H*], 4.16 [1H, dd, $J_{4,5}$ 5.6, $J_{5,1'}$ 3.8, C(5)*H*]; δ_C(125.7 MHz; CD_3OD) 18.4 [*C*(2′)], 39.5 [*C*(1″)], 52.9 [*C*(4)], 59.4 [*C*(2″)], 68.3 [*C*(1′)], 86.7 [*C*(5)], 161.5 [*C*(2)].

Preparation of (3*S*,4*R*,5*R*,α*R*)- and (3*S*,4*S*,5*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxyhexano-4-lactone 34 and 35

To a solution of methyl (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate **7** (1.0 g, 2.96 mmol) in *tert*-butyl alcohol (10 cm^3) was added a solution of potassium hexacyanoferrate(III) (2.93 g, 8.88 mmol) and potassium carbonate (1.23 g, 8.88 mmol) in water (15 cm^3). A solution of osmium tetroxide (38 mg, 0.15 mmol) in *tert*-butyl alcohol (5 cm^3) was added, and the biphasic mixture stirred at 20 °C overnight, during which time the colour darkened considerably. Sodium sulfite (5.0 g, 39.7 mmol) was added and, after being stirred for 30 min (whereupon the colour of the mixture, especially the organic phase, lightened), the reaction mixture was extracted with ethyl acetate (4 × 30 cm^3). The organic extracts were dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The residue was found to consist of two diastereomeric lactones, which were separated by column chromatography on silica gel [petrol–diethyl ether 4 : 5]. Analytical samples of the two lactones were prepared by recrystallisation from diethyl ether–petrol.

The more polar fraction yielded *(3S,4R,5R,αR)-3-[N-benzyl-N-(α-methylbenzyl)amino]-5-hydroxyhexano-4-lactone* **34** as fine, white needles (0.48 g, 48%), mp 132–136 °C (Found: C, 74.34; H, 7.71; N, 4.18. $C_{21}H_{25}NO_3$ requires C, 74.31; H, 7.42; N, 4.13%); $[\alpha]_D^{26}$ +101.2 (*c* 1.62 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3601 (m, free OH), 3397 (br, H-bonded OH), 1775 (s, γ-lactone C=O); *m/z* (electrospray) 340 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.41 [3H, d, *J* 6.2, C(6)H_3], 1.47 [3H, d, *J* 7.0, C(α)*Me*], 1.97 [1H, dd, $J_{2A,2B}$ 17.8, $J_{2B,3}$ 6.5, C(2)H_B], 2.13 [1H, dd, $J_{2A,2B}$ 17.8, $J_{2A,3}$ 8.2, C(2)H_A], 2.64 [1H, d, *J* 3, C(5)O*H*], 3.76 [2H, s, NCH_2Ph], 3.94 [1H, q, *J* 7.0, C(α)*H*], 4.04 [1H, ddd, $J_{2A,3}$ 8.2, $J_{3,4}$ 6.5, $J_{2B,3}$ 6.5, C(3)*H*], 4.32 [1H, dd, $J_{3,4}$ 6.5, $J_{4,5}$ 5.6, C(4)*H*], 4.39 [1H, app. qnd, *J* 6 and 3, C(5)*H*], 7.23–7.41 [10H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 15.6 and 18.4 [C(6) and C(α)*Me*], 32.6 [*C*(2)], 52.5 [N*C*H_2Ph], 55.5 and 56.6 [*C*(3) and *C*(α)], 66.4 [*C*(5)], 86.6 [*C*(4)], 127.4 [*p*-*Ph*], 127.6, 127.8, 128.6 and 128.9 [*p*-, *o*- and *m*-*Ph*], 138.7 and 140.4 [*i*-*Ph*], 175.7 [*C*(1)].

The less polar fraction yielded *(3S,4S,5S,αR)-3-[N-benzyl-N-(α-methylbenzyl)amino]-5-hydroxyhexano-4-lactone* **35** as white needles (0.32 g, 32%), mp 126–128 °C (Found: C, 74.57; H, 7.47; N, 4.05%); $[\alpha]_D^{26}$ +169.9 (*c* 0.73 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3592 (m, free OH), 3395 (br, H-bonded OH), 1774 (s, γ-lactone C=O); *m/z* (electrospray) 340 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.36 [3H, d, *J* 6.3, C(6)H_3], 1.41 [3H, d, *J* 7.1, C(α)*Me*], 1.77 [1H, d, *J* 7.7, C(5)O*H*], 2.01 [1H, dd, $J_{2A,2B}$ 18.4, $J_{2A,3}$ 9.0, C(2)H_A], 2.12 [1H, dd, $J_{2A,2B}$ 18.4, $J_{2B,3}$ 7.1, C(2)H_B], 3.66 [1H, d, *J* 14.8, NC$H_A$$H_B$Ph], 3.72 [1H, d, *J* 14.8, NCH$_A$$H_B$-Ph], 3.82 [1H, q, *J* 7.1, C(α)*H*], 3.96–4.05 [2H, m, C(3)*H* and C(5)*H*], 4.12 [1H, dd, *J* 5.6 and 2.3, C(4)*H*], 7.25–7.43 [10H, m,

Ph]; δ_C(50.3 MHz; $CDCl_3$) 18.8 and 20.2 [*C*(6) and C(α)*Me*], 29.9 [*C*(2)], 50.3 [N*C*H_2Ph], 54.4 and 57.5 [*C*(3) and *C*(α)], 67.2 [*C*(5)], 87.0 [*C*(4)], 127.3 [*p-Ph*], 127.6, 128.0 and 128.6 [*p*-, *o*- and *m-Ph*], 139.4 and 141.0 [*i-Ph*], 176.6 [*C*(1)].

Use of other co-oxidants (*N*-methylmorpholine *N*-oxide or trimethylamine *N*-oxide) resulted in more complex product mixtures, which appeared to be mixtures of cyclised and uncyclised products.

Preparation of (3*S*,4*S*,5*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-5-hydroxyhexano-4-lactone 35 and *tert*-butyl (3*S*,4*R*,5*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxy-hexanoate 36

tert-Butyl (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-hex-4-enoate **4**[18] (2.0 g, 5.3 mmol) was dihydroxylated under the same conditions as for the methyl ester above. This gave two products, which were separated by column chromatography on silica gel [petrol–diethyl ether 4:5]. The more polar fraction yielded (3*S*,4*S*,5*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxyhexano-4-lactone **35** (0.55 g, 31%); data as in the previous section.

The less polar fraction yielded *tert-butyl (3S,4R,5R,αR)-3-[N-benzyl-N-(α-methylbenzyl)amino]-4,5-dihydroxyhexanoate* **36** as a white solid (1.12 g, 51%). An analytical sample was prepared by recrystallisation from hexane, to give white needles, mp 86–87 °C (Found: C, 72.43; H, 8.82; N, 3.29. $C_{25}H_{35}NO_4$ requires C, 72.61; H, 8.53; N, 3.39%); $[\alpha]_D^{24}$ +28.0 (*c* 2.02 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3492 (br, OH), 1712 (s, ester C=O); *m*/*z* (CI, NH_3) 414 (MH^+, 100%); δ_H(300 MHz; $CDCl_3$) 1.34 [3H, d, *J* 6.3, C(6)H_3], 1.41 [9H, s, OCMe_3], 1.47 [3H, d, *J* 7.1, C(α)*Me*], 1.71 [1H, d, $J_{2A,2B}$ 17.2, C(2)H_A], 2.01 [1H, dd, $J_{2A,2B}$ 17.2, $J_{2B,3}$ 9.5, C(2)H_B], 3.22 [1H, d, $J_{3,4}$ 7.7, C(4)*H*], 3.50 [1H, d, *J* 14.1, NC$H_A$$H_B$Ph], 3.66 [1H, m, (after D_2O shake: q, $J_{5,6}$ 6.3) C(5)*H*], 3.73–3.81 [3H, m, O*H*, NC$H_A$$H_B$Ph and C(3)*H*], 3.89 [1H, q, *J* 7.1, C(α)*H*], 3.89 [1H, s, O*H*], 7.32–7.41 [10H, m, *Ph*]; δ_C(50.3 MHz; $CDCl_3$) 19.5 and 20.1 [*C*(6) and C(α)*Me*], 27.9 [OCMe_3], 33.4 [*C*(2)], 51.2 [N*C*H_2Ph], 53.3 and 56.7 [*C*(3) and *C*(α)], 66.3 and 74.6 [*C*(4) and *C*(5)], 81.3 [O*C*Me_3], 127.6 and 127.8 [*p-Ph*], 128.4, 128.6, 128.9 and 129.0 [*o*- and *m-Ph*], 139.1 and 139.9 [*i-Ph*], 172.5 [*C*(1)].

Dihydroxylation of methyl (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 7 employing the Sharpless AD ligands

A solution of osmium tetroxide (0.5 mg, 0.006 mmol) in *tert*-butyl alcohol (0.5 cm^3) was added to a biphasic solution of potassium hexacyanoferrate(III) (0.296 g, 0.90 mmol), potassium carbonate (0.124 g, 0.90 mmol), methanesulfonamide (0.029 g, 0.30 mmol), and the appropriate ligand (0.024 g, 0.03 mmol) in aq. *tert*-butyl alcohol (3.0 cm^3 water and 2.0 cm^3 alcohol). [The 'α' ligand is $(DHQ)_2PHAL$, while the 'β' ligand is $(DHQD)_2PHAL$]. A solution of methyl (3*S*,α*R*)-(*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate **7** (0.101 g, 0.30 mmol) in *tert*-butyl alcohol (0.5 cm^3) was added, and the biphasic mixture was stirred at 20 °C overnight, during which time the colour darkened considerably. Sodium sulfite (0.75 g, 6.0 mmol) was added and, after being stirred for 30 min (whereupon the colour of the mixture, especially the organic phase, lightened), the reaction mixture was extracted with ethyl acetate (4 × 10 cm^3). The organic extracts were dried (magnesium sulfate), filtered, and concentrated *in vacuo*. After short-column chromatography on silica gel (diethyl ether), the product mixtures were examined by ^{1}H NMR spectroscopy. The 'α' ligand, in the mismatched-pair reaction, gave lactones **34** and **35** in the ratio 1:3, whereas the 'β' ligand, in the matched-pair reaction, gave the same lactones **34** and **35** in the ratio 9:2.

Preparation of (3*S*,4*R*,5*R*)-3-amino-4,5-dihydroxyhexanoic acid 37

A solution of (3*S*,4*R*,5*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-5-hydroxyhexano-4-lactone **34** (0.20 g, 0.59 mmol) in acetic acid (10 cm^3) was placed in a Fischer–Porter bottle under argon, and 10% palladium on charcoal (40 mg) was added. The suspension was stirred rapidly under hydrogen (7 atm) at 20 °C for 30 h, then filtered (Whatman No. 1 filter paper), and the solvent removed *in vacuo*. The residue was dissolved in saturated methanolic hydrogen chloride, and the solution once again concentrated *in vacuo*. The resulting white solid was dissolved in water and loaded onto an ion-exchange column (DOWEX 50X8-200; 20 g), which was eluted with aq. hydrochloric acid (1 M) followed by aq. ammonia (1 M). The basic fractions were combined, and concentrated *in vacuo*. The residue was recrystallised from aq. methanol to give *(3S,4R,5R)-3-amino-4,5-dihydroxyhexanoic acid* **37** as white needles (0.030 g, 31%), mp 206–208 °C (Found: C, 43.93; H, 8.15; N, 8.54. $C_6H_{13}NO_4$ requires C, 44.17; H, 8.03; N, 8.58%); $[\alpha]_D^{21}$ −28.6 (*c* 1.48 in H_2O); ν_{max}(KBr disk)/cm^{-1} 3600–2400 (v br, OH and NH), 1623 and 1584 (zwitterionic amino acid); *m*/*z* (DCI, NH_3) 164 (MH^+, 100%); δ_H(500 MHz; D_2O) 1.14 [3H, d, *J* 6.4, C(6)H_3], 2.43 [1H, dd, $J_{2A,2B}$ 16.9, $J_{2A,3}$ 8.0, C(2)H_A], 2.53 [1H, dd, $J_{2A,2B}$ 16.9, $J_{2B,3}$ 5.2, C(2)H_B], 3.46 [1H, dd, $J_{3,4}$ 5.7, $J_{4,5}$ 2.4, C(4)*H*], 3.54 [1H, app dt, *J* 8.0 and 5.4, C(3)*H*], 3.88 [1H, qd, $J_{5,6}$ 6.4, $J_{4,5}$ 2.4, C(5)*H*]; δ_C(50.3 MHz; D_2O) 18.4 [*C*(6)], 36.0 [*C*(2)], 51.7 [*C*(3)], 67.5 and 72.4 [*C*(4) and *C*(5)], 177.8 [*C*(1)].

Preparation of (3*S*,4*R*,5*R*)-3-[*N*-(*tert*-butoxycarbonyl)amino]-5-hydroxyhexano-4-lactone 38

10% Palladium hydroxide on charcoal (0.700 g) was suspended in ethyl acetate (2 cm^3) in a Fischer–Porter bottle under argon, and presaturated with hydrogen (6 atm). A solution of (3*S*,4*R*,5*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxyhexano-4-lactone **34** (0.700 g, 2.06 mmol) and di-*tert*-butyl dicarbonate (0.540 g, 2.47 mmol) in ethyl acetate (10 cm^3) was added, and the suspension was stirred rapidly under hydrogen (6 atm) at 20 °C for 18 h. The reaction mixture was filtered through Celite and the solvents removed *in vacuo*. The residue was purified by short-column chromatography on silica gel (ethyl acetate) to give *(3S,4R,5R)-3-[N-(tert-butoxycarbonyl)amino]-5-hydroxyhexano-4-lactone* **38** as a white solid (0.455 g, 90%). An analytical sample was prepared by recrystallisation from dichloromethane–petrol to give white needles, mp 159–162 °C (Found: C, 53.48; H, 7.83; N, 5.62. $C_{11}H_{19}NO_5$ requires C, 53.87; H, 7.81; N, 5.71%); $[\alpha]_D^{24}$ −52.5 (*c* 2.10 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 3467 and 3364 (s, NH), 1750 (s, lactone C=O), 1680 (s, carbamate C=O), 1524 (s, carbamate NH); *m*/*z* (CI, NH_3) 263 (MNH_4^+, 95%), 207 (100, $MNH_4^+ - C_4H_8$); δ_H(300 MHz; $CDCl_3$) 1.38 [3H, d, *J* 6.6, C(6)H_3], 1.45 [9H, s, OCMe_3], 1.82 [1H, br d, *J* 8, O*H*], 2.58 [1H, dd, $J_{2A,2B}$ 17.7, $J_{2B,3}$ 8.1, C(2)H_B], 2.81 [1H, dd, $J_{2A,2B}$ 17.7, $J_{2A,3}$ 9.3, C(2)H_A], 4.10 [1H, br app qn, *J* 7, C(5)*H*], 4.44 [1H, br d, *J* 7.1, C(4)*H*], 4.75 [1H, br app qn, *J* 8.5, C(3)*H*], 5.46 [1H, br d, *J* 7.6, N*H*]; δ_C(50.3 MHz; $CDCl_3$) 19.6 [*C*(6)], 28.3 [OCMe_3], 35.4 [*C*(2)], 48.3 [*C*(3)], 66.6 [*C*(5)], 80.2 [O*C*Me_3], 83.5 [*C*(4)], 155.4 [N*C*O], 175.5 [*C*(1)].

Preparation of (3*S*,4*S*,5*S*)-3-[*N*-(*tert*-butoxycarbonyl)amino]-5-hydroxyhexano-4-lactone 39

(3*S*,4*S*,5*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxyhexano-4-lactone **35** (0.500 g, 1.47 mmol) was hydrogenated over 10% palladium hydroxide on charcoal (0.500 g) in the presence of di-*tert*-butyl dicarbonate (0.385 g, 1.76 mmol) under the same conditions as for the diastereoisomer **34** above to give *(3S,4S,5S)-3-[N-(tert-butoxycarbonyl)amino]-5-hydroxyhexano-4-lactone* **39** as a white solid (0.320 g, 89%). An analytical sample was prepared by recrystallisation from

dichloromethane–petrol to give fine white needles, mp 111–113 °C (Found: C, 53.77; H, 8.11; N, 5.62. $C_{11}H_{19}NO_5$ requires C, 53.87; H, 7.81; N, 5.71%); $[\alpha]_D^{24}$ −0.7 (*c* 2.24 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 3479 and 3376 (s, NH), 1751 (s, lactone C=O), 1682 (s, carbamate C=O), 1526 (s, carbamate NH); *m/z* (CI, NH_3) 263 (MNH_4^+, 30%), 207 (100, $MNH_4^+ - C_4H_8$); δ_H(300 MHz; $CDCl_3$) 1.34 [3H, d, *J* 6.7, C(6)H_3], 1.45 [9H, s, OCMe_3], 2.07 [1H, br s, O*H*], 2.42 [1H, dd, $J_{2A,2B}$ 18.0, $J_{2B,3}$ 5.2, C(2)H_B], 3.03 [1H, dd, $J_{2A,2B}$ 18.0, $J_{2A,3}$ 8.7, C(2)H_A], 4.02 [1H, br m, C(5)*H*], 4.21 [1H, app t, *J* 3.5, C(4)*H*], 4.35 [1H, br m, C(3)*H*], 4.80 [1H, br app s, N*H*]; δ_C(50.3 MHz; $CDCl_3$) 19.1 [*C*(6)], 28.3 [OCMe_3], 35.3 [*C*(2)], 49.2 [*C*(3)], 67.6 [*C*(5)], 80.5 [O*C*Me$_3$], 89.1 [*C*(4)], 155.2 [N*C*O], 175.6 [*C*(1)].

Preparation of (4*R*,4a*R*,7a*S*)-1-(*tert*-butoxycarbonyl)-2,2,4-trimethyl-1,2,4,4a,7,7a-hexahydrofuro[3,2-*d*][1,3]oxazin-6-one 42

(3*S*,4*R*,5*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-5-hydroxyhexano-4-lactone **38** (0.200 g, 0.815 mmol) was dissolved in acetone–2,2-dimethoxypropane (1:1; 10 cm^3). (+)-Camphor-10-sulfonic acid (0.015 g) was added, and the mixture was heated at reflux for 16 h. Triethylamine (0.1 cm^3) was added, and the solvents were removed *in vacuo*. The residue was subjected to column chromatography on silica gel [petrol–diethyl ether (3:2)].

The less polar fraction gave *methyl (3S,4R,5R)-3-[N-(tert-butoxycarbonyl)amino]-4,5-(isopropylidenedioxy)hexanoate* as a white solid [0.035 g, 13% (17% based on consumed starting material)], mp 103–109 °C (Found: C, 56.73; H, 8.36; N, 4.20. $C_{15}H_{27}NO_6$ requires C, 56.77; H, 8.57; N, 4.41%); $[\alpha]_D^{26}$ −11.0 (*c* 0.98 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 3420 and 3335 (s, NH), 1741 (s, ester C=O), 1687 (s, carbamate C=O), 1533 (s, carbamate NH); *m/z* (CI, NH_3) 318 (MH^+, 20%), 262 (30, $MH^+ - C_4H_8$), 218 (100, $MH^+ - C_4H_8 - CO_2$); δ_H(300 MHz; $CDCl_3$) 1.31 [3H, d, *J* 6.0, C(6)H_3], 1.38 [6H, s, NCMe_2O], 1.43 [9H, s, OCMe_3], 2.60 [2H, d, *J* 6.9, C(2)H_2], 3.59 [1H, app d, *J* 8.3, C(4)*H*], 3.68 [3H, s, O*Me*], 3.85 [1H, dq, $J_{4,5}$ 8.3, $J_{5,6}$ 6.0, C(5)*H*], 4.13 [1H, br app q, *J* 7, C(3)*H*], 4.97 [1H, br d, *J* 9.6, N*H*]; δ_C(50.3 MHz; $CDCl_3$) 17.1 [*C*(6)], 26.7 and 27.2 [OCMe_2O], 28.2 [OCMe_3], 38.4 [*C*(2)], 45.9 [*C*(3)], 51.7 [O*Me*], 73.3 [*C*(5)], 79.7 [O*C*Me$_3$], 83.4 [*C*(4)], 108.6 [O*C*Me$_2$O], 155.7 [N*C*O], 171.7 [*C*(1)].

The more polar fraction gave *(4R,4aR,7aS)-1-(tert-butoxycarbonyl)-2,2,4-trimethyl-1,2,4,4a,7,7a-hexahydrofuro[3,2-d]-[1,3]oxazin-6-one* **42** as a white solid [0.140 g, 60% (75% based on consumed starting material)]. An analytical sample was prepared by recrystallisation from diethyl ether–petrol to give white needles, mp 103–109 °C (Found: C, 58.67; H, 8.13; N, 4.87. $C_{14}H_{23}NO_5$ requires C, 58.93; H, 8.12; N, 4.87%); $[\alpha]_D^{21}$ +17.2 (*c* 1.27 in $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 1756 (s, lactone C=O), 1689 (s, carbamate C=O); *m/z* (electrospray) 286 (MH^+); δ_H(300 MHz; $CDCl_3$) 1.27 [3H, d, *J* 6.6, C(4)*CH*$_3$], 1.47 [9H, s, OCMe_3], 1.59 [3H, s, C(2)*Me*Me], 1.70 [3H, s, C(2)Me*Me*], 2.69 [1H, dd, $J_{7A,7B}$ 18.4, $J_{7B,7a}$ 7.4, C(7)H_B], 2.85 [1H, dd, $J_{7A,7B}$ 18.4, $J_{7A,7a}$ 10.2, C(7)H_A], 4.02 [1H, qd, $J_{4,Me}$ 6.6, $J_{4,4a}$ 2.9, C(4)*H*], 4.64 [1H, dd, $J_{4a,7a}$ 9.6, $J_{4,4a}$ 2.9, C(4a)*H*], 5.18 [1H, app td, *J* 9.8 and 7.4, C(7a)*H*]; δ_C(50.3 MHz; $CDCl_3$) 15.7 [*C*(6)], 26.1 [NCMe_AO], 28.3 [OCMe_3], 28.7 [NCMe_BO], 34.2 [*C*(2)], 49.2 [*C*(3)], 65.7 [*C*(5)], 78.9 [*C*(4)], 81.3 and 89.4 [O*C*Me$_3$ and N*C*Me$_2$O], 153.8 [N*C*O], 174.9 [*C*(1)].

Finally, elution of the column with diethyl ether gave some unchanged starting material (0.040 g, 20% recovery).

Use of dimethoxypropene (10 equiv.) and pyridinium toluene-*p*-sulfonate (catalytic) in refluxing toluene for 2 h gave complete conversion to the acetonide **42**, with no starting material **38** or by-product detectable by ^{1}H NMR.

The corresponding isopropylidene aminal of the (3*S*,4*S*,5*S*)-isomer **39** could not be formed under either of these conditions.

Preparation of methyl 3-*epi*-D-daunosaminide hydrochloride 43

(3*S*,4*R*,5*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-5-hydroxyhexano-4-lactone **38** (0.150 g, 0.612 mmol) was dissolved in anhydrous dichloromethane (10 cm^3) and the solution was stirred at −78 °C under nitrogen. DIBAL (1.0 M solution in dichloromethane; 2.14 cm^3, 2.14 mmol) was added by syringe over 2 min, and the solution was stirred for 30 min, before being quenched by the dropwise addition of methanol (1.0 cm^3). After warming of the mixture to 20 °C, saturated aq. Rochelle's salt (6 cm^3) was added, and the mixture was stirred for 1 h before being filtered through Celite, dried (magnesium sulfate), and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with diethyl ether, to give a mixture of lactols, which was not characterised, but was immediately treated with methanolic hydrogen chloride (*vide infra*).

Elution of the column with a more polar solvent mixture (diethyl ether–methanol 20:1) gave the over-reduction product *(3S,4R,5R)-3-[N-(tert-butoxycarbonyl)amino]hexane-1,4,5-triol* **40** as a clear, colourless, glassy oil (0.021 g, 14%) (Found: C, 52.77; H, 9.47; N, 5.29. $C_{11}H_{23}NO_5$ requires C, 53.00; H, 9.30; N, 5.62%); $[\alpha]_D^{21}$ −6.6 (*c* 2.44 in $CHCl_3$); ν_{max}($CHCl_3$ solution)/cm^{-1} 3622 (m, OH), 3439 (s, NH), 1688 (s, carbamate C=O), 1520 (s, carbamate NH); *m/z* (CI, NH_3) 250 (MH^+, 50%), 194 (70, $MH^+ - C_4H_8$), 150 (100, $MH^+ - C_4H_8 - CO_2$); δ_H(250 MHz; $C_5D_5CD_3$; 70 °C) 1.01 [3H, d, *J* 6.2, C(6)H_3], 1.37 [9H, s, OCMe_3], 1.50–1.68 [2H, m, C(2)H_2], 3.02 [1H, br d, *J* 6.7, C(4)*H*], 3.42–3.53 and 3.79–3.88 [3H and 1H, m, C(1)H_2, C(3)*H* and C(5)*H*], 4.90 [1H, br app s, N*H*]; δ_C(50.3 MHz; $CDCl_3$) 19.2 [*C*(6)], 28.3 [OCMe_3], 36.1 [*C*(2)], 47.9 [*C*(3)], 58.4 [*C*(1)], 68.5 [*C*(5)], 77.9 [*C*(4)], 80.0 [O*C*Me$_3$], 157.1 [N*C*O].

Use of THF instead of dichloromethane as the solvent led to lower yields of the lactols, together with larger quantities of the over-reduced triol **40**, and some recovered starting material **38**.

The mixture of lactols was dissolved in anhydrous methanol (20 cm^3), and a saturated solution of hydrogen chloride in anhydrous methanol (2.0 cm^3) was added. After being stirred for 48 h, the solution was concentrated *in vacuo*. Column chromatography on silica gel (methanol–ethyl acetate 3:7) gave methyl 3-*epi*-D-daunosaminide hydrochloride **43** as a clear, colourless, viscous oil (0.045 g, 37% from the lactone), and as a mixture of anomers [α:β 5:1 (by ^{1}H NMR spectroscopy)]. This oil was highly hygroscopic, and darkened rapidly on exposure to air. Thus it was not characterised, but the major anomer of the free base was isolated for comparison purposes. Hence the hydrochloride was dissolved in water (0.5 cm^3) and passed through an ion-exchange column (Amberlite IRA-400, Na-form; 1 g), eluting with water. The solution was concentrated *in vacuo* to give the methyl 3-*epi*-D-daunosaminide as a clear, yellow, viscous oil (0.035 g, 36% from the lactone), which was twice subjected to column chromatography on silica gel [first column acetone; second column dichloromethane–methanol (10:1)], allowing isolation of a sample of pure methyl 3-*epi*-α-D-daunosaminide as a clear, colourless, viscous oil, $[\alpha]_D^{21}$ +126 (*c* 0.61 in $CHCl_3$) {lit.,[35] $[\alpha]_D^{20}$ −132 (*c* 2.4 in $CHCl_3$) for enantiomer}; δ_H(500 MHz; $CHCl_3$) 1.26 [3H, d, *J* 6.7, C(6)H_3], 1.65 [1H, d, $J_{2A,2B}$ 14.6, C(2)H_B], 1.78 [3H, br s, N*H* and O*H*], 2.12 [1H, app dt, *J* 14.6 and 4.5, C(2)H_A], 3.10 [1H, app br s, C(3)*H*], 3.33 [1H, d, $J_{3,4}$ 3.3, C(4)*H*], 3.36 [3H, s, O*Me*], 4.22 [1H, q, $J_{5,6}$ 6.7, C(5)*H*], 4.74 [1H, d, $J_{1,2A}$ 3.9, C(1)*H*]. Selected peaks for methyl 3-*epi*-β-D-daunosaminide[34b] (from the ^{1}H NMR spectrum of the anomeric mixture): δ_H(300 MHz; $CHCl_3$) 1.28 [3H, d, *J* 6.7, C(6)H_3], 1.54–1.60 [1H, obscured m, C(2)H_e], 1.86 [1H, ddd, $J_{2a,2e}$ 13.7, $J_{1,2a}$ 8.7, $J_{2a,3}$ 4.4, C(2)H_a], 3.16–3.19 [1H, m, C(3)*H* or C(4)*H*], 3.46 [3H, s, O*Me*], 4.10 [1H, dq, $J_{5,6}$ 6.7, $J_{4,5}$ 1.4, C(5)*H*], 4.70 [1H, dd, $J_{1,2a}$ 8.7, $J_{1,2e}$ 2.6, C(1)*H*].

Alternatively, a solution of compound **42** (0.069 g, 0.24 mmol) in anhydrous dichloromethane (5 cm^3) under nitrogen at −78 °C was treated with DIBAL (1.0 M solution in hexane;

0.36 cm³, 0.36 mmol) for 2 h. Methanol (0.1 cm³) was added dropwise, and the solution was warmed to 20 °C. Saturated aq. Rochelles's salt (1 cm³) was added, and the mixture was stirred for 30 min before being filtered through Celite, dried (magnesium sulfate), and concentrated *in vacuo*. The crude product contained starting material, a mixture of the desired lactols, and a third compound, assumed to be the compound arising from over-reduction. The mixture of lactols was isolated by column chromatography on silica gel [dichloromethane–diethyl ether (5:1)], and immediately dissolved in anhydrous methanol (5 cm³). A saturated solution of hydrogen chloride in anhydrous methanol (1.0 cm³) was added, and the solution was stirred for 48 h before being concentrated *in vacuo*. This gave the same mixture of anomers of methyl 3-*epi*-D-daunosaminide hydrochloride **43** as above (0.015 g, 31%).

Preparation of methyl α-L-daunosaminide hydrochloride 44

(3*S*,4*S*,5*S*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-5-hydroxyhexano-4-lactone **39** (0.150 g, 0.612 mmol) was reduced with DIBAL in dichloromethane under the same conditions as for the (3*S*,4*R*,5*R*)-diastereomer **38** above. The residue was purified by column chromatography on silica gel, eluting with diethyl ether, to give a mixture of lactols, which was not characterised, but was immediately treated with methanolic hydrogen chloride (*vide infra*).

Elution of the column with a more polar solvent mixture (diethyl ether–methanol 20:1) gave the over-reduction product *(3S,4S,5S)-3-[N-(tert-butoxycarbonyl)amino]hexane-1,4,5-triol* **41** as an off-white solid (0.030 g, 20%), mp 98–100 °C (Found: C, 53.11; H, 9.21; N, 5.92. $C_{11}H_{23}NO_5$ requires C, 53.00; H, 9.30; N, 5.62%); $[a]_D^{21}$ −4.6 (*c* 1.15 in $CHCl_3$); ν_{max}-($CHCl_3$ solution)/cm^{-1} 3620 (m, OH), 3439 (m, NH), 1686 (s, carbamate C=O), 1520 (s, carbamate NH); *m/z* (CI, NH_3) 250 (MH^+, 10%), 194 (50, $MH^+ - C_4H_8$), 150 (60, $MH^+ - C_4H_8 - CO_2$); δ_H(250 MHz; $C_5D_5CD_3$; 70 °C) 1.10 [3H, d, *J* 6.4, C(6)H_3], 1.37 [9H, s, OCMe_3], 1.63–1.77 [2H, m, C(2)H_2], 3.00 [1H, dd, *J* 6.7 and 3.0, C(4)*H*], 3.43–3.57 and 3.64–3.78 [2H and 2H, m, C(1)H_2, C(3)*H* and C(5)*H*], 5.09 [1H, br d, *J* 7.3, N*H*]; δ_C(50.3 MHz; $CDCl_3$) 19.1 [*C*(6)], 28.2 [OCMe_3], 32.8 [*C*(2)], 49.8 [*C*(3)], 58.7 [*C*(1)], 66.9 [*C*(5)], 76.9 [*C*(4)], 80.3 [O*C*Me$_3$], 157.7 [N*C*O].

The mixture of lactols was treated with methanolic hydrogen chloride as before. Column chromatography of the residue on silica gel (methanol–ethyl acetate 3:7) gave methyl α-L-daunosaminide hydrochloride **44** as a white solid (0.044 g, 36% from the lactone), mp 179–181 °C (decomp.) [lit.,[2g] mp 188–190 °C (decomp.)]; $[a]_D^{23}$ −123 (*c* 0.97 in MeOH) {lit.,[2g] $[a]_D$ −140 (*c* 1 in MeOH)}. Further purification was achieved by recrystallisation from methanol–diethyl ether to give material (11 mg), mp 184 °C (decomp.); $[a]_D^{23}$ −146 (*c* 0.64 in MeOH); δ_H(500 MHz; d_5-pyridine) 1.37 [3H, d, *J* 6.5, C(6)H_3], 2.38 [1H, dd, $J_{2A,2B}$ 12.5, $J_{2B,3}$ 4.6, C(2)H_B], 2.47 [1H, app td, *J* 12.5 and 3.5, C(2)H_A], 3.26 [3H, s, O*Me*], 3.92 [1H, q, $J_{5,6}$ 6.5, C(5)*H*], 4.22 [1H, ddd, $J_{2A,3}$ 12.5, $J_{2B,3}$ 4.6, $J_{3,4}$ 2.9, C(3)*H*], 4.47 [1H, d, $J_{3,4}$ 2.9, C(4)*H*], 4.85 [1H, d, $J_{1,2A}$ 3.5, C(1)*H*], 5.0 [4H, br s, N*H* and O*H*]. This material was identical by mixed ^{1}H NMR with authentic methyl α-L-daunosaminide hydrochloride, prepared from methyl β-L-daunosaminide hydrochloride (purchased from Sigma Chemical Company) by treatment with methanolic hydrogen chloride, followed by two recrystallisations from methanol–diethyl ether.

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Paper 9/07017F