Reduction of 4-Oxo α-Amino Acids as a Route to 4-Hydroxylated α-Amino Acids. Concise Approaches to the Synthesis of Clavalanine, *erythro*-4-Hydroxyornithine and (+)-Bulgecinine

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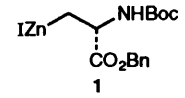
The stereochemical course of reduction of derivatives of 4-oxo α-amino acids **3** to give *cis*- and *trans*-γ-substituted α-aminobutano-4-lactones **9** and **10** using a range of hydride reducing agents is reported. Although reduction with sodium boranuide (sodium borohydride) in protic solvents proceeds with low stereoselectivity, use of triethylsilane–boron trifluoride–diethyl ether gives good selectivity in favour of the *cis*-isomer, provided that the 4-substituent is phenyl. Moderate to excellent stereoselectivity in favour of the *trans*-isomer may be obtained by using L-Selectride® in tetrahydrofuran. The presence of an additional stereogenic centre at C-5 completely overwhelms the effect of the α-centre. Applications of this method in approaches to the synthesis of clavalanine, *erythro*-4-hydroxyornithine and (+)-bulgecinine are described.

We have recently demonstrated that 4-oxo α-amino acid derivatives **3** can be prepared in enantiomerically pure form by the palladium-catalysed coupling of the serine-derived organozinc reagent **1** with acid chlorides.[1] Transmetallation of the zinc reagent **1** to the zinc/copper reagent **2** is possible, and permits reaction with a range of other electrophiles.[2] So far, however, we have not achieved a direct reaction of either the organozinc reagent **1** or the zinc/copper reagent **2** with aldehydes, which would allow direct access to 4-hydroxy α-amino acids. This appears to be due to the relatively low reactivity of both these reagents. In this paper, we describe the use of 4-oxo α-amino acid derivatives **3** as precursors to a range of naturally occurring 4-hydroxy α-amino acids **4**, which effectively circumvents this restriction.[3]



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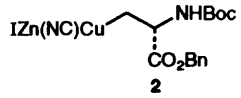

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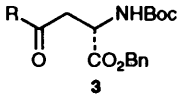

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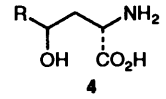
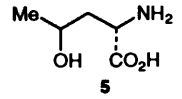


4

4-Hydroxylated α-amino acids **4** are relatively common in nature. For example, both diastereoisomers of 4-hydroxynorvaline **5** have been isolated from natural sources,[4] as have the related γ-lactones.[5] 4-Hydroxyornithine **6** is a component of marine organisms[6] and plants,[7] as well as a constituent of biphenomycin cyclic peptide antibiotics.[8] 4-Hydroxylated proline derivatives, exemplified by (−)-bulgecinine **7**,[9] a constituent of the bulgecin glycopeptides, are also widely distributed. In addition, access to 4,5-dihydroxynorvaline **8** is of interest, since a derivative of this compound is a key intermediate in the synthesis[10] of the unusual β-lactam antibiotic clavalanine.[11]

Previous stereoselective routes to 4-hydroxylated α-amino acids, or the corresponding lactones, have principally relied on the use of transformations of carbohydrate building blocks.[10,12,13] The reaction of a chiral glycine anion equivalent with oxiranes has been used for the preparation of simple 4-hydroxylated α-amino acids.[14] Several 4-hydroxylated α-amino acids have been prepared by homogeneous asymmetric hydrogenation of enantiomerically pure 4-hydroxylated dehydroamino acid derivatives,[15] although the additional stereogenic centre can sometimes interfere with the normally high enantioselectivity of such hydrogenations.[16] 4-Hydroxyglutamic acid has been prepared by hydroxylation of an enolate derived from protected glutamic acid.[17] Under some circumstances, indirect 4-hydroxylation of α-amino acids is possible using radical methods.[18] Stereoselective halogenolactonization of allylglycine derivatives has also been used as a route to 4-hydroxylated α-amino acids.[19] Finally, the enzymic resolution of γ-substituted α-aminobutano-4-lactones has been reported.[20]



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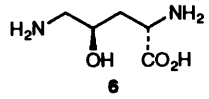

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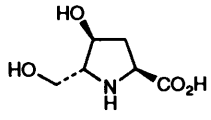
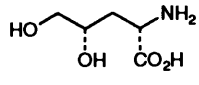
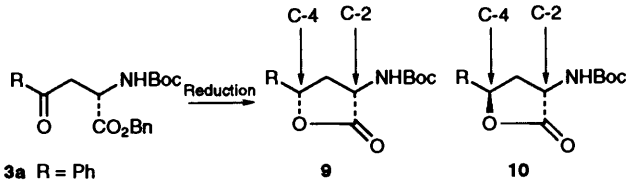


7 (–)-Bulgecinine



8

Our ready access to a wide range of 4-oxo α-amino acid derivatives **3** has allowed us to investigate the diastereoselectivity of the reduction of these compounds as a stereoselective route for the preparation of a wide range of 4-hydroxylated α-amino acids. It was our major concern to establish the effect of the existing stereogenic centre on the diastereoselectivity of such reductions. Upon reduction of 4-oxo α-amino acid derivatives **3**, fast cyclization to the corresponding γ-substituted α-aminobutano-4-lactones **9** and **10** is generally observed. The ^{1}H NMR spectra of the *cis* **9** and *trans* **10** isomers are clearly distinguishable.[21] In the *cis*-isomer, the signals due



3a R = Ph
3b R = $AcOCH_2$
3c R = $FmocHNCH_2$
9 **10**

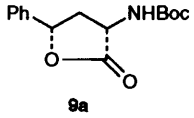
Table 1 Reduction of keto ester **3a**

Reagent	**9a** *cis*-Isomer	**10a** *trans*-Isomer	Yield (%)
$NaBH_4$, MeOH	1	1	62
$NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH	1[a]	1[a]	77
$NaBH_4$, diglyme	2	1	52
$Zn(BH_4)_2$, Et_2O	1	1	70
L-Selectride®, THF	1	2	77

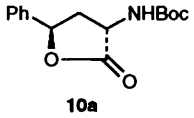
[a] Isolated as the open-chain benzyl esters **11a** and **12a**; configuration assigned by lactonization using toluene-*p*-sulfonic acid in MeOH.

to each of the protons of the methylene group at C-3 are widely separated, whilst in the *trans* isomer the corresponding protons have very similar chemical shifts. This observation has been rationalized by proposing that there is a single stable conformation for the *cis* lactone, in which the two substituents at C-2 and C-4 are *pseudo*-equatorial, while the *trans* lactone is conformationally mobile, giving rise to signals of very similar chemical shift for each of the C-3 protons.[22] This observation allows the assignment of configuration of the products of reduction of 4-oxo α-amino acids in a reliable and straightforward manner.[19,23]

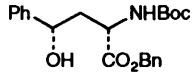
In the first instance, we investigated the stereoselectivity of reduction of the 4-oxo-4-phenyl amino acid derivative **3a**, using a variety of reducing agents to give the lactones **9a** and **10a**.[24] Our results are summarized in Table 1. In general, the stereoselectivity of the reduction process is low. The main point of note is that reduction under Luche conditions[25] prevents lactonization, presumably by buffering the reaction medium, thereby giving a mixture of the 4-hydroxy esters **11a** and **12a**.



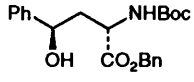
9a



10a

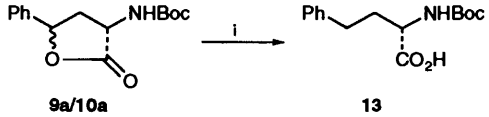


11a



12a

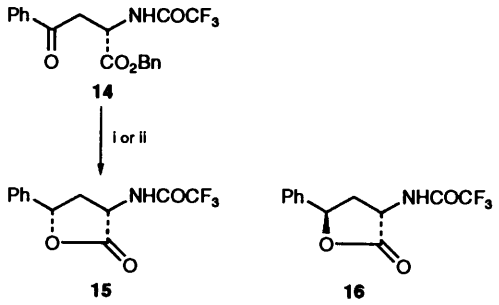
In order to establish that no loss of stereochemical integrity at C-2 had occurred during these reduction processes, a sample of the lactone (as a diastereoisomeric mixture) was subjected to catalytic hydrogenation to give Boc-homophenylalanine **13** (90%), which was optically pure by comparison of optical



9a/10a **13**

rotation data with those in the literature,[26] and with a sample prepared by direct hydrogenolysis of compound **3a**.[1]

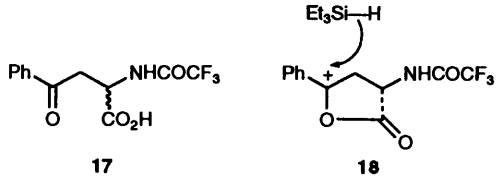
In view of the poor stereocontrol in these reduction reactions, we sought to explore the role of the protecting group on nitrogen, and to this end prepared the trifluoroacetyl derivative **14** by treatment of compound **3a** with trifluoroacetic acid (TFA) followed by trifluoroacetic anhydride (TFAA) in pyridine. Reduction using sodium boranuide in methanol again gave a mixture of *cis* **15** and *trans* **16** isomers (ratio *cis* to *trans*, 7:3, 79%) indicating that the protecting group does play a role in the stereoselectivity of the reduction. However, we finally established that reduction of keto ester **14** using triethylsilane–boron trifluoride–diethyl ether gave a much higher selectivity in



Scheme 1 *Reagents and conditions:* i, $NaBH_4$, MeOH, room temp., 15 min; ii, $BF_3 \cdot Et_2O$, Et_3SiH, room temp., 48 h

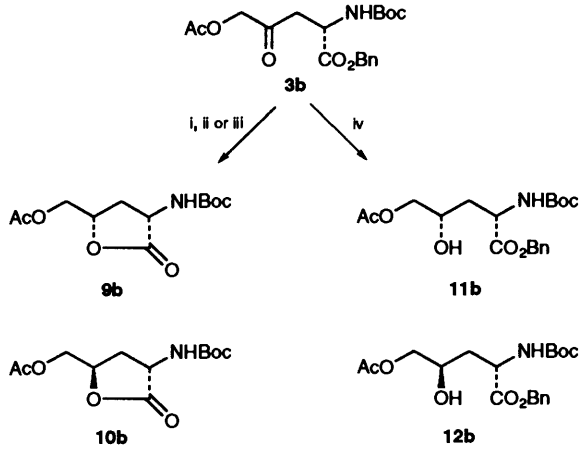
favour of the *cis*-lactone, and in excellent yield (ratio *cis* to *trans*, 9:1, 99%).

This latter result is closely related to Nordlander's observation of the formation of the same (racemic) lactone on reduction of the free carboxylic acid **17**, although no explicit comment was made about the relative configuration of the product.[27] We believe that the stereochemical outcome of this reaction is best rationalized by hydride delivery to the less hindered face of a benzylic cation such as **18**. Unfortunately,



it is self-evident that reduction using triethylsilane–boron-trifluoride–diethyl ether is only suitable for aromatic substrates without acid-sensitive functionality.

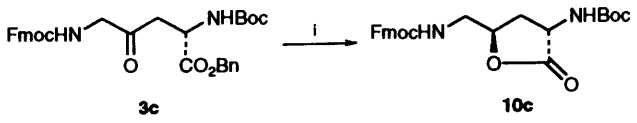
We then considered the reduction of the 5-acetoxy-4-oxo-norvaline derivative **3b** as a route to a protected 4,5-dihydroxynorvaline **11b**,[13b] an analogue of an intermediate in Weigele's synthesis of clavalanine.[10] Reduction of keto ester **3b** with sodium boranuide in bis-(2-methoxyethyl) ether (diglyme) gave a 1:1 mixture of the *cis* **9b** and *trans* **10b** lactones (60%). Use of L-Selectride® in THF at −78 °C gave a preponderance of the *trans* lactone (ratio of *cis* to *trans*, 1:4, 66%), whilst use of zinc boranuide in diethyl ether at −10 °C allowed isolation and separation of both the desired unlactonized 4,5-dihydroxynorvaline **11b** and its C-4 epimer **12b**. We believe that the lower



Scheme 2 *Reagents and conditions:* i, $NaBH_4$, MeOH, room temp., 15 min; ii, $NaBH_4$, diglyme, room temp., 15 min; iii, L-Selectride®, THF, −78 °C, 3 h; iv, $Zn(BH_4)_2$, Et_2O, −10 °C, 40 min

temperature used for this reduction compared with that used for the reduction of the 4-phenyl derivative **3a** suppresses lactonization. Since opening of the lactone is required in Weigele's synthesis of clavalanine, [10] this result provides access to an analogue of an even later intermediate in this synthesis.

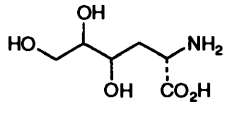
In the context of a proposed synthesis of biphenomycin B, we required a synthesis of *erythro*-4-hydroxyornithine **6**.[15] This stereoisomer requires the reduction of a 5-amino-4-oxo α-amino acid derivative to give a *trans* lactone, and in view of the moderate stereoselectivity in the desired sense which we had observed with reduction of 5-acetoxy-4-oxonorvaline derivative **3b** using L-Selectride in THF at −78 °C, we explored these conditions for reduction of the fluorenylmethoxycarbonyl derivative **3c**. The ^{1}H NMR spectrum of the unpurified product showed that only the *trans* lactone **10c** had been formed, and this compound was isolated in good yield (85%).



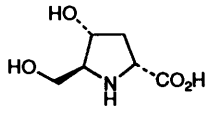
3c **10c**

Scheme 3 *Reagents and conditions:* i, L-Selectride®, THF, −78 °C, 3 h

Finally, we have explored the reduction of 4-oxo α-amino acid derivatives which have an additional stereogenic centre at C-5, in the context of an approach to the stereoselective synthesis of 4,5,6-trihydroxynorleucines **19**[28] and (+)-bulgecinine **20**,[29] the enantiomer of the naturally occurring component of the bulgecin glycopeptide antibiotics.



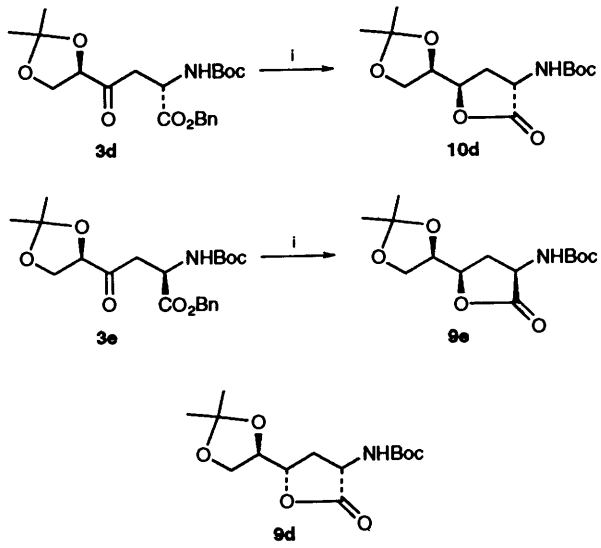
19



20 (+)-Bulgecinine

The desired diastereoisomeric 4-oxo α-amino acid derivatives were prepared as follows. (*R*)-Isopropylideneglyceroyl chloride, prepared from (*R*)-isopropylideneglyceric acid calcium salt, was coupled with the L-serine-derived zinc reagent **1** under palladium catalysis to give protected 5,6-dihydroxy-4-oxonorleucine derivative **3d** (51%). Reaction of the D-serine-derived zinc reagent under the same conditions gave the 5,6-dihydroxy-4-oxonorleucine derivative **3e** (45%), without any detectable contamination by the diastereoisomeric compound **3d**, as determined by ^{1}H NMR spectroscopy. This confirmed that no loss of stereochemical integrity had occurred either at the α-centre, consistent with our previous observations,[1] or at the stereogenic centre of the isopropylideneglyceroyl moiety. In order to complete the synthesis of the 4,5,6-trihydroxynorleucines **19**, we investigated the reduction of the ketones **3d** and **3e**. Reduction of ketone **3d** with sodium boranuide in methanol gave a mixture of *cis* **9d** and *trans* **10d** lactones (ratio *cis* to *trans* 1:3, 69%). Since we had already established that L-Selectride® gave enhanced selectivity for the *trans* lactone, we were not surprised that reduction of the ketone **3d** with L-Selectride® gave the *trans* lactone **10d** (69%), with no trace of the *cis* lactone **9d**. However, analogous reduction of the ketone **3e** with L-Selectride® gave the *cis* lactone **9e** (67%), with no detectable amount of the corresponding *trans* lactone.

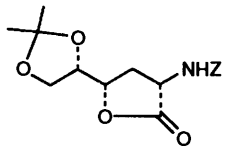
Other reducing agents which we investigated (sodium boranuide in methanol; tetrabutylammonium boranuide in dichloromethane) also gave a preponderance of the *cis* lactone **9e**. Our overall conclusion is that the steric course of the reduction is controlled by the stereogenic centre at C-5, which is known to exert a powerful effect in simpler systems to give



Scheme 4 *Reagents and conditions:* i, L-Selectride®, THF, −78 °C, 3 h

products of *syn*-relative configuration.[30] The stereochemical assignments for the lactones **9e** and **10d** were based on analysis of their ^{1}H NMR spectra as previously described. Thus for the *cis* lactone **9e**, the signals corresponding to the C-3 protons are at δ 2.03 and 2.75, whereas in the *trans* lactone **10d** the analogous signals are at δ 2.41 and 2.71.

Corroboration of the stereochemical assignment for the lactone **9e** was provided by comparison of its ^{1}H NMR spectrum with that of the corresponding enantiomeric Z-protected lactone **21**, provided by Dr. G. W. J. Fleet. The spectra were identical, apart from those signals attributable to the protecting group.



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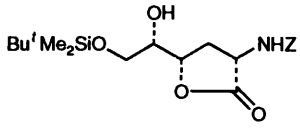
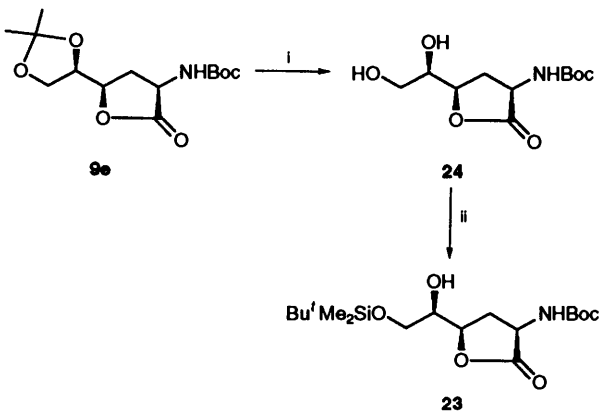


22

Conversion of lactone **9e** into lactone **23**, the enantiomer of the Boc-protected analogue of a late intermediate **22** in Fleet's synthesis of (−)-bulgecinine, was carried out using a two-stage deprotection/reprotection sequence. Removal of the isopropylidene acetal to give the diol **24** was achieved in good yield (71%) using iodine in methanol,[31] and selective protection of the primary hydroxy group was carried out under standard conditions to give the silyl ether **23** (52%). This sequence illustrates the effectiveness of our approach to the stereoselective synthesis of 4,5,6-trihydroxynorleucines, which is applicable to the preparation of the enantiomeric series simply by suitable choice of starting materials.

Our overall conclusion is that only moderate stereochemical control is exerted by the α-centre in the reduction of 4-oxo α-amino acids, although useful levels of stereoselectivity in favour of *trans* lactones can usually be obtained [especially by the use of L-Selectride® in tetrahydrofuran (THF)]. Other asymmetric centres in the substrate can control completely the stereochemical sense of any reduction. In this context a very recent report has described the highly stereoselective preparation of a *trans*-γ-substituted α-aminobutano-4-lactone using high-pressure hydrogenation in the presence of an [(*R*)-2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl]ruthenium(II) complex.[32] However, apart from the case of the 4-phenyl system **15**, effective



Scheme 5 *Reagents and conditions:* i, I_2 in MeOH (1%), room temp., 48 h; ii, TBDMSCl, NEt_3, DMAP, CH_2Cl_2–DMF

methods for the selective preparation of the corresponding *cis*-lactones are still required.

Experimental

For general experimental procedures see ref. 1. All NMR spectra were recorded in $CDCl_3$ as solvent. *J* Values are given in Hz. Specific optical rotations are given in units of 10^{-1} deg cm^2 g^{-1}. Light petroleum refers to that fraction with boiling range 40–60 °C. L-Selectride® was obtained from Aldrich as a 1 mol dm^{-3} solution in THF. Compounds **3a–c** were obtained by the method already described in ref. 1.

Reduction of Benzyl (S)-3-*Benzoyl*-2-[(tert-*butoxycarbonyl*)-*amino*]*propanoate* **3a** *with Sodium Boroanuide.*—Benzyl (*S*)-3-benzoyl-2-[(*tert*-butoxycarbonyl)amino]propanoate **3a** (0.192 g, 0.50 mmol) was dissolved in methanol (4 cm^3) and solid sodium boranuide (0.019 g, 0.52 mmol) was added in four portions. The resulting solution was stirred at room temp. for 1 h, after which TLC analysis (30% ethyl acetate–light petroleum) showed no starting material remained. The mixture was concentrated under reduced pressure then was partitioned between diethyl ether (10 cm^3) and aq. hydrochloric acid (2 cm^3; 1 mol dm^{-3}). The aqueous phase was further extracted with diethyl ether (2 × 10 cm^3). The combined organic extracts were then washed with distilled water and dried (Na_2SO_4). Removal of solvent gave a pale yellow solid (0.165 g). Flash chromatography over silica gel (light petroleum–ethyl acetate, 9:1) gave: a high running component, (2S,4R)-2-[(tert-*butoxycarbonyl*)*amino*]-4-*phenylbutano*-4-*lactone* **10a** (0.045 g, 32%), m.p. 154–155 °C (from Et_2O) (Found: C, 64.8; H, 6.6; N, 4.9. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.9; N, 5.05%); $[\alpha]_D$ −31.5 (*c* 0.2, CH_2Cl_2); ν_{max}(film)/cm^{-1} 3422, 1789 and 1697; δ_H(300 MHz) 1.45 (9 H, s), 2.68 (1 H, m, 3-H), 2.82 (1 H, m, 3-H), 4.37 (1 H, m, 2-H), 5.07 (1 H, br, NH), 5.71 (1 H, d, *J* 8, 4-H), 7.33 (2 H, m) and 7.41 (3 H, m); *m*/*z* (FAB) 278 (15%, MH$^+$), 222 [100, MH$^+$ −$(CH_3)_2C{=}CH_2$] and 161 (52); and a low running component, (2S, 4S)-2′-[(tert-*butoxycarbonyl*)-*amino*]-4-*phenylbutano*-4-*lactone* **9a** (0.041 g, 30%), m.p. 158–160 °C (Found: MH$^+$, 278.1384. $C_{15}H_{20}NO_4$ requires *m*/*z* 278.1392); $[\alpha]_D$ +23.0 (*c* 0.3, CH_2Cl_2); ν_{max}(film)/cm^{-1} 3360, 1778 and 1682; δ_H(300 MHz) 1.46 (9 H, s), 2.15 (1 H, m, 3-H), 3.12 (1 H, m, 3-H), 4.58 (1 H, m, 2-H), 5.30 (1 H, br, NH), 5.40 (1 H, dd, *J* 11.2 and 5.2, 4-H) and 7.38 (5 H, m); *m*/*z* (FAB) 278 (12%, MH$^+$), 222 [100, MH$^+$ − $(CH_3)_2C{=}CH_2$] and 161 (58).

Reduction of Benzyl (S)-3-*Benzoyl*-2-[(tert-*butoxycarbonyl*)-*amino*]*propanoate* **3a** *with Sodium Boranuide and Cerium*(III) *Chloride Heptahydrate.*—Benzyl (*S*)-3-benzyl-2-[(*tert*-butoxycarbonyl)amino]propanoate **3a** (0.053 g, 0.16 mmol) and cerium(III) chloride heptahydrate (0.060 g, 0.16 mmol) were dissolved in ethanol (2 cm^3) and the solution was cooled to −10 °C. Solid sodium boranuide (0.006 g, 0.16 mmol) was added, and the resulting solution was stirred at −10 °C for 3 h, after which TLC analysis showed no starting material remained. The mixture was concentrated under reduced pressure then was partitioned between diethyl ether (5 cm^3) and aq. hydrochloric acid (2 cm^3; 1 mol dm^{-3}). The aqueous phase was further extracted with diethyl ether (2 × 5 cm^3). The combined organic extracts were then washed with distilled water and dried (Na_2SO_4). Removal of solvent on a rotary evaporator gave a pale yellow solid (0.052 g). Flash chromatography over silica gel (light petroleum–ethyl acetate gradient 9:1 to 4:1) gave: a high running component *benzyl* (2S,4S)-2-[(tert-*butoxycarbonyl*)*amino*]-4-*hydroxy*-4-*phenylbutanoate* **11a** (0.021 g, 36%) (Found: MH$^+$, 386.1957. $C_{22}H_{28}NO_5$ requires *m*/*z*, 386.1967); $[\alpha]_D$ −32.8 (*c* 0.3, EtOH); ν_{max}(film)/cm^{-1} 3410, 1740 and 1700; δ_H(300 MHz) 1.47 (9 H, s), 1.86 (1 H, ddd, *J* 12.0, 12.0 and 2.2, 3-H), 2.17 (1 H, ddd, *J* 14.1, 10.8 and 3.2, 3-H), 3.94 (1 H, d, *J* 3.2, 4-H), 4.69 (2 H, m, 2-H and OH), 5.17 (2 H, s, OCH_2Ph), 5.64 (1 H, d, *J* 8, NH), 7.30 (5 H, m) and 7.34 (5 H, m); *m*/*z* (FAB) 771 (1%, M_2H^+), 386 (10, MH$^+$) and 312 (100); and a low running component *benzyl* (2S,4R)-2-[(tert-*butoxycarbonyl*)*amino*]-4-*hydroxy*-4-*phenylbutanoate* **12a** (0.022 g, 41%), m.p. 103–104 °C (Found: MH$^+$, 386.1965); $[\alpha]_D$ −21.6 (*c* 0.3, EtOH); ν_{max}(film)/cm^{-1} 3435, 1740 and 1700; δ_H(300 MHz) 1.44 (9 H, s), 2.20 (2 H, m, 3-H_2), 2.51 (1 H, br, OH), 4.45 (1 H, m, 4-H), 4.82 (1 H, m, 2-H), 5.14 (1 H, d, *J* 12.2), 5.21 (1 H, d, *J* 12.2), 5.45 (1 H, br, NH) and 7.36 (10 H, m); *m*/*z* (FAB) 386 (1%, MH$^+$), 312 (10) and 91 (100).

Correlation of Benzyl (2S,4S)-2-[(tert-*Butoxycarbonyl*)-*amino*]-4-*hydroxy*-4-*phenylbutanoate* **11a** *with* (2S,4S)-2-[(tert-*Butoxycarbonyl*)*amino*]-4-*phenylbutano*-4-*lactone* **9a**.—Benzyl (2*S*,4*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-4-phenylbutanoate **11a** (0.002 g) was dissolved in methanol (1 cm^3) and toluene-*p*-sulfonic acid (PTSA) (0.001 g) was added. The mixture was stirred at room temp. for 2 h, after which TLC analysis showed no starting material remained. Concentration of the flask contents under reduced pressure gave a crude product, shown to contain exclusively (2*S*,4*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-phenylbutano-4-lactone **9a** by ^{1}H NMR analysis.

Correlation of Benzyl (2S,4R)-2-[(tert-*Butoxycarbonyl*)-*amino*]-4-*hydroxy*-4-*phenylbutanoate* **12a** *with* (2S,4R)-2-[(tert-*Butoxycarbonyl*)*amino*]-4-*phenylbutano*-4-*lactone* **10a**.—Benzyl (2*S*,4*R*)-2-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-4-phenylbutanoate **12a** (0.002 g) was dissolved in methanol (1 cm^3) and PTSA (0.001 g) added. The mixture was stirred at room temp. for 2 h, after which TLC analysis (20% ethyl acetate–light petroleum) showed no starting material remained. Concentration under reduced pressure gave a crude product, shown to contain exclusively (2*S*,4*R*)-2-[(*tert*-butoxycarbonyl)amino]-4-phenylbutano-4-lactone **10a** by ^{1}H NMR analysis.

Reduction of Benzyl (S)-3-*Benzoyl*-2-[(tert-*Butoxycarbonyl*)-*amino*]*propanoate* **3a** *with Zinc Boranuide.*—An ethereal solution of zinc boranuide (0.14 mol dm^{-3}; 0.88 cm^3, 0.13 mmol) was added dropwise to an ice-cooled solution of benzyl (*S*)-3-benzoyl-2-[(*tert*-butoxycarbonyl)amino]propanoate **3a** (0.096 g, 0.25 mmol) in dry diethyl ether (3 cm^3) under nitrogen. The cooling bath was removed and the mixture was stirred at room temp. for 30 min, after which TLC analysis showed no starting material remained. Distilled water (5 cm^3) was added, and the

ethereal layer was removed, dried (Na_2SO_4), and concentrated under reduced pressure to give a coloured oil. Flash chromatography over silica gel (light petroleum–ethyl acetate, 9:1) gave (2*S*,4*S*/*R*)-2-[(*tert*-butoxycarbonyl)amino]-4-phenylbutano-4-lactone **9a**/**10a** (0.048 g, 0.18 mmol, 70%) as a 1:1 mixture of diastereoisomers.

Reduction of Benzyl (S)-3-*Benzoyl*-2-[(tert-*Butoxycarbonyl*)-*amino*]*propanoate* **3a** *with Sodium Boranuide in Anhydrous Diglyme.*—Benzyl (*S*)-3-benzoyl-2-[(*tert*-butoxycarbonyl)-amino]propanoate **3a** (0.096 g, 0.25 mmol) was dissolved in dry diglyme (1 cm^3) and solid sodium boranuide (0.008 g, 0.26 mmol) was added. The resulting solution was stirred at room temp. for 1 h, after which TLC analysis showed no starting material remained. The mixture was concentrated under reduced pressure and then partitioned between diethyl ether (5 cm^3) and aq. hydrochloric acid (2 cm^3; 1 mol dm^{-3}). The aqueous phase was further extracted with diethyl ether (2 × 5 cm^3). The combined organic extracts were washed with distilled water and dried (Na_2SO_4). Removal of solvent on the rotary evaporator followed by further pumping at 1 mmHg gave a crude product free of diglyme. Flash chromatography over silica gel (light petroleum–ethyl acetate 9:1) gave (2*S*,4*S*/*R*)-2-(*tert*-butoxycarbonyl)amino]-4-phenylbutano-4-lactone (0.035 g, 0.13 mmol, 52%) as a mixture of diastereoisomers, with 33% d.e. in favour of the 4*S* or *cis* lactone **9a** as judged by ^1H NMR spectroscopy.

Reduction of Benzyl (S)-3-*Benzoyl*-2-[(tert-*butoxycarbonyl*)-*amino*]*propanoate* **3a** *with L-Selectride®.*—A solution of L-Selectride® (1.0 mol dm^{-3}; 0.2 cm^3, 0.20 mmol) in THF was added dropwise to a stirred solution of benzyl (*S*)-3-benzoyl-2-[(*tert*-butoxycarbonyl)amino]propanoate **3a** (0.077 g, 0.20 mmol) in dry THF (2 cm^3) at −78 °C under nitrogen. The resulting mixture was stirred at −78 °C for 3 h, after which TLC analysis showed no starting material remained. Saturated aq. ammonium chloride (2 cm^3) was added and the mixture was warmed to room temp. Extraction with diethyl ether (3 × 10 cm^3) followed by drying of the combined organic extracts (Na_2SO_4) and concentration under reduced pressure gave a coloured oil. Flash chromatography over silica gel (10% ethyl acetate–light petroleum) afforded (2*S*,4*S*/*R*)-2-[(*tert*-butoxycarbonyl)amino]-4-phenylbutano-4-lactone (0.040 g, 0.14 mmol, 72%) as a mixture of diastereoisomers, with 33% d.e. in favour of the 4*R* or *trans* lactone **10a** as judged by ^1H NMR spectroscopy.

Hydrogenation of(2S,4S/R)-2-[(tert-*Butoxycarbonyl*)*amino*]-4-*phenylbutano-4-lactone* **9a**/**10a** *Mixture.*—Palladium on charcoal (5%) (0.05 g; 50% wet) was added to a solution of the lactone mixture **9a**/**10a** (0.080 g, 0.29 mmol) in ethanol (5 cm^3)–water (0.5 cm^3). The resulting mixture was agitated under hydrogen at 40 psi for 24 h, after which TLC analysis showed no starting material remained. The reaction mixture was then filtered through a Celite pad and concentrated under reduced pressure to give (*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-phenylbutanoic acid **13** as a foam (0.073 g, 0.26 mmol, 90%); $[\alpha]_D$ +7.0 (*c* 1.2, EtOH) [lit.,[26] +6.0 (*c* 1.0, EtOH)]; ν_{max}(film)/cm^{-1} 3335, 2978 and 1720; δ_H(300 MHz) 1.48 (9 H, s), 2.05 (1 H, m), 2.22 (1 H, m), 2.75 (2 H, m), 4.40 (1 H, m), 5.16 (1 H, br d, *J* 6), 7.23 (3 H, m), 7.32 (2 H, m) and 9.4 (1 H, br s).

Benzyl (S)-3-*Benzoyl*-2-[(*trifluoroacetyl*)*amino*]*propanoate* **14**.—Benzyl (*S*)-3-benzoyl-2-[(*tert*-butoxycarbonyl)amino]-propanoate **3a** (0.239 g, 0.62 mmol) was dissolved in dry dichloromethane (2 cm^3) and the resulting solution was cooled to −10 °C under nitrogen. TFA (5 cm^3) was added dropwise and the mixture was then stirred at room temp. for 30 min, after which TLC analysis showed no starting material remained. The flask contents were then concentrated under reduced pressure to give a solid residue (0.240 g), which was dissolved in a mixture of dry dichloromethane (2 cm^3) and dry pyridine (1 cm^3). TFAA (0.158 g, 0.105 cm^3, 0.75 mmol) was added and the mixture was stirred under nitrogen at room temp. for 2 h. Dilution with diethyl ether (30 cm^3), followed by washing successively with aq. hydrochloric acid (10 cm^3; 1 mol dm^{-3}) and distilled water (3 × 10 cm^3), drying (Na_2SO_4), and concentration under reduced pressure gave a pale yellow oil. Flash chromatography over silica gel (30% ethyl acetate–light petroleum) afforded *benzyl* (S)-3-*benzoyl*-2-[(*trifluoroacetyl*)*amino*]*propanoate* **14** as a pale oil which solidified with time (0.180 g, 0.48 mmol, 77%), m.p. 71–72 °C (from Et_2O) (Found: C, 59.8; H, 4.2; N, 3.7. $C_{19}H_{16}F_3NO_4$ requires C, 60.2; H, 4.25; N, 3.7%); $[\alpha]_D$ +54.0 (*c* 1.0, CH_2Cl_2); ν_{max}(film)/cm^{-1} 3412, 3329, 1725 and 1685; δ_H(300 MHz) 3.54 (1 H, dd, *J* 18.5 and 4.0), 3.87 (1 H, dd, *J* 18.5 and 4.0), 4.96 (1 H, dt, *J* 8.1 and 4.0), 5.19 (2 H, s), 7.28 (6 H, m), 7.5 (3 H, m) and 7.88 (2 H, dd, *J* 8 and 1); *m*/*z* (FAB) 380 (52%, MH^+) and 91 (100).

Reduction of Benzyl (S)-3-*Benzoyl*-2-[(*trifluoroacetyl*)*amino*]-*propanoate* **14** *with Triethylsilane in Boron Trifluoride–Diethyl Ether.*—Triethylsilane (0.150 cm^3, 0.110 g, 0.95 mmol) was added dropwise to a stirred solution of benzyl (*S*)-3-benzoyl-2-[(trifluoroacetyl)amino]propanoate **14** (0.095 g, 0.25 mmol) in boron trifluoride–diethyl ether (0.58 cm^3, 0.67 g, 4.8 mmol) under nitrogen. The resulting solution was stirred at room temp. for 48 h, then was quenched by being poured into saturated aq. sodium hydrogen carbonate (5 cm^3). Extraction with diethyl ether (3 × 5 cm^3), followed by drying of the combined organic extracts (Na_2SO_4) and concentration under reduced pressure, gave a crude product (0.107 g) which solidified on storage. Flash chromatography over silica gel (50% ethyl acetate–light petroleum) gave (2S,4S/R)-4-*phenyl*-2-[(*trifluoroacetyl*)-*amino*)*butano*-4-*lactone* **15**/**16** as a mixture of diastereoisomers with an 80% diastereoisomeric excess (d.e.) in favour of the 4*S* or *cis*-isomer **15** (0.068 g, 99%), m.p. 131–132 °C (Found: C, 52.8; H, 3.9; N, 4.9. $C_{12}H_{10}F_3NO_3$ requires C, 52.8; H, 3.7; N, 5.1%); ν_{max}(KBr disc)/cm^{-1} 3348, 1749, 1710 and 1681; *m*/*z* (EI) 273 (2%, M^+), 245 (2), 229 (4) and 116 (100).

(a)(2*S*,4*S*)-4-Phenyl-2-[(trifluoroacetyl)amino]butano-4-lactone **15**. δ_H(300 MHz) 2.29 (1 H, dddd, *J* 12.4, 12.6, 11.2 and 1.3), 3.18 (1 H, dddd, *J* 12.6, 8.3, 5.2 and 1.3), 4.90 (1 H, ddd, *J* 8.3, 12.4 and 5.7), 5.49 (1 H, dd, *J* 5.2 and 11.2), 7.37 (5 H, s) and 7.50 (1 H, d, *J* 5.7).

(b) (2*S*,4*R*)-4-Phenyl-2-[(trifluoroacetyl)amino]butano-4-lactone **16**. δ_H(300 MHz) 2.70 (1 H, ddd, *J* 12.9, 11.0 and 8.5), 2.92 (1 H, ddd, *J* 12.9, 8.8 and 2.0), 4.65 (1 H, ddd, *J* 8.8, 11.0 and 6.3), 5.80 (1 H, dd, *J* 2.0 and 8.5) and 7.37 (6 H, m).

Reduction of Benzyl (S)-3-*Benzoyl*-2-[(*trifluoroacetyl*)-*amino*]*propanoate* **14** *with Sodium Boroanuide.*—Benzyl (*S*)-3-benzoyl-2-[(trifluoroacetyl)amino]propanoate **14** (0.052 g, 0.14 mmol) was dissolved in methanol (1 cm^3) and solid sodium boranuide (0.006 g, 0.16 mmol) was added. The resulting solution was stirred at room temp. for 15 min, after which TLC analysis showed no starting material remained. The reaction mixture was then partitioned between diethyl ether (10 cm^3) and aq. hydrochloric acid (2 cm^3; 1 mol dm^{-3}). The aqueous layer was then further extracted with diethyl ether (2 × 10 cm^3). The organic extracts were combined, washed with distilled water (10 cm^3), and dried (Na_2SO_4). Removal of solvent on a rotary evaporator gave a crude product (0.048 g). Flash chromatography over silica gel (50% ethyl acetate–light petroleum) then afforded (2*S*,4*S*/*R*)-4-phenyl-[(trifluoroacetyl)-amino]butano-4-lactone as a mixture of diastereoisomers with

a 40% d.e. in favour of the 4*S* or *cis*-isomer **15** (0.30 g, 0.11 mmol, 79%).

Reduction of Benzyl (S)-5-*Acetoxy*-2-[(tert-*butoxycarbonyl*)*amino*]-4-*oxopentanoate* **3b** *with Sodium Boranuide in Diglyme.*—This reaction was carried out as described for the corresponding reduction of compound **3a**, although only 0.25 mol equiv. of sodium boranuide was used. This allowed isolation of (2S,4S/R)-4-*acetoxymethyl*-2-[(tert-*butoxycarbonyl*)*amino*]*butano*-4-*lactone* **9b**/**10b** (0.080 g, 0.30 mmol, 60%) as a 1:1 mixture of diastereoisomers, judged by ^{1}H NMR analysis; m.p. 93–96 °C (Found: C, 53.0; H, 7.1; N, 5.1. $C_{12}H_{19}NO_6$ requires C, 52.7; H, 7.0; N, 5.1%); ν_{max}(KBr disc)/cm^{-1} 3354, 3334, 1779, 1740 and 1705; *m*/*z* (FAB) 274 (12%, MH$^+$), 218 [100, MH$^+$ − $(CH_3)_2C{=}CH_2$] and 174 [35, MH$^+$ − $(CH_3)_2C{=}CH_2$ − CO_2]; (a) (2*S*,4*S*)-4-acetoxymethyl-2-(*tert*-butoxycarbonyl)amino]butano-4-lactone **9b**. δ_H(300 MHz) 1.45 (9 H, s), 1.96 (1 H, m, 3-H), 2.10 (3 H, s), 2.75 (1 H, m, 3-H), 4.16 (1 H, dd, *J* 12.5 and 4.5), 4.29 (1 H, dd, *J* 12.5 and 3.0), 4.44 (1 H, m, 2-H), 4.61 (1 H, m, 4-H) and 5.11 (1 H, m, NH); (b) (2*S*,4*R*)-4-acetoxymethyl-2-[(*tert*-butoxycarbonyl)-amino]butano-4-lactone **10b**. δ_H(300 MHz) 1.45 (9 H, s), 2.11 (3 H, s), 2.42 (1 H, m, 3-H), 2.74 (1 H, m, 3-H), 4.16 (1 H, dd, *J* 12.5 and 5.8), 4.36 (1 H, dd, *J* 12.5 and 3.0), 4.44 (1 H, m, 2-H), 4.82 (1 H, m, 4-H) and 5.11 (1 H, m, NH).

Reduction of Benzyl (S)-5-*Acetoxy*-2-[(tert-*butoxycarbonyl*)*amino*]-4-*oxopentanoate* **3b** *with L-Selectride®.*—This reaction was carried out as described for the L-Selectride® reduction of compound **3a** in THF, and gave (2*S*,4*R*/*S*)-4-acetoxymethyl-2-[(*tert*-butoxycarbonyl)amino]butano-4-lactone (0.090 g, 0.33 mmol, 66%) as a mixture of diastereoisomers with a 58% d.e. in favour of the 4*R* or *trans*-isomer **10b**, as judged by ^{1}H NMR analysis.

Reduction of Benzyl (S)-5-*Acetoxy*-2-[(tert-*butoxycarbonyl*)*amino*]-4-*oxopentanoate* **3b** *with Zinc Boranuide.*—An ethereal solution of zinc boranuide (0.14 mol dm^{-3}; 1.75 cm^3, 0.25 mmol) was added dropwise to a stirred solution of benzyl (*S*)-5-acetoxy-2-[(*tert*-butoxycarbonyl)amino]-4-oxopentanoate **3b** (0.190 g, 0.50 mmol) in dry diethyl ether (5 cm^3) under nitrogen at −10 °C. The resulting solution was stirred at −10 °C for 40 min, after which TLC analysis (50% ethyl acetate–light petroleum) showed no starting material remained. The reaction was quenched with distilled water (5 cm^3), the ethereal layer was removed, and the aqueous phase was extracted with diethyl ether (2 × 10 cm^3). The organic extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure to give a coloured oil. Flash chromatography over silica gel (20% ethyl acetate–light petroleum) afforded *benzyl* (2S,4R/S)-5-*acetoxy*-2-[(tert-*butoxycarbonyl*)*amino*]-4-*hydroxypentanoate* as a 1:1 mixture of diastereoisomers **11b**/**12b** (0.140 g, 0.38 mmol, 74%) (Found: C, 59.4; H, 7.3; N, 3.6. $C_{19}H_{27}NO_7$ requires C, 59.8; H, 7.1; N, 3.7%); ν_{max}(film)/cm^{-1} 3380br, 1740 and 1715; *m*/*z* (FAB) 382 (13%, MH$^+$), 326 [10, MH$^+$ − $(CH_3)_2C{=}CH_2$], 308 [12, MH$^+$ − $(CH_3)_2C{=}CH_2$ − H_2O], 282 [38, MH$^+$ − $(CH_3)_2C{=}CH_2$ − CO_2] and 264 [5, MH$^+$ − $(CH_3)_2C{=}CH_2$ − CO_2 − H_2O]. Careful flash chromatography over silica gel (100 cm^3 dry volume) (10% ethyl acetate–light petroleum) allowed separation of this diastereoisomeric mixture to give: a high running component, *benzyl* (2S,4S)-5-*acetoxy*-2-[(tert-*butoxycarbonyl*)*amino*]-4-*hydroxypentanoate* **11b** (0.065 g, 0.17 mmol, 34%) (Found: MH$^+$, 382.1880. $C_{19}H_{28}NO_7$ requires *m*/*z*, 382.1865); $[\alpha]_D$ −4.2 (*c* 0.6, EtOH); ν_{max}(film)/cm^{-1} 3385, 2978 and 1760–1700; δ_H(200 MHz) 1.44 (9 H, s), 1.62 (1 H, m), 1.96 (1 H, ddd, *J* 14.0, 11.2 and 3.0), 2.08 (3 H, s), 3.85 (1 H, br), 4.06 (3 H, m), 4.58 (1 H, m, 2-H), 5.19 (2 H, s), 5.46 (1 H, d, *J* 8, NH), and 7.36 (5 H, m); *m*/*z* (EI) 382 (2%, MH$^+$), 326 (6), 308 (6), 282 (18), 264 (5) and 57 (100); and a low running component, *benzyl* (2S,4R)-5-*acetoxy*-2-[(tert-*butoxycarbonyl*)*amino*]-4-*hydroxypentanoate* **12b** (0.070 g, 0.18 mmol, 36%) (Found: MH$^+$, 382.1864); $[\alpha]_D$ −3.2 (*c* 1.0, EtOH); ν_{max}(film)/cm^{-1} 3378, 2978 and 1760–1700; δ_H(200 MHz) 1.45 (9 H, s), 1.96 (2 H, m), 2.09 (3 H, s), 2.60 (1 H, br), 4.03 (3 H, m), 4.61 (1 H, m), 5.21 (2 H, s), 5.45 (1 H, d, *J* 8, NH) and 7.36 (5 H, m); *m*/*z* (EI) 382 (7%, MH$^+$), 326 (15), 308 (12), 282 (32), 264 (8) and 57 (100).

(2S,4R)-2-[(tert-*Butoxycarbonyl*)*amino*]-4-{[(*fluoren*-9-*ylmethoxycarbonyl*)*amino*]*methyl*}*butano*-4-*lactone* **10c**.—Benzyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-5-[(fluoren-9-ylmethoxycarbonyl)amino]-4-oxopentanoate **3c** (0.070 g, 0.13 mmol) was dissolved in dry THF (1 cm^3) and the solution was cooled to −78 °C under nitrogen. A solution of L-Selectride® (1.0 mol dm^{-3}; 0.13 cm^3, 0.13 mmol) in THF was added dropwise and the mixture was stirred at −78 °C for 1 h, after which TLC analysis (30% ethyl acetate–light petroleum) showed no starting material remained. Saturated aq. ammonium chloride was added and the mixture was warmed to room temp. Extraction with diethyl ether (3 × 5 cm^3), followed by drying of the combined organic extracts (Na_2SO_4), and concentration under reduced pressure gave a crude product. Flash chromatography over silica gel (light petroleum–ethyl acetate gradient, 7:3 to 1:1) then afforded (2S,4R)-2-[(tert-*butoxycarbonyl*)*amino*]-4-{[(*fluoren*-9-*ylmethoxycarbonyl*)*amino*]*methyl*}*butano*-4-*lactone* **10c** as a crystalline solid (0.050 g, 0.11 mmol, 85%), m.p. 128–129 °C (Found: M$^+$, 452.2007. $C_{25}H_{28}N_2O_6$ requires *M*, 452.1947); $[\alpha]_D$ −38.0 (*c* 0.3, EtOH); ν_{max}(KBr disc)/cm^{-1} 3364, 1799 and 1693; δ_H(200 MHz) 1.44 (9 H, s), 2.40 (2 H, m, 3-H_2), 3.37 (1 H, m), 3.49 (1 H, m), 4.20 (2 H, m), 4.42 (2 H, m), 4.74 (1 H, m), 5.14 (1 H, br d, *J* 6.5), 5.23 (1 H, br t, *J* 6), 7.34 (4 H, m), 7.57 (2 H, d, *J* 7) and 7.77 (2 H, dd, *J* 6.7 and 1.1); *m*/*z* (EI) 453 (4%, MH$^+$), 452 (8, M$^+$), 396 [5, MH$^+$ − $(CH_3)_2C{=}CH_2$], 352 [10, MH$^+$ − $(CH_3)_2C{=}CH_2$ − CO_2] and 178 (100).

2,2-*Dimethyl*-1,3-*dioxolane*-4-*carbonyl Chloride.*—Oxalyl dichloride (4.44 cm^3, 34.5 mmol) was added to a stirred suspension of 2,2-dimethyl-1,3-dioxolane-4-carboxylic acid calcium salt (5.05 g, 16.95 mmol) in dry benzene (20 cm^3) under nitrogen. Dimethylformamide (DMF) (0.1 cm^3) was added carefully and the mixture was stirred for 2 h. Benzene was removed under reduced pressure and the residue was distilled to give 2,2-dimethyl-1,3-dioxolane-4-carbonyl chloride[33] (2.26 g, 41%), b.p. 76 °C at 28 mmHg).

Preparation of the 4-*Oxo Amino Acids* **3d** *and* **3e**.—A mixture of the appropriate benzyl 2-[(*tert*-butoxycarbonyl)amino]-3-iodopropanoate (0.304 g, 0.75 mmol), zinc–copper couple (90 mg), dry dimethylacetamide (200 mm^3) and dry benzene (3 cm^3) was sonicated for 30 min until all the starting material was consumed [TLC (5:1) toluene–ethyl acetate eluent]. 2,2-Dimethyl-1,3-dioxolane-4-carbonyl chloride (1 mmol) and bis(triphenylphosphine)palladium dichloride (28 mg) were added and the mixture was sonicated for a further 2 h. Ethyl acetate (60 cm^3) was added and the mixture was filtered and washed successively with dil. HCl (2 × 10 cm^3), saturated aq. $NaHCO_3$ (10 cm^3) and distilled water (3 × 10 cm^3). The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness. The residues were purified by flash chromatography with a toluene–ethyl acetate gradient (10:1 to 5:1) to give the required 4-oxo amino acids.

Benzyl (2S,5R)-2-[(tert-*Butoxycarbonyl*)*amino*]-5,6-*isopropylidenedioxy*-4-*oxohexanoate* **3d**.—The *title compound* was prepared from benzyl L-2-[(*tert*-butoxycarbonyl)amino]-3-

iodopropanoate and isolated as an oil (156 mg, 51%) (Found: MH^+, 408.2078. $C_{21}H_{30}NO_7$ requires *m/z*, 408.2022); $[\alpha]_D$ −6.7 (*c* 0.75, EtOH); ν_{max}(film)/cm^{-1} 3385–3359br, 1719, 1215 and 1165; δ_H(500 MHz) 1.35 (3 H, s), 1.41 (9 H, s), 1.42 (3 H, s), 3.11 (1 H, dd, *J* 18.9 and 4.2), 3.32 (1 H, dd, *J* 18.9 and 4.6), 3.79 (1 H, dd, *J* 8 and 5.5), 4.07 (1 H, t, *J* 8), 4.35 (1 H, dd, *J* 7 and 5.5), 4.61 (1 H, m), 5.08 (1 H, d, *J* 12.3), 5.19 (1 H, d, *J* 12.3), 5.49 (1 H, d, *J* 8.7) and 7.33 (5 H, m); δ_C(125 MHz) 24.9, 25.9, 28.3, 41.1, 49.1, 66.1, 67.7, 73.8, 80.0, 111.3, 128.0, 128.4, 128.7, 135.1, 155.5, 170.7 and 209.2; *m/z* (EI) 408 (18%, MH^+), 352 [70, $MH^+ - (CH_3)_2C{=}CH_2$], 308 [65, $MH^+ - (CH_3)_2C{=}CH_2 - CO_2$) and 91 (100).

Benzyl (2R,5R)-2-[(tert-*Butoxycarbonyl*)*amino*]-5,6-*isopropylidenedioxy*-4-*oxohexanoate* **3e**.—The *title compound* was prepared from benzyl D-2-[(*tert*-butoxycarbonyl)amino]-3-iodopropionate, and was isolated as an oil (138 mg, 45%) (Found: M^+, 407.1909. $C_{21}H_{29}NO_7$ requires M, 407.1944); $[\alpha]_D$ +39.2 (*c* 0.79, EtOH); ν_{max}(film)/cm^{-1} 3359, 1719, 1501, 1370, 1352, 1215, 1165 and 1062; δ_H(500 MHz) 1.37 (3 H, s), 1.42 (9 H, s), 1.46 (3 H, s), 3.20 (1 H, dd, *J* 18.8 and 4.1), 3.30 (1 H, dd, *J* 18.8 and 4.5) 3.95 (1 H, dd, *J* 8.9 and 5.3), 4.14 (1 H, dd, *J* 8.9 and 7.8), 4.36 (1 H, dd, *J* 7.8 and 5.3), 4.61 (1 H, m), 5.16 (2 H, s), 5.47 (1 H, d, *J* 8.4) and 7.34 (5 H, m); δ_C(125 MHz) 24.9, 26.0, 28.3, 41.0, 49.2, 66.2, 67.3, 72.1, 80.0, 111.2, 128.2, 128.5, 128.6, 135.3, 155.5, 171.2 and 209.0; *m/z* (FAB) 408 (71%, MH^+), 352 [$MH^+ - (CH_3)_2C{=}CH_2$] and 308 [$MH^+ - (CH_3)_2C{=}CH_2 - CO_2$]; *m/z* (EI) 408 (0.6%, MH^+), 407 (0.1, M^+), 352 [18, $MH^+ - (CH_3)_2C{=}CH_2$], 308 [25, $MH^+ - (CH_3)_2C{=}CH_2 - CO_2$] and 91 (100).

(2S,4R,5R)-2-[(tert-*Butoxycarbonyl*)*amino*]-5,6-*isopropylidenedioxy*)*hexan*-4-*olide* **10d**.—A solution of L-Selectride® (1.0 mol dm^{-3} in THF; 0.506 cm^3, 0.506 mmol) was added dropwise to a stirred solution of benzyl (2*S*,5*R*)-2-[(*tert*-butoxycarbonyl)amino]-5,6-isopropylidenedioxy-4-oxohexanoate **3d** (187 mg, 0.46 mmol) in dry THF (4 cm^3) at −78 °C under nitrogen. The resulting mixture was stirred at −78 °C for 3 h, until no starting material was present [TLC (5:1) toluene–ethyl acetate]. Saturated aq. NH_4Cl (3 cm^3) was added and the mixture was warmed to room temperature. Extraction with ethyl acetate (3 × 10 cm^3), drying ($MgSO_4$), filtration, and evaporation gave an oil. The oil was chromatographed on silica gel (toluene–ethyl acetate gradient, 10:1 to 5:1) to give (2S,4R,5R)-2-[(tert-*butoxycarbonyl*)*amino*]-5,6-*isopropylidenedioxyhexan*-4-*olide* **10d** (96 mg, 69%), m.p. 79–80 °C (Found: C, 55.5; H, 7.9; N, 4.7. $C_{14}H_{23}NO_6$ requires C, 55.8; H, 7.6; N, 4.7%); $[\alpha]_D$ −53.5 (*c* 0.64, EtOH); ν_{max}(film)/cm^{-1} 3434, 1744, 1665, 1470, 1175 and 1120; δ_H(500 MHz) 1.36 (6 H, s), 1.46 (9 H, s), 2.41 (1 H, m, 3-H), 2.71 (1 H, m, 3-H), 3.95 (1 H, m), 4.08 (1 H, dd, *J* 8.4 and 6.8), 4.19 (1 H, m), 4.57 (2 H, m) and 5.05 (1 H, br); *m/z* (FAB) 302 (73%, MH^+) and 246 [100, $MH^+ - (CH_3)_2C{=}CH_2$].

(2R,4R,5R)-2-[(tert-*Butoxycarbonyl*)*amino*]-5,6-(*isopropylidenedioxy*)*hexan*-4-*olide* **9e**.—A solution of L-Selectride® (1.0 mol dm^{-3} in THF; 0.96 cm^3, 0.96 mmol) was added dropwise to a stirred solution of benzyl (2*R*,5*R*)-2-[(*tert*-butoxycarbonyl)amino]-5,6-isopropylidenedioxy-4-oxohexanoate **3e** (355 mg, 0.872 mmol) in dry THF (12 cm^3) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 3 h until no starting material was present [TLC (5:1) toluene–ethyl acetate eluent]. Saturated aq. NH_4Cl (6 cm^3) was added, and the mixture was warmed to room temperature. Extraction with ethyl acetate (3 × 10 cm^3), drying ($MgSO_4$), filtration, and evaporation gave an oil. The oil was chromatographed on silica gel (toluene–ethyl acetate gradient, 10:1 to 5:1) to give as a solid (2R,4R,5R)-2-[(tert-*butoxycarbonyl*)*amino*]-5,6-(*isopropylidenedioxy*)*hexan*-4-*olide* **9e** (175 mg, 67%), m.p. 124–126 °C (from ethyl acetate–light petroleum) (Found: C, 56.05; H, 7.30; N, 4.65%); $[\alpha]_D$ +6.2 (*c* 1.0, EtOH); ν_{max}(film)/cm^{-1} 3366, 1752, 1688, 1524, 1184 and 1171; δ_H(500 MHz) 1.38 (3 H, s), 1.43 (3 H, s), 1.46 (9 H, s), 2.03 (1 H, m, 3-H), 2.75 (1 H, m, 3-H), 3.92 (1 H, dd, *J* 8.2 and 6.5), 4.10 (1 H, dd, *J* 8.2 and 7.0), 4.23 (1 H, m), 4.47 (2 H, m) and 5.18 (1 H, br); *m/z* (FAB) 302 (70%, MH^+) and 246 [100, $MH^+ - (CH_3)_3C{=}CH_2$].

(2R,4R,5R)-2-[(tert-*Butoxycarbonyl*)*amino*]-5,6-*dihydroxyhexan*-4-*olide* **24**.—(2*R*,4*R*,5*R*)-2-[(*tert*-Butoxycarbonyl)amino]-5,6-isopropylidenedioxyhexan-4-olide **9e** (150 mg, 0.50 mmol) was stirred in a 1% solution of iodine in methanol (20 cm^3) for 48 h until no starting material remained [TLC (5:1) toluene–ethyl acetate]. The solvent was removed under reduced pressure, the residue was extracted with ethyl acetate (4 × 20 cm^3), and the extract was evaporated to dryness. The residue was chromatographed on silica gel (ethyl acetate eluent) to give (2*R*,4*R*,5*R*)-2-[(*tert*-butoxycarbonyl)amino]-5,6-dihydroxyhexan-4-olide **24** as needles (92 mg, 71%), m.p. 147–149 °C (from $CHCl_3$); $[\alpha]_D$ +34.4 (*c* 0.27, EtOH); ν_{max}(film)/cm^{-1} 3372, 1763, 1684, 1522, 1163 and 1022; δ_H(500 MHz) 1.44 (9 H, s), 2.26 (1 H, m, 3-H), 2.56 (1 H, br), 2.80 (1 H, m, 3-H), 3.65 (1 H, m), 3.75 (2 H, m), 3.93 (1 H, br s), 4.45 (1 H, m), 4.60 (1 H, m), 5.03 (1 H, br s); *m/z* (FAB) 284 (12%, MNa^+), 262 (10, MH^+) and 206 [100, $MH^+ - (CH_3)_2C{=}CH_2$].

(2R,4R,5R)-2-[(tert-*Butoxycarbonyl*)*amino*]-6-(tert-*butyldimethylsiloxy*)-5-*hydroxyhexan*-4-*olide* **23**.—4-(Dimethylamino)pyridine (DMAP) (2 mg), triethylamine (0.06 cm^3) and *tert*-butylchlorodimethylsilane (TBDMSCl) (0.065 g, 0.43 mmol) were added to a solution of (2*R*,4*R*,5*R*)-2-[(*tert*-butoxycarbonyl)amino]-5,6-dihydroxyhexan-4-olide **24** (100 mg, 0.383 mmol) in a mixture of dichloromethane (2.5 cm^3) and DMF (0.72 cm^3) under nitrogen. The mixture was stirred at room temperature for 20 h. Distilled water (3 cm^3) was added, and the flask contents were extracted with dichloromethane (3 × 10 cm^3). The combined organic extracts were washed with distilled water (10 cm^3), dried ($MgSO_4$), and evaporated to dryness. The residue was purified by flash chromatography [(2:1) light petroleum–diethyl ether as eluent] to give (2R,4R,5R)-2-[(tert-*butoxycarbonyl*)*amino*]-6-(tert-*butyldimethylsiloxy*)-5-*hydroxyhexan*-4-*olide* **23** (75 mg, 52%), m.p. 85–86 °C (from CCl_4–Et_2O) (Found: C, 54.8; H, 9.1; N, 3.6. $C_{17}H_{33}NO_6Si$ requires C, 54.4; H, 8.9; N, 3.7%); $[\alpha]_D$ −24.3 (*c* 0.61, $CHCl_3$); ν_{max}(film)/cm^{-1} 3416br, 2957, 2932, 1782, 1709, 1367, 1265, 1165, 1115, 839 and 739; δ_H(500 MHz) 0.07 (6 H, s), 0.88 (9 H, s), 1.45 (9 H, s), 2.18 (1 H, m, 3-H), 2.66 (1 H, br s), 2.72 (1 H, m, 3-H), 3.64–3.75 (3 H, m), 4.48 (1 H, m), 4.54 (1 H, m) and 5.29 (1 H, br d); *m/z* (FAB) 376 (10%, MH^+), 320 [100, $MH^+ - (CH_3)_2C{=}CH_2$] and 276 [95, $MH^+ - (CH_3)_2C{=}CH_2 - CO_2$].

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