Asymmetric Synthesis of β-Amino-α-Hydroxy Acids *via* Diastereoselective Hydroxylation of Homochiral β-Amino Enolates

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The highly diastereoselective conjugate addition of lithium *N*-benzyl-*N*-α-methylbenzylamide with enoate acceptors, and the electrophilic hydroxylation of the resultant β-amino enolates with (camphorsulfonyl)oxaziridine, is identified as a direct and general strategy for the asymmetric synthesis of homochiral β-amino-α-hydroxy acids and their derivatives. A structurally diverse array of β-amino enolate substrates can be hydroxylated with generally excellent *anti* diastereoselectivity (>90% d.e.) using this protocol; an alternative stepwise hydroxylation procedure, where the β-amino enolate is prepared by enolisation of the preformed conjugate adduct is also found to lead to formation of the *anti* diastereoisomer. The diastereofacial selectivity of enolate hydroxylation appears to be under predominantly substrate-controlled asymmetric induction, although a measurable degree of chirality recognition with the oxaziridine reagent can be observed. Homochiral β-amino-α-keto esters are also prepared and their stereoselective reductions examined.

Homochiral β-amino-α-hydroxy acids are the pivotal components in a variety of compounds with important biological activity and recent years have witnessed a dramatic flurry of interest in their asymmetric synthesis.[1-3] The remarkable efficacy of the anticancer agent taxol is dependent upon the presence of a β-amino-α-hydroxy acid derived side chain and an expeditious stereocontrolled synthesis of this important component has been the primary objective of much current research.[4] Furthermore, an increasing number of protease inhibitors have been found to derive their activity from the ability of the β-amino-α-hydroxy acid motif to act as a transition state mimic of peptide hydrolysis and, importantly, activity is often found to reside predominantly in a single stereoisomer of this crucial amino acid moiety. For example, whilst phenylnorstatine **1** (Fig. 1) is the stereoisomer essential

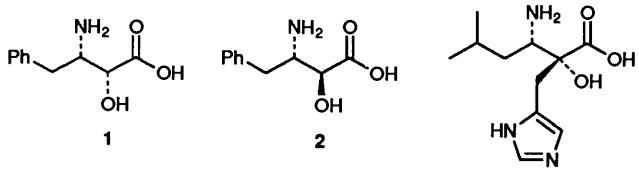
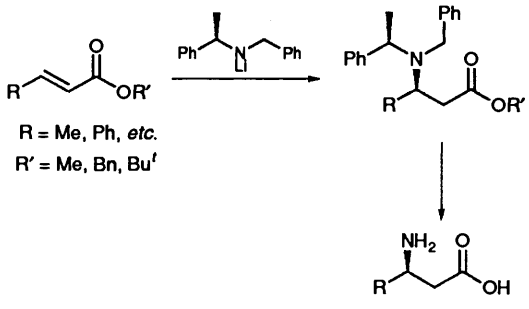


Fig. 1

for activity in a variety of renin inhibitors,[5,6] its α-epimer allophenylnorstatine **2** (Fig. 1) is the preferred component for incorporation into the kynostatin class of HIV protease inhibitors.[7,8] Further to such stereochemical issues, the asymmetric synthesis of β-amino-α-hydroxy acids may also be complicated by more complex structural requirements; the potent aminopeptidase M inhibitor leuhistin **3** (Fig. 1), for example, contains the α-hydroxy group at a quaternary stereogenic centre.[9] It is thus evident that effective synthetic approaches to β-amino-α-hydroxy acid derivatives of defined absolute and relative stereochemistry is of prime importance and, as the number of interesting β-amino-α-hydroxy acids continues to expand, a direct and efficient protocol for their synthesis is becoming increasingly desirable.

We have previously reported that the homochiral lithium amide derived from (*R*)-benzyl(α-methylbenzyl)amine undergoes conjugate addition to a variety of enoate acceptors to afford, upon protic work-up, β-amino acid derivatives with excellent diastereoselectivity (>95% d.e.).[10,11] Furthermore, these conjugate adducts are conveniently deprotected, thus providing an efficient protocol for the synthesis of homochiral free β-amino acids (Scheme 1). In view of the importance of

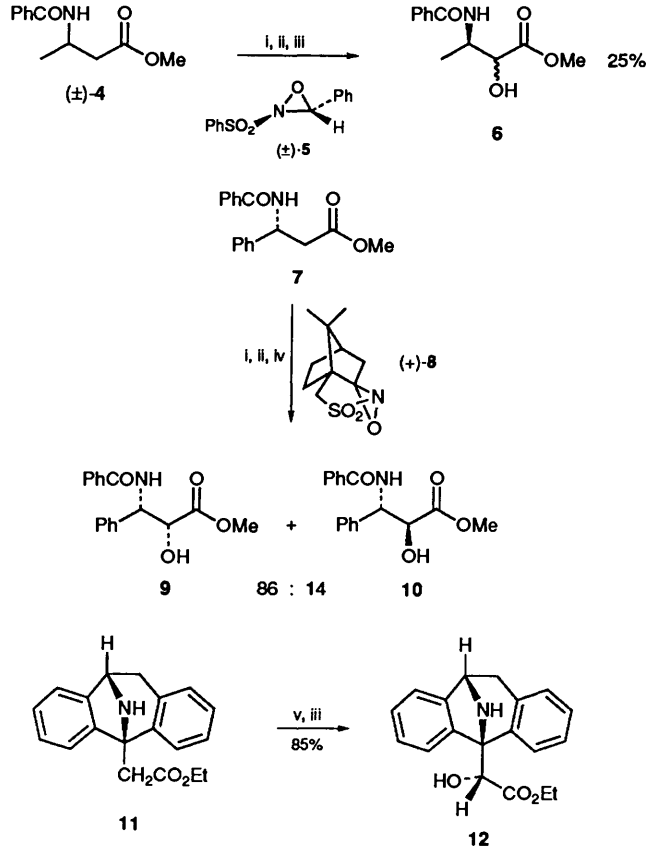


Scheme 1

homochiral β-amino-α-hydroxy acids in a variety of biologically active compounds, it was of great interest to ascertain whether the β-amino enolates available from the lithium amide conjugate addition reactions could give rise to useful levels of 1,2-asymmetric induction upon reaction with suitable sources of electrophilic oxygen.

At the commencement of the present study, the hydroxylation of β-amino enolates had received only scant attention. Seebach, for example, had shown the enolate dianion derived from the racemic *N*-benzoyl-β-aminobutanoate (±)-**4** underwent hydroxylation with the oxaziridine (±)-**5** to afford the corresponding α-hydroxy derivative **6** as an undefined mixture of diastereoisomers in only 25% yield (Scheme 2).[12] During the course of this work, Davis also reported[3] the hydroxylation of an enolate dianion derived from a related (non-racemic) β-acylamino ester. Thus, treatment of the enolate derived from compound **7** with the (camphorsulfonyl)oxaziridine (+)-**8** afforded the corresponding α-hydroxy derivatives as an 86:14 mixture of *syn* and *anti* diastereoisomers (compounds **9** and **10**)

in 58% combined yield (Scheme 2). Interestingly, utilisation of the alternative antipode of the oxaziridine reagent in this reaction was reported to lead to a 'similar' level of diastereoselectivity, thus suggesting that any molecular recognition effects were minimal and the hydroxylation was mediated solely by substrate-controlled 1,2-asymmetric induction.[3] Despite the poor selectivities observed by Seebach and Davis, at least one example of a high-yielding and highly diastereoselective hydroxylation of a β-amino enolate has been reported. Thus, treatment of the unusual β-amino ester **11** with potassium hexamethyldisilazanide (KHMDS) and hydroxylation of the resultant enolate with the oxaziridine (±)-**5**, afforded the β-amino-α-hydroxy acid derivative **12** in 85% yield as a single diastereoisomer (Scheme 2).[13]

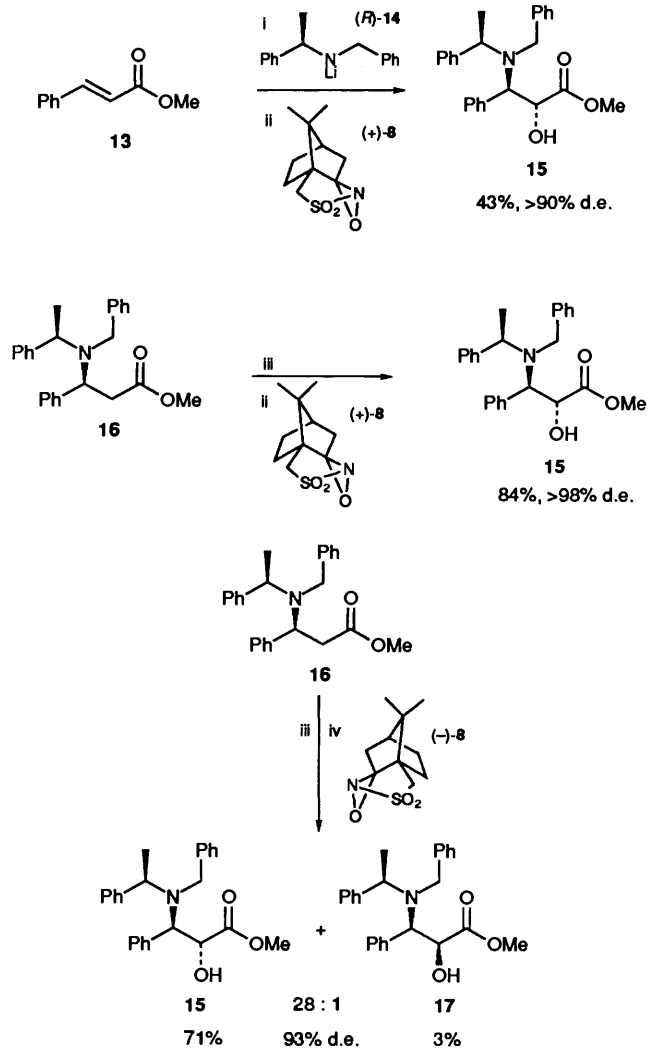


Scheme 2 *Reagents:* i, LiCl; ii, LDA (> 2 equiv.); iii, (+)-**5**; iv, (+)-**8**; v, KHMDS

Results and Discussion

Undeterred by the general lack of precedent, we decided to screen a variety of reagents for the stereoselective hydroxylation of the β-amino enolates obtainable from our lithium amide asymmetric conjugate addition reactions. Two alternative methods for enolate generation were investigated, namely: a 'tandem' approach, whereby the β-amino enolate resulting from the initial lithium amide conjugate addition was trapped *in situ*, and an alternative 'stepwise' approach, where the β-amino enolate was generated from a preformed conjugate adduct. Using methyl crotonate and methyl cinnamate as representative substrates, the tandem and stepwise approaches were investigated using molecular oxygen,[14] Vedejs' MoOPH reagent,[15] and the Davis oxaziridine[16] (±)-**5** as sources of electrophilic oxygen. Unfortunately, all experiments were unsatisfactory in terms of yield and selectivity; furthermore, on one occasion the use of molecular oxygen, in the presence of dimethyl sulfide as peroxide scavenger, resulted in an explosion. Nevertheless, an investigation into the utility of the (camphorsulfonyl)oxaziridine[17] reagent **8** met with success and these results provide the focus of this article.

Hydroxylation of Cinnamate Derived β-Amino Enolates.— The tandem addition–hydroxylation with methyl cinnamate **13** was attempted at −78 °C using the homochiral lithium amide (*R*)-**14** and the oxaziridine (+)-**8** (Scheme 3). Although the



Scheme 3 *Reagents:* i, (*R*)-**14**; ii, (+)-**8**; iii, LHMDS; iv, (−)-**8**

corresponding β-amino-α-hydroxy ester **15** appeared to be formed with good diastereoselectivity (>90% d.e.), the presence of by-products precluded an accurate assessment. Furthermore, isolation of the hydroxylated product **15** by flash chromatography was complicated by the co-elution of recovered amine starting material. The amine could be removed from the product by heating *in vacuo* at high temperature, although this was evidently unsatisfactory. The *anti* relative stereochemistry assigned to compound **15** was later unambiguously confirmed (*vide infra*).

In order to avoid the aforementioned isolation problems, the alternative stepwise protocol was attempted. Firstly, the β-amino ester **16** was prepared (>95% d.e.) by a conjugate addition of the lithium amide (*R*)-**14** to the acceptor **13**, followed by protic work-up in the standard manner.[10,11] Enolisation of the adduct **16** using lithium hexamethyldisilazanide (LHMDS), followed by hydroxylation at −78 °C with the oxaziridine (+)-**8**, furnished the desired product **15** with excellent diastereoselectivity (Scheme 3). This selectivity could

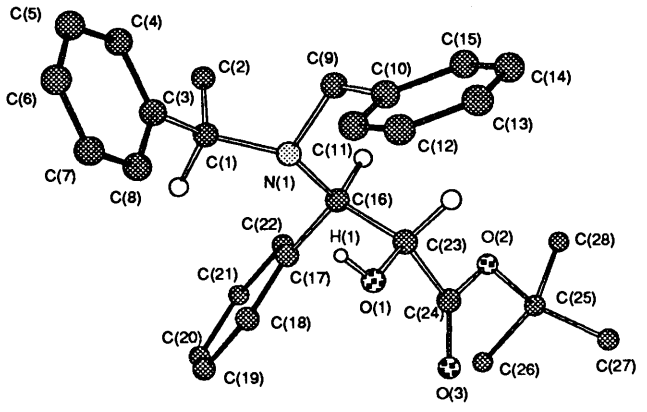


Fig. 2

be confirmed as >98% d.e. since the alternative *syn* diastereoisomer, which was later independently prepared (*vide infra*), could not be identified in the ^{1}H NMR spectrum of the crude product. Interestingly, the corresponding hydroxylation using the antipodal oxaziridine reagent, namely (−)-**8**, led to only a slight reduction in diastereoselectivity (93% d.e.) and thus confirmed that the hydroxylation was pedominantly under substrate controlled asymmetric induction (Scheme 3). The minor *syn* diastereoisomer **17** generated in this 'mismatched' reaction could be separated from the adduct **15** by chromatography.

It was postulated that the origin of the by-products in the tandem reaction with the cinnamate acceptor **13** was a consequence of competing 1,2-addition of the lithium amide to the methyl ester. In order to arrest any 1,2-addition, the tandem protocol was repeated using *tert*-butyl cinnamate **18** as the substrate. Analysis of the crude product by ^{1}H NMR spectroscopy, indicated a 25:1 selectivity (92% d.e.) in favour of the *anti* diastereoisomer (−)-**19**. The major diastereoisomer (−)-**19** and the minor *syn* diastereoisomer **20** were readily isolated in 86% and 3% yields, respectively. The excellent yield and selectivity procured in this reaction provided the basis of our approach to the synthesis of the taxol side chain.[4]

Single crystals of the hydroxy ester (−)-**19** were grown from hexane and analysed by X-ray crystallography. The refined structure (Fig. 2) unambiguously confirmed the *anti* relative stereochemistry within (−)-**19** [the absolute configuration follows directly from that of homochiral (*R*)-benzyl(α-methylbenzyl)amine]. Interestingly, the hydroxyl group was found to adopt a conformation *gauche* to the nitrogen moiety (Fig. 2 includes the hydrogen atoms at stereogenic centres for clarity). Such a conformation might have been predicted due to the possibility of an intramolecular hydrogen bond, and the nitrogen and hydroxyl oxygen atoms were found to be suitably proximate [N(1)–O(1) 2.79 Å] to accommodate such an interaction. Furthermore, the hydroxyl hydrogen atom was refined and, although the O(1)–H(1)···N(1) angle (110.8°) was far from ideal for hydrogen bonding, the location of the hydrogen atom (Fig. 2) was supportive of an association with the proximate nitrogen centre. Selected bond lengths and bond angles for compound (−)-**19** are given in Table 1 and Table 2.

Although the tandem procedure using the cinnamate **18** was particularly successful, for completeness the stepwise procedure in the *tert*-butyl ester series was also investigated. The enolisation–hydroxylation of the readily prepared[11] amino ester **21** was attempted using LHMDS and the oxaziridine (+)-**8** in a manner identical with that employed in the successful hydroxylation of compound **16**. Surprisingly, however, the ^{1}H NMR spectrum of the crude product in this reaction only indicated *ca.* 10% conversion of starting material to the desired product **16**. Nevertheless, if enolisation was performed using LDA as base, the reaction was successful and compound (−)-**19** was secured with excellent diastereoselectivity (97% d.e.) and in excellent yield (90%) (Scheme 4). These results suggest that LHMDS is too bulky to effect enolisation at appreciable rates with the more sterically encumbered *tert*-butyl β-amino ester substrates. More significantly, however, these results also demonstrated that both the tandem and the stepwise procedures with *tert*-butyl cinnamate **18** as substrate led to the preferential formation of the *anti* diastereoisomer of the β-amino-α-hydroxy acid derivative.

With the stereochemical identity of the adduct (−)-**19** confirmed, the *anti* stereochemistry in the methyl ester series could now be demonstrated by an independent synthesis of compound **15** starting from compound (−)-**19**. Thus, the free acid **22** was readily secured by treatment of (−)-**19** with trifluoroacetic acid (TFA) and subsequent basification using sodium hydrogen carbonate (Scheme 5). Interestingly, the free acid, and not the corresponding sodium carboxylate, was obtained under these conditions suggesting that compound **22**, once formed, may be protected from deprotonation by the surrounding lipophilic benzyl groups. In any event, the acid **22** was readily methylated with diazomethane to afford a sample of the ester **15** which was identical by ^{1}H NMR spectroscopy to the product secured from the hydroxylation reactions in the methyl ester series, thus confirming the *anti* relative stereochemistry therein (Scheme 5).

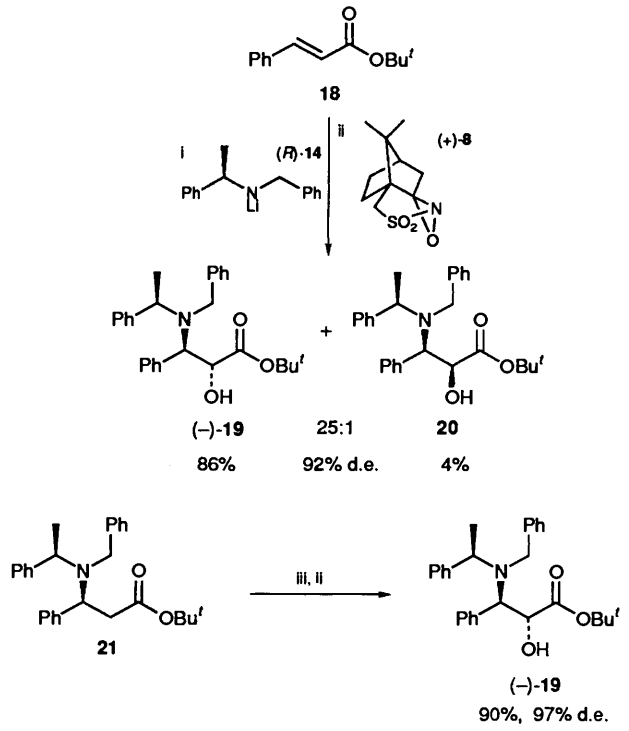
The observation that both the tandem and stepwise procedures using cinnamate esters afforded the same sense, and comparable levels, of 1,2-asymmetric induction was particularly intriguing in view of our previous observations of stereodivergent β-amino enolate generation[11] in these alternative

Table 1 Selected bond lengths (Å) for the hydroxylated adduct (−)-**19**

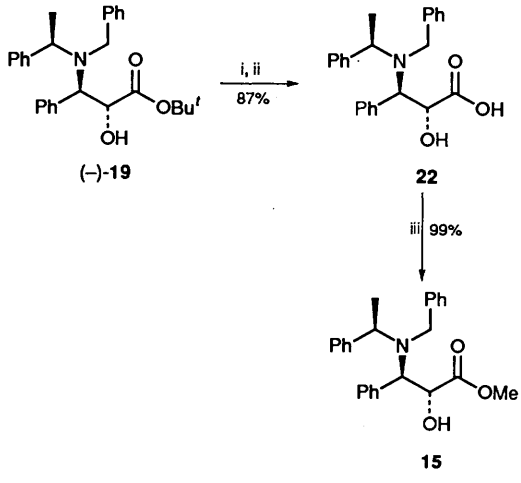
O(1)–C(23)	1.407(5)
O(2)–C(24)	1.332(5)
O(2)–C(25)	1.481(4)
O(3)–C(24)	1.187(5)
N(1)–C(1)	1.480(4)
N(1)–C(9)	1.480(4)
N(1)–C(16)	1.492(4)
C(1)–C(2)	1.522(6)
C(1)–C(3)	1.526(5)
C(9)–C(10)	1.503(5)
C(16)–C(17)	1.513(5)
C(16)–C(23)	1.551(5)
C(23)–C(24)	1.507(5)
O(1)–H(1)	0.80(5)

Table 2 Selected bond angles (°) for the hydroxylated adduct (−)-**19**

C(24)–O(2)–C(25)	122.4(3)
C(1)–N(1)–C(9)	111.2(2)
C(1)–N(1)–C(16)	114.5(2)
C(9)–N(1)–C(16)	111.8(2)
N(1)–C(1)–C(2)	114.6(3)
N(1)–C(1)–C(3)	109.2(3)
C(2)–C(1)–C(3)	113.7(3)
N(1)–C(9)–C(10)	115.8(3)
N(1)–C(16)–C(17)	114.5(2)
N(1)–C(16)–C(23)	107.7(3)
C(17)–C(16)–C(23)	112.3(3)
O(1)–C(23)–C(16)	111.9(2)
O(1)–C(23)–C(24)	107.7(3)
C(16)–C(23)–C(24)	111.6(3)
O(2)–C(24)–O(3)	125.6(3)
O(2)–C(24)–C(23)	108.8(3)
O(3)–C(24)–C(23)	125.6(4)
C(23)–O(1)–H(1)	113.0(46)



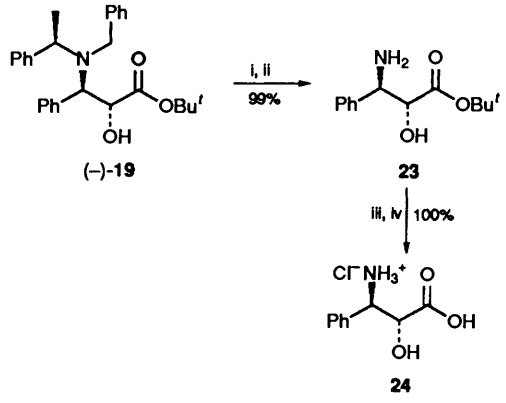
Scheme 4 *Reagents:* i, (*R*)-**14**; ii, (+)-**8**; iii, LHMDS



Scheme 5 *Reagents:* i, TFA; ii, $NaHCO_3$; iii, CH_2N_2

procedures. Consequently, we came to the initial conclusion that the sense of 1,2-asymmetric induction in the hydroxylation of related β-amino enolates would be independent of enolate generation procedure. Whilst generally being sustained, our studies concerning the asymmetric synthesis of allophenylnorstatine **2** have highlighted a significant exception to this conjecture.[8] Furthermore, we have also discovered that, contrary to the observations of Davis,[3] there is an observable degree of molecular recognition between the chiral β-amino enolate and the chiral oxaziridine in these reactions (*vide infra*).

Debenzylation of β-Amino-α-Hydroxy Ester Adducts.—It is evident that the successful deprotection of β-amino-α-hydroxy ester adducts such as (–)-**19** is a fundamental prerequisite of any synthetic application. It was anticipated that the *N*-benzyl groups would be easily removed *via* catalytic hydrogenolysis, however the debenzylation of the cinnamate adducts presented the potential problem of over-reduction. Nevertheless, we were gratified to discover that, in keeping with the observations on the α-unsubstituted analogues,[11] the desired *N*-benzyl moiety was remarkably resistant towards our hydrogenolysis conditions. Thus, debenzylation of (–)-**19** under 7 atm of hydrogen using palladium on activated carbon as catalyst, and basification of the resultant acetate salt, readily furnished the free β-amino-α-hydroxy ester **23** in 99% yield (Scheme 6). This



Scheme 6 *Reagents:* i, 7 atm H_2, Pd–C, AcOH; ii, $NaHCO_3$; iii, TFA; iv, HCl

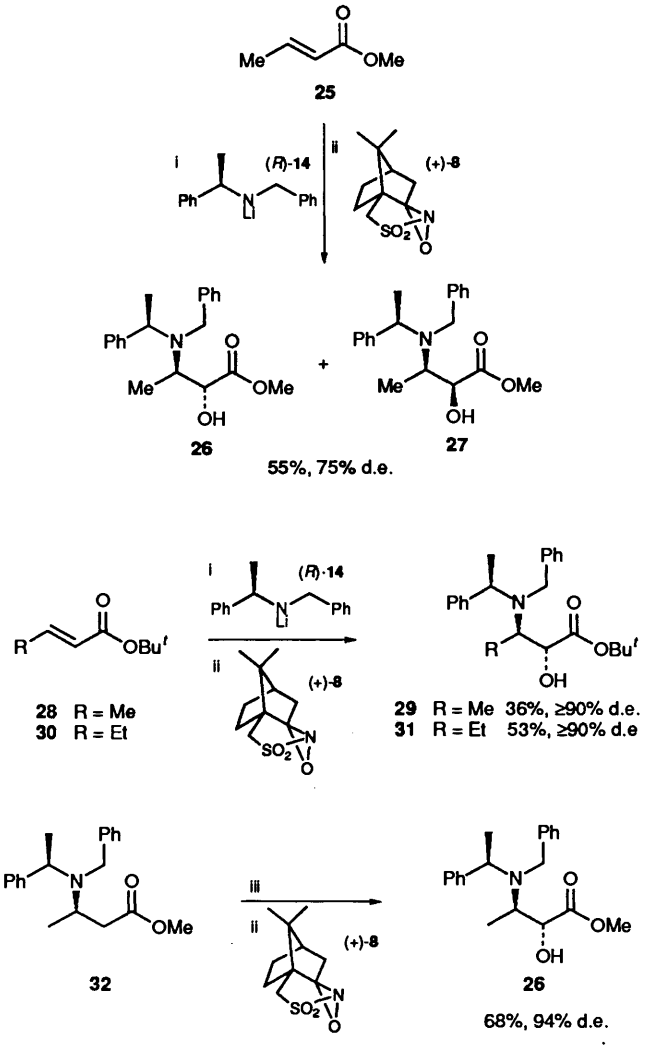
hydrogenolysis procedure has also been employed for the debenzylation of a variety of other β-amino-α-hydroxy ester and amide (*vide infra*) adduct substrates without complication.

Finally, the parent β-amino acid (2*R*,3*R*)-3-amino-2-hydroxy-3-phenylpropionate was readily obtained in quantitative yield as the hydrochloride salt **24** by initial treatment of the ester **23** with trifluoroacetic acid (TFA) and subsequent ion-exchange of the resultant TFA salt by the addition of hydrochloric acid (Scheme 6).

Hydroxylation of β-Alkyl-β-amino Enolates.—In order to investigate the generality of the above procedures, it was of interest to examine the possibility of diastereoselective hydroxylations using crotonate analogues and related β-alkyl-β-amino enolates.

The tandem addition–hydroxylation of methyl crotonate **25** using the lithium amide (*R*)-**14** and the oxaziridine (+)-**8** furnished the *anti* and *syn* diastereoisomers **26** and **27** with moderate *anti* diastereoselectivity (7:1, 75% d.e.) and these inseparable diastereoisomers were secured in a combined yield of 55% (Scheme 7). Interestingly, the corresponding tandem addition–hydroxylation using *tert*-butyl crotonate **28** as the substrate afforded the adduct **29** with improved diastereoselectivity (≥90% d.e.) and this could be isolated as a single diastereoisomer after chromatography, although the isolated yield (36%) was only moderate (Scheme 7). The tandem addition–hydroxylation of *tert*-butyl pent-2-enoate **30** was also attempted and the adduct **31** was generated with good diastereoselectivity (≥90% d.e.) and readily isolated by chromatography as a single diastereoisomer in 53% yield (Scheme 7).

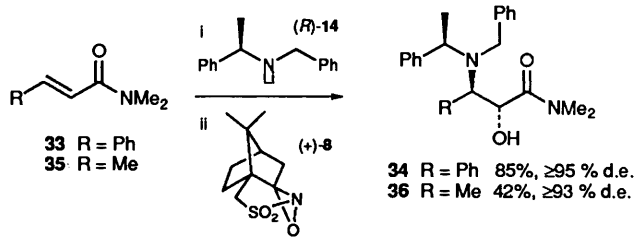
The diastereoselectivity obtained in the formation of the hydroxy ester **26** could be improved if the alternative stepwise protocol was employed. Thus, enolisation of the known β-amino ester **32** with LHMDS, and hydroxylation with the oxiziridine (+)-**8** in the standard manner afforded the hydroxylated adduct **26** with excellent diastereoselectivity (94% d.e.) and in 68% yield (Scheme 7). The *anti* relative stereochemistry was assigned to all the above β-amino-α-hydroxy ester derivatives by analogy with the results in the corresponding cinnamate series.



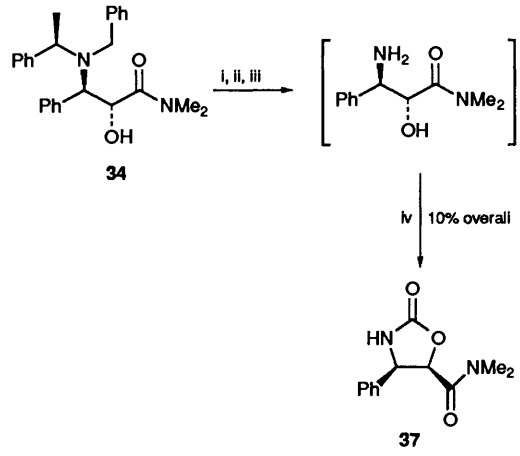
Scheme 7 *Reagents:* i, (*R*)-**14**; ii, (+)-**8**; iii, LHMDS

Hydroxylation of β-Amino Enolates Derived from Enamide Acceptors.—We anticipated that enamide acceptors could also prove suitable substrates for use in the tandem addition–hydroxylation procedure, especially since the reduced electrophilicity of the amide moiety should curtail any 1,2-addition of the lithium amide and thus lead to improved yields of the desired adducts. Indeed, the tandem addition–hydroxylation of *N,N*-dimethylcinnamide **33** with the lithium amide (*R*)-**14** and the oxiziridine (+)-8 occurred with excellent diastereoselectivity (≥95% d.e.) to afford the hydroxy amide **34** in 85% isolated yield (Scheme 8).

Although it has been demonstrated that the conjugate addition of the lithium amide (*R*)-**14** occurs at the *Si*-face of both the cinnamate and cinnamide acceptors,[18] it would not have been acceptable to assume that the sense of diastereofacial control over electrophilic hydroxylation of the derived β-amino enolates would be the same. Consequently, a convenient method for assessing the relative stereochemistry in compound **34** was required. Thus, debenzylation of compound **34** under standard conditions and treatment of the liberated free β-amino-α-hydroxy ester with carbonyl diimidazole (CDI) afforded the oxazolidinone **37** in 10% yield (Scheme 9). The disappointing yield in this reaction was presumably a result of competing intermolecular condensations of the free β-amino-α-hydroxy amide intermediate with CDI. The coupling constant for the ring protons in the oxazolidine **27** ($J_{4,5}$ 8.9) was consistent with the *cis* ring stereochemistry[19] which follows



Scheme 8 *Reagents:* i, (*R*)-**14**; ii, (+)-**8**

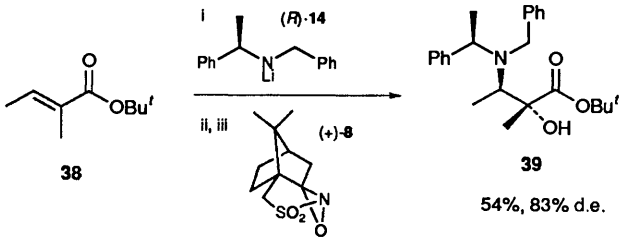


Scheme 9 *Reagents:* i, 7 atm H_2, Pd–C, AcOH; ii, HCl, MeOH; iii, Et_3N; iv, CDI

directly from an *anti* arrangement in compound **34**, thus confirming that the use of amide acceptors did not affect the sense of π-facial selectivity of the β-amino enolate hydroxylation. The tandem addition–hydroxylation using *N,N*-dimethyl crotonamide **35** was also attempted and the adduct **36** was secured in moderate yield (42%) and with excellent diastereoselectivity (≥93% d.e.) (Scheme 8). The *anti* relative stereochemistry was assigned to **36** by analogy with the above cinnamide result.

Hydroxylation of α-Alkyl β-Amino Enolates.—We have previously shown that the asymmetric protonation of β-amino-α-alkyl enolates derived from the conjugate addition of the lithium amide (*R*)-**14** to appropriate α-alkyl enoate acceptors can occur with excellent diastereoselectivity to afford the corresponding *syn* β-amino-α-alkyl ester products.[20] In view of the interest in β-amino-α-alkyl-α-hydroxy acids such as leuhistin **3**, it was of interest to investigate whether the above asymmetric hydroxylation protocol could be applied to such a system. Although the asymmetric hydroxylation of fully-substituted enolates has received some attention,[21] these enolates were generated using standard enolisation procedures and not by a conjugate addition strategy.

tert-Butyl (*E*)-2-methylbut-2-enoate **38** was chosen as a model substrate and the tandem addition–hydroxylation procedure was attempted in THF using the lithium amide (*R*)-**14** and the oxaziridine (+)-**8** under standard conditions. Unfortunately, although the product **39** was generated with excellent diastereoselectivity (94% d.e.), the isolated yield was poor (18%). Interestingly, however, if the addition of the amide (*R*)-**14** was performed using toluene as solvent and an excess of THF was added before the addition of the oxaziridine (+)-**8**, then only a slight compromise in diastereoselectivity was observed (83% d.e.) and the isolated yield of the adduct **39** was significantly improved (54%) (Scheme 10). It is also noteworthy



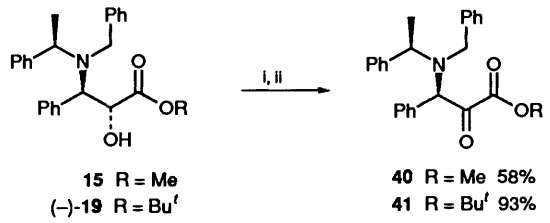
Scheme 10 *Reagents:* i, (*R*)-**14**, toluene; ii, xs. THF; iii, (+)-**8**

that if the addition–hydroxylation sequence was performed in neat toluene, with the addition of THF omitted, then essentially no control over the α-stereoselectivity was obtained. The importance of THF for good control over the π-facial selectivity of electrophilic hydroxylation in this system is consistent with the observations[20] in the corresponding asymmetric protonation reactions and is presumably related to the ability of THF to complex with the lithium atom in the intermediate β-enolate. The relative stereochemistry of compound **39** was assigned as *anti* by analogy with the asymmetric protonation results[20] and the hydroxylation results described herein.

Preparation and Reduction of Homochiral β-Amino-α-Keto Esters.—Although the above methodology provides a direct approach to β-amino-α-hydroxy acids with *anti* relative stereochemistry, we required a procedure for the preparation of the *syn* diastereoisomers. In our studies on the taxol side chain synthesis,[8] we have shown that, after debenzylation, the *anti* diastereoisomers can be efficiently converted to their *syn* alternatives by inversion of the α-hydroxyl stereochemistry *via* an oxazoline intermediate. Nevertheless, it was desirable to develop alternative procedures for the preparation of the *syn* diastereoisomers from the initial *anti* adducts in order to aid an accurate measurement of reaction diastereoselectivities. One potentially direct approach to the *syn* diastereoisomers could be *via* the stereoselective reduction of the keto moiety in the corresponding β-amino-α-keto esters. Despite the evident destruction of a precious stereogenic centre, it was anticipated that the necessary β-amino-α-keto ester starting materials could be prepared by the oxidation of the original *anti* diastereomeric adducts. After screening a number of oxidation procedures using the hydroxy methyl ester **15** as a model substrate, the Swern oxidation[22] protocol was found to be the most efficient. Thus, Swern oxidation of compound **15** and subsequent chromatography of the crude product, provided the β-amino-α-keto ester **40** as a single diastereoisomer in 58% yield (Scheme 11). It was found that prolonged standing of the keto ester **40** as the pure oil resulted in gradual epimerisation of the β-stereogenic centre and consequently it was necessary to effect immediate reduction of the α-keto moiety in order to avoid this compromise of stereochemical integrity. Under identical oxidation conditions, the β-amino-α-keto ester **41** was also prepared and isolated in excellent yield (93%) as a single diastereoisomer (Scheme 11).

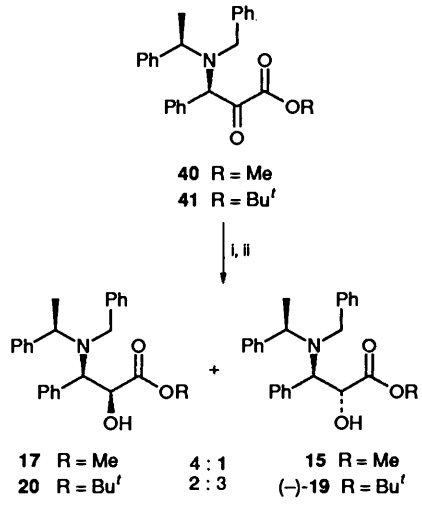
In view of the vulnerability towards epimerisation, it was considered frivolous to undertake a systematic survey of asymmetric reductions of the keto esters **40** and **41** with different reducing agents. Nevertheless, even the stereorandom reduction of both **40** and **41** was anticipated to provide samples of the desired *syn* β-amino-α-hydroxy esters.

Consequently, a solution of freshly prepared keto ester **40** in methanol was reduced with an excess of sodium borohydride. Interestingly, the reduction proceeded cleanly to afford a 4:1 mixture of the β-amino-α-hydroxy esters in favour of the



Scheme 11 *Reagents:* i, $(COCl)_2$, DMSO, −60 to −10 °C; ii, Et_3N

desired *syn* α-epimeric product **17** which was isolated by chromatography in 53% yield (Scheme 12). The ^1H NMR



Scheme 12 *Reagents:* i, $NaBH_4$, MeOH

spectrum of this material was identical to the sample of compound **17** secured in the 'mismatched' hydroxylation of compound **16** described above, thus confirming the previous stereochemical assignment.

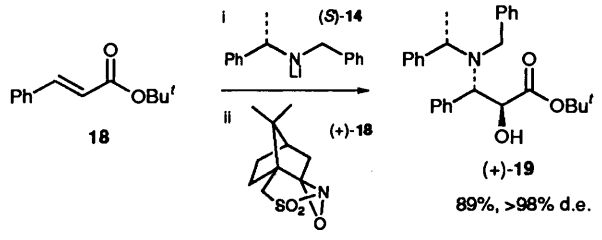
Despite the moderate *syn* selectivity obtained in the reduction of the ketone **40**, treatment of compound **41** with sodium borohydride under identical conditions led to the formation of a 3:2 mixture of α-epimeric products with the *anti* diastereoisomer (−)-**19** now predominating (Scheme 12). Purification by chromatography afforded (−)-**19** and the desired *syn* diastereoisomer **20** in 52% and 31% yields respectively. Again, the ^1H NMR spectrum of compound **20** was identical with that obtained in the aforementioned tandem addition–hydroxylation reaction and confirmed the previous stereochemical assignment. The reasons for the observation that changing the ester substituent has such a significant effect on the diastereofacial selectivity of reduction in the above reactions are not yet clear.

Molecular Recognition in the Tandem Addition–Hydroxylation Protocol.—It initially appeared that the stereochemical outcome of the β-amino enolate hydroxylation reactions was under almost exclusive substrate control and the stereochemistry of the oxaziridine was of only minor significance. As described above, Davis has reported that the oxaziridine stereochemistry is of negligible importance in the hydroxylation of the enolate derived from compound **7** (*vide supra*) and our observations in the stepwise hydroxylation procedure supported this observation. Nevertheless, we did note a slight improvement in selectivity in the hydroxylation of compound **16** if the oxaziridine (+)-**8** was employed, and this led us to use

this reagent for the hydroxylation of the lithium amide (*R*)-**14** derived β-amino enolates in general.

Nevertheless, the identification of stereodivergent enolate generation in the tandem and stepwise procedures,[11] together with the confirmation of the stereochemistry of the minor *syn* diastereoisomer **20** by the independent preparation described above, prompted us to investigate the effect of chirality recognition in the tandem protocol with *tert*-butyl cinnamate **18**. Since the effects of chirality recognition can be readily ascertained by inverting the stereochemistry of either homochiral reaction partner, the requirement for the enantiomer (+)-**19** in a synthetic study[4] encouraged us to investigate any recognition effects by using the enantiomeric lithium amide (*S*)-**14**, with the oxaziridine configuration being maintained (+)-**8**.

Thus, the tandem addition–hydroxylation of compound **18** was attempted using the lithium amide (*S*)-**14** and the oxaziridine (+)-**8** and, to our surprise, the *anti* diastereoisomer (+)-**19** was formed exclusively under these conditions (>98% d.e.) (Scheme 13). This improvement in diastereoselectivity



Scheme 13 *Reagents:* i, (*S*)-**14**; ii, (+)-**8**

indicates that the pairing of reagents described here corresponds to the 'matched' reaction (cf. 92% d.e. for the 'mismatched pair', *vide supra*). Consequently, it appears that the 'matched' pairing of reagents in the stepwise protocol corresponds to the 'mismatched' pairing in the alternative tandem procedure, the origin of this divergence presumably being that of enolate geometry. The corollary to this observation is that the diastereoselectivities in the aforementioned tandem addition–hydroxylation reactions may be slightly improved if the reactions were repeated using the complementary pairings of reagents. Nevertheless, the premise that the chirality of the substrate is the predominate stereodirecting feature in both the stepwise and the tandem protocols appears secure, and any improvement might be expected to be only slight.

Conclusion

The asymmetric hydroxylation of homochiral β-amino enolates has been developed into an efficient procedure for the synthesis of β-amino-α-hydroxy acids of defined absolute and relative stereochemistry. Furthermore, the excellent diastereoselectivities and yields obtained in these reactions renders the methodology described herein ideal for the synthesis of structurally diverse β-amino-α-hydroxy acids of biological significance.[4,8]

Experimental

General.—M.p.s were determined using either a Gallenkamp or a Koffler hot stage apparatus and are uncorrected. Optical rotations were recorded using a Perkin-Elmer 241 Polarimeter with a thermally jacketted 10 cm cell and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were obtained on a Perkin-Elmer 781 or Perkin-Elmer 1750 spectrophotometer with solution spectra generally being recorded in chloroform using 0.1 mm or 1.0 mm NaCl cells. NMR spectra were generally recorded in deuteriochloroform and referenced with respect to residual protio solvent as the internal standard. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00) and coupling constants (J) are measured in Hertz. ^{1}H NMR spectra were recorded using either Bruker WH300 or AM500 spectrometers and ^{13}C NMR spectra were recorded with DEPT editing as necessary using either the latter instrument or a Varian Gemini 200. Mass spectra were recorded on a VG MASSLAB VG 20-250 instrument using the chemical ionisation (CI) technique. Elemental analyses were performed by the Dyson Perrins Laboratory analytical department. Flash column chromatography was undertaken on silica gel (kieselgel 60). Tetrahydrofuran was distilled from sodium–benzophenone under an atmosphere of dry nitrogen. Petroleum refers to that fraction of light petroleum which boils in the range 40–60 °C and was redistilled before use. Reactions involving lithium amides were performed under an atmosphere of dry nitrogen and reaction diastereoselectivities were determined by integration of the appropriate peaks in the ^{1}H NMR spectrum of the crude reaction product.

Standard Procedure A.—A solution of the β-amino ester (1.00 mmol) in anhydrous THF (5 cm^3) was cooled to 0 °C and 1.0 mol dm^{-3} lithium hexamethyldisilylazanide (LHMDS) (1.50 mmol) added dropwise *via* a syringe. After being stirred at 0 °C for 30 min, the resultant yellow enolate solution was cooled to −78 °C and solid (camphorsulfonyl)oxaziridine was added (2.00 mmol) to it. The mixture was then stirred for 1.5 h at −78 °C, warmed to 0 °C over 15 min, quenched by the addition of sat. aq. ammonium chloride and evaporated under reduced pressure. The residue was diluted with water (20 cm^3) and then extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford an oily solid residue. This material was either directly subjected to flash chromatography on silica gel or, if desired for recycling; the oxaziridine–sulfonimine residues could first be precipitated by the addition of diethyl ether.

Standard Procedure B.—A solution of the homochiral benzyl(α-methylbenzyl)amine[23] (1.60 mmol) in anhydrous THF (5 cm^3) was cooled to 0 °C and 1.60 mol dm^{-3} butyllithium (1.50 mmol) added dropwise to it *via* a syringe. The resultant pink lithium amide solution was stirred at 0 °C for 45 min and subsequently cooled to −78 °C. The Michael acceptor (1.00 mmol) was then added to it as a solution in anhydrous THF (2 cm^3) and stirring was continued for 2 h. After this the resultant yellow to pink enolate solution was treated with solid (camphorsulfonyl)oxaziridine (1.60 mmol). After being stirred for a further 1 h at −78 °C, the mixture was warmed to 0 °C (15 min), quenched by the addition of sat. aq. ammonium chloride and subjected to the work-up procedure described in Standard Procedure A.

Tandem Preparation of Methyl (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxy*-3-*phenylpropionate* **15**.—Methyl cinnamate **13** (200 mg, 1.23 mmol) was treated with the lithium amide derived from (*R*)-benzyl(α-methylbenzyl)amine and hydroxylated with the oxaziridine (+)-**8** in accordance with the Standard Procedure B. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 2:1) gave the title compound as a colourless oil, contaminated with (*R*)-benzyl(α-methylbenzyl)amine. The amine was removed by heating *in vacuo* at 150 °C for 4 h to afford the title compound as a colourless oil (207 mg, 43%), which was spectroscopically identical with a sample prepared *via* the stepwise hydroxylation protocol (*vide infra*).

Stepwise 'Matched' Preparation of Methyl (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxy*-3-*phenylpropionate* **15**.—The β-amino ester **16** (5.40 g, 14.5 mmol) was deprotonated with LHMDS and hydroxylated with the oxaziridine (+)-**8** in accordance with the Standard Procedure A. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 2:1) gave the title compound as a colourless oil (4.75 g, 84%); $[\alpha]_D^{23}$ −5.5 (*c* 1.10, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3528m (OH) and 1736vs (C=O); δ_H(300 MHz; $CDCl_3$) 7.49–7.20 (15 H, m, Ph), 4.55 and 4.25 [2 H, AB, J_{AB} 4.5, C*H*(OH)C*H*N), 4.18 (1 H, q, *J* 6.9, NC*H*Me), 4.12 and 3.71 (2 H, AB, J_{AB} 14.8, NCH_2Ph), 3.53 (3 H, s, CO_2Me), 2.36 (1 H, br s, CH(O*H*)] and 1.23 (3 H, d, *J* 6.9, NCH*Me*); δ_C(50 MHz; $CDCl_3$) 173.2 (CO_2), 143.9, 141.4 and 138.0 (Ph: C_{ipso}), 129.7, 128.7, 128.5, 128.3, 128.2 and 127.2 (Ph: C_{ortho}, C_{meta} and C_{para}), 72.7 [*C*H(OH)], 67.3 [CH(OH)*C*HN], 59.7 (N*C*HMe), 52.2 (NCH_2Ph), 52.1 (CO_2Me) and 12.4 (NCH*Me*); *m*/*z*(CI) 390 (MH^+, 30%), 300 (34), 196 (48), 105 (52) and 91 (100) (Found: C, 77.3; H, 6.9; N, 3.4. $C_{25}H_{27}NO_3$ requires C, 77.09; H, 6.99; N, 3.60%).

Stepwise 'Mismatched' Preparation of Methyl (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxy*-3-*phenylpropionate* **15**.—The β-amino ester **16** (1.30 g, 3.48 mmol) was deprotonated with LHMDS and hydroxylated with the oxaziridine (−)-**8** in accordance with Standard Procedure A. In contrast to the analogous reaction using the opposite enantiomer (+)-**8** (*vide supra*), analysis of the crude product by ^1H NMR spectroscopy (and by TLC) indicated the generation of a small amount of the *syn*- diastereoisomer **17** (28:1, 93% d.e. in favour of compound **16**). Consequently, the pairing described herein constitutes the 'mismatched' reaction. Purification by flash chromatography on silica gel (petrol–diethyl ether, 2:1) afforded first a small amount of the *syn*-diastereoisomer **17** as a colourless oil (40 mg, 3%) followed by the more polar title compound, also as a colourless oil (963 mg, 71%). The ^1H NMR spectrum of the minor diastereoisomer was identical with that of an authentic sample prepared by an oxidation–reduction sequence (*vide infra*).

Tandem Preparation of tert-*Butyl* (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxy*-3-*phenylpropionate* (−)-**19**.—*tert*-Butyl cinnamate **18** (2.00 g, 9.80 mmol) was treated with the lithium amide derived from (*R*)-benzyl(α-methylbenzyl)amine and hydroxylated with the oxaziridine (+)-**8** in accordance with Standard Procedure B. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 5:1) afforded the title compound **19** as a colourless oil (3.61 g, 86%) and the more polar α-epimeric (*syn*) diastereoisomer **20** as a colourless oil, which crystallised upon storage (150 mg, 3%). This minor diastereoisomer was later prepared independently by an oxidation–reduction sequence (*vide infra*) and fully characterised. The title compound could be readily crystallised from hexane; m.p. 87–88 °C; $[\alpha]_D^{20}$ −27.2 (*c* 0.98, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3484br (OH) and 1720s (C=O): δ_H(300 MHz; $CDCl_3$) 7.50–7.22 (15 H, m, Ph), 4.39 [1 H, br s, C*H*(OH)], 4.22 [2 H, m, CH(OH)C*H*N and NC*H*Me], 4.14 and 3.84 (2 H, AB, J_{AB} 15.0, NCH_2Ph), 2.77 [1 H, br s, CH(O*H*)], 1.22 (3 H, d, obscured, NCH*Me*) and 1.21 (9 H, s, CO_2CMe); D_2O shake: *inter alia* δ_H(300 MHz; $CDCl_3$) 4.39 [1 H, d, *J* 3.1, C*H*(OH)]; δ_C(125 MHz; $CDCl_3$) 172.2 (CO_2), 144.2, 141.9 and 138.4 (Ph: C_{ipso}), 129.9, 128.2, 128.1, 128.0, 127.5, 126.8 and 126.6 (Ph: C_{ortho}, C_{meta} and C_{para}), 82.2 [CO_2CMe_3], 73.6 [*C*H(OH)], 65.4 [CH(OH)*C*HN], 57.4 (N*C*HMe), 52.3 (NCH_2Ph), 27.7 (CO_2CMe_3) and 14.4 (NCH*Me*); *m*/*z*(CI) 432 (MH^+, 100%), 300 (66) and 196 (63) (Found: C, 78.15; H, 7.75; N, 3.05. $C_{28}H_{33}NO_3$ requires C, 77.93; H, 7.71; N, 3.25%).

Stepwise Preparation of tert-*Butyl* (2R,3R,αR)-3-[N-*Benzyl*-N-(α-methylbenzyl)*amino*]-2-*hydroxy*-3-*phenylpropionate* (−)-**19**.—A solution of diisopropylamine (78 mg, 0.771 mmol) in anhydrous THF (10 cm^3) was cooled to 0 °C and treated with 1.49 mol dm^{-3} butyllithium (0.49 cm^3, 0.723 mmol). After being stirred at 0 °C for 20 min, the colourless LDA solution was cooled to −78 °C and the β-aminoester **21** (200 mg, 0.482 mmol) in anhydrous THF (2 cm^3) was added. Stirring was continued for 1 h at −78 °C and then the resultant enolate solution was treated with the solid oxaziridine (+)-**8**. The mixture was then stirred for 1.5 h at −78 °C, warmed to 0 °C over 15 min, quenched by the addition of sat. aq. ammonium chloride and then subjected to the work-up procedure described in the Standard Procedure A. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 5:1) afforded the title compound as a colourless oil (187 mg, 90%) which was identical with that prepared using the previous tandem addition–hydroxylation procedure (*vide supra*).

Preparation of (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxy*-3-*phenylpropionic Acid* **22**.—A solution of the ester (−)-**19** (1.07 g, 2.48 mmol) in dichloromethane (10 cm^3) was treated with trifluoroacetic acid (5 cm^3) and stirred at room temp. overnight. The mixture was subsequently diluted with dichloromethane (50 cm^3) and cautiously treated with sat. aq. sodium hydrogen carbonate (80 cm^3). The organic layer was then separated and the aqueous. layer extracted with dichloromethane (2 × 60 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound (813 mg, 87%) as a colourless foam; m.p. 74 °C (decomp.) (from dichloromethane); $[\alpha]_D^{20}$ +21.2 (*c* 0.98, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3405s (OH), 2530m (acid OH) and 1718s (C=O); δ_H(300 MHz; $CDCl_3$) 7.56–7.22 (15 H, m, Ph), 4.52 and 4.42 [2 H, AB, J_{AB} 10.6, C*H*(OH)C*H*N], 4.31 (1 H, q, *J* 6.9, NC*H*Me), 4.10 and 3.75 (2 H, AB, J_{AB} 13.8, NCH_2Ph) and 1.51 (3 H, d, *J* 6.9, NCH*Me*); δ_C(50 MHz; $CDCl_3$) 176.1 (CO_2), 138.5, 134.4 and 133.0 (Ph: C_{ipso}), 130.6–128.6 (Ph: C_{ortho}, C_{meta}, C_{para}), 67.3 [*C*H(OH)], 65.0 and 60.8 [N*C*HMe, CH(OH)*C*HN], 52.1 (NCH_2Ph) and 15.5 (NCH*Me*); *m*/*z*(FAB) 376 (MH^+, 18%), 300 (14), 272 (28), 196 (22), 105 (100) and 91 (62) (Found: C, 76.5; H, 6.8; N, 4.0. $C_{24}H_{25}NO_3$ requires C, 76.77; H, 6.71; N, 3.73%).

Preparation of Methyl (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxy*-3-*phenylpropionate* **15**.—A solution of the acid **22** (289 mg, 0.77 mmol) in diethyl ether (15 cm^3) was cooled to 0 °C and treated with an excess of diazomethane (as a diethyl ether solution) which had been freshly prepared from Diazald™ (2.14 g, 10.0 mmol) according to a literature procedure.[24] After being stirred for 15 min, the mixture was warmed to room temp. and stirring continued for a further 15 min. The excess of diazomethane was then removed with a stream of nitrogen until the yellow solution became colourless. After this it was evaporated under reduced pressure to afford the title compound (296 mg, 99%) which was spectroscopically identical with the sample previously prepared (*vide supra*).

Preparation of [tert-*Butyl* (2R,3R)-3-*Amino*-2-*hydroxy*-3-*phenylpropionate* **23**.—The β-amino ester (−)-**19** (500 mg, 1.16 mmol) was dissolved in acetic acid (8 cm^3) and 10% palladium on activated carbon (200 mg) was added to the solution. The mixture was then stirred at room temp. overnight under 7 atm of hydrogen. After the catalyst had been filtered off, the filtrate was evaporated and the resultant acetate salt was diluted with dichloromethane (30 cm^3) and treated with sat. aq. sodium hydrogen carbonate (20 cm^3). After thorough mixing, the organic layer was separated and the aqueous layer extracted with further dichloromethane (2 × 30 cm^3). The combined

organic layer and extracts were washed with a further portion of sat. aq. sodium hydrogen carbonate (10 cm^3), dried ($MgSO_4$), filtered and then evaporated under reduced pressure to afford the title compound as a colourless oil, which crystallised upon storage (272 mg, 99%); m.p. 63–64 °C (from dichloromethane); $[\alpha]_D^{25}$ −29.0 (*c* 0.50, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725m (C=O); δ_H(300 MHz; $CDCl_3$) 7.35–7.23 (5 H, m, Ph), 4.36 and 4.28 [2 H, AB, J_{AB} 3.6, C*H*(OH)C*H*N], 2.13 [3 H,br s, CH(O*H*) and CH(NH_2)] and 1.33 (9 H, s, CO_2CMe_3]; δ_C(125 MHz; $CDCl_3$) 171.7 (CO_2), 140.9 (Ph: C_{ipso}), 128.2 and 127.3 (Ph: C_{ortho}, C_{meta}), 127.6 (Ph: C_{para}), 82.7 (CO_2CMe_3), 75.0 [*C*H(OH)], 58.3 [CH(OH)*C*HN] and 27.9 (CO_2CMe_3); *m*/*z* (CI) 238 (MH^+, 62%), 182 (55) and 106 (100) (Found: C, 65.8; H, 8.3; N, 5.9. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%).

Preparation of (2R,3R)-3-*Carboxy*-2-*hydroxy*-1-*phenylpropanylammonium hydrochloride* **24**.—The β-amino ester **23** (272 mg, 1.15 mmol) was dissolved in trifluoroacetic acid (2 cm^3) and the solution stirred at room temp. overnight. The trifluoroacetic acid was subsequently removed under reduced pressure and the resultant oil dissolved in the minimum amount of hydrochloric acid (10%). The solvent was then removed under reduced pressure to afford the title compound as a white solid in quantitative yield. An analytical sample was obtained by recrystallisation from methanol–isopropyl alcohol; m.p. 240 °C (decomp.); $[\alpha]_D^{20}$ +25.1 (*c* 0.98, MeOH); ν_{max}(KBr)/cm^{-1} 1723vs (C=O); δ_H(300 MHz; CD_3OD) 7.55–7.51 (2 H, m, Ph), 7.42–7.40 (3 H, m, Ph) and 4.70 and 4.67 [2 H, AB, J_{AB} 3.9, C*H*(OH)C*H*N]; δ_C(125 MHz; CD_3OD) 173.1 (CO_2), 134.0 (Ph: C_{ipso}), 130.6 (Ph: C_{para}), 129.8 and 129.7 (Ph: C_{ortho} and C_{meta}), 72.0 [*C*H(OH)] and 57.9 [CH(OH)*C*HN]; *m*/*z*(CI) 182 (M^+, 100%) and 106 (58) (Found: C, 49.6; H, 5.8; N, 6.3. $C_9H_{12}ClNO_3$ requires C, 49.67; H, 5.56; N, 6.44%).

Tandem Preparation of Methyl (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxybutyrate* **26**.—Methyl crotonate **25** (250 mg, 2.50 mmol) was treated with the lithium amide derived from (*R*)-benzyl(α-methylbenzyl)amine and hydroxylated with the oxaziridine (+)-**8** in accordance with Standard Procedure B. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 3:1) furnished an inseparable mixture of the α-epimeric products, contaminated with (*R*)-benzyl(α-methylbenzyl)amine. This secondary amine was removed by heating *in vacuo* overnight to afford the title compound (75% d.e.) as a colourless oil (446 mg, 55%). The major diastereoisomer was seen to be the same as that observed in the stepwise procedure (*vide infra*); minor (*syn*): *inter alia* δ_H(300 MHz; $CDCl_3$) 3.52 (3 H, s, CO_2Me).

Preparation of tert-*Butyl* (2R,3R,αR)-3-N-*Benzyl*-N-α-*methylbenzyl*)*amino*-2-*hydroxybutyrate* **29**.—*tert*-Butyl crotonate **28** (500 mg, 3.52 mmol) was treated with the lithium amide derived from (*R*)-benzyl(α-methylbenzyl)amine and hydroxylated with the oxaziridine (+)-**8** in accordance with the Standard Procedure B. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 5:1) afforded the title compound (≥98% d.e.) as a white, crystalline solid (463 mg, 36%); m.p. 88–89 °C (from diethyl ether–hexane); $[\alpha]_D^{22}$ −35.2 (*c* 1.00, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1719s (C=O); δ_H(300 MHz; $CDCl_3$) 7.57–7.19 (10 H, m, Ph), 4.02 [3 H, m, C*H*(OH), NC*H*Me and NC*H*HPh], 3.88 (1 H, part AB, J_{AB} 14.8, NCH*H*Ph), 3.27 (1 H, dq, *J* 7.0 and 2.6, CH(OH)C*H*Me), 2.94 [1 H, br d, *J* 6.1, CH(O*H*)], 1.37 (9 H, s, CO_2CMe_3), 1.33 (3 H, d, *J* 6.8, NCH*Me*) and 1.09 [3 H, d, *J* 7.0, CH(OH)CH*Me*]; δ_C(50 MHz; $CDCl_3$) 174.2 (CO_2), 144.6 and 142.6 (Ph: C_{ipso}), 128.6, 128.4, 128.0, 127.0 and 126.8 (Ph: C_{ortho}, C_{meta}, C_{para}), 82.1 (CO_2CMe_3), 73.6 [*C*H(OH)], 57.9 (N*C*HMe), 54.2 [CH(OH)*C*HN], 50.7 (N*C*H_2Ph), 27.8 (CO_2CMe_3) and 16.5 and 12.5 [NCH*Me*, CH(OH)CH*Me*]; *m*/*z*(CI) 370 (MH^+, 100%), 238 (66), 134 (67), 105 (36) and 91 (40) (Found: C, 75.0; H, 8.6; N, 3.6. $C_{23}H_{31}NO_3$ requires C, 74.76; H, 8.46; N, 3.79%).

Preparation of tert-*Butyl* (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxypentanoate* **31**.—*tert*-Butyl (*E*)-pent-2-enoate **30** (300 mg, 1.92 mmol) was treated with the lithium amide derived from (*R*)-benzyl(α-methylbenzyl)amine and hydroxylated with the oxaziridine (+)-**8** in accordance with the Standard Procedure B. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 9:1) afforded the title compound (≥90% d.e.) as a colourless oil (392 mg, 53%); $[\alpha]_D^{20}$ −12.5 (*c* 1.00, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3511w (OH) and 1717vs (C=O); δ_H(300 MHz; $CDCl_3$) 7.51–7.21 (10 H, m, Ph), 4.23 and 3.72 (2 H, AB, J_{AB} 15.3, NCH_2Ph), 3.97 (1 H, q, *J* 7.0, NC*H*Me), 3.88 [1 H, m, C*H*(OH)], 3.15 [1 H, m, CH(OH)C*H*N], 2.94 [1 H, br d, *J* 6.0, CH(O*H*)], 1.64 (2 H, m, MeCH_2CHN), 1.44 (9 H, s, CO_2CMe_3), 1.33 (3 H, d, *J* 7.0, NCH*Me*), 1.00 (3 H, t, *J* 7.4, *Me*CH_2CHN); D_2O shake: *inter alia* δ_H(300 MHz; $CDCl_3$) 3.88 [1 H, d, *J* 1.9, C*H*(OH)]; δ_C(50 MHz; $CDCl_3$) 174.8 (CO_2), 143.6 and 142.7 (Ph: C_{ipso}), 128.4, 128.3, 127.1 and 126.6 (Ph: C_{ortho}, C_{meta}, C_{para}), 82.4 (CO_2CMe_3), 71.1 [*C*H(OH)], 60.8 [CH(OH)*C*HN], 58.1 (N*C*HMe), 51.0 (N*C*H_2Ph), 27.9 (CO_2CMe_3), 20.4 (MeCH$_2$-CHN), 18.6 (NCH*Me*) and 11.8 (*Me*CH_2CHN); *m*/*z*(CI) 384 (MH^+, 100%), 252 (79) and 148 (35) (Found: C, 75.1; 8.9; N, 3.6. $C_{24}H_{33}NO_3$ requires C, 75.16; H, 8.67; N, 3.65%).

Stepwise Preparation of Methyl (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)]*amino*-2-*hydroxybutyrate* **26**.—The β-amino ester **32** (500 mg, 1.61 mmol) was deprotonated with LHMDS and hydroxylated with the oxaziridine (+)-**8** in accordance with the Standard Procedure A. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 2:1) afforded the title compound (94% d.e.) as a colourless oil (355 mg, 68%); $[\alpha]_D^{25}$ −9.2 (*c* 0.97, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3531w (OH) and 1730vs (C=O); δ_H(300 MHz; $CDCl_3$) 7.49–7.20 (10 H, m, Ph), 3.98 [2 H, m, C*H*(OH) and NC*H*Me], 3.84 and 3.81 (2 H, AB system, J_{AB} 14.3, NCH_2Ph), 3.65 (3 H, s, CO_2Me), 3.25 [1 H, m, CH(OH)C*H*N], 2.92 [1 H, br s, CH(O*H*], 1.36 (3 H, d, *J* 6.9, NCH*Me*) and 1.19 [3 H, d, *J* 7.0, CH(OH)CH*Me*]; δ_H(50 MHz; $CDCl_3$) 174.7 (CO_2), 143.9 and 141.4 (Ph: C_{ipso}) 128.9, 128.5, 128.4, 128.0 and 127.0 (Ph: C_{ortho}, C_{meta} and C_{para}), 73.3 [*C*H(OH)], 56.9 (N*C*HMe), 54.1 [CH(OH)*C*HN], 52.0 (CO_2Me), 50.9 (N*C*H_2Ph) and 14.2 and 13.1 [NCH*Me* and CH(OH)CH*Me*]; *m*/*z*(CI) 328 (MH^+, 100%), 238 (89) 134 (64), 105 (34) and 91 (37) (Found: C, 73.6; H, 8.0; N, 4.4. $C_{20}H_{25}NO_3$ requires C, 73.37; H, 7.70; N, 4.28%).

Preparation of (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)-*amino*]-2-*hydroxy*-N,N-*dimethyl*-3-*phenylpropionamide* **34**.—(*E*)-*N*,*N*-Dimethylcinnamide **33** (500 mg, 2.86 mmol) was treated with the lithium amide derived from (*R*)-benzyl-(α-methylbenzyl)amine and hydroxylated with the oxaziridine (+)-**8** in accordance with the Standard Procedure B. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 1:1) afforded the title compound (≥95% d.e.) as a colourless oil (977 mg, 85%); $[\alpha]_D^{20}$ −73.9 (*c* 1.03, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400m (OH) and 1646vs (C=O); δ_H(300 MHz; $CDCl_3$) 7.69–7.17 (15 H, m, Ph), 4.77 [1 H, d, *J* 2.1, C*H*(OH)], 4.71 and 3.90 (2 H, AB J_{AB} 14.0, NCH_2Ph), 4.32 (1 H, q, *J* 6.9, NC*H*Me), 3.86 [1 H, d, *J* 2.1, CH(OH)C*H*N], 3.81 [1 H, br s, CH(O*H*)], 2.71 [3 H, s, CON(*Me*)Me], 2.25 [3 H, s, CON(Me)*Me*] and 1.03 (3 H, d, *J* 6.9, NCH*Me*); δ_C(50 MHz; $CDCl_3$) 172.5 (CO_2), 144.9, 141.9 and 138.4 (Ph: C_{ipso}), 130.2, 129.0, 128.5, 128.2, 127.8 and 127.0 (Ph: C_{ortho}, C_{meta} and C_{para}), 74.3 [*C*H(OH)], 62.3 [CH(OH)*C*HN], 56.2 (N*C*HMe),

52.3 (NCH$_2$Ph), 35.8 and 35.5 (CONMe) and 12.9 (NCH*Me*); *m/z*(CI) 403 (MH^+, 100%), 300 (66), 196 (50), 105 (31), 91 (58) and 72 (27) (Found: C, 77.6; H, 7.2; N, 7.0. $C_{26}H_{30}N_2O_2$ requires C, 77.58 H, 7.51; N, 6.96%).

Preparation of (4R,5R)-5-(*Dimethylcarbamoyl*)-4-*phenyloxazolidin*-2-*one* **37**.—The β-amino amide **34** (960 mg, 2.39 mmol) was debenzylated in an analagous manner to that described above for (−)-**19**. The resultant acetate salt was dissolved in a solution of anhydrous methanol saturated with gaseous HCl and the solution stirred for 5 min; the solvent was then evaporated under reduced pressure and dichloromethane (20 cm^3) added to the residue. Triethylamine (1.21 g, 11.9 mmol) was then added to the mixture which was then stirred for 30 min at room temp. The resultant solution was then treated with solid carbonyldiimidazole (580 mg, 3.58 mmol) and stirring was continued overnight. The solution was subsequently treated with dilute (1.0 mol dm^{-3}) hydrochloric acid (20 cm^3) and extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification of the residue by flash chromatography on silica gel (ethyl acetate), trituration of the resultant solid with diethyl ether and recrystallisation from chloroform afforded the title compound as colourless plates (58 mg, 10%); m.p. 182–184 °C; $[\alpha]_D^{20}$ −85.6 (*c* 0.55, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3455m (NH), 1773vs (oxazolidinone C=O) and 1671s (amide C=O); δ_H(300 MHz; $CDCl_3$) 7.37 (5 H, s, Ph), 5.60 (1 H, br s, CON*H*), 5.59 (1 H, d, *J* 8.9, CHC*H*CON), 5.25 (1 H, d, *J* 8.9, C*H*CHCON), 2.59 [3 H, s, $CO_2N(Me)Me$] and 2.52 [3 H, s, $CO_2N(Me)Me$]; δ_C(50 MHz; $CDCl_3$); 165.5 ($CONMe_2$), 159.0 (CONH), 135.4 (Ph: C_{ipso}), 129.5 (Ph: C_{para}), 128.7 and 127.6 (Ph: C_{ortho} and C_{meta}), 76.6 (CHCHCON), 58.9 (CHCHCON) and 36.2 and 35.3 (CO_2NMe_2); *m/z*(CI) 252 (MNH_4^+, 22%), 235 (MH^+, 100), 102 (23) and 42 (39) (Found: C, 61.7; H, 6.1; N, 12.2. $C_{12}H_{14}N_2O_3$ requires C, 61.53; H, 6.02; N, 11.96%).

Preparation of (2R,3R,αR)-3-[N-*Benzyl*-N-(α-methylbenzyl)-*amino*]-2-*hydroxy*-N,N-*dimethylbutanamide* **36**.—(*E*)-*N*,*N*-Dimethylcrotonamide **35** (200 mg, 1.77 mmol) was treated with the lithium amide derived from (*R*)-benzyl(α-methylbenzyl)-amine and hydroxylated with the oxaziridine (+)-**8** in accordance with the Standard Procedure B. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 1:1) afforded the title compound as a colourless crystalline solid (251 mg, 42%) m.p. 119–120 °C (from diethyl ether); $[\alpha]_D^{21}$ −92.5 (*c* 0.93, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3438w (OH) and 1640vs (C=O); δ_H(300 MHz; $CDCl_3$) 7.51–7.17 (10 H, m, Ph), 4.44 [1 H, dd, *J* 7.0, 1.4, C*H*(OH)CHMe], 4.29 and 3.75 (2 H, AB, J_{AB} 13.8, NC*H*$_2$Ph), 4.13 (1 H, q, *J* 6.9, NC*H*Me), 3.84 [1 H, d, *J* 7.0, CH(O*H*)], 2.86 [1 H, qd, *J* 6.9, 1.4, CH(OH)C*H*Me], 2.81 [3 H, s, CON(*Me*)Me], 1.99 [3 H, s, CON(Me)*Me*], 1.38 (3 H, d, *J* 6.9, NCH*Me*) and 1.04 [3 H, d, *J* 6.9, CH(OH)CH*Me*]; δ_C(125 MHz; $CDCl_3$) 173.3 (CO_2), 145.3 and 142.0 (Ph: C_{ipso}), 129.0, 128.2, 128.1 and 128.0 (Ph: C_{ortho} and C_{meta}), 126.6 and 126.5 (Ph: C_{para}), 74.8 (*C*H(OH)], 56.0 (NC*H*Me), 52.2 [CH(OH)*C*HN], 50.9 (NCH$_2$Ph), 35.8 and 35.0 ($CONMe_2$) and 13.5 and 10.5 [NCH*Me*, CH(OH)CH*Me*]; *m/z*(CI) 341 (MH^+, 100%), 238 (44) and 134 (23) (Found: C, 74.2; H, 8.4; N, 8.1. $C_{21}H_{28}N_2O_2$ requires C, 74.08 H, 8.29; N, 8.23%).

Preparation of tert-*Butyl* (2R,3R,αR)-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxy*-2-*methylbutyrate* **39**.—A solution of (*R*)-benzyl(α-methylbenzyl)amine (433 mg, 2.05 mmol) in anhydrous toluene (8 cm^3) was cooled to −78 °C and 1.60 mol dm^{-3} butyllithium (1.20 cm^3, 1.92 mmol) added to it dropwise *via* a syringe. The resultant pale pink lithium amide solution was stirred at −78 °C for 30 min and *tert*-butyl (*E*)-2-methylbut-2-enoate **38** (200 mg, 1.56 mmol) was then added to it as a solution in anhydrous toluene (2 cm^3). Stirring was continued for 1 h at −78 °C after which the mixture was stored in a freezer (−30 °C) for a further 3 h. The pale pink solution was recooled to −78 °C and diluted with anhydrous THF (40 cm^3). After being stirred at −78 °C for 5 min, the now deep red-pink solution was treated with the oxaziridine (+)-**8** (470 mg, 2.05 mmol) and the stirred solution then allowed to warm to room temp. overnight. The mixture was subsequently quenched with sat. aq. ammonium chloride, evaporated under reduced pressure and the residue diluted with water (20 cm^3) before extraction with dichloromethane (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum–diethyl ether, 9:1) afforded the title compound as a colourless oil (267 mg, 54%); $[\alpha]_D^{23}$ −25.8 (*c* 1.00, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1714m (C=O); δ_H(300 MHz; $CDCl_3$) 7.51–7.17 (10 H, m, Ph), 4.16 and 3.62 (2 H, AB, J_{AB} 13.3, NC*H*$_2$Ph), 4.03 (1 H, br q, *J* 6.9, NC*H*Me), 3.59 [1 H, s, C(O*H*)], 3.01 [1 H, q, *J* 6.9, C(OH)C*H*Me], 1.40 (9 H, s, CO_2CMe), 1.38 (3 H, d, obscured, NCH*Me*), 1.20 [3 H, d, *J* 6.9, C(OH)CH*Me*] and 0.93 [3 H, s, C(OH)*Me*]; δ_C(125 MHz; $CDCl_3$) 176.5 (CO_2), 143.8 and 141.2 (Ph: C_{ipso}), 129.5, 128.4, 128.2 and 127.9 (Ph: C_{ortho}, C_{meta}) 126.8 and 126.7 (Ph: C_{para}), 81.6 (CO_2CMe_3), 78.0 [*C*(OH)Me], 56.2 and 55.7 (NCHMe and C(OH)CHMe), 51.5 (NCH$_2$Ph), 27.8 (CO_2CMe_3), 24.4 [C(OH)*Me*] and 12.2 and 11.9 [NCH*Me* and C(OH)CH*Me*]; *m/z*(CI) 384 (MH^+, 100%), 238 (81), 134 (58), 105 (30) and 91 (33) (Found: C, 75.2; H, 8.4; N, 3.5. $C_{24}H_{33}NO_3$ requires C, 75.16; H, 8.67; N, 3.65%).

Preparation of Methyl (3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*oxo*-3-*phenylpropionate* **40**.—A solution of oxalyl chloride (82 mg, 0.646 mmol) in anhydrous dichloromethane (5 cm^3) was cooled to −60 °C and dimethyl sulfoxide (100 mg, 1.28 mmol) in anhydrous dichloromethane (1 cm^3) added to it. The mixture was stirred for 4 min, after which the alcohol **15** (100 mg, 0.257 mmol) in anhydrous dichloromethane (2 cm^3) was added to it and the whole stirred for 2 min at −60 °C. The mixture was then warmed to −10 °C (ice–salt bath), stirred for 30 min and treated with triethylamine (260 mg, 2.57 mmol); this resulted in rapid yellow colouration of the mixture. Stirring was continued for a further 5 min at −10 °C, the cold bath then removed and the solution allowed to warm to room temp. The mixture was then stirred for 1.5 h, diluted with water (20 cm^3), and extracted with dichloromethane (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Immediate purification of the residue by flash chromatography on silica gel (petroleum–diethyl ether, 9:1) afforded the diastereomerically pure title compound as a deep yellow oil (58 mg, 58%); $[\alpha]_D^{23}$ −116.4 (*c* 1.34, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1745m (ester C=O) and 1730s (ketone C=O); δ_H(300 MHz; $CDCl_3$) 7.40–7.25 (15 H, m, Ph), 5.47 (1 H, s, C*H*CO), 4.15 and 3.95 (2 H, AB, J_{AB} 15.1, NC*H*$_2$Ph), 4.12 (1 H, q, *J* 6.9, NC*H*Me), 3.65 (3 H, s, CO_2Me) and 1.24 (3 H, d, *J* 6.9, NCH*Me*$_3$); δ_C(125 MHz; $CDCl_3$) 167.2 (CO_2), 143.1, 140.5, 139.4 and 136.7 (Ph: C_{ipso} and *C*OCO$_2$), 130.3–126.1 (Ph: C_{ortho}, C_{meta} and C_{para}), 59.1 (*C*HCO and NCHMe), 51.7 (CO_2Me), 48.8 (NCH$_2$Ph) and 18.5 (NCH*Me*$_3$); *m/z*(CI) 388 (MH^+, 69%), 212 (100), 196 (89), 108 (59) and 91 (89) (Found: C, 77.4; H, 6.6; N, 3.5. $C_{25}H_{25}NO_3$ requires C, 77.49; H, 6.50; N, 3.61%).

Preparation of tert-*Butyl* (3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*oxo*-3-*phenylpropionate* **41**.—A solution of oxalyl chloride (221 mg, 1.74 mmol) in anhydrous dichloromethane (10 cm^3) was cooled to −60 °C and dimethyl sulfoxide (271 mg, 3.47 mmol) in anhydrous dichloromethane

($2\ cm^3$) added to it. After the mixture had been stirred for 4 min, the alcohol (−)-**19** (300 mg, 0.696 mmol) in anhydrous dichloromethane ($2\ cm^3$) was added to it and the whole stirred for 2 min at −60 C. The mixture was then warmed to −10 °C (ice–salt bath), stirred for 30 min and treated with triethylamine (703 mg, 6.96 mmol); this resulted in a rapid yellow colouration of the mixture. Stirring was continued for a further 5 min at −10 °C, after which the cold bath was removed and the solution allowed to warm to room temp. The mixture was then stirred for 1.5 h, diluted with water ($20\ cm^3$) and extracted with dichloromethane ($3 \times 30\ cm^3$). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Immediate purification of the residue by flash chromatography on silica gel (petroleum–diethyl ether, 9:1) afforded the title compound as a deep yellow oil; $[\alpha]_D^{23}$ −158.5 (*c* 0.84, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1737s (ester C=O and ketone C=O); δ_H(300 MHz; $CDCl_3$) 7.46–7.13 (15 H, m, Ph), 5.36 (1 H, C*H*CO), 4.16 and 3.97 (2 H, AB, J_{AB} 15.4, NCH_2Ph), 4.15 (1 H, q, *J* 6.8, NC*H*Me), 1.27 (9 H, s, CO_2CMe_3] and 1.20 (3 H, d, *J* 6.8, NCH*Me*); δ_C(50 MHz; $CDCl_3$) 197.0 (*C*OCO$_2$), 161.1 (*C*O$_2$), 144.5, 142.3 and 135.7 (Ph: C_{ipso}), 130.2, 128.9, 128.7, 128.4, 128.2, 128.1, 127.9, 127.5 and 126.6 (Ph: C_{ortho}, C_{meta} and C_{para}), 83.8 (CO_2CMe_3), 68.1 and 59.8 (*C*HCO and N*C*CHMe), 51.4 (N*C*H$_2$Ph), 27.4 (CO_2CMe_3) and 19.4 (NCH*Me*); *m*/*z*(CI) 430 (MH^+, 68%), 330 (39), 300 (33), 224 (39), 196 (38), 135 (85) and 91 (100) (Found: C, 78.3; H, 7.4; N, 3.6. $C_{28}H_{31}NO_3$ requires C, 78.29; H, 7.27; N, 3.26%).

Preparation of Methyl (2S,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxy*-3-*phenylpropionate* **17** via α-*Keto Ester Reduction*.—A solution of the freshly prepared α-keto ester **40** (70 mg, 0.181 mmol) in methanol ($5\ cm^3$) was stirred at room temp. Sodium borohydride (14 mg, 0.370 mmol) was added as a solid to the yellow solution which immediately became colourless. After the mixture had been stirred overnight, the methanol was evaporated under reduced pressure and the residue diluted with water ($15\ cm^3$) before extraction with dichloromethane ($3 \times 15\ cm^3$). The combined organic extracts were then dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford a mixture of the α-epimers **17** and **15** (4:1 by ^{1}H NMR spectroscopy). Purification by flash chromatography on silica gel (petroleum–diethyl ether, 3:1) afforded the desired title compound as a colourless oil (36 mg, 53%); $[\alpha]_D^{22}$ −99.8 (*c* 0.55, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1743vs (C=O); δ_H(300 MHz; $CDCl_3$) 7.47–7.25 (15 H, m, Ph), 4.53 [1 H, dd, *J* 8.0 and 2.6, C*H*(OH)CHN], 4.25 (1 H, q, *J* 6.9, NC*H*Me), 4.07 and 3.68 (2 H, AB, J_{AB} 13.4, NCH_2Ph), 4.05 [1 H, d, *J* 8.0, CH(OH)C*H*N], 3.91 [1 H, d, *J* 2.6, CH(O*H*)], 3.37 (3 H, s, CO_2Me) and 1.03 (3 H, d, *J* 6.9, NCH*Me*); D_2O shake: *inter alia* δ_H(300 MHz; $CDCl_3$) 4.53 [1 H, d, *J* 8.0, C*H*(OH)CHN]; δ_C(125 MHz; $CDCl_3$) 172.7 (CO_2), 143.5, 139.5 and 137.6 (Ph: C_{ipso}), 129.6, 129.1, 128.6, 128.5, 128.4, 128.0, 127.9, 127.3 and 127.2 (Ph: C_{ortho}, C_{meta} and C_{para}), 72.0 [*C*H(OH)], 63.4 [CH(OH)*C*HN], 56.4 (N*C*HMe), 51.9 (CO_2Me), 51.0 (N*C*H$_2$Ph) and 13.9 (NCH*Me*); *m*/*z*(CI) 390 (MH^+, 100%), 300 (44), 196 (52), 105 (40) and 91 (56) (Found: C, 77.0; H, 7.35; N, 3.4. $C_{25}H_{27}NO_3$ requires C, 77.09; H, 6.99; N, 3.60%).

Preparation of tert-*Butyl* (2S,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxy*-3-*phenylpropionate* **20** via α-*Keto Ester Reduction*.—A solution of the freshly prepared α-keto ester **41** (166 mg, 0.387 mmol) in methanol ($5\ cm^3$) was stirred at room temp. whilst sodium borohydride (29 mg, 0.775 mmol) was added to it as a solid; the yellow solution immediately became colourless. After the mixture had been stirred overnight, the methanol was evaporated under reduced pressure and the residue diluted with water ($15\ cm^3$) before extraction with dichloromethane ($3 \times 15\ cm^3$). The combined organic extracts were then dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford a mixture of the α-epimers **20** and (−)-**19** (1:1.5 by ^{1}H NMR spectroscopy) as a colourless oil (157 mg, 94%). Separation of these diastereoisomers by flash chromatography on silica gel (petroleum–diethyl ether, 5:1) afforded the *anti* diastereoisomer (−)-**19** as a colourless oil (87 mg, 52%) and a more polar fraction of the desired title compound as a white solid (52 mg, 31%) which was crystallised from diethyl ether–hexane; m.p. 110–112 °C; $[\alpha]_D^{23}$ −95.1 (*c* 0.81, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3383br (OH), 1737vs (C=O); δ_H(300 MHz; $CDCl_3$) 7.52–7.26 (15 H, m, Ph), 4.46 [1 H, d, *J* 9.9, C*H*(OH)CHN], 4.21 (1 H, q, *J* 6.9, NC*H*Me), 4.06 and 3.66 (2 H, AB, J_{AB} 13.4, NCH_2Ph), 3.90 [1 H, d, *J* 9.9, CH(OH)C*H*N], 3.84 [1 H, br s, CH(O*H*)], 1.08 (3 H, d, *J* 6.9, NCH*Me*) and 1.05 (9 H, s, CO_2Me_3); δ_C(125 MHz; $CDCl_3$) 171.1 (CO_2), 143.2, 139.3 and 136.8 (Ph: C_{ipso}), 129.9, 128.9, 128.5, 128.4, 128.1 and 127.8 (Ph: C_{ortho} and C_{meta}), 127.9, 127.3 and 127.2 (Ph: C_{para}), 80.9 (CO_2CMe_3), 71.1 [*C*H(OH)], 64.4 [CH(OH)*C*HN], 56.1 (N*C*HMe), 50.3 (N*C*H$_2$Ph), 27.3 [CO_2-C*Me*$_3$] and 13.9 (NCH*Me*); *m*/*z*(CI) 432 (MH^+, 52%), 300 (36), 212 (100), 196 (88), 105 (40) and 91 (76) (Found: C, 77.7; H, 7.4; N, 2.9. $C_{28}H_{33}NO_3$ requires C, 77.93; H, 7.71; N, 3.25%).

Tandem 'Matched' Preparation of tert-*Butyl* (2S,3S,αS)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)*amino*]-2-*hydroxy*-3-*phenylpropionate* (+)-**19**.—tert-*Butyl cinnamate* **18** (2.00 g, 9.80 mmol) was treated with the lithium amide derived from (S)-benzyl(α-methylbenzyl)amine and hydroxylated with the oxaziridine (+)-**8** in accordance with the Standard Procedure B. In contrast to the analogous reaction using (*R*)-benzyl(α-methylbenzyl)amine and the oxaziridine (+)-**8** (*vide supra*), analysis of the crude product by ^{1}H NMR spectroscopy (and TLC) failed to show the presence of the *syn* diastereoisomer (>98% d.e.). Consequently, the pairing described herein constitutes the 'matched' reaction. Purification by flash chromatography on silica gel (petroleum–diethyl ether, 5:1) afforded the title compound as a colourless oil (3.76 g, 89%), which could be crystallised from hexane; $[\alpha]_D^{20}$ +27.2 (*c* 0.99, $CHCl_3$) {(−)-**19** (*vide supra*), $[\alpha]_D^{20}$ −27.2 (*c* 0.98, $CHCl_3$)}.

Crystallographic Analysis of tert-*Butyl* (2R,3R,αR)-3-[N-*Benzyl*-N-(α-*methylbenzyl*)-*amino*]-2-*hydroxy*-3-*phenylpropionate* (−)-**19**.—*Crystal data*. $C_{28}H_{33}NO_3$, *M* = 431.6, monoclinic, *a* = 13.080(2), *b* = 6.6019(7), *c* = 14.408(2) Å, β = 95.17(1)°, *V* = 1239.0(3) Å^3 (by least-squares refinement of diffractometer angles for 24 automatically centred reflections, λ = 0.710 69 Å), space group ($P2_1$, *Z* = 2, D_c = 1.16 g cm^{-3}, *F*(000) = 464, colourless plates, crystal dimensions 0.25 × 0.31 × 0.50 mm, μ(Mo-Kα) = 0.69 cm^{-1}.

Data collection and processing. CAD4 Diffractomer, $\omega/2\theta$ mode, ratio of the scanning rates ω/θ = 1.2, ω scan width = 0.71 + 0.34 tan θ, ω scan speed 1.1–5.0 deg min^{-1}, graphite-monochromated Mo-Kα radiation, 3436 reflection measured ($1 \leqslant \theta \leqslant 26°$, $\bar{h},h\ \bar{2},k,\ \bar{l},l$), 2511 unique [merging *R* = 0.026] giving 1445 with $I > 3\sigma(I)$. Linear and approx. isotropic crystal decay, *ca.* 27% corrected during processing.

Structure analysis and refinement. Direct methods, full-matrix least squares refinement with all non-hydrogen atoms anisotropic. All hydrogen atoms were located in the difference Fourier maps and included in the final refinement with the fixed positional and thermal parameters [only atom H(1) was refined isotropically]. The Chebushew weighting scheme[25] with the coefficients 5.19, 0.38, 4.43 was applied. Final *R* and R_w values were 0.035 and 0.041. The observations/variables ratio was 4.93. $(\Delta\rho)_{max}$ = 0.10, $(\Delta\rho)_{min}$ = −0.08 e Å^{-3}. Crystallographic

calculations were carried out using the CRYSTALS[26] program package on a Micro VAX3800 computer. Neutral atom scattering factors were taken from the usual sources.[27] Full details are available from the Cambridge Crystallographic Data Centre.

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