Synthesis and Reduction of α-Amino Ketones Derived from Leucine

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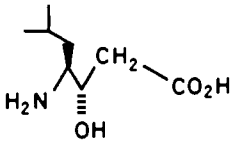
New α-amino ketones (**5**) derived from leucine have been synthesized by reaction of organometallics on *N*-methoxy-*N*-methylamide (**4**). The stereoselectivity of reduction of the α-amino ketones (**5**) was studied. The stereochemistry of the resulting α-amino alcohols (**6**) was established by transforming them into the oxazolidinones (**8**) by means of a new procedure.

Stereochemical control of the reduction of α-amino ketones to α-amino alcohols is an increasingly important challenge in peptide and peptidomimetic chemistry and in pharmacological research.

Enzyme receptors are greatly stereoselective towards drugs, and it is well known that chiral amino alcohols derived from amino acids have inhibiting properties towards some classes of proteolytic enzymes. A naturally occurring pentapeptide, pepstatin (**1**), inhibits aspartyl proteases and incorporates two units of the modified α-amino alcohol statine (**2**) in its sequence.[1] It has been postulated that the 3*S* hydroxy group of statine in pepstatin, which interacts with both aspartates of the active site, mimics the *pro-S* hydroxy group of the tetrahedral amide-bound hydrolysis intermediate.[2] This assumption has been extensively used as a guide in the preparation of numerous other novel potent peptide inhibitors which contain statine as a key residue.[3] The synthesis of statine and other transition-state analogues has proved to be the decisive step in new protease inhibitor elaboration.[4,5] For this purpose we have prepared several α-amino ketones (**5**) derived from leucine and have studied their reduction by readily accessible reagents.

Iva - Val - Val - Sta - Ala - Sta

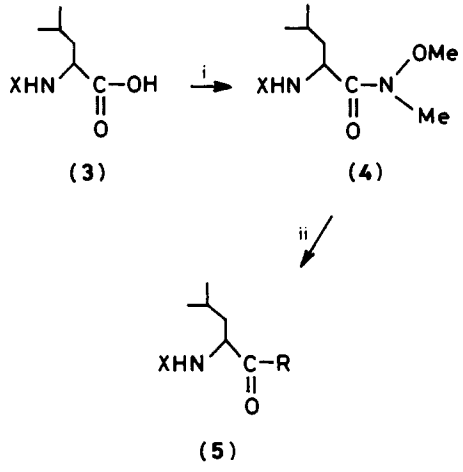
(1) pepstatin (Iva = isovaleric)



(2) statine

Results and Discussion

The ketone intermediates (**5a—d**), derived from *N*-blocked L-leucine, were obtained by the *N*-methoxy-*N*-methylamide (**4**) approach (Scheme 1, Table 1). The convenient method, previously developed by Nahm and Weinreb for the preparation of non-functionalized ketones,[6] was successfully extended to the synthesis of ketones (**5a—d**) with highly reactive functions such as ester or phosphonate. The *N*-methoxy-*N*-methylamide intermediate (**4**) was routinely synthesized by the condensation of commercially available *N,O*-dimethylhydroxylamine hydrochloride with *N*-protected leucine using BOP [benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate] as the coupling reagent.[7] The amide (**4**) was obtained in almost quantitative yield after purification by silica gel chromatography. This product was allowed to react with an excess of various Grignard or organolithium reagents in tetrahydrofuran



Scheme 1. General pathway for preparation of ketones (**5**). *Reagents:* i, MeNHOMe–BOP; ii, RMgHal or RLi

(THF) or diethyl ether. The reaction mixture hydrolysis provided the expected ketones (**5a—d**) with good yields (Table 1).[8] We also synthesized the t-butylstatine derivative (**5c**) starting from the *N*-methoxy-*N*-methylamide (**4a**) and following the Grignard procedure modified by Dubois and Molnarfi.[9]

The chloromethyl ketone (**5e**) was successfully prepared by an attractive alternative procedure elaborated in our laboratory including isopropenyl chloroformate (IPCF) activation of the acid function of compound (**3**; X = Boc), followed by treatment with diazomethane and acidolysis (Scheme 2, Table 1). This process avoids the risks of racemization when one uses the acyl chloride activation method,[10] and the risk of formation of an ester since decomposition of the isopropenyl mixed anhydride

Table 1. 360 MHz ^{1}H N.m.r. data for compound (**6**) and (**8**)

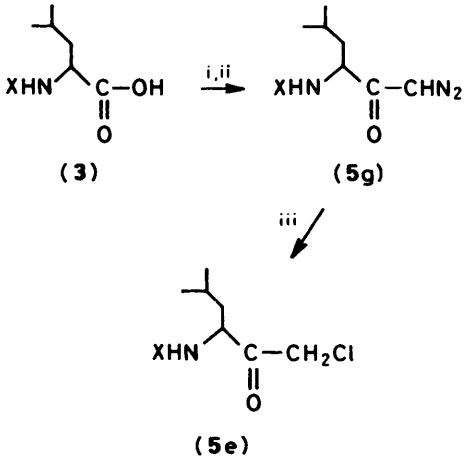
Entry	X	R	Ketone (**5**) yield from (**3**) (%)	Alcohol (**6**) δ_{NH} *syn*; *anti*	Oxazolidinone (**8**) $\delta_{5\text{-}H}$ *syn*; *anti*	Oxazolidinone (**8**) $J_{4,5}$ (Hz) *syn*; *anti*
a	Boc	$[CH_2]_2CHMe_2$	95	6.4; 6.1	4.6; 4.1	7.5; 4.8
b	Boc	CH_2OCHMe_2	90	6.4; 5.9	*a*	*a*
c	Z	$CH_2CO_2Bu^t$	60	7.0; 6.8	*a*	*a*
d	Boc	$CH_2\overset{O}{\overset{\|\|}{P}}(OMe)_2$	97	6.5; 6.3	4.8; 4.2	7.9; 4.8
e	Boc	CH_2Cl	70	6.6; 6.4	4.7; 4.3	7.9; 5.4
f	Boc	CH_2CO_2Me		6.5; 6.2	4.9; 4.4	7.8; 5.4

[a] Not determined.

Table 2. Stereoselectivity data for the reduction of ketones (5)

Ketone (5)	Alcohol (6) *anti*:*syn* (%) $NaBH_4$–MeOH	$NaBH_4$–Et_2O or THF	$LiAlH_4$–Et_2O	LiAlH-$(OBu^t)_3$–Et_2O	$Zn(BH_4)_2$–Et_2O
(5a)	15:85	40:60	23:77	70:30	40:60
(5b)	26:74	33:67			34:66
(5c)	20:80	40:60	*a*		33:67
(5d)	20:80	40:60			
(5e)	15:85	36:64	32:68	75:25	
(5f)	20:80	40:60	*a*		

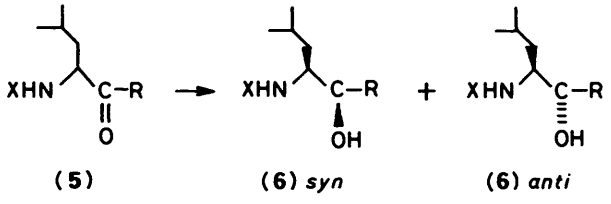
[a] Reduction of the ester function also occurs.



Scheme 2. Synthesis of chloromethyl ketone (5e). *Reagents:* i, IPCF; ii, CH_2N_2; iii, HCl

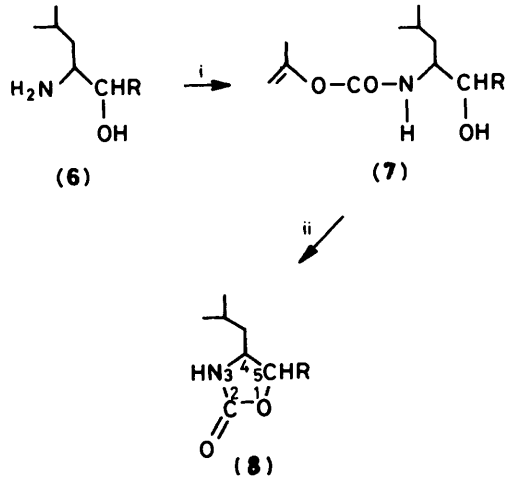
liberates acetone and not an alcohol as in the case of the usual mixed anhydrides (ethyl or isobutyl).

Reduction of α-amino ketones (5a—f) provides the two diastereoisomeric alcohols (6a—f) *syn* and *anti* in quantitative yield (Scheme 3, Table 1). Experimental results, including diastereoisomeric ratio of α-amino alcohols, are listed in Table 2.



Scheme 3. Reduction of ketones (5)

To assign the absolute stereochemistry of the diastereoisomers (6 *syn,anti*) the oxazolidinones (8 *syn,anti*) were prepared according to Scheme 4. For the preparation of these oxazolidinones, we chose to develop a method avoiding the obvious phosgene approach, respecting the hazards of this reagent. After some exploratory and unsatisfactory work with benzyl or methyl chloroformate, the choice fell on isopropenyl chloroformate. Addition of isopropenyl chloroformate to the deblocked amino alcohol leads to the corresponding *N*-isopropenyloxycarbonyl alcohols (7); by heating these compounds in dimethylformamide (DMF) we obtained the oxazolidinones (8 *syn,anti*) in quantitative yield (Table 1). The difference of reactivity between the *N*-alkyloxycarbonyl and the *N*-isopropenyloxycarbonyl alcohols could be explained by the thermodynamically favourable liberation of acetone in the case of the latter consecutive to the attack of the hydroxy group on the carbamate. Such a mechanism does not involve either of the two asymmetric centres, so no racemization was expected. This was confirmed by synthesizing the oxazolidinones (8f *anti*) and (8f *syn*) from each epimerically pure (3*S*,4*S*)-(*anti*)- and (3*S*,4*S*)-(*syn*)-statine methyl ester (6f). In the 360 MHz ^1H n.m.r. spectrum of each oxazolidinone (8f), no signal due to the other diastereoisomer was detected, and the chemical shifts and coupling constants for the 5-H protons were in excellent agreement with those reported by Rich and Sun.[3] Moreover an Overhauser effect of 8% was measured for the 4-H proton by irradiating the 5-H proton in the oxazolidinone (8f *syn*) prepared from (3*R*,4*S*)-statine methyl ester. No apparent effect was observed when the same experiment was performed on the oxazolidinone (8f *anti*) obtained from the (3*S*,4*S*) derivative, thus confirming the assignment of the *syn* configuration to the compound having the higher coupling constant $J_{4,5}$.



Scheme 4. Preparation of oxazolidinones (8). *Reagents:* i, IPCF; ii, DMF (heat)

Consequently, the oxazolidinones (8a, d, and e) were synthesized from the *anti,syn* mixture of amino alcohols (6a, d, and e). The assignments of each epimeric 5-H proton relative to the compounds (8a, d, and e) were deduced from the coupling constant $J_{4,5}$ measurements (Table 1); the relative ratios of these epimers were determined by integration of the 5-H or NH signals. Since the transformation of the amino alcohols (6) into the oxazolidinones (8) was quantitative, the *syn versus anti* ratio of epimers (6a, d, and e) could be determined from these preceding studies. The ratio of the other α-amino alcohols epimeric mixtures (6b and c) was evaluated by extensive chemical-shift correlation of the NH proton, this signal in *syn* compounds being at a lower field than in *anti* compounds (Table 1).

The data listed in Table 2 show that the reduction of the ketones (5) preferentially leads to the alcohols (6) with the *syn* configuration. This observed stereoselectivity is in agreement with the results previously reviewed by Tramontini concerning the reduction of amino ketones.[11] This author pointed out that α-aminocarbonyl systems with the chiral centre in the α-position generally prefer to undergo attack leading to the alcohol with the *syn* configuration, regardless of the reducing

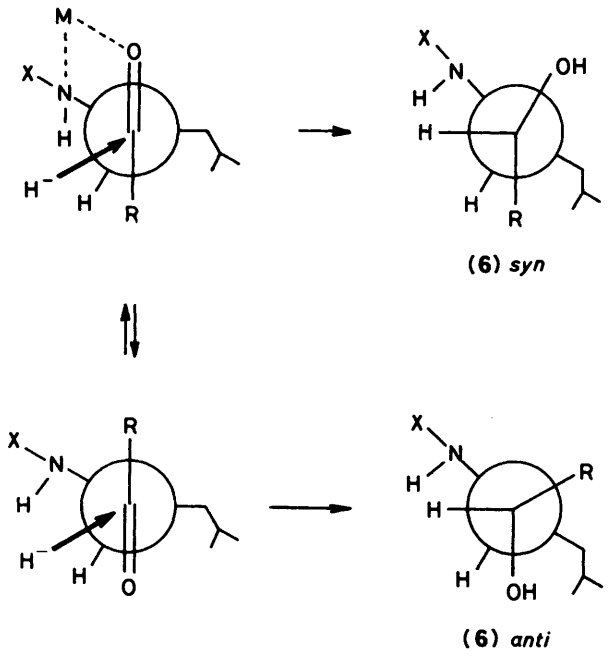


Figure. Likely conformations in the transition state

agent employed. In the case of the carbamate derivatives of leucine discussed herein, we make the assumption that this *syn* orientation results from the formation of a chelate between the hydride, the ketone, and the carbamate (the lone pair being delocalized between the nitrogen and the carbonyl group) (Figure). This model is first supported by the dramatic lack of influence in the nature of the R substituent whatever its chemical nature (alkyl, halogen, ester, ether, or phosphonate); otherwise a different stereoselectivity could be expected depending on the ability of this substituent to interact with the metal hydride. The invariability of the diastereoisomeric ratio with respect to the nature of the metal (Na, Zn, Li) corroborates our hypothesis. In addition, the extent of *syn* reduction is increased in a dissociating solvent such as methanol; under these conditions the formation of the chelate could be favoured. However, we have predominantly obtained an *anti* reduction using a bulky aluminium hydride such as $AlLiH(OBu^t)_3$; this *anti* orientation could be interpreted by the destabilization of the chelate due to steric effects, thus favouring the transition state with the carbonyl and the carbamate in a *trans* conformation as shown in the Figure.[12]

Therefore we have shown the usefulness of the hydroxamate derivatives of α-amino acids in the synthesis of multifunctionalized chiral ketones in good yield. Further studies on the α-amino alcohols stereoselective preparation from α-aminoketones. including enzymatic reduction, are in progress. The interesting use of IPCF for the synthesis of oxazolidinones from α-amino alcohols has been demonstrated.

Experimental

BOP Reagent was obtained from Sempa-Chimie. All amino acid derivatives used were of the L form and were purchased commerically from Bachem or Fluka. ^1H N.m.r. data were recorded on a Brucker 360 MHz instrument with $SiMe_4$ as internal reference. The spectra were recorded in $CDCl_3$ or $(CD_3)_2SO$. The products were purified by chromatography on silica gel (Merck; 0.05—0.2 mm).

(S)-2,8-*Dimethyl*-4-(*t-butoxycarbonylamino*)*nonan*-5-*one* (**5a**).—To a suspension of magnesium (1.2 g, 50 mmol) and mercury(II) chloride (0.27 g, 1 mmol) in dry THF (10 ml) under an inert atmosphere were added a few drops of isopentyl bromide. Once spontaneous reflux had been initiated, isopentyl bromide (7.55 g, 50 mmol) was gently added at such a rate as to maintain reflux conditions, and the mixture was stirred for 1 h at room temperature. Then a solution of *N*-methoxy-*N*-methylamide (**4**; X = Boc) (2.74 g, 10 mmol) in dry THF (10 ml) was slowly added to the Grignard reagent. After being stirred for 30 min, the complex was hydrolysed by addition of 3M-HCl until neutral pH. The mixture was extracted with diethyl ether, and the organic phase was then washed successively with 1M-HCl, saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography on silica gel with hexane–ethyl acetate (80:20 v/v) as eluant gave the *title compound* (**5a**) as white crystals (2.70 g, 95%), m.p. 51 °C (Found: C, 67.2; H, 10.9; N, 5.0. $C_{16}H_{31}NO_3$ requires C, 67.33; H, 10.95; N, 4.91%); R_F 0.7 [ethyl acetate–hexane (20:80)]; $[\alpha]_D^{20}$ −34.9° (*c* 1 in MeOH); $\delta_H[(CD_3)_2SO]$ 0.82—0.87 (12 H, m, Me), 1.27—1.37 (2 H, m, 3-H_2), 1.42 (9 H, s, Bu^{t}O), 1.42—1.45 (1 H, m, 8-H), 1.45—1.47 (2 H, m, 7-H_2), 1.56—1.61 (1 H, m, 2-H), 2.40—2.44 (2 H, m, 6-H_2), 3.88 (1 H, m, 4-H), and 7.20 (1 H, d, *J* 6.5 Hz, NH).

(S)-1-*Isopropoxy*-5-*methyl*-3-(*t-butoxycarbonylamino*)*hexan*-2-*one* (**5b**).—The procedure was the same as described above except that chloromethyl isopropyl ether was the reagent, and a temperature of −10 °C was maintained throughout the procedure. Work-up as for compound (**5a**), and chromatography on silica gel with hexane–ethyl acetate (80:20) as eluant, gave *compound* (**5b**) as white crystals (2.58 g, 90%), m.p. 50 °C (Found: C, 62.3; H, 10.0; N, 4.9. $C_{15}H_{29}NO_4$ requires C, 62.69; H, 10.17; N, 4.87%); $[\alpha]_D^{20}$ −10° (*c* 1 in MeOH); R_F 0.3 [ethyl acetate–hexane (10:80)]; $\delta_H[(CD_3)_2SO]$ 0.85—0.88 (6 H, d, *J* 6.4 Hz, 5-Me_2), 1.05—1.10 (6 H, d, *J* 6.4 Hz, CHMe_2), 1.37 (9 H, s, Bu^{t}O), 1.42 (2 H, m, 4-H_2), 1.61—1.64 (1 H, m, 5-H), 3.52—3.54 (1 H, m, OCH), 4.08—4.29 (2 H, q, 1-H_2), 4.16 (1 H, m, 3-H), and 7.09—7.11 (1 H, d, *J* 6.5 Hz, NH).

t-Butyl (S)-4-(*Benzyloxycarbonylamino*)-6-*methyl*-3-*oxoheptanoate* (**5c**).—This compound was prepared according to the procedure of Dubois *et al.*[9] To a suspension of magnesium (1.20 g, 50 mmol) in anhydrous diethyl ether (10 ml) was added dropwise isopropyl chloride (0.79 g, 10 mmol). After being stirred for 1 h, the solution was cooled to −20 °C and t-butyl acetate (0.09 g, 1 mmol) was added. The mixture was allowed to reach 0 °C, and the hydroxamate (**4**) (0.27 g, 1 mmol) was added. Usual work-up afforded *compound* (**5c**) as white crystals (0.20 g, 60%), m.p. 40 °C (Found: C, 66.0; H, 8.05; N, 4.0. $C_{20}H_{29}NO_5$ requires C, 66.09; H, 8.04; N, 3.85%); $[\alpha]_D^{20}$ −36° (*c* 1 in MeOH); R_F 0.4 [ethyl acetate–hexane (20:80)]; $\delta_H(CDCl_3)$ 0.82—0.84 (6 H, m, 6-Me_2), 1.37 (9 H, s, Bu^{t}O), 1.42 (2 H, m, 5-H_2), 1.51 (1 H, m, 6-H), 3.3—3.4 (2 H, q, 2-H_2), 4.4 (1 H, m, 4-H), 5.0 (2 H, s, CH_2Ph), 5.2 (1 H, d, *J* 7.5 Hz, NH), and 7.3 (5 H, m, Ph).

(S)-1-(*Dimethoxyphosphoryl*)-5-*methyl*-3-(*t-butoxycarbonylamino*)*hexan*-2-*one* (**5d**).— To a cooled solution (−45 °C) of n-butyl-lithium (1.6mM in hexane; 8 ml) in dry THF (10 ml) under argon was added dropwise a solution of dimethyl methylphosphonate (1.49 g, 12 mmol) in dry THF (10 ml). The mixture was stirred for 20 min until the formation of a white precipitate was complete. Then a solution of compound (**4**) (1.37 g, 5 mmol) in THF (10 ml) was added over a period of 15 min. The temperature was raised to 0 °C, and the mixture was hydrolysed with 1M-HCl (20 ml), diluted with diethyl ether (30 ml), decanted, and washed with water to neutral pH. The organic phase was

dried over sodium sulphate, and concentrated under reduced pressure to afford pure phosphonate (**5d**) as an oil (1.56 g, 97%), R_F 0.31 [ethyl acetate–hexane (80:20)]; $[\alpha]_D^{20}$ −49·4° (*c* 1 in MeOH); $\delta_H[(CD_3)_2SO]$ 0.87 (6 H, t, *J* 6.3 Hz, 5-Me_2), 1.39 (9 H, s, t-Bu^{t}O), 1.30—1.50 (2 H, m, 4-H_2), 1.50—1.65 (1 H, m, 5-H), 3.29 (2 H, d, *J* 21.4 Hz, 1-H_2), 3.65 (6 H, d, *J* 11.9 Hz, OMe), 4.04 (1 H, m, 3-H), and 7.20 (1 H, d, *J* 7.9 Hz, NH).

(S)-1-*Chloro*-5-*methyl*-3-(*t-butoxycarbonylamino*)*hexan*-2-*one* (**5e**).—To a cooled solution (−10 °C) of *N*-t-butoxycarbonyl-L-leucine (2.31 g, 10 mmol) and isopropenyl chloroformate (1.3 ml, 11 mmol) in ethyl acetate (20 ml) was added dropwise di-isopropylethylamine (1.72 ml, 11 mmol). The mixture was stirred for 5 min at −10 °C, and precipitated amine hydrochloride was rapidly filtered off in the cold; then a solution of diazomethane (12 mmol) in diethyl ether was added dropwise to the filtrate, and the resulting yellow solution was stirred for 30 min at 0 °C. The mixture was concentrated under reduced pressure at room temperature. The residue was diluted with diethyl ether (50 ml), and washed with water (20 ml). The organic phase was dried with sodium sulphate, and concentrated under reduced pressure to afford a yellow oil (2.6 g) which was subject to chromatography on silica gel (60 g) with ethyl acetate–hexane (20:80) as eluant to give the diazo ketone (**5g**) as yellow crystals (2.05 g, 80%), m.p. 81 °C; R_F 0.30 [ethyl acetate–hexane (20:80)]; $[\alpha]_D^{20}$ −69.1° (*c* 1 in MeOH); $\delta_H[(CD_3)_2SO]$ 0.83 (3 H, d, *J* 6.3 Hz, Me), 0.87 (3 H, d, *J* 6.3 Hz, Me), 1.39 (9 H, s, Bu^{t}O), 1.38—1.48 (2 H, m, CH_2), 1.50—1.67 (1 H, m, 5-H), 3.87—3.97 (1 H, m, 3-H), 6.02 (1 H, s, 1-H), and 7.22 (1 H, d, *J* 8.4 Hz, NH).

To an ice-cooled solution of diazo-ketone (**5g**) (2.8 g) in diethyl ether (30 ml) was added dropwise a solution of 3M-HCl in diethyl ether until the yellow colour disappeared. The resulting mixture was washed with 5% aqueous sodium hydrogen carbonate, dried (sodium sulphate), and concentrated under reduced pressure to afford pure *chloro ketone* (**5e**) as white crystals (2.49 g, 87%), m.p. 59 °C (Found: C, 54.7; H, 8.3; Cl, 13.3; N, 5.5. $C_{12}H_{22}ClNO_3$ requires C, 54.64; H, 8.41; Cl, 13.44; N, 5.31%); R_F 0.55 [ethyl acetate–hexane (20:80)]; $[\alpha]_D^{20}$ −46.6° (*c* 1 in MeOH); $\delta_H(CDCl_3)$ 0.95 (3 H, d, *J* 6.5 Hz, Me), 0.99 (3 H, d, *J* 6.5 Hz, Me), 1.42 (9 H, s, Bu^{t}O), 1.34—1.47 (1 H, m, 4-H), 1.50—1.63 (1 H, m, 4-H), 1.63—1.76 (1 H, m, 5-H), 4.24 (2 H, q, *J* 18 Hz, 1-H_2), 4.44—4.45 (1 H, m, 3-H), and 4.91 (1 H, d, *J* 4.5 Hz, NH).

Reduction of Amino Ketones (**5**) *to Amino Alcohols* (**6**).—*Sodium borohydride reduction; general procedure.* Sodium borohydride (4 mmol) was added gradually at 0 °C to a stirred solution of the amino ketone (1 mmol) in methanol, DMF or THF (5 ml). The reaction mixture was further stirred for 1 h, then neutralised with acetic acid, and the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate, and the extract was dried (sodium sulphate), and concentrated under reduced pressure.

Lithium aluminium hydride reduction; general procedure. Amino ketone (1 mmol) was added gradually to a stirred and cooled solution of lithium aluminium hydride (4 mmol) in dry THF or diethyl ether (5 ml) under dry nitrogen. The mixture was stirred for 1 h and the excess of hydride was decomposed with ethanol. The solution was neutralized with dil. hydrochloric acid, and concentrated. The residue was extracted with ethyl acetate, and the solution was dried (sodium sulphate) and concentrated.

The diastereoisomeric ratio of the resulting mixture of *syn* and *anti* amino alcohols was evaluated using n.m.r. spectroscopy (Table 2).

(3R,4S)-N-(*Isopropenyloxycarbonyl*)*statine Methyl Ester* (**7f** syn).—(3*R*,4*S*)-*N*-(t-Butoxycarbonyl)statine methyl ester (**6f** *syn*) (0.58 g, 2 mmol) was treated with trifluoroacetate acid for 5 min. The solvent was evaporated off under reduced pressure and the trifluoroacetate salt was precipitated by trituration with diethyl ether, filtered with suction, and dried *in vacuo* over potassium hydroxide. The trifluoroacetate salt was then dissolved in dichloromethane (5 ml) and cooled to 0 °C; triethylamine (0.28 ml, 2 mmol) and isopropenyl chloroformate (0.26 ml, 2.2 mmol) were successively added. After being stirred for 30 min the mixture was evaporated under reduced pressure. The residue was partitioned between ethyl acetate (20 ml) and water (10 ml) and the mixture was decanted. The organic phase was worked successively with 1M-HCl, saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride, dried (sodium sulphate), and concentrated under reduced pressure. The oily residue was crystallized from diethyl ether–hexane at −20 °C to afford the *alcohol* (**7f** *syn*) as white crystals (0.49 g, 90%), m.p. 63 °C (Found: C, 56.9; H, 8.5; N, 5.1. $C_{13}H_{23}NO_5$ requires C, 57.13; H, 8.48; N, 5.12%); R_F 0.50 [ethyl acetate–hexane (50:50)]; $[\alpha]_D^{20}$ −28.5° (*c* 1 in MeOH); $\delta_H[(CD_3)_2SO]$ 0.83 (3 H, d, *J* 6.4 Hz, 6-Me), 0.88 (3 H, d, *J* 6.4 Hz, 6-Me), 1.22—1.43 (2 H, m, 5-H_2), 1.52—1.67 (1 H, m, 6-H), 1.84 (3 H, s, CH_2=C*Me*), 2.25 (1 H, q, J_1 9.5, J_2 14.9 Hz, 2-*H*H), 2.56 (1 H, q, J_1 2.7, J_2 14.9 Hz, 2-H*H*), 3.32—3.44 (1 H, m, 4-H), 3.58 (3 H, s, OMe), 3.65—3.78 (1 H, m, 3-H), 4.57 (1 H, s, =C*H*H), 4.59 (1 H, s, =CH*H*), 4.99 (1 H, d, *J* 6.4 Hz, OH), and 7.19 (1 H, d, *J* 9.3 Hz, NH).

(3S,4S)-N-(*Isopropenyloxycarbonyl*)*statine Methyl Ester* (**7f** anti).—By the same procedure as described above for compound (**7f** *syn*) (3*S*,4*S*)-*N*-(t-butoxycarbonyl)statine methyl ester (**6f**) (0.135 g, 0.5 mmol) afforded the derivative (**7f** *anti*) as an oil, R_F 0.55 [ethyl acetate–hexane (50:50)]; $\delta_H[(CD_3)_2SO]$ 0.85 (3 H, d, *J* 6.4 Hz, 6-Me), 0.88 (3 H, d, *J* 6.4 Hz, 6-Me), 1.18—1.41 (2 H, m, 5-H_2), 1.51—1.68 (1 H, m, 6-H), 1.84 (3 H, s, CH_2=C*Me*), 2.23 (1 H, q, J_1 9.8, J_2 15.1 Hz, 2-*H*H), 2.44 (1 H, q, J_1 3.9, J_2 15.1 Hz, 2-H*H*), 3.47—3.61 (1 H, m, 4-H), 3.58 (3 H, s, OMe), 3.83—3.93 (1 H, m, 3-H), 4.58 (1 H, s, =C*H*H), 4.59 (1 H, s, =CH*H*), 4.93 (1 H, d, *J* 5.4 Hz, OH), and 7.06 (1 H, d, *J* 8.8 Hz, NH).

Isopropenyloxycarbonyl derivatives (**7a**, **d**, and **e**) were synthesized quantitatively as described for (**7f** *syn*) on a 1 mmol scale starting from the epimeric mixture of alcohols (**6a**, **d**, and **e**). The crude residues were directly submitted to cyclization (*vide infra*).

Methyl (4S,5R)-(4-*Isobutyl*-2-*oxo*-*oxazolidin*-5-*yl*)*acetate* (**8f** syn).—The alcohol (**7f** *syn*) (0.136 g, 0.5 mmol) was dissolved in DMF (3 ml) and the solution was heated at 130 °C during 1 h. The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate (20 ml), and the solution was washed successively with 1M-HCl, saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride. The organic phase was dried (sodium sulphate), and concentrated under reduced pressure. The pale yellow oily residue was crystallized from diethyl ether–hexane at −20 °C to afford the *oxazolidinone* (**8f** *syn*) as white crystals (0.090 g, 84%), m.p. 91 °C (Found: C, 55.8; H, 8.1; N, 6.6. $C_{10}H_{17}NO_4$ requires C, 55.80; H, 7.96; N, 6.51%); R_F 0.30 [ethyl acetate–hexane (50:50)]; $[\alpha]_D^{20}$ −6.5° (*c* 1 in MeOH); $\delta_H[(CD_3)_2SO]$ 0.83 (3 H, d, *J* 6.3 Hz, CH*Me*), 0.89 (3 H, d, *J* 6.3 Hz, CH*Me*), 1.02—1.17 (1 H, m, C*H*H), 1.26—1.41 (1 H, m, CH*H*) 1.56—1.74 (1 H, m, CH), 2.63 (1 H, q, J_1 9.5, J_2 16.4 Hz, C*H*H), 2.76 (1 H, q, J_1 4.6, J_2 16.4 Hz, CH*H*), 3.63 (3 H, s, OMe), 3.81—3.94 (1 H, m, 4-H), 4.84—4.95 (1 H, m, 5-H), and 7.84 (1 H, s, NH). On irradiation of the signal centred at δ 2.70, the signal of 5-H became a doublet (δ 4.89, *J* 7.8 Hz). An n.O.e. experiment was carried out in $CDCl_3$; on irradiation of the 5-H proton at δ 5.63,

an Overhauser effect of 8% was measured for the 4-H proton at δ 4.58.

Methyl (4S,5S)-(4-*Isobutyl*-2-*oxo*-*oxazolidin*-5-*yl*)*acetate* (**8f** anti).—The title compound was prepared from compound (**7f** *anti*) (0.136 g, 0.5 mmol) by the procedure described above. The yield after crystallization from diethyl ether–hexane at −20 °C was 70% (0.075 g), m.p. 48 °C (Found: C, 55.6; H, 8.0; N, 6.6%); R_F 0.40 [ethyl acetate–hexane (50:50)]; $[\alpha]_D^{20}$ −77.2° (*c* 1 in MeOH); $\delta_H[(CD_3)_2SO]$ 0.85 (3 H, d, *J* 6.8 Hz, CH*Me*), 0.88 (3 H, d, *J* 6.8 Hz, CH*Me*), 1.27—1.42 (2 H, m, CH_2), 1.60—1.74 (1 H, m, CH), 2.71 (1 H, q, J_1 7.8, J_2 16.1 Hz, C*H*H), 2.82 (1 H, q, J_1 5.1, J_2 16.1 Hz, CH*H*), 3.47—3.55 (1 H, m, 4-H), 3.63 (3 H, s, OMe), 4.33—4.40 (1 H, m, 5-H), 7.83 (1 H, s, NH). By irradiating the signal centred at δ 2.77, the signal of 5-H became a doublet (δ 4.37, *J* 5.4 Hz). An n.O.e. experiment was carried out under the same conditions as for (**8f** *syn*); on irradiation of 5-H at δ 5.13, no Overhauser effect was detectable for the 4-H proton at δ 4.18.

Oxazolidinones (**8a**, **d**, and **e**) were obtained almost quantitatively by heating the crude epimeric mixtures (**7a**, **d**, and **e**) in DMF at 130 °C. The reaction was checked by t.l.c. [ethyl acetate–hexane (50:50)]. When the reaction was complete, the solvent was evaporated under reduced pressure and the crude residue was submitted to ^1H n.m.r. spectroscopy, without further purification.

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