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Synthesis of Metallo-β-Lactamase Inhibitors

Magnus W. Walter, Robert M. Adlington, Jack E. Baldwin, and Christopher J. Schofield*

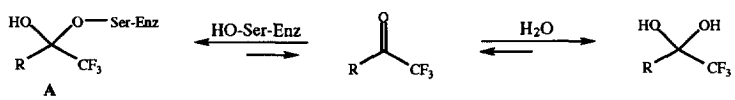
The Dyson Perrins Laboratory and the Oxford Centre for Molecular Sciences, South Parks Road, Oxford OX1 3QY, UK.

e-mail: christopher.schofield@dpl.ox.ac.uk

Abstract: α-Amido trifluoromethyl alcohols and ketones were synthesised *via* two independent routes using the Ruppert Reagent (TMS-CF_3) and shown to be inhibitors of metallo-β-lactamases.

Introduction

Trifluoromethyl ketones form an important group of biologically useful fluorinated molecules.[1] The interest in this class of compounds largely derives from their utility as protease inhibitors as first described by Abeles.[2] Serine proteases contain a nucleophilic serinyl-residue at their active-sites which attacks the amide-carbonyl of peptide substrates leading to hydrolysis *via* an acyl enzyme intermediate. Fluorination of ketones in the α-position of the carbonyl group increases their electrophilicity (trifluoromethyl ketones exist as mixtures of ketones and hydrate in organic solvents such as aqueous chloroform). Thus, nucleophilic attack by the active site serinyl residue onto the highly electrophilic trifluoromethyl ketone carbonyl group leads to the formation of tetrahedral adduct **A** which is believed to mimic the intermediate of hydrolysis reactions (**Scheme 1**). Since adduct **A** is relatively stable, trifluoromethyl ketones have been classified as 'transition state analogue' inhibitors of hydrolytic enzymes.[3,4]



Scheme 1

Class B or metallo-β-lactamases form a group of hydrolytic enzymes which confer resistance against β-lactam antibiotics to bacteria.[5] Unlike the Class A, C, and D β-lactamases which contain a nucleophilic serinyl residue in their active sites, the Class B enzymes belong to the group of hydrolytic metallo enzymes,[6] which includes carboxypeptidase A (CPA)[7], angiotensin converting enzyme (ACE)[8], and thermolysin[9]. These enzymes require a bivalent metal-cation, normally zinc, for activity.[10] Metallo-β-lactamases have only recently emerged as being clinically important, but given their broad-spectrum activity against conventional β-lactam antibiotics including carbapenems the spread of genes coding for this type of β-lactamase is of major concern.[11]

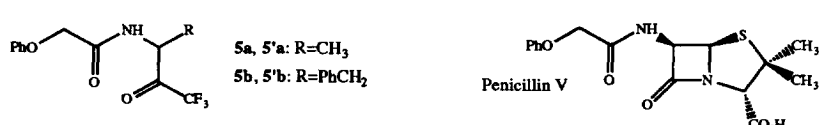
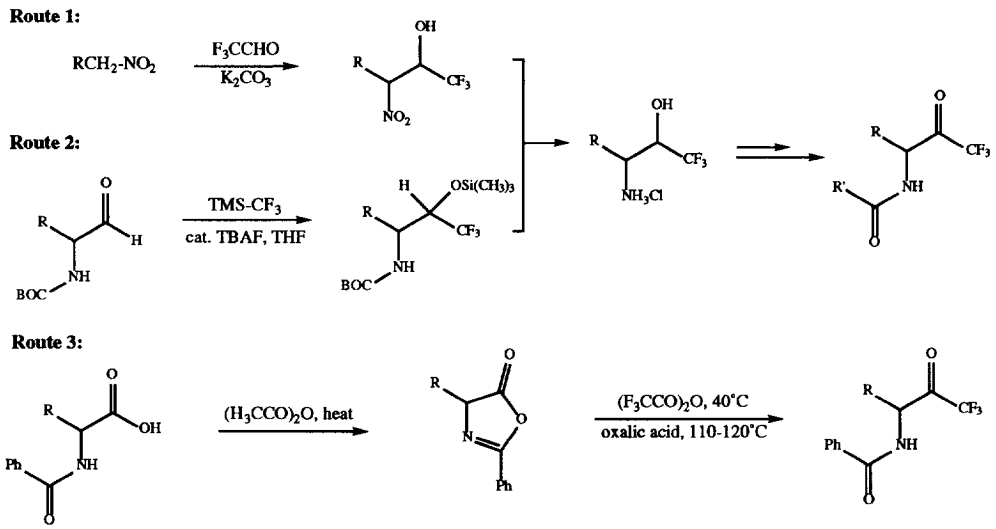


Figure 1

Recently, we reported that α-amido trifluoromethyl ketones exhibit inhibitory activity against metallo-β-lactamases.[12, 13] Our inhibitor design was based on the assumption that the active site zinc-ion would bind the trifluoromethyl ketone in its hydrated form and that the side-chain attached to the nitrogen would mimic the side-chains of β-lactam antibiotics, such as penicillin V (**Figure 1**). Herein, we disclose full experimental details of our synthesis of α-amido trifluoromethyl ketones.

Results and Discussion

A number of syntheses of α-amido trifluoromethyl ketones have been reported. The majority adopt a similar overall strategy, namely acylation and oxidation of an α-amino trifluoromethyl alcohol intermediate. In their pioneering work Abeles and Imperiali obtained the intermediate α-amino trifluoromethyl alcohol *via* a nitro-aldol (Henry) reaction between a nitroalkane and trifluoroacetaldehyde (Route 1 in **Scheme 2**).[14] Subsequently, Skiles reported a synthesis of peptidic trifluoromethyl ketones in which addition of (trifluoromethyl)trimethylsilane (the Ruppert Reagent/TMS-CF_3)[15-18] to amino aldehydes gave access to the alcohol precursors (Route 2 in **Scheme 2**).[19]



Scheme 2

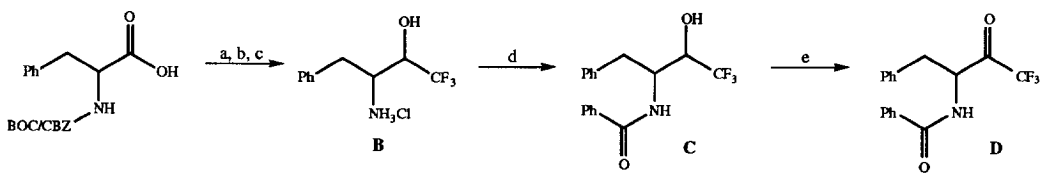
As a source of trifluoromethyl anions, the commercially available Ruppert Reagent is superior to other organometallic reagents due to its stability and ease of handling.[20-22] The oxidation of trifluoromethyl alcohols to the corresponding ketones is reportedly difficult and requires the use of the relatively expensive Dess-Martin reagent.[23] The elegant approach of Kolb *et al.* circumvents this problem by converting amino acid derived azlactones directly into *N*-benzoyl α-amino trifluoromethyl ketones *via* a modified Dakin-West procedure (Route 3 in **Scheme 2**).[24-26] However, this approach tolerates only benzoyl groups as nitrogen substituents and the products are obtained as racemates.[27]

Recently, we reported a synthesis of α-carbamoyl trifluoromethyl ketones based on reaction of (trifluoromethyl)trimethylsilane with oxazolidin-5-ones.[28] Hydrolysis of the adducts gave trifluoromethyl

ketone derivatives. The advantages of this approach are the use of readily available optically pure amino acids as starting materials and flexibility with regard to the nitrogen substituent on the substrate.

Initially synthesis of the target structures **5** (**Figure 1**) was based on the addition of a trifluoromethyl anion equivalent to an α-amino aldehyde according to Route 2 in **Scheme 2**.[29] Subsequently, we compared the established methodology to our new approach to *N*-substitued α-amino trifluoromethyl ketones *via* amino acid derived oxazolidin-5-ones as key intermediates.

Based on Skiles' work, BOC or CBZ-protected amino acids were converted into α-amino trifluoromethyl alcohols by addition of the Ruppert Reagent to protected α-amino aldehydes (**Scheme 3**). Given the configurational instability of α-amino aldehydes it is important to avoid purification by column chromatography on silica which facilitates epimerisation of C-2.[30] In this respect we found Weinreb's procedure superior to other methods.[31] Thus, BOC- and CBZ-protected alanine and phenylalanine were converted into the 'Weinreb-amides' by coupling with *N,O*-dimethylhydroxylamine using 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI). Reduction with lithium aluminium hydride furnished clean *N*-BOC or *N*-CBZ protected α-amino aldehydes which were used without purification.

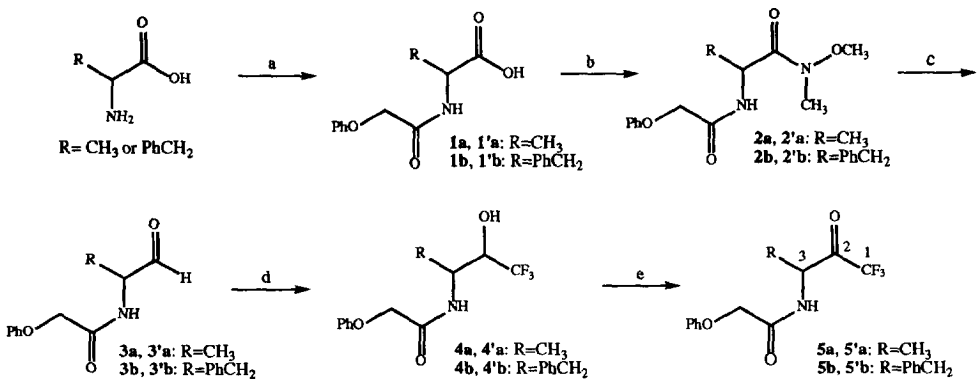


Reagents: (a) EDCI, $NHCH_3OCH_3HCl$, Et_3N, DMF; (b) $LiAlH_4$,THF; (c) TMS-CF_3, cat. CsF, THF, then HCl, *ca.* 30% yield; (d) PhCOCl, Et_3N, THF; (e) Dess-Martin reagent.

Scheme 3

Addition of the Ruppert Reagent to *N*-BOC or *N*-CBZ protected α-amino aldehydes using commercially available tetrabutylammoniun fluoride trihydrate proceeded only in poor yields. Better results were obtained when using caesium fluoride as a flouride source. After deprotection to give trifluoromethyl alcohol **B** followed by acylation with benzoyl chloride and oxidation using the Dess-Martin reagent the known trifluoromethyl ketone **D** was obtained in low overall yield. The spectral data for **D** were identical within the expected error margins to the data published by Kolb *et al.*[24, 25]

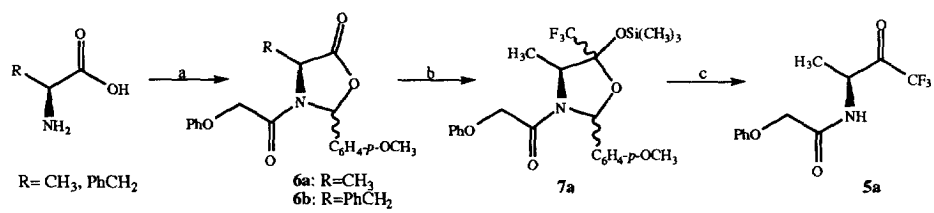
Because of the low yielding trifluoromethylation step (c) the approach outlined in **Scheme 3** was modified for the synthesis of the target compounds **5** and acylation of the amino acid with phenoxyacetyl chloride was carried out first (**Scheme 4**). Weinreb's procedure worked equally well for the conversion of *N*-phenoxyacetyl amino acids **1** into the corresponding amino aldehydes **3**. No sign of reduction of the α-amide moiety was observed by ^1H NMR analysis (200 MHz) and aldehydes **3** were judged sufficiently pure by ^1H NMR analysis to be used in the next step without any further purification. Addition of TMS-CF_3 to the aldehydes **3** using catalytic amounts of caesium fluoride with sonication, followed by acidic work-up gave *N*-phenoxyacetyl α-amino trifluoromethyl alcohols **4** in reproducible yields of 40-44%. Oxidation of the alcohols **4** using the Dess-Martin reagent gave trifluoromethyl ketones **5** in yields of 53-81%. Since purification of the products by column chromatography on silica gel led to significant loss of material trifluoromethyl ketones **5** were purified by crystallisation from petroleum ether (30-40)/diethyl ether.



Reagents: (a) $PhOCH_2COCl$, NaOH, 65-85%; (b) EDCI, $NHCH_3OCH_3HCl$, Et_3N, DMF, 57-99%; (c) $LiAlH_4$, THF, 69-93%; (d) TMS-CF_3, cat. CsF, THF, then HCl, 40-44%; (e) Dess-Martin reagent, 53-81%.

Scheme 4

The alternative approach to the target compounds **5** was based on the addition of the Ruppert Reagent to amino acid derived oxazolidin-5-ones (**Scheme 5**).[28] Reaction of the sodium salt of alanine or phenylalanine with anisaldehyde gave Schiff base salts which were subsequently *N*-phenoxyacetylated and cyclised *in situ*.[32] *N*-Phenoxyacetyl substituted oxazolidin-5-one **6a** reacted with TMS-CF_3 to give the silylated adduct **7a** in excellent yield using catalytic amounts of a solution of tetrabutylammonium fluoride in THF. In the case of phenylalanine derived oxazolidin-5-one **6b** no addition of TMS-CF_3 was observed under the same conditions, or when using ceasium fluoride under sonication. It is possible that the lack of reactivity in this case is due to steric hindrance around the five-membered ring caused by the three aromatic groups. (Note that a trifluoromethyl group is comparable in size to the isopropyl group using a half-sphere approximation.[33]) Alanine derived adduct **7a** was desilylated using tetrabutylammonium fluoride and hydrolysed using acidic ion-exchange resin to give the target molecule **5a** in good overall yield (~43% over 3 steps without any silica gel chromatography, compared to 7.5% over 5 steps for the synthesis of **5a** according to **Scheme 4**).



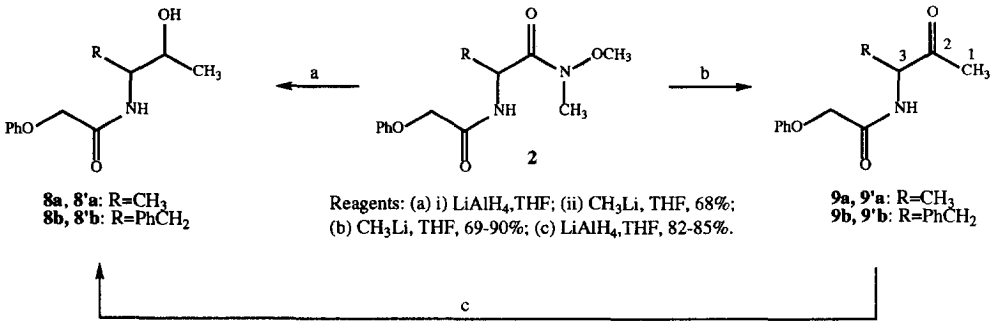
Reagents: (a) NaOH, anisaldehyde then $PhOCH_2COCl$, CH_2Cl_2, reflux, 56%; (b) TMS-CF_3, cat. TBAF-THF, THF; (c) 1 eq. TBAF-THF, then Amberlite, CH_3CN, 80% over 2 steps.

Scheme 5

N-Phenoxyacetyl-substituted trifluoromethyl ketones and alcohols **4** and **5** were tested and shown to be inhibitors of metallo-β-lactamases from *Xanthomonas maltophilia* ULA-511, *Aeromonas hydrophilia* AE036, *Bacillus cereus* 569H, and *Pseudomonas aeruginosa* 101. The details of the kinetic assays and the test

results have been published elsewhere.[12] Of particular interest is the fact that the enzyme from *A. hydrophilia* AE036 was irreversibly inhibited both by trifluoromethyl alcohols and ketones. The mechanistic basis of this type of inhibition is currently under investigation.

The non-fluorinated analogues of **4** and **5** were synthesised according to **Scheme 6** as a control for the influence of the trifluoromethyl group on the inhibitory activity.



Scheme 6

Addition of methyllithium to Weinreb amides **2** furnished ketones **9** directly.[31] The corresponding alcohols **8** were obtained by reduction of the Weinreb amides to the aldehydes followed by addition of methyllithium or by reduction of the ketones with lithium aluminium hydride. The non-fluorinated analogues of **4** and **5** (**8** and **9**) did not display any significant inhibitory activity.

Conclusion

In summary, α-amido trifluoromethyl ketone inhibitors of metallo-β-lactamases were obtained *via* two independent routes. Their synthesis *via* a route utilising addition of the Ruppert Reagent to oxazolidin-5-ones followed by mild acid hydrolysis proceeded in better yields and was more convenient than the precedented alternative which proceeds *via* addition of the Ruppert Reagent to α-amino aldehydes followed by oxidation. The scope of the TMS-CF_3 oxazolidine route is seemingly somewhat limited by steric constraints.

Acknowledgements:

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Experimental

Experimental Techniques

Melting points (mp) were determined using a Thermogalen® III melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at approximately 20°C with a path length of 1dm. Concentrations (c) are given in g/100ml. Infrared spectra were recorded as thin films between NaCl plates, as KBr discs or in $CHCl_3$ solution on a Perkin-Elmer 1750 Fourier Transform spectrometer. Absorptions are reported in wavenumbers (cm^{-1}). The following abbreviations are used: w, weak; m, medium; s, strong and br, broad.

Proton magnetic resonance spectra (^1H NMR) were recorded at 200 MHz on a Varian Gemini 200 or a Bruker AC200 spectrometer and at 500 MHz on a Bruker AM500 spectrometer. For ^1H NMR spectra recorded in $CDCl_3$ and D_2O chemical shifts (δ_H) are quoted in parts per million (p.p.m.) and are referenced to the residual solvent peak. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; m, multiplet and br, broad. Coupling constants (*J*) were recorded in Hertz to the nearest 0.5Hz. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 50.31 MHz on a Bruker AC200 and at 125.77 MHz on a Bruker AMX500 spectrometer using DEPT editing. Chemical shifts (δ_C) are quoted in p.p.m. and referenced to $CDCl_3$ unless otherwise stated. Spectra in D_2O are referenced to internal 1,4-dioxane. Fluorine magnetic resonance spectra (^{19}F NMR) were recorded at 235.19 MHz on a Bruker AC250 spectrometer. Chemical shifts (δ_F) are quoted in p.p.m. at 235.19 MHz and referenced externally to $CFCl_3$ at 0.00 p.p.m.

Low resolution mass spectra (m/z) were recorded on a V. G. Micromass ZAB 1F (CI/DCI), a V. G. Masslab 20-250 (CI/DCI) or a V. G. BIO Q (electrospray ionisation) mass-spectrometer, with only molecular ions (M^+), fragments from molecular ions and major peaks being reported.

High resolution mass spectra (HRMS) were recorded by the Mass Spectrometry Service Swansea.

Sonication was carried out using a Kerry Pulsatron® sonicator with a water bath at ambient temperature.

Microanalyses were performed by Mrs. V. Lamburn, Dyson Perrins Laboratory, University of Oxford.

Flash chromatography was accomplished on silica gel using Sorbsil® C60. Thin layer chromatography was performed on aluminium plates pre-coated with Merck silica gel F_{254} which were visualised by the quenching of UV fluorescence (λ_{max}=254nm) or by staining with 5% w/v phosphomolybdic acid in 95% ethanol.

All solvents were distilled before use. Anhydrous dichloromethane was obtained by stirring over calcium hydride for 24 hours followed by distillation under argon. Anhydrous diethyl ether and anhydrous tetrahydrofuran were obtained by distillation from sodium/benzophenone ketyl under nitrogen. All other reagents were purified in accordance with the instructions in D. D. Perrin and W. L. F. Armarego, "Purification of Laboratory Chemicals", 3rd edition, Pergamon Press, London, 1988 or used as obtained from commercial sources.

Experimental Procedures

(*S*)-*N*-Phenoxyacetyl-alanine (1a): To an ice-cooled solution of (*S*)-alanine (1.78g, 20.0mmol) in 1N sodium hydroxide (20.0ml, 20.0mmol) were added phenoxyacetylchloride (3.38ml, 20.0mmol) and 1N sodium hydroxide solution (20.0ml, 20.0mmol) dropwise under ice cooling. After stirring for 20 minutes, 1N hydrochloric acid solution was added (20.0ml, 20.0mmol) whereupon a thick, white precipitate formed which was dissolved in ethyl acetate (heating was required to effect solution). After separation, the organic layer was extracted with saturated sodium bicarbonate solution (3x20ml). The combined aqueous layers were then acidified to pH 2-3 with 1N hydrochloric acid. The resulting white precipitate was dissolved in hot ethyl acetate/ethanol (50ml), washed with brine (50ml) and dried over magnesium sulphate. After removal of solvents *in vacuo*, the crude product was obtained as an off-white solid which was recrystallised from hot ethanol to gave **1a** as fine white needles (2.90g, 65%); $[\alpha]_D^{20}$ = +17.0 (c = 1.0, AcOH); m.p. 188-190°C (lit.[34]: 166°C); ν_{max} (KBr): 3410s, 3300-2400br, 1740s, 1650s, 1600s, 1500s, 1420m, 1175m; δ_H (200 MHz, $(D_3C)_2SO$): 1.28 (3H, d, *J* 7Hz, CH_3), 4.27 (1H, qui, *J* 7Hz, H-2), 4.41 (2H, s, $PhOCH_2$), 6.90-6.95 (5H, m, Ph), 8.36 (1H, d, br, *J* 7Hz, NH); δ_C (50.3 MHz, $(D_3C)_2SO$): 17.0 (CH_3), 47.3 (C-2), 66.5 ($PhOCH_2$), 114.7, 121.2, 129.5 (all CH aryl), 157.7 (*ipso* aryl), 167.6, 173.4 (amide and acid C=O); m/z (NH_3): 241 (MNH_4^+, 50%), 224 (MH^+, 100%), 208 (10%), 149 (15%), 132 (10%), 90 (10%); required for $C_{11}H_{13}NO_4$: C: 59.19, H: 5.87, N: 6.23%; found: C: 59.39, H: 5.83, N: 6.23%.

(*R*)-*N*-Phenoxyacetyl-alanine (1'a): 1'a was obtained following the same procedure as given for **1a**, (4.70g, 85%) from (*R*)-alanine (2.25g, 25.0mmol). **1'a** was identical to **1a** by comparison of their respective spectroscopic data except for: $[\alpha]_D^{20}$ = -17.0 (c = 1.0, AcOH).

(*S*)-*N*-Phenoxyacetyl-*N'*-methoxy-*N'*-methyl-alanylamide (2a): To an ice-cooled solution of **1a** (2.78g, 12.5mmol) in dry DMF (15ml) were added *N*-*O*-dimethylhydroxylamine hydrochloride (0.99g, 10.0mmol), triethylamine (1.40ml; 10.0mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI) (2.27g, 10.0mmol). After stirring for 24 hours water (20ml) was added and stirring was continued for 30 minutes. The mixture was extracted with ethyl acetate (3x20ml) and the combined organic layers were thoroughly washed with brine (3x50ml) to remove residual DMF. After drying over magnesium sulphate and removal of solvents *in vacuo* **2a** was obtained as a pale yellow oil, sufficiently pure to be used in the next reaction without further purification (2.00g, 75%). A small analytical sample for spectroscopic characterisation was purified by column chromatography; $[\alpha]_D^{20}$ = +11.6 (c = 1, $CHCl_3$); ν_{max} ($CHCl_3$): 3300m, 2940m, 1655s, 1600m, 1525m, 1495s, 1240m, 1175m; δ_H (200 MHz, $CDCl_3$): 1.40 (3H, d, *J* 7Hz, CH_3), 3.23 (3H, s, N-CH_3), 3.69 (3H, s, OCH_3), 4.49 (2H, s, $PhOCH_2$), 5.04 (1H, qui, *J* 7Hz, H-2), 6.91-7.02 (3H, m, Ph), 7.26-7.31 (2H, m, Ph), 7.43 (1H, d, br, *J* 7Hz, NH); δ_C (50.3 MHz, $CDCl_3$): 17.8 (CH_3), 32.8 (NCH_3), 45.6 (C-2), 62.5 (OCH_3), 67.5 ($PhOCH_2$), 114.3, 122.0, 129.8 (all CH aryl), 156.9 (*ipso* aryl), 168.1, 173.4 (2xC=O); m/z (NH_3): 267 (MH^+, 5%), 237 (10%), 206 (30%), 178 (40%), 107 (100%); HRMS: calculated for $C_{13}H_{19}N_2O_4$ (MH^+): 267.1345; found: 267.1345.

(*R*)-*N*-Phenoxyacetyl-*N'*-methoxy-*N'*-methyl-alanylamide (2'a): 2'a was obtained following the same procedure as given for **2a**, (2.20g, 83%) from **1'a** (2.78g, 12.5mmol). **2'a** was identical to **2a** by comparison of their respective spectroscopic data except for: $[\alpha]_D^{20}$ = -12.0 (c = 1.0, $CHCl_3$).

(*S*)-*N*-Phenoxyacetyl-alaninal (3a): To a solution of **2a** (345mg, 1.30mmol) in dry THF (25ml) was added $LiAlH_4$ (38mg, 1.00mmol) carefully under ice cooling (violent reaction). The reaction was quenched after 20 minutes by addition of 1M sodium hydrogen sulphate solution (2ml). The mixture was then extracted with ethyl acetate (3x15ml) and the combined organic layers washed with 1N hydrochloric acid (3x5ml), saturated sodium carbonate solution (3x5ml) and brine (15ml), dried over magnesium sulphate and the solvents removed *in vacuo*. The product was obtained as a pale yellow oil and immediately used in the next reaction (185mg, 69%); δ_H (200 MHz, $CDCl_3$): 1.44 (3H, d, *J* 7Hz, CH_3), 4.55 (2H, s, $PhOCH_2$), 4.59 (1H, q, *J* 7Hz, H-2), 6.94-6.98 (3H, m, Ph), 7.26-7.34 (3H, m, Ph and NH), 9.59 (1H, s, CHO).

(*R*)-*N*-Phenoxyacetyl-alaninal (3'a): **3'a** was obtained following the same procedure as given for **3a**, (170mg, 73%) from **2'a** (300mg, 1.13mmol). The ^1H NMR spectrum of **3'a** was identical to the one of **3a** within the expected error margins.

(2*S*,3*S*)- and (2*R*,3*S*)-3-Amino-*N*-phenoxyacetyl-1,1,1-trifluorobutan-2-ol (4a) (mixture of two diastereomers in a ratio of 4:1 by ^{19}F NMR analysis)**:** To a solution of **3a** (139mg, 0.67mmol) in dry THF (5ml) were added TMS-CF_3 (128µl, 0.87mmol, 1.3eq) and caesium fluoride (1.5mg, 1mol%). The suspension was sonicated and the reaction followed by t.l.c analysis. The initiation of the reaction was indicated by the formation of a yellow colour. 25 minutes after initiation 1N hydrochloric acid (5ml) was added and stirring continued for another 10 minutes. The product mixture was extracted with ethyl acetate (3x10ml), the combined organic layers washed with saturated sodium bicarbonate solution (15ml) and brine (15ml), dried over magnesium sulphate and reduced *in vacuo*. The product was obtained as a pale yellow oil and purified by column chromatography to give **4a** as a clear oil (75mg, 40%); ν_{max} ($CHCl_3$): 3400-2900br, 1650s, 1600m, 1545m, 1500s, 1440m, 1390m; NMR data for more polar diastereomer: δ_H (500 MHz, $CDCl_3$): 1.40 (3H, d, *J* 7Hz, CH_3), 3.95-3.98 (1H, m, 3-H), 4.30 (1H, dqui, *J* 3, 6Hz, 2-H), 4.51 (2H, s, $PhOCH_2$), 6.92-7.39 (5H, m, Ph); δ_C (125.7 MHz, $CDCl_3$): 17.2 (CH_3), 45.7 (C-3), 67.2 ($PhOCH_2$), 72.6 (q, $J_{C\text{-}F}$ 30Hz, C-2), 114.7, 122.3 (both CH aryl), 124.7 (q, $J_{C\text{-}F}$ 284Hz, CF_3), 129.8 (CH aryl), 156.9 (*ipso* aryl), 169.5 (amide C=O); δ_F (235.19 MHz, $CDCl_3$): -77.5 (d, $J_{F\text{-}H}$ 8Hz, $CHOHCF_3$); NMR-spectroscopic data for less polar diastereomer: δ_H (500 MHz, $CDCl_3$): 1.36 (3H, d, *J* 7Hz, CH_3), 4.13-4.20 (1H, m, 3-H), 4.39 (1H, m, 2-H), 4.52 (2H, s, $PhOCH_2$), 6.81-7.36 (5H, m, Ph); δ_C (125.7 MHz, $CDCl_3$): 15.0 (CH_3), 45.9 (C-3), 67.1 ($PhOCH_2$), 72.2 (q, $J_{C\text{-}F}$ 30Hz, C-2), 114.6, 122.4 (both CH aryl), 124.7 (q, $J_{C\text{-}F}$ 284Hz, CF_3), 128.9 (CH aryl), 156.0 (*ipso* aryl), 169.6 (amide C=O); δ_F (235.19 MHz, $CDCl_3$): -75.7 (d, $J_{F\text{-}H}$ 8Hz, $CHOHCF_3$); m/z (NH_3): 295 (MNH_4^+, 10%), 278 (MH^+, 100%), 208 (40%), 178 (10%); HRMS: calculated for $C_{12}H_{15}F_3NO_3$ (MH^+): 278.1006; found: 278.1004.

(2*R*,3*R*)- and (2*S*,3*R*)-3-Amino-*N*-phenoxyacetyl-1,1,1-trifluorobutan-2-ol (4'a) (mixture of two diastereomers in a ratio of 4:1 by ^{19}F NMR analysis): **4'a** was obtained following the same procedure as given for **4a**, (78mg, 42%) from **3'a** (140mg, 0.67mmol). **4'a** was identical to **4a** by comparison of their respective spectroscopic data.

(*S*)-3-Amino-*N*-phenoxyacetyl-1,1,1-trifluorobutanone (5a): Dess-Martin reagent[35] (90mg, 0.21mmol, 1.5eq) was added to an ice-cooled solution of **4a** (40mg, 0.14mmol) in dry dichloromethane (15ml) at 0°C. The resulting suspension was stirred for 2 hours under an argon atmosphere. The reaction mixture was then diluted with dichloromethane (50ml) and washed with 1M sodium thiosulphate (25ml) and saturated sodium bicarbonate solution (25ml). The layers were separated and the aqueous layer

was extracted with ethyl acetate (3x10ml). The combined organic layers were washed with brine (15ml), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was obtained as a pale yellow oil and purified by column chromatography to yield the title compound as a slowly solidifying clear oil (21mg, 53%); **5a** was obtained as a $CDCl_3$ solution mixture of ketone and hydrate in a ratio of 3:2 by ^{19}F NMR (235.19 MHz, $CDCl_3$); $[\alpha]_D^{20}$ = +12.0 (c= 0.5, $CHCl_3$); m.p. 178-180°C; ν_{max} (KBr): 3410s, 3200-2700br, 1740s, 1725s, 1640s, 1600m, 1545m, 1490s, 1420m; δ_H (500 MHz, $CDCl_3$): 1.40 (3H, d, *J* 5Hz, hydrate CH_3), 1.44 (3H, d, *J* 5Hz, ketone CH_3), 4.22 (1H, qui, *J* 5Hz, hydrate 3-H), 4.54 (2H, s, ketone $PhOCH_2$), 4.55 (2H, s, hydrate $PhOCH_2$), 5.12 (1H, qui, *J* 5Hz, hydrate 3-H), 6.93-7.37 (6H, m, Ph and NH); δ_C (125.7 MHz, $CDCl_3$): 14.6 (hydrate CH_3), 16.6 (ketone CH_3), 49.8 (ketone C-3), 51.2 (hydrate C-3), 94.6 (q, $J_{C\text{-}F}$ 30Hz, C-2, hydrate), 115.6 (q, $J_{C\text{-}F}$ 292Hz, $CO\underline{C}F_3$), 114.7, 122.4, 122.6 (all CH aryl), 122.5 (q, $J_{C\text{-}F}$ 289Hz, $C(OH)_2\underline{C}F_3$), 129.8 (CH aryl), 156.8, 157.0 (both *ipso* aryl), 168.2, 171.6 (2xC=O), 190.2 (q, $J_{C\text{-}F}$ 35Hz, $\underline{C}OCF_3$); δ_F (235.19 MHz, $CDCl_3$): -76.5 and -82.4 (ketone and hydrate CF_3); m/z (NH_3): 293 (MNH_4^+, 20%), 276 (MH^+, 100%), 169 (15%), 152 (10%), 107 (5%); required for $C_{12}H_{12}F_3NO_3$: C: 52.37, H: 4.39, N: 5.09%; found: C: 52.51, H: 4.25, N: 5.09%.

(*R*)-3-Amino-*N*-phenoxyacetyl-1,1,1-trifluorobutanone (5'a): 5'a was obtained following the same procedure as given for **5a**, (24mg, 44%, the low yields are probably due to the difficulties in recovering the product from the silica gel) from **4'a** (55mg, 0.20mmol). **5'a** was identical to **5a** by comparison of their respective spectroscopic data except for: $[\alpha]_D^{20}$ = -11.4 (c = 0.5, $CHCl_3$).

(*S*)-*N*-Phenoxyacetyl-phenylalanine (1b): To a solution of (*S*)-phenylalanine (3.30g, 20.0mmol) in 1N sodium hydroxide solution (20.0ml, 20.0mmol) were added phenoxyacetyl chloride (3.38ml, 20.0mmol) and 1N sodium hydroxide solution (20.0ml, 20.0mmol) dropwise under ice cooling. After stirring for 20 minutes, 1N hydrochloric acid solution was added (20.0ml, 20.0mmol) whereupon a thick, white precipitate formed which was dissolved in ethyl acetate. The aqueous layer was extracted with ethyl acetate (3x20ml). The combined organic layers were extracted with saturated sodium bicarbonate solution (3x20ml). The aqueous layers were then carefully acidified to pH 2-3 with 1N hydrochloric acid. The resulting oil was taken up in ethyl acetate (50ml), washed with brine (50ml), dried over magnesium sulphate and the solvents removed *in vacuo*. The crude product was obtained as an off-white solid which was recrystallised from ethyl acetate to give **1b** as colourless prisms (4.19g, 70%); $[\alpha]_D^{20}$ = +15.0 (c = 1.0, MeOH); lit.[36]: $[\alpha]_D^{20}$ = +14.01 (c= 0.5, MeOH); m.p. 143-145°C; lit.[36]: 137-138°C; ν_{max} (KBr): 3390s, 3200-2400br, 1725s, 1625s, 1535m, 1495s, 1375s, 1290m; δ_H (200 MHz, $(D_3C)_2SO$): 2.99 (1H, dd, *J* 9, 14Hz, $PhCH_2$), 3.13 (1H, dd, *J* 5, 14Hz, $PhCH_2$), 4.46-4.56 (3H, m, 2-H overlapping with $PhOCH_2$), 6.84-6.99 (3H, m, Ph), 7.17-7.30 (7H, m, 2xPh), 8.29 (1H, d, br, *J* 8Hz, NH); δ_C (50.3 MHz, $(D_3C)_2SO$): 36.4 ($PhCH_2$), 53.1 (C-2), 66.4 ($PhOCH_2$), 114.6, 121.3, 126.6, 128.3, 129.1, 129.6 (all CH aryl), 137.4, 157.6 (*ipso* aryl), 168.0, 172.7 (2xC=O); m/z (NH_3): 317 (MNH_4^+, 25%), 300 (MH^+, 100%), 284 (5%), 254 (5%), 225 (5%), 151 (30%), 120 (10%); required for $C_{17}H_{17}NO_4$: C: 68.23, H: 5.68, N: 4.68%; found: C: 68.18, H: 5.48, N: 4.42%.

(*R*)-*N*-Phenoxyacetyl-phenylalanine (1'b): 1'b was obtained following the same procedure as given for **1b**, (1.70g, 81%) from (*R*)-phenylalanine (1.15g, 7.0mmol). **1'b** was identical to **1b** by comparison of their respective spectroscopic data except for: $[\alpha]_D^{20}$ = -16.5 (c = 1.0, MeOH).

(*S*)-*N*-Phenoxyacetyl-*N'*-methoxy-*N'*-methyl-phenylalanylamide (2b): To a solution of **1b** (3.74g, 12.5mmol) in dry DMF (15ml) cooled to 0°C were added *N-O*-dimethylhydroxylamine hydrochloride (0.99g, 10.0mmol), triethylamine (1.38ml, 10.0mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI) (2.27g, 10.0mmol). After stirring for 24 hours water (20ml) was added and stirring was continued for 30 minutes. The mixture was extracted with ethyl acetate (3x50ml), the organic layer separated and thoroughly washed with brine (3x20ml). After drying over magnesium sulphate and removal of solvents *in vacuo*, the crude product was obtained as a pale yellow oil which was purified by column chromatography to give **2b** as an off-white solid (3.40g, 99%); $[\alpha]_D^{20}$ = +15.0 (c = 1.0, $CHCl_3$); m.p. 90-91°C; ν_{max} (KBr): 3410m, 1815m, 1795m, 1655s, 1600m, 1565m, 1495s, 1465m, 1385s; δ_H (200 MHz, $CDCl_3$): 2.96 (1H, dd, *J* 7, 13Hz, $PhCH_2$), 3.08-3.19 (4H, m, 1x$PhCH_2$ overlapping with N-CH_3), 3.69 (3H, s, OCH_3), 4.45 (2H, s, $PhOCH_2$), 5.34 (1H, q, *J* 7Hz, 2-H), 6.87-7.35 (11H, m, 2xPh and NH); δ_C (50.3 MHz, $CDCl_3$): 32.0 (NCH_3), 38.3 ($PhCH_2$), 49.8 (C-2), 61.6 (OCH_3), 67.2 ($PhOCH_2$), 114.7, 122.0, 127.1, 128.4, 129.0, 129.7 (all CH aryl), 136.0, 157.0 (both *ipso* aryl), 167.8, 171.2 (2xC=O); m/z (NH_3): 343 (MH^+, 100%), 313 (40%), 282 (55%), 254 (45%), 226 (10%), 151 (10%), 132 (30%), 120 (20%); required for: $C_{19}H_{22}N_2O_4$: C: 66.65, H: 6.48, N: 8.18%; found: C: 66.58, H: 6.42, N: 8.16%.

(*R*)-*N*-Phenoxyacetyl-*N'*-methoxy-*N'*-methyl-phenylalanylamide (2'b): 2'b was obtained following the same procedure as given for **2b**, (0.55g, 57%) from **1'b** (0.85g, 2.84mmol). **2'b** was identical to **2b** by comparison of their respective spectroscopic data except for: $[\alpha]_D^{20}$ = -16.3 (c = 1.0, $CHCl_3$).

(*S*)-*N*-Phenoxyacetyl-phenylalaninal (3b): To a solution of **2b** (365mg, 1.07mmol) in dry THF (25ml) was added $LiAlH_4$ (29mg, 0.75mmol) carefully at 0°C (violent reaction). The reaction was quenched after 20 minutes by careful addition of 1M sodium hydrogen sulphate solution (2ml). The mixture was then extracted with ethyl acetate (3x10ml); the combined organic layers were washed with 1N hydrochloric acid (3x15ml), saturated sodium carbonate solution (3x15ml), and brine (15ml), dried over magnesium sulphate and concentrated *in vacuo*. The product was obtained as a white, waxy solid and was immediately used in the next reaction (280mg, 93%); δ_H (200 MHz, $CDCl_3$): 3.17-3.20 (2H, m, $PhCH_2$), 4.53 (2H, s, $PhOCH_2$), 4.81 (1H, q, *J* 7Hz, H-2), 6.85-7.36 (11H, m, 2xPh and NH), 9.65 (1H, s, CHO).

(*R*)-*N*-Phenoxyacetyl-phenylalaninal (3'b): 3'b was obtained following the same procedure as given for **3b**, (170mg, 86%) from **2'b** (240mg, 0.70mmol). The ^1H NMR spectrum of **3'b** was identical to the one of **3b** within the expected error margins.

(2*S*,3*S*)- and (2*R*,3*S*)-3-Amino-*N*-phenoxyacetyl-4-phenyl-1,1,1-trifluorobutan-2-ol (4b) (mixture of 2 diastereomers in a ratio of 10:1 by ^{19}F NMR analysis): To a solution of **3b** (280mg, 1.00mmol) in dry THF (5ml) were added TMS-CF_3 (195µl, 1.30mmol, 1.3eq) and caesium fluoride (1.5mg, 1mol%). The suspension was sonicated and the reaction followed by t.l.c analysis. The initiation of the reaction was indicated by the formation of a yellow colour. 25 minutes after initiation 1N hydrochloric acid (5ml) was added and stirring continued for another 10 minutes. The product mixture was extracted with ethyl acetate (3x10ml), the combined organic layers washed with saturated sodium bicarbonate solution (15ml) and brine (15ml), dried over magnesium sulphate and reduced *in vacuo*. The product was obtained as a pale yellow oil and purified by column chromatography (140mg, 40%). Spectroscopic data for the major

diastereomer: ν_{max} ($CHCl_3$): 3400-2800br, 1710m, 1680m, 1600m, 1525s, 1495s, 1365m; δ_H (500 MHz, $CDCl_3$): 2.94-3.16 (2H, m, $PhCH_2$), 3.97-4.00 (1H, m, 3-H), 4.37 (1H, dq, *J* 2, 8Hz, 2-H), 4.48 (2H, s, $PhOCH_2$), 4.81 (1H, br, d, *J* 7Hz, OH), 6.87-7.35 (11H, m, 2xPh and NH); δ_C (125.7 MHz, $CDCl_3$): 37.1 ($PhCH_2$), 51.1 (C-3), 67.3 ($PhOCH_2$), 69.5 (q, J_{C-F} 30Hz, C-2), 114.8, 122.3 (both CH aryl), 124.6 (q, J_{C-F} 284Hz, CF_3), 127.1, 128.8, 129.2, 129.7 (all CH aryl), 136.6, 157.0 (both *ipso* aryl), 169.6 (C=O); δ_F (235.19 MHz, $CDCl_3$): -77.4 (d, J_{F-H} 8Hz, CF_3); m/z (NH_3): 371 (MNH_4^+, 40%), 354 (MH^+, 100%), 284 (15%), 263 (55%), 218 (15%); 210 (5%), 120 (5%); required for $C_{18}H_{18}F_3NO_3$: C: 61.19, H: 5.13, N: 3.96%; found: C: 61.18, H: 5.35, N: 4.19%.

(2*R*,3*R*)- and (2*S*,3*R*)-3-Amino-*N*-phenoxyacetyl-4-phenyl-1,1,1-trifluorobutan-2-ol (4'b) (mixture of two diastereomers in a ratio of 10:1 by ^{19}F NMR): **4'b** was obtained following the same procedure as given for **4b**, (125mg, 44%) from **3'b** (230mg, 0.81mmol). **4'b** was identical to **4b** by comparison of their respective spectroscopic data.

(*S*)-3-Amino-*N*-phenoxyacetyl-4-phenyl-1,1,1-trifluorobutanone (5b): Dess-Martin reagent[35] (42.5mg, 0.10mmol, 1.4eq) was added to a cooled solution of **4b** (25mg, 0.07mmol) in dry dichloromethane (15ml). The resulting suspension was stirred for 2 hours under an argon atmosphere. The reaction mixture was then diluted with 50ml of dichloromethane and washed with 1M sodium thiosulphate (25ml) and saturated sodium bicarbonate solution (25ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (3x10ml). The combined organic layers were washed with brine (15ml), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was obtained as a yellow oil which was purified by crystallization from petroleum ether (30-40)/diethyl ether to yield **5b** as a white solid (18mg, 73%). **5b** was obtained as a $CDCl_3$ solution mixture of ketone and hydrate in a ratio of 3:2 by ^{19}F NMR (235.19 MHz, $CDCl_3$); $[\alpha]_D^{20}$ = +16.6 (c = 0.5, $CHCl_3$); m.p. 75-77°C; ν_{max} ($CHCl_3$): 3415m, 1770m, 1600m, 1520s, 1495s, 1440m, 1240m; δ_H (500 MHz, $CDCl_3$): 3.03 (1H, dd, *J* 7.5, 14Hz, ketone $PhCH_2$), 3.08 (1H, dd, *J* 11, 14Hz, hydrate $PhCH_2$), 3.30 (1H, dd, *J* 7.5, 14Hz, ketone $PhCH_2$), 3.35 (1H, dd, *J* 3, 14Hz, hydrate $PhCH_2$), 4.13-4.18 (1H, m, hydrate 3-H), 4.39/4.44 (2H, ABq, *J* 12Hz, hydrate $PhOCH_2$), 4.46/4.50 (2H, ABq, *J* 12Hz, ketone $PhOCH_2$), 5.29 (1H, dt, *J* 5.5, 7.5Hz, ketone 3-H), 6.75-7.37 (10H, m, 2xPh); δ_C (125.7 MHz, $CDCl_3$): 33.3 (hydrate $PhCH_2$), 36.2 (ketone $PhCH_2$), 54.3 (ketone C-3), 57.8 (hydrate C-3), 67.0 (ketone $PhOCH_2$), 67.1 (hydrate $PhOCH_2$), 94.5 (q, J_{C-F} 31Hz, hydrate C-2), 115.6 (q, J_{C-F} 292Hz, hydrate CF_3), 114.6, 114.8, 122.4, 122.6 (all CH aryl), 122.5, 122.7 (q, J_{C-F} J 289Hz, ketone CF_3), 127.0, 127.8, 128.0, 128.4, 129.0, 129.2, 129.8 (all CH aryl), 133.7, 136.7, 156.9 (all *ipso* aryl), 168.3, 172.3 (ketone and hydrate C=O), 189.2 (q, J_{C-F} 31Hz, $\underline{C}OCF_3$); δ_F (235.19 MHz, $CDCl_3$): -76.3 and -82.3 (ketone and hydrate CF_3); m/z (NH_3): 352 (MH^+, 100%), 334 (10%), 169 (5%), 151 (15%), 108 (10%); HRMS: calculated for $C_{18}H_{20}F_3N_2O_3$ (MNH_4^+): 369.1425; found: 369.1425.

(*R*)-3-Amino-*N*-phenoxyacetyl-4-phenyl-1,1,1-trifluorobutanone (5'b): 5'b was obtained following the same procedure as given for **5b**, (20mg, 81%) from **4'b** (25mg, 0.07mmol). **5'b** was identical to **5b** by comparison of their respective spectroscopic data except for: $[\alpha]_D^{20}$ = -17.2 (c = 1.0, $CHCl_3$).

(2*S*,4*S*)-2-(4'-Methoxyphenyl)-4-methyl-3-phenoxyacetyl-1,3-oxazolidin-5-one (6a): Preparation of the intermediate Schiff base salt:[32] (*S*)-Alanine (0.89g, 10.0mmol) was

dissolved in sodium hydroxide (10.0ml of a 1N solution, 10.0mmol). The solution was then evaporated *in vacuo* until solid began to appear at which time anisaldehyde (1.21ml, 10.0mmol) was added. Evaporation was continued until the reaction mixture solidified. Diethyl ether was added and the solid filtered, washed thoroughly with the same solvent and dried *in vacuo* (1.90g. 83%).

Preparation of 6a: The finely ground Schiff base salt (3.66g, 16.0mmol) was dissolved in refluxing dry dichloromethane (190ml) and phenoxyacetyl chloride (3.00ml, 20.0mmol, 1.25eq) was added under an argon atmosphere. The resulting solution was kept at reflux for 12 hours after which time a yellow solution had formed. The solvent was removed *in vacuo* and the resulting yellow suspension was taken up in ethyl acetate (150ml), washed with saturated sodium bicarbonate solution (75ml), aqueous hydrochloric acid solution (75ml), brine (75ml) and dried over magnesium sulphate. **6a** was obtained after column chromatography and crystallisation from hot diethyl ether as fine white needles (3.70g, 68%); $[\alpha]_D^{20}$ = +224 (c = 1.0, $CHCl_3$); m.p. 95-97°C; ν_{max} (KBr): 2960s, 1795s, 1715s, 1670m, 1500m, 1465m; 1380m; δ_H (500 MHz, $C_6D_5CD_3$, 90°C): 1.41 (3H, d, *J* 7Hz, CH_3), 3.31 (3H, s, OCH_3), 3.81 and 4.06 (2H, ABq, J_{AB} 14Hz, $PhOCH_2$), 4.50 (1H, q, *J* 7Hz, 4-H), 6.44 (1H, s, 2-H), 6.45-7.09 (9H, m, 2xPh); δ_C (50.3 MHz, $CDCl_3$): 16.1 (CH_3), 52.7 (C-4), 55.4 (OCH_3), 67.8 ($PhOCH_2$), 89.6 (C-2), 114.0, 114.6, 122.1, 128.1, 128.5 (all CH aryl), 129.0, 156.7, 161.4 (all *ipso* aryl), 167.3 and 172.1 (2xC=O); m/z (NH_3): 342 (MH^+, 100%), 248 (20%), 206 (5%), 162 (10%), 135 (15%); required for $C_{19}H_{19}NO_5$: C: 66.85, H: 5.61, N: 4.10%; found: C: 66.69, H: 5.59, N: 4.01%.

(2*S*,4*S*)-4-Benzyl-2-(4'-methoxyphenyl)-*N*-phenoxyacetyl-1,3-oxazolidin-5-one (6b): Preparation of the intermediate Schiff base salt: (*S*)-Phenylalanine (1.65g, 10.0mmol) was dissolved in sodium hydroxide (10.0ml of a 1N solution, 10.0mmol). The solution was then evaporated *in vacuo* until solid began to appear at which time anisaldehyde (1.21ml, 10.0mmol) was added. Evaporation was continued until the reaction mixture solidified. Diethyl ether was added and the solid filtered, washed thoroughly with the same solvent and dried *in vacuo* (2.98g, 98%).

Preparation of 6b: The carefully ground Schiff base salt (3.05g, 10.0mmol) was dissolved in refluxing dry dichloromethane (200ml) and phenoxyacetyl chloride (1.88ml, 12.5mmol, 1.25eq) was added under an argon atmosphere. The resulting solution was kept at reflux for 12 hours after which time a yellow solution had formed. The solvent was removed *in vacuo* and the resulting yellow suspension was taken up in ethyl acetate (150ml), washed with saturated sodium bicarbonate solution (75ml), aqueous hydrochloric acid solution (75ml), brine (75ml) and dried over magnesium sulphate. **6b** was obtained as a pale yellow oil and as a single diastereomer after purification by flash column chromatography, using 20% ethyl acetate/petroleum ether (30-40) as eluant (2.65g, 64%); $[\alpha]_D^{20}$ = +223.6 (c = 1.0, $CHCl_3$); ν_{max} (KBr): 2840m, 1785s, 1645s, 1615m, 1600s, 1590m, 1405s, 1320s, 1250s cm^{-1}; δ_H (500 MHz, $CDCl_3$): 3.24 (1H, dd, *J* 2 and 14Hz, $PhCH_2$), 3.68 (1H, dd, *J* 5 and 14Hz, $PhCH_2$), 3.78 (3H, s, OCH_3), 3.72 and 4.18 (2H, ABq, J_{AB} 14Hz, $PhOCH_2$), 5.15 (1H, dd, *J* 2 and 5Hz, 4-H), 5.84 (1H, s, 2-H), 6.80-6.90 (2H, m, Ph), 7.02-7.32 (12H, m, 3xPh); δ_C (125.7 MHz, $CDCl_3$): 34.2 ($PhCH_2$), 55.3 (C-4), 58.6 (OCH_3), 67.3 ($PhOCH_2$), 90.2 (C-2), 114.0, 121.9, 126.7, 127.5, 128.6, 128.7, 129.6, 129.7 (all CH aryl), 129.9, 134.4, 156.6, 161.4 (all *ipso* aryl), 166.8, 170.4 (lactone and amide C=O); m/z (EI): 418 (MH^+, 100%), 324 (10%), 282 (10%), 253 (15%), 238 (10%), 136 (15%); required for $C_{25}H_{23}NO_5$: C: 71.94, H: 5.51, N: 3.36%; C: 71.93, H: 5.46, N: 3.14%.

(2*S*,4*S*,5*RS*)-2-(4'-Methoxyphenyl)-4-methyl-*N*-phenoxyacetyl-5-trifluoromethyl-5-trimethylsilyloxy-1,3-oxazolidine (7) (mixture of two diastereomers in a ratio of 1.5:1 by high temperature ^{19}F NMR analysis): To a solution of **6a** (0.55g, 1.61mmol) in dry THF (15ml) were added (trifluoromethyl)trimethylsilane (294μl, 2.00mmol) and tetrabutylammonium fluoride (30μl of a 1M solution in THF, 0.03mmol) under an argon atmosphere at room temperature. The resulting yellow solution was stirred for 3 hours after which time t.l.c. analysis indicated completion. The mixture was taken up in ethyl acetate (10ml), washed with water (2x10ml), brine (10ml), and dried over magnesium sulphate. The crude product was sufficiently clean by ^1H NMR to be taken over to the next step (0.74g, 95%). An analytical sample for characterisation was obtained by preparative thin layer chromatography; ν_{max} ($CHCl_3$): 2965m, 1655s, 1615m, 1515m, 1495m, 1415m; δ_H (250 MHz, $C_6D_5CD_3$, 90°C): 0.05 (9H, s, $Si(CH_3)_3$, major diastereomer)/0.13 (9H, s, $Si(CH_3)_3$, minor diastereomer), 1.31 (3H, d, *J* 6Hz, CH_3, minor diastereomer)/1.38 (3H, d, *J* 6Hz, CH_3, major diastereomer), 3.30 (3H, s, OCH_3, major diastereomer)/3.31 (3H, s, OCH_3, minor diastereomer), 3.65-4.04 (2x2H, m, $PhOCH_2$, both diastereomers), 4.76 (1H, q, *J* 6Hz, 4-H, minor diastereomer)/4.78 (1H, q, *J* 6Hz, 4-H, major diastereomer), 6.37 (1H, s, 2-H, major diastereomer)/6.48 (1H, s, 2-H, minor diastereomer), 6.69-7.21 (9H, m, Ph); δ_C (125.7 MHz, $CDCl_3$): 1.1 ($Si(CH_3)_3$), 13.9/16.2 (CH_3), 55.2/56.1 (OCH_3), 67.1/67.2 ($PhOCH_2$), 90.2/90.3 (C-2), 101.0-102.0 (m, C-5), 113.6/113.8 (CH aryl), 123.5 (q, J_{C-F} 287Hz, CF_3), 124.0 (q, J_{C-F} 290Hz, CF_3) , 127.5, 128.2, 128.0, 128.2, 128.4, 128.5 (all CH aryl), 130.4, 136.0, 152.4, 153.5 (all *ipso* aryl), 160.1/160.4 (C=O); δ_F (235.19 MHz, $C_6D_5CD_3$, 90°C): -89.0 (CF_3, major diastereomer), -90.2 (CF_3, minor diastereomer); m/z (NH_3): 484 (MH^+, 25%), 398 (10%), 348 (30%), 276 (20%), 137 (100%); HRMS: calculated for $C_{23}H_{29}F_3NO_5Si$ (MH^+): 484.177; found: 484.178.

(*S*)-3-Amino-*N*-phenoxyacetyl-1,1,1-trifluorobutanone (5a) obtained by hydrolysis of **(7)**: To a solution of **(7)** (0.74g, 1.53mmol) in THF (10ml) was added tetrabutylammonium fluoride solution in THF (1.70ml of a 1M solution, 1.70mmol). After stirring for 15 minutes ethyl acetate (15ml) was added and the organic layer was washed with aqueous hydrochloric acid. After evaporation of solvents *in vacuo* acetonitrile (15ml) and strongly acidic cation exchange resin (250mg) were added and the mixture stirred at 45°C until all starting material had disappeared by ^{19}F NMR analysis (4-6 hours). The crude reaction mixture was diluted with acetonitrile (25ml), filtered and the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate (25ml), washed with saturated sodium bicarbonate solution (25ml) and brine (25ml). After removal of solvents the crude product was obtained as a brown solid and was purified by crystallisation from diethyl ether/petroleum ether (30-40) (0.36g, 80%). The spectroscopic data (^1H, ^{13}C, ^{19}F NMR) obtained for **5a** by this procedure were identical to those of **5a** obtained *via* the aldehyde route ($[\alpha]_D^{20}$ = +12.3 (c = 0.5 $CHCl_3$).

(2*S*,3*S*)- and (2*R*,3*S*)-3-Amino-*N*-phenoxyacetylbutan-2-ol (8a): To a solution of **(9a)** (85mg, 0.38mmol) in dry THF (5ml) was added $LiAlH_4$ (15mg, 0.39mmol) under ice-cooling. The reaction was quenched after 25 minutes by addition of sodium hydrogen sulphate solution (5ml of a 1M solution, 5.00mmol). The reaction mixture was extracted with ethyl acetate (3x10ml), the combined organic layers were washed with saturated sodium bicarbonate solution (15ml) and brine (5ml), dried over magnesium sulphate and concentrated *in vacuo*. **8a** was obtained as a pale yellow, slowly solidifying oil (73mg, 85%, mixture of 2 diastereomers in a ratio of 3:2 by ^1H NMR (500 MHz, $CDCl_3$)); ν_{max} (KBr): 3300-2900br,

1655s, 1600m, 1540m, 1495s, 1375m; δ_H (500 MHz, $CDCl_3$): 1.15 (3H, d, *J* 6Hz, $CHOHC\underline{H}_3$), 1.16 (3H, d, *J* 7Hz, $CHOHC\underline{H}_3$), 3.97-4.10 (1H, m, 3-H), 3.85-4.15 (1H, m, 2-H), 4.50/4.51 (2H, s, $PhOC\underline{H}_2$), 6.70-6.85 (H, m, NH), 6.91-7.34 (5H, m, Ph); δ_C (50.3 MHz, $CDCl_3$): 14.2/17.7 (CH_3), 18.8/20.4 ($CHOH\underline{C}H_3$), 50.2 (C-3), 67.3/70.1 ($PhO\underline{C}H_2$), 114.7, 122.1, 122.2 (all CH aryl), 157.1 (*ipso* aryl), 168.4/168.5 (amide C=O); m/z (NH_3): 224 (MH^+, 100%), 206 (10%), 179 (10%), 107 (5%); HRMS: calculated for $C_{12}H_{18}NO_3$ (MH^+): 224.1287; found: 224.1287.

(2*R*,3*R*)- and (2*S*,3*R*)-3-Amino-*N*-phenoxyacetylbutan-2-ol (8'a): 8'a was obtained from **9'a** (55mg, 0.25mmol) following the same procedure as given for **8a** (41mg, 74%). **8'a** was identical to **8a** by comparison of their respective spectroscopic data .

(*S*)-3-Amino-*N*-phenoxyacetylbutanone (9a): A solution of **2a** (360mg, 1.35mmol) in dry THF (15ml) was cooled to 0°C and methyllithium (3.00ml of a 1M solution, 3.00mmol, 2.22eq) was added dropwise. The solution was stirred for 30 minutes, quenched by the addition of 1N hydrochloric acid (5ml), and extracted with ethyl acetate (3x15ml). The combined organic layers were washed with brine (15ml), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was obtained as a pale yellow oil and purified by column chromatography using 30% ethyl acetate/petroleum ether (30-40) to give **9a** as a slowly solidifying clear oil (205mg, 69%); $[\alpha]_D^{20}$ = -53.0 (c = 1.0, $CHCl_3$); ν_{max} (KBr): 3400-2900br, 1720s, 1675s, 1600m, 1525m, 1445s, 1360m 1140m; δ_H (500 MHz, $CDCl_3$): 1.43 (3H, d, *J* 7Hz, CH_3), 2.24 (3H, s, $COCH_3$), 4.55 (2H, s, $PhOCH_2$), 4.69 (1H, qui, *J* 7Hz, H-3), 6.95-7.04 and 7.27-7.36 (5H, m, Ph), 7.52 (1H, d, br, *J* 7Hz, NH); δ_C (50.3 MHz, $CDCl_3$): 17.1 (CH_3), 26.6 ($CO\underline{C}H_3$), 54.6 (C-3), 67.2 ($PhOCH_2$), 114.8, 122.1, 129.7 (all CH aryl), 156.9 (*ipso* aryl), 168.8 (amide C=O), 206.4 (ketone C=O); m/z (NH_3): 222 (MH^+, 100%), 179 (10%), 107 (5%); HRMS: calculated for $C_{12}H_{16}NO_3$ (MH^+): 222.113, found: 222.113.

(*R*)-3-Amino-*N*-phenoxyacetylbutanone (9'a) was obtained from **2'a** (55mg, 0.21mmol) following the same procedure as given for **9a** (41mg, 90%). **9'a** was identical to **9a** by comparison of their respective spectroscopic data except for: $[\alpha]_D^{20}$ = +53.0 (c = 1.0, $CHCl_3$).

(2*S*,3*S*)- and (2*R*,3*S*)-3-Amino-*N*-phenoxyacetyl-4-phenylbutan-2-ol (8b):

Procedure A: To a solution of **3b** (140mg, 0.49mmol) in dry THF (5ml) was added methyl magnesium bromide (0.25ml of a 3M solution, 0.75mmol, 1.53eq) under ice-cooling. The reaction was quenched after 25 minutes by addition of sodium hydrogen sulphate solution (5ml of a 1M solution, 5mmol). After extraction with ethyl acetate (3x10ml) the combined organic layers were washed with saturated sodium bicarbonate solution (3x5ml) and brine (5ml), dried over magnesium sulphate and concentrated *in vacuo*. The product was obtained as a white solid which was crystallised from diethyl ether to give **8b** as fine white needles (100mg, 68%) and as a mixture of diastereomers in a ratio of 9:1 by ^1H NMR analysis (see below).

Procedure B: To an ice-cooled solution of **9b** (40mg, 0.13mmol) in dry THF was added lithium aluminium hydride (5mg, 0.13mmol). The resulting suspension was stirred for 30 minutes and then carefully quenched by the addition of sodium hydrogen sulphate solution (5ml of a 1M solution, 5mmol). After addition of aqueous hydrochloric acid (15ml) the aqueous layer was extracted with ethyl acetate (3x15ml) and the combined organic layers were dried over magnesium sulphate. The product was obtained as a white solid which was crystallised from diethyl ether to give **8b** as fine white needles (33mg, 82%) and as a mixture of diastereomers in a ratio of 10:1 by ^1H NMR analysis (only the data for the major diastereomer is reported);

m.p. 115°C; ν_{max} (KBr): 3300-2900br, 1655s, 1495s, 1445m, 1240m cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.15 (3H, d, *J* 6Hz, CH_3), 2.92 (2H, m, $PhCH_2$), 3.87 (1H, dq, *J* 2, 8Hz, 3-H), 4.12 (1H, dq, *J* 2, 6Hz, 2-H), 4.48 (2H, s, $PhOCH_2$), 6.87-7.36 (11H, m, 2xPh and NH); δ_C (125.7 MHz, $CDCl_3$): 20.8 (C-1), 38.2 ($PhCH_2$), 55.3 (C-3), 65.8 (C-2), 67.3 ($PhOCH_2$), 114.7, 122.1, 126.5, 128.5, 129.3, 129.7 (all CH aryl), 137.8, 157.1 (both *ipso* aryl), 168.6 (amide C=O); m/z (NH_3): 300 (MH^+, 100%), 254 (10%), 282 (45%), 208 (10%); 190 (10%), 102 (5%); required for $C_{18}H_{21}NO_3$: C: 72.24, H: 7.02, N: 4.68%; found: C: 72.02, H: 7.05, N: 4.44%.

(2*R*,3*R*)- and (2*S*,3*R*)-3-Amino-*N*-phenoxyacetyl-4-phenylbutan-2-ol (8'b) was obtained following procedure B as given for **8b** (120mg, 85%), from **9'b** (140mg, 0.47mmol). **8'b** was identical to **8b** by comparison of their respective spectroscopic data.

(*S*)-3-Amino-*N*-phenoxyacetyl-4-phenylbutanone (9b): A solution of **2b** (150mg, 0.44mmol) in dry THF (15ml) was cooled to 0°C and methyllithium (1.00ml of a 1M solution, 1.00mmol, 2.3eq) was added dropwise. The solution was stirred for 30 minutes and then quenched by the addition of 1M sodium hydrogen sulphate solution (5ml). After extraction with ethyl acetate (3x15ml) the combined organic layers were washed with brine (15ml), dried over magnesium sulphate and concentrated *in vacuo*. Crystallisation from diethyl ether yielded **9b** as fine white needles (111mg, 85%); $[\alpha]_D^{20}$ = -56.0 (c = 1.0, $CHCl_3$); m.p. 95-96°C, ν_{max} (KBr): 3285s, 1715s, 1675s, 1600m, 1545s, 1495s, 1315m, 1110m cm^{-1}; δ_H (500 MHz, $CDCl_3$): 2.15 (3H, s, CH_3), 3.07-3.12 (2H, m, $PhCH_2$), 4.48 (2H, s, $PhOCH_2$), 4.92 (1H, q, *J* 7Hz, 3-H), 7.05-7.20 (11H, m, 2xPh, NH); δ_C (125.7 MHz, $CDCl_3$): 28.1 (CH_3), 37.2 ($PhCH_2$), 58.9 (C-3), 67.2 ($PhOCH_2$), 114.7, 122.1, 127.2, 128.7, 129.1, 129.8 (all CH aryl), 135.5, 156.9 (both *ipso* aryl), 172.3 (amide C=O), 206.5 (ketone C=O); m/z (NH_3): 298 (MH^+, 100%), 254 (10%), 226 (5%), 196 (5%), 151 (5%), 132 (10%), 120 (25%), 107 (10%); required for $C_{18}H_{19}NO_3$: C: 72.72, H: 6.40, N: 4.71%; found: C: 73.03, H: 6.70, N: 4.87%.

(*R*)-3-Amino-*N*-phenoxyacetyl-4-phenylbutanone (9'b) was obtained from **2'b** (80mg, 0.23mmol) following the same procedure as given for **9b** (53mg, 76%). **9'b** was identical to **9b** by comparison of their respective spectroscopic data except for: $[\alpha]_D^{20}$ = +55.8 (c = 1.0, $CHCl_3$).

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