Oxidation of didehydro-α-amino acids as a route to β-hydroxy- or β-amino-pyruvic derivatives and to α-acylglycinates

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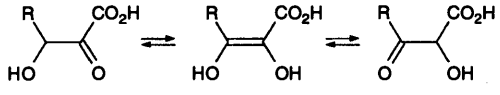
Oxidation of protected didehydro-α-amino acids with *N*-bromosuccinimide or lead tetraacetate affords imines of β-bromo- or β-acetoxy-pyruvates. The hydrolysis of brominated imines proceeds through addition of water followed by intramolecular displacement of bromine. According to experimental procedures, intermediate hydroxyaziridines, hydroxyoxazolines or aminoepoxides have to be considered. Two pathways are examined for hydrolysis of β-acetoxyimines: cyclisation to oxazolones or conversion to acylglycinates when imines are converted to the isomeric enamines prior to deprotection.

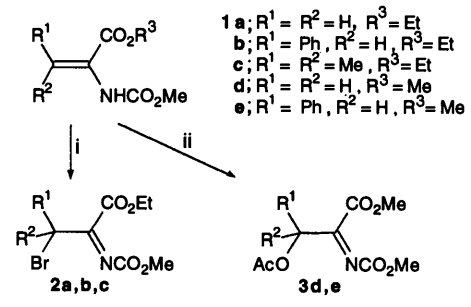
Introduction

β-Hydroxypyruvic acid (HPA) and its derivatives are related to reductones[1] and three tautomeric forms have to be taken in account.



These compounds are of biological interest as intermediates in metabolism of β-hydroxy-α-amino acids[2] or as substrates for enzymic reactions with transketolases[3] or pyruvate dehydrogenases.[4] Such highly functionalised small molecules are also valuable intermediates in heterocyclic synthesis.[5]

In a previous paper we reported that *N*-bromosuccinimide (NBS) oxidation of didehydroamino esters **1** allowed convenient access to β-bromo-α-imino esters **2** (Scheme 1).[6] The present work will deal with our studies on the mechanistic pathways for hydrolysis of these pyruvic imines. Rearrangements related to neighbouring-group assistance are of prime importance, in good agreement with the chemistry of α-halogeno ketones[7] or the related methanesulfonates,[8] triflates[8] or sulfonates.[9] These results prompted us to investigate a new approach through lead tetraacetate (LTA) oxidation of compounds **1** which allows access to β-acetoxy-α-imino esters **3** (Scheme 1).

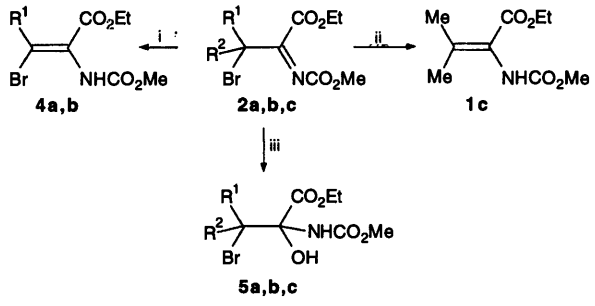


Scheme 1 *Reagents:* i, NBS; ii, LTA

Results and discussion

Hydrolysis of β-bromo-α-imino esters 2

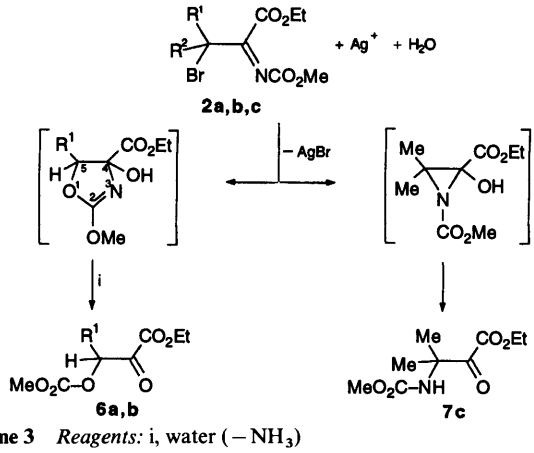
Strongly basic or nucleophilic media have to be avoided. They promote isomerisation to enamines **4** (R^2 = H) or reduction to didehydroamino esters **1** (R^1, R^2 ≠ H) (Scheme 2).[10] However,



Scheme 2 *Reagents:* i, B^-; ii, Nu^- (−NuBr); iii, H_3O^+

under acid catalysis, addition of water was quantitative in a few minutes, affording hemiaminals **5** in good yield (Scheme 2). α-Hydroxy-α-amino acids are known to be stable, readily isolable compounds.[11]

Two procedures were then investigated for displacement of bromine. Hydrolysis of imino esters **2** in aq. silver nitrate occurred smoothly at room temperature, affording β-hydroxy-α-keto esters as the carbonates **6a,b** or a β-amino-α-keto ester as the carbamate **7c** (Scheme 3). These derivatives were readily



Scheme 3 *Reagents:* i, water (−NH_3)

characterised after conversion to their 2,4-dinitrophenylhydrazones.

To account for this result, two intramolecular rearrangements have to be considered. Carbamate **7c** results from a 1,2-nitrogen migration through an intermediate hydroxyaziridine. Such a mechanism was previously evidenced during aminolysis of β-chloropyruvic esters.[12] Obtention of carbonates **6a,b** involves an acyl migration which can be explained by a competitive cyclisation to an hydroxyoxazoline which opens to a readily hydrolysed iminocarbonate.

In a second procedure, bromohydrins **5** were treated with potassium *tert*-butoxide in tetrahydrofuran (THF) at room temperature. Compound **5a** proved to be unstable, and compound **5b** gave a complex mixture which slowly turned into the crystalline oxazolone **8b**. Compound **5c** reacted smoothly, giving a mixture of two compounds (85:15, NMR determination) isolated after crystallisation. The major product was identified as the 4-methoxyoxazolidinone **9c** and the minor product was the related 4-(methoxycarbonylamino)oxazolidinone **10c** (Scheme 4). An X-ray structural determination of compound **9c** was performed (Fig. 1) because, with spectroscopic data, it was difficult to exclude isomeric structures such as the expected epoxyamine.

Probably this epoxyamine, related to those previously noticed during aminolysis of chloropyruvates,[12] occurs only as an unstable intermediate, which accounts well for the formation of oxazolone or oxazolidinone products. Ring opening to a β-hydroxy-α-imino ester is followed by intramolecular cyclisation. Isomerisation to oxazolone **8b** (R^2 = H) or formation of oxazolidinones **9c** and **10c** through nucleophilic addition of methanol or methyl carbamate (R^1, $R^2 \neq$ H) can then occur. An alternative mechanism with nucleophilic addition prior to cyclisation can be conceived as well. Methyl carbamate probably occurs from a competitive decomposition of hemiacetals **5** and such a reaction could account for the degradation of compound **5a**.

Lead tetraacetate oxidation of didehydroamino esters 1

This approach was investigated to prevent extensive rearrangements of halogenopyruvic derivatives. LTA oxidation of enamides is a preparatively useful reaction which can lead to a variety of products according to experimental conditions or substitution pattern.[13] Didehydroamino esters **1d,e** reacted readily at room temperature in dichloromethane. The oxidation proceeds through the β-acetoxy imines **3d,e** which can add the liberated acetic acid to afford α,β-diacetoxy amino esters **11d,e** (Scheme 5). Compound **1d** (R^1 = R^2 = H) afforded only compound **11d**, as a stable crystalline compound, but with substrate **1e** (R^1 = Ph, R^2 = H) a mixture of imine **3e** and the diastereoisomeric diacetoxy derivatives **11e** was obtained. This mixture was converted to the stable β-acetoxydidehydrophenylalaninate **12e** with triethylamine (Scheme 5).

Deprotection followed either of two different routes. The diacetoxyalaninate **11d** was treated with a suspension of potassium carbonate in methanol[14] to afford oxazolone **14d** (≡ **8d**) after 1.5 h at 0 °C. Such oxazole derivatives are uncommon[15] but some were obtained by Huisgen[16] through 1,3-dipolar cycloadditions. It was possible to characterise the intermediate hydroxy hemiaminal **13d** after 3 min at 0 °C. Mechanistic pathways are probably very similar to those previously discussed for ring opening of epoxyamines.

The β-acetoxydidehydrophenylalaninate **12e** was also readily deprotected at 0 °C with potassium *tert*-butoxide but cyclisation doesn't occur and the isolated product was the benzoylglycinate **15e**. It should be noted that potassium hydroxide promoted a β-ketonic cleavage with formation of benzoic acid. As a general rule, such acylglycine derivatives are obtained through acylation of nucleophilic glycine synthons.[17]

Conclusions

Mild oxidation of protected didehydroamino acids with NBS or LTA affords (*O*,*N*)-acetals of β-bromo- or β-acetoxy-α-keto esters. Hydrolytic behaviour of these polyfunctional molecules is strongly dependent on the nature of the leaving group but a

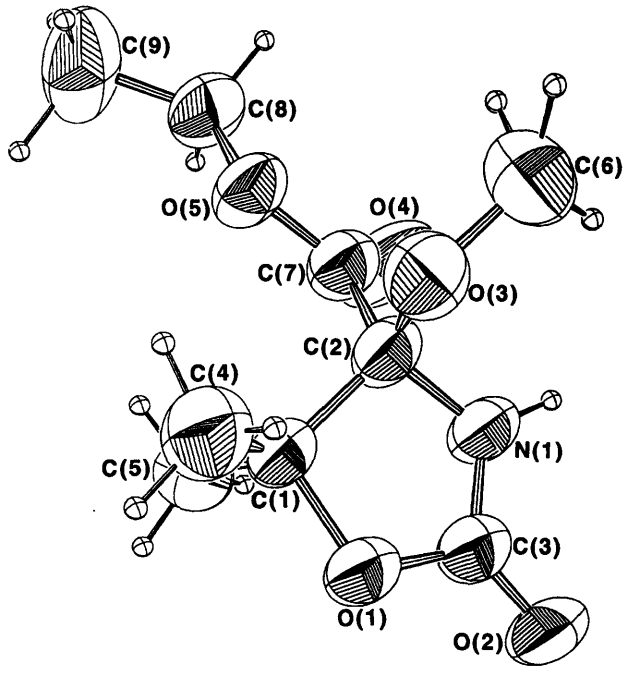
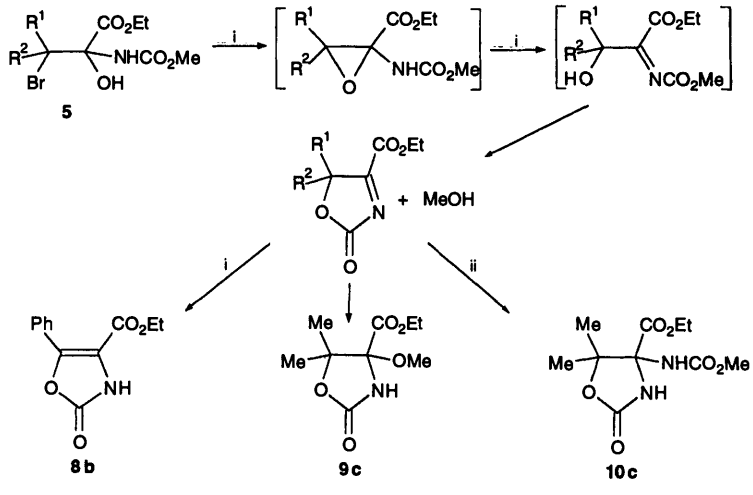
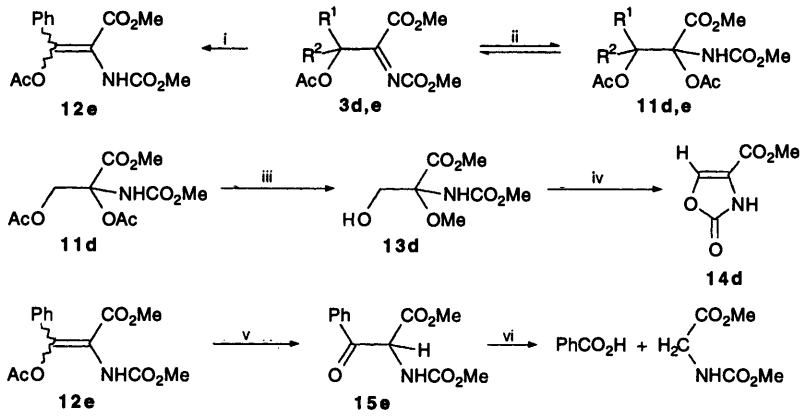


Fig. 1 X-Ray molecular structure of compound **9c** with crystallographic numbering scheme



Scheme 4 *Reagents:* i, Bu^tO^-; ii, H_2NCO_2Me



Scheme 5 *Reagents and conditions:* i, NEt_3; ii, AcOH; iii, K_2CO_3, MeOH, 0 °C, 3 min; iv, K_2CO_3, MeOH, 0 °C, 90 min; v, Bu'OK, 0 °C, 10 min; vi, ^-OH

proper choice of experimental conditions allows selective access to β-amino- and β-hydroxy-pyruvic derivatives or to isomeric acylglycines and oxazolones resulting from intramolecular cyclisation.

A further study of amino-protecting groups should improve the selectivity of these reactions.

Experimental

Mps were determined with a Köfler apparatus and are uncorrected. IR spectra were determined neat (liquid) or as Nujol mulls (solids) on a Perkin-Elmer 1420 spectrophotometer. NMR spectra were recorded in $CDCl_3$, with tetramethylsilane as internal standard, on a Bruker AC 300 P (300 MHz for ^1H and 75.5 MHz for ^{13}C) spectrometer. *J* Values are given in Hz. Microanalyses were performed by the 'Laboratoire Central de Microanalyse du CNRS' (Lyon). Mass spectra were recorded on a Varian MAT 311 spectrometer. Chromatography was performed using silica gel 60 (Merck, 230–400 mesh).

General procedure for preparation of β-bromo-α-imino esters 2[6]

NBS (1.1 g, 6.2 mmol) was added to a solution of a didehydroamino ester **1** (5.8 mmol) in freshly distilled CH_2Cl_2 (20 cm^3). After 12 h at room temperature, the solvent was evaporated off under reduced pressure. Succinimide precipitated with addition of hot heptane (50 cm^3); after filtration and removal of heptane, the corresponding imino ester **2** was isolated as a yellow oil and was immediately used in the next step.

General procedure for the synthesis of β-bromo-α-hydroxy amino esters 5

To a solution of 0.5 g of an imino ester **2** in a mixture of acetone and water (80:20, 10 cm^3) were added 5 drops of conc. HCl. The solution was stored at room temperature for 2 h before dilution with water and extraction with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the corresponding α-hydroxy-α-amino ester **5**.

*β-Bromo-α-hydroxy-*N*-methoxycarbonylalanine ethyl ester* **5a** (61%), mp 77 °C (from hexane) (Found: C, 31.35; H, 4.45; N, 5.2. $C_7H_{12}BrNO_5$ requires C, 31.1; H, 4.45; N, 5.2%); δ_H 1.34 (3 H, t, CH_2CH_3), AB pattern 3.70 and 3.77 (2 H, *J* 10.5, CH_2Br), 3.71 (3 H, s, OCH_3), AB of ABX_3 pattern 4.33 and 4.35 (2 H, J_{AB} 19.8, OCH_2CH_3), 5.00 (1 H, s, OH) and 6.24 (1 H, s, NH); δ_C 14.0 (CH_2CH_3) 35.4 (C^β), 52.7 (OCH_3), 63.5 (OCH_2), 81.5 (C^α), 155.6 (NCO) and 168.7 ($CO_2C_2H_5$).

*β-Bromo-α-hydroxy-*N*-(methoxycarbonyl)phenylalanine ethyl ester* **5b** (68%), isolated as a mixture of two diastereoisomers, **5bM** (major) and **5bm** (minor) (80:20), mp 96 °C (from diethyl ether–hexane) (Found: C, 45.25; H, 4.7; N, 4.1. $C_{13}H_{16}BrNO_5$ requires C, 45.1; H, 4.6; N, 4.05%).

Isomer **5bM**: δ_H 1.37 (3 H, t, CH_2CH_3), 3.59 (3 H, s, OCH_3), AB of ABX_3 pattern 4.38 and 4.42 (2 H, J_{AB} 10.0, OCH_2CH_3), 5.00 (1 H, s, OH), 5.13 (1 H, s, PhCH), 5.16 (1 H, s, NH) and 7.38–7.42 (3 H, m) and 7.60–7.64 (2 H, m) (ArH); δ_C 14.1 (CH_2CH_3), 52.7 (OCH_3), 54.6 (C^β), 63.8 (OCH_2), 83.4 (C^α), 128.4, 128.9, 130.0 and 134.8 (ArC), 154.8 (NCO) and 169.7 ($CO_2C_2H_5$).

Isomer **5bm**: δ_H 1.14 (3 H, t, CH_2CH_3), 3.69 (3 H, s, OCH_3), AB of ABX_3 pattern 4.07 and 4.11 (2 H, J_{AB} 10.7, OCH_2CH_3), 4.79 (1 H, s, OH), 5.21 (1 H, s, PhCH), 6.20 (1 H, s, NH) and 7.27–7.34 (3 H, m) and 7.44–7.51 (2 H, m) (ArH); δ_C 13.9 (CH_2CH_3), 52.7 (OCH_3), 57.5 (C^β), 63.5 (OCH_2), 83.6 (C^α), 128.4, 129.0, 129.5 and 135.2 (ArC), 155.5 (NCO) and 168.0 ($CO_2C_2H_5$).

*β-Bromo-α-hydroxy-*N*-methoxycarbonylvaline ethyl ester* **5c** (75%), mp 58 °C (from heptane) (Found: C, 36.1; H, 5.5; N, 4.65. $C_9H_{16}BrNO_5$ requires C, 36.25; H, 5.4; N, 4.7%); δ_H 1.32 (3 H, t, CH_2CH_3), 1.80 (3 H, s) and 1.88 (3 H, s) [$(CH_3)_2C$], 3.68 (3 H, s, OCH_3), AB of ABX_3 pattern 4.30 and 4.33 (2 H, J_{AB} 10.8, OCH_2CH_3), 4.99 (1 H, s, OH) and 6.10 (1 H, s, NH); δ_C 14.0 (CH_2CH_3), 29.3 and 30.3 [$(CH_3)_2C$], 52.6 (OCH_3), 63.4 (OCH_2), 67.8 (C^β), 86.1 (C^α), 156.1 (NCO) and 168.8 ($CO_2C_2H_5$).

General procedure for the hydrolysis of imino esters 2 under silver nitrate catalysis

To a solution of an imino ester **2** (1 g) in CH_3CN (5 cm^3) were added 2 mol equiv. of $AgNO_3$ in 5 cm^3 of a mixture of acetone and water (50:50). After 2 h at room temperature, AgBr was filtered off and the solvents were eliminated. After addition of water (20 cm^3) the residue was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent was removed to afford a crude keto ester **6** or **7**. Analytical samples of the corresponding 2,4-dinitrophenylhydrazones were obtained by the usual procedure.

Ethyl 3-[(methoxycarbonyl)oxy]-2-oxopropanoate **6a** (83%), oil; 2,4-DNPH (81%), mp 157 °C (from diethyl ether). The two compounds were identical with those previously obtained from imine **2a** by a three-step procedure.[10]

Ethyl 3-[(methoxycarbonyl)oxy]-2-oxo-3-phenylpropanoate **6b** (96%), oil; δ_H 1.26 (3 H, t, CH_2CH_3), 3.82 (3 H, s, OCH_3), AB of ABX_3 pattern 4.22 and 4.26 (2 H, J_{AB} 10.8, OCH_2CH_3), 6.61 (1 H, s, PhCH) and 7.38–7.47 (5 H, m, C_6H_5); δ_C 13.8 (CH_2CH_3), 55.5 (OCH_3), 62.9 (OCH_2), 80.5 (C^3), 129.1, 129.3, 130.0 and 130.3 (ArC), 154.9 (OCO_2), 159.2 (C^1) and 186.5 (C^2). 2,4-DNPH (72%), mp 107 °C (from diethyl ether) (Found: C, 51.15; H, 4.25; N, 12.35. $C_{19}H_{18}N_4O_9$ requires C, 51.1; H, 4.05; N, 12.55%); δ_H 1.33 (3 H, t, CH_2CH_3), 3.84 (3 H, s, OCH_3), AB of ABX_3 pattern 4.37 and 4.40 (2 H, J_{AB} 11.1, OCH_2CH_3), 6.71 (1 H, s, PhCH), 7.38–7.48 (5 H, m, C_6H_5), 7.92 (1 H, d, *J* 9.5), 8.37 (1 H, dd, *J* 9.5 and 2.5) and 9.13 (1 H,

d, J 2.5) (3 × ArH); δ_C 13.9 (CH_2CH_3), 55.3 (OCH_3), 62.7 (OCH_2), 77.2 (C^3), 117.0, 122.9, 127.8, 128.6, 129.0, 129.9, 131.9, 135.5, 135.8 and 140.3 (ArC), 144.1 (C^2), 154.9 (OCO_2) and 160.7 (C^1).

Ethyl 3-[(methoxycarbonyl)amino]-3-methyl-2-oxobutanoate **7c** (88%), oil, 2,4-DNPH (85%), mp 126 °C (from diethyl ether). The two compounds were identical with those previously obtained from imine **2c**.[10]

Reactions of β-bromo-α-hydroxy amino esters 5 with potassium *tert*-butoxide

To a solution of a bromohydrin **5** (0.5 g) in THF (10 cm^3) was added 1.1 mol equiv. of potassium *tert*-butoxide. After reaction (30 min at 0 °C for **5a**, 15 h at room temp. for **5c**), the mixture was diluted with diethyl ether (30 cm^3), then was washed with water (30 cm^3). The organic layer was dried ($MgSO_4$) and the solvents were evaporated off.

Ethyl 2-oxo-5-phenyl-2,3-dihydrooxazole-4-carboxylate **8b** (34%), mp 168 °C (from ethanol) (Found: C, 60.85; H, 4.6; N, 5.8. $C_{12}H_{11}NO_4 \cdot 0.25H_2O$ requires C, 60.65; H, 4.85; N, 5.9%); m/z 233 (Found: 233.069. $C_{12}H_{11}NO_4$ requires M, 233.069); ν_{max}/cm^{-1} 3190, 3105, 1765, 1720 and 1630; δ_H 1.39 (3 H, t, CH_2CH_3), 4.39 (2 H, q, OCH_2CH_3), 7.42–7.47 (3 H, m), 8.00–8.05 (2 H, m) (ArH) and 9.28 (1 H, s, NH); δ_C 14.1 (CH_2CH_3), 62.1 (OCH_2), 113.8 (C^4), 126.1, 128.0, 128.4 and 130.6 (ArC), 145.9 (C^5), 153.3 (C^2) and 158.3 ($CO_2C_2H_5$).

Ethyl 4-methoxy-5,5-dimethyl-2-oxooxazolidine-4-carboxylate **9c** *and ethyl 4-methoxycarbonylamino-5,5-dimethyl-2-oxooxazolidine-4-carboxylate* **10c**. Compound **10c** was obtained after addition of diethyl ether, then the residual oil gave compound **9c** after dilution with hexane. *Compound* **9c** (52%), mp 84 °C (from hexane) (Found: C, 49.35; H, 6.9; N, 6.45. $C_9H_{15}NO_5$ requires C, 49.75; H, 6.9; N, 6.45%); m/z 186 $[(M - {}^{\bullet}OCH_3)]^+$ (Found: 186.076. $C_8H_{12}NO_4$ requires M, 186.076); ν_{max}/cm^{-1} 3250, 3145, 1760 and 1750; δ_H 1.35 (3 H, t, CH_2CH_3), 1.36 (3 H, s) and 1.54 (3 H, s) [$C(CH_3)_2$], 3.25 (3 H, s, OCH_3), 4.32 (2 H, q, OCH_2CH_3) and 7.55 (1 H, s, NH); δ_C 14.1 (CH_2CH_3), 20.3 and 24.2 [$C(CH_3)_2$], 51.4 (OCH_3), 62.6 (OCH_2), 86.4 (C^5), 93.3 (C^4), 157.2 (NCO) and 166.5 ($CO_2C_2H_5$). Compound **10c** (10%), mp 153 °C (from diethyl ether); m/z 187 $[(M - {}^{\bullet}CO_2C_2H_5)]^+$ (Found: 187.071. $C_7H_{11}N_2O_4$ requires M, 187.071); ν_{max}/cm^{-1} 3315, 3230, 1750 and 1715; δ_H 1.33 (3 H, t, CH_2CH_3), 1.41 (3 H, s) and 1.57 (3 H, s) [$C(CH_3)_2$], 3.72 (3 H, s, OCH_3), 4.30 (2 H, q, OCH_2CH_3), 5.92 (1 H, s, NH) and 6.43 (1 H, s, NH); δ_C 14.0 (CH_2CH_3), 21.8 and 24.1 [$C(CH_3)_2$], 53.0 (OCH_3), 63.1 (OCH_2), 77.1 (C^5), 83.2 (C^4), 155.9 (NCO) and 167.4 ($CO_2C_2H_5$).

General procedure for lead tetraacetate oxidation of didehydroamino esters 1

1.1 Mol equiv. of LTA was added to a solution of 1 g of a didehydroamino ester **1d**,**e** in CH_2Cl_2 (20 cm^3). The mixture was stirred for 48 h (**1d**) or 24 h (**1e**) at room temperature. Lead diacetate was filtered off and the solvent was evaporated off under reduced pressure.

α,β-Diacetoxy-N-(methoxycarbonyl)alanine methyl ester **11d** (70%); the crude product was subjected to chromatography on silica gel and then crystallised, mp 94 °C (from diethyl ether–hexane) (Found: C, 43.15; H, 5.5; N, 5.1. $C_{10}H_{15}NO_8$ requires C, 43.3; H, 5.45; N, 5.05%); ν_{max}/cm^{-1} 3400 and 1750–1720; δ_H 1.98 (3 H, s) and 2.04 (3 H, s) (2 × $OCOCH_3$), 3.63 (3 H, s) and 3.75 (3 H, s) (2 × OCH_3), AB pattern 4.45 and 5.09 (2 H, J_{AB} 11.1, CH_2) and 6.48 (1 H, s, NH); δ_C 20.5 and 20.7 (2 × $OCOCH_3$), 52.4 and 53.8 (2 × OCH_3), 62.0 (C^β), 83.3 (C^α), 153.9 (NCO) and 167.3, 169.4 and 169.8 (CO_2CH_3, 2 × $OCOCH_3$).

β-Acetoxy-*N*-(methoxycarbonyl)didehydrophenylalanine methyl ester 12e. The crude product was a mixture of the two diastereoisomeric diacetoxyphenylalaninates **11e** and of the β-acetoxyimino ester **3e** (25:75). It was treated with an excess of triethylamine (2.5 mol equiv.) in CH_2Cl_2 (20 cm^3) for 1 h at room temperature. The mixture was then washed with water (20 cm^3) and dried ($MgSO_4$). Then evaporation off of the solvent afforded *compound* **12e** (72%), mp 144 °C (from ethanol) (Found: C, 57.05; H, 5.25; N, 4.8. $C_{14}H_{15}NO_6$ requires C, 57.35; H, 5.15; N, 4.75%); ν_{max}/cm^{-1} 3270, 1730–1770 and 1690; δ_H 2.22 (3 H, s, $OCOCH_3$), 3.66 (3 H, s) and 3.81 (3 H, s) (2 × OCH_3), 6.15 (1 H, s, NH) and 7.35–7.41 (3 H, m) and 7.48–7.52 (2 H, m) (ArH); δ_C 20.8 ($OCOCH_3$), 52.5 and 53.0 (2 × OCH_3), 118.4 (C^α), 127.9, 128.7, 130.1 and 133.1 (ArC), 149.2 (C^β), 154.8 (NCO) and 163.9 and 168.4 (CO_2CH_3, $OCOCH_3$).

Methyl 2-oxo-2,3-dihydrooxazole-4-carboxylate 14d (≡ 8d)

To a solution of diacetoxyalaninate **11d** (0.5 g, 1.8 mmol) in CH_3OH (15 cm^3) was added 2 mol equiv. of K_2CO_3 (3.6 mmol) and the mixture was stirred at 0 °C for 1.5 h then was diluted with water (20 cm^3), made acidic with citric acid, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was eliminated under reduced pressure to give oxazolone **14d** (78%), mp 134 °C (from diethyl ether); m/z 143 (Found: 143.021. $C_5H_5NO_4$ requires M, 143.021); ν_{max}/cm^{-1} 3310, 3130, 1760 and 1710; δ_H 3.90 (3 H, s, OCH_3), 7.42 (1 H, s, HC=) and 9.02 (1 H, s, NH); δ_C 52.7 (OCH_3), 120.0 (C^4), 134.7 (C^5), 154.8 (C^2) and 158.5 (CO_2CH_3).

When the same reaction was performed at 0 °C for only 3 mn, the β-hydroxy-α-methoxyalaninate **13d** was isolated but characterised only by IR and NMR spectra of the crude product. Oil, ν_{max}/cm^{-1} 3550–3200 and 1750–1690; δ_H 2.45 (1 H, br s, OH), 3.34 (3 H, s, OCH_3), 3.71 (3 H, s) and 3.86 (3 H, s) (2 × OCH_3), AB pattern 3.87 and 4.15 (2 H, J_{AB} 11.3, CH_2) and 6.14 (1 H, s, NH); δ_C 51.8, 52.6 and 53.3 (3 × OCH_3), 64.9 (C^β), 87.5 (C^α), 155.3 (NCO) and 169.3 (CO_2CH_3).

α-Benzoyl-*N*-methoxycarbonylglycine methyl ester 15e

To a solution of β-acetoxydidehydrophenylalaninate **12e** (0.5 g, 1.7 mmol) in methanol (20 cm^3) was added potassium *tert*-butoxide (1.87 mmol). The mixture was stirred at 0 °C for 10 min then was diluted with water, made acidic with citric acid, and extracted with diethyl ether. The organic layer was dried (Na_2SO_4) and the solvent was eliminated under reduced pressure to give *title compound* **15e** (88%), mp 75 °C (from diethyl ether–hexane) (Found: C, 57.1; H, 5.3; N, 5.6. $C_{12}H_{13}NO_5$ requires C, 57.35; H, 5.2; N, 5.6%); ν_{max}/cm^{-1} 3320 and 1740–1680; δ_H 3.71 (6 H, s, 2 × OCH_3), AB pattern 6.03 and 6.20 (2 H, J_{AB} 8.1, CHNH) and 7.49–7.54 (2 H, m), 7.61–7.67 (1 H, m) and 8.09–8.12 (2 H, m) (ArH); δ_C 52.7 and 53.2 (2 × OCH_3), 59.3 (C^α), 128.8, 129.5, 134.0 and 134.5 (ArC), 156.3 (NCO), 167.4 (CO_2CH_3) and 191.4 (C^β).

When the reaction was performed with potassium hydroxide, under the same conditions, the only isolated product was benzoic acid.

X-Ray crystallography of compound 9c

$C_9H_{15}NO_5$, M = 217.22, monoclinic, space group $P2_1/a$, a = 19.514(8), b = 10.666(3), c = 10.982(3) Å, β = 92.74(3)°, Z = 8, V = 2283(1) Å^3, D_c = 1.264 g cm^{-3}, μ(Mo-Kα) = 0.968 cm^{-1}, crystal size = 0.25 × 0.25 × 0.35 mm^3. Intensity data were collected on an automatic diffractometer (CAD4 ENRAF-NONIUS) with graphite-monochromatised Mo-Kα radiation. The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta \leq 50°$, scan $\omega/2\theta$ = 1, $t \leq 60$ s, range hkl: h −23.23; k, 0.12; l, 0.13, intensity control without appreciable decay (0.3%) gives 4476 reflections from which 2410 independent (R = 0.010) with $I > 3\sigma(I)$. After Lorentz and polarisation corrections, the structure was solved by direct method with the program SHELX-86[18] which revealed all the non-hydrogen atoms of the compound. After isotropic (R = 0.115), then anisotropic refinement (R = 0.086), all the hydrogen atoms are found with

a Fourier Difference (between 0.47 and 0.21 e Å^{-3}). The whole structure was refined by the full-matrix least-square techniques {use of F magnitude; x, y, z, β_{ij} for N-, C- and O-atoms and x, y, z fixed for H-atoms; 370 variables and 2410 observations; $w = 1/\sigma(F_o)^2 = [\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}\}$ with the resulting $R = 0.051$, $R_w = 0.048$ and $S_w = 1.085$ (residual $\Delta\rho \leq 0.49$ e Å^{-3}). Atomic scattering factors were from International Tables for X-ray Crystallography.[19] The calculations were performed on a Hewlett Packard 9000-710 for structure determination and on a Digital MicroVAX 3100 computer with the MOLEN package for refinement and ORTEP calculations.†[,20]

† Full lists of fractional atomic coordinates, bond lengths and angles have been deposited as supplementary material with the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/23.

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