CSIRO PUBLISHING

www.publish.csiro.au/journals/ajc *Aust. J. Chem.* **2003**, *56*, 897–901

The Synthesis of Some Chiral 2-Aminoalkyloxazole-5-carboxylates from Isoxazol-5(2*H*)-ones

Matthew Cox,[A] *Rolf H. Prager*,[A,B] *Carina E. Svensson*[A] *and Max R. Taylor*[A]

[A] School of Chemistry, Physics and Earth Sciences, Flinders University, Adelaide 5001, Australia.
[B] Author to whom correspondence should be addressed (e-mail: rolf.prager@flinders.edu.au).

Ethyl 5-oxo-2,5-dihydroisoxazole-4-carboxylates have been *N*-acylated by a number of natural and synthetic phthalimidylamino acids in the presence of carbodiimides. The *N*-acylated products form the corresponding 2-aminoalkyloxazole-5-carboxylates smoothly when irradiated at 300 nm in acetone.

Manuscript received: 20 February 2003.
Final version: 23 April 2003.

Introduction

As part of our aim to synthesize oxazole and thiazole subunits of modified cyclic peptide mimetics[1,2] based on natural products with marked cytotoxic properties,[3] such as ulicyclamide (1)[4] or bistratamide C (2) (see Diagram 1),[5] we have examined the possible application of our synthesis of oxazoles[6] and thiazoles[7] to the synthesis of such potential building blocks. Initially, we concentrated on 2-aminoalkyloxazole-4-carboxylic acids (3),[2] as this substitution pattern, which results from the peptide origin of these cyclic molecules, is the norm. By contrast, naturally occurring molecules based on 2-aminoalkyloxazole-5-carboxylic acids (4), exemplified by almazoles A and B ((5) and (6), respectively), are rare.[8,9] We have already demonstrated that our methodology is applicable to such products by the synthesis of almazole A and B.[10] A convenient synthesis of a group of 2,5-disubstituted oxazoles would allow us to synthesize both linear and cyclic peptide mimetics, in which we would be able to selectively orientate the ring nitrogen or oxygen atoms towards the centre of the macrocycle, see (7). A preliminary account of some of this work has been published.[1]

Discussion

As observed previously with the 2,4-disubstituted oxazoles,[2] we were unable to obtain good yields of the Schiff bases of the aminomethyloxazole-5-carboxylates (8) or (9) (see

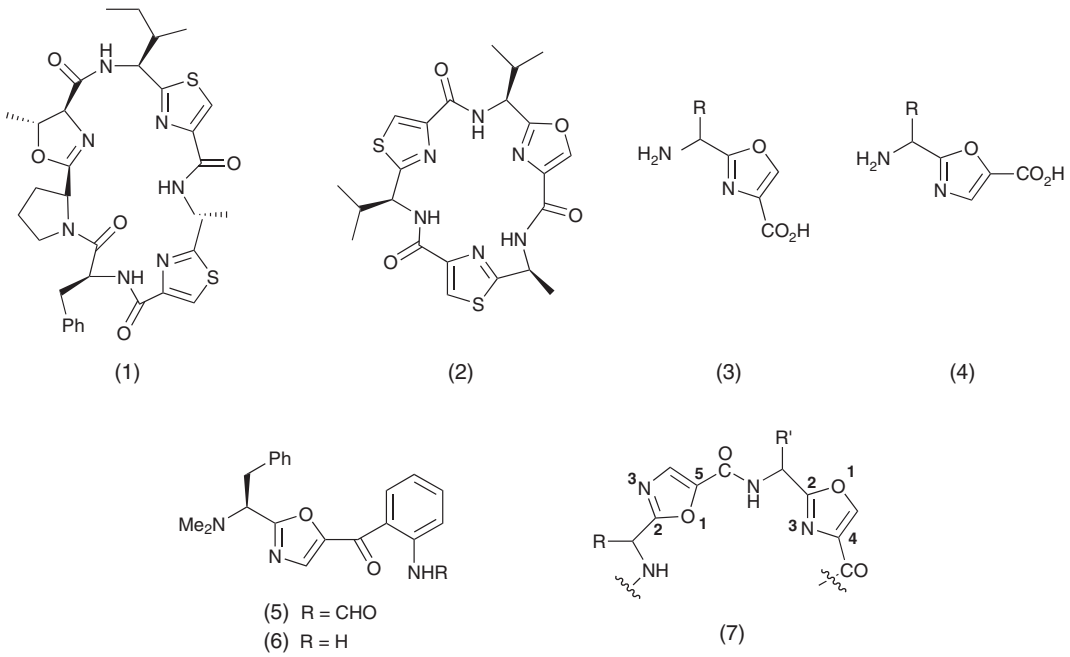
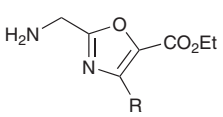
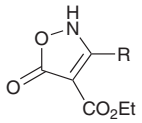


Diagram 1.

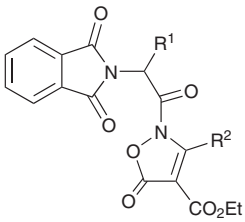
 10.1071/CH03053 0004-9425/03/090897



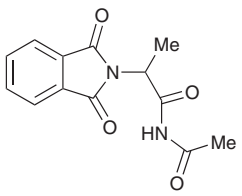
(8) R = H
(9) R = Me



(10) R = H
(11) R = Me

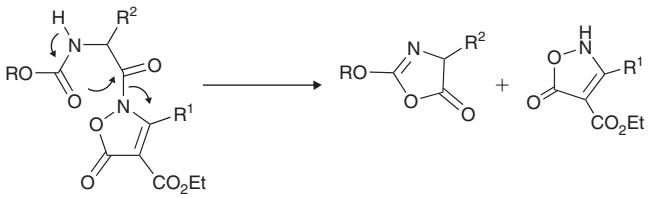


	R^1	R^2
(12)	Me	Me
(14)	Me	H
(15)	H	Me
(16)	H	H
(17)	4-BzO-$C_6H_4CH_2$	H

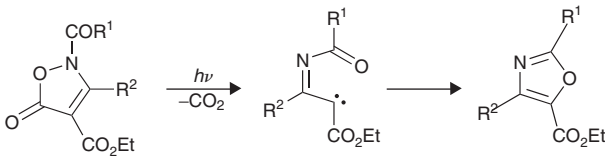


(13)

Diagram 2.



Scheme 1.

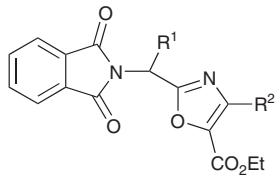


Scheme 2.

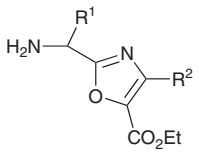
Diagram 2) with either camphor or hydroxypinanone. Both ketones gave about 20% of the corresponding imine with either (8) or (9). Thus, enantioselective alkylations[2,11] of derivatives of (8) or (9) were not pursued further.

Our synthetic strategy involved *N*-acylation of isoxazolones with *N*-protected amino acids and subsequent photolysis of the products. The protecting group of choice for the amino group was confirmed to be the phthalimido group, which was resistant to the complications observed with other monofunctional protecting groups such as the benzyloxycarbonyl or *tert*-butoxycarbonyl (BOC) groups. Amino acids protected as carbamates failed to give acylated isoxazolones, presumably because they formed azalactones[12] due to the relatively good nucleophilicity of the isoxazolone group, particularly those with a carboxylate group at C4 (Scheme 1).

Accordingly, phthalimido amino acids have been reacted with the isoxazolones (10) and (11) under conditions that gave essentially only *N*-acylated products.[2] Photolysis of the *N*-acylisoxazolones proceeds through the carbene to give the oxazole (Scheme 2).[6]



	R^1	R^2
(18)	H	H
(19)	H	Me
(20)	Me	Me
(21)	Me	H
(24)	4-BzO-$C_6H_4CH_2$	H



	R^1	R^2
(8)	H	H
(9)	H	Me
(22)	Me	Me
(23)	Me	H
(25)	4-BzO-$C_6H_4CH_2$	H

Diagram 3.

N-acylation of the isoxazolones was best achieved, as previously described, using a carbodiimide at 0°C, as acylation with an acid chloride gave considerable *O*-acylation.[13] Coupling yields with (10) and (11) using dicyclohexylcarbodiimide (DCC) at 0°C were in the range 77–80%, with close to 100% *N*-acylation. Lack of racemization was determined by analysis of the Mosher amides[14] of the derived aminoalkyloxazole-5-carboxylates.

As with the photolysis of the isomeric isoxazolone-4-carboxylates,[2] photolysis of the 5-carboxylates gave small quantities of by-products, which suggests that the intermediate carbene had been intercepted by traces of water. In all cases, such products were separated by chromatography and were generally not characterized. However, in the case of photolysis of (12) in acetone (see Diagram 3), small quantities of the imide (13) were isolated, the formation of which is consistent with previous observations.[2] In addition, the photolysis of (17) was unusual. It was best carried out in ethyl acetate, but the desired product ((24), 43%) was also accompanied with 4-benzyloxyphthalimidotyrosine (36%). Since the solvent was dried and freshly distilled, it is possible that the acyl radical[2] reacted with traces of residual oxygen to form the carboxylic acid.

The above acylation–photolysis procedure was used to synthesize the *N*-acylated isoxazolones (14)–(17), and then the corresponding oxazoles (18)–(21) and (24). Hydrazinolysis then readily cleaved the phthalimido group without effecting the ethyl ester[15] to give the aminoalkyloxazoles (8), (9), (22), (23), and (25). The molecular structure of (18) was confirmed by X-ray crystallography (Fig. 1). All bond lengths and angles have expected values.

The optical integrity of the stereogenic centre in the resulting chiral oxazoles was again determined by conversion of the amines to their (*R*)-α-methoxy-α-(trifluoromethyl) phenylacetamides.[2,14] The two diastereomeric amides could be clearly differentiated by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy.

Conclusion

The *N*-acylation of 4-ethoxycarbonylisoxazolones with (*R*)- or (*S*)-2-phthalimido acids, and subsequent photolysis of the products, leads to a convenient synthesis of a series of 2-aminoalkyloxazole-5-carboxylates in moderate yields.

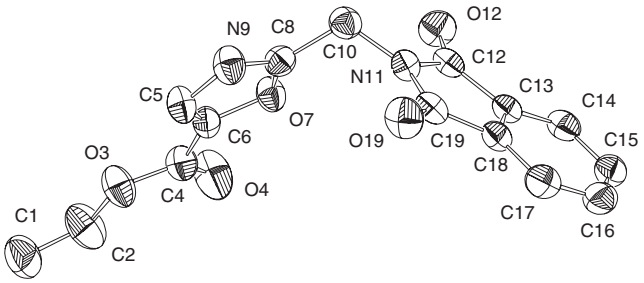


Fig. 1. ORTEP diagram of ethyl 2-[(l,3-dioxo-l,3-dihydro-2*H*-isoindol-2-yl)methyl]-l,3-oxazole-5-carboxylate (18) with 50% displacement ellipsoids.

Experimental

General experimental details were the same as in the preceding paper.[2]

*Ethyl 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetyl]-5-oxo-2,5-dihydroisoxazole-4-carboxylate (16)*

DCC (3.0 g, 14.2 mmol) was added to a mixture of phthalimidylglycine[16] (2.00 g, 9.75 mmol) and the isoxazolone (10)[17] (2.00 g, 12.7 mmol) in dichloromethane (60 mL) at ambient temperature and the mixture was stirred for 16 h. The crude product was redissolved in dichloromethane, the volume was reduced under vacuum to about 3 mL and the residue was then diluted with diethyl ether, whereupon the N-*acylated product* (16) precipitated as a white solid (3.21 g, 96%), mp 151–153°C (Found: C 55.5, H 3.3, N 8.2%; $[M-CO_2]^{+\bullet}$, 300.0739. $C_{16}H_{12}N_2O_7$ requires C 55.8, H 3.5, N 8.1%; $[M-CO_2]^{+\bullet}$, 300.0746). ν_{max}/cm^{-1} 3087, 1800, 1776, 1741, 1715, 1600, 1232, 1114. δ_H 8.99 (1 H, s) 7.93 (2 H, m), 7.80 (2 H, m), 4.92 (2 H, s), 4.38 (2 H, q, *J* 7.1), 1.38 (3 H, t, *J* 7.1). δ_C 167.1, 161.8, 159.7, 159.6, 145.8, 134.7, 131.8, 124.0, 101.3, 61.8, 39.1, 14.0. *m*/*z* 300 (0.5%, $[M-CO_2]^{+\bullet}$), 188 (24), 160 (100).

*Ethyl 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanoyl]-5-oxo-2,5-dihydroisoxazole-4-carboxylate (14)*

DCC (1.30 g, 6.17 mmol) was added to a mixture of phthalimidylalanine[18] (1.00 g, 4.56 mmol) and the isoxazolone (10) (932 mg, 5.93 mmol) in dichloromethane (28 mL) at 0°C. The reaction was stirred for 3 h on ice, then allowed to reach room temperature and stirring was continued for two days at ambient temperature. The crude product was redissolved in dichloromethane, the volume was reduced under vacuum to about 5 mL and the residue was diluted with ether, whereupon the N-*acylated product* (14) was collected by filtration, after cooling on ice, as white crystals (1.26 g, 77%), mp 114–121°C [(*S*)-isomer], 142–152°C (racemic), $[\alpha]_D$ + 53.3° (*c* 0.713 in $CHCl_3$) (Found; C 56.8, H 3.9, N 7.7%; $[M-CO_2]^{+\bullet}$, 314.0911. $C_{17}H_{14}N_2O_7$ requires C 57.0, H 3.9, N 7.8%; $[M-CO_2]^{+\bullet}$, 314.0903). ν_{max}/cm^{-1} 3069, 1807, 1780, 1758, 1743, 1716, 1691, 1646, 1595, 1228, 1191, 1157, 1025. δ_H 9.02 (1 H, s), 7.89 (2 H, m), 7.78 (2 H, m), 5.37 (1 H, q, *J* 7.1), 4.34 (2 H, q, *J* 7.1), 1.80 (3 H, d, *J* 7.1), 1.34 (3 H, t, *J* 7.1). δ_C 166.8, 162.2, 161.8, 159.6, 146.3, 134.6, 131.3, 123.8, 100.4, 61.3, 47.5, 14.5, 13.9. *m*/*z* 314 (2%, $[M-CO_2]^{+\bullet}$), 202 (15), 174 (100).

*Ethyl 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetyl]-3-methyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate (15)*

Using the method described above, a mixture of phthalimidylglycine (2.0 g, 9.7 mmol) and the isoxazolone (11)[19] (1.80 g, 10.5 mmol) gave the N-*acylated product* (15) as a white powder (3.11 g, 89%), mp 141–144°C (Found: C 57.2, H 3.9, N 8.0%; $[M-CO_2]^{+\bullet}$, 314.0910. $C_{17}H_{14}N_2O_7$ requires C 57.0, H 3.9, N 7.8%. $[M-CO_2]^{+\bullet}$, 314.0903). ν_{max}/cm^{-1} 1800, 1738, 1712, 1600, 1228, 1188. δ_H 7.93 (2 H, m), 7.79 (2 H, m), 4.92 (2 H, s), 4.38 (2 H, q, *J* 7.1), 2.96 (3 H, s), 1.39 (3 H, t, *J* 7.1). δ_C 167.1, 163.6, 161.7, 161.4, 161.0, 134.5, 131.8, 123.8, 98.9, 40.3, 14.3, 14.2. *m*/*z* 314 (3%, $[M-CO_2]^{+\bullet}$), 188 (22), 160 (100).

*Ethyl 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanoyl]-3-methyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate (12)*

Using the above procedure, phthalidylalanine (800 mg, 3.65 mmol) and the isoxazolone (11) (693 mg, 4.05 mmol) gave, after crystallization from diethyl ether, the *N-acylated product* (12) as colourless crystals (1.09 g, 80%), mp 159–163°C [(*S*)-isomer], 155–159°C (racemate), $[\alpha]_D$ + 67.3° (*c* 0.847 in $CHCl_3$) (Found: C 57.8, H 4.2, N 7.5%; $[M-CO_2]^{+\bullet}$, 328.1061. $C_{18}H_{16}N_2O_7$ requires C 58.1, H 4.3, N 7.5%; $[M-CO_2]^{+\bullet}$, 328.1059). ν_{max}/cm^{-1} 1787, 1748, 1718, 1695, 1579, 1336, 1214, 1187, 1008. δ_H 7.87 (2 H, m), 7.77 (2 H, m), 5.42 (1 H, q, *J* 7.1), 4.33 (2 H, q, *J* 7.1), 2.99 (3 H, s), 1.80 (3 H, d, *J* 7.1), 1.34 (3 H, t, *J* 7.1). δ_C 166.9, 164.5, 163.9, 161.4, 161.0, 134.5, 131.4, 123.7, 98.3, 61.2, 48.8, 14.8, 14.5, 14.1. *m*/*z* 328 (4%, $[M-CO_2]^{+\bullet}$), 202 (19), 174 (100).

(S)-Ethyl 5-Oxo-2-[3-(benzyloxyphenyl)-2-phthalimidopropanoyl]-2,5-dihydroisoxazole- 4-carboxylate (17)

1-(3-(Dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (1.59 g, 7.7 mmol) was added to a solution of 4-benzyloxyphthalimidophenylalanine[20] (2.06 g, 5.1 mmol) and the isoxazolone (10) (0.89 g, 5.6 mmol) in anhydrous dichloromethane (100 mL) and anhydrous dimethylformamide (10 mL) at 0°C. The reaction was maintained under N_2 at 0°C for 3 h before being allowed to warm up to rt for 16 h. After this time the reaction mixture was washed with 1 M HCl (2 × 50 mL) and the solvent was evaporated. The residue was dissolved in diethyl ether (50 mL) and ethyl acetate (100 mL), and the organic layer was washed with water (3 × 50 mL), dried (Na_2SO_4), filtered, and evaporated to give (21) (2.29 g, 85%) as a *pale-yellow glass* $[\alpha]_D^{20}$ −60° [(*S*)-isomer, *c* 1.0 in $CHCl_3$] (Found: $[M+H]^{+\bullet}$, 541.1613. $C_{30}H_{24}N_2O_8$ requires $[M+H]^{+\bullet}$, 541.1611). ν_{max}/cm^{-1} 1789, 1716, 1384. δ_H9.00 (1 H, s), 7.81 (2 H, m), 7.75 (2 H, m), 7.37–7.32 (5 H, m), 7.15 (2 H, d, *J* 8.8), 6.83 (2 H, d, *J* 8.8), 5.50 (1 H, dd, *J* 6.6 and 8.9), 4.97 (2 H, s), 4.32 (2 H, q, *J* 7.1), 3.52 (2 H, m), 1.33 (3 H, t, *J* 7.1). δ_C 166.8, 161.5, 161.2, 159.5, 158.0, 146.1, 136.7, 134.5, 131.1, 130.3, 128.5, 127.9, 127.4, 127.2, 123.8, 115.0, 100.8, 69.1, 61.7, 53.4, 33.3, 14.1. *m*/*z* 541 (10%, $[M+H]^{+\bullet}$), 497 (3), 395 (12), 385 (54), 357 (100).

*Ethyl 2-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-4-methyl-1,3-oxazole-5-carboxylate (19)*

The isoxazolone (15) (1.018 g, 2.84 mmol) was irradiated in acetone (1000 mL) for 6 h as described above. The solvent was then removed under reduced pressure and the solid residue was recrystallized from ethanol yielding the *title compound* as an off-white powder (400 mg, 45%), mp 145–147°C (Found: C 61.0, H 4.7, N 8.8%; $M^{+\bullet}$, 314.0899. $C_{16}H_{14}N_2O_5$ requires C 61.1, H 4.5, N 8.9%; $M^{+\bullet}$, 314.0903). ν_{max}/cm^{-1} 1778, 1716, 1617, 1560, 1423, 1332, 1153, 1116, 1104. δ_H 7.91 (2 H, m), 7.77 (2 H, m), 4.99 (2 H, s), 4.36 (2 H, q, *J* 7.1), 2.40 (3 H, s), 1.37 (3 H, t, *J* 7.1). δ_C 167.1, 159.4, 158.4, 146.0, 138.3, 134.3, 131.9, 123.7, 61.1, 34.8, 14.2, 13.3. *m*/*z* 314 (28%, $M^{+\bullet}$), 160 (100).

*Ethyl 2-[1-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-4-methyl-1,3-oxazole-5-carboxylate (20)*

Method 1. The isoxazolone (12) (606 mg, 1.628 mmol) was irradiated in acetone (300 mL) for 6.5 h as described above. The solvent was then removed under reduced pressure and the crude product was purified by flash column chromatography, eluting with dichloromethane/ethyl acetate (9 : 1). Removal of the solvent under reduced pressure yielded the *product* as a colourless oil (273 mg, 51%), $[\alpha]_D$ −18.8° [(*S*)-isomer, *c* 1.333 in $CHCl_3$] (Found: $M^{+\bullet}$, 328.1060. $C_{17}H_{16}N_2O_5$ requires $M^{+\bullet}$, 328.1059). ν_{max}/cm^{-1} 1776, 1718, 1615, 1551, 1149, 1100, 1021. δ_H 7.85 (2 H, m), 7.74 (2 H, m), 5.58 (1 H, q, *J* 7.1), 4.33 (2 H, q, *J* 7.1), 2.45 (3 H, s), 1.92 (3 H, d, *J* 7.1), 1.35 (3 H, t, *J* 7.1). δ_C 166.8, 162.5, 158.3, 145.6, 138.0, 134.0, 131.6, 123.3, 60.8, 43.2, 15.9, 14.0, 13.2. *m*/*z* 328 (50%, $M^{+\bullet}$), 254 (12), 174 (71), 43 (100).

Method 2. Isoxazolone (12) (410 mg) was irradiated as described above in acetonitrile (200 mL), and the product was purified by flash

chromatography (dichloromethane/ethyl acetate) to give the oxazole above (167 mg, 46%), and the acetamide of phthalimidylalanine (13) (11 mg, 4%), mp 145–153°C (lit.[21] 135–137°C) (Found (Electrospray MS): $[M+Na]^{+\bullet}$, 283.1; $[M+H]^{+\bullet}$, 261.2. $C_{13}H_{12}N_2O_6$ requires $[M+Na]^{+\bullet}$, 283.2; $[M+H]^{+\bullet}$, 261.2). ν_{max}/cm^{-1} 3255, 3173, 1782, 1740, 1718, 1523, 1240, 1199, 1100, 1087. δ_H 9.00 (1 H, br s, NH exchangeable), 7.87 (2 H, m), 7.77 (2 H, m), 5.00 (1 H, q, *J* 7.2), 2.30 (3 H, s), 1.67 (3 H, d, *J* 7.2). δ_C 173.4, 169.0, 167.6, 134.5, 132.0, 123.7, 49.5, 25.0, 14.6.

*Ethyl 2-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-1,3-oxazole-5-carboxylate (18)*

The isoxazolone (16) (1.820 g, 5.29 mmol) was irradiated in acetone (900 mL) for 3 h as described above. The solvent was then removed under reduced pressure and the solid residue was suspended in hot ethanol (70 mL), cooled on ice, then diluted with water (30 mL). The product was collected by filtration as a slightly yellow powder (1.390 g, 88%), mp 169–170°C (sublimation at 160–169°C). A sample was recrystallized from ethanol/water (Found: C 59.8, H 4.1, N 9.3%; $M^{+\bullet}$, 300.0745. $C_{15}H_{12}N_2O_5$ requires C 60.0, H 4.0, N 9.3%; $M^{+\bullet}$, 300.0746). ν_{max}/cm^{-1} 1771, 1732, 1719, 1544, 1422, 1395, 1148. δ_H 7.92 (2 H, m), 7.77 (2 H, m), 7.65 (1 H, s), 5.05 (2 H, s), 4.37 (2 H, q, *J* 7.1), 1.37 (3 H, t, *J* 7.1). δ_C 167.1, 161.3, 157.3, 143.3, 134.3, 134.0, 131.9, 123.8, 61.5, 34.8, 14.2. *m/z* 300 (71%, $M^{+\bullet}$), 255 (6, $[M-OC_2H_5]^{+\bullet}$), 160 (100).

*Ethyl 2-[1-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1,3-oxazole-5-carboxylate (21)*

The isoxazolone (14) (159 mg, 0.444 mmol) was irradiated in acetone (200 mL) for 2 h as described above. The crude residue was passed through a short plug of silica using dichloromethane as eluent to give the *title compound* as a colourless oil, which solidified on standing as iridescent crystals (99 mg, 71%). A sample was recrystallized from dichloromethane/hexane, mp 96–100°C, $[\alpha]_D$ −6.4° [(*S*)-isomer, *c* 1.093 in $CHCl_3$] (Found: C 61.2, H 4.6, N 8.6%; $M^{+\bullet}$, 314.0900. $C_{16}H_{14}N_2O_5$ requires C 61.1, H 4.5, N 8.9%; $M^{+\bullet}$, 314.0903). ν_{max}/cm^{-1} 1779, 1694, 1614, 1587, 1535, 1303, 1157, 1074, 1019. δ_H 7.87 (2 H, m), 7.76 (2 H, m), 7.70 (1 H, s), 5.62 (1 H, q, *J* 7.1), 4.35 (2 H, q, *J* 7.1), 1.95 (3 H, d, *J* 7.1),1.35 (3 H, t, *J* 7.1). δ_C 167.0, 164.6, 157.4, 143.0, 134.2, 133.9, 131.6, 123.5, 61.2, 43.3, 15.8, 13.9. *m/z* 314 (27%, $M^{+\bullet}$), 174 (100).

*(*S*)-Ethyl 2-[2-(4-Benzyloxyphenyl)-1-phthalimidoethyl]oxazole-5-carboxylate (24)*

The isoxazolone (17) (1.0 g, 1.9 mmol) was photolyzed through pyrex at 300 nm in anhydrous ethyl acetate (1000 mL) under N2 at rt for 5 h. The solvent was evaporated and the residue was purified by radial chromatography (10% ethyl acetate/light petroleum) to give two fractions.

The first fraction contained *(S)-ethyl 2-[2-(4-benzyloxyphenyl)-1-phthalimidoethyl]oxazole-5-carboxylate* (24) (0.438 g, 48%), which was isolated as a yellow oil, $[\alpha]_D^{20}$ −101° (*c* 2.8 in $CHCl_3$) (Found: $M^{+\bullet}$, 496.1634. $C_{29}H_{24}N_2O_6$ requires $M^{+\bullet}$, 496.1635). ν_{max}/cm^{-1} 1717, 1458, 1381, 1244, 1145. δ_H 7.78 (2 H, m), 7.71 (1 H, s), 7.70 (2 H, m), 7.37–7.32 (5 H, m), 7.13 (2 H, d, *J* 8.8), 6.82 (2 H, d, *J* 8.8), 5.72 (1 H, dd, *J* 6.5 and 10.0), 4.96 (2 H, s), 4.36 (2 H, q, *J* 7.1), 3.73 (2 H, m), 1.36 (3 H, t, *J* 7.1). δ_C 167.1, 163.7, 157.8, 143.1, 136.8, 134.2, 134.0, 131.4, 130.0, 128.4, 128.1, 127.8, 127.4, 123.6, 115.0, 105.5, 69.9, 61.5, 49.4, 34.7, 14.2. *m/z* 496 (3%, $M^{+\bullet}$), 451 (2), 423 (6), 350 (32), 83 (100), 43 (74).

The second fraction contained *O*-benzylphthalimidotyrosine (0.265 g, 36%), which was isolated as a white solid. The spectral data was identical to that above, mp 210–212°C.

Ethyl 2-(Aminomethyl)-1,3-oxazole-5-carboxylate Hydrochloride (8)

A suspension of (18) (400 mg, 1.33 mmol) and hydrazine hydrate (78 μL, 1.60 mmol) in ethanol (16 mL) was stirred for 2 h at 60°C. After evaporation, the residue was stirred with 1.5 M aqueous hydrochloric acid (10 mL) for 20 min at ambient temperature. Dichloromethane (10 mL) was added, the mixture was filtered, and the organic layer was discarded. The aqueous layer was extracted once more with dichloromethane (10 mL) and then evaporated to dryness. The *title compound* was isolated as a yellow oil, which crystallized on standing as rosettes (185 mg, 67%). A sample was recrystallized from ethanol/diethyl ether, mp 114–116°C (Found: C 40.5, H 4.4, N 13.7%; $M^{+\bullet}$, 170.0693. $C_7H_{11}ClN_2O_3$ requires C 40.7, H 4.1, N 13.6%; $M^{+\bullet}$, 170.0691). ν_{max}/cm^{-1} 3400, 1732, 1614, 1556, 1146, 1021. δ_H (D_2O/CD_3OD) 7.94 (1 H, s), 4.95 (3 H, br s), 4.57 (2 H, s), 4.45 (2 H, q, *J* 7.2), 1.42 (3 H, t, *J* 7.2). δ_C (D_2O/CD_3OD) 159.2, 157.3, 142.8, 132.9, 61.5, 35.0, 12.3. *m/z* 170 (77%, $M^{+\bullet}$), 125 (18), 69 (100).

Ethyl 2-(Aminomethyl)-4-methyl-1,3-oxazole-5-carboxylate Hydrochloride (9)

A suspension of the phthalimide (19) (2.27 g, 7.24 mmol) and hydrazine hydrate (460 mg, 9.00 mmol) in ethanol (45 mL) was stirred for 3.5 h at 65°C. After evaporation, the residue was stirred with 1.5 M aqueous HCl (20 mL) for 20 min at ambient temperature. Dichloromethane (20 mL) was added, the mixture was filtered, and the organic layer was discarded. The aqueous layer was extracted once more with dichloromethane (10 mL) and then evaporated to dryness, azeotroping with toluene (2 × 3 mL). The residue was suspended in hot dichloromethane (30 mL) and then cooled on ice. After addition of diethyl ether (15 mL) and cooling overnight, the product (9) was collected as light-yellow, lustrous crystals (1.23 g, 77%), mp 100–108°C (Found: C 43.1, H 6.2, N 12.5%; $M^{+\bullet}$, 184.0843. $C_8H_{13}ClN_2O_3$ requires, C 43.5, H 5.9, N 12.7%; $M^{+\bullet}$, 184.0848). ν_{max}/cm^{-1} 3423, 3108, 1712, 1616, 1577, 1507, 1338, 1107. δ_H ($CDCl_3$/[D_6]DMSO) 8.90 (3 H, br s), 4.36 (2 H, q, *J* 7.2), 4.25 (2 H, br s), 2.46 (3 H, s), 1.38 (3 H, t, *J* 7.2). δ_C ($CDCl_3$/[D_6]DMSO) 158.5, 158.1, 145.5, 138.6, 61.2, 36.0, 14.1, 13.1. *m/z* 184 (55%, $M^{+\bullet}$), 156 (15), 139 (13), 83 (100).

Ethyl 2-(1-Aminoethyl)-4-methyl-1,3-oxazole-5-carboxylate Hydrochloride (22)

A mixture of (20) (150 mg, 0.457 mmol) and hydrazine hydrate (27 μL, 0.555 mmol) in ethanol (6 mL) was reacted as described above to give the product (22) as a colourless oil (62 mg, 58%) (Found: $[M+H]^{+\bullet}$, 199.1080. $C_9H_{14}N_2O_3$ requires $[M+H]^{+\bullet}$, 199.1083). ν_{max} (film)/cm^{-1} 3400br, 1716, 1651. δ_H ($CDCl_3$) 9.20 (3 H, br s), 4.92 (1 H, br s), 4.33 (2 H, br s), 2.40 (3 H, s), 1.89 (3 H, br s), 1.36 (3 H, br s). δ_C ($CDCl_3$) 161.6, 158.6, 145.7, 138.6, 61.4, 45.4, 17.4, 14.0, 13.1.

Ethyl 2-(1-Aminoethyl)-1,3-oxazole-5-carboxylate Hydrochloride (23)

A mixture of (21) (160 mg, 0.509 mmol) and hydrazine hydrate (30 μL, 0.617 mmol) in ethanol (6 mL) yielded the *title compound* as a yellow oil (77 mg, 69%) (Found: $[M+H]^{+\bullet}$, 185.0920. $C_8H_{12}N_2O_3$ requires $[M+H]^{+\bullet}$, 185.0926). ν_{max}/cm^{-1} 3600–2400br, 1726, 1593, 1315, 1146. δ_H 9.10 (3 H, br s), 7.76 (1 H, s), 5.00 (1 H, br s), 4.37 (2 H, q, *J* 6.9), 1.87 (3 H, br s), 1.37 (3 H, t, *J* 6.9). δ_C 163.5, 157.5, 143.4, 133.9, 61.7, 45.5, 17.3, 14.0.

*(*S*)-Ethyl 2-[1-Amino-2-(4-benzyloxyphenyl)ethyl]-1,3-oxazole-5-carboxylate (25)*

A solution containing the protected oxazole (24) (0.438 g, 0.88 mmol) and hydrazine hydrate (176 μL, 3.96 mmol) in ethanol (20 mL) was reacted as described above to give (25) (0.3 g, 93%) as an orange oil, which required no further purification, $[\alpha]_D^{20}$ −16.6° (*c* 0.84 in $CHCl_3$) (Found: $[M+H]^{+\bullet}$, 367.1655. $C_{21}H_{22}N_2O_4$ requires $[M+H]^{+\bullet}$, 367.1658). ν_{max}/cm^{-1} 3290, 1724 (ester C=O), 1511, 1302, 1241, 1145. δ_H 7.66 (1 H, s), 7.43–7.31 (5 H, m), 7.05 (2 H, d, *J* 8.5), 6.88 (2 H, d, *J* 8.5), 5.02 (2 H, s), 4.38 (2 H, q, *J* 7.1), 4.32 (1 H, dd, *J* 5.5 and 8.0), 4.01 (2 H, br s), 3.21 (1 H, dd, *J* 5.5 and 13.6), 2.99 (1 H, dd, *J* 8.0 and 13.6), 1.38 (3 H, t, *J* 7.14). δ_C 169.6, 157.7, 142.3, 136.9, 133.7, 130.2, 128.8, 128.6, 128.4, 127.8, 127.3, 114.9, 69.9, 61.4, 51.6, 41.1, 14.1. *m/z* 367 (5%, $[M+H]^{+\bullet}$), 322 (10), 294 (12), 276 (2), 260 (4), 91 (100).

General Procedure for the Synthesis of the Mosher Amides

(*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (2 eq.) was refluxed in oxalyl chloride for 1.5 h and excess oxalyl chloride was evaporated. A solution of aminoalkyloxazoles (22), (23), (25) (24–37 mg) and 4-dimethylaminopyridine (1 eq.) at 0°C in dichloromethane (0.5 mL) was added to a solution of the above acid chloride and 4-dimethylaminopyridine (1 eq.) in dichloromethane (1 mL) at 0°C. The reaction was stirred at 0°C (40 min–1.5 h) and then at rt until TLC analysis showed the formation of the Mosher amide was complete. The mixture was evaporated and the oily residue was dissolved in diethyl ether (20 mL), washed with aqueous 1 M HCl (3 × 15 mL), water (10 mL), dried, and evaporated.

Racemic (22) and (23) were reacted as described above and the diastereomers were characterized by ^{1}H and ^{19}F NMR spectroscopy of the methoxy group, the methyl group α to the amide moiety, and the trifluoromethyl group. Both the methoxy group and the trifluoromethyl groups showed a ratio of 98 : 2 of the diastereomers.

Structure Determination and Refinement of (18)

A hemisphere of intensity data with k positive were collected on a CAD-4PC diffractometer (monochromatic $Mo_{K\alpha}$ radiation 0.71069 Å, *T* 293(2) K). A total of 5262 reflections were measured which when averaged (R_{int} 0.024) gave 2412 unique reflections, of which there were 1670 with $F^2 > 2\sigma(F^2)$. Using Xtal 3.7[22] the structure was solved by direct methods and refined on 2199 reflections with $F^2 > 0$ and 199 variables to convergence [*R* ($F^2 > 2\sigma(F^2)$] 0.042, *wR* 0.084, *S* 1.301, $w = (\sigma(F^2)^{-2})$]. Hydrogen atoms were placed in calculated positions and not refined.

Crystal Data for (18)

Compound (18) was crystallized from ethyl acetate. $C_{15}H_{12}N_2O_5$, *M* 300.27, monoclinic, space group $P2_1/n$, *a* 13.414(1), *b* 7.035(1), *c* 15.410(1) Å, β 108.45(1)°, θ 12.1–15.5°, *V* 1379.5(3) Å^3, *T* 293(2) K, D_c 1.446 Mg m^{-3}, *Z*4, μ_{Mo} 0.111 mm^{-1}, crystal 0.40 × 0.30 × 0.04 mm^3, $\Delta\rho$ 0.30(2) e Å^{-3}, R_{int} 0.024, $\omega/2\theta$ scans, θ_{max} 24.97°, no absorption correction; $-15 \le h \le 15$ for 5262 measured reflections, $0 \le k \le 8$ for 2412 independent reflections, $-18 \le l \le 18$ for 2199 reflections with $F^2 > 2\sigma(F^2)$.

Refinement

Refinement on F^2, $(\Delta/\sigma)_{max}$ 0.0005, $R(F)$ 0.066, $\Delta\rho_{max,min}$ 0.25, −0.32 eÅ^{-3}, $wR(F^2)$ 0.101, *S* 1.338. Scattering factors taken from the International Tables Vol. IV, Tables 2.2B and 2.3.1, 2199 reflections, 199 parameters, hydrogen atoms in calculated positions, weighting scheme based on measured s.u. values.

Acknowledgments

M.C. acknowledges the award of a Flinders University research scholarship and C.E.S is grateful for the award of an OPRS scholarship from Flinders University. The project was supported by the Australian Research Council.

Accessory Materials

A cif file of (18) is available from the *Australian Journal of Chemistry* until September 2008, from the Cambridge Crystallographic Data Centre (deposition 215 089), or from the author.

References

[1] J. Khalafy, C. E. Svensson, R. H. Prager, C. M. Williams, *Tetrahedron Lett*. **1998**, *39*, 5405.
[2] M. Cox, R. H. Prager, C. E. Svensson, *Aust. J. Chem*. **2003**, *56*, 887.
[3] P. Wipf, *Chem. Rev*. **1995**, *95*, 2115.
[4] K. Kohda, Y. Ohta, Y. Kawazoe, T. Kato, Y. Suzumura, Y. Hamada, T. Shioiri, *Biochem. Pharmacol*. **1989**, *38*, 4500.
[5] M. P. Foster, G. P. Concepción, G. B. Caraan. C. M. Ireland, *J. Org. Chem*. **1992**, *57*, 6671.
[6] R. H. Prager, J. A. Smith, B. Weber, C. M. Williams, *J. Chem. Soc., Perkin Trans. 1,* **1997**, 2665.
[7] R. H. Prager, M. R. Taylor, C. M. Williams, *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2673.
[8] (*a*) I. N'Diaye, G. Guella, G. Chiasera, F. Mancini, F. Pietra, *Tetrahedron Lett*. **1994**, *35*, 4827. (*b*) F. Pietra, G. Guella, I. Mancini, I. N'Diaye, *Helv. Chim. Acta*. **1994**, *77*, 1999.
[9] I. N'Diaye, G. Guella, I. Mancini, F. Pietra, *Tetrahedron Lett*. **1996**, *37*, 3049.
[10] J. Khalafy, R. H. Prager, C. M. Williams, *Aust. J. Chem*. **1999**, *52*, 31.
[11] N. Irako, Y. Hamada, T. Shioiri, *Tetrahedron* **1995**, *51*, 12731.
[12] J. O. Greenstein, *Chemistry of Amino Acids* Vol. 2, **1961** (Wiley: New York, NY).
[13] R. H. Prager, J. A. Smith, B. Weber, C. M. Williams, *J. Chem. Soc., Perkin Trans. 1,* **1997**, 2659.
[14] J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org Chem*. **1969**, *34*, 2543.
[15] (*a*) J. C. Sheehan, W. A. Bolhofe, *J. Am. Chem. Soc*. **1950**, *72*, 2786. (*b*) F. E. King, J. W. Clark-Lewis, D. A. A. Kidd, G. R. Smith, *J. Chem. Soc*. **1954**, 1039. (*c*) J. C. Sheehan, W. L. Richardson, *J. Am. Chem. Soc*. **1954**, *76*, 6329. (*d*) F. E. King, J. W. Clark-Lewis, W. A. Swindin, *J. Chem. Soc*. **1959**, 2259.
[16] R. Shapiro, *J. Org. Chem*. **1993**, *58*, 5759.
[17] R. H. Prager, Y. Singh, *Aust. J. Chem*. **1992**, *45*, 1811.
[18] E. Fischer, *Ber. Dtsch. Chem. Ges*. **1907**, *40*, 489.
[19] G. Grassi, F. Foti, F. Risitano, F. Caruso, *J. Chem. Res., Synop*. **1983**, 172.
[20] M. F. Francis, N. Chen, L. Benoiton, *Synthesis* **1979**, 709.
[21] H. Takamatsu, S. Umemoto, T. Tatsumi, K. Nakamura, *Japanese Patent 8539*, **1964**; *Chem. Abstr*. **1964**, *61*, 13 419b.
[22] *Xtal3.7 System* (Eds S. R. Hall, D. J. du Boulay, R. Olthof-Hazekamp) **2001** (University of Western Australia: Perth).