The Chemistry of Pseudomonic Acid,† Part II.[1] Dehydrative Cyclisation of α-Acylamino Ketones to Oxazoles

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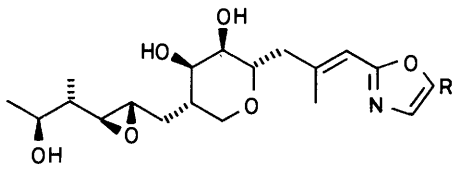
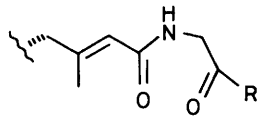
A number of mild methods for the preparation of 2-substituted 5-normonyloxazoles (**1**) by dehydrative cyclisation of the corresponding monamides (**2**) have been developed and are described. The preferred conditions involve using trichloroacetyl chloride, pyridine, and 4-*N*,*N*-dimethylaminopyridine. The stabilities of the vinyloxazoles to both the reaction conditions and to light are also reported.

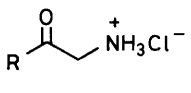
The preparation of a series of normonyl¶ heterocycles by cyclisation and olefination reactions was described in the preceding paper. Of particular biological interest were the oxazoles (**1**). This paper describes the methods developed for the cyclodehydration of the keto amides (**2**) to the oxazoles (**1**) using conditions which are compatible with the sensitive monate nucleus.[2]



(**1**)



(**2**)



(**3**)

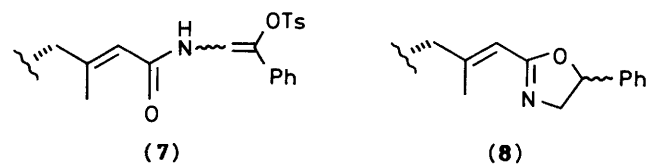
Results and Discussion

The cyclodehydration of α-acylamino ketones, the Robinson–Gabriel synthesis, is one of the oldest syntheses of oxazoles.[3] Reagents which allow this transformation include concentrated sulphuric acid, phosphorus pentachloride, polyphosphoric acid, and thionyl chloride.[4] In contrast, a milder method which has been reported is the use of phosgene with base[4] and such a combination was investigated in the monate series.

Condensation of monic acid (**6**) with phenacylamine hydrochloride (**3a**) as previously described [1] for the synthesis of monic acid amides, gave the keto amide (**2a**) in 52% yield. Treatment with trimethylsilyl chloride and triethylamine to protect the nucleus as its tris(trimethylsilyl ether) and subsequent reaction with phosgene and triethylamine gave, after mild acidic hydrolysis, the phenyloxazole (**1a**) in 11% overall yield from the keto amide. Also isolated was the acyloxazolone (**4a**), derived by addition of phosgene to the keto amide.

Application of this reaction to substituted phenyl analogues of (**1a**), in particular to nitrophenyloxazole (**1b**), led to exclusive formation of the acyloxazolone (**4b**). A number of alternative reagents were subsequently investigated for the dehydration of protected (**2b**). No products were obtained with phosphorus pentachloride, thionyl chloride, or thiophosgene. With tosyl chloride and pyridine, the enol tosylate (**7**) was obtained after deprotection. In contrast, phosphoryl chloride and pyridine effected cyclisation to the oxazoles. Phosphoryl chloride alone has previously been described for the synthesis of oxazoles.[5] With silyl protection as before, (**1b**) was formed in 8% yield from the amide (**2b**).

A recent literature report described the condensation of carboxylic acids with β-amino alcohols in the presence of tetrachloromethane and triphenylphosphine to produce dihydro-oxazoles.[6] Presumably the reaction proceeds *via* an intermediate hydroxyamide which is cyclised under the reaction conditions. Application to the condensation of monic acid and 2-hydroxy-2-phenylethylamine afforded the dihydro-oxazole (**8**) in 43% yield. Protection of the hydroxy groups of the monate nucleus was not required under these conditions since the rate of chlorination is very slow. These conditions were successfully



(**4**) (**5**) (**6**)

(**7**)

(**8**)

For formulae (1)—(5) R = : **a**, Ph; **b**, $C_6H_4NO_2$-*o*-P; **c**, C_6H_4SMe-*p*; **d**, $C_6H_4SO_2Me$-P; **e**, Et

† The approved generic name for pseudomonic acid is mupirocin.

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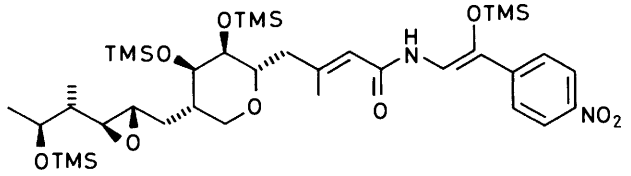
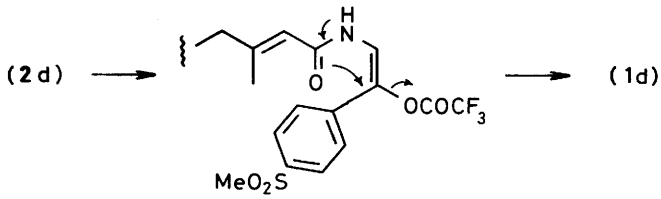
¶ Normonyl, the trivial name for the 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(*E*)-en-1-yl radical, is used throughout for convenience.

applied to the preparation of oxazoles (**1**) using α-amino ketones and, in this case, monic acid protected as its tris(trimethylsilyl ether). The overall sequence from monic acid and phenacylamine gave the oxazole (**1a**) in 21% yield. In a separate experiment, the tris(trimethylsilyl ether) of the amide (**2a**) was shown to cyclise to (**1a**) in 49% overall yield after deprotection. In general, better overall yields were obtained by preparing and isolating the amides (**2**) separately and this sequence was shown to be more widely applicable than any of the previous processes. It was used to convert (**2b**) and (**2c**) into the corresponding oxazoles (**1b**) (28%) and (**1c**) (64%). For nitrophenyloxazole (**1b**) better yields were obtained without silyl protection as variable amounts of silyl enol ether (**9**) were formed at the protection stage, which reverted to unchanged amide (**2b**) after deprotection.



(**9**)

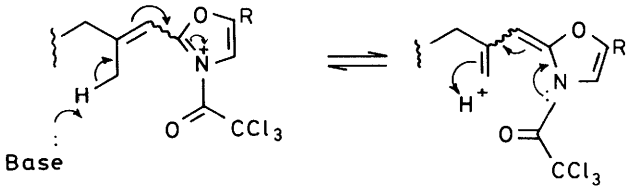
Biological interest in an oxazole (**1d**) necessitated a more efficient preparation of this oxazole. Dehydration of α-acylamino ketones to oxazoles has previously been effected with acetic anhydride,[7] and it was felt that a more electrophilic acid anhydride, *e.g.* trifluoroacetic anhydride, should effect cyclisation more easily. The keto amide (**2d**) was therefore dissolved in an excess of trifluoroacetic anhydride at room temperature, and upon evaporation, the tris(trifluoroacetate) of the oxazole (**1d**) was found to have been formed. Removal of the trifluoroacetate esters with potassium carbonate in methanol then gave (**1d**) in 48% yield. It is known that in the Robinson–Gabriel cyclisation the amide oxygen is retained and the keto oxygen is lost.[8] It is possible therefore that in this case an enol trifluoroacetate is formed which is sufficiently electrophilic to cyclise to the oxazole (Scheme 1).



Scheme 1.

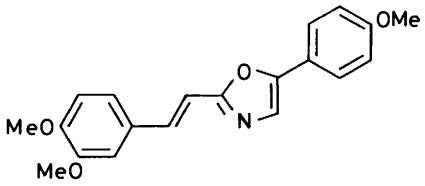
Trichloroacetic anhydride was also found to be effective in the reaction, giving (**1d**) in 35—40% yield and, in addition, the trichloroacetate esters were more easily hydrolysed than the corresponding trifluoroacetates. Base was not required in these reactions, and no oxazole was obtained when triethylamine was present. Acid chlorides are known to be more electrophilic than anhydrides and trichloroacetyl chloride also afforded (**1d**). The combination of a weak base such as pyridine with trichloroacetyl chloride and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine was found to be the optimum reagent. As with the anhydrides, strong bases such as triethylamine were found to inhibit oxazole formation. Using trichloroacetyl chloride and pyridine, (**1d**) was prepared in 60% overall yield from monic aid. This method was used to synthesise a wide range of other substituted oxazoles.

In contrast to the previously described olefination procedure,[1] this method affords only the desired *E* olefins in most cases. However, the cyclisation of (**2e**) gave not only (**1e**) (64%) but also (**5e**) (7%). To determine the origin of (**5e**) both 5-alkyl- and 5-aryl-normonyloxazoles (*E* isomers) were treated with trichloroacetyl chloride, pyridine, and 4-*N*,*N*-dimethylaminopyridine, and it was found that for the alkyloxazoles, slow isomerisation occurred. No isomerisation took place when the trichloroacetyl chloride was omitted. It is suggested that isomerisation occurs through a base-catalysed reaction of the acylated oxazole (Scheme 2). The preferential isomerisation



Scheme 2.

of the alkyloxazoles probably reflects the greater electron density of the oxazole rings in these compounds. Although the 5-aryloxazoles were not isomerised by the trichloroacetyl chloride–pyridine reagent, samples of aryloxazoles (**1b**) and (**1d**) were in some cases obtained contaminated with their *Z* isomers (**5b**), (**5d**). Investigation revealed that photoisomerisation in solution was the cause and even diffuse laboratory light was sufficient. A search of the literature revealed that a naturally occurring oxazole, annuloline (**10**), had been reported to



(**10**)

undergo a similar photoisomerisation.[9] Although the equilibrium ratios of isomers were similar for the aryloxazoles studied, *E*:*Z* *c.a.* 2:1, the rates at which photoisomerisation occurred under similar conditions varied greatly. In general, aryloxazoles substituted on the phenyl group with electron withdrawing groups were found to isomerise in solution most rapidly and the greatest rate was found for nitrophenyloxazole (**1b**). Alkyloxazoles did not undergo photoisomerisation in solution and no isomerisation of the solid materials took place.

Some of the aryloxazoles described were found to be highly potent antimycoplasmal agents, and showed significant improvements in metabolic stability over monate esters. Details of these biological properties will be published elsewhere.

Experimental

For general experimental conditions see the preceding paper.

2-Normonyl-5-phenyloxazole (**1a**).—(i) *In one step from monic acid* (**6**). To a solution of monic acid (1.03 g, 3 mmol) in dry THF (50 ml) were added 4-*N*,*N*-dimethylaminopyridine (50 mg), triethylamine (1.82 ml, 13 mmol), and chlorotrimethylsilane (1.65 ml, 13 mmol). After 3 h the solution was filtered and solvent removed under reduced pressure. The resulting residue was partitioned between aqueous ammonium chloride and ethyl acetate, and the organic phase was then washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The resulting residue was dissolved in a mixture of acetonitrile (10 ml), pyridine (10 ml), tetrachloromethane (1.5 ml, 15 mmol), and triethylamine (1.6 ml, 12 mmol). Phenacylammonium

chloride (0.51 g, 3 mmol) and triphenylphosphine (0.7 g, 3 mmol) were added, and after 1 h more triphenylphosphine (1.6 g, 6 mmol). After a further 16 h the reaction mixture was poured into a mixture of brine and aqueous sodium hydrogen carbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give an oil, which was dissolved in a mixture of THF (60 ml) and water (15 ml). Concentrated hydrochloric acid (20 drops) was added and after 12 min the solution poured into aqueous sodium hydrogen carbonate. The resulting mixture was extracted with ethyl acetate, and the extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to leave a brown oil which was purified by chromatography on silica gel (50 g), eluting with 0—8% methanol in dichloromethane. 2-Normonyl-5-phenyloxazole was obtained as a white foam (0.28 g, 21%) identical with that obtained previously.[1]

(ii) *From phenacyl monamide* (**2a**). A solution of phenacyl monamide[1] (1.4 g, 3 mmol) in THF (30 ml) was treated with chlorotrimethylsilane (1.3 ml, 10 mmol), triethylamine (1.4 ml, 10 mmol), and 4-*N*,*N*-dimethylaminopyridine (50 mg) for 2 h at 20 °C. The mixture was then filtered and evaporated under reduced pressure, and the resulting residue extracted with ether. The combined ether extracts were filtered and evaporated under reduced pressure and the resulting residue dissolved in a mixture of acetonitrile (15 ml), pyridine (15 ml), triethylamine (0.8 ml, 6 mmol), and tetrachloromethane (1.2 ml, 12 mmol). Triphenylphosphine (1.6 g, 6 mmol) was then added and the mixture stood set aside at 20 °C for 2 h and then at 50 °C for 16 h. The reaction mixture was poured into aqueous sodium hydrogen carbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give an oil, which was dissolved in dioxane (40 ml) and water (10 ml). Concentrated aqueous hydrochloric acid (12 drops) was added and after 12 min the solution neutralised with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to leave a brown oil which was purified by chromatography on silica gel (50 g) eluting with a gradient of 4—10% methanol in dichloromethane to give 2-normonyl-5-phenyloxazole as a white foam (0.65 g, 49%).

N-(p-*Nitrophenacyl*)*monamide* (**2b**). This was obtained according to the general method[1] from *p*-nitrophenacylammonium chloride[10] as a yellow foam (31% yield); $\nu_{max.}$(film) 3 380, 1 660, 1 630, 1 605, 1 525, and 1 350 cm^{-1}; $\lambda_{max.}$(EtOH) 223 nm (ε_m 18 200); $\delta_H(CD_3OD)$ 0.90 (3 H, d, 17-H_3), 1.95 (3 H, d, 14-H_3), 2.13 (3 H, s, 15-H_3), 4.73 (2 H, s, 1′-H), 5.91 (1 H, s, 2-H), and 8.28 (4 H, m, aryl); $\delta_C(CDCl_3)$ 196.1 (C-2′), 169.5 (C-1), 153.3 (C-3), 152.0 (C-4″), 141.2 (C-1″), 130.3 (C-3″ and -5″), 124.9 (C-2″ and -6″), 120.6 (C-2), 76.4 (C-5), 71.7 (C-13), 70.8 (C-7), 70.1 (C-6), 66.4 (C-16), 61.4 (C-11), 56.9 (C-10), 47.5 (C-1′), 43.7 (C-4 and -12), 41.7 (C-8), 33.1 (C-9), 19.6 (C-14), 19.1 (C-15), and 12.3 (C-17) (Found: *m*/*z*, M^+, 506.2231. $C_{25}H_{34}N_2O_9$ requires 506.2264).

5-p-*Nitrophenyl*-2-*normonyloxazole* (**1b**).—(i) *Using phosphoryl chloride*. *p*-Nitrophenacyl monamide (1.01 g, 2 mmol) (**2b**) was treated with chlorotrimethylsilane (0.76 ml, 6 mmol) and triethylamine (0.84 ml, 6 mmol) in THF (20 ml) until protection was complete as indicated by t.l.c. (16 h). The resulting solution was filtered and evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 ml) and treated with phosphoryl chloride (0.3 ml, 3.5 mmol) and pyridine (0.5 ml, 6 mmol) for 16 h at 20 °C. The reaction mixture was poured into aqueous sodium hydrogen carbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give an oil, which was dissolved in dioxane (40 ml) and water (10 ml). Concentrated aqueous hydrochloric acid (12 drops) was added and after 12 min the solution neutralised with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to leave an oil which was purified by chromatography on silica gel (50 g) eluting with a gradient of 4—10% methanol in dichloromethane to give the oxazole (**1b**) as a yellow foam (0.08 g, 8%); $\nu_{max.}$(film) 3 400, 1 650, 1 605, and 1 520 cm^{-1}; $\lambda_{max.}$(EtOH) 267 nm (ε_m 18 200); $\delta_H(CDCl_3)$ 0.90 (3 H, d, 17-H_3), 1.21 (3 H, d, 14-H_3), 2.34 (3 H, s, 15-H_3), 6.32 (1 H, s, 2-H), 7.56 (1 H, s, heteroaryl) and 8.3—7.8 (4 H, m, aryl); $\delta_C(CDCl_3)$ 162.7 (C-1), 147.8 and 147.1 (C-3 and -4″), 134.0 (C-5′), 131.3 (C-1″), 126.3 (C-4′), 124.5 and 124.3 (C-3″ and -5″, and C-2″ and -6″), 112.9 (C-2), 75.3 (C-5), 71.3 (C-13), 70.6 (C-7), 69.1 (C-6), 65.5 (C-16), 61.3 (C-11), 55.6 (C-10), 43.0 (C-12), 42-9 (C-4), 39.7 (C-8), 31.8 (C-9), 20.9 (C-14), 19.8 (C-15), and 12.7 (C-17) (Found: M^+, 488.2168. $C_{25}H_{32}N_2O_8$ requires 488.2259).

(ii) *Using triphenylphosphine–tetrachloromethane*. To a solution containing *p*-nitrophenacyl monamide (**2b**) (0.50 g, 1 mmol), tetrachloromethane (0.40 ml. 4 mmol), triethylamine (0.28 ml, 2 mmol), pyridine (6 ml), and acetonitrile (6 ml) at 60 °C was added triphenylphosphine (0.53 g, 2 mmol). After 1 h at 60 °C the solution was evaporated under reduced pressure and the residue purified by chromatography (silica gel, 0—10% methanol in dichloromethane) to give the title compound as a yellow foam (0.08—0.14 g, 15—28%).

N-(p-*Methylthiophenacyl*)*monamide* (**2c**). This was prepared according to the general method[1] from *p*-methylthiophenacylammonium chloride[11] as white rhombs (56%), m.p. 84—87 °C (diethyl ether); $\nu_{max.}$(film) 3 400, 1 685, 1 660, 1 620, and 1 590 cm^{-1}; $\lambda_{max.}$(EtOH) 223 nm (ε_m 18 100); $\delta_H(CD_3OD)$ 0.97 (3 H, d, 17-H_3), 1.21 (3 H, d, 14-H_3), 2.19 (3 H, s, 15-H_3), 2.54 (3 H, s, SMe), 4.69 (2 H, s, 1′-H), 5.91 (1 H, s, 2-H), and 7.3—7.9 (4 H, m, aryl); $\delta_C(CD_3OD)$ 195.4 (C-2′), 169.7 (C-1), 153.0 (C-3), 148.4 (C-4″), 132.4 (C-3″ and -5″), 129.3 (C-2″ and -C6″), 126.1 (C-1″), 120.7 (C-2), 76.2 (C-5), 71.6 (C-13), 70.7 (C-7), 70.0 (C-6), 66.3 (C-16), 61.3 (C-11), 56.8 (C-10), 46.7 (C-1′), 43.6 (C-4 and -12), 41.5 (C-8), 32.9 (C-9), 20.3 (C-14), 19.0 (C-15), 14.6 (SMe) and 12.2 (C-17); *m*/*z* 507 (M^+, 0.7%), 489 (0.8), and 151 (100) (Found: M^+, 507.2251. $C_{26}H_{37}NO_7S$ requires 507.2291).

5-p-*Methylthiophenyl*-2-*normonyloxazole* (**1c**).—*p*-Methylthiophenacyl monamide (**2c**) (0.50 g, 1 mmol) in THF (20 ml) was treated with chlorotrimethylsilane (0.8 ml, 6 mmol), triethylamine (0.9 ml, 6 mmol), and 4-*N*,*N*-dimethylaminopyridine (50 mg) for 16 h at 20 °C. The mixture was then filtered and evaporated under reduced pressure, and the resulting residue extracted with ether. The combined ether extracts were filtered and evaporated under reduced pressure and the resulting residue dissolved in mixture of acetonitrile (6 ml), pyridine (6 ml), triethylamine (0.28 ml, 2 mmol), and tetrachloromethane (0.4 ml, 4 mmol). Triphenylphosphine (0.53 g, 2 mmol) was then added and the mixture stirred for 3 h at 20 °C and then poured into aqueous sodium hydrogen carbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give an oil, which was dissolved in dioxane (40 ml) and water (10 ml). Concentrated aqueous hydrochloric acid (12 drops) was added and after 12 min the solution neutralised with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to leave a brown oil which was purified by chromatography on silica gel (10 g) eluting with a gradient of 4—10% methanol in dichloromethane to give the oxazole as a yellow oil (314 mg, 64%); $\nu_{max.}$(film) 3 300, 1 655, and 1 485 cm^{-1}; $\lambda_{max.}$(EtOH) 223

(ε_m 15 300), 267 (9 200), and 326 nm (34 100); $\delta_H(CDCl_3)$ 0.93 (3 H, d, 17-H_3), 1.21 (3 H, d, 14-H_3), 2.30 (3 H, s, 15-H_3), 3.50 (3 H, s, SMe), 6.26 (1 H, s, 2-H), 7.25 (1 H, s, oxazole-H), and 7.52 and 7.23 (4 H, m, aryl); $\delta_C(CDCl_3)$ 161.0 (C-1), 149.7 (C-3), 146.8 (C-5′), 139.1 (C-4″), 126.8 (C-3″ and -5″), 124.8 (C-4′), 124.4 (C-2″ and -6″), 122.2 (C-1″), 113.2 (C-2), 75.4 (C-5), 71.2 (C-13), 70.5 (C-7), 69.0 (C-6), 65.6 (C-16), 61.2 (C-11), 55.6 (C-10), 42.9 (C-12), 42.8 (C-4), 39.6 (C-8), 31.8 (C-9), 20.8 (C-14), 19.7 (C-15), 15.7 (SMe) and 12.7 (C-17); *m/z* 489 (M^+, 17%) and 245 (100) (Found: 489.2218. $C_{26}H_{35}NO_6S$ requires 489.2185).

N-(p-*Methylsulphonylphenacyl*)*monamide* (**2d**). This was obtained according to the general method[1] from *p*-methylsulphonylphenacylammonium chloride[12] as a white foam (68%); $\nu_{max.}$(film) 3 400, 2 950, 1 705, 1 665, 1 635, and 750 cm^{-1}; $\lambda_{max.}$(EtOH) 230 (ε_m 28 500) and 238 nm (28 200); $\delta_H(CD_3OD)$ 0.89 (3 H, d, 17-H_3), 1.15 (3 H, d, 14-H_3), 2.10 (3 H, s, 15-H_3), 3.09 (3 H, s, SO_2Me), 5.82 (1 H, s, 2-H), and 8.17 (4 H, m, aryl); $\delta_C(CD_3OD)$ 195.7 (C-2′), 169.7 (C-1), 153.4 (C-3), 146.0 (C-4″), 140.4 (C-1″), 129.9 (C-3″ and -5″), 128.8 (C-2″ and -6″), 120.5 (C-2), 76.2 (C-5), 71.6 (C-13), 70.7 (C-7), 70.0 (C-6), 66.3 (C-16), 61-2 (C-11), 56.8 (C-10), 47.4 (C-1′), 44.1 ($MeSO_2$), 43.7 (C-4 and -12), 41.5 (C-8), 32.9 (C-9), 20.4 (C-14), 19.0 (C-15), and 12.3 (C-17) (Found: M^+, 539.2205. $C_{26}H_{37}NO_9S$ requires *M*, 539.2189).

5-p-*Methylsulphonylphenyl*-2-*normonyloxazole* (**1d**).—(i) *From the sulphide* (**1c**). A mixture of 5-*p*-methylthiophenyl-2-normonyloxazole (**1c**) (0.20 g, 0.4 mmol), sodium hydrogen carbonate (0.26 g, 3.2 mmol), and *m*-chloroperbenzoic acid (0.32 g, 1.6 mmol) in dichloromethane (10 ml) was stirred at 20 °C for 20 h and then diluted with ethyl acetate. The solution was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by chromatography (silica gel, 0—10% methanol in dichloromethane) to give the title compound (0.011 g, 53%) as white rhombs m.p. 169—171 °C (MeOH) (Found; C, 59.8; H, 6.8; N, 2.8. $C_{26}H_{35}NO_8S$ requires C, 59.9; H, 6.8; N, 2.7%); $\nu_{max.}$(film) 3 450, 1 655, 1 605, 1 305, and 1 150 cm^{-1}; $\lambda_{max.}$(EtOH) 323 nm (ε_m 23 500); $\delta_H(CDCl_3)$ 0.89 (3 H, d, 17-H_3), 1.20 (3 H, d, 14-H_3), 2.34 (3 H, s, 15-H_3), 3.09 (3 H, s, SO_2Me), 6.35 (1 H, s, 2-H), 7.57 (1 H, s, oxazole-H) and 7.9 (4 H, m, aryl); $\delta_C(CD_3OD$–$CDCl_3)$ 163.5 (C-1), 150.4 (C-3), 149.3 (C-5′), 140.6 (C-4″), 133.9 (C-1″), 129.0 (C-3″ and -5″), 126.3 (C-4′), 125.3 (C-2″ and -6″), 113.2 (C-2), 76.1 (C-5), 71.3 (C-13), 70.5 (C-7), 69.7 (C-6), 66.2 (C-16), 61.2 (C-1), 56.6 (C-10), 44.4 (SO_2Me), 43.8 (C-4), 43.4 (C-12), 41.2 (C-8), 32.8 (C-9), 20.3 (C-14), 19.9 (C-15), and 12.2 (C-17); *m/z* 521 (M^+, 9%), 306 (12), and 277 (100) (Found: M^+, 521.2050. $C_{26}H_{35}NO_8S$ requires *M*, 521.2083).

(ii) *From the amide* (**2d**) *with trifluoroacetic anhydride*. *p*-Methylsulphonylphenacylmonamide (**2d**) 0.054 g, 0.1 mmol) was dissolved in trifluoroacetic anhydride (0.140 ml, 1.0 mmol) at 20 °C. After 1 h volatiles were removed under reduced pressure, and the resulting oil was dissolved in methanol. Excess of potassium carbonate was added and after 2 h at 20 °C the mixture was partitioned between water and ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give the oxazole (**1d**) as a white solid collected with ether (0.025 g, 48%).

(iii) *From the amide* (**2d**) *with trichloroacetic anhydride*. *p*-Methylsulphonylphenacyl monamide (**2d**) (1.30 g, 2.4 mmol) was dissolved in trichloroacetic anhydride (9.00 ml, 50 mmol) at 20 °C. After 1 h at 20 °C the solution was poured into aqueous sodium hydrogen carbonate and the mixture extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated under reduced pressure and the resulting residue was dissolved in methanol (50 ml) to which potassium carbonate (1.40 g, 10 mmol) was added. After 10 min at 20 °C the mixture was partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$), and evaporated under reduced pressure. The resulting oil was purified by chromatography (20 g silica gel, 0–8% methanol in dichloromethane) to give the oxazole (**1d**) as a white solid collected with methanol (0.43 g, 35%).

(iv) *From the amide* (**2d**) *with trichloroacetyl chloride–pyridine*. *p*-Methylsulphonylphenacyl monamide (**2d**) (2.16 g, 4.0 mmol), 4-dimethylaminopyridine (10 mg), and pyridine (3.24 ml, 40 mmol) were dissolved in dichloromethane (20 ml). The solution was placed in an ice-bath and a solution of trichloroacetyl chloride (2.01 ml, 18 mmol) in dichloromethane (5 ml) was added at such a rate that the temperature of the reaction remained in the range 10—15 °C. After a further 30 min at this temperature the solution was washed with aqueous sodium hydrogen carbonate and then evaporated under reduced pressure. The resulting residue was dissolved in methanol (20 ml) and the solution cooled to 0 °C. Potassium carbonate (1.66 g, 12 mmol) was added, and after 10 min at 0 °C, water and brine were added. The pH of the solution was adjusted to 7 (HCl), and the solution was then extracted 3 times with ethyl acetate. The combined extracts were washed with brine and evaporated under reduced pressure. Chromatography of the residue (20 g silica gel, 0—10% methanol in dichloromethane) then gave the oxazole (**1a**) as a white solid collected with methanol (1.25 g, 60%).

N-(2-*Oxobutyl*)*monamide* (**2e**). This was obtained according to the general method[1] from 1-aminobutan-2-one[13] as a foam (15%); $\nu_{max.}$(film) 3 600—2 200, 1 720, 1 660, and 1 630 cm^{-1}; $\lambda_{max.}$(EtOH) 222 nm (ε_m 13 800); $\delta_H(CDCl_3)$ 0.93 (3 H, d, 17-H_3), 1.12 (3 H,t, 4′-H_3), 1.22 (3 H, d, 14-H_3), 2.18 (3 H, s, 15-H_3), 2.50 (2 H, m, 3′-H_2), 4.17 (2 H, d, 1′-H_2), 5.76 (1 H, s, 2-H) and 6.47 (1 H, t, NH); $\delta_C(CDCl_3)$ 206.9 (C-2′), 167.4 (C-1), 152.2 (C-3), 119.4 (C-2), 74.5 (C-5), 70.9 (C-13), 70.4 (C-7), 68.8 (C-6), 65.3 (C-16), 61.0 (C-11), 55.6 (C-10), 48.6 (C-1′), 42.7 (C-12), 42.5 (C-4), 39.6 (C-8), 33.4 (C-3′), 31.6 (C-9), 20.8 (C-14), 18.9 (C-15), 12.6 (C-17), and 7.5 (C-4′); *m/z* 413 (M^+, 1%), 169 (98), 111 (100), 83 (83), 82 (81), 69 (73), 55 (68), 43 (84), and 41 (68) (Found: M^+, 413.2399. $C_{21}H_{35}NO_7$ requires *M*, 413.2413).

5-*Ethyl*-2-*normonyloxazole* (**1e**).—Trichloroacetyl chloride (2.2 ml, 20 mmol) was added to a solution of *N*-(2-oxobutyl)monamide (1.0 g, 2.3 mmol) (**2e**), 4-dimethylaminopyridine (50 mg), and pyridine (4.0 ml, 50 mmol) in dichloromethane (25 ml) at 0 °C. After 0.5 h the solution was washed with aqueous sodium hydrogen carbonate and then evaporated under reduced pressure. The resulting residue was dissolved in methanol (15 ml) and the solution cooled to 0 °C before addition of potassium carbonate (1.0 g, 7.0 mmol). After 15 min at 0 °C, brine and ethyl acetate were added and the organic layer separated. The aqueous layer was further extracted with ethyl acetate and the combined extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The resulting residue was chromatographed on silica (0—10% methanol in dichloromethane) to give oxazole (**1e**) (0.6 g, 64%); $\nu_{max.}$(film) 3 600—3 200, 1 720, 1 660, 1 370, and 910 cm^{-1}, $\lambda_{max.}$(EtOH) 266 nm (ε_m 5 010); $\delta_H(CD_3OD)$ 0.94 (3 H, d, *J* Hz, 17-H_3), 1.20 (3 H, d, *J* 7 Hz, 14-H_3), 1.26 (3 H, t, *J* 7 Hz, 2″-H_3), 1.40 (1 H, m, 12-H), 1.69 (2 H, m, 9-H_2) 1.96 (1 H, m, 8-H), 2.19 (3 H, s, 15-H_3), 2.28 (1 H, dd, *J* 15, 10 Hz, 4-H), 2.50 (1 H, m, 4-H′), 2.70 (3 H, m, 11-H and 1″-H_2), 2.81 (1 H, dt, *J* 2.5, 6 Hz, 10-H), 6.13 (1 H, s, 2-H), and 6.78 (1 H, s, 4′-H); $\delta_C(CD_3OD)$ 12.2 and 12.1 (C-17 and -2″), 19.5 and 19.8 (C-15 and -1″), 20.3 (C-14), 33.0 (C-9), 41.6 (C-8), 43.7 (C-12 and -4), 56.9 (C-10), 61.2 (C-11), 66.3 (C-16), 70.0 (C-6), 10.7 (C-7), 71.6 (C-13), 76.4 (C-5), 113.7 (C-2), 122.4 (C-4′), 147.6 (C-3), 154.8 (C-5′), and 160.6 (C-1); *m/z* 395 (M^+, 1%), 151 (100), 83 (25), 82 (23), 71 (27), 70 (27), 69 (25), 57 (60), and 55 (45) (Found: M^+,

395.2302. $C_{21}H_{33}NO_6$ requires *M*, 395.2308); and the *Z* isomer (**5e**) (14 mg, 7%); $\nu_{max.}$(film) 3 600—3 200, 1 720, 1 650, 1 605, and 930 cm^{-1}; $\delta_H(CDCl_3)$ 0.94 (3 H, d, *J* 7 Hz, 17-H_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.24 (3 H, t, *J* 7 Hz, 2″-H_3), 1.30 (1 H, m, 12-H), 1.56 (1 H, dt, *J* 14, 6 Hz, 9-H), 1.80 (1 H, ddd, *J* 6, 8, 14 Hz, 9-H′), 2.02 (1 H, m, 8-H), 2.08 (3 H, s, 15-H_3), 2.65 (3 H, m, 11-H and 1″-H_2), 2.77 (2 H, m, 10- and 4-H), 3.03 (1 H, dd, *J* 13, 4 Hz, 4-H′), 6.18 (1 H, s, 2-H), and 6.69 (1 H, s, 4′-H); $\delta_C(CDCl_3)$ 11.8 (C-2″), 12.9 (C-17), 19.0 (C-1″), 20.7 (C-14), 27.5 (C-15), 31.7 (C-9), 36.1 (C-4), 38.8 (C-8), 43.1 (C-12), 56.2 (C-10), 61.7 (C-11), 65.6 (C-16), 66.4 (C-6), 70.3 (C-7), 71.5 (C-13), 77.2 (C-5), 112.8 (C-2), 121.1 (C-4′), 148.7 (C-3), 153.2 (C-5′) and 160.2 (C-1); *m*/*z* 395 (M^+, 5%), 180 (26), 163 (48), 151 (100), 55 (22), 45 (23), 43 (279, and 41 (34) (Found: M^+, 395.2316. $C_{21}H_{33}NO_6$ requires *M*, 395.2308).

2-*Normonyl*-5-*phenyl*-4,5-*dihydro-oxazol* (**8**).—To a solution containing monic acid (**6**) (0.34 g, 1 mmol), 1-phenyl-2-aminoethanol (0.14 g, 1 mmol), triethylamine (0.42 ml, 3 mmol), tetrachloromethane (0.50 ml, 5 mmol), pyridine (3 ml), and acetonitrile (3 ml), was added, at 20 °C and over 20 min, another solution containing triphenylphosphine (0.80 g, 3 mmol), pyridine (2 ml), and acetonitrile (2 ml). After 3 days at 20 °C the mixture was poured into aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated under reduced pressure and the resulting residue purified by chromatography (silica gel, 0—12% methanol in dichloromethane) to give the title compound as a reddish foam (0.19 g, 43%); $\nu_{max.}$(film) 3 400, 1 660, 1 600, and 730 cm^{-1}; $\lambda_{max.}$(EtOH) 220 nm (ε_m 22 300); $\delta_H(CDCl_3)$ 0.93 (3 H, d, 17-H_3), 1.22 (3 H, d, 14-H_3), 2.21 (3 H, s, 15-H_3), 4.30 and 3.80 (2 H, 2 m, heterocycle 4-H_2), 5.50 (1 H, t, heterocycle 5-H_2), 5.92 (1 H, s, 2-H), and 7.25—7.40 (5 H, m, aryl); *m*/*z* 445 (M^+, 8%), 230 (24), 201 (82), and 41 (100) (Found: M^+, 445.2443. $C_{25}H_{35}NO_6$ requires *M*, 445.2464.

2-p-*Nitrophenyl*-2-*trimethylsilyloxyvinylmonamide Tris*(*trimethylsilyl ether*) (**9**).—A solution containing 5-*p*-nitrophenacyl monamide (**2b**) (1.0 g, 2 mmol), trimethylchlorosilane (1.3 ml, 10 mmol), triethylamine (1.4 ml, 10 mmol), and 4-*N*,*N*-dimethylaminopyridine (50 mg) in acetonitrile (20 ml) was stirred for 3 h at 20 °C and then set aside for 18 h at 0 °C. The mixture was diluted with ether and filtered, and the filtrate evaporated under reduced pressure to give the above silyl ether (**9**) as a bright yellow foam (1.3 g, 57%); $\nu_{max.}(CHCl_3)$ 1 675, 1 640, and 1 590 cm^{-1}; $\delta_H(CDCl_3)$ 0.8 (3 H, d, 17-H_3), 1.1 (3 H, d, 14-H_3), 2.2 (3 H, s, 15-H_3), 5.6 (1 H, s, 2-H), 7.2 (1 H, s, 1′-H), and 7.5—8.1 (4 H, ABq, aryl).

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