The Chemistry of Pseudomonic Acid.† 15.[1] Synthesis and Antibacterial Activity of a Series of 5-Alkyl, 5-Alkenyl, and 5-Heterosubstituted Oxazoles

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The synthesis of a range of 5-alkyl, 5-alkenyl, and 5-heterosubstituted 2-(1-normon-2-yl) oxazoles is described. The antibacterial activity was determined as the minimum inhibitory concentration against a range of Gram-positive and Gram-negative organisms using a standard Agar dilution procedure. Compounds possessing an acid functionality directly on, or close to, the ring were found to be of greatly decreased potency, while increasing lipophilicity with greater chain length led to increased potency of these derivatives.

Introduction

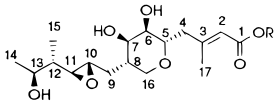
Pseudomonic acid (**1a**), marketed by SmithKline Beecham as the topical antibacterial agent, Bactroban, is potent against Gram-positive bacteria and some Gram-negative organisms such as *Haemophilus* and *Pasteurella*.[2] The mechanism of action is the inhibition of bacterial isoleucyl tRNA synthetase,[3a,b] for which pseudomonic acid shows a much greater affinity than for the corresponding mammalian enzyme.[3b] However, *in vivo*, the ester function of **1a** is hydrolyzed to the antibacterially inactive monic acid **1b**.

We had previously searched for linker groups which would act as bioisosteres of the ester group in **1a** and had found that the 2,5-substituted oxazoles of general structure **2** constituted a particularly useful series.[4,5] In an attempt to more closely define the factors controlling the potency of these oxazole derivatives, we have prepared a variety of alkyl, alkenyl, and heterosubstituted oxazoles and determined their antibacterial activity *in vitro*.

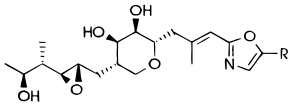
In carrying out this study of structure−activity relationships, our strategy was 3-fold. First we sought to investigate the effect of chain length in 5-alkyloxazoles bearing a carboxylic acid or ester functionality. Second we sought to extend this study to alkenyl analogues to investigate the effect of increased conjugation and rigidity. Third we set out to alter the electronic nature of the oxazole ring by the synthesis of 5-heterolinked systems and to compare these with the corresponding carbon counterparts.

Chemistry

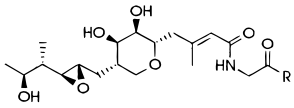
5-Alkyl-substituted oxazoles **2a**−**f** were prepared from monic acid **1b** by the modified Robinson−Gabriel Synthesis (Scheme 1), utilized previously in the synthesis of 1-normon-2-yloxazoles[5] (normonyl = 3-[5(*S*)-(2(*S*),3-(*S*)-epoxy-5(*S*)-hydroxy-4(*S*)-methylhexyl)-3(*R*),4(*R*)-dihydroxytetrahydropyran-2(*S*)-yl]-2-methylprop-1(*E*)-en-1-yl). The required α-amino ketones **5a**−**d** were prepared by reaction of the corresponding α-bromo ketones **4a**−**d** with potassium phthalimide, followed by liberation of the hydrobromide salt of the amine with concentrated acid (Scheme 2). The α-amino ketones prepared in this way were sufficiently pure for the use in the reaction with the isobutoxyformic anhydride of monic acid.



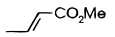
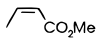
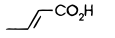
1(a) R = $(CH_2)_8CO_2H$
(b) R = H

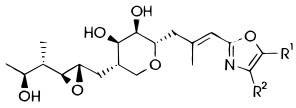


(2)



(3)

	R		R
(a)	$-CH_2CH_3$	(m)	H
(b)	$-(CH_2)_3CH_3$	(n)	$-CO_2^-Na^+$
(c)	$-(CH_2)_3CO_2CH_3$	(o)	
(d)	$-(CH_2)_8CO_2CH_3$	(p)	
(e)	$-(CH_2)_3CO_2^-Na^+$	(q)	$-OCH_2CH_3$
(f)	$-(CH_2)_8CO_2^-Na^+$	(r)	-OPh
(g)	-CHO	(s)	$-SCH_2CH_3$
(h)	$-CH_2OH$	(t)	-SPh
(i)		(u)	
(j)		(v)	
(k)		(w)	$-OCO_2CH_2CH_3$
(l)		(x)	$-CO_2CH_3$



(9) (a) R^1 = $R^2 = CO_2CH_3$

(b) $R^1 = OCH_3$ $R^2 = CO_2CH_3$

Compounds bearing a carboxylic acid functionality (**2e,f**) were prepared by hydrolysis of the corresponding methyl ester (**2c,d**). In the case of **2f**, this was carried

† The approved generic name for pseudomonic acid is Mupirocin.
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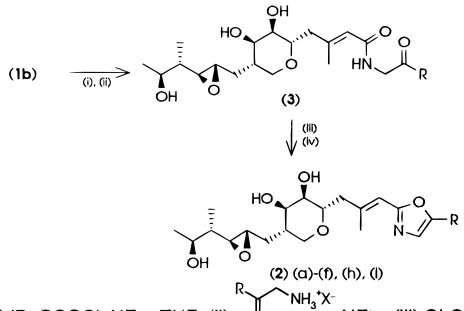
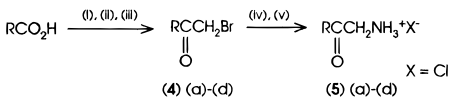
Scheme 1

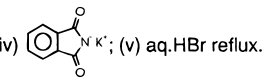


Reagents: (i) iBuOCOCl, NEt_3, THF; (ii) NEt_3; (iii) Cl_3CCOCl, Pyridine, 4-DMAP, CH_2Cl_2; (iv) K_2CO_3, MeOH.

Scheme 2

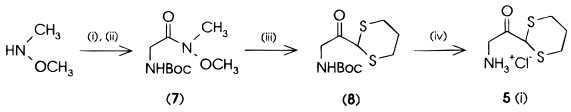


Reagents: (i) $(COCl)_2$, DMF, CH_2Cl_2; (ii) CH_2N_2, Et_2O; (iii) aq.HBr;



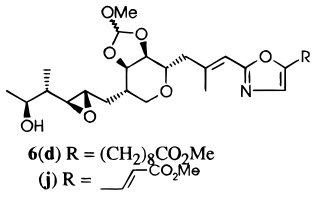
(iv); (v) aq.HBr reflux.

Scheme 3



Reagents: (i) NEt_3, DCCl, DMF; (ii) N-tBoc glycine; (iii)  THF, -70°C; (iv) MeOH, conc.HCl.

out by protecting the glycol as the cyclic ortho ester **6d** followed by hydrolysis with sodium hydroxide.[6] Alternatively, the ester could be hydrolyzed enzymatically using either bakers' yeast or the protease enzyme Subtilisin Carlsberg.[7]

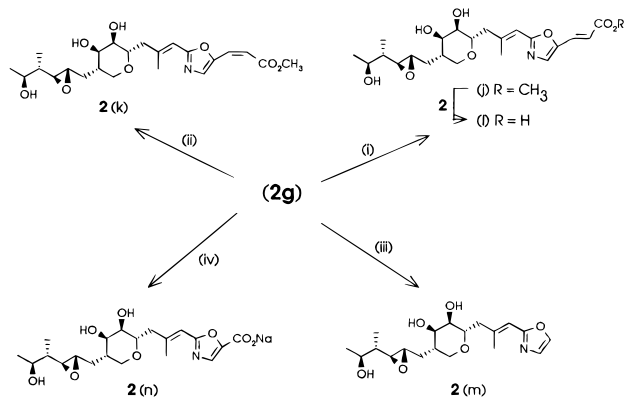


6(d) R = $(CH_2)_8CO_2Me$
(j) R =

Our strategy for the synthesis of alkenyloxazoles was *via* the aldehyde **2g**. We envisaged that double-bond formation *via* Wittig methodology would lead to a variety of alkenyl derivatives.

The first approach to **2g** was *via* the (hydroxymethyl)-oxazole **2h**, which was prepared from monic acid and 1-amino-3-hydroxypropan-2-one hydrochloride according to Scheme 1. However, in our hands, difficulties were encountered in attempted oxidation of **2h** to the aldehyde **2g** and we therefore sought another approach using the dithiane group as a masked aldehyde. The required oxazole **2i** was synthesized by the modified Robinson−Gabriel synthesis (Scheme 1). Preparation of the required α-amino ketone **5i** was *via* the method of Weinreb,[8] in which the anion of dithiane was reacted with the *N*-methyl-*N*-methoxyamide **7** (Scheme 3). Deblocking of the masked aldehyde was accomplished *via*

Scheme 4



Reagents: (i) $Ph_3P{=}CHCO_2CH_3$, CH_2Cl_2; (ii) $(CF_3CF_2O)_2PCH_2CO_2CH_3$, K_2CO_3, 18-crown-6, $PhCH_3$; (iii) $(Ph_3P)_3RhCl$, benzene, reflux; (iv) $NaClO_2$, resorcinol, tBuOH, NaH_2PO_4.

the method of Corey[9] using *N*-chlorosuccinimide and silver nitrate.

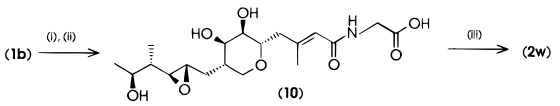
The aldehyde **2g** proved to be a versatile synthetic intermediate for the synthesis of a variety of oxazole derivatives (Scheme 4). Reaction with (carbomethoxymethylene)triphenylphosphorane gave the (*E*)- and (*Z*)-alkenes **2j** and **2k** in a 6:1 ratio. Protection of the diol as the cyclic ortho ester **6j** followed by hydrolysis with sodium hydroxide gave the acid **2l**, which, after chromatography, was still contaminated with a small amount of the *Z* isomer. Using the Clark Still modification[10] of the Horner−Emmons olefination, it was possible to prepare the (*Z*)-alkenyloxazole **2k** selectively. It was of particular interest to us to prepare the parent oxazole ring system **2m** to understand the effect of 5-substituents on the ring, and the aldehyde **2g** provided a convenient route to this, *via* decarbonylation with Wilkinson's catalyst.[11]

The 5-carboxylic acid **2n**, important for comparison with the alkenyl and alkyl carboxylic acids, was prepared by oxidation with sodium chlorite in the presence of resorcinol[12] using a buffered system. Although pseudomonic acid derivatives are sensitive to acid,[13] this buffered system proved to be an extremely mild oxidative procedure.

The synthesis of 5-heterosubstituted oxazoles was investigated, again *via* the dehydrative cyclization (Scheme 1), using as starting material the corresponding glycine ester or amide. Cyclization of the substituted glycinamide **3o** under the standard conditions, however, gave the 4,5-disubstituted derivative **9a**. This presumably arose by initial formation of the 4-(trichloroacetyl)-oxazole followed by methanolysis under the reaction conditions. This electrophilic attack to form 4-acylated derivatives has been noted previously by Fleury and coworkers.[14] 4-Substitution could be avoided, however, by the use of triphenylphosphine/tetrachloromethane as the dehydrating agent,[5] and this technique was used in the preparation of oxazoles **2o**−**t**.

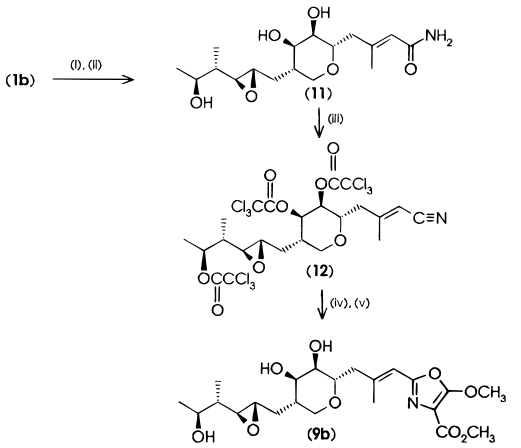
Oxidation of the sulfides **2s,t** to the corresponding sulfoxides **2u,v** was carried out with *m*-chloroperoxybenzoic acid. To prevent acid-catalyzed rearrangement of the nucleus, a two-phase buffered system of dichloromethane/ saturated aqueous sodium bicarbonate was used. The carbonate **2w** was prepared from the glyci-

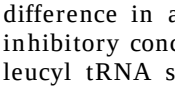
Scheme 5



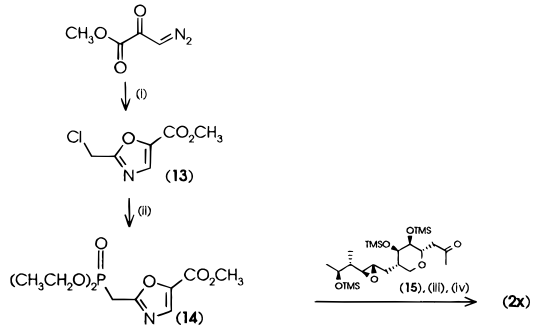
Reagents: (i) iBuOCOCl, NEt_3, THF; (ii) $NH_2CH_2CO_2H$; (iii) EtOCOCl, NEt_3, THF.

Scheme 6



Reagents: (i) iBuOCOCl, NEt_3, THF; (ii) NH_3 (g); (iii) Cl_3CCOCl, Pyridine, 4-DMAP; (iv) $Rh_2(OAc)_4$ (cat), PhH,  ; (v) MeOH, K_2CO_3.

Scheme 7



Reagents: (i) $ClCH_2CN$, PhH, $Cu(acac)_2$, reflux; (ii) $P(OCH_2CH_3)_3$, reflux; (iii) LDA, -70°C - room temp.; (iv) H^+/H_2O/THF

namide **10** on treatment with ethyl chloroformate (Scheme 5).

An alternative strategy for the synthesis of oxazoles involves a formal 1,3-dipolar cycloaddition of a transition-metal stabilized carbenoid species to a nitrile.[16,17] To this end, monic acid **1b** was converted to the protected nitrile **12** *via* dehydration of the corresponding amide **11** (Scheme 6). Reaction of this with methyl diazomalonate in the presence of a catalytic amount of rhodium(**II**) acetate gave the 4-(methoxycarbonyl)-5-methoxyoxazole (**9b**). However, reaction with ethyl diazopyruvate failed to yield any of the desired 5-ethoxycarbonyl analogue.

For the synthesis of the (methoxycarbonyl)oxazole **2x**, the (chloromethyl)oxazole **13** was prepared by a 1,3-dipolar cycloaddition using copper *bis*(acetyl acetonate) as catalyst[16] and converted to the phosphonate **14** as shown in Scheme 7. Reaction of this with the ketone **15** under the previously-described Horner−Wittig conditions[4] gave the (methoxycarbonyl)oxazole **2x**. Attempted synthesis of **2x** *via* the dehydrative cyclization route was not possible due to the instability of the α-amino ketone **5x**.

Results and Discussion

Compounds **2a**−**x** and **9a,b** were tested against a range of Gram-positive and Gram-negative bacteria using a standard agar dilution procedure, and the minimum inhibitory concentration (MIC in $\mu g\ mL^{-1}$) determined. The results are reported in Table 1, and the data for pseudomonic acid (**1a**) given for comparison.

Taking as the base level the activity of the parent oxazole **2m**, it can be seen that the activity of derivatives can be improved by the addition of a substituent of the required lipophilicity. For example, enhanced activity is obtained with the butyl side chain **2b**, with an alkyl-linked ester **2c**, or by the lipophilic dithiane unit **2i**. However, with the very polar acid substituent **2n**, activity is lost.

Lipophilicity is clearly an important factor in the activity of these analogues, since it is believed that there is no active transport mechanism for the uptake of pseudomonic acid derivatives into bacterial cells.[18] In the case of the parent oxazole **2m**, dithiane **2i**, and acid **2n**, the lipophilicity appears to be responsible for the difference in activity in whole cells, since when the inhibitory concentration was determined against isoleucyl tRNA synthetase from *Staphylococcus aureus* Oxford[19] all were found to inhibit the enzyme with IC_{50}s within the range 29−40 ng mL^{-1} . The effect of this optimum lipophilicity can also be seen in the ester series (**2x,c**,**d**) where the optimal chain length is three methylene groups, and in the acid series (**2n,e**,**f**) where very poor activity is observed until a chain length of eight methylene groups is reached. In the alkyl series, the butyl substituent (**2b**) shows increased activity over the ethyl analogue (**2a**). The insertion of a double bond between the oxazole and ester or acid moiety was investigated with the synthesis of compounds (**2j**−**l**), but no increase in potency was noted with the increased conjugation.

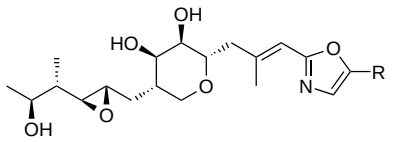
It is known that the electronic nature of the oxazole ring can be altered by electron-withdrawing or -donating substituents at C-5,[20] and this was probed with the O-, N-, and S-linked oxazoles. The N-linked system **2o** offered no improvement over the parent oxazole; however, this derivative was found to be unstable in solution.[21] The more stable analogue **2p** offered no improvement however. 5-O-Substitution **2q,r** did, however, offer an improvement over the parent compound, the *O*-ethyl derivative **2q** having comparable activity to the butyloxazole **2b**. However, with the carbonate **2w**, activity was lost.

The alkylthio analogue **2s** was less active than the corresponding O-linked counterpart **2q**, as was the corresponding sulfoxide **2u**, indicating no relationship between electron-donating ability of the 5-substituent and potency of the compounds. Again, in the arylthio series **2t,v**, no relationship between electron-donating ability and activity was seen.

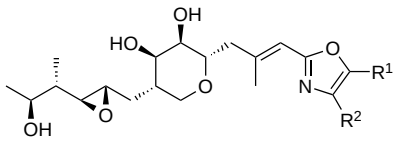
The 5-formyl and 5-hydroxymethyl analogues **2g, h** again showed no improvement over the parent system. 4,5-Disubstitution (**9a,b**) was clearly detrimental to activity.

In conclusion, we have shown that for a range of C-5-substituted 1-normonyloxazoles, alteration of the elec-

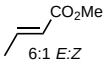
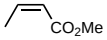
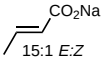
Table 1. Biological Activity of 5−Substituted Oxazoles **2a**−**x**, 4,5-Disubstituted Oxazoles **9a,b**, and Pseudomonic Acid (**1a**)



2a-x



9a,b

			MIC (μg mL−1)				
no.	R (R[1])	R[2]	*Haemophilus influenzae* Q1	*Moraxella catarrhalis* 1502	*Staphylococcus aureus* Oxford NCTC 6571	*Streptococcus pyogenes* CN10	*Streptococcus pneumoniae* PU7
1a			0.03	0.25	0.25	0.13	0.25
2a	CH_2CH_3		2	16	2	NT[h]	16
2b	$(CH_2)_3CH_3$		1	4	1	0.5	4
2c	$(CH_2)_3CO_2Me$		1[a]	2	1	0.5	4
2d	$(CH_2)_8CO_2Me$		4	64	4	4	8
2e	$(CH_2)_3CO_2Na$		8[a]	32	32	64	64
2f	$(CH_2)_8CO_2Na$		4	8	4	1	4
2g	CHO		4	8	2	16	64
2h	CH_2OH		2	8	32	32	NG[g]
2i			1	0.5	1	1	4
2j	 6:1 *E:Z*		0.5	NT[h]	2	4[d]	1
2k			0.25[a]	8	8	16	16
2l	 15:1 *E:Z*		16	16	64	64	64
2m	H		2	4	16	32	128[b]
2n	CO_2Na		>128	>128	>128	>128	>128
2o			0.5	8[e]	8	4	8
2p			16[f]	32	16	16	32
2q	OCH_2CH_3		0.5	4	2	2	2
2r	OPh		8[f]	16	8	8	16
2s	SCH_2CH_3		1	8	8	4	8
2t	SPh		8	8	16[c]	4	32
2u			0.13	16[e]	8	8	4
2v			2	16	16	4	16
2w	$OCO_2CH_2CH_3$		32	32	>128	>128	>128
2x	CO_2CH_3		1	8	4	8	8
9a		CO_2Me	2	NG	16	128	32
9b	OCH_3	CO_2Me	128	>128	>128	>128	>128

[a] *H. influenzae* WY21. [b] *S. pneumoniae* 1629. [c] *S. aureus* Russell. [d] *S. pyogenes* BCA. [e] *M. catarrhalis* H. [f] *H. influenzae* H128. [g] NG = no bacterial growth. [h] NT = not tested.

tronic nature of the oxazole ring by incorporation of a heteroatom link at C-5 or by increasing the conjugation by the preparation of alkenyl derivatives offers no advantages over an alkyl-linked system. The activity of acid-containing derivatives is highly dependent on chain length. Optimum activity lies with lipophilic derivatives such as the dithiane system **2i** or the alkyl ester **2c**. However, in none of the analogues prepared did the activity approach that of pseudomonic acid (**1a**) itself. Further results on 5-aryl-substituted oxazoles will be reported elsewhere.

Experimental Section

Melting points were determined on a Reichert apparatus and are uncorrected. Infrared spectra were determined either in dichloromethane on a Philips PU 9706 spectrophotometer or in KBr on a Perkin-Elmer PE 983 spectrophotometer. NMR spectra were recorded on a Bruker AC-250F or a JEOL GX-270 spectrometer. Chemical shifts are expressed in ppm (δ) relative to internal tetramethylsilane. Mass spectra were obtained on a VG ZAB mass spectrometer. All organic phases were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure with a Büchi rotary evaporator. Merck Kieselgel 60 (<230 mesh ASTM) was used for column chromatography unless otherwise stated. Polar, water-soluble compounds were purified by chromatography on the hydrophobic absorption resin Diaion HP20SS (Mitsubishi Chem. Corp), eluting with water/THF mixtures. Tetrahydrofuran (THF) was dried by distillation from calcium hydride followed by distillation from sodium in the presence of benzophenone.

Target compounds were obtained as gums or freeze-dried solids and were pure by ^{1}H NMR, ^{13}C NMR, and HPLC at two wavelengths. Elemental composition was determined by high-

resolution mass spectrometry (HRMS). The HPLC system was developed to detect acid- or base-catalyzed rearrangement products of the epoxide, which would be undetected by elemental analysis. HPLC was performed on a Waters Associates instrument using a C_{18} μ-Bondapak reverse-phase column with pH 4.5 0.05 M ammonium acetate buffer−methanol solutions as eluant. Detection was by UV at 240 nm and at the λ_{max} of the test compound.

General Method of Preparation of Monamides 3. To a solution of monic acid in dry THF (5 mL/mmol) at 0 °C were added triethylamine (1.1 equiv) and isobutyl chloroformate (1 equiv). After 0.5 h at 0 °C the appropriate ammonium salt (1 equiv) and triethylamine (1 equiv) were added, and the reaction mixture was stirred at 0 °C for 3 h. Ethyl acetate was added and the solution washed with aqueous $NaHCO_3$ and brine, then dried ($MgSO_4$), and evaporated under reduced pressure. The resulting residue was purified by chromatography eluting with 0−6% methanol in dichloromethane to yield pure amide.

General Method of Preparation of Oxazoles 2 via Dehydrative Cyclization. Trichloroacetyl chloride (9 equiv) was added to a solution of monamide, 4-(dimethylamino)-pyridine (few crystals/mmol), and pyridine (20 equiv) in dichloromethane (10 mL/mmol), and the mixture was cooled in an ice bath. After 0.5 h the solution was washed with aqueous $NaHCO_3$ and then evaporated under reduced pressure. The resulting residue was dissolved in methanol (5 mL/mmol) and the solution cooled to 0 °C before addition of potassium carbonate (3 equiv). After 15 min at 0 °C, brine and ethyl acetate were added, and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate, and the combined extracts were washed with brine, dried ($MgSO_4$), and then evaporated under reduced pressure. The resulting residue was chromatographed on silica (0−10% methanol in dichloromethane) to give pure oxazole.

***N*-(2-Oxobutyl)monamide (3a).** The general procedure was followed on a 5.0 mmol scale using 1-aminobutan-2-one (prepared *in situ* from the hydrochloride, 618 mg, 5.0 mmol, and triethylamine) to give **3a** after column chromatography (305 mg, 0.74 mmol, 15%): IR (film) 3400, 1720, 1660, and 1630 cm^{-1}; UV (EtOH) λ_{max} 222 nm (ϵ_m 13 830); ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, J = 7 Hz, 17-H_3), 1.12 (3H, t, J = 7 Hz, 4-H_3), 1.22 (3H, d, J = 7 Hz 14-H_3), 1.36 (1H, q, J = 7 Hz, 12-H), 1.72 (2H, m, 9-H_2), 2.02 (1H, m, 8-H), 2.18 (3H, s, 15-H_3), 2.24 (1H, dd, J = 14, 8 Hz, 4-H), 2.50 (3H, m, 4-H′ and 3′-H_2), 2.72 (1H, dd, J = 8, 2 Hz, 11-H), 4.17 (2H, d, J = 5 Hz, 1′-H_2), 5.76 (1H, s, 2-H), 6.47 (1H, t, J = 4.0 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 7.5 (C-4′), 12.6 (C-17), 18.9 (C-15), 20.8 (C-14), 31.6 (C-9), 33.4 (C-3′), 39.6 (C-8), 42.5 (C-4), 42.7 (C-12), 48.6 (C-1′), 55.6 (C-10), 61.0 (C-11), 65.3 (C-16), 68.8 (C-6), 70.4 (C-7), 70.9 (C-13), 74.5 (C-5), 119.4 (C-2), 152.2 (C-3), 167.4 (C-1), 206.9 (C-2′); MS (EI, m/z) 413 (M^+, 1), 169 (98), 111 (100); HRMS calcd for $C_{21}H_{35}NO_7$ 413.2413, found 413.2399.

5-Ethyl-2-(1-normon-2-yl)oxazole (2a). *N*-(2-Oxobutyl)-monamide (**3a**) (960 mg, 2.32 mmol) was cyclized as described in the general procedure to give **2a** after column chromatography (589 mg, 1.49 mmol, 64%): IR (film) 3400, 1720, 1660, 1370, and 910 cm^{-1}; UV (EtOH) λ_{max} 266 nm (ϵ_m 5010); ^1H NMR (CD_3OD) δ 0.94 (3H, d, J = 7 Hz, 17-H_3), 1.20 (3H, d, J = 7.0 Hz, 14-H_3), 1.26 (3H, t, J = 7 Hz, 2″-H_3), 1.40 (1H, m, 12-H), 1.69 (2H, m, 9-H_2), 2.19 (3H, s, 15-H_3), 2.28 (1H, dd, 4-H, J = 15.0, 10.0 Hz), 2.50 (1H, m, 4-H′), 2.70 (3H, m, 11-H and 1″-H_2), 2.81 (1H, dt, J = 2.6, 6.0 Hz, 10-H), 6.13 (1H, s, 2-H), and 6.78 ppm (1H, s, 4′-H); ^{13}C NMR (CD_3OD) δ 12.1, 12.2, (C-17, -2″), 19.5, 19.8 (C-15, -1″), 20.3 (C-14), 33.0 (C-9), 41.6 (C-8), 43.7 (C-12, -4), 56.9 (C-10), 61.2 (C-11), 66.3 (C-16), 70.0 (C-6), 70.7 (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-3′); MS (EI m/z) 395 (M^+, 1), 151 (100); HRMS calcd for $C_{21}H_{33}NO_6$ 395.2308, found 395.2309.

***N*-(2-Oxohexyl)monamide (3b).** The general procedure was followed on a 5 mmol scale using 1-aminohexan-2-one (prepared *in situ* from the hydrochloride, 758 mg, 5.0 mmol and triethylamine) to give **3b** after column chromatography (1.05 g, 2.38 mmol, 48%): IR (film) 3400, 1720, 1660, 1640, and 910 cm^{-1}; UV (EtOH) λ_{max} 222 nm (ϵ_m 12 030); ^1H NMR ($CDCl_3$) δ 0.92 (6H, m, 17-H_3 and 6′-H_3), 1.21 (3H, d, J = 7.0 Hz, 14-H_3), 2.19 (3H, s, 15-H_3), 2.24 (1H, dd, J = 15.0, 10.0 Hz, 4-H), 2.48 (2H, t, J = 8.0 Hz, 3′-H_2), 2.57 (1H, d, J = 15.0 Hz, 4′-H), 2.72 (1H, dd, J = 8.0, 1.0 Hz, 11-H), 2.80 (1H, dt, J = 1.0, 4.0 Hz, 10-H), 3.50−4.00 (6H, m), 4.18 (2H, d, J = 6 Hz, 1′-H_2), 5.75 (1H, s, 2-H), and 6.42 (1H, t, J = 5 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 12.6 (C-17), 13.8 (C-6′), 18.9 (C-15), 20.8 (C-14), 22.3 (C-5′), 25.7 (C-4′), 31.7 (C-9), 39.6 (C-8), 40.0 (C-3′), 42.6 (C-4), 42.8 (C-12), 49.0 (C-1′), 55.6 (C-10), 61.1 (C-11), 65.4 (C-16), 68.8 (C-6), 70.4 (C-7), 71.0 (C-13), 75.0 (C-5), 119.5 (C-2), 152.1 (C-3), 167.3 (C-1), and 206.4 ppm (C-2′); MS (EI m/z) 442 (MH^+, 2), 441 (M^+, 2), 197 (69), and 111 (74); HRMS calcd for $C_{23}H_{39}NO_7$ 441.1716, found 441.2727.

5-Butyl-2-(1-normon-2-yl)oxazole (2b). *N*-(2-Oxohexyl)-monamide (**3b**) (940 mg, 2.13 mmol) was cyclized as described in the general procedure to give, after column chromatography, oxazole **2b** (182 mg, 0.43 mmol, 20%): IR ($CHCl_3$) 3600−3200, 2960, 2930, 1720, 1660, 1640, and 1450 cm^{-1}; UV (EtOH) λ_{max} 265 (ϵ_m 12 980) and 222 nm (ϵ_m 6240); ^1H NMR ($CDCl_3$) δ 1.22 (3H, d, J = 7.0 Hz, 14-H_3), 1.37 (3H, m, 3″-H_2 and 12-H), 1.61 (2H, q, J = 7 Hz, 2″-H_2), 1.72 (2H, t, J = 5 Hz, 9-H_2), 2.01 (1H, m, 8-H), 2.21 (3H, s, 15-H_3), 2.38 (1H, m, 4-H), 2.63 (3H, m, 1″-H_2 and 4-H), 2.71 (1H, dd, J = 8, 2 Hz, 11-H), 2.82 (1H, m, 10-H), 3.4−4.0 (6H, m), 6.16 (1H, s, 2-H), and 6.72 (1H, s, 4′-H); ^{13}C NMR ($CDCl_3$) δ 12.6 (C-17), 13.7 (C-4″), 19.3 (C-15), 20.7 (C-14), 22.1 (C-3″), 25.2 (C-2″), 29.6 (C-1″), 31.7 (C-9), 39.6 (C-8), 42.7 (C-12, -4), 55.6 (C-10), 61.1 (C-11), 65.5 (C-16), 68.8 (C-6), 70.3 (C-7), 70.9 (C-13), 75.3 (C-5), 113.2 (C-2), 122.3 (C-4′), 145.5 (C-3), 151.9 (C-3′), 160 (C-1); MS (EI, m/z) 423 (M^+, 5), 180 (7), 179 (100); HRMS calcd for $C_{23}H_{37}NO_6$ 423.2621, found 423.2616.

***N*-(5-(Methoxycarbonyl)-2-oxopentyl)monamide (3c).** 4-(Methoxycarbonyl)butyryl chloride[22] (6.65 g, 40 mmol) was added slowly in a small volume of ether to a freshly prepared ethereal solution of diazomethane (∼3.4 g, 80 mmol) at 0 °C with stirring. The mixture was then stirred at 0 °C for 1.5 h. After this time concentrated hydrobromic acid (50 mL) was added dropwise with ice bath cooling. The mixture was stirred at room temperature for 30 min. Brine and ethyl acetate were then added, and the organic layer was separated, washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to give the crude methyl 6-bromo-5-oxohexanoate as an oil (5.75 g, 63%).

This material (5.5 g, 24 mmol) was heated together with potassium phthalimide (4.8 g, 0.25 mmol) in DMF (50 mL) at 100 °C for 30 min. After cooling, ethyl acetate was added to the mixture, and the solution was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was taken up in concentrated hydrobromic acid (80 mL) and heated under reflux for 3 h and then left at room temperature overnight. The solution was filtered and the filtrate evaporated under reduced pressure to give a brown oil which was taken up in methanol and concentrated hydrobromic acid (1 mL). After heating under reflux for 5 h the mixture was evaporated to give a brown oily solid which was triturated with acetone to yield a cream-colored solid, [5-(methoxycarbonyl)-2-oxopentyl]ammonium bromide (4.7 g, 80%); ^1H NMR (DMSO-d_6, DCl) δ 3.9 (2H, s, H-1), 3.6 (3H, s, CH_3), 2.4 (4H, m, H-3 and H-5), 1.8 (2H, m, H-4).

This ammonium salt (8.85 g) was using in the general method on a 39 mmol scale to give **3c** as a colorless oil (4.8 g, 24%) after purification by chromatography on silica: IR (film) 3400, 1730, 1600, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.33 (1H, t, NH), 5.75 (1H, s, H_2), 4.17 (2H, d, H_1′), 3.67 (3H, s, OCH_3), 2.18 (3H, s, CH_3-15), 1.22 (3H, d, CH_3-14), 0.93 (3H, d, CH_2-17); MS (EI, m/z) 485 (M^+, 5), 454 (14), 327 (17), 309 (11), 241 (65); HRMS calcd for $C_{24}H_{39}NO_9$ 485.2624, found 485.2628.

5-(3-(Methoxycarbonyl)propyl)-2-(1-normon-2-yl)oxazole (2c). *N*-(5-(Methoxycarbonyl)-2-oxopentyl)monamide (**3c**) (4.37 g) was cyclized as described in the general procedure to give, after column chromatography, the oxazole **2c** (1.55 g): IR (film) 3410, 1740, 1660, and 1600 cm^{-1}; UV (EtOH) λ_{max} 266 nm (ϵ_m 14 877); ^1H NMR δ ($CDCl_3$) 6.77 (1H, s, H4′), 6.17 (1H, s, H2), 3.67 (s, OCH_3), 2.61 (2H, t, H1″), 2.37 (2H, t, H3″), 2.23 (3H, s, CH_3-15), 1.23 (3H, d, J = 6.4 Hz CH_3-14), 0.93 (3H, d, J = 7.0 Hz, CH_3-17); ^{13}C NMR ($CDCl_3$) δ 173.5 (ester

CO), 160.9 (C-1), 150.4 (C-5′), 145.5 (C-3), 123.2 (C-4′), 113.3 (C-2), 75.2 (C-5), 71.3 (C-13), 70.5 (C-7), 70.0 (C-6), 65.4 (C-16), 61.3 (C-11), 55.6 (C-10), 51.6 (OCH_3), 42.8 and 42.7 (C-4 and -12), 39.5 (C-8), 33.1 (C-3″), 31.7 (C-9), 24.9 (C-1″), 23.0 (C-2″), 20.8 (C-14), 19.4 (C-15), 12.7 (C-17); MS (EI, *m/z*) 467 (M^+, 5), 436 (4), 286 (19), 259 (20), 223 (100); HRMS calcd for $C_{24}H_{37}NO_8$ 467.2519, found 467.2517.

***N*-(10-(Methoxycarbonyl)-2-oxodecyl)monamide (3d).** Methyl 11-bromo-10-oxoundecanoate (1.47 g, 5 mmol) was heated with potassium phthalimide (1.06 g, 5.5 mmol) in dry DMF (20 mL) at 100 °C for 30 min. The reaction mixture was cooled, diluted with ethyl acetate (60 mL), washed with saturated aqueous $NaHCO_3$ (3 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and evaporated to a pale yellow solid.

The crude phthalimido derivative was heated to reflux with concentrated hydrobromic acid (40 mL) for 3 h. The mixture was cooled, filtered to remove a dark brown solid, and evaporated under reduced pressure. Acetone (100 mL) was added to the residue and the mixture allowed to stand in the refrigerator overnight. The resultant white solid was collected by filtration and dried *in vacuo* to give [10-(methoxycarbonyl)-2-oxodecyl]ammonium bromide (**5d**), which was not purified further (0.996 g, 64%): IR (Nujol) 3450, 3150 (sh), 1730, 1580, and 1460 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.25−1.65 (m, CH_2), 2.21−2.65 (4H, m, CH_2), 3.60 (3H, s, CH_3), 3.98 (2H, br s, C*H*NH_3^+) and 8.20 (3H, br s, N*H*$_3^+$).

This material (0.840 g, 2.7 mmol) was reacted with the mixed anhydride of monic acid (2.7 mmol) as described in the general method to give *N*-(10-(methoxycarbonyl)-2-oxodecyl)-monamide (**3d**) as a colorless glassy solid (0.500 g, 33%): IR (CH_2Cl_2) 3620, 3430, 1735, 1670, and 1640 cm^{-1}; UV (EtOH) λ_{max} 221 nm (ϵ_m 15 401); ^1H NMR ($CDCl_3$) *inter alia* δ 0.93 (3H, d, J = 6.9 Hz, 17-H_3), 1.21 (3H, d, J = 6.2 Hz, 14-H_3), 2.17 (3H, s, 15-H_3), 3.67 (3H, s, OCH_3), 4.16 (2H, d, J = 4.6 Hz, 1′-H_2), 5.76 (1H, s, 2-H), and 6.58 (1H, t, NH); ^{13}C NMR ($CDCl_3$) δ 206.2 (C-2′), 174.4 (C-10′), 167.1 (C-1), 152.1 (C-3), 119.5 (C-2), 74.9 (C-5), 70.4 (C-7), 68.8 (C-6), 65.4 (C-16), 61.2 (C-11), 55.6 (C-10), 51.5 (OCH_3), 49.0 (C-1′), 42.8 and 42.6 (C-12 and −4), 40.3 (C-3′), 39.55 (C-8), 34.06 (C-10′), 31.66 (C-9), 29.1, 29.0 and 24.9 (*C*H_2 in side-chain), 20.8 (C-14), 18.9 (C-15), and 12.7 (C-17); MS (EI, *m/z*) 555 (M^+, 10), 311 (100); HRMS calcd for $C_{29}H_{49}NO_9$ requires 555.3407, found 555.3418.

5-(8-(Methoxycarbonyl)octan-1-yl)-2-(1-normon-2-yl)-oxazole (2d). (10-(Methoxycarbonyl)-2-oxodecyl)monamide (4.0 g, 7.2 mmol) was cyclized under the conditions described in the general method to give **2d** as a colorless oil after workup and chromatography (1.49 g, 37%): IR (CH_2Cl_2) 3610, 3560, 3420, 1735, and 1665 cm^{-1}; UV (EtOH) λ_{max} 266 nm (ϵ_m 16 100); ^1H NMR ($CDCl_3$, *inter alia*) δ 0.92 (3H, d, J = 6.9 Hz, 17-H_3), 1.21 (3H, d, J = 6.2 Hz, 14-H_3), 2.21 (3H, s, 15-H_3), 3.66 (3H, s, OCH_3), 6.16 (1H, s, 2-H), and 6.71 (1H, s, oxazole-H); ^{13}C NMR ($CDCl_3$) δ 174.3 (C═O), 160.5 (C-1), 151.7 and 145.0 (C-3 and -5′), 122.4 (C-4′), 113.3 (C-2), 71.2 and 70.3 (C-13 and -7), 68.8 (C-6), 65.4 (C-16), 61.3 (C-11), 55.5 (C-10), 51.4 (CO_2CH_3), 42.7 (C-12), 42.6 (C-4), 39.4 (C-8), 34.0 (C-8″), 31.6 (C-9), 29.1, 29.0, 28.9, 27.5, 25.5 and 24.9 (side-chain CH_2s), 20.8 (C-14), 19.3 (C-15), and 12.7 (C-17); MS (EI, *m/z*) 537 (M^+, 6), 293 (100); HRMS calcd for $C_{29}H_{47}NO_8$ 537.3302, found 537.3275.

Sodium 5-(3-Carboxylatopropyl)-2-(1-normon-2-yl)oxazole (2e). 5-(3-(methoxycarbonyl)propyl)-2-(1-normon-2-yl)-oxazole (**2c**) (100 mg), DMF (1 mL), bakers' yeast (5.0 g), and phosphate buffer (pH 7) were stirred at room temperature for 18 h and then filtered through Kieselguhr. The filtrate was evaporated under reduced pressure, and the residue was taken up in methanol and filtered. The filtrate was evaporated, and this residue was dissolved in water containing $NaHCO_3$ (54 mg). This aqueous solution was washed with dichloromethane, then acidified (2 M HCl) to pH 4, and extracted with ethyl acetate. The ethyl acetate was dried ($MgSO_4$) and evaporated to give a gum which was taken up in water (6 mL) containing $NaHCO_3$ (22 mg). The product (**2e**) was obtained after chromatography on HP20SS and freeze-drying as a white solid, (46 mg, 45%): UV (EtOH) λ_{max} 266 nm (ϵ_m 9896); ^1H NMR (CD_3OD) 6.61 (1H, s, 4′-H), 6.13 (1H, s, 2-H), 2.19 (3H, s, 15-H_3), 1.2 (3H, d, 14-H_3), and 0.94 (3H, d, 17-H_3); MS (FAB, *m/z*) 476 (MH^+, 100), 454 (88).

Sodium 5-(8-Carboxylatooctan-1-yl)-2-(1-normon-2-yl)-oxazole (2f). (i)Preparation via Sodium Hydroxide Hydrolysis. 2d (0.600 g, 1.1 mmol) was dissolved in trimethyl orthoformate (6.0 mL) and treated with a catalytic amount of *p*-toluenesulfonic acid, and the mixture was stirred at room temperature for 30 min. The resultant solution was diluted with ethyl acetate (60 mL) and washed with saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL), and the organic phase was dried ($MgSO_4$) and evaporated to an oil. This was dissolved in THF (6 mL), 1 M aqueous NaOH (6 mL) was added, and the mixture was heated to 65 °C for 4 h. The reaction mixture was cooled, the organic solvent was removed under reduced pressure, and the pH was adjusted to 7.0 with concentrated HCl. Methanol (25 mL) was added, the pH was adjusted to 2.0 with 2M HCl, and the solution was stirred at room temperature for 15 min. The pH was then raised to 9.95 with 1 M NaOH , ethyl acetate (60 mL) and water (60 mL) were added, and the pH was adjusted to 3.0 with 2 M HCl. The layers were separated, and the aqueous layer was extracted into ethyl acetate (2 × 60 mL). The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure, redissolved in THF (30 mL), and treated with a solution of $NaHCO_3$ (100 mg, 1.2 mmol) in water (60 mL). The solution was concentrated under reduced pressure and purified by chromatography on HP20SS, eluting with 0−8% THF in water. Product-containing fractions were combined and freeze-dried to give **2f** as a white solid (147 mg, 24%): IR (KBr) 3400, 1655, 1565 cm^{-1}; UV (H_2O) λ_{max} 267 nm (ϵ_m 15 760); ^1H NMR (D_2O, *inter alia*) δ 0.91 (3H, d, J = 7.0 Hz, 17-H_3), 1.17 (3H, d, J = 6.5 Hz, 14-H_3), 2.33 (3H, s, 15-H_3), 6.07 (1H, s, 2-H), and 6.75 (1H, s, oxazole-H); ^{13}C NMR (D_2O) δ 12.3 (C-17), 19.6 (C-15), 19.3 (C-14), 26.1, 27.3, 28.2, 29.8, 29.9, 30.0 and 30.3 (CH_2 in side chain), 32.3 (C-9), 38.9 (side chain), 40.2 (C-8), 43.2 and 42.9 (C-12 and C-4), 57.9 (C-10), 62.5 (C-11), 66.1 (C-16), 69.8 (C-6), 70.8 and 70.9 (C-13 and C-7), 76.0 (C-5), 114.0 (C-2), 123.1 (C-4′), 147.1 and 153.7 (C-3 or C-5′), 161.6 (C-1), and 184.8 (*C*O_2Na); MS (FAB, *m/z*) 546 (MH^+, 71), 524 (MH^+ free acid, 100).

(ii) Preparation via Enzymic Hydrolysis. 2f Was also prepared by hydrolysis of the corresponding methyl ester (0.27 g, 0.5 mmol) with protease enzyme (Subtilisin Carlsberg) at 37 °C in 1% DMSO/water keeping the pH at 7.5 over a period of 20 h. After extraction, **2f** was obtained as a white solid on precipitation from ether (0.083 g, 31%).

***N*-(3-Hydroxy-2-oxopropyl)monamide (3h).** To a solution of monic acid (0.344 g, 1 mmol) in dry THF (5 mL) at 0 °C were added triethylamine (0.15 mL, 1.1 equiv) and isobutyl chloroformate (0.14 mL, 1 equiv). After 0.5 h at 0 °C the reaction mixture was filtered and evaporated to a white foam. This was dissolved in dry methanol (10 mL), cooled to 0 °C, and treated with triethylamine (0.15 mL, 1.1 equiv) and a solution of 1-amino-3-hydroxypropan-2-one hydrochloride (0.125 g, 1 mmol) in methanol (10 mL). The reaction mixture was stirred at 0 °C for 0.5 h and at room temperature for a further 1.5 h. Silica gel (Merck Kieselgel 60, ca. 5 g) was added and the mixture evaporated to dryness. This was then applied to a column of Kieselgel 60. Elution with 0−15% methanol in dichloromethane gave **3h** as a pale yellow foam (0.107 g, 26%): IR (KBr) 3427, 1733, 1660 (sh), 1628 cm^{-1}; UV (EtOH) λ_{max} 221 nm (ϵ_m 13 496); ^1H NMR (CD_3OD, *inter alia*) δ 0.95 (3H, d, J = 7.0 Hz, 7-H_3), 1.21 (3H, d, J= 6.5 Hz, 14-H_3), 2.14 (3H, s, 15-CH_3), 2.72 (1H, dd, J = 2.0, 7.5 Hz, 11-H), 4.12 (2H, s, NHC*H*$_2$CO), 4.26 (2H, s, CO*CH*$_2$OH), 5.83 (1H, s, 2-H);^{13}C NMR (CD_3OD) δ 12.3 (C-17), 19.0 (C-15), 20.4 (C-14), 33.0 (C-9), 41.7 (C-8), 43.8 (C-4), 44.8 (C-12), 46.9 (C-2′), 57.0 (C-10), 61.3 (C-11), 66.4 (C-16), 67.5 (*C*H_2OH), 70.0 (C-6), 70.8 (C-13), 71.7 (C-7), 76.2 (C-5), 120.5 (C-2), 153.5 (C-3), 169.9 (C-1), 208.1 (C═O); MS (FAB, *m/z*) 438 (MNa^+, 41), 416 (MH^+, 100).

5-(Hydroxymethyl)-2-(1-normon-2-yl)oxazole (2h). Trichloroacetyl chloride (2.1 mL, 12 equiv) was added to a solution of *N*-(3-hydroxy-2-oxopropyl)monamide (**3h**) (0.690 g, 1.66 mmol), 4-(dimethylamino)pyridine (few grains), and pyridine (1.5 mL) in dichloromethane (15 mL), and the mixture

was cooled in an ice bath. After 0.5 h, the reaction mixture was diluted with dichloromethane (10 mL) and washed with water and brine. The organic phase was dried ($MgSO_4$) and evaporated to a yellow foam, which was redissolved in methanol (15 mL) and treated with potassium carbonate (0.916 g, 4 molar equiv) at 0 °C. After 0.5 h the reaction mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous phase was neutralized to pH 7.0 with 5 M HCl and continuously extracted with ether for 60 h. The organic extracts were combined and evaporated, and the crude product was purified by chromatography on Kieselgel 60. Elution with 0−12% methanol in dichloromethane gave **2h** as a yellow foam (0.060 g, 9%): IR (KBr) 3405, 1662, 1510, 1451 cm^{-1}; UV (EtOH) λ_{max} 263 nm (ϵ_m 11 889); ^1H NMR (CD_3OD, *inter alia*) δ 0.93 (3H, d, J = 7.1 Hz, 17-H_3), 1.18 (3H, d, J = 6.4 Hz, 14-H_3), 2.33 (3H, d, J = 0.6 Hz, 15-H_3), 4.58 (2H, s, CH_2OH), 6.18 (1H, s, 2-H), 7.02 (1H, s, oxazole-H); ^{13}C NMR (CD_3OD) δ 12.3 (C-17), 19.6 (C-15), 20.3 (C-14), 33.0 (C-9), 41.7 (C-8), 43.7 (C-12) and C-4), 55.1 (CH_2OH), 56.9 (C-10), 61.3 (C-11), 66.4 (C-16), 70.0 (C-6), 70.7 (C-9), 77.6 (C-13), 76.2 (C-5), 113.6 (C-2), 125.3 (C-4′), 149.1 (C-3), 152.0 (C-5′), 163.2 (C-1); MS 397 (M^+, 8), 153 (100); HRMS calcd for $C_{20}H_{31}NO_7$ 397.2101, found 397.2116.

***N*-α-(tert-Butoxycarbonyl)glycine *N*-Methyl-*N*-methoxyamide (7).** A suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (7.34 g, 75 mmol) in DMF (40 mL) was treated at 0 °C with triethylamine (10.4 mL, 7.6 g, 75 mmol). After 0.5 h the resulting slurry was treated over 10 min with a solution of *N*,*N*′-dicyclohexylcarbodiimide (15.45 g, 75 mmol) in THF (70 mL), and then a solution of *N*-(*tert*-butoxycarbonyl)-glycine (12.97 g, 74 mmol) in THF (50 mL). The reaction mixture was stirred at 0 °C for a further 2 h and then at room temperature for 20 h. The resulting slurry was poured onto ethyl acetate (300 mL) and filtered, and the filtrate was washed with acidified brine and brine, dried ($MgSO_4$), and evaporated to a white solid (17 g). Recrystallization from ethyl acetate−hexane gave the product as a white crystalline solid (6.22 g, 38%): mp 100−101 °C. The mother liquor was concentrated and set aside in the fridge overnight. A second crop of white crystals was collected (4.04 g, 25%): mp 98−100 °C; IR (CH_2Cl_2) 3400, 2940, 1715, 1675, 1500, and 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (9H, s, Bu^t), 3.20 (3H, s, NCH_3), 3.70 (3H, s, OCH_3), 4.10 (1H, d, J = 5 Hz, CH_2CO), and 5.25 (1H, bs, N*H*); MS 219 (MH^+, 90), 163 (100); HRMS calcd for $C_9H_{18}N_2O_4$ 218.1267, found 218.1269.

1-(1,3-Dithian-2-yl)-2-(*tert*-butoxycarbonylamino)ethan-1-one (8). To a solution of 1,3-dithiane (5.76 g, 44 mmol) in dry THF (20 mL) at −30 °C under an argon atmosphere was added a solution of *n*-butyllithium (1.55 M, 25 mL, 40 mmol). After 30 min the resultant mixture was cooled to −70 °C, and a solution of *N*-α-(*tert*-butoxycarbonyl)glycine *N*-methyl-*N*-methoxyamide (**7**) (2.62 g, 12 mmol) in dry THF (50 mL) added over a period of 20 min. The resulting yellow solution was allowed to warm to −10 °C over a period of 2 h. The solution was poured into a stirred mixture of ether (200 mL) and aqueous sodium dihydrogen phosphate buffer (1 M, 200 mL). The layers were separated, and the ether layer was washed with buffer (100 mL) and saturated aqueous sodium chloride (100 mL), dried, and evaporated. The resulting oil was purified by chromatography on Kieselgel 60, eluting with 0−30% ethyl acetate/hexane mixtures. **8** was obtained as a colorless oil which solidified on standing (3.63 g, containing 14% ethyl acetate by weight, 94% yield): IR (CH_2Cl_2) 3430, 1710, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (9H, s, $(CH_3)_3$), 2.0−2.2 (2H, m, CH_2), 2.46−2.76 (2H, m, CH_2), 3.10−3.40 (2H, m, CH_2), 4.20−4.28 (3H, m, CH_2CO and $HC(S\text{-})_2$), 5.27 (1H, br s, N-H).

2-Amino-1-(1,3-dithian-2-yl)ethanone Hydrochloride (5i). 1-(1,3-Dithian-2-yl)-2-((*tert*-butoxycarbonyl)amino)ethanone (9.2 g, 33.2 mmol) was suspended in methanol (60 mL), cooled to 0 °C, and treated with concentrated hydrochloric acid (16.5 mL). The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The resulting precipitate was collected by filtration, washed with a small amount of cold methanol, and dried *in vacuo*. The filtrate was allowed to stand at room temperature for 16 h to give a second crop of product which was collected, washed, and dried. Concentration of the filtrate under reduced pressure gave a third crop of the solid amine hydrochloride (combined yield 5.67 g, 84%): IR (Nujol) 1715, 1510, 1435 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.75−2.10 (2H, m, CH_2), 2.40−3.22 (4H, m, 2 × CH_2), 4.10 (2H, s, $NHCH_2$), 5.02 (1H, s, $HC(S\text{-})_2$), 8.55 (1H, br s, N-H); MS (EI, *m*/*z*) 177 (M^+, 10), 119 (100); HRMS calcd for $C_6H_{11}S_2ON$ 177.0282, found 177.0284.

***N*-[2-(1,3-Dithian-2-yl)-2-oxoethyl]monamide (3i).** To a solution of monic acid (17.2 g, 50 mmol) in dry THF (250 mL) at 0 °C were added triethylamine (7.64 mL, 55 mmol) and isobutyl chloroformate (50 mmol). After 20 min, the reaction mixture was filtered and the filtrate evaporated under reduced pressure. The residue was redissolved in methanol (150 mL) and treated with triethylamine (7.64 mL, 55 mmol) followed by a solution of 2-amino-1-(1,3-dithian-2-yl)ethanone hydrochloride (**5i**) (10.0 g, 50 mmol) in methanol (150 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h and then evaporated to a yellow oil. This was dissolved in ethyl acetate (300 mL) and washed with water (200 mL) and saturated brine. The aqueous phase was back-extracted with ethyl acetate (3 × 100 mL) and dichloromethane (3 × 100 mL). The combined organic extracts were dried and evaporated. The crude product was chromatographed on Kieselgel 60 eluting with 0−8% methanol in dichloromethane. Product-containing fractions were combined and evaporated to give **3i** as a pale yellow foam (12.99 g, 52%): IR (CH_2Cl_2) 3420, 1715, 1650, 1640 cm^{-1}; UV (EtOH) λ_{max} 220 nm (ϵ_m 17 730); ^1H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 7.0 Hz, 17-H_3), 1.22 (3H, d, J = 6.2 Hz, 14-H_3), 2.20 (3H, s, 15-H_3), 4.34 (1H, s, $HC(S\text{-})_2$), 4.40 (2H, d, J = 5.0 Hz, $NHCH_2$), 5.80 (1H, s, 2-H), 6.63 (1H, t, J = 5.0 Hz, N-H); ^{13}C NMR ($CDCl_3$) δ 12.8 (C-17), 19.0 (C-15), 20.9 (C-14), 25.0 (CH_2), 26.2 (2 × CH_2), 3.71 (C-9), 39.6 (C-8), 42.7 (C-4), 42.6 (C-12), 44.2 ($CH(S\text{-})_2$), 46.5 ($NHCH_2$), 55.7 (C-10), 61.2 (C-11), 65.4 (C-16), 66.9 (C-6), 70.5 (C-13), 75.0 (C-5), 119.4 (C-2), 152.6 (C-3), 167.4 (C-1), 199.0 (C═O); MS (EI, *m*/*z*) 503 (M^+, 0.2%), 485 ($M^+ - H_2O$, 0.2), 119 (100); HRMS calcd for $C_{23}H_{37}NO_9S_2$ 503.2011, found 503.2022.

5-(1,3-Dithian-2-yl)-2-(1-normon-2-yl)oxazole (2i). Cyclization of the monamide **3i** (9.5 g, 18.9 mmol) as described in the general method gave **2i** as a pale yellow foam (2.68 g, 28%): IR (CH_2Cl_2) 3600, 3550, 3400, 1680 cm^{-1}; UV (EtOH) λ_{max} 267 nm (ϵ_{max} 17 190); ^1H NMR ($CDCl_3$) δ 0.95 (3H, d, J = 6.9 Hz, 17-H_3), 1.22 (3H, d, J = 6.2 Hz, 14-H_3), 2.25 (3H, s, 15-H_3), 5.14 (1H, s, $HC(S\text{-})_2$), 6.20 (1H, s, 2-H), 7.10 (1H, s, oxazole-H); ^{13}C NMR ($CDCl_3$) δ 12.7 (C-17), 19.5 (C-15), 20.6 (C-14), 25.2 (CH_2), 29.3 (2 × CH_2), 31.7 (C-9), 39.0 and 39.5 (C-8 and $CH(S\text{-})_2$), 42.6 (C-12 and C-4), 55.6 (C-10), 61.3 (C-11), 65.3 (C-16), 66.7 (C-6), 70.3 (C-13), 71.3 (C-7), 75.1 (C-5), 112.9 (C-2), 125.3 (C-4′), 147.5 (C-3 or C-5′), 148.0 (C-3 or C-5′), 161.4 (C-1); MS (EI, *m*/*z*) 485 (M^+, 66), 241 (100); HRMS calcd for $C_{23}H_{35}NO_6S_2$ 485.1906, found 485.1897.

5-Formyl-2-(1-normon-2-yl)oxazole (2g). A solution of **2i** (0.240 g, 0.5 mmol) in acetonitrile (1 mL) was added to a mixture of *N*-chlorosuccinimide (0.467 g, 3.5 mmol), silver nitrate (0.637 g, 3.75 mmol), and 2,6-lutidine (0.93 mL, 8 mmol) in acetonitrile (12 mL) and water (3 mL) at 0 °C. After 15 min the reaction mixture was warmed to room temperature, stirred for a further 15 min, and then treated sequentially with saturated aqueous sodium sulfite (0.5mL), saturated aqueous sodium carbonate (0.5 mL), and saturated sodium chloride (0.5 mL) at 1 min intervals. 1:1 Hexane:dichloromethane (10 mL) was then added, and the mixture was filtered through Kieselguhr. The filtrate was separated, the aqueous phase was extracted with dichloromethane, and the combined organic extracts were dried and evaporated. The residue was chromatographed on Kieselgel 60, eluting with 0−8% methanol in dichloromethane. Product-containing fractions were combined and evaporated to give **2g** as a white foam (72 mL, 36%): IR (CH_2Cl_2) 3600, 3550, 3400, 1680, 1650 cm^{-1}; UV (CH_3CN) λ_{max} 298 nm (ϵ_m 18 410); ^1H NMR ($CDCl_3$) δ 0.96 (3H, d, J = 7.0 Hz, 17-H_3), 1.23 (3H, d, J = 6.2 Hz, 14-H_3), 2.37 (3H, s, 15-H_3), 2.43 (1H, dd, J = 9.2, 14.8 Hz, 4′-H), 6.33 (1H, s, 2-H), 7.91 (1H, s, oxazole-H), 9.73 (1H, s, C*H*O); ^{13}C NMR ($CDCl_3$) δ 12.7 (C-17), 20.1 (C-15), 20.8 (C-14), 31.6 (C-9), 39.6 (C-8), 42.6 (C-12), 43.2 (C-4), 55.6 (C-10), 61.3 (C-11), 65.5 (C-16),

68.8 (C-6), 70.3 (C-13), 71.3 (C-7), 75.0 (C-5), 112.3 (C-2), 139.1 (C-4′), 148.2 (C-3 or C-5′), 154.3 (C-3 or C-5′), 165.4 (C-1), 176.3 (CHO); MS (EI, *m*/*z*) 395 (M^+, 0.2), 151 (55); HRMS calcd for $C_{20}H_{29}NO_7$ 395.1944, found 395.1948.

5-(2-(Methoxycarbonyl)ethenyl)-2-(1-normon-2-yl)oxazole (2j). 5-Formyl-2-(1-normon-2-yl)oxazole (**2g**) (50 mg) was dissolved in dry dichloromethane (1 mL) and treated with (carbomethoxymethylene)triphenylphosphorane (64 mg, 1.5 equiv) and the mixture stirred at room temperature for 3 h. The crude solution was applied to a column of Kieselgel 60 and eluted with 0−6% methanol in dichloromethane to give **2j** (45 mg, 77%) as a mixture of isomers. Fractions richest in the *E*-isomer were combined and evaporated to a white foam (26 mg) containing **2j** as a 6:1 ratio of *E*:*Z* isomers at the newly-formed double bond: IR (CH_2Cl_2) 3400, 1710, 1670 cm^{-1}; UV (EtOH) λ_{max} 324 (ϵ_m 25 751), 228 nm (11 656); ^1H NMR ($CDCl_3$) δ 0.96 (3H, d, J = 7.0 Hz, 17-H_3), 1.22 (3H, d, J = 6.3 Hz, 14-H_3), 2.30 (3H, s, 15-H_3), 3.82 (3H, s, CO_2CH_3), 6.28 (1H, s, 2-H), 5.87 and 6.80 (2H, AB q, J = 12.7 Hz, C*H*═C*H* minor isomer), 6.30 and 7.46 (2H, AB q, J = 15.6 Hz, C*H*═C*H* major isomer), 7.29 (oxazole-H major isomer), 8.28 (oxazole-H minor isomer); MS (EI, *m*/*z*) (M^+, 12), 207 (100); HRMS calcd for $C_{22}H_{33}NO_8$ 451.2206, found 451.2146.

5-[(*E*)-2-Carboxyethenyl]-2-(1-normon-2-yl)oxazole (2l). 5-(2-(Methoxycarbonyl)ethenyl)-2-(1-normon-2-yl)oxazole (6:1 ratio of *E*:*Z* isomers, 100 mg) was dissolved in trimethyl orthoformate (1.2 mL) and treated with *p*-toluene sulfonic acid (few grains). After stirring at room temperature for 40 min the mixture was diluted with ethyl acetate (10 mL), washed with aqueous $NaHCO_3$ (10 mL) and saturated brine (5 mL), dried ($MgSO_4$), and evaporated to an oil. This was dissolved in methanol (2 mL) and treated with 1 M sodium hydroxide solution (1 mL) and the mixture was stirred at room temperature for 40 min. The pH was adjusted to 2.0 with 5 N hydrochloric acid and the mixture stirred for 15 min. The pH was then adjusted to 9.5 with 1 M sodium hydroxide solution and the mixture stirred at room temperature for 1 h until formate removal was complete. The methanol was evaporated under reduced pressure and the pH adjusted to 3.5 with 5 M HCl. The product was extracted into ethyl acetate. The organic phase was layered with water, and the pH was adjusted to 7.0 with saturated sodium hydrogen carbonate. The aqueous phase was concentrated and applied to a column of HP20SS. Elution with 20% THF in water gave **2l** as the free acid. Product-containing fractions were combined and freeze-dried to a white fluffy solid (24 mg, 25%) which was shown to contain a 15:1 ratio of *E*:*Z* isomers: IR (KBr) 3413, 2971, 2331, 1691, 1636 cm^{-1}; UV (H_2O) λ_{max} 223 (ϵ_m 11 730), 313 nm (20 495); ^1H NMR (*inter alia*, D_2O) δ 0.91 (3H, d, J = 7.0 Hz, 17-H_3), 1.15 (3H, d, J = 6.4 Hz, 14-H_3), 2.13 (3H, s, 15-H_3), 2.84 (1H, dd, J = 2.5, 8.1 Hz, 11-H), 5.95 and 6.64 (2H, minor isomer, AB q, J = 12.8 Hz, CH═CH *Z* isomer), 6.13 (1H, s, 2-H), 6.18 and 7.37 (2H, major isomer AB q, J = 15.7 Hz, CH═CH *E* isomer), l7.31 (1H, s, oxazole-H); MS (EI, *m*/*z*) 437 (M^+, 2), 193 (20); HRMS calcd for $C_{22}H_{31}NO_8$ 437.2050, found 437.2056.

5-[(*Z*)-2-(Methoxycarbonyl)ethenyl]-2-(1-normon-2-yl)-oxazole (2k). To a solution of **2g** (109 mg, 0.25 mmol) in dry THF (4 mL) was added triethylamine (141 μL), chlorotrimethylsilane (127 μL 1.0 mmol), and 4-(*N*,*N*-dimethylamino)-pyridine (few crystals). The reaction mixture was stirred at room temperature for 2.5 h, filtered, and evaporated to a colorless oil. 18-Crown-6 (0.792 g, 3 mmol) was stirred with finely-ground potassium carbonate (0.207 g, 1.5 mmol) in dry toluene (2 mL) at room temperature for 1.5 h, cooled to −20 °C, and treated with a solution of the tris(trimethylsilyl)-protected oxazole in dry toluene (2 mL) and bis(2,2,2-trifluoroethyl) [(methoxycarbonyl)methyl]phosphonate (0.053 mL, 0.25 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 30 min. Ethyl acetate (10 mL) and water (10 mL) were added, the layers were separated, and the organic phase was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. The crude product was redissolved in THF (8 mL) and water (2 mL) and treated with 5 M HCl (8 drops). After 5 min the reaction mixture was quenched with saturated $NaHCO_3$. Ethyl acetate (10 mL) was added, and the mixture was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography on Kieselgel 60, eluting with 0−6% methanol in dichloromethane to give **2k** as a white foam (65 mg, 58%): IR (CH_2Cl_2) 3600, 3550, 3400, 1740, 1630 cm^{-1}; UV (EtOH) λ_{max} 224 (ϵ_m 7290), 324 nm (26 640); ^1H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 7.0 Hz, 17-H_3), 1.22 (3H, d, J = 6.2 Hz, 14-H_3), 2.27 (3H, s, 15-H_3), 3.78 (3H, s, CO_2CH_3), 5.87 and 6.70 (2H, 2 × d, J = 12.7 Hz, CH═CH), 6.25 (1H, s, 2-H), 8.29 (1H, s, oxazole-H); ^{13}C NMR ($CDCl_3$) δ 12.7 (C-17), 19.7 (C-15), 20.8 (C-14), 31.6 (C-9), 39.5 (C-8), 42.8 (C-12), 42.9 (C-4), 51.5 (OCH_3), 55.6 (C-10), 61.3 (C-11), 65.4 (C-16), 68.8 (C-6), 70.4 (C-13), 71.3 (C-7), 75.2 (C-5), 112.7 (C-2), 116.1 (═*C*H), 127.4 (═*C*H), 134.1 (C-4′), 146.6 (C-3 or C-5′), 49.2 (C-3 or C-5′), 162.2 (C-1), 166.1 (CO_2Me); MS (EI, *m*/*z*) 451 (M^+, 10), 207 (100); HRMS calcd for $C_{23}H_{33}NO_8$ 451.2206, found 451.2206.

2-(1-Normon-2-yl)oxazole (2m). 5-Formyl-2-(1-normon-2-yl)oxazole (**2g**) (122 mg, 0.3 mmol) was converted to the tris-(trimethylsilyl) ether as described in the synthesis of **2k**. This was dissolved in dry benzene (5 mL) and treated with tris-(triphenylphosphine)rhodium(I) chloride (0.273 g, 0.3 mmol), and the mixture was heated to reflux for 2.5 h. The reaction mixture was cooled in an ice bath, treated with ethanol (15 mL), and filtered through Kieselguhr. The filtrate was evaporated to a brown oil, ethanol (15 mL) was added, and the process was repeated. Evaporation of the filtrate gave the crude protected product which was purified by column chromatography on Kieselgel 60, eluting with 0−30% ethyl acetate in hexane. Product-containing fractions were combined and evaporated to an oil (36 mg), which was dissolved in THF (3 mL) and water (0.75 mL) and treated with 5 M HCl (2 drops). After stirring at room temperature for 5 min the mixture was quenched with aqueous $NaHCO_3$. The product was extracted into ethyl acetate (2 × 15 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to an oil. Chromatography on Kieselgel 60 eluting with 0−8% methanol in dichloromethane gave **2m** as a white foam (16 mg, 14%): IR (CH_2Cl_2) 3610, 3580, 3400, 1660 cm^{-1}; UV (EtOH) λ_{max} 257 nm (ϵ_m 15 103); ^1H NMR ($CDCl_3$) δ 0.92 (3H, d, J = 7.0 Hz, 17-H_3), 1.21 (3H, d, J = 6.3 Hz, 14-H_3), 2.25 (3H, s, 15-H_3), 2.38 (1H, dd, J = 8.7, 14.6 Hz, 4-H), 2.72 (1H, dd, J = 2.2, 7.8 Hz, 11-H), 2.81 (1H, dt, J = 2.2, 5.6 Hz, 10-H), 6.25 (1H, s, 2-H), 7.12 [1H, s, 4′-H (resolution enhancement shows J = 1 Hz)], 7.66 [1H, s, 5′-H (resolution enhancement shows J = 1 Hz)]; ^{13}C NMR ($CDCl_3$) δ 12.7 (C-17), 18.6 (C-15), 19.4 (C-14), 31.7 (C-9), 39.5 (C-8), 42.7 (C-4), 42.8 (C-12), 55.6 (C-10), 61.3 (C-11), 65.4 (C-16), 68.9 (C-6), 70.4 (C-13), 71.4 (C-7), 75.2 (C-5), 113.1 (C-2), 127.5 (C-4′), 137.2 (C-5′), 146.6 (C-3), 161.8 (C-1); MS (EI, *m*/*z*) 367 (M^+, 7), 1233 (100); HRMS calcd for $C_{19}H_{29}NO_6$ 367.1995, found 367.2006.

Sodium 5-Carboxylato-2-(1-normon-2-yl)oxazole (2n). 5-Formyl-2-(1-normon-2-yl)oxazole (**2g**) (50 mg, 0.124 mmol) was dissolved in *tert*-butyl alcohol (1 mL) together with resorcinol (138 mg, 10 equiv). A solution of sodium chlorite (14 mg, 0.16 mmol) in 0.5 M sodium dihydrogen phosphate buffer (0.126 mL) was added dropwise, and the mixture was stirred at room temperature for 0.5 h. The reaction was quenched with saturated $NaHCO_3$ and the solution concentrated under reduced pressure. The resultant aqueous solution was washed with ethyl acetate (3 × 5 mL) and the aqueous phase applied to a column of HP20SS. Elution with water gave the product **2n**. Product-containing fractions were freeze-dried to a fluffy white solid (30 mg). To remove residual resorcinol from this sample, the product was rechromatographed and freeze-dried to a white solid (17 mg, 30%): IR (KBr) 3401, 1609, 1514, 1380 cm^{-1}; UV (H_2O) λ_{max} 273 nm (ϵ_m 19 325); ^1H NMR (D_2O) δ 0.92 (3H, d, J = 7.1 Hz, 17-H_3), 1.17 (3H, d, J = 6.4 Hz, 14-H_3), 1.34−1.48 (1H, m, 12-H), 1.63 (1H, ddd, J = 6.8, 7.7, 14.5 Hz, 9-H), 1.78 (1H, ddd, J = 5.4, 6.7, 14.5 Hz, 9′-H), 2.00−2.10 (1H, m, appears as eight lines, 8-H), 2.18 (3H, d, J = 1.2 Hz, 15-H_3), 2.43 (1H, dd, J = 9.9, 15.0 Hz, 4-H), 2.70 (1H, ddd, J = 14.7, 1.95, 1.0 Hz, 4′-H), 2.87 (1H, dd, J = 2.6, 8.0 Hz, 11-H), 3.02 (1H, ddd, J = 2.6, 5.4, 6.4 Hz, 10-H), 3.55 (1H, dd, J = 3.2, 11.3 Hz, 16-H), 3.59 (1H, dd, J = 3.1, 7.8 Hz, 6-H), 3.81−3.98 (4H, m, 16′-H, 5-H, 7-H and 13-

H), 6.20 (1H, s, 2-H), 7.52 (1H, s, oxazole-H); MS (FAB, thioglycerol, *m/z*) 456 (MNa^+), 434 (MH^+, 100).

***N*-(2-Oxo-2-piperidin-1-ylethyl)monamide (3o).** *N*-(((*tert*-Butoxycarbonyl)amino)acetyl)piperidine (0.484 g) was dissolved in trifluoroacetic acid (4 mL) and stirred at room temperature for 1 h. The solution was then evaporated to dryness to give *N*-(aminoacetyl)piperidine trifluoroacetate salt (0.5 g). This was reacted with the isobutoxyformic anhydride of monic acid on a 2 mmol scale according to the general procedure to give **3o** as a foam (0.48 g, 51%): IR (CH_2Cl_2) 3610, 3390, 1660, and 1630 cm^{-1}; UV (EtOH) λ_{max} 217 nm (ϵ_m 19 300); ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, 17-H_3), 1.23 (3H, d, 14-H_3), 1.5−1.70 (6H, m, $(CH_2)_3$), 2.20 (3H, s, 15-H_3), 3.5−4.0 (4H, m, CH_2NCH_2), 4.15 (2H, m, $NHCH_2$), 5.80 (1H, s, 2H), and 6.80 (1H, m, NH); ^{13}C NMR ($CDCl_3$) δ 166.9 and 166.4 (C-2 and -2′), 151.2 (C-3), 120.0 (C-2), 74.6 (C-5), 71.4 (C-13), 70.5 (C-7), 68.7 (C-6), 65.3 (C-16), 61.3 (C-11), 55.3 (C-10), 45.5 (C-1′), 43.2 (C-2″), 42.7 (C-12), 42.5 (C-4), 41.0 (C-6″), 39.4 (C-8), 31.6 (C-9), 26.1 and 25.4 (C-3″ and -5″), 24.3 (C-4″), 20.9 (C-14), 18.9 (C-15) and 12.6 (C-17); MS (EI, *m/z*) 468 (M^+, 7%), 224 (25), 143 (52), and 85 (100); HRMS calcd for $C_{24}H_{40}N_2O_7$ 468.2836, found 468.2828.

4-(Methoxycarbonyl)-2-(1-normon-2-yl)-5-piperidin-1-yloxazole (9a). The amide **3o** (0.15 g) was cyclized according to the general procedure to give the oxazole **9a** as an oil (0.085 g, 52%): IR (CH_2Cl_2) 3610, 3450, 1695, and 1600 cm^{-1}; UV (EtOH) λ_{max} 215 (ϵ_m 8692) and 296 nm (18 627); ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, 17-H_3), 1.23 (3H, d, 14-H_3), 1.41 (6H, m, $(CH_2)_3$), 2.18 (3H, s, 15-H_3), 3.65 (4H, m, CH_2NCH_2), 3.85 (3H, s, CO_2CH_3), and 6.05 (1H, s, 2-H); ^{13}C NMR ($CDCl_3$) δ 162.8 (C-1), 158.9 (CO_2), 150.6 (C-5′), 144.3 (C-3), 112.5 (C-2), 106.0 (C-4′), 75.0 (C-5), 71.2 (C-13), 70.2 (C-7), 68.7 (C-6), 65.3 (C-16), 61.2 (C-11), 55.5 (C-10), 51.4 (OCH_3), 49.4 (C-2″ and −6″), 42.7 (C-12), 42.5 (C-4), 39.3 (C-8), 31.5 (C-9), 25.5 (C-3″ and −5″), 24.0 (C-4″), 20.7 (C-17), 19.3 (C-15) and 12.6 (C-14); MS (EI, *m/z*) 509 (MH^+, 93), and 263 (100); HRMS calcd for $C_{26}H_{40}N_2O_8$ 508.2785, found 508.2773.

5-(Piperidin-1-yl)-2-(1-normon-2-yl)oxazole (2o). *N*-(2-Oxo-2-piperidin-1-yl ethyl)monamide (**3o**) (100 mg, 0.21 mmol) was dissolved in dry acetonitrile (1.5 mL) and treated with triethylamine (0.1 mL), tetrachloromethane (0.14 mL), and triphenylphosphine (0.18 g). After 45 min the reaction mixture was diluted with ethyl acetate (15 mL) and washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) and the organic phase dried ($MgSO_4$) and evaporated. The residue was chromatographed on Kieselgel 60, eluting with 0−40% ethyl acetate in hexane to give **2o** as a pale yellow oil (17 mg, 15%): IR (CH_2Cl_2) 3400, 1635 (sh), 1595 cm^{-1}; UV (EtOH) λ_{max} 311 nm (ϵ_m 5436); ^1H NMR δ 0.93 (3H, d, J = 7.0 Hz, 17-H_3), 1.21 (3H, d, J = 6.4 Hz, 14-H_3), 1.62−1.71 (6H, m, 3 × CH_2), 2.17 (3H, s, 15-H_3), 2.34 (1H, dd, J = 8.5, 14.6 Hz, 4-H), 2.62 (1H, dd, J = 2.7, 14.6 Hz, 4′-H), 2.71 (1H, dd, J = 2.2, 7.8 Hz, 11-H), 2.80 (1H, dt, J = 2.1, 5.7 Hz, 10-H), 3.04−3.10 (4H, m, 2 × CH_2), 6.00 (1H, s, oxazole-H), 6.05 (1H, s, 2-H); MS (EI, *m/z*) 450 (M^+, 58,), 205 (100); HRMS calcd for $C_{24}H_{38}N_2O_6$ 450.2730, found 450.2731.

***N*-[2-Oxo-2-(*N*-methyl-*N*-phenylamino)ethyl]monamide (3p).** The trifluoroacetate salt of 2-amino-*N*-methyl-*N*-phenylacetamide was reacted with the isobutoxyformic anhydride of monic acid on a 3.8 mmol scale according to the general procedure. The product was obtained as a white foam (1.04 g, 56%): IR (CH_2Cl_2) 3400, 1660 (sh), 1640, 1600, 1500 cm^{-1}; UV (EtOH) λ_{max} 223.5 nm (ϵ_m 21 780); ^1H NMR ($CDCl_3$) δ 0.95 (3H, d, J = 7.1 Hz, 17-H_3), 1.24 (3H, d, J = 6.3 Hz, 14-H_3), 2.15 (3H, s, 15-H_3), 2.75 (1H, dd, J = 2.0, 7.6 Hz, 11-H), 2.81 (1H, dt, J = 2.0, 5.7 Hz, 10-H), 3.30 (3H, s, N-CH_3), 5.75 (1H, s, 2-H), 6.71 (1H, t, J = 4.3 Hz, N-H), 7.23−7.28 (2H, m, Ar-H), 7.37−7.49 (3H, m, Ar-H); ^{13}C NMR ($CDCl_3$) δ 12.6 (C-17), 18.9 (C-15), 20.8 (C-4), 31.7 (C-9), 37.6 (C-8), 39.5 (N-CH_3), 41.9 (CH_2CO), 42.5 (C-4), 42.7 (C-12), 55.5 (C-10), 61.1 (C-11), 65.4 (C-16), 66.7 (C-6), 70.4 (C-13), 71.1 (C-7), 74.5 (C-5), 119.7 (C-2), 127.2 (2 × Ar-C), 128.7 (Ar-C), 130.2 (Ar-C), 141.9 (C-N), 151.6 (C-3), 167.2 (C═O), 168.9 (C═O); MS (EI, *m/z*) 490 (M^+, 5), 107 (100); HRMS calcd for $C_{26}H_{38}N_2O_7$ 490.2679, found 490.2683.

5-(*N*-methyl-*N*-phenylamino)-2-(1-normon-2-yl)oxazole (2p). The monamide **3p** (200 mg, 0.4 mmol) was cyclized according to the method described in the preparation of **2o** to give **2p** as a white foam (38 mg, 19%): IR (CH_2Cl_2) 3600, 3550, 1595, 1500 cm^{-1}; UV (EtOH) λ_{max} 240 nm (ϵ_m 12 175), 315 (10 295); ^1H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 7.0 Hz, 17-H_3), 1.24 (3H, d, J = 6.3 Hz, 14-H_3), 2.21 (3H, s, 15-H_3), 2.72 (1H, dd, J = 2.2, 7.9 Hz, 11-H), 2.82 (1H, dt, J = 2.2, 5.6 Hz, 10-H), 3.30 (3H, s, N-CH_3), 6.14 (1H, s, 2-H); 6.58 (1H, s, oxazole-H), 6.94−7.00 (3H, m, Ar-H), 7.27−7.34 (2H, m, Ar-H); ^{13}C NMR ($CDCl_3$) δ 12.6 (C-17), 19.2 (C-15), 20.7 (C-14), 31.6 (C-9), 39.41 and 38.77 (C-8 and N-CH_3), 42.66 (C-4), 42.71 (C-12), 55.5 (C-10), 61.2 (C-11), 65.4 (C-16), 68.9 (C-6), 70.3 (C-13), 71.2 (C-7), 75.1 (C-5), 112.7 and 113.2 (C-2 and C-4′), 116.7 (2 × Ar-C), 121.2 (Ar), 129.1 (2 × Ar), 144.7 (N-C), 146.1 (C-3), 151.9 (C-5′), 156.4 (C-1); MS (EI, *m/z*) 472 (M^+, 57), 227 (100); HRMS calcd for $C_{26}H_{36}N_2O_6$ 472.2573, found 472.2586.

***N*-[(Ethoxycarbonyl)methyl]monamide (3q).** Monic acid (344 mg, 1 mmol) was dissolved in dry THF (15 mL) and treated with triethylamine (0.15 mL, 1 equiv) and isobutyl chloroformate (0.14 mL, 1 equiv). After 20 min the reaction mixture was filtered and the filtrate treated with triethylamine (0.15 mL) and glycine ethyl ester hydrochloride (152 mg, 1.1 equiv). Water (2 drops) was added to achieve complete solution, and the mixture was stirred at room temperature for 30 min. The reaction mixture was evaporated to dryness, dissolved in dichloromethane, dried ($MgSO_4$), and evaporated. The residue was chromatographed on Kieselgel 60, eluting with 0−8% methanol in dichloromethane to give **3q** as a white foam (320 mg, containing 16% triethylamine hydrochloride, 63% overall yield: IR (CH_2Cl_2) 3430, 1736, 1660, 1640, 1606 cm^{-1}; UV (EtOH) λ_{max} 276 nm; ^1H NMR (CD_3OD) δ 0.95 (3H, d, J = 7.1 Hz, 17-H_3), 1.21 (3H, d, J = 6.5 Hz, 14-H_3), 1.28 (3H, t, J = 7.2 Hz, CH_3CH_2), 2.14 (3H, d, 15-H_3), 2.71 (1H, dd, J = 2.0, 7.6 Hz, 11-H), 2.82 (1H, dt, J = 2.0, 5.8 Hz, 10-H), 3.93 (2H, s, $NHCH_2$), 4.19 (2H, q, J = 7.2 Hz, CH_2CH_3, 5.82 (1H, s, 2-H); MS (EI, *m/z*) 411 (M^+, 20), 167 (100); HRMS calcd for: $C_{21}H_{33}NO_7$ 411.2257, found 411.2260.

5-Ethoxy-2-(1-normon-2-yl)oxazole (2q). *N*-[(Ethoxycarbonyl)methyl]monamide (**3q**) (100 mg, containing 0.23 mmol) was dissolved in dry THF (6 mL) and treated with triethylamine (0.16 mL, 1.1 mmol), chlorotrimethylsilane (0.15 mL, 1.1 mmol), and 4-(dimethylamino)pyridine (few crystals). The mixture was stirred at room temperature for 1.5 h, filtered, and evaporated under reduced pressure. The residue was dissolved in acetonitrile (1.2 mL) and treated with triethylamine (0.1 mL, 0.7 mmol), tetrachloromethane (0.14 mL, 1.45 mmol), and triphenylphosphine (0.18 g, 0.68 mmol). The reaction mixture was stirred at room temperature for 2.5 h, diluted with ethyl acetate (10 mL), and washed with $NaHCO_3$ (5 mL) and brine (5 mL). The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in THF (3 mL) and water (0.75 mL), treated with 5 M hydrochloric acid (2 drops), stirred for 5 min at room temperature, and then quenched with aqueous $NaHCO_3$. The product was extracted into ethyl acetate (2 × 7 mL), and the combined organic extracts were washed with brine (7 mL), dried ($MgSO_4$), and evaporated to an oil. This was chromatographed on Kieselgel 60, eluting with 0−6% methanol in dichloromethane to give **2q** as a colorless oil (15 mg, 16%): IR (CH_2Cl_2) 3600, 3550, 3400, 1610 cm^{-1}; UV (EtOH) λ_{max} 276 nm; ^1H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 7.0 Hz, 17-H_3), 1.22 (3H, d, J = 6.2 Hz, 14-H_3), 1.45 (3H, t, J = 7.1 Hz, CH_2CH_3), 2.19 (3H, s, 15-H_3), 2.72 (1H, dd, J = 2.0, 7.8 Hz, 11-H), 4.12 (2H, q, J = 7.1 Hz, CH_2CH_3), 6.05 (1H, s, 2-H), 6.11 (1H, s, oxazole-H); MS (EI, *m/z*) 411 (M^+, 20), 167 (100); HRMS calcd for $C_{21}H_{33}NO_7$ 411.2257, found 411.2260.

***N*-[(Phenyloxycarbonyl)methyl]monamide (3r).** Monic acid (0.688 g, 2 mmol) was converted to the isobutoxyformic anhydride as described in the general method of preparation of monamides. The reaction mixture was filtered and evaporated to dryness, and the residue was redissolved in methanol (30 mL). This was treated with triethylamine (0.30 mL, 1.1 equiv) followed by phenylglycinate hydrobromide (0.464 g, 1 equiv). The reaction mixture was stirred at room temperature for 1.5 h and worked up as described in the general method. After chromatography on Kieselgel 60, eluting with 0−10%

methanol in dichloromethane, **3r** was obtained as a white foam (0.379 g, 40%): IR (CH_2Cl_2) 3570, 3440, 1770, 1670, 1640 cm^{-1}; UV (EtOH) λ_{max} 219 nm (ϵ_m 178 736); ^1H NMR (CD_3OD) δ 0.94 (3H, d, J = 7.5 Hz, 17-H_3), 1.20 (3H, d, J = 6.4 Hz, 14-H_3), 1.33−1.44 (1H, m, appears as 8 lines, 12-H), 2.18 (3H, d, J = 0.7 Hz, 15-H_3), 2.64 (1H, d, J = 14.4 Hz, 4-H), 2.70 (2H, dd, J = 2.1, 7.5 Hz, 11-H), 2.80 (1H, dt, J = 2.1, 5.7 Hz, 10-H), 4.20 (2H, s, CH_2NH), 5.85 (1H, s, 2-H), 7.10−7.14 (2H, m, Ar-H), 7.21−7.27 (1H, m, Ar-H), 7.35−7.42 (2H, m, Ar-H); ^{13}C NMR ($CDCl_3$) δ 12.7 (C-17), 17.0 (C-15), 20.9 (C-14), 21.6 (C-9), 39.6 (C-8), 41.3 (*C*H_2CO), 42.5 (C-4), 42.7 (C-12), 55.6 (C-10), 61.1 (C-11), 65.3 (C-16), 66.8 (C-6), 70.4 (C-7), 71.2 (C-13), 74.9 (C-5), 119.4 (C-2), 121.3 (2 × Ph), 126.2 (Ph), 129.5 (2 × Ph), 150.4 (O-*C*), 152.6 (C-3), 167.6 (C-1), 169.2 (*C*O_2Ph); MS (FAB, 3-NOBA-Na, m/z) 500 (MNa^+, 52), 329, 176 (100).

5-(Phenyloxy)-2-(1-normon-2-yl)oxazole (2r). **3r** (100 mg, 0.2 mmol) was dissolved in dry THF (6 mL) and treated with triethylamine (0.16 mL, 1.1 mmol), chlorotrimethylsilane (0.15 mL, 1.1 mmol), and 4-(dimethylamino)pyridine (few crystals). The mixture was stirred at room temperature for 1.5 h, filtered, and evaporated under reduced pressure. The residue was dissolved in acetonitrile (1.2 mL) and treated with triethylamine (0.1 mL, 0.7 mmol), tetrachloromethane (0.14 mL, 1.45 mmol), and triphenylphosphine (0.18 g, 0.68 mmol). The reaction mixture was stirred at room temperature for 2.5 h, diluted with ethyl acetate (10 mL), and washed with $NaHCO_3$ (5 mL) and brine (5 mL). The organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in THF (3 mL) and water (0.75 mL), treated with 5 M hydrochloric acid (2 drops), stirred for 5 min at room temperature, and then quenched with aqueous $NaHCO_3$. The product was extracted into ethyl acetate (2 × 7 mL), and the combined organic extracts were washed with brine (7 mL), dried ($MgSO_4$), and evaporated to an oil. This was chromatographed on Kieselgel 60, eluting with 0−6% methanol in dichloromethane, to give **2r** as a pale yellow foam (32 mg, 33%): IR (CH_2Cl_2) 3600, 3570, 3420, 1630, 1590 cm^{-1}; UV (EtOH) λ_{max} 270 nm (ϵ_m 14 694); ^1H NMR (CD_3OD) δ 0.95 (3H, d, J = 7.2 Hz, 17-H_3), 1.20 (3H, d, J = 6.4 Hz, 14-H_3), 1.36−1.47 (1H, m, 12-H), 2.15 (3H, s, 15-H_3), 2.24 and 2.32 (1H, 2 × d, AB q, J = 9.5 Hz, 4-H), 2.72 (1H, dd, J = 2.1, 7.6 Hz, 11-H), 2.82 (1H, dt, J = 2.2, 5.8 Hz, 10-H), 6.07 (1H, s, 2-H), 6.53 (1H, s, oxazole-H), 7.10−7.23 (3H, m, Ar-H), 7.37−7.43 (2H, m, Ar-H); MS (EI, m/z) 459 (M^+, 30), 215 (100); HRMS calcd for $C_{25}H_{33}NO_7$ 459.2257, found 459.2246.

***N*-[[(Ethylthio)carbonyl]methyl]monamide (3s).** Monic acid was converted to the isobutoxyformic anhydride on a 5 mmol scale followed by reaction with the trifluoroacetate salt of glycine ethyl thiolester according to the procedure given in the general scheme to give **3s** as a white foam (1.55 g, 70%); IR ($CHCl_3$) 3440, 1665, 1640 (sh), 1500 cm^{-1}; UV (EtOH) λ_{max} 227 nm (ϵ_m 18 866); ^1H NMR ($CDCl_3$) δ 0.95 (3H, d, J = 6.9 Hz, 17-H_3), 1.24 (3H, d, J = 5.8 Hz, 15-H_3), 1.27 (3H, t, J = 7.4 Hz, *C*H_3CH$_2$S), 2.20 (3H, s, 15-H_3), 2.74 (1H, dd, J = 2.1, 7.8 Hz, 11-H), 2.82 (1H, dt, J = 2.1, 8.9 Hz, 10-H), 2.94 (1H, q, J = 7.4 Hz, CH_2S), 4.23 (2H, d, CH_2NH), 5.78 (1H, s, 2-H), 6.40 (1H, br s, N-H); MS (+ve ion FAB, thioglycerol, m/z) 446 (MH^+, 100).

5-(Ethylthio)-2-(1-normon-2-yl)oxazole (2s). The monamide **3s** (445 mg, 1 mmol) was cyclized using the procedure described in the preparation of **2o** to give **2s** as a yellow oil (101 mg, 23%): IR ($CHCl_3$) 3530, 3400, 1650 cm^{-1}; UV (EtOH) λ_{max} 277 nm (ϵ_m 13 785); ^1H NMR ($CDCl_3$) δ 0.95 (3H, d, J = 6.9 Hz, 17-H_3), 1.23 (3H, d, J = 6.3 Hz, 14-H_3), 1.29 (3H, t, J = 7.4 Hz, C*H_3*CH$_2$), 2.27 (3H, s, 15-H_3), 2.77 (2H, q, J = 7.5 Hz, CH$_3$C*H_2*), 6.21 (1H, s, 2-H), 7.26 (1H, s, oxazole-H); MS (EI, m/z) 427 (M^+, 8), 183 (62); HRMS calcd for $C_{21}H_{33}NO_6S$ 427.2029, found 427.2037.

***N*-[[(Phenylthio)carbonyl]methyl]monamide (3t).** Monic acid was converted to the isobutoxyformic anhydride on a 3 mmol scale followed by reaction with the TFA salt of glycine phenyl thiolester according to the procedure given in the general scheme to give **3t** as a white foam (0.592 g, 40%): IR (CH_2Cl_2) 3550, 3440, 1700, 1665, 1638 cm^{-1}; UV (EtOH) λ_{max} 225 nm (ϵ_m 21 790); ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, J = 7.0 Hz, 17-H_3), 1.22 (3H, d, J = 6.2 Hz, 14-H_3), 2.21 (3H, s, 15-H_3), 4.33 (2H, d, J = 5.7 Hz, CH_2), 5.75 (1H, s, 2-H), 6.32 (1H, t, J = 5.6 Hz, NH), 7.42 (5H, s, Ar-H); MS (+ve ion FAB, 3-NOBA-Na, m/z) 516 (MNa^+, 43), 494 (MH^+, 5), 176 (100).

5-(Phenylthio)-2-(1-normon-2-yl)oxazole (2t). The monamide **3t** (198 mg, 0.4 mmol) was cyclized according to the conditions described in the preparation of **2o** to give **2t** as a pale yellow foam (31 mg, 16%); IR (CH_2Cl_2) 3600, 3550, 3440, 1700, 1580 cm^{-1}; UV (EtOH) λ_{max} 272 nm (ϵ_m 16 000); ^1H NMR ($CDCl_3$) δ 0.92 (3H, d, J = 7.0 Hz, 17-H_3), 1.20 (3H, d, J = 6.3 Hz, 14-H_3), 2.24 (3H, s, 15-H_3), 2.50 (1H, dd, J = 2.2, 7.8 Hz, 11-H), 2.79 (1H, dt, J = 2.2, 5.8 Hz, 10-H), 6.20 (1H, s, 2-H), 7.22−7.30 (5H, m, Ar-H), 7.34 (1H, s, oxazole-H); ^{13}C NMR ($CDCl_3$) δ 12.7 (C-17), 19.6 (C-15), 20.8 (C-14), 31.6 (C-9), 39.5 (C-8), 42.8 (C-12 and C-4), 55.6 (C-10), 61.3 (C-11), 65.4 (C-16), 68.9 (C-6), 70.4 (C-7), 71.4 (C-13), 75.1 (C-5), 113.1 (C-2), 127.1 (C-4′), 128.5 (2 × Ar-C), 129.3 (2 × Ar-C), 134.6 (S-C), 135.2 (Ar-C), 140.2 (C-5′), 148.6 (C-3), 165.0 (C-1); MS (EI, m/z) 475 (M^+, 30), 366, 231 (100); HRMS calcd for $C_{25}H_{33}NO_6S$ 475.2029, found 475.2038.

5-(Ethylsulfinyl)-2-(1-normon-2-yl)oxazole (2u). The oxazole **2s** (130 mg, 0.3 mmol) was dissolved in dichloromethane (10 mL). Saturated aqueous $NaHCO_3$ (5 mL) was then added, followed by *m*-chloroperbenzoic acid (75 mg, 0.42 mmol). The reaction mixture was stirred at 0 °C for 20 min and then diluted with dichloromethane (50 mL). The phases were separated, and the organic phase was washed with brine (10 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography on Kieselgel 60, eluting with 5% methanol in dichloromethane to give **2u** as a white foam (41 mg, 30%): IR (CH_2Cl_2) 3550, 3400, 1645 cm^{-1}; UV (EtOH) λ_{max} 273.5 (ϵ_m 19 315); ^1H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 7.0 Hz, 17-H_3), 1.24 (3H, d, J = 6.3 Hz, 14-H_3), 1.30 (3H, t, J = 7.4 Hz, CH$_2$*CH*$_3$), 2.30 (3H, s, 15-H_3), 2.72 (1H, dd, J = 1.6, 8.0 Hz, 11-H), 2.79 (1H, dt, J = 2.0, 5.5 Hz, 10-H), 3.23−3.25 [2H, 2 × q, S(O)CH_2 (2 isomers)], 6.28 (1H, s, 2-H), 7.58 (1H, s, oxazole-H); MS (EI, m/z) 427 (M^+, 4), 366 (38), 121 (100); HRMS calcd for $C_{21}H_{33}NO_7S$ 433.1978, found 433.1979.

5-(Phenylsulfinyl)-2-(1-normon-2-yl)oxazole (2v). The oxazole **2t** (40 mg, 0.084 mmol) was dissolved in dichloromethane (2 mL) and treated with *m*-chloroperbenzoic acid (29 mg of 50−55% pure, 1 equiv) at 0 °C under an argon atmosphere. After 30 min the reaction mixture was treated with saturated aqueous $NaHCO_3$ (3 mL), warmed to room temperature and diluted with dichloromethane (5 mL). The phases were separated, and the organic phase was washed with brine (3 mL), dried ($MgSO_4$), and evaporated. The crude product was chromatographed on Kieselgel 60, eluting with 5% methanol in dichloromethane to give **2v** as a pale yellow foam (13 mg, 31%): IR (CH_2Cl_2) 3600, 3550, 3440, 1645 cm^{-1}; UV (EtOH) λ_{max} 279 nm; ^1H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 7.0 Hz, 17-H_3), 1.23 (3H, d, J = 6.2 Hz, 14-H_3), 2.17 (3H, s, 15-H_3), 2.70 (1H, dd, J = 2.2, 7.8 Hz, 11-H), 2.77−2.83 (1H, m, 10-H), 6.18 (1H, s, 2-H), 7.37 and 7.40 [1H, 2 × s, oxazole-H (2 sulfoxide isomers)], 7.56−7.58 (3H, m, Ar-H), 7.73−7.78 (2H, m, Ar-H); MS (EI, m/z) 491 (M^+, 7), 474 (30), 456 (40), and 366 (100); HRMS calcd for $C_{25}H_{33}NO_2S$ 491.1978, found 491.1975.

***N*-(Carboxymethyl)monamide (10).** The isobutoxy mixed anhydride of monic acid (10 mmol) was converted to **10** on reaction with glycine under the conditions described in the general method for preparation of monamides. The addition of water (10 mL) was required to effect complete solubility. After a reaction time of 1 h, the mixture was concentrated to a colorless oil under reduced pressure, dissolved in water, and applied to a column of HP20SS. Elution with water rapidly eluted the product as its triethylamine salt. Product-containing fractions were combined and freeze-dried to a crisp foam (3.25 g) which was found to be contaminated with 20% monic acid triethylamine salt. This material was purified as follows: 1 g of crude product was dissolved in water (10 mL) and the pH adjusted to 3.0 with 2 M hydrochloric acid. This solution was applied to a column of HP20SS. Elution with 0−4% THF/water mixtures gave the desired product free from monic acid contaminant. Product-containing fractions were combined and freeze-dried to give **10** as a fluffy white solid (overall yield 35%): IR (KBr) 3409, 1734, 1659, 1630, 1534

cm^{-1}; ^1H NMR (D_2O) δ 0.94 (3H, d, J = 7.1 Hz, 17-H_3), 1.18 (3H, d, J = 6.4 Hz, 14-H_3), 1.37−1.50 (1H, m, 12-H), 2.04 (3H, s, 15-H_3), 2.30 (1H, dd, J = 10.1, 15.0 Hz, 4-H), 2.60 (1H, d, J = 15.0 Hz, 4′-H), 2.88 (1H, dd, J = 2.6, 8.1 Hz, 11-H), 3.03 (1H, dt, J = 2.5, 6.0 Hz, 10-H), 3.98 (2H, s, CH_2CO_2), 5.84 (1H, s, 2-H); ^{13}C NMR (D_2O) δ 12.0 (C-17), 18.5 (C-15), 19.7 (C-14), 31.7 (C-9), 39.8 (C-8), 41.8 (CH_2CO), 42.1 (C-4), 42.8 (C-12), 57.7 (C-10), 62.3 (C-11), 65.9 (C-16), 69.4 (C-6), 70.4 and 70.6 (C-13 and C-7), 75.3 (C-5), 120.0 (C-2), 152.8 (C-3), 170.9 (C-1), 174.5 (CO_2H); MS (FAB, thioglycerol, m/z) 402 (MH^+, 42), 126 (100).

5-[(Ethoxycarbonyl)oxy]-2-(1-normon-2-yl)oxazole (2w). The amide **10** (200 mg, 0.5 mmol) was dissolved in dry THF (7 mL, 0.5 mmol) followed by ethyl chloroformate (0.048 mL, 0.5 mmol). After 0.5 h at room temperature the reaction mixture was treated with a further equivalent of triethylamine and ethyl chloroformate and stirred for a further hour. The mixture was diluted with ethyl acetate (30 mL), washed with water (30 mL) and saturated brine (30 mL), dried ($MgSO_4$), and evaporated. The crude product was chromatographed on Kieselgel 60, eluting with 0−8% methanol in dichloromethane, to give **2w** (141 mg, 62%): IR (CH_2Cl_2) 3600, 3500, 3440, 1785, 1650, 1620 cm^{-1}; UV (EtOH) λ_{max} 262 nm (ϵ_m 18 780); ^1H NMR ($CDCl_3$) δ 0.95 (3H, d, J = 7.0 Hz, 17-H_3), 1.22 (3H, d, J = 6.3 Hz, 14-H_3), 1.41 (3H, t, J = 7.0 Hz, CH_3CH_2), 2.20 (3H, s, 15-H_3), 4.36 (2H, q, J = 7.1 Hz, CH_3CH_2), 6.10 (1H, s, 2-H), 6.73 (1H, s, oxazole-H); ^{13}C NMR (acetone-d_6) δ 12.3 (C-17), 14.2 (CH_3), 19.5 (C-15), 20.8 (C-14), 32.7 (C-9), 41.2 (C-8), 43.4 (C-4), 43.6 (C-12), 55.8 (C-10), 60.5 (C-11), 66.0 (C-16), 66.8 (CH_2), 69.5 (C-6), 70.1 (C-7), 71.1 (C-13), 76.1, (C-5), 110.7 (C-2), 112.8 (C-4′), 148.4 (C-3), 150.7, 151.5, and 155.9 (C5′, C1′, and CO_2-Et); MS (EI, m/z) 456 (MH^+), 139 (100); HRMS calcd for $C_{22}H_{23}NO_9$ 455.2155, found 455.2163.

2-(1-Normon-2-yl)-5-methoxy-4-(methoxycarbonyl)oxazole (9b). A solution of monic acid (6.88 g, 20 mmol) in THF (200 mL) was treated at 0 °C with triethylamine (3.0 mL, 2.2 g, 22 mmol) and then isobutyl chloroformate (2.7 mL, 2.8 g, 20.7 mmol). A white precipitate formed. After 0.75 h gaseous ammonia was bubbled into the reaction mixture for *ca.* 1 min. A thick white slurry formed. After 0.25 h the reaction mixture was evaporated to dryness, and the residue was dissolved in methanol (200 mL). Silica was added, and the methanol was removed by evaporation. The residue was subjected to a high vacuum for 1 h and then applied to a column of Kieselgel 60. Elution with a methanol−dichloromethane gradient (0−20%) gave monamide **11** as a white foam (5.43 g, 79%).

A suspension of monamide **11** (343 mg, 1 mmol) in THF (15 mL) at 0 °C under nitrogen was treated with triethylamine (0.76 mL, 555 mg, 5.5 mmol) and then trichloroacetyl chloride (0.5 mL, 800 mg, 4.4 mmol). After 0.75 h the reaction mixture was partitioned between ethyl acetate (40 mL) and 1 M hydrochloric acid (40 mL). The organic phase was washed with brine (40 mL), dried ($MgSO_4$), and evaporated, giving a white foam (1.0 g). The product was chromatographed, eluting with hexane then *via* a gradiant through to dichloromethane, giving the tris(trichloroacetyl) ester of mononitrile **12** as a white foam (515 mg, 94%): IR (CH_2Cl_2) 2950, 2200, and 1770 cm^{-1}; ^1H NMR ($CHCl_3$) δ 1.05 (3H, d, J = 7 Hz, 17-H_3), 1.40 (3H, d, J = 7 Hz, 14-H_3), 2.05 (3H, s, 15-H_3), 4.80−5.20 (2H, m, 7- and 13-H), 5.25 (1H, s, 2-H), and 5.55 (1H, m, 6-H); MS (+ve ion FAB, 3-NOBA/Na, m/z) 784 (MNa^+, 25), 176 (100).

A solution of the above nitrile (548 g, 1 mmol) and rhodium-(II) acetate dimer (10 mg) in ethanol-free chloroform (0.5 mL) at reflux under nitrogen was treated with a solution of dimethyl diazomalonate (158 mg, 1 mmol) in ethanol-free chloroform (0.5 mL) over 0.5 h. After a further 0.5 h the reaction mixture was allowed to cool to room temperature and chromatographed with methanol−dichloromethane (0−1%) to give a pale yellow foam (374 mg): IR (CH_2Cl_2) 1765, 1715, and 1620 cm^{-1}.

A portion of this material (185 mg) in methanol (8 mL) was treated at 0 °C with potassium carbonate (180 mg). After 10 min the reaction mixture was partitioned between ethyl acetate (40 mL) and brine (40 mL). The aqueous phase was further extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to a yellow foam (100 mg). This was chromatographed, eluting with 0−1% ethanol in ethyl acetate, to give **9b** as a white foam (50 mg, 22% overall yield from the nitrile): IR (CH_2Cl_2) 3400−3600, 2950, 1715, 1660, 1620, and 1560 cm^{-1}; UV (EtOH) λ_{max} 268 nm (ϵ_m 18 250); ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, J = 6.9 Hz, 17-H_3), 1.21 (3H, d, J = 6.2 Hz, 14-H_3), 1.33 (1H, q, J = 6.9 Hz, 12-H), 1.73 (2H, t, J = 7.5 Hz, 9-Hz), 2.00 (1H, m, 8-H), 2.21 (3H, s, 15-H_3), 2.34 (1H, m, 4-H), 2.60−2.80 (3H, m, 4-, 10-, and 11-H), 3.20 (1H, br s, OH), 3.35 (1H, br s, OH), 3.50 (1H, br.s, OH), 3.55 and 3.75−4.00 (1H, m, and 5H, m, 5-, 6-, l7-, and 13-H, and 16-H_2), 3.87 (3H, s, OMe), 4.18 (3H, s, OMe), and 6.07 (1H, s, 2-H); ^{13}C NMR ($CDCl_3$) δ 162.1 (C-1), 160.8 (CO_2Me) 150.9 (C-5′), 146.8 (C-3), 112.1 (C-2), 106.2 (C-4′), 75.0 (C-5), 71.4 (C-13), 70.3 (C-7), 68.8 (C-6), 65.4 (C-16), 61.3 (C-11), 59.5 (OCH_3), 55.5 (C-10), 51.7 (OCH_3), 42.8 (C-4), 42.6 (C-12), 39.5 (C-8), 31.6 (C-9), 45.9 (C-15), 19.4 (C-14), and 12.7 (C-17); MS (EI, m/z) 455 (M^+), 211 (100); HRMS calcd for $C_{22}H_{33}NO_9$ 422.2155, found 455.2159.

5-(Methoxycarbonyl)-2-(1-normon-2-yl)oxazole (2x). To a stirred suspension of copper(II) acetyl acetonate (2.6 mg) in benzene (1 mL) and chloroacetonitrile (0.64 mL) at reflux under an argon atmosphere was added a solution of methyl diazopyruvate (0.64 g, 5 mmol) in benzene (10 mL) over a period of 3 h. The crude reaction mixture was applied to a column of Kieselgel 60. Elution with 0−15% ethyl acetate in hexane gave **13** as a colorless oil (0.075 g, 8.6%): IR (CH_2Cl_2) 1735, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (3H, s, OCH_3), 4.65 (2H, s, CH_2Cl), 7.72 (1H, s, oxazole-H).

This material was heated to reflux with triethyl phosphite (0.146 mL, 0.86 mmol) for 2 h. Excess triethyl phosphite was removed under reduced pressure, and the residue was subjected to flash chromatography on Kieselgel 60, eluting with hexane/ethyl acetate mixtures, to give 2-[(diethylphosphono)-methyl]-5-(methoxycarbonyl)oxazole (**14**) as a pale yellow oil (50.0 mg, 48%): ^1H NMR ($CDCl_3$) δ 1.34 (6H, t, J = 8 Hz, CH_3), 3.45 (2H, d, J = 22 Hz, CH_2P), 3.90 (3H, s, OCH_3), 4.17 (4H, q, J = 8, 9 Hz, CH_2CH_3), 7.70 (1H, s, oxazole-H).

To a solution of lithium diisopropylamide [prepared from diisopropylamine (0.03 mL, 0.2 mmol) and *n*-butyllithium (0.146 mL, 1.51 M solution)] in THF (1 mL) at −70 °C under an argon atmosphere was added a solution of **14** (50 mg, 0.021 mmol) in THF (0.5 mL). The reaction mixture was stirred at −70 °C for 30 min and at 0 °C for 30 min. To this solution at 0 °C was added [(2*S*,3*R*,4*R*,5*S*)-3,4-bis[(trimethylsilyl)oxy]-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-epoxy-5-[(trimethylsilyl)oxy]-4-methylhexyl]-tetrahydropyran-2-yl] acetone[4] (**15**). The reaction was stirred at 0 °C for 30 min, allowed to warm to room temperature, and stirred for 18 h. The mixture was quenched with saturated ammonium chloride solution, and the product was extracted into ethyl acetate. The combined extracts were dried and evaporated to an oil. This was dissolved in THF (5 mL) and water (1.5 mL). Hydrochloric acid (5 M, 3 drops) was added and the mixture stirred for 5 min. After this time the mixture was quenched with saturated $NaHCO_3$. The product was extracted into ethyl acetate, and the combined organic extracts were washed with sodium chloride solution, dried, and evaporated. Chromatography on Kieselgel 60, eluting with 0−6% methanol in dichloromethane, gave 5-(methoxycarbonyl)-2-(1-normon-2-yl)oxazole (**2x**) as a colorless oil (10 mg, 12%): IR (KBr) 3421, 1726, 1648, 1578 cm^{-1}; UV (EtOH) λ_{max} 280 nm (ϵ_m 12 750); ^1H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 7.0 Hz, 17-H_3), 1.22 (3H, d, J = 6.3 Hz, 14-H_3), 2.33 (3H, s, 15-H_3), 2.40 (1H, dd, J = 14.8, 9.1 Hz, 4′-H), 3.92 (3H, s, OCH_3), 6.29 (1H, s, 2-H), 7.77 (1H, s, oxazole-H); MS (EI, m/z) 425 (M^+, 12), 181 (100); HRMS calcd for $C_{21}H_{31}NO_8$ 425.2050, found 425.2055.

Determination of Minimum Inhibitory Concentrations (MICs). Compounds were serially diluted in Blood Agar Base (Oxoid) containing 5% chocolated horse blood. Organisms were grown overnight in nutrient broth media. Then 1 μL spots were inoculated onto the surface of the agar plates, giving an inoculum of *ca.* 10^6 colony-forming units per spot. Plates were incubated for 18−24 h at 37 °C. The minimum inhibitory concentration was determined as the lowest concentration fully inhibiting bacterial growth.

Determination of IC_{50} against Isoleucyl tRNA Synthetase. IC_{50} values, defined as the concentration of inhibitor

resulting in 50% inhibition of (U-^{14}C)isoleucine charging of tRNA,[19] were determined after preincubation of increasing concentrations of compound with crude isoleucyl tRNA synthetase from *S. aureus* Oxford for 5 min, followed by addition of substrates and cofactors and reaction for 10 min at 37 °C.

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