1,3-Dipolar cycloaddition route to nitrogen heterocyclic triones

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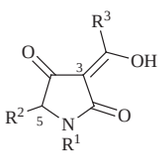
1,3-Dipolar cycloaddition of nitrile oxides, formed *in situ* by dehydration of primary nitro compounds, with pyrrolidine enamines of protected γ- or δ-amino-β-keto esters affords isoxazole-4-carboxylates; these undergo lactam formation and N–O bond cleavage to afford 3-acyltetramic acids and 3-acyl-4-hydroxypyridin-2-ones.

Introduction

The 3-acyltetramic acids (3-acylpyrrolidine-2,4-diones) **1** and



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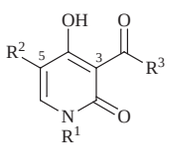

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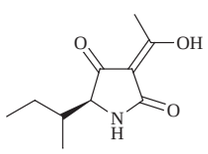

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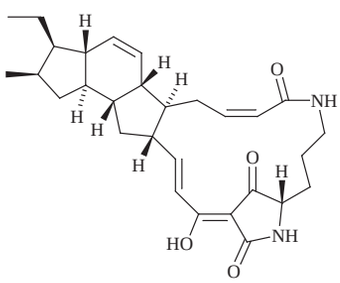

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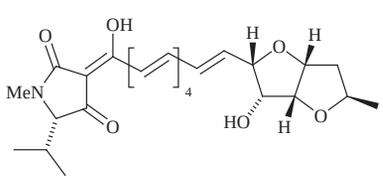

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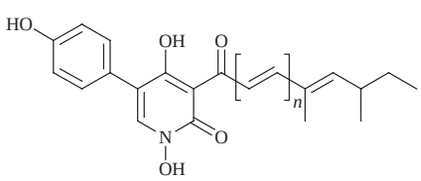


6 $n = 1$
7 $n = 2$

their six-membered ring analogues, the 3-acyl-4-hydroxypyridin-2-ones **2**, are a structurally diverse group of biologically active natural products having in common an enolised heterocyclic tricarbonyl moiety.† [1,2] This nitrogen heterocyclic unit incorporates an acyl group at C-3, forming a β,β′-triketo system and causing the acyltetramic acids to be acidic (pK_a 3–7).

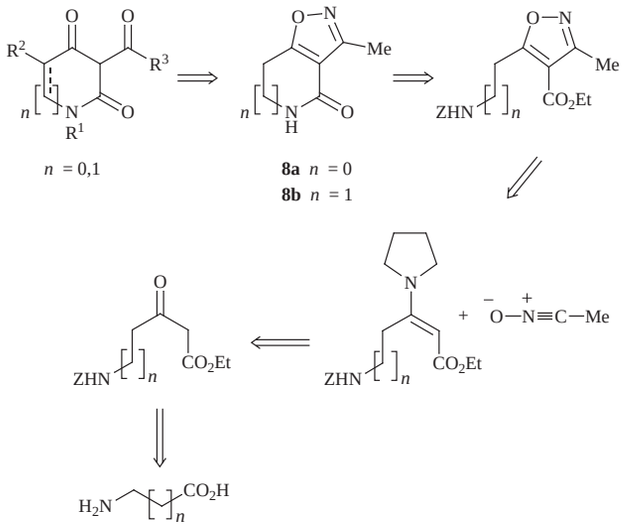
The simplest acyltetramic acid natural product is tenuazonic acid **3**, originally isolated from *Alternaria tenuis*[3] and shown to inhibit the incorporation of thymidine into DNA.[4] Other natural products having a saturated 3-acyl side-chain include the antiprotozoal compound malonomycin,[5] and α-cyclopiazonic acid, a mycotoxin isolated from the fungus *Penicillium cyclopium* Westling[6] which grows on agricultural products. Another group has the acyltetramic acid unit embedded within a macrocyclic lactam, exemplified by the antiprotozoal agent ikarugamycin **4**, isolated from *Streptomyces phaeochromogenes* var. ikaruganensis Sakai,[7] and whose structure elucidation[8] has been followed by several syntheses.[9,10] A larger group of acyltetramic acids carry a dienoyl or polyenoyl side chain at C-3, for example, the antimicrobial and antileukemic streptolydigin,[11] and the highly toxic pigment erythroskyrine **5** from *P. islandicum*, which has shown antibiotic action against *Staphylococcus* species.[12]

In the 3-acyl-4-hydroxypyridin-2-one group, two of the simplest natural products are tenellin **6** and bassianin **7**, closely related bright yellow pigments from the insect pathogenic fungi *Beauveria tenella* and *B. bassiana*, respectively.[13,14] Others include the elfamycin antibiotics, kirromycin (mocimycin),[15,16] and aurodox (goldinodax, antibiotic X-5108), the *N*-methyl analogue of kirromycin.[17] Related structures to aurodox are heneicomycin[18] and efrotomycin.[19] Total syntheses of aurodox and efrotomycin have been completed by Nicolaou *et al.*[20]

There is considerable interest in the heterocyclic triones, particularly as antibiotics, antiviral and antifungal agents, and this range of biological properties makes them interesting targets for synthesis and biological evaluation. Problems associated with handling these highly polar moieties have prompted us to develop strategies which avoid forming the enolic unit until the final stages of the synthetic sequence.[21]

We propose a new approach (Scheme 1) combining the known disconnection of tetramic acids to β-keto esters[22] with the concept of isoxazoles as masked 1,3-dicarbonyl compounds.[23] The required isoxazoles could be assembled by 1,3-dipolar cycloaddition of a nitrile oxide to the pyrrolidine enamine of an amino-substituted β-keto ester, followed by spontaneous elimination of pyrrolidine to leave an isoxazole-4-carboxylate ester.[24] The β-keto esters are available from α- or β-amino acids by a number of protocols.[25] The formation of 4-carboxyisoxazoles *via* 1,3-dipolar cycloaddition of β-enamino esters is known to occur regiospecifically.[24] Deprotection of the amino group and closure of the required nitrogen heterocycle to form **8a**,**b** would be followed by opening of the

† For **1** we illustrate a 3-*exo*-enol tautomer, the major tautomer in non-polar solvents or the solid state.[1,2] Compounds **2** exist as the illustrated *endo*-enol tautomer.



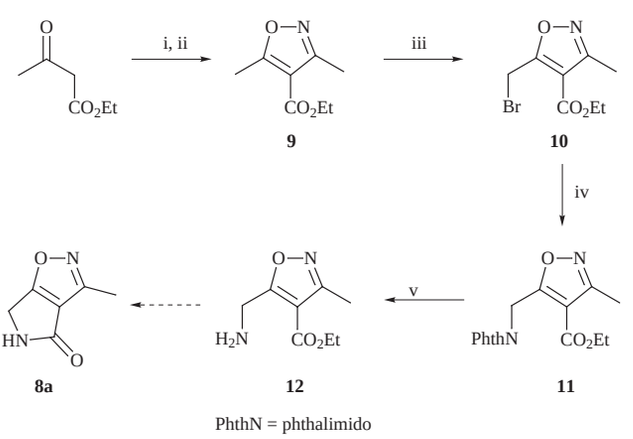
Scheme 1

isoxazole ring by hydrogenation[26] or another N–O bond cleavage method,[27–29] to 'unmask' the acyltetramic acid or acylpyridone at a late stage of the sequence. Using isoxazole building blocks allows elaboration of the nitrogen heterocyclic triones *via* non-polar intermediates. The key C–C bond formation, to attach the 3-acyl side-chain, occurs in the 1,3-dipolar cycloaddition which ensures *C*-acylation of a 1,3-dicarbonyl compound.

We report herein details of our studies[30] which demonstrate application of this strategy to heterocyclic triones **1** and **2** (we have recently described our findings with the analogous oxygen heterocyclic systems[31]).

Results and discussion

Before arriving at the strategy of Scheme 1, our first isoxazole-based approach began with ethyl 3,5-dimethylisoxazole-4-carboxylate **9** (Scheme 2). There was precedent for



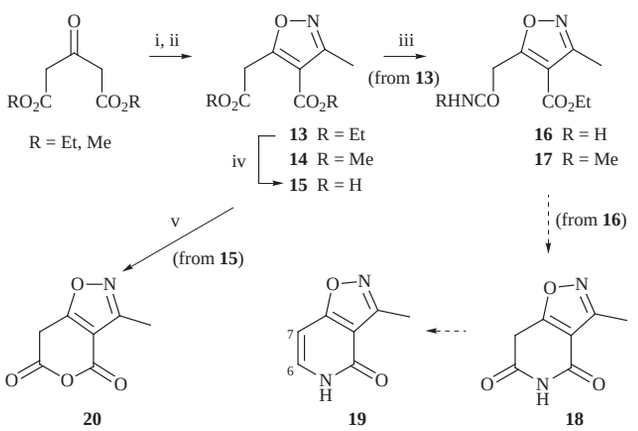
PhthN = phthalimido

Scheme 2 *Reagents*: i, pyrrolidine, benzene, reflux; ii, $EtNO_2$, Et_3N, $POCl_3$, 0–5 °C; iii, NBS, UV, CCl_4 reflux; iv, potassium phthalimide, DMF, 25 °C; v, H_2NNH_2, MeOH, reflux.

functionalization of this molecule at the C-5 methyl group,[32] so we proposed to introduce the amino substituent after isoxazole formation. Our initial strategy was thus to brominate at the C-5(Me), convert the bromide into a primary amine and cyclize to give the required bicyclic precursor to the 3-acylpyrrolidine-2,4-diones.

Isoxazole **9** was synthesised by a variant of the method of Stork *et al.*[24] The enamine of ethyl acetoacetate was formed quantitatively under Dean–Stark conditions with pyrrolidine in benzene, and reacted with acetonitrile oxide, formed *in situ* by slow addition of $POCl_3$ to a solution of $EtNO_2$ and Et_3N with the enamine. Distillation afforded ethyl 3,5-dimethylisoxazole-4-carboxylate **9** (42%). Phosphorus oxychloride was preferred to phenyl isocyanate[24] as dehydrating agent, since its use avoids the problematic (to separate) diphenylurea by-product without compromising the yield. Functionalisation at the C-5 methyl group was achieved with NBS using photolytic initiation in CCl_4 at reflux to yield the sensitive ethyl 5-bromomethyl-3-methylisoxazole-4-carboxylate **10** (90%). Treatment of the crude bromide with potassium phthalimide in DMF afforded ethyl 3-methyl-5-phthalimidomethylisoxazole-4-carboxylate (41%) **11** which was deprotected with hydrazine hydrate to yield 5-aminomethylisoxazole **12** (84%). We hoped for spontaneous cyclisation of this amino ester to the pyrroloisoxazole **8a** but there was no evidence of this under the deprotection conditions (MeOH, reflux). More forcing conditions, such as heating in xylene in a sealed tube, also led to recovery of amino ester **12** unchanged.

A modification of this approach was used in an attempted synthesis of the 3-acyl-4-hydroxypyridin-2-one unit. The pyrrolidine enamine of diethyl 3-oxopentane-1,5-dioate, formed in benzene under Dean–Stark conditions, was reacted with acetonitrile oxide as before to produce ethyl 5-ethoxycarbonylmethyl-3-methylisoxazole-4-carboxylate **13** (44%) (Scheme 3). The same sequence using dimethyl 3-oxopentane-1,5-dioate



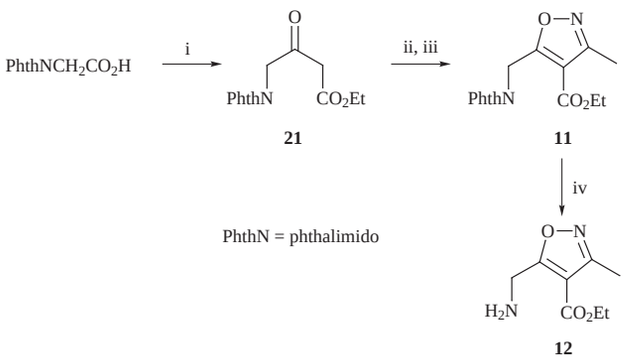
Scheme 3 *Reagents*: i, pyrrolidine, benzene, reflux; ii, $EtNO_2$, Et_3N, $POCl_3$, 0–5 °C; iii, for **16**: NH_4OH aq., 25 °C; for **17**: $MeNH_2$ aq., 25 °C; iv, NaOH aq.; v, DCC.

gave the corresponding isoxazole **14** (44%). Regioselective reaction of the C-5 side-chain ester of **13** with aqueous ammonia led to ethyl 5-carbamoylmethyl-3-methylisoxazole-4-carboxylate **16** (92%), while methylamine gave the *N*-methylamide **17** (99%).

Our intention had been to cyclise the amide **16** to generate the imide **18** (Scheme 3), which should undergo regioselective reduction (to an aminal) and dehydration to **19** to introduce the C-6/7 double bond required for most of the pyridone natural products. Despite several attempts we were unable to form the imide **18**. Saponification of the diester **13** led to the diacid **15**, from which the cyclic anhydride **20** was prepared in good yield using DCC. This is potentially another precursor to imide **18**, but at this point these approaches were superseded.

In the ultimately successful alternative strategy of Scheme 1 as a route to the 3-acylpyrrolidine-2,4-diones and 3-acyl-4-hydroxypyridin-2-ones, the amino group is built into the starting materials. Our initial targets were the key bicyclic intermediates **8a**,**b** which we envisaged being formed ultimately from an α- or β-amino acid, respectively.

The first requirement was to elaborate the carboxylic acid function to generate a β-keto ester. β-Keto ester synthesis from amino acids has been achieved by a number of protocols, from which we selected the approach of Pollet and Gelin.[25] Thus



Scheme 4 *Reagents*: i, 1,1′-carbonyldiimidazole, THF, 25 °C; then ethyl hydrogen malonate Mg-chelate; ii, pyrrolidine, toluene, reflux; iii, $EtNO_2$, Et_3N, $POCl_3$, 0–5 °C; iv, H_2NNH_2, MeOH, reflux.

phthalimidoacetic acid was activated as the imidazolide, which was added to the magnesium chelate formed from ethyl hydrogen malonate and propan-2-ylmagnesium bromide, to yield the β-keto ester **21** (99%) (Scheme 4). This β-keto ester was smoothly converted into the pyrrolidine enamine under Dean–Stark conditions in toluene, followed by reaction with acetonitrile oxide to produce ethyl 3-methyl-5-phthalimidomethylisoxazole-4-carboxylate **11** (43%), which was deprotected with hydrazine hydrate to give the amino ester **12** (see earlier).

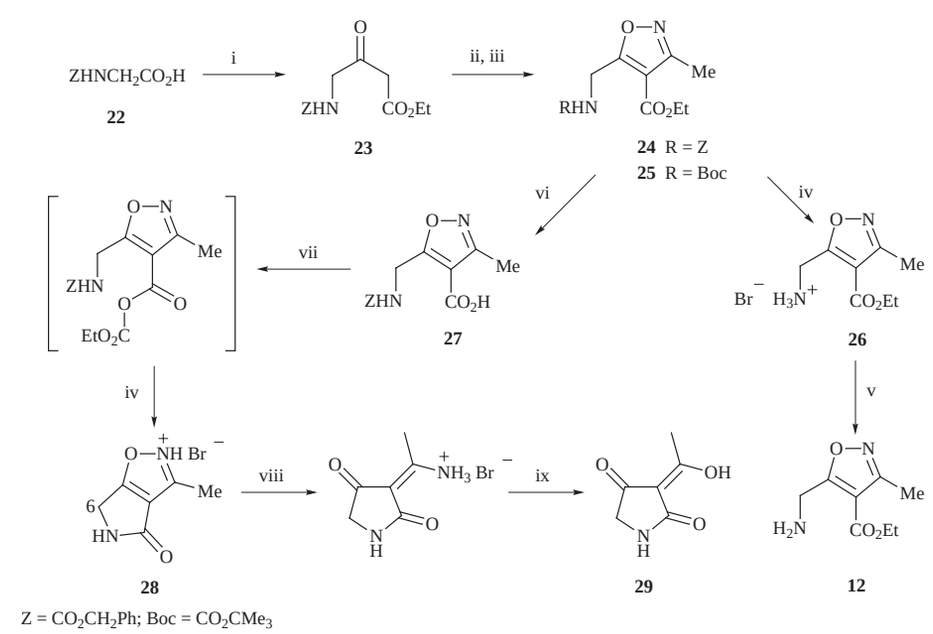
This sequence was repeated using different *N*-protecting groups. *N-tert*-Butoxycarbonylglycine was taken through to the corresponding isoxazole **25** in low yield, but the benzyloxycarbonyl group was introduced more efficiently. *N*-Benzyloxycarbonylglycine **22** was converted to ethyl 4-benzyloxycarbonylamino-3-oxobutanoate **23** (88%) and then, by reaction of the pyrrolidine enamine of this β-keto ester with acetonitrile oxide, into ethyl 5-benzyloxcarbonylaminomethyl-3-methylisoxazole-4-carboxylate **24** (30%) (Scheme 5). The benzyloxycarbonyl group was removed with HBr in glacial acetic acid (33% w/v) to give the amine hydrobromide **26** (86%), and treatment of this salt with aqueous base led again to the amino ester **12**. As observed above, there was no evidence of cyclisation to form the bicyclic lactam **8a**. We presume this is due to the strain that would arise in the new ring from the three sp^2 centres and the amide bond, in conjunction with deactivation of the C-4 carboxy group *via* conjugation.

To achieve the required cyclisation, further activation of the ester carbonyl was clearly necessary. The isoxazole ester **24** was hydrolysed (aqueous NaOH) to afford 5-benzyloxycarbonylaminomethyl-3-methylisoxazole-4-carboxylic acid **27** (73%), which was activated as a mixed anhydride by reaction with triethylamine and ethyl chloroformate. This intermediate was not normally isolated (although it has been identified by ^1H NMR spectroscopy) but used directly. Addition of HBr in glacial acetic acid to this material resulted in the removal of the benzyloxycarbonyl protecting group and cyclisation to form 3-methyl-5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one **8a** as its hydrobromide salt **28** (80%) (Scheme 5). Various methods to isolate the free isoxazole proved unsuccessful.

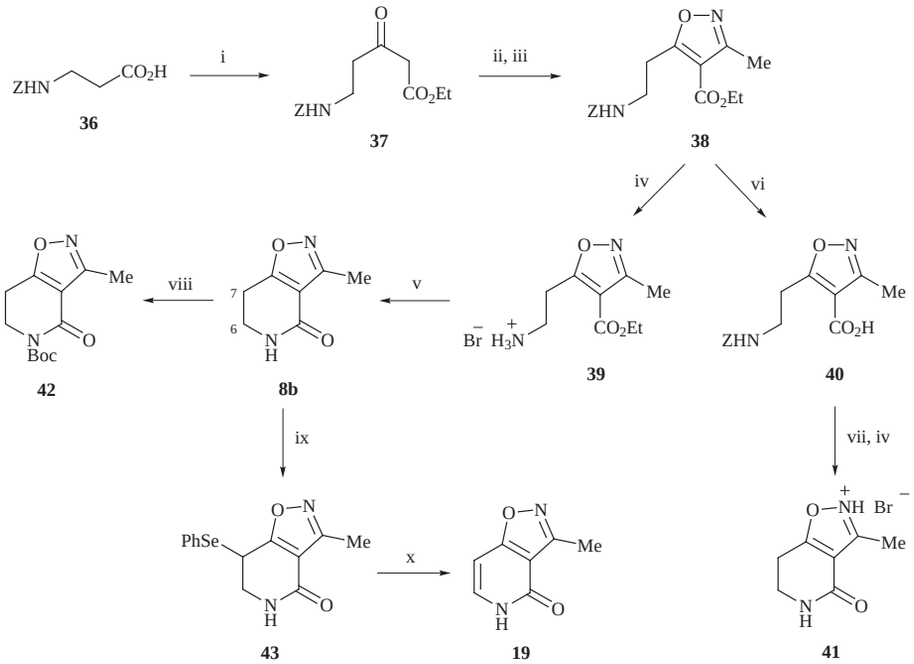
To complete this strategy, catalytic hydrogenation over palladium–charcoal was successfully applied for the reduction of the N–O bond of salt **28**, so long as the reaction was stopped after uptake of one equivalent of H_2. The intermediate enaminone salt was isolated and base hydrolysis efficiently released 3-(1-hydroxyethylidene)pyrrolidine-2,4-dione (3-acetyltetramic acid) **29** (91%) (Scheme 5). If hydrogenation was allowed to continue, a complex mixture of polar materials was isolated; further investigation showed the acyltetramic acid **29** to be unstable under the hydrogenation conditions. This N–O cleavage method is suitable if the side-chains are saturated, but if reducible side-chains have been introduced, these could also react under hydrogenation conditions. Various other reagents have been used to facilitate cleavage in these cases, and our studies with SmI_2 and $Mo(CO)_6$ will be reported in detail elsewhere.[33]

To position a substituent at C-6 of 3-methyl-5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one hydrobromide **28**, *i.e.* at C-5 of the eventual 3-acyltetramic acid, an obvious method would be to introduce the substituent as the side-chain of the original amino acid. We thus prepared the corresponding β-keto esters from *N*-benzyloxycarbonyl-alanine, -isoleucine and -valine, but were unable to convert these into the pyrrolidine enamines, even with use of Lewis acids.

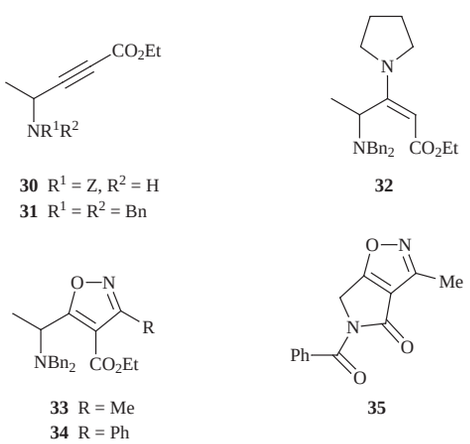
We briefly examined alkyne esters as an alternative source of the desired pyrrolidine enamines, derived from amino acids other than glycine. Ethyl 4-(benzyloxycarbonylamino)pent-2-



Scheme 5 *Reagents*: i, 1,1′-carbonyldiimidazole, THF; then ethyl hydrogen malonate Mg-chelate; ii, pyrrolidine, toluene, reflux; iii, $EtNO_2$, Et_3N, $POCl_3$, 0–5 °C; iv, HBr–AcOH; v, Na_2CO_3 aq.; vi, NaOH aq., reflux; vii, EtOCOCl, Et_3N, 0 °C; viii, H_2, Pd–C, ethanol; ix, NaOH aq., 25 °C.



Scheme 6 *Reagents*: i, 1,1′-carbonyldiimidazole, THF; then ethyl hydrogen malonate Mg-chelate; ii, pyrrolidine, toluene, reflux; iii, $EtNO_2$, Et_3N, $POCl_3$, 0–5 °C; iv, HBr–AcOH; v, Na_2CO_3 aq.; vi, NaOH aq., reflux; vii, EtOCOCl, *N*-methylmorpholine, 0 °C; viii, BuLi, Boc_2O; ix, $LiNPr^i_2$ (2 equiv.), THF, −78 °C, PhSeCl; x, H_2O_2, AcOH aq.



30 R^1 = Z, R^2 = H
31 R^1 = R^2 = Bn

32

33 R = Me
34 R = Ph

35

ynoate **30** was prepared[34] from 2-(benzyloxycarbonylamino)-propanal (itself derived from the *N*-protected alanine methyl ester), but in only a low yield that was not easily reproducible. This led us to prepare an alternative, ethyl 4-(dibenzylamino)-pent-2-ynoate **31**, from *N,N*-dibenzylalanine benzyl ester,[35] *via* the corresponding aldehyde. Although direct 1,3-dipolar cycloaddition of alkyne ester **31** with acetonitrile oxide was unsuccessful, treatment with pyrrolidine in refluxing EtOH produced the enamine **32** which did undergo cycloaddition with nitrile oxides, but not in synthetically useful yields. Thus reaction with acetonitrile oxide gave ethyl 5-(1-dibenzylaminoethyl)-3-methylisoxazole-4-carboxylate **33** (10%), and with benzonitrile oxide (formed from benzaldehyde oxime) gave ethyl 5-(1-dibenzylaminoethyl)-3-phenylisoxazole-4-carboxylate **34** (5%). These low yields and the need for a simple deprotection protocol for the amino group halted further efforts in this direction.

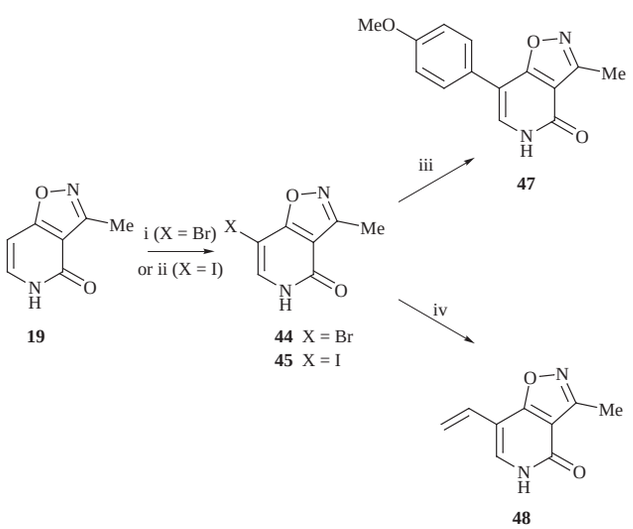
An attempt was made to introduce substituents at C-6 of bicycle **28** by deprotonation–alkylation. The salt was treated at −78 °C in HMPA–THF with LDA (3 equiv.) followed by $PhCH_2Br$, but no 6-benzyl product was observed. To avoid the need for dianion formation, the lactam nitrogen was protected as the benzoyl derivative **35**, by treatment of the salt **28** with BuLi and PhCOCl at −78 °C (56%). However, attempted deprotonation of imide **35** with either LDA or BuLi, followed by addition of iodomethane, led only to recovery of starting material.

Having devised successful methodology for the 3-acylpyrrolidine-2,4-dione (3-acyltetramic acid) series, we extended the same methodology to the six-membered 3-acyl-4-hydroxypyridone series. The disconnections of Scheme 1 (n = 1) lead to the amino acid β-alanine. Thus *N*-benzyloxycarbonyl-β-alanine **36** was elaborated *via* the protocol described above to produce the β-keto ester ethyl 5-benzyloxycarbonylamino-3-oxopentanoate **37** (91%) (Scheme 6). The enamine of the β-keto ester was generated as usual with pyrrolidine under Dean–Stark conditions, and reacted directly with acetonitrile oxide to form ethyl 5-(2-benzyloxycarbonylaminoethyl)-3-methylisoxazole-4-carboxylate **38** (68%). The benzyloxycarbonyl protecting group was readily removed by treatment with HBr in glacial acetic acid to give the hydrobromide salt **39** (90%). Basification of this salt (aqueous Na_2CO_3) presumably formed the free amino ester, although this was not isolated because spontaneous closure of the six-membered ring occurred to form 3-methyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **8b** (96%). Alternatively, but less directly, saponification of the ester **38** to acid **40** (86%), activation as the mixed anhydride and treatment with HBr in glacial acetic acid, afforded the isoxazolopyridone as its hydrobromide salt **41** (62%) in a parallel to the preparation of bicycle **28**.

For most of the natural products of the 3-acyl-4-hydroxypyridin-2-one group, a double bond is required between C-5 and C-6, corresponding to C-7 and C-6, respectively, of the isoxazolopyridone **8b** (*cf.* Scheme 6). A phenylselenation–oxidative elimination approach was used to introduce this double bond.[36] Initially we prepared the *N*-protected derivative **42** from pyridone **8b** using di-*tert*-butyl dicarbonate and BuLi (69%); LDA was less effective. However, attempted *C*-deprotonation (BuLi or LDA) of **42** followed by treatment with phenylselenenyl chloride led to partial decomposition. In contrast, formation of the dianion from pyridone **8b** with LDA (2 equiv.) and reaction with phenyl selenenyl chloride resulted in the formation of the phenyl selenide **43** (79%). Oxidative elimination of the 7-phenylselenyl group on treatment with H_2O_2 and aqueous acetic acid cleanly introduced the C-6,7 double bond to yield 3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **19** (92%) (Scheme 6).

A remaining task was the introduction of substituents at C-7 of the tetrahydroisoxazolopyridone **8b** or the unsaturated derivative **19**, and a palladium-catalysed coupling seemed appropriate to introduce aryl side chains. Heck coupling[37] was initially attempted between bicycle **19** and 4-bromoanisole with $Pd(OAc)_2$–PPh_3 as the catalyst system, but the required 7-phenyl species was not formed.

We therefore turned to another palladium-catalysed process, the Stille reaction,[38] which involves coupling between an organo halide and an organotin species. It was thus necessary to introduce a halogen at C-7 in 3-methyl-4,5-dihydroisoxazolo-[4,5-*c*]pyridin-4-one **19**. Bromination of the pyridone **8b** was attempted using LDA (3 equiv.) followed by excess bromine, in the hope that this would lead to dibromination at C-7 and subsequent elimination of HBr (in the presence of diisopropylamine) to yield the required vinyl bromide, thereby bypassing the phenylselenation–oxidative elimination, but only starting material was recovered. An alternative route, however, proved successful: bromination of the enamide **19** by addition of a solution of Br_2 in $CHCl_3$, followed by Et_3N, afforded 7-bromo-3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **44** (62%) (Scheme 7). There is precedent for improved Stille coup-



Scheme 7 *Reagents*: i, Br_2, Et_3N, 25 °C; ii, I_2 (4 equiv.), $CHCl_3$–C_5H_5N; or ICl, CH_2Cl_2–MeOH; iii, $MeOC_6H_4SnBu_3$ (**46**), $Pd_2(dba)_3$, $AsPh_3$ (1 : 4 Pd : As), THF, reflux; iv, $H_2C{=}CHSnBu_3$, $Pd_2(dba)_3$, $AsPh_3$ (1 : 4 Pd : As), THF, reflux.

lings when the organo halide is an iodide rather than a bromide. We therefore attempted iodination of **19** at C-7 following the same protocol as for bromination, using either Et_3N or pyridine as base, but this returned only starting material. However, alternative procedures using I_2 in $CHCl_3$–pyridine (1 : 1 v/v),[39] or ICl in CH_2Cl_2–MeOH did give the required 7-iodo-3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **45** (40 and 43%, respectively).

The 3-acyl-4-hydroxypyridin-2-one natural products tenellin **6** and bassianin **7** carry a 4-hydroxyphenyl group at C-5 (C-7 in the isoxazolopyridone). We therefore selected (4-methoxyphenyl)tributyltin **46** as the organotin coupling partner, which would lead to the introduction of a 4-alkoxyphenyl group that could be later transformed into the required 4-hydroxyphenyl group. 4-Bromoanisole was therefore converted into the corresponding Grignard reagent, which was treated with tributyltin chloride to form the trialkylorganotin **46**.[40]

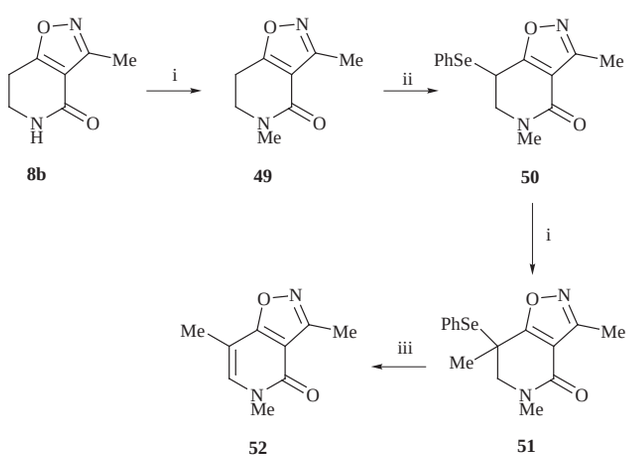
The 7-bromo- and 7-iodo-isoxazolopyridones, **44** and **45** respectively, were then subjected to Stille coupling conditions. Initial investigation was undertaken with the alkenyl bromide **44**. Early reports[38] used $Pd(PPh_3)_4$ as catalyst in either anhydrous THF or DMF, but we observed no coupling to (4-methoxyphenyl)tributyltin **46** under these conditions. Pd-$(OAc)_2$–PPh_3 and the alternative, much more active, catalyst $(MeCN)_2PdCl_2$[41] were similarly ineffective.

We therefore turned our attention to the alkenyl iodide **45**, which precedent indicated would be more reactive than bromide **44** in couplings with organotin **46**. $(MeCN)_2PdCl_2$ proved unsuccessful as catalyst in anhydrous THF or DMF, but $CHCl_3$ as solvent at 25 °C did yield the coupling product, 7-(4-methoxyphenyl)-3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **47** in low yield (19%). It has been shown that $Pd(AsPh_3)_4$, generated *in situ* from tris(dibenzylideneacetone)dipalladium and $AsPh_3$, causes a large rate acceleration relative to $Pd(PPh_3)_4$.[42] At 2 mol% this catalyst gave the arylated pyridone **47** in slightly better yield (25%), but increase in the proportion of catalyst and optimisation of the conditions delivered the product **47** with a much improved yield (78%) (Scheme 7).

Using this active catalyst and the same conditions, coupling was achieved with the bromopyridone **44** to again afford the arylated pyridone **47**, but in only 20% yield, confirming the large difference in reactivity between the 7-bromo- and 7-iodopyridones. The iodopyridone **45** was also coupled to vinyltributyltin to give the 7-vinylpyridone **48** (74%).

The NMR spectroscopic data for compound **47** are worthy of comment. In the ^1H NMR spectrum taken in $(CD_3)_2SO$, there are two sets of peaks for the four protons of the newly introduced 1,4-disubstituted phenyl ring, and the ^{13}C NMR spectrum shows signals additional to those predicted. Using variable temperature ^1H NMR spectroscopy, and heating the sample to 100 °C in $(CD_3)_2SO$, peak broadening was observed although complete coalescence of the peaks did not occur. It is possible that we are observing a mixture of pyridone and hydroxypyridine tautomers, although we have no definitive evidence on this point. Cleavage of the isoxazole ring of bicyclic pyridone **47** to produce a 3-acyl-4-hydroxypyridin-2-one confirms its structure, and is discussed later.

Methods for the introduction of alkyl chains at C-7 of isoxazolopyridone **19** were also explored. *N*-Methylation of tetrahydroisoxazolopyridone **8b** using LDA and MeI was successful, yielding the product **49** (65%) (Scheme 8). Phenyl-



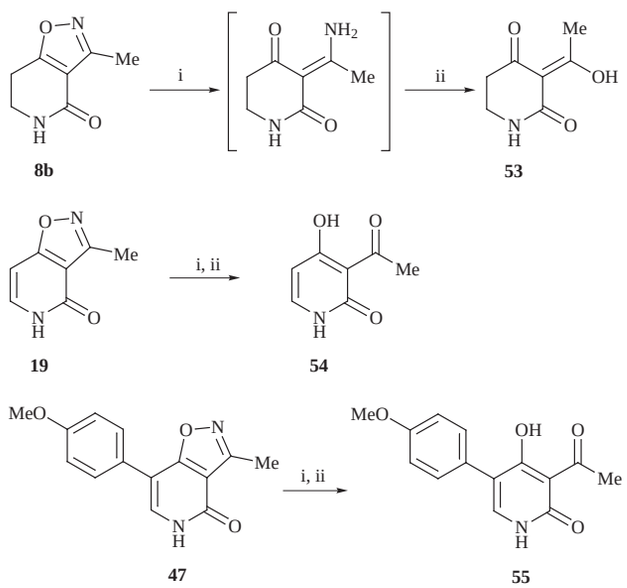
Scheme 8 *Reagents*: i, LDA, THF, −78 °C, MeI; ii, LDA, THF, −78 °C, PhSeCl; iii, H_2O_2, AcOH aq., 0 °C.

selenation of this material using LDA and PhSeCl gave the 7-phenylseleno derivative **50** (38%), which was treated with LDA and MeI to afford 3,5,7-trimethyl-7-phenylseleno-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **51** (84%) by methylation at C-7. Oxidative elimination then gave the desired 3,5,7-trimethyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **52** (95%). The alternative sequence of C-7 phenylselenation of **8b** to form compound **43** (see above), followed by reaction with excess base and MeI, did not produce the trimethylpyridone **51**.

Several of the acylpyridone natural products carry an oxygen substituent on the nitrogen atom, and we made preliminary

attempts to introduce oxygen on to N-5 of the isoxazolopyridones. Deprotonation of the amide nitrogen atom of 3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **19** with BuLi followed by treatment with gaseous oxygen, or reaction of the tetrahydroisoxazolopyridone **8b** with MCPBA or H_2O_2, resulted only in recovery of the starting material. Reaction of pyridone **19** with *O*-benzylhydroxylamine, in the expectation of substitution of NH by NOBn, proved fruitless under a variety of conditions. At this point we ceased our studies but Rigby *et al.*[43] have reported an efficient protocol for late introduction of the *N*-hydroxy group.

To validate this strategy for the 3-acyl-4-hydroxypyridones, all that remained was to cleave the isoxazole N–O bond to unmask the tricarbonyl moiety. Catalytic hydrogenation[27] of the isoxazole ring again proved successful in the six-membered ring series. Thus tetrahydroisoxazolopyridone **8b** produced a moisture sensitive enaminone, which after basic hydrolysis afforded 3-(1-hydroxyethylidene)piperidine-2,4-dione **53**‡ (this compound can also be called 3-acetylhomotetramic acid) in 97% yield over the two steps (Scheme 9). The hydrogenolysis–



Scheme 9 *Reagents*: i, H_2, Pd–C, EtOH; ii, NaOH aq., 25 °C.

hydrolysis was also performed on the isoxazolopyridone **19** to give 3-acetyl-1,2-dihydro-4-hydroxypyridin-2-one **54**, (97%), and with 7-(4-methoxyphenyl)-3-methyl-4,5-dihydroisoxazolo-[4,5-*c*]pyridin-4-one **47** to afford a quantitative yield of 3-acetyl-1,2-dihydro-4-hydroxy-5-(4-methoxyphenyl)pyridin-2-one **55**, thus revealing a cyclic trione system closely related to some of the natural products. The NMR spectra of this pyridone **55** exhibited the expected patterns, with one set of proton signals for the 1,4-disubstituted phenyl ring, *cf.* the observations outlined earlier for the precursor **47**.

These studies have clearly demonstrated the validity of the new cycloaddition strategy for the synthesis of the nitrogen heterocyclic triones, and further efforts are underway to apply this approach.

Experimental

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1720X FT spectrometer. UV Spectra were recorded on a Philips Pu 8720 spectrometer, in EtOH unless otherwise stated. ^{1}H NMR spectra were recorded using the following instruments: at 80 MHz on a Bruker WP80SY, at 250 MHz on a Bruker WM250, at 270 MHz on a JEOL JNM-EX270 or at 400 MHz on a Bruker AM400. ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 instrument at 68 MHz or a Bruker AM400 at 100 MHz and multiplicites were determined using DEPT sequences. *J* Values are given in Hz. Mass spectra were recorded on AEI MS902, VG 7070E or VG Autospec spectrometers using electron impact as the ionisation technique, unless FAB (fast atom bombardment) is indicated. Microanalytical data were obtained using a Perkin-Elmer 240B elemental analyser. All solvents were dried and distilled prior to use.[44]

‡ The 3-*exo*-enol tautomer is illustrated, by analogy with 3-acyltetramic acids.[1,2]

Ethyl 3,5-dimethylisoxazole-4-carboxylate 9

Ethyl acetoacetate (26.0 g, 0.2 mol) and pyrrolidine (14.2 g, 0.2 mol) were heated together in benzene (100 cm^3) at reflux under Dean–Stark conditions. After 2 h water (3.6 cm^3, 0.2 mol) had separated, the mixture was cooled and the excess solvent evaporated under reduced pressure. To the residue was added Et_3N (80.0 cm^3, 0.6 mol) and $EtNO_2$ (15.8 cm^3, 0.22 mol) in $CHCl_3$ (200 cm^3) and the solution cooled to 0 °C. To this cooled solution was added $POCl_3$ (34.00 g, 0.22 mol) in $CHCl_3$ (40 cm^3) dropwise over 1.5 h and the mixture stirred at room temperature for a further 15 h. The resultant dark mixture was poured into water (200 cm^3) and the organic phase washed successively with 6 M hydrochloric acid (70 cm^3), aqueous NaOH (5% w/v, 100 cm^3) and saturated brine (100 cm^3) before drying ($MgSO_4$), filtering and evaporating under reduced pressure to yield an orange oil which was purified by fractional distillation to give the title compound (14.31 g, 42%) as a colourless oil, bp 60–63 °C at 0.5 mmHg (lit.,[32] 60–62 °C at 0.5 mmHg); ν_{max}(film)/cm^{-1} 2983, 2939, 1721, 1612, 1460, 1427, 1303, 1109 and 782; δ_H(250 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7, OCH_2CH_3), 2.40 and 2.65 (each 3H, s, 3- and 5-CH_3) and 4.32 (2H, q, *J* 7, OCH_2CH_3).

Ethyl 5-bromomethyl-3-methylisoxazole-4-carboxylate 10

To ethyl 3,5-dimethylisoxazole-4-carboxylate **9** (2.0 g, 11.82 mmol) in CCl_4 (200 cm^3) was added NBS (2.73 g, 15.37 mol), and the mixture exposed to a UV lamp and allowed to reflux under nitrogen for 4.5 h. The brown mixture was dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield the title compound as a yellow oil (2.63 g, 90%) that was used directly; ν_{max}(film)/cm^{-1} 3031, 2983, 2938, 1720, 1609, 1425, 1310, 1130, 1094 and 788; δ_H(250 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7, OCH_2CH_3), 2.45 (3H, s, 3-CH_3), 4.30 (2H, q, *J* 7, OCH_2CH_3) and 4.75 (2H, s, CH_2Br).

Ethyl 3-methyl-5-phthalimidomethylisoxazole-4-carboxylate 11 (by bromide substitution)

To 5-bromomethyl-3-methylisoxazole-4-carboxylate **10** (1.00 g, 4.03 mmol) in DMF (40 cm^3) was added potassium phthalimide (0.75 g, 4.03 mol) and the mixture heated under nitrogen at 65 °C for 10 h. The cooled dark brown mixture was extracted with diethyl ether (2 × 25 cm^3) and the combined extracts were washed with water (5 × 30 cm^3). The organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield the *title compound* as an off-white solid (0.52 g, 41%), mp 95–97 °C (Found: C, 61.4; H, 4.7; N, 8.9%; M$^+$, 314.0946. $C_{16}H_{14}N_2O_5$ requires C, 61.14; H, 4.49; N, 8.91%; *M*, 314.0903); ν_{max}(KBr)/cm^{-1} 2975, 2925, 1710, 1600, 1450, 1410, 1390, 1300 and 1100; δ_H(250 MHz; $CDCl_3$) 1.40 (3H, t, *J* 7, OCH_2CH_3), 2.45 (3H, s, 3-CH_3), 4.40 (2H, q, *J* 7, OCH_2CH_3), 5.30 (2H, s, *J* 7, NCH_2), 7.80 (2H, m, Ar-H) and 7.95 (2H, s, Ar-H); δ_C(68 MHz; $CDCl_3$) 11.6 and 14.2 (CH_3), 34.4 and 61.1 (CH_2), 109.3 (C), 123.6 (CH), 131.8 (C), 134.2 (CH), 160.2, 161.2, 167.2 and 170.6 (C); *m/z* 314 (M$^+$), 268 (100%), 241, 160, 104 and 76.

Ethyl 5-aminomethyl-3-methylisoxazole-4-carboxylate 12 (from the *N*-phthalimido derivative 11)

To the phthalimide **11** (2.0 g, 6.36 mmol) in EtOH (25 cm^3) was

added hydrazine hydrate (0.8 cm^3, 25.44 mol), and the mixture heated at reflux for 8 h. After this period it was cooled and water (10 cm^3) added, the solution acidified to pH 5 using 1 M hydrochloric acid (30 cm^3) and the mixture filtered and extracted with diethyl ether (3 × 25 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield the *title compound* as a pale yellow oil (0.98 g, 84%) (Found: C, 52.2; H, 6.8; N, 15.2%; M^+, 184.0831. $C_8H_{12}N_2O_3$ requires C, 52.17; H, 6.57; N, 15.21%; *M*, 184.0848); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 221 (5876); ν_{max}(film)/cm^{-1} 3350, 2985, 2950, 1700, 1600, 1420, 1295 and 1100; δ_H(250 MHz; $CDCl_3$) 1.25 (3H, t, *J* 7, OCH_2CH_3), 1.73 (2H, br s, NH_2), 4.03 (2H, s, *J* 7, CH_2NH_2) and 4.18 (2H, q, *J* 7, OCH_2CH_3); δ_C(68 MHz; $CDCl_3$) 11.6 and 14.1 (CH_3), 38.5 and 60.8 (CH_2), 107.9, 159.9, 162.0 and 178.2 (C); *m*/*z* 184 (M^+), 155, 137, 110 and 82 (100%).

Ethyl 5-ethoxycarbonylmethyl-3-methylisoxazole-4-carboxylate 13

Prepared as described above for ethyl 3,5-dimethylisoxazole-4-carboxylate **9**, but using diethyl 3-oxopentane-1,5-dioate (36.91 g, 0.183 mol) and pyrrolidine (12.98 g, 0.183 mol) in toluene to form the enamine, Et_3N (55.4 g, 0.548 mol), $EtNO_2$ (15.07 g, 0.2 mol) and $POCl_3$ (30.78 g, 0.2 mol). Workup afforded a brown oil which was fractionally distilled to yield the title compound as a pale yellow oil (19.2 g, 44%), bp 118–120 °C at 0.6 mmHg (Found: MH^+, 242.1052. $C_{11}H_{15}NO_5$ requires *MH*, 242.1028); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 218 (6723); ν_{max}(film)/cm^{-1} 2975, 2925, 1710, 1600, 1470, 1380 and 1100; δ_H(250 MHz; $CDCl_3$) 1.20 and 1.35 (each 3H, t, *J* 7, OCH_2CH_3), 2.45 (3H, s, 3-CH_3), 4.05 (2H, s, CH_2CO), 4.15 and 4.30 (each 2H, q, *J* 7, OCH_2CH_3); δ_C(68 MHz; $CDCl_3$) 11.7 and 14.1 (CH_3), 33.4, 60.8 and 61.7 (CH_2), 110.3, 159.9, 161.8, 166.9 and 170.5 (C); *m*/*z* (FAB) 242 (M^+ + 1, 100%), 196, 168, 140 and 82.

Methyl 5-methoxycarbonylmethyl-3-methylisoxazole-4-carboxylate 14

Prepared as described above for ethyl 3,5-dimethylisoxazole-4-carboxylate **9**, but using dimethyl 3-oxopentane-1,5-dioate (40.0 g, 0.229 mol) and pyrrolidine (16.33 g, 0.229 mol) in toluene to form the enamine, Et_3N (68.72 g, 0.689 mol), $EtNO_2$ (19.0 g, 0.252 mol) and $POCl_3$ (38.64 g, 0.252 mol). Workup afforded a brown oil which was fractionally distilled to yield the title compound as a pale yellow oil (21.30 g, 44%), bp 105–106 °C at 0.20 mmHg (Found: M^+, 213.0667. $C_9H_{11}NO_5$ requires *M*, 213.0637); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 220 (5847); ν_{max}(film)/cm^{-1} 3000, 2950, 1725, 1600, 1440, 1300 and 1100; δ_H(250 MHz; $CDCl_3$) 2.43 (3H, s, 3-CH_3), 3.71 and 3.84 (each 3H, s, OCH_3) and 4.10 (2H, s, CH_2CO); δ_C(68 MHz; $CDCl_3$) 11.5 (CH_3), 32.9 (CH_2), 51.7 and 52.5 (CH_3), 110.1, 159.7, 162.7, 170.4 and 175.1 (C); *m*/*z* (FAB) 214 (M^+ + 1, 100%), 182, 154, 72 and 59.

Ethyl 5-carbamoylmethyl-3-methylisoxazole-4-carboxylate 16

To ethyl 5-ethoxycarbonylmethyl-3-methylisoxazole-4-carboxylate **13** (1.00 g, 4.15 mmol) was added an excess of conc. aqueous ammonia (d = 0.88 kg m^{-3}, 5.0 cm^3) and EtOH (3.0 cm^3), and the suspension stirred vigorously at room temperature for 14 h. After this period a white solid had precipitated which was filtered and recrystallised (EtOAc) to yield the *title compound* as a white solid (0.81 g, 92%), mp 141–141.5 °C (Found: C, 51.1; H, 6.0; N, 13.1%; $M^+ - NH_2$, 196.0605. $C_9H_{12}N_2O_4$ requires C, 50.94; H, 5.70; N, 13.20%; $M - NH_2$, 196.0610); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 218 (7301); ν_{max}(KBr)/cm^{-1} 3410, 3300, 3200, 2975, 2950, 1720, 1630, 1600, 1430, 1410, 1300 and 1110; δ_H(250 MHz; $CDCl_3$) 1.24 (3H, t, *J* 7, OCH_2CH_3), 2.46 (3H, s, 3-CH_3), 4.08 (2H, s, CH_2CO) and 4.26 (2H, q, *J* 7, OCH_2CH_3); δ_C(68 MHz; $CDCl_3$) 11.2 and 14.71 (CH_3), 35.2 and 61.6 (CH_2), 110.0, 160.6, 162.9, 168.6 and 173.7 (C); *m*/*z* 196 ($M^+ - NH_2$, 81%), 169, 141 and 82.

Ethyl 5-(*N*-methylcarbamoylmethyl)-3-methylisoxazole-4-carboxylate 17

Prepared as described above for ethyl 5-carbamoylmethyl-3-methylisoxazole-4-carboxylate **16** but using 5-ethoxycarbonylmethyl-3-methylisoxazole-4-carboxylate **13** (1.00 g, 4.15 mmol) and methylamine in toluene (30% w/v, 10.0 cm^3), to yield the *title compound* as a white solid (0.93 g, 99%), mp 143.5–144 °C (Found: C, 53.1; H, 6.3; N, 12.4%; $M^+ - C_2H_3NO$, 169.0753. $C_{10}H_{14}N_2O_4$ requires C, 53.09; H, 6.24; N, 12.38%; $M - C_2H_3NO$, 169.0739); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 216 (7584); ν_{max}(KBr)/cm^{-1} 3290, 2975, 2925, 1710, 1620, 1600, 1460, 1400 and 1110; δ_H(250 MHz; $CDCl_3$) 1.30 (3H, t, *J* 7, OCH_2CH_3), 2.45 (3H, s, 3-CH_3), 2.85 (3H, d, *J* 5, $NHCH_3$), 4.00 (2H, s, CH_2CO), 4.45 (2H, q, *J* 7, OCH_2CH_3) and 6.30 (1H, br s, $NHCH_3$); δ_C(68 MHz; $CDCl_3$) 11.7, 14.0 and 26.5 (CH_3), 35.2 and 61.1 (CH_2), 110.0, 159.9, 162.4, 166.1 and 171.8 (C); *m*/*z* 169 ($M^+ - C_2H_3NO$, 100%), 141, 123, 82 and 58.

5-(Carboxymethyl)-3-methylisoxazole-4-carboxylic acid 15

Ethyl 5-ethoxycarbonylmethyl-3-methylisoxazole-4-carboxylate **13** (5.35 g, 22.17 mmol) was heated at reflux with NaOH (0.9 g, 22.17 mmol) in water (75 cm^3) for 4.5 h. After this time the solution was cooled, filtered and acidified carefully to pH 1 with conc. hydrochloric acid. The precipitate was filtered and washed with diethyl ether (20 cm^3) to yield the *title compound* as a white solid (3.97 g, 97%), mp 199–200 °C (Found: C, 45.6; H, 3.6; N, 7.8%. $C_7H_7NO_5$ requires C, 45.41; H, 3.81; N, 7.57%); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 217 (6491); ν_{max}(KBr)/cm^{-1} 3180–2900, 1740, 1700, 1610, 1460 and 1110; δ_H [250 MHz; $(CD_3)SO$] 2.45 (3H, s, 3-CH_3), 4.25 (2H, s, CH_2CO) and 13.1 (2H, br s, 2 × OH); δ_C(68 MHz; $CDCl_3$) 11.6 (CH_3), 33.4 (CH_2), 110.6, 160.0, 163.2, 168.9 and 171.7 (C); *m*/*z* 141 ($M^+ - CO_2H$), 123, 82 and 43 (100%).

3-Methyl-4,6-dioxo-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazole 20

To 5-(Carboxymethyl)-3-methylisoxazole-4-carboxylic acid **15** (1.0 g, 5.4 mmol) in THF (30 cm^3) was added DCC (1.12 g, 5.4 mmol) in THF (20 cm^3), and the mixture stirred at room temperature for 8 h. After this time the mixture was filtered and evaporated under reduced pressure to yield the *title compound* as an off-white solid (0.72 g, 80%), mp 140–143 °C (Found: M^+, 167.0194. $C_7H_5NO_4$ requires *M*, 167.0211); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 209 (10440); ν_{max}($CHCl_3$)/cm^{-1} 2938, 1825, 1782, 1638, 1461, 1045 and 748; δ_H [250 MHz; $(CD_3)CO$] 2.40 (3H, s, 3-CH_3) and 4.20 (2H, s, CH_2CO); δ_C(68 MHz; $CDCl_3$) 11.2 (CH_3), 38.6 (CH_2), 110.2, 159.6, 162.9, 168.6 and 171.3 (C); *m*/*z* 167 (M^+), 126, 82 (100%) and 81.

Ethyl 4-phthalimido-3-oxobutanoate 21

To phthalimidoacetic acid (30.0 g, 146.22 mmol) in dry THF (200 cm^3) was added 1,1′-carbonyldiimidazole (23.71 g, 146.22 mmol) and the solution stirred under nitrogen at room temperature for 12 h to form the acid imidazolide. To ethyl hydrogen malonate (19.32 g, 146.22 mmol) in dry THF (150 cm^3) at 0 °C was added over 0.5 h propan-2-ylmagnesium bromide, prepared from magnesium turnings (7.00 g, 293.0 mmol) and 2-bromopropane (36.0 g, 293.0 mmol), in dry THF (200 cm^3). After stirring at room temperature for 0.5 h and warming to 40 °C for 0.5 h, the solution was cooled to 0 °C and the imidazolide solution added. The resultant gummy precipitate was stirred vigorously at room temperature for 4 h, before 0.3 M orthophosphoric acid (800 cm^3) was carefully added and the mixture extracted with EtOAc (3 × 600 cm^3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$

(800 cm^3) and saturated brine (800 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to yield the *title compound* as a white solid (39.71 g, 99%), mp 110.5–111 °C (Found: C, 61.2; H, 4.7; N, 5.0%. $C_{14}H_{13}NO_5$ requires C, 61.09; H, 4.76; N, 5.09%); $\lambda_{max}(CH_3CN)$/nm (ε/dm^3 mol^{-1} cm^{-1}) 218 (35296); $\nu_{max}(CHCl_3)$/cm^{-1} 2975, 2945, 1720, 1600, 1400, 1270, 1080 and 1015; δ_H(250 MHz; $CDCl_3$) 1.21 (3H, t, *J* 7, OCH_2CH_3), 3.55 (2H, s, $COCH_2CO$), 4.20 (2H, q, *J* 7, OCH_2 CH_3), 4.65 (2H, s, NCH_2), 7.60 (2H, m, Ar-H) and 7.80 (2H, s, Ar-H); δ_C(68 MHz; $CDCl_3$) 14.0 (CH_3), 46.6, 46.9 and 61.8 (CH_2), 123.6 (CH), 131.9 (C), 134.3 (CH), 166.2, 167.4 and 194.9 (C); *m*/*z* (FAB) 276 ($M^+ + 1$), 230 (100%), 160, 137 and 77.

Ethyl 5-phthalimidomethyl-3-methylisoxazole-4-carboxylate 11 (by direct cycloaddition)

Prepared as described above for ethyl 3,5-dimethylisoxazole-4-carboxylate **9**, but using ethyl 4-phthalimido-3-oxobutanoate **21** (35.74 g, 0.13 mol) and pyrrolidine (9.23 g, 0.13 mol) in toluene to form the enamine, Et_3N (43.41 g, 0.429 mol), $EtNO_2$ (10.74 g, 0.143 mol) and $POCl_3$ (22.0 g, 0.143 mol). Workup afforded an orange oil which was purified by column chromatography on silica gel, eluting with light petroleum (bp 40–60 °C)–EtOAc (1 : 1 v/v) to yield the *title compound* as a white solid (17.42 g, 43%), mp 95.5–97 °C, identical to a sample prepared by bromide substitution, see above.

Ethyl 4-benzyloxycarbonylamino-3-oxobutanoate 23

Prepared as described above for the preparation of ethyl 4-phthalimido-3-oxobutanoate **21**, but using *N*-benzyloxycarbonylglycine **22** (50.0 g, 239.0 mmol), 1,1′-carbonyldiimidazole (38.8 g, 239.0 mmol), ethyl hydrogen malonate (34.74 g, 263.0 mmol), magnesium (11.4 g, 480.0 mmol) and 2-bromopropane (60.0 g, 420.0 mmol), to yield the *title compound* as an orange oil (58.56 g, 88%) (Found: C, 59.9; H, 6.1; N, 5.1%. $C_{14}H_{17}NO_5$ requires C, 60.20; H, 6.14; N, 5.02%); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 208 (5208); ν_{max}(film)/cm^{-1} 3360, 3033, 2981, 1720, 1522, 1454, 1368, 1320, 1252, 1162, 1027, 915, 776 and 698; δ_H(250 MHz; $CDCl_3$) 1.25 (3H, t, *J* 7, OCH_2CH_3), 2.50 (2H, s, $COCH_2CO$), 4.15 (2H, s, $NHCH_2$), 4.20 (2H, q, *J* 7, OCH_2 CH_3), 5.10 (2H, s, $PhCH_2$), 5.45 (1H, br s, NH) and 7.34 (5H, s, Ar-H); δ_C(68 MHz; $CDCl_3$) 13.8 (CH_3), 46.0, 50.7, 61.0 and 66.6 (CH_2), 127.7, 127.8 and 128.1 (CH), 136.0, 156.1, 166.4 and 198.5 (C); *m*/*z* (FAB) 280 (M + 1), 235 and 91 (100%).

Ethyl 5-benzyloxycarbonylaminomethyl-3-methylisoxazole-4-carboxylate 24

Prepared as described above for ethyl 3,5-dimethylisoxazole-4-carboxylate **9**, but using ethyl 4-benzyloxycarbonylaminomethyl-3-oxobutanoate **23** (50.0 g, 0.179 mol) and pyrrolidine (12.74 g, 0.179 mol) in toluene to form the enamine, Et_3N (54.34 g, 0.537 mol), $EtNO_2$ (14.78 g, 0.197 mol) and $POCl_3$ (30.21 g, 0.197 mol). Workup and column chromatography on silica gel eluting with light petroleum (bp 40–60 °C)–EtOAc (1 : 1 v/v) afforded the *title compound* as a pale cream solid (16.51 g, 30%), mp 66–68 °C (Found: C, 60.3; H, 5.8; N, 8.7%; MH^+, 319.1338. $C_{16}H_{18}N_2O_5$ requires C, 60.37; H, 5.70; N, 8.80%; *MH*, 319.1294); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 209 (10440); $\nu_{max}(CHCl_3)$/cm^{-1} 3022, 1722, 1613, 1498, 1300, 1108 and 972; δ_H(250 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7, OCH_2CH_3), 2.44 (3H, s, 3-CH_3), 4.33 (2H, q, *J* 7, OCH_2CH_3), 4.76 (2H, d, *J* 7, $NHCH_2$), 5.13 (2H, s, $PhCH_2$), 5.57 (1H, br s, NH) and 7.35 (5H, s, Ar-H); δ_C(68 MHz; $CDCl_3$) 11.5 and 14.2 (CH_3), 37.4, 60.9 and 67.0 (CH_2), 109.0 (C), 128.0 and 128.2 (CH), 136.0, 156.1, 159.8, 161.8 and 173.7 (C); *m*/*z* 319 (MH^+), 211 and 91 (100%).

Ethyl 5-aminomethyl-3-methylisoxazole-4-carboxylate 12 (from the *N*-benzyloxycarbonyl derivative)

Ethyl 5-benzyloxycarbonylaminomethyl-3-methylisoxazole-4-carboxylate **24** (2.0 g, 6.36 mmol) was treated with HBr in glacial acetic acid (33% w/v, 1.7 g, 6.93 mmol) at 20 °C for 4 h. To this was added dry diethyl ether (100 cm^3) and the precipitate collected by filtration and washed with dry diethyl ether (3 × 30 cm^3) to afford the hydrobromide salt **26** as a pale brown solid (5.41 g, 86%). To this salt was added Na_2CO_3 (2.4 g, 22.44 mmol) in water (75 cm^3) and the mixture stirred at 20 °C for 16 h. The mixture was then extracted with $CHCl_3$ (3 × 50 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure to leave the *title compound* as a pale yellow oil (2.97 g, 72%), identical to a sample prepared from the phthalimido derivative **11**.

5-Benzyloxycarbonylaminomethyl-3-methylisoxazole-4-carboxylic acid 27

Ethyl 5-benzyloxycarbonylaminomethyl-3-methylisoxazole-4-carboxylate **24** (3.70 g, 11.63 mmol) was treated with NaOH (0.47 g, 11.63 mmol) in water (25 cm^3) at reflux for 4 h. The mixture was cooled, washed with $CHCl_3$ (10 cm^3) and the aqueous layer acidified to pH 3 with conc. hydrochloric acid. The precipitate was filtered under suction, dissolved in $CHCl_3$ and the solution dried ($MgSO_4$) and evaporated under reduced pressure to yield the *title compound* as a pale cream solid (2.48 g, 73%), mp 171–172 °C (Found: C, 57.9; H, 4.8; N, 9.5%; M^+, 290.0860. $C_{14}H_{14}N_2O_5$ requires C, 57.93; H, 4.86; N, 9.65%; *M*, 290.0919); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 211 (11120); ν_{max}(Nujol)/cm^{-1} 3311 (v br), 1741, 1697 and 1275; δ_H [250 MHz; $(CD_3)_2SO$] 2.35 (3H, s, 3-CH_3), 4.60 (2H, d, *J* 7, $NHCH_2$), 5.05 (2H, s, $PhCH_2$), 7.35 (5H, s, Ar-H) and 8.00 (1H, br s, NH); δ_C [68 MHz; $(CD_3)_2SO$] 11.2 (CH_3), 37.1 and 65.74 (CH_2), 108.7 (C), 127.8, 127.9 and 128.4 (CH), 136.8, 156.3, 159.7, 162.9 and 174.1 (C); *m*/*z* 290 (M^+), 109 and 91 (100%).

3-Methyl-5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one hydrobromide 28

To 5-benzyloxycarbonylaminomethyl-3-methylisoxazole-4-carboxylic acid **27** (2.3 g, 7.94 mmol) in THF (50 cm^3) was added Et_3N (0.85 g, 8.4 mmol) at 0 °C and the mixture stirred for 10 min, before ethyl chloroformate (0.91 g, 8.4 mmol) was added dropwise and the suspension stirred a further 12 h at 20 °C. After this period the mixture was filtered and the solvent evaporated under reduced pressure to yield the mixed anhydride, which was used directly; δ_H(250 MHz; $CDCl_3$) 1.40 (3H, t, *J* 7, OCH_2CH_3), 2.45 (3H, s, 3-CH_3), 4.40 (2H, q, *J* 7, OCH_2CH_3), 4.65 (2H, d, *J* 5, CH_2NH), 5.10 (2H, s, $PhCH_2$), 5.50 (1H, br s, NH) and 7.40 (5H, s, Ar-H).

To the mixed anhydride was added HBr in glacial acetic acid (33% w/v, 0.7 g, 8.4 mmol) and the mixture stirred a further 16 h. Dry diethyl ether was then added (30 cm^3) and the precipitate filtered under suction, washed with dry diethyl ether (3 × 30 cm^3) and dried to yield the *title compound* (1.4 g, 80%) as an off-white solid, mp 270–272 °C (Found: M^+ − HBr, 138.0422. $C_6H_7N_2O_2Br$ requires *M* − HBr, 138.0429); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 213 (3929); ν_{max}(Nujol)/cm^{-1} 1747, 1604, 1575, 1516, 1305, 1227, 1115, 1075, 865 and 734; δ_H [400 MHz; $(CD_3)_2SO$] 2.58 (3H, s, 3-CH_3), 4.69 (2H, s, CH_2NH) and 8.50 (2H, br s, 2 × NH); δ_C [125 MHz; $(CD_3)_2SO$] 11.3 (CH_3), 34.5 (CH_2), 111.1, 160.1, 162.6 and 169.4 (C); *m*/*z* 138 (M^+ − HBr), 128, 110, 80 (100%), 79 and 52.

3-(1-Hydroxyethylidene)pyrrolidine-2,4-dione (3-acetyltetramic acid) 29

3-Methyl-5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one hydrobromide **28** (170 mg, 0.776 mmol) and palladium on charcoal (10% Pd, 0.50 mg) were stirrred together in EtOH (30 cm^3) at 20 °C under hydrogen (1 atm) until 1 equiv. of hydrogen (18.63 cm^3, 0.776 mmol) had been absorbed. The mixture was then filtered through kieselgühr and the filtrate evaporated under

reduced pressure to yield a white solid. To this was added 2 M aqueous NaOH (10 cm^3) and the mixture stirred at 20 °C for 3 h before acidification to pH 1 with conc. hydrochloric acid. The precipitate was collected by filtration to yield the *title compound* as a white solid (100 mg, 91%), mp 156–158 °C (lit.,[45] 155 °C) (Found: C, 50.7; H, 4.9; N, 9.5%; M^+, 141.0404. $C_6H_7NO_3$ requires C, 51.07; H, 5.00; N, 9.92%; *M*, 141.0426); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 275 (11053); ν_{max}(Nujol)/cm^{-1} 3210, 1712, 1459 and 962; δ_H(250 MHz; $CDCl_3$/CF_3CO_2D) 2.65 (3H, s, CH_3CO) and 4.20 (2H, br s, CH_2); δ_C(68 MHz; CD_3OD) 20.5 (CH_3), 52.2 (CH_2), 97.8, 110.7, 167.9 and 196.5 (C); *m*/*z* 141 (M^+, 100%), 126, 113 and 84.

5-Benzoyl-3-methyl-5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one 35

To 3-methyl-5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one hydrobromide **28** (25 mg, 0.02 mmol) in dry THF (2 cm^3) at −78 °C under nitrogen was added n-butyllithium (1.6 M solution in hexanes, 72 µl, 0.02 mmol). The mixture was stirred at −78 °C for 1 h before the dropwise addition of PhCOCl (15 µl, 0.022 mmol), and then for a further 4 h whilst being allowed to warm to 20 °C. The mixture was then added to saturated aqueous NH_4Cl (2 cm^3), extracted with CH_2Cl_2 (3 × 10 cm^3), and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to yield the *title compound* (15.5 mg, 56%) as a white solid, mp 157–159 °C (Found: M^+ − PhCO, 137.0332. $C_{13}H_{10}N_2O_3$ requires *M* − PhCO, 137.0351); ν_{max}($CHCl_3$)/cm^{-1} 2385, 1707, 1666 and 1126; δ_H(250 MHz; CD_3OD) 2.45 (3H, s, 3-CH_3), 5.05 (2H, s, CH_2) and 7.50–7.92 (5H, m, Ph); δ_C(68 MHz; CD_3OD) 11.6 (CH_3), 37.5 (CH_2), 110.4 (C), 128.4, 129.6 and 133.0 (CH), 161.7, 164.7, 175.3 and 197.5 (C); *m*/*z* 137 (M^+ − PhCO), 105 (PhCO, 100%) and 91.

Ethyl 5-benzyloxycarbonylamino-3-oxopentanoate 37

Prepared as described for the preparation of ethyl 4-phthalimido-3-oxobutanoate **21**, but using *N*-benzyloxycarbonyl-β-alanine **36** (30.0 g, 134.0 mmol), 1,1′-carbonyldiimidazole (21.8 g, 134.0 mmol), ethyl hydrogen malonate (19.5 g, 147.0 mmol), magnesium (6.43 g, 268.0 mmol) and 2-bromopropane (33.0 g, 268.0 mmol), to yield the *title compound* (35.6 g, 91%) as a yellow oil (Found: C, 61.2; H, 6.6; N, 4.9%. $C_{15}H_{19}NO_5$ requires C, 61.42; H, 6.53; N, 4.78%); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 208 (6492); ν_{max}(film)/cm^{-1} 3353, 3032, 2981, 1715, 1526, 1454 and 1248; δ_H(270 MHz; $CDCl_3$) 1.27 (3H, t, *J* 7, OCH_2CH_3), 2.80 (2H, t, *J* 6, $NHCH_2CH_2$), 3.43 (2H, s, $COCH_2CO$), 3.44 (2H, t, *J* 6, $NHCH_2CH_2$), 4.18 (2H, q, *J* 7, OCH_2CH_3), 5.08 (2H, s, $PhCH_2$), 5.27 (1H, br s, NH) and 7.34 (5H, s, Ph); δ_C(68 MHz; $CDCl_3$) 13.9 (CH_3), 35.2, 42.4, 48.8, 61.1 and 66.2 (CH_2), 127.7, 127.8 and 128.2 (CH), 136.2, 156.1, 166.7 and 201.9 (C); *m*/*z* (FAB) 294 (M^+ + 1), 250, 204, 120 and 91 (100%).

Ethyl 5-(2-benzyloxycarbonylaminoethyl)-3-methylisoxazole-4-carboxylate 38

Prepared as described above for ethyl 3,5-dimethylisoxazole-4-carboxylate **9**, but using ethyl 5-benzyloxycarbonylamino-3-oxopentanoate **37** (44.76 g, 0.153 mol) and pyrrolidine (10.85 g, 0.153 mol) in toluene to form the enamine, Et_3N (46.36 g, 0.459 mol), $EtNO_2$ (12.63 g, 0.168 mol) and $POCl_3$ (25.81 g, 0.168 mol). Workup afforded an orange oil which was purified by column chromatography on silica gel, eluting with light petroleum (bp 40–60 °C)–EtOAc (1:1 v/v) to yield the *title compound* (35.73 g, 68%) as a pale yellow oil (Found: C, 61.4; H, 6.1; N, 8.2%; M^+, 332.1356. $C_{17}H_{20}N_2O_5$ requires C, 61.44; H, 6.07; N, 8.43%; *M*, 332.1372); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 210 (10200); ν_{max}(film)/cm^{-1} 3346, 3064, 3032, 1720, 1607, 1531, 1455, 1374, 1301, 1244 and 1106; δ_H(250 MHz; $CDCl_3$) 1.35 (3H, t, *J* 7, OCH_2CH_3), 2.40 (3H, s, 3-CH_3), 3.30 and 3.60 (each 2H, t, *J* 6, $NHCH_2CH_2$), 4.35 (2H, q, *J* 7, OCH_2CH_3), 5.10 (2H, s, $PhCH_2$), 5.25 (1H, br s, NH) and 7.35 (5H, s, Ph); δ_C(68 MHz; $CDCl_3$) 11.5 and 13.9 (CH_3), 27.8, 38.4, 60.6 and 66.4 (CH_2), 109.2 (C), 127.8, 128.0 and 128.2 (CH), 136.2, 156.1, 159.7, 162.0 and 175.5 (C); *m*/*z* 332 (M^+), 225, 169 and 91 (100%).

Ethyl 5-(2-aminoethyl)-3-methylisoxazole-4-carboxylate hydrobromide 39

Ethyl 5-(2-benzyloxycarbonylaminoethyl)-3-methylisoxazole-4-carboxylate **38** (16.54 g, 49.8 mmol) was treated with HBr in glacial acetic acid (32% w/v, 15.11 cm^3, 59.7 mmol) and stirred at room temperature for 4 h. To this was added dry diethyl ether (80 cm^3) and the precipitate was filtered under suction, washed with dry ether (3 × 40 cm^3) and dried to yield the *title compound* (12.4 g, 90%) as a pale cream solid, mp 174–176 °C (Found: C, 38.4; H, 5.5; N, 9.9; Br, 28.5%; M^+ − HBr, 198.1040. $C_9H_{15}N_2O_3Br$ requires C, 38.73; H, 5.42; N, 10.04; Br, 28.63%; *M* − HBr, 198.1004); ν_{max}(KBr)/cm^{-1} 3399, 2982, 2700, 1609, 1428, 1367, 1307, 1130 and 940; δ_H [250 MHz; $(CD_3)_2SO$] 1.47 (3H, t, *J* 7, OCH_2CH_3), 2.52 (3H, s, 3-CH_3), 3.35 and 3.55 (each 2H, t, *J* 6, $CH_2CH_2NH_3^+$), 4.45 (2H, q, *J* 7, OCH_2CH_3) and 8.15 (3H, br s, NH_3^+); δ_C [68 MHz; $(CD_3)_2SO$] 12.0 and 14.7 (CH_3), 25.8, 36.6 and 61.3 (CH_2), 109.9, 160.1, 162.0 and 174.3 (C); *m*/*z* 198 (M^+ − HBr), 169 (100%), 97, 82 and 79.

3-Methyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one 8b

To ethyl 5-(2-aminoethyl)-3-methylisoxazole-4-carboxylate hydrobromide **39** (10.0 g, 35.83 mmol) was added Na_2CO_3 (3.8 g, 35.83 mmol) in water (100 cm^3) and the solution stirred at room temperature for 16 h. The light brown solution was extracted with EtOAc (3 × 75 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield the *title compound* as an off-white solid (5.2 g, 96%), mp 166–168 °C (Found: C, 55.0; H, 5.35; N, 18.3%; M^+, 152.0580. $C_7H_8N_2O_2$ requires C, 55.26; H, 5.30; N, 18.41%; *M*, 152.0586); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 215 (3373); ν_{max}($CHCl_3$)/cm^{-1} 3422, 3007, 1685, 1605, 1498, 1466, 1323 and 919; δ_H(250 MHz; $CDCl_3$) 2.50 (3H, s, 3-CH_3), 3.07 (2H, t, *J* 7, $NHCH_2CH_2$), 3.67 (2H, dt, *J* 7 and 2.5, $NHCH_2CH_2$) and 6.02 (1H, br s, NH); δ_C(68 MHz; $CDCl_3$) 10.9 (CH_3), 23.3 and 40.58 (CH_2), 109.5, 158.0, 164.6 and 174.1 (C); *m*/*z* 152 (M^+, 100%), 123 (100%), 81 and 67.

5-(2-Benzyloxycarbonylaminoethyl)-3-methylisoxazole-4-carboxylic acid 40

Prepared as described above for 5-benzyloxycarbonylaminomethyl-3-methylisoxazole-4-carboxylic acid **27**, but using ethyl 5-(2-benzyloxycarbonylaminoethyl)-3-methylisoxazole-4-carboxylate **38** (9.00 g, 29.49 mmol) and NaOH (1.20 g, 29.24 mmol) in water (100 cm^3). The cooled solution was filtered, carefully acidified to pH 1 (conc. hydrochloric acid), and the precipitate collected and washed with diethyl ether (30 cm^3) to afford the *title compound* as a white solid (7.65 g, 86%), mp 165–167 °C (Found: M^+, 304.1078. $C_{15}H_{16}N_2O_5$ requires *M*, 304.1059); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 208 (1538); ν_{max}(Nujol)/cm^{-1} 3309, 1682, 1606, 1548 and 1121; δ_H [250 MHz; $(CD_3)_2CO$] 2.45 (3H, s, 3-CH_3), 3.30 and 3.60 (each 2H, t, *J* 8, $NHCH_2CH_2$), 5.05 (2H, s, $PhCH_2$), 5.25 (1H, br s, NH) and 7.20–7.35 (5H, s, Ph); δ_C [68 MHz; $(CD_3)_2SO$] 11.4 (CH_3), 27.6, 39.3 and 65.3 (CH_2), 109.3 (C), 127.7, 128.4 and 134.1 (CH), 137.2, 156.1, 159.6, 163.2 and 175.7 (C); *m*/*z* 304 (M^+), 169, 100 and 91 (100%).

3-Methyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one hydrobromide 41

Prepared as described above for 3-methyl-5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one hydrobromide **28**, but using 5-(2-benzyloxycarbonylaminoethyl)-3-methylisoxazole-4-carboxylic acid **40** (4.04 g, 13.28 mmol) in THF (75 cm^3), *N*-methylmorpholine (1.34 g, 13.28 mmol) as tertiary amine, ethyl chloro-

formate (1.44 g, 13.28 mmol) and HBr in glacial acetic acid (33% w/v, 3.30 cm^3, 13.28 mmol), to yield the *title compound* (1.92 g, 62%) as a pale buff solid, mp 194–197 °C (Found: $M^+ - HBr$, 152.0585. $C_7H_9N_2O_2Br$ requires $M - HBr$, 152.0586); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 216 (4544); ν_{max}(Nujol)/cm^{-1} 3380, 1745, 1605, 1268 and 929; δ_H [250 MHz; $(CD_3)_2SO$] 2.40 (3H, s, 3-CH_3), 3.20 and 3.50 (each 2H, m, NHCH_2CH_2), 5.05 (2H, s, PhCH_2), 5.25 (1H, br s, NH) and 8.20 (2H, br s, 2 × NH); δ_C [68 MHz; $(CD_3)_2SO$] 11.8 (CH_3), 25.5 and 36.5 (CH_2), 110.2, 159.9, 163.4 and 173.8 (C); *m*/*z* 152 ($M^+ - HBr$), 141 and 23 (100%).

5-*tert*-Butoxycarbonyl-3-methyl-4,5,6,7-tetrahydroisoxazolo-[4,5-*c*]pyridin-4-one 42

To 3-methyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **8b** (0.5 g, 3.28 mmol) in dry THF (20 cm^3) at −78 °C under nitrogen was added n-butyllithium (1.5 M in hexanes, 2.20 cm^3, 3.28 mmol) and the mixture stirred at −78 °C for 0.5 h before the addition of di-*tert*-butyl dicarbonate (0.79 g, 3.61 mmol) in dry THF (5 cm^3). After stirring at room temperature for 3 h, saturated aqueous NH_4Cl (30 cm^3) was added and the mixture extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil which was purified by column chromatography on silica gel eluting with a solvent gradient of CH_2Cl_2 to CH_2Cl_2–MeOH (98 : 2 v/v) to afford the *title compound* as a white solid (0.572 g, 69%), mp 30 °C (Found: C, 57.1; H, 6.5; N, 10.8%; $MH^+ - CO_2CMe_3$, 152.0570. $C_{12}H_{16}N_2O_4$ requires C, 57.13; H, 6.39; N, 11.10%; $MH - CO_2CMe_3$, 152.0586); ν_{max}($CHCl_3$)/cm^{-1} 1764, 1715, 1369, 1318, 1297, 1130 and 1073; δ_H(270 MHz; $CDCl_3$) 1.56 [9H, s, C(CH_3)$_3$], 2.50 (3H, s, 3-CH_3), 3.08 and 4.16 (each 2H, t, *J* 7, NCH_2CH_2); δ_C(68 MHz; $CDCl_3$) 10.5 (CH_3), 23.1 (CH_2), 28.1 (3 × CH_3), 44.2 (CH_2), 83.5, 110.7, 152.5, 158.0, 160.3 and 175.6 (C); *m*/*z* 152 ($MH^+ - CO_2CMe_3$) and 57 (100%).

3-Methyl-7-phenylseleno-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]-pyridin-4-one 43

n-Butyllithium (1.6 M in hexanes, 9.10 cm^3, 14.50 mmol) was added dropwise to a solution of diisopropylamine (2.10 cm^3, 14.50 mmol) in dry THF (40 cm^3) stirred at 0 °C under a nitrogen atmosphere. The resultant solution was stirred for 20 min, cooled to −78 °C, and 3-methyl-4,5,6,7-tetrahydroisoxazolo-[4,5-*c*]pyridin-4-one **8b** (1.00 g, 6.57 mmol) in dry THF (20 cm^3) was added. After stirring at −78 °C for 2 h, phenylselenenyl chloride (1.26 g, 6.57 mmol) in dry THF (10 cm^3) was added and the mixture stirred at 20 °C for 1.5 h. Saturated aqueous NH_4Cl (30 cm^3) was then added and the mixture extracted with chloroform (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield a brown oil which was purified by column chromatography on silica gel eluting with light petroleum (bp 40–60 °C)–EtOAc (1 : 2 v/v) to yield the *title compound* as a pale beige solid (1.60 g, 79%), mp 164–165 °C (Found: C, 50.8; H, 3.9; N, 9.1%; M^+, 308.0070. $C_{13}H_{12}N_2O_2Se$ requires C, 50.83; H, 3.94; N, 9.12%; *M*, 308.0064); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 221 (13159); ν_{max}($CHCl_3$)/cm^{-1} 3421, 1682, 1603, 1580, 1490, 1305, 1159 and 999; δ_H(250 MHz; $CDCl_3$) 2.42 (3H, s, 3-CH_3), 3.74 (1H, ddd, *J* 14, 5 and 3, CHC*H*HNH), 4.18 (1H, ddd, *J* 14, 5 and 1, CHCH*H*NH), 4.56 (1H, dd, *J* 5 and 3, C*H*CHH), 6.29 (1H, br s, NH) and 7.25–7.59 (5H, m, Ph); δ_C(68 MHz; $CDCl_3$) 10.4 (CH_3), 31.6 (CH), 47.9 (CH_2), 109.4 (C), 126.1 (CH), 129.1 (CH), 136.5 (CH), 158.1 (C), 163.0 (C) and 174.1 (C); *m*/*z* 308 (M^+), 151 (100%), 91 and 77.

3-Methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one 19

3-Methyl-7-phenylseleno-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **43** (1.00 g, 3.85 mmol) was treated with aqueous hydrogen peroxide (30% w/v, 1.35 cm^3, 15.4 mmol) at 0 °C followed by glacial acetic acid (0.95 cm^3) and water (0.60 cm^3) and the mixture stirred at 0 °C for 0.5 h and at 20 °C for 2 h. After this period the mixture was extracted with CH_2Cl_2 (3 × 200 cm^3) and the combined organic extracts were washed with saturated brine (200 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to yield the *title compound* as a white solid (0.45 g, 92%), mp 215–218 °C (Found: C, 55.6; H, 3.9; N, 18.4%; M^+, 150.0425. $C_7H_6N_2O_2$ requires C, 56.00; H, 4.03; N, 18.66%; *M*, 150.0429); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 279.2 (1627); ν_{max}($CHCl_3$)/cm^{-1} 3043, 2399, 1681, 1424, 1204 and 1044; δ_H(250 MHz; $CDCl_3$) 2.66 (3H, s, 3-CH_3), 6.61 and 7.41 (each 1H, d, *J* 7, C*H*=C*H*NH) and 11.49 (1H, br s, NH); δ_C(68 MHz; $CDCl_3$) 10.8 (CH_3), 94.3 (CH), 110.0 (C), 135.7 (CH), 157.0, 161.4 and 171.0 (C); *m*/*z* 150 (M^+, 100%).

7-Bromo-3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one 44

To 3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **19** (0.045 g, 0.270 mmol) in $CHCl_3$ (2 cm^3) was added bromine (0.015 cm^3, 0.270 mmol) in $CHCl_3$ (1 cm^3) over 0.5 h. The yellow solution was stirred 0.75 h before treatment with Et_3N (0.110 g, 1.06 mmol) and stirring a further 20 h at 20 °C. After this time, saturated aqueous sodium hydrogen carbonate (4 cm^3) was added and the mixture extracted with $CHCl_3$ (3 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield a brown solid, purified by flash column chromatography on silica gel eluting with CH_2Cl_2–MeOH (96 : 4 v/v) to yield the *title compound* as an off-white solid (0.042 g, 62%), mp 226–228 °C (Found: C, 36.2; H, 2.2; N, 12.0%; M^+, 227.9539 and 229.9519. $C_7H_5N_2O_2Br$ requires C, 36.59; H, 2.20; N, 12.23%; *M*, 227.9350 and 229.9514); ν_{max}(Nujol)/cm^{-1} 1673, 1606, 1496, 1300, 1268, 1210, 1082, 940, 869, 740 and 634; δ_H [250 MHz; $(CD_3)_2SO$] 2.50 (3H, s, 3-CH_3) and 7.91 (1H, s, CH); δ_C [68 MHz; $(CD_3)_2SO$] 10.7 (CH_3), 82.4 and 109.4 (C), 138.4 (CH), 158.3, 158.4 and 168.0 (C); *m*/*z* 228 and 230 (M^+, 100%), 149, 81 and 79.

7-Iodo-3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one 45

Method A. 3-Methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **19** (0.010 g, 0.066 mmol) in $CHCl_3$–pyridine (1 : 1 v/v, 0.5 cm^3) under a nitrogen atmosphere was treated with I_2 (0.068 g, 0.53 mmol) in $CHCl_3$–pyridine (1 : 1 v/v, 0.5 cm^3) at 0 °C and the brown solution stirred for a further 36 h at 20 °C. The mixture was then diluted with diethyl ether (5 cm^3), and washed with water (2 cm^3), 2 M hydrochloric acid (2 × 2 cm^3), water (2 cm^3) and aqueous sodium thiosulfate (2 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a brown solid purified by flash column chromatography on silica gel eluting with EtOAc to yield the *title compound* as a white solid (0.007 g, 40%), mp 129–132 °C (Found: M^+, 275.9401. $C_7H_5N_2O_2I$ requires *M*, 275.9396); ν_{max}(Nujol)/cm^{-1} 3583, 1697, 1588, 1556, 1288, 1185, 1069, 859, 803, 777 and 722; δ_H [400 MHz; $(CD_3)_2SO$] 2.48 (3H, s, 3-CH_3), 7.83 (1H, s, CH) and 11.97 (1H, br s, NH); δ_C [100 MHz; $(CD_3)_2SO$] 10.7 (CH_3), 49.8 and 108.5 (C), 142.5 (CH), 158.1, 158.5 and 170.4 (C); *m*/*z* 276 (M^+, 100%) and 149 ($M^+ - I$).

Method B. To 3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **19** (0.52 g, 3.50 mmol) in dry CH_2Cl_2 (20 cm^3) and dry MeOH (5 cm^3) at 20 °C under nitrogen, was added ICl (1.0 M in CH_2Cl_2, 5.2 cm^3, 5.18 mmol) and the reaction mixture was stirred for 16 h. The precipitate was collected and washed with a minimum of CH_2Cl_2 to yield the *title compound* (0.41 g, 43%) as a white solid, identical with material prepared by Method A (see above).

7-(4-Methoxyphenyl)-3-methyl-4,5-dihydroisoxazolo[4,5-*c*]-pyridin-4-one 47

7-Iodo-3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **45** (23 mg, 0.08 mmol) in dry THF (5 cm^3) was treated with

tris(dibenzylideneacetone)dipalladium (3.9 mg, 0.004 mmol) and $AsPh_3$ (5 mg, 0.016 mmol) in dry THF (1 cm^3) and the mixture stirred at 20 °C for 10 min, until the deep red solution turned straw coloured. (4-Methoxyphenyl)tributyltin **46** (37 mg, 0.092 mol) in dry THF (1 cm^3) was then added and the mixture heated under reflux for 9 h. Evaporation under reduced pressure afforded a residue purified by column chromatography on silica gel eluting with light petroleum (bp 40–60 °C)–EtOAc (1:2 v/v) to yield the *title compound* as an off-white solid (17 mg, 78%), mp 238 °C (Found: M^+, 256.0844. $C_{14}H_{12}N_2O_3$ requires *M*, 256.0848); $\nu_{max}(CHCl_3)/cm^{-1}$ 3623 and 1683; δ_H [400 MHz; $(CD_3)_2SO$] 2.49 (3H, s, 3-CH_3), 3.79 (3H, s, OCH_3), 6.66 and 7.53 (each 1.26 H, d, *J* 7, tautomer A), 7.03 and 7.64 (each 0.74H, d, *J* 8.5, tautomer B) and 7.61 (1H, s, C*H*NH); δ_C [100 MHz; $(CD_3)_2SO$] 10.2 and 55.2 (CH_3), 92.1 (CH), 106.7 and 108.9 (C), 114.3 (CH), 123.9 (C), 128.0, 134.0 and 137.7 (CH), 156.7, 157.1, 158.3, 158.8, 168.8 and 170.7 (C); *m*/*z* 256 (M^+, 100%), 226, 150 and 76.

7-Ethenyl-3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one 48

To 7-iodo-3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **45** (37 mg, 0.13 mmol), tris(dibenzylideneacetone)dipalladium (1 mg, 0.001 mmol) and $AsPh_3$ (2 mg, 0.0065 mmol) under nitrogen was added dry THF (4 cm^3) and left to stir at 20 °C for 5 min, until the red solution became straw coloured. Vinyltributyltin (47 mg, 0.15 mmol) was added and the reaction mixture left to stir at 20 °C for 16 h and then at 50 °C for 1 h. After cooling, the reaction mixture was concentrated under reduced pressure, the residue taken up in acetonitrile (10 cm^3), washed with hexane (2 × 10 cm^3), concentrated under reduced pressure and purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (20:1 v/v) to yield the *title compound* as a white solid (18 mg, 74%), mp >230 °C (Found: M^+, 176.0585. $C_9H_8N_2O_2$ requires *M*, 176.0586); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 229 (8700), 264 (10300) and 299 (3300); ν_{max}(KBr)/cm^{-1} 1698, 1640, 1607, 1569, 1527, 1497, 1427, 1371, 1320, 1303, 1265 and 1207; δ_H [400 MHz; $(CD_3)_2SO$] 2.50 (3H, s, 3-C*H*$_3$), 5.30 (1H, dd, *J* 1 and 11, CH=C*H*H), 5.90 (1H, dd, *J* 1 and 18, CH=CH*H*), 6.63 (1H, dd, *J* 11 and 18, C*H*=CH_2), 7.68 (1H, d, *J* 4.5, C*H*NH) and 11.91 (1H, br s, NH); δ_C [100 MHz; $(CD_3)_2SO$] 10.9 (CH_3), 106.2 and 109.7 (C), 115.5 (CH_2), 129.1 and 137.6 (CH), 157.5, 158.9 and 169.6 (C); *m*/*z* 176 (M^+, 100%), 161, 147, 133, 119, 105 and 67.

3,5-Dimethyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one 49

Prepared as described above for 3-methyl-7-phenylseleno-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **43**, but using n-butyllithium (1.6 M in hexanes, 3.89 cm^3, 6.22 mmol), diisopropylamine (0.63 g, 6.22 mmol), 3-methyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **8b** (0.86 g, 5.65 mmol) and iodomethane (0.40 cm^3, 6.22 mmol) as electrophile. Workup afforded a yellow solid that was purified by flash column chromatography on silica gel eluting with EtOAc–light petroleum (bp 40–60 °C) (3:1 v/v) to yield the *title compound* as a pale yellow solid (0.61 g, 65%), mp 90.5–91 °C (Found: C, 57.7; H, 6.0; N, 16.7%; M^+, 166.0740. $C_8H_{10}N_2O_2$ requires C, 57.82; H, 6.07; N, 16.86%; *M*, 166.0742); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 218 (4420); $\nu_{max}(CHCl_3)/cm^{-1}$ 1667, 1611 and 1326; δ_H(400 MHz; $CDCl_3$) 2.47 (3H, s, 3-CH_3), 3.04 (3H, s, NCH_3), 3.11 and 3.70 (each 2H, t, *J* 7, CH_2CH_2); δ_C(100 MHz; $CDCl_3$) 10.1 (CH_3), 22.4 (CH_2), 33.1 (CH_3), 47.8 (CH_2), 109.6, 158.0, 162.0 and 173.2 (C), confirmed by $^1H/^{13}C$ COSY; *m*/*z* 166 (M^+) and 123 (100%).

3,5-Dimethyl-7-phenylseleno-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]-pyridin-4-one 50

Prepared as described above for 3-methyl-7-phenylseleno-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **43**, but using n-butyllithium (1.6 M in hexanes, 1.80 cm^3, 2.85 mmol), diisopropylamine (0.40 cm^3, 2.85 mmol), 3,5-dimethyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **49** (0.43 g, 2.59 mmol) and phenylselenenyl chloride (0.55 g, 2.55 mmol) as electrophile. Workup afforded a yellow solid that was purified by flash column chromatography on silica gel eluting with EtOAc–light petroleum (bp 40–60 °C) (2:1 v/v) to yield the *title compound* as a pale beige oil (0.24 g, 38%) (Found: M^+, 322.0225. $C_{14}H_{14}N_2O_2Se$ requires *M*, 322.0220); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 252.5 (27246); $\nu_{max}(CHCl_3)/cm^{-1}$ 1668, 1609, 1309 and 1096; δ_H(250 MHz; $CDCl_3$) 2.35 (3H, s, 3-CH_3), 2.90 (3H, s, NCH_3), 3.60 (1H, dd, *J* 14 and 3, CHC*H*H), 4.12 (1H, dd, *J* 14 and 5, CHCH*H*), 4.50 (1H, dd, *J* 5 and 3, C*H*CHH) and 7.15–7.45 (5H, m, Ph); δ_C(68 MHz; $CDCl_3$) 10.4 (CH_3), 31.2 (CH), 33.5 (CH_3), 55.9 (CH_2), 110.2 (C), 126.0, 129.2, 129.3 and 136.6 (CH), 158.4, 161.0 and 172.7 (C); *m*/*z* 322 (M^+) and 165 (100%).

3,5,7-Trimethyl-7-phenylseleno-4,5,6,7-tetrahydroisoxazolo-[4,5-*c*]pyridin-4-one 51

Prepared as described above for 3-methyl-7-phenylseleno-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **43**, but using n-butyllithium (1.6 M in hexanes, 0.45 cm^3, 0.726 mmol), diisopropylamine (0.10 cm^3, 0.726 mmol), 3,5-dimethyl-7-phenylseleno-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **50** (0.16 g, 0.660 mmol) and iodomethane (0.11 g, 0.726 mmol) as electrophile, to yield the *title compound* as an orange oil (0.14 g, 84%) (Found: M^+ − SePh, 179.0821. $C_{15}H_{16}N_2O_2Se$ requires *M* − SePh, 179.0821); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 252.5 (19178); $\nu_{max}(CHCl_3)/cm^{-1}$ 1682, 1550, 1320 and 1122; δ_H(250 MHz; $CDCl_3$) 1.75 (3H, s, 7-CH_3), 2.35 (3H, s, 3-CH_3), 2.95 (3H, s, NCH_3), 3.60 and 4.00 (each 1H, d, *J* 7.5, C*HH*) and 7.20–7.40 (5H, m, Ph); δ_C(68 MHz; $CDCl_3$) 10.5 and 22.5 (CH_3), 33.5 (CH_2), 40.5 (C), 63.0 (CH_2), 103.0 and 109.5 (C), 128.0 (CH), 131.2, 138.5, 158.5, 161.5 and 176.1 (C); *m*/*z* 179 (M^+ − SePh, 100%), 77 and 42.

3,5,7-Trimethyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one 52

Prepared as described for 3-methyl-4,5-dihydroisoxazolo[4,5-*c*]-pyridin-4-one **19**, but using 3,5,7-trimethyl-7-phenylseleno-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **51** (0.10 g, 0.40 mmol), aqueous hydrogen peroxide (30% w/v, 165 mg, 1.60 mmol), glacial acetic acid (50 mg) and water (30 mg) to yield the *title compound* as a pale yellow solid (0.68 g, 95%), mp 100–102 °C (Found: M^+, 178.0756. $C_9H_{10}N_2O_2$ requires *M*, 178.0742); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 291.6 (4358); $\nu_{max}(CHCl_3)/cm^{-1}$ 1667, 1614, 1573, 1161 and 1061; δ_H(250 MHz; $CDCl_3$) 2.25 (3H, s, 7-CH_3), 2.65 (3H, s, 3-CH_3), 3.55 (3H, s, NCH_3) and 7.10 (1H, s, CH); δ_C(68 MHz; $CDCl_3$) 10.7, 11.8 and 36.2 (CH_3), 103.1 and 109.0 (C), 137.5 (CH), 158.0, 158.8 and 170.0 (C); *m*/*z* 178 (M^+), 151, 96 and 68.

3-(1-Hydroxyethylidene)piperidine-2,4-dione

Prepared as described for 3-(1-hydroxyethylidene)pyrrolidine-2,4-dione **29**, but using 3-methyl-4,5,6,7-tetrahydroisoxazolo-[4,5-*c*]pyridin-4-one **8b** (0.045 g, 0.30 mmol) and palladium on charcoal (10% Pd, 45 mg), to yield the *title compound* as a white solid (0.046 g, 97%), mp 174–176 °C (Found: M^+, 155.0548; $C_7H_9NO_3$ requires *M*, 155.0582); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 272 (5000); ν_{max}(Nujol)/cm^{-1} 3170, 1660, 1628, 1331, 1248, 1039 and 720; δ_H(250 MHz; CF_3CO_2D–$CDCl_3$) 2.55 (3H, s, CH_3), 2.90 (2H, br s, CH_2CH_2N) and 3.70 (2H, br s, CH_2CH_2N); δ_C [68 MHz; $(CD_3)_2SO$] 25.1 (CH_3), 35.0 and 36.9 (CH_2), 100.8, 171.5, 191.0 and 192.5 (C); *m*/*z* 155 (M^+, 100%), 140, 85 and 55.

3-Acetyl-1,2-dihydro-4-hydroxypyridin-2-one 54

Prepared as described for 3-(1-hydroxyethylidene)pyrrolidine-2,4-dione **29**, but using 3-methyl-4,5-dihydroisoxazolo[4,5-*c*]-pyridin-4-one **19** (40.50 mg, 0.27 mmol) and palladium on charcoal (10% Pd, 0.50 mg) to yield the *title compound* as a

white solid (40.0 mg, 97%), mp 220–221 °C (lit.,[46] 212–214 °C) (Found: M^+, 153.0438. $C_7H_7NO_3$ requires *M*, 153.0426); λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 323 (5800); ν_{max}(Nujol)/cm^{-1} 3500, 1864, 1623, 1253, 1228 and 765; δ_H(250 MHz; CD_3OD) 2.60 (3H, s, CH_3), 5.95 and 7.40 (each 1H, d, *J* 7, CH=CH); δ_C(68 MHz; CD_3OD) 31.6 (CH_3), 101.5 (CH), 108.6 (C), 142.6 (CH), 164.5, 178.7 and 206.8 (C); *m*/*z* 153 (M^+, 100%), 111 and 70.

5-(4-Methoxyphenyl)-3-acetyl-1,2-dihydro-4-hydroxypyridin-2-one 55

Prepared as described for 3-(1-hydroxyethylidene)pyrrolidine-2,4-dione **29**, but using 7-(4-methoxyphenyl)-3-methyl-4,5-dihydroisoxazolo[4,5-*c*]pyridin-4-one **47** (12.5 mg, 0.049 mmol) and palladium on charcoal (10% Pd, 5 mg) to yield the *title compound* as an off-white solid (13 mg, 100%), mp 230–232 °C (Found: M^+, 259.0784. $C_{14}H_{13}NO_4$ requires *M*, 259.0844); $\nu_{max}(CHCl_3)$/cm^{-1} 1682; δ_H [500 MHz; $(CD_3)_2SO$] 2.41 (3H, s, 3-CH_3), 3.76 (3H, s, OCH_3), 6.94 and 7.36 (each 2H, d, *J* 7, Ar-H), 7.60 (1H, s, CHN) and 11.68 (1H, br s, NH); δ_C [125 MHz; $(CD_3)_2SO$] 30.8 and 55.1 (CH_3), 106.4 and 111.7 (C), 113.6 (CH), 124.9 (C), 130.0 and 141.1 (CH), 158.5, 161.6, 175.1 and 205.5 (C); *m*/*z* 259 (M^+), 83, 71 and 57.

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