

Dehydrogenation–halogenation of a 4,5,6,7-tetrahydroisoxazolo[4,3-*c*]pyridin-4-one to provide a scaffold for acylpyridones

Raymond C. F. Jones,^{*a} Abdul K. Choudhury,^a Claire E. Dawson,^b Christopher Lumley,^a and Vickie McKee^a

^aDepartment of Chemistry, Loughborough University, Loughborough, Leics. LE11 3TU, UK

^bDepartment of Chemistry, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK

E-mail: r.c.f.jones@lboro.ac.uk

Dedicated to Professor Keith Smith on the occasion of his 65th anniversary

Abstract

The dehydrogenation and halogenation of 3-methyl-4,5,6,7-tetrahydroisoxazolo[4,3-*c*]pyridin-4-one has been investigated to provide a suitable 7-halo-4,5-dihydroisoxazolo[4,3-*c*]pyridine-4-one to act as a masked scaffold for the acylpyridone natural products and analogues.

Keywords: Heterocycles, photolysis, halogenations, cross-coupling, pyridone

Introduction

The 3-acyl-4-hydroxypyridin-2-one moiety **1** (Figure 1) is the common structural unit of a family of natural products with a range of interesting biological activities.¹ Examples are the pigments tenellin **2a** and bassianin **2b** from insect pathogenic fungus *Beauveria bassiana*,² pyridovericin **2c**³ (a tyrosine kinase inhibitor) and the elfamycin antibiotics.⁴ Farinosone A **2d**, isolated from *Paecilomyces farinosus*, induces and enhances neurite outgrowth in the PC-12 cell line, although it is not clear whether the pyridines in general display neuritogenic properties.⁵ The 5-substituent is commonly an aryl ring or derivative (biogenesis from tyrosine), and the 3-acyl substituent is commonly polyenoyl. The biosynthesis of tenellin and bassianin in *Beauveria bassiana* has recently been studied in detail using genetic techniques, and been shown to involve conversion from an acyltetramic acid via oxidative ring expansion.⁶

As part of an ongoing programme of synthesis towards metabolites and analogues containing the enolised heterocyclic tricarbonyl motif **3**,⁷⁻¹⁰ we have reported a nitrile oxide dipolar cycloaddition strategy which affords 3-methyl-4,5-dihydroisoxazolo[4,3-*c*]pyridin-4-one **4** as a 2nd generation masked non-polar scaffold for the 3-acyl-4-hydroxypyridin-2-one nucleus.^{8,9} We have reported two syntheses of building block **4**, from 3-aminopropanoic acid (β -alanine) or

from 2,3-diaminopropanoic acid;¹⁰ the more economical starting material for the synthesis is β -alanine and a key intermediate is the tetrahydroisoxazopyridone **5**. Furthermore, elaboration of dihydroisoxazopyridone **4** at C-7 to append the aromatic rings found at C-5 of many of the pyridone natural products is an important step in our sequence.^{8,10} Two key conversions for our overall strategy are thus the 6,7-desaturation of lactam **5** to give scaffold **4**, and generation of a suitable alkenyl halide at C-7 to facilitate Pd-mediated cross-couplings. We report here in detail our investigations to establish reliable methodology for these two conversions.¹¹

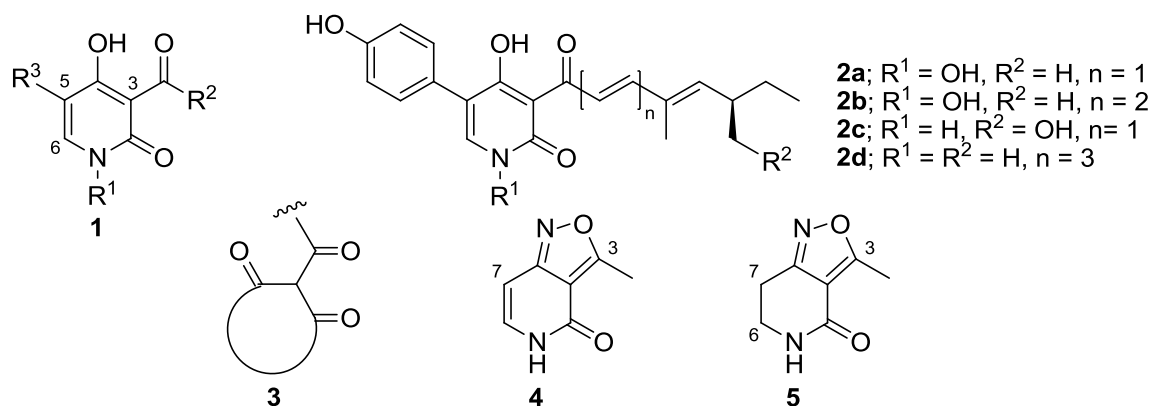


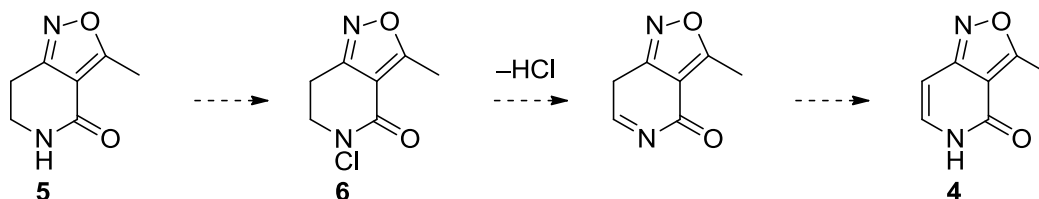
Figure 1. The 3-acyl-4-hydroxypyridin-2-one motif **1**, natural products **2** and scaffold **4**.

Results and Discussion

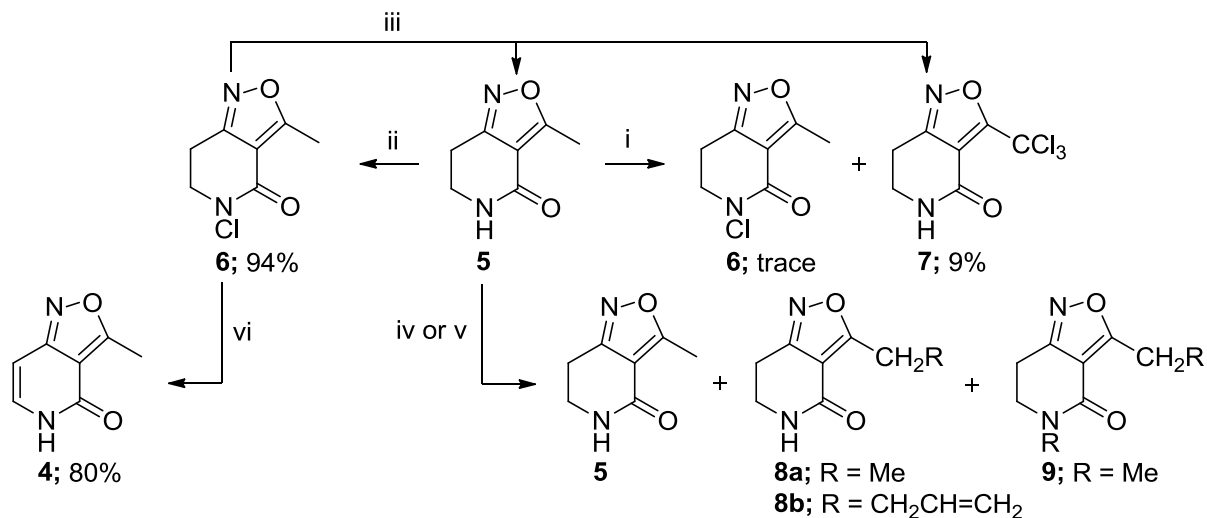
Having in hand the tetrahydroisoxazopyridone **5**,¹⁰ we needed to introduce C-6,7 unsaturation to generate the dehydro compound **4**. Our initial attempts were using dehydrogenation reagents, thus we investigated the following methods: DDQ in 1,4-dioxane at reflux, and also in the presence of *N,O*-bis(trimethylsilyl)trifluoroacetamide as this reagent had been shown to improve the dehydrogenation of steroidal lactams by facilitating the breakdown of the intermediate quinone-lactam complex;¹² 10% Pd-C in 1,4-dioxane at reflux, and in diphenyl ether at 200 °C;¹³ Pb(OAc)₄ in acetic acid.¹⁴ In all except the latter case, none of the desired pyridone was detected, and only in the latter case was a trace of the dehydrogenation product observed spectroscopically (NMR, MS), although not in synthetically useful quantities.

The next approach to be investigated was *N*-chlorination to give **6** followed by elimination of HCl, on the presumption that an imine so-produced would tautomerize to the required enamine **4** (Scheme 1). Our initial studies used a reported procedure: potassium hexamethyldisilazide (KHMDS) as base, and a positive chlorine source, *N*-chlorosuccinimide (NCS; THF, 20 °C).¹⁵ After purification, some of the desired *N*-chlorolactam **6** was observed, contaminated by NCS, but to our surprise the major product was the 3-trichloromethyl compound **7** (9%) (Scheme 2).¹⁶ The formation of the *C*-chloro compound **7** can be rationalized by competitive deprotonation at

C-3(Me) (which we have observed separately¹⁰) and chlorination either directly by NCS, or with the *N*-chlorolactam **6** as an alternative chlorinating agent. Once mono-chlorination has taken place, successive deprotonation-chlorination is favoured by the existing chloro-substituent, in a sequence mirroring the haloform reaction.¹⁷ NCS used in the absence of base did afford the *N*-chloro compound **6** but contaminated with NCS and succinimide, such that a pure sample could not be isolated. In an alternative *N*-chlorination protocol, treatment of the pyrroloisoxazole **5** with freshly prepared *t*-butyl hypochlorite (MeOH, 0 °C)¹⁸ in the absence of direct light did provide the *N*-chlorolactam **6** in good yield (94%).



Scheme 1. Plan for C-6,7 desaturation of lactam **5** via *N*-chlorination and dehydrochlorination.

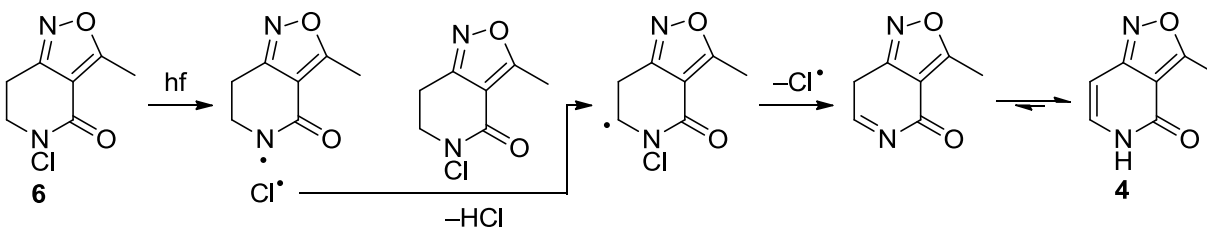


Scheme 2. *N*-Chlorination & photolysis, and base mediated reactions of lactam **5**. *Reagents:* i, KHMDS, NCS, THF, 20 °C; ii, *t*-BuOCl, MeOH, 0 °C; iii, DBU, benzene, 20 °C; iv, BuLi, THF, -78 °C, MeI; v, BuLi, THF, -78 °C, H₂C=CHCH₂Br; vi, hv, Hanovia Hg-lamp, MeOH.

We next attempted elimination of HCl from **6** using DBU as base (benzene, 20 °C), but the products observed were the *N*-H lactam **5** and the trichloromethylisoxazolopyridone **7** (Scheme 2). It is probable that the *N*-chlorolactam **6** acted as a chlorinating agent for anions formed at the C-3 substituent, as proposed above. The competitive deprotonation at C-3(Me) of *N*-H lactam **5** was further illustrated by alkylation experiments. In the first, methylation was investigated (1 mole equiv BuLi, THF, -78 °C; 1 mol equiv MeI) to afford a mixture containing unchanged

lactam **5**, the C-methyl compound **8a** and the *C,N*-dimethyl-lactam **9**, that was not separated (Scheme 2). An allylation experiment (excess BuLi, THF, $-78\text{ }^{\circ}\text{C}$; 1.5 mol equiv prop-2-enyl bromide) afforded recovered **5** and C-allyl compound **8b** (20%), identified by the presence of an NH signal (δ 5.82, 1H, br s) in the ^1H NMR spectrum along with the appropriate alkene proton signals, and the absence of the C-3(Me) signal. It was therefore deemed necessary to avoid basic conditions for dehydrohalogenation of chlorolactam **6**, to avoid reaction at C-3(Me).

Our attention was therefore drawn to a report of the photolysis of *N*-chlorolactams to afford *N*-(α -methoxyalkyl)lactams.¹⁹ After some experimentation, a solution of *N*-chloro compound **6** in MeOH was degassed (N_2 flow, 10 min) and irradiated with a medium-pressure mercury lamp for 1 h to afford the desired dihydropyrroloisoxazole **4** in an optimum yield of 80%, along with some recovered N-H compound **5** (Scheme 2). In some experiments the yield of **4** was lower but more dechlorinated material was returned so that the yield based on recovered N-H lactam was maintained around 80%. Other light sources were less efficient; for example, use of two home Solaria UV lamps gave **4** in just 40% (60% based on recovered **5**). The mechanism for the dehydrochlorination of **5** is proposed to be via a radical chain process (Scheme 3):¹⁹ homolysis of the N-Cl bond followed by H-atom abstraction from C-6 of **6**, would leave a carbon radical at C-6 which, if it fragments to expel a chlorine atom, would generate an imine that could simply tautomerize to the stable acyl enamine form **4**. The accompanying production of the N-H lactam **5** is proposed to arise from H-abstraction from the MeOH solvent; the HCl so-formed may also cause acid-promoted decomposition of **6** with generation of chlorine. The structure of target dihydroisoxazolopyridone **4** was confirmed by an X-ray crystal structure determination (Figure 2);²⁰ the solid-state structure shows H-bonded pyridone dimers with some π - π stacking.



Scheme 3. A proposed mechanism for photolytic dehydrochlorination of *N*-chlorolactam **6**.

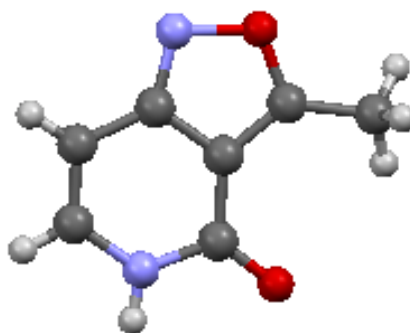
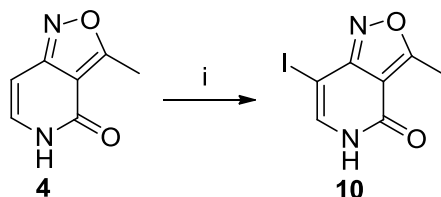


Figure 2. X-Ray crystal structure of 3-methyl-4,5,6,7-dihydroisoxazolo[4,3-*c*]pyridin-4-one **4**.

Having secured the desired overall dehydrogenation of tetrahydroisoxazopyridone **5**, we required a substituent at C-7 to enable cross-coupling to the aromatic residues commonly found in the acylpyridone natural products. This proved straightforward (Scheme 4); treatment of **4** with iodine monochloride (CH_2Cl_2 -MeOH, 20 °C, 16 h) provided 7-iodo compound **10** (70%).²¹



Scheme 4. C-7 Iodination of unsaturated lactam **4**. Reagents: i, ICl, CH_2Cl_2 -MeOH, 20 °C, 16 h.

Meanwhile, we had identified additional trace products in the photolysis reaction of *N*-chlorolactam **6**, as the 7-chloroisoxazopyridone **11** and 7-chloro-6-methoxy-adduct **12a** (which co-eluted on column chromatography), and pseudo-dimer **13**. The 7-chloro derivatives are believed to arise by interaction of major product **4** with chlorine formed during the radical process, and either proton loss or MeOH addition to an imine intermediate in the chlorination. The dimer is attributed to chlorination of MeOH solvent to provide methanal or an equivalent.¹⁹

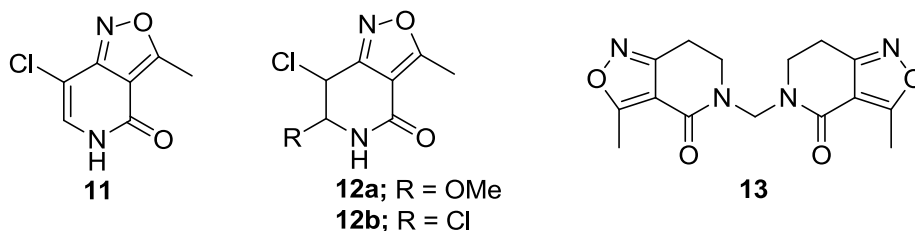
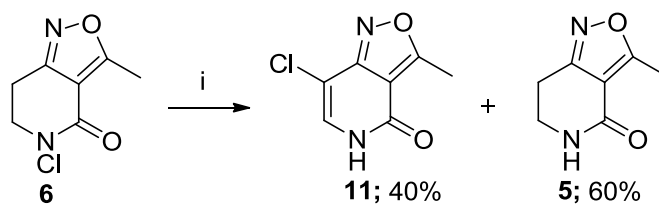


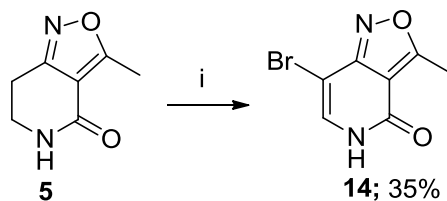
Figure 3. Minor products of Hanovia Hg-lamp photolysis of chlorolactam **6**.

The identification of 7-chloroisoxazopyridone **11** prompted us to investigate further, as the direct one-step formation of a 7-haloisoxazopyridone from chlorolactam **6** would shorten the synthetic sequence. During investigation of alternative light sources, a tungsten UV lamp was employed (Scheme 5). After complete disappearance of starting material **6** (TLC), only low yields of the dihydroisoxazopyridone **4** were obtained and the N-H lactam **5** was the major compound returned (up to 60%). However, the main product of interest was the 7-chloroisoxazopyridone **11** (optimum yield 40%), sometimes isolated with the 6,7-dichloro adduct **12b**; in these instances the mixture could be converted on base treatment (K_2CO_3 aq, 50 °C) to 7-chlorodihydroisoxazopyridone **11** by an HCl elimination. As outlined above, we propose the 7-chloro compound **11** to arise from chlorination of the dihydroisoxazopyridone **4**. In an attempt to increase the yield of **11** we thus added a potential chlorine source (NCS, 1 mol equiv) to the photolysis reaction mixture but no change to the outcome was observed.



Scheme 5. Formation of 7-chlorolactam **11** by photolysis of *N*-chlorolactam **6**. *Reagents:* i, hv, tungsten UV lamp, MeOH.

For the planned cross-coupling of 7-haloisoxazolopyridones, it was anticipated that a 7-bromo derivative would be more effective than the above 7-chloro compound. We thus investigated access to 7-bromodihydroisoxazolopyridone **14**. As the photolysis route was believed to proceed via a radical mechanism, we attempted bromination of lactam **5** using *N*-bromosuccinimide (NBS) under radical initiation. After less successful attempts using 1,1-azobis(cyclohexanecarbonitrile) (ACCN) initiation in cyclohexane at reflux, and azobis(isobutyronitrile) (AIBN) in cyclohexane or toluene at reflux, we found that AIBN in carbon tetrachloride at reflux afforded 7-bromo compound **14** in 30% yield; changing to *t*-butanol solvent at reflux, and adding AIBN in portions every hour for 5 h, afforded an improved 35% yield (Scheme 6). As we did not find any evidence for dihydroisoxazolopyridone **4** in these experiments, we propose that this conversion proceeds as a ‘benzylic’ bromination via H-atom abstraction at C-7,²² and that the 7-bromo compound so-formed undergoes a second H-abstraction/bromination followed by HBr elimination, rather than elimination to form enamine **4** and a polar bromination. Attempts to extend this protocol to radical iodination of **5** using *N*-iodosuccinimide (NIS) were unsuccessful, producing only traces of iodo compound **10**.

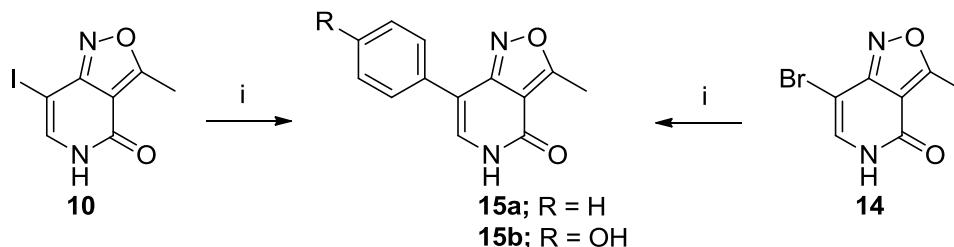


Scheme 6. Radical bromination of lactam **5**. *Reagents:* i, NBS, AIBN, *t*-butanol reflux, 5 h.

We thus had available 7-iodo, 7-bromo and 7-chloroisoxazolopyridones (**10**, **14** and **11**, respectively) in yields based on tetrahydroisoxazolopyridone **5** of 53, 35 and 38%, respectively. Thus proceeding via the iodo compound was the most efficient despite involving three steps.

The next part of the sequence involved cross-coupling to the alkenyl halides at C-7, so comparative investigations were undertaken with all three 7-halo compounds under Suzuki reaction conditions.²³ Using phenylboronic acid [Pd(PPh₃)₄ (8 mol %), Na₂CO₃ aq, 1,4-dioxane-EtOH reflux], 7-phenylisoxazolopyridone **15a** was isolated in 67% yield from 7-iodo substrate

10 (Scheme 7) but no reaction was observed with less reactive 7-chloro substrate **11**. With 4-hydroxyphenylboronic acid and using the same conditions, the coupled product **15b** was produced in 85% yield from 7-iodo starting material **10** but just 35% yield from 7-bromo reactant **14**. A range of different ligands and Pd-based catalysts were investigated with the chloro substrate **11** but without success in coupling. Similarly, the corresponding *N*-benzyl and *N*-(4-methoxybenzyl) derivatives were prepared from **11** (ArCH₂Br, MeCN, K₂CO₃, 0 °C) but failed to deliver any cross-coupling. Attempts to prepare a C-7-magnesium or zinc derivative from the chloride **11** for Pd-mediated coupling to a boronic acid, were also fruitless.²⁴



Scheme 7. Cross-coupling reactions of 7-haloisoxazopyridones **10,14**. *Reagents:* i, PhB(OH)₂ for **15a**, 4-HOC₆H₄B(OH)₂ for **15b**, Pd(PPh₃)₄ (8 mol %), Na₂CO₃ aq, 1,4-dioxane-EtOH reflux.

In one further approach, we very briefly experimented with direct arylation of the nucleophilic acyl enamine **4** via a presumed electrophilic substitution [Pd(PPh₃)₄, Ag₂CO₃, water, 60 °C, 24 h] to afford the 7-phenylisoxazopyridone **15a** but in low yield (12%).²⁵ This process would potentially avoid the iodination step, but we have not optimized further.

Conclusions

We can therefore conclude that 7-iododihydroisoxazopyridone **10** was both the most accessible 7-halo derivative from intermediate **5**, and (as expected) the best substrate for cross-coupling, and have proceeded using this sequence for the key conversions in our programme of synthesis towards the acylpyridones.

Experimental Section

General. ¹H NMR spectra were recorded using Bruker DPX 400 MHz or Varian 400 MHz spectrometers, and ¹³C NMR spectra the Bruker instrument operating at 100.62 MHz. Chemical shift, δ, values are given in ppm, coupling constants in Hertz and multiplets denoted by: s, singlet; d, doublet; t, triplet; q, quartet and m, multiplet. All spectra were recorded using tetramethylsilane (TMS) as the internal reference in CDCl₃ or *d*₆-DMSO solvent. IR spectra were

determined using a Perkin Elmer FT-IR Paragon 1000 spectrometer or a Perkin Elmer Spectrum One spectrometer and recorded in the range 4000-600 cm^{-1} . Mass spectra were recorded on a Joel SX-102 spectrometer (FAB and EI) and the Thermo Exactive (Orbi) accurate mass spectrometer (ESI), fitted with a Triversa Advion Nanomate sample delivery system using nano-ESI of MeOH or MeOH-AcOH (99:1 w/w). GC-MS used was Fisons GC 800 with autosampler, Fisons mass lab MD 800 EI⁺ and DB5-MS 30 m column. Melting points (m.p.; °C) were determined using an Electrothermal-IA 9100 and are uncorrected. TLC using silica gel as the absorbent was carried out with aluminium backed plates; column chromatography using silica gel was carried out with Zeoprep 60 HYD 40-63 Micron silica. HPLC analysis was conducted in a Waters Fraction Lynx system comprising a 2767 injector/collector with a 2525 gradient pump, CFO, 2996 photodiode array, 2420 ELSD and Micromass ZQ2000 equipped with a Waters XBridge dC18 column (column length 20 mm, internal diameter of column 3 mm, particle size 3.5 micron). The analysis was conducted using a three minute run time using H₂O with 10mM NH₄OAc and CH₃CN. Distillation of reagents was carried out at atmospheric pressure unless otherwise stated. Solvents were distilled before use. Light petroleum (b.p. 40-60 °C) and EtOAc were distilled from CaCl₂, CH₂Cl₂ from CaH₂; THF was freshly distilled from sodium and benzophenone under an atmosphere of nitrogen, MeOH from Mg(OMe)₂.

Procedure for *N*-chloro-3-methyl-4,5,6,7-tetrahydroisoxazolo[4,3-*c*]pyridin-4-one (6)

To 3-methyl-4,5,6,7-tetrahydroisoxazolo[4,3-*c*]pyridin-4-one **5** (1.09 g, 7.17 mmol) in dry MeOH (50 mL) under N₂ at 0 °C was added dropwise *t*-butyl hypochlorite (1.17 g, 10.76 mmol) in the absence of direct light. The mixture was left to stir at 0 °C for 2 h, at 20 °C for 2 h and then concentrated under reduced pressure. The residue in CH₂Cl₂ (50 mL) was washed with water (50 mL), dried (MgSO₄) and concentrated under reduced pressure to yield title compound **6** (1.26 g, 94%) as a white solid; a portion of the title compound was purified by chromatography on silica gel, eluting with hexane:EtOAc (1:1 v/v) to yield a white solid, m.p. 108 °C, IR (ν_{max} , CDCl₃/cm⁻¹), 2249, 1693, 1630, 1516, 1471, 1451, 1428, 1385, 1303, 1266, 1144, 1066. UV (λ_{max} , EtOH/nm), 229 ($\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 10 900). ¹H NMR (400 MHz; CDCl₃), δ_{H} 2.71 (3H, s, CH₃), 3.21, 4.02 (each 2H, t, *J* = 6.4, CH₂CH₂N). ¹³C NMR (100MHz; CDCl₃), δ_{C} 12.3 (CH₃), 22.5, 55.3 (2 x CH₂), 107.6 (C-3a), 159.3 (C-7a), 160.3 (C-3), 173.3 (CONH). MS, *m/z* (CI) = 189 (MH⁺, 2%), 187 (MH⁺, 6), 170, 153 (100), 123, 109, 81. HRMS: Calcd for C₇H₇N₂O₂³⁵Cl: MH⁺ 187.0269; found: MH⁺ 187.0274. Anal. Calcd for C₇H₇N₂O₂Cl: C, 45.06; H, 3.78; N, 15.01; Cl, 19.00%, Found: C, 45.36; H, 3.82; N, 14.81; 19.28%.

Procedure for 3-methyl-4,5-dihydroisoxazolo[4,3-*c*]pyridin-4-one (4)

N-Chlorolactam **6** (150 mg, 0.802 mmol) in freshly distilled MeOH (200 mL) was degassed for 10 min. Under a constant flow of N₂ the solution was stirred for 1 h under irradiation by a medium pressure mercury Hanovia lamp. Concentrating the solvent under reduced pressure and purification of the crude residue using column chromatography, eluting with light petroleum:EtOAc (1:1 v/v) yielded the title compound **4** as a white solid (96 mg, 80%), m.p.

205-207 °C (from EtOAc-MeOH), IR (ν_{\max} , CH₂Cl₂/cm⁻¹), 3425, 3224, 2987, 1696, 1643, 1382, 1324. UV (λ_{\max} , EtOH/nm), 233 ($\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 7 100), 294 (3 500). ¹H NMR (400 MHz; CDCl₃), δ_{H} 2.81 (3H, s, CH₃), 6.32 (1H, d, $J = 7.6$, CHCHNH), 6.89 (1H, dd, $J = 7.6, 5.6$, CHCHNH), 8.92 (1H, br, NH). ¹³C NMR (100MHz; CDCl₃), δ_{C} 13.1 (CH₃), 95.1 (CHCHN), 108.2 (C-3a), 132.8 (CHCHN), 158.7 (C-7a), 162.5 (C-3), 171.2 (CONH). MS, m/z (EI) = 150 (M⁺, 80%), 108, 95, 80, 53, 43 (100). HRMS: Calcd for C₇H₆N₂O₂: M⁺ 150.0429; found: M⁺ 150.0427. Anal. Calcd for C₇H₆N₂O₂: C, 56.00; H, 4.03; N, 18.66%, Found: C, 56.01; H, 4.02; N, 18.65%.

Crystal data for 4. C₇H₆N₂O₂, $M = 150.14$, orthorhombic, $a = 7.4800(7)$, $b = 12.9880(9)$, $c = 13.529(2)$ Å, $U = 1314.3(2)$ Å³, $T = 150(2)$ K, space group *Pbca*, Mo-K α radiation, $\lambda = 0.71069$ Å, $Z = 8$, $D_c = 1.517$ Mg m⁻³, $F(000) = 624$, crystal dimensions 0.18 x 0.14 x 0.12 mm, $\mu(\text{Mo-K}\alpha) = 0.115$ mm⁻¹, $3.01 < 2\theta < 25.08^\circ$, 4823 reflections measured, 1042 unique reflections. Solved by direct methods and refined by full-matrix least-squares on F^2 . The final cycle (for 124 parameters) converged with $wR2 = 0.0993$ (for all data) and $R1 = 0.0416$ [$I > 2\sigma(I)$].

Procedure for 7-iodo-3-methyl-4,5-dihydroisoxazolo[4,3-*c*]pyridine-4-one (10)

To dihydroisoxazolopyridone **4** (0.35 g, 2.33 mmol) in dry CH₂Cl₂ (8 mL) and dry MeOH (1 mL) at 20 °C, under N₂, was added ICl (1.0M in CH₂Cl₂, 3.5 mL, 3.50 mmol) and the reaction mixture was stirred at room temperature for 16 h. The precipitate was collected and washed with a minimum of CH₂Cl₂ to yield the title compound **11** (0.45 g, 70%) as a white solid, m.p. 223-225°C (decomp.), IR (ν_{\max} , CH₂Cl₂/cm⁻¹), 3260, 1665, 1620, 1519 & 1330. UV (λ_{\max} , EtOH/nm), 239 ($\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 7 100), 310 (2 300). ¹H NMR (400 MHz; *d*₆-DMSO), δ_{H} 2.82 (3H, s, CH₃), 7.50 (1H, d, $J = 5.0$ Hz, CHNH), 11.12 (1H, br, s, NH). ¹³C NMR (100MHz; *d*₆-DMSO), δ_{C} 12.9 (CH₃), 51.6 (C-7), 107.4 (C-3a), 140.4 (CHN), 158.9 (C-7a), 159.0 (C-3), 175.2 (CONH). MS, m/z (EI) = 276 (M⁺, 9%), 127, 107, 94, 79, 52, 43 (100). HRMS: Calcd for C₇H₅N₂O₂I: M⁺ 275.9398; found: M⁺ 275.9396. Anal. Calcd for C₇H₅N₂O₂I: C, 30.46; H, 1.83; N, 10.15%, Found: C, 30.60; H, 1.83; N, 10.02%; M⁺.

Procedure for 3-(but-2-enyl)4,5,6,7-tetrahydroisoxazolo[4,3-*c*]pyridine-4-one (8b)

To lactam **5** (20 mg, 0.13 mmol) in THF (10 mL) at -78 °C was added *n*-BuLi (0.13 mL, 2.5M in hexanes, 0.33 mmol) The solution was stirred for 2 h before prop-2-enyl bromide (0.02 mL, 0.2 mmol) was added, and then stirred for 2 h at -78 °C. The reaction was quenched with water (10 mL) and the mixture acidified with hydrochloric acid (2M; 10 mL) at -78 °C. The mixture was extracted with EtOAc (3 x 20 mL), the organic layers were combined, washed with brine (25 mL), dried (MgSO₄), filtered and the solvent was removed under reduced pressure to leave a yellow oil, purified by column chromatography, eluting with EtOAc:light petroleum (1:1 v/v) to afford the title compound **8b** as a white solid (5 mg, 20%), m.p. 107 -109 °C. UV ν_{\max} CH₂Cl₂/cm⁻¹), 3128, 3017, 1628, 1616, 1461, 1419. ¹H NMR (400 MHz; CDCl₃), δ_{H} 2.47 (2H, m, CHCH₂), 2.95 (2H, t, $J = 6.4$ Hz, CH₂CH₂N), 3.13 (2H, t, $J = 7.2$ Hz, CHCH₂CH₂), 3.53 (2H, dt, $J = 2.8, 6.4$ Hz, CH₂CH₂N), 4.96 (1H, dd, $J = 1.6, 10.0$ Hz, CH=CHH), 5.03 (1H, dd, $J = 1.6,$

17.2 Hz, CH=CHH), 5.78 (1H, m, CH=CH₂), 5.82 (1H, br, NH). ¹³C NMR (100MHz; CDCl₃), δ_C 21.4, 25.9, 31.0, 40.7 (4 x CH₂), 107.6 (C-3a), 116.2 (=CH₂), 136.1 (=CH), 160.5 (C-7a), 163.0 (C-3), 175.1 (CONH). HRMS (ESI): Calcd for C₁₀H₁₂N₂O₂: MH⁺ 193.0971; found: MH⁺ 193.0971.

Procedure for 7-chloro-3-methyl-4,5-dihydroisoxazolo[4,3-c]pyridine-4-one (11)

N-Chlorolactam **6** (2.21 g, 11.9 mmol) in freshly distilled MeOH (50 mL) was stirred at 23 °C for 5 h under a constant flow of N₂, while being irradiated by a tungsten halogen UV lamp. The solvent was concentrated under reduced pressure and the residue purified by column chromatography, eluting with light petroleum:EtOAc (1:1 v/v) to yield the title compound **11** as a white solid (0.88 g, 40%), m.p. 230-232 °C, IR (ν_{max} CH₂Cl₂/cm⁻¹), 2898, 1672, 1632, 1519, 1342. ¹H NMR (400 MHz; *d*₆-DMSO), δ_H 2.71 (3H, s, CH₃), 7.38 (1H, s, CH). ¹³C NMR (100MHz; *d*₆-DMSO), δ_C 12.6 (CH₃), 98.1 (C-7), 107.9 (C-3a), 133.8 (CHN), 156.4 (C-7a), 158.8 (C-3), 175.2 (CONH). HRMS (FAB): Calcd for C₇H₅N₂O₂³⁵Cl: MH⁺ 185.0112; found: MH⁺ 185.0114.

Procedure for 7-bromo-3-methyl-4,5-dihydroisoxazolo[4,3-c]pyridine-4-one (14)

To degassed *t*-butanol (10 mL) were added lactam **5** (100 mg, 0.658 mmol) and recrystallised *N*-bromosuccinimide (0.14 g, 0.789 mmol) under an N₂ atmosphere. AIBN (9 mg, 0.05 mmol) was added portionwise every hour for 5 h, and the mixture heated at reflux overnight. The solvent was removed under reduced pressure, water (20 mL) was added, and the mixture extracted with CH₂Cl₂ (4 x 40 mL). The combined organic extracts were dried (MgSO₄), filtered and the solvent was removed under reduced pressure to leave a residue that was purified by column chromatography, eluting with light petroleum:EtOAc (1:1 v/v) to yield the title compound **14** as an off-white solid (35 mg, 35%), m.p. 268-269 °C, IR (ν_{max} CH₂Cl₂/cm⁻¹), 3436, 1774, 1665, 1427, 1370, 1296, 1188. ¹H NMR (400 MHz; *d*₆-DMSO), δ_H 2.78 (3H, s, CH₃), 7.48 (1H, s, CHNH), 11.32 (1H, br, s, NH). ¹³C NMR (100MHz; *d*₆-DMSO), δ_C 12.7 (CH₃), 104.5 (C-7), 107.4 (C-3a), 136.7 (CHN), 156.9 (C-7a), 159.6 (C-3), 174.2 (CONH). HRMS (EI): Calcd for C₇H₅N₂O₂⁷⁹Br: M⁺ 227.9535; found: M⁺ 227.9534.

Procedure for 3-methyl-7-phenyl-4,5-dihydroisoxazolo[4,3-c]pyridin-4-one (15a)

Prepared according to method A as for **15b** (see below), but using tetrakis(triphenylphosphine)palladium (4.2 mg, 0.004 mmol) in 1,4-dioxane (10 mL), 7-iodo-3-methyl-4,5-dihydroisoxazolo[4,3-c]pyridin-4-one **10** (20 mg, 0.072 mmol), phenylboronic acid (13 mg, 0.11 mmol) in ethanol (10 mL), and aqueous Na₂CO₃ (2M; 0.02 mL, 0.14 mmol). The residue was purified by column chromatography, eluting with light petroleum:EtOAc (1:1, v/v) to leave the title compound **15a** as a white solid (10 mg, 67%), m.p. 253-254 °C, IR (ν_{max} CH₂Cl₂/cm⁻¹), 3245, 2359, 1676, 1629, 1404. ¹H NMR (400 MHz; CDCl₃), δ_H 2.86 (3H, s, CH₃), 7.33 (1H, d, *J* = 6.0 Hz, CHNH), 7.36 (1H, t, *J* = 7.2 Hz, Ar-CH), 7.43 (2H, m, Ar-CH), 7.75 (2H, d, *J* = 7.2 Hz, Ar-CH), 8.72 (1H, br, NH). ¹³C NMR (100 MHz; CDCl₃), δ_C 13.0 (CH₃),

108.6 (C-7), 112.5 (C-3a), 127.3, 128.0, 128.8, 129.1 (4 x CH), 133.2 (Ar-C), 158.8 (C-7a), 161.7 (C-3), 174.2 (CONH). HRMS (FAB): Calcd for C₁₃H₁₀N₂O₂: MH⁺ 227.0815; found: MH⁺ 227.0825.

Procedure for 7-(4-hydroxyphenyl)-3-methyl-4,5-dihydroisoxazolo[4,3-c]pyridin-4-one (15b)

Method A. Tetrakis(triphenylphosphine)palladium (12 mg, 0.014 mmol) was added to degassed 1,4-dioxane (10 mL), followed by addition of 7-iodo-3-methyl-4,5-dihydroisoxazolo[4,3-c]pyridin-4-one **10** (100 mg, 0.36 mmol) and the solution was purged with gaseous N₂ for ten minutes at 23 °C. Separate solutions of 4-hydroxyphenylboronic acid (75 mg, 0.54 mmol) in EtOH (10 mL) and aqueous Na₂CO₃ (2M; 0.36 mL, 0.72 mmol) were degassed with N₂, and added to the reaction sequentially. The resulting mixture was heated at reflux for 18 h under an N₂ atmosphere, cooled, water (50 mL) added and the mixture extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄), filtered and the solvent was removed under reduced pressure to give a brown oil that was purified using column chromatography eluting with EtOAc to leave the title compound **15b** as a white solid (70 mg, 80%), m.p. 268-269°C, IR (ν_{max} CH₂Cl₂/cm⁻¹), 3425, 2359, 1642, 1436, 1177, 1118. ¹H NMR (400 MHz; *d*₆-DMSO), δ_H 2.87 (3H, s, CH₃), 6.86 (2H, d, *J* = 8.4 Hz, Ar-CH), 7.29 (1H, d, *J* = 6.0 Hz, CHNH), 7.60 (2H, d, *J* = 8.4 Hz, Ar-CH), 11.05 (1H, br, NH), OH not observed. ¹³C NMR (100 MHz; *d*₆-DMSO), δ_C 12.4 (CH₃), 107.1 (C-7), 108.1 (C), 115.3 (CH), 124.2 (Ar-C), 128.7, 131.5 (2 x CH), 156.7, 157.6, 159.0 (3 x C), 173.7 (CONH). MS, *m/z* = 243 (MH⁺, 32), 242 (M⁺, 100), 227 (46), 171 (33), 133 (18), 118 (20), 77 (10), 51 (16). HRMS (EI): Calcd for C₁₃H₁₀N₂O₃: M⁺ 242.0691, found: M⁺ 242.0694

Method B. The same procedure was applied as method A above, but using: tetrakis(triphenylphosphine)palladium (11 mg, 0.001 mmol), 1,4-dioxane (10 mL), 7-bromo-3-methyl-4,5-dihydroisoxazolo[4,3-c]pyridin-4-one **14** (73 mg, 0.32 mmol), 4-hydroxyphenylboronic acid (65 mg, 0.48 mmol) in EtOH and aqueous Na₂CO₃ (2M; 0.32 mL, 0.64 mmol) to afford a brown oil, purified using column chromatography eluting with EtOAc:light petroleum (1:1 v/v) to leave the title compound **15b** as a white solid (25 mg, 36%), identical to a sample prepared from method A.

Acknowledgements

We thank the EPSRC and Loughborough University (studentships to C. E. D. & A. K. C.), AgrEvo UK & Syngenta for additional support (C. E. D. & A. K. C.), Drs. D. A. Whiting, M. J. O'Mahony & N. B. Carter for helpful discussions, and the EPSRC Mass Spectrometry Service Centre (Swansea) for some high resolution MS data.

References and Notes

1. For a review, see: Jessen, H. J.; Gademann, K. *Nat. Prod. Rep.* **2010**, *27*, 1168.
2. El Basyouni, S. H.; Brewer, D.; Vining L. C. *Can. J. Bot.* **1968**, *46*, 441. Wat, C.-K.; McInnes, A. G.; Smith, D. G. *Can. J. Chem.* **1977**, *55*, 4090.
3. Takahashi, S.; Uchida, K.; Kakinuma, N.; Hashimoto, R.; Yanagisawa, T.; Nakagawa, A. *J. Antibiot.* **1998**, *51*, 1051.
4. For leading references, see: Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691.
5. Cheng, Y.; Schneider, B.; Riese, U.; Schubert, B.; Li, Z.; Hamburger, M. *J. Nat. Prod.* **2004**, *67*, 1854.
6. Halo, L. M.; Marshall, J. M.; Yakasai, A. A.; Song, Z.; Butts, C. P.; Crump, M. P.; Heneghan, M.; Bailey, A. M.; Simpson, T. J.; Lazarus C. M.; Cox, R. J. *ChemBioChem* **2008**, *9*, 585. Halo, L. M.; Heneghan, M. N.; Yakasai, A. A.; Song, Z.; Williams, K.; Bailey, A. M.; Cox, R. J.; Lazarus, C. M.; Simpson, T. J. *J. Am. Chem. Soc.* **2008**, *130*, 17988.
7. For 3-acyltetramic acids, see: Jones, R.C.F.; Dawson, C.E.; O'Mahony, M.J. *Synlett* **1999**, 873. Jones, R. C. F.; Pillainayagam, T. A. *Synlett* **2004**, 2815. Law, C. C. M., Ph.D. Thesis, Loughborough University **2008**.
8. Jones, R.C.F.; Dawson, C.E.; O'Mahony, M.J.; Patel, P. *Tetrahedron Lett.*, **1999**, *40*, 4085.
9. For our 1st generation approach, see: Jones, R. C. F.; Duller, K. A. M.; Vulto, S. I. E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 411. Jones, R.C.F.; Bhalay, G.; Carter, P.A.; Duller K.A.M.; Dunn, S.H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 765. Jones, R. C. F.; Duller, K. A. M. *Arkivoc* **2002** (viii) 34.
10. Jones, R. C. F.; Choudhury, A. K.; Iley, J. N.; Loizou, G.; Lumley, C.; McKee, V. *Synlett* **2010**, 654.
11. For preliminary communication of a small part of this work, see refs. 8, 10.
12. Bhattacharya, A.; DiMichele, L. M.; Dolling, U.-H.; Douglas A. W.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 3318.
13. See, for example: Hua, D. H.; Saha, S.; Maeng J. C.; Bensoussan, D. *Synlett* **1990**, 233. Nelson, P. H.; Nelson, J. T. *Synthesis* **1991**, 192.
14. Cf. Laduree, D.; Lancelot J.-C.; Robba, M. *Tetrahedron Lett.* **1985**, *26*, 1295.
15. Back, T. G.; Lai E. K. Y.; Morzycki, J. W. *Heterocycles* **1991**, *32*, 481.
16. In our preliminary communication, the structure of **7** was mistakenly assigned as the corresponding 4,5-dihydroisoxazolopyridone.
17. For a historical review, see: Fuson R. C.; Bull, B. A. *Chem. Rev.* **1934**, *15*, 275.
18. Mintz M. J.; Walling, C. *Org. Synth.* **1973**, Coll. Vol. V, p. 184.
19. Phan X. T.; Shannon, P. J. *J. Org. Chem.* **1983**, *48*, 5164.
20. For crystal data, see Experimental Section. Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the number CCDC846796. These data can be obtained free of charge from The Director,

CCDC, 12 Union Road, Cambridge CB2 1RZ, England, or via www.ccdc.cam.ac.uk/data_request/cif.

21. Cf. Robbins, M. J.; Barr P. J.; Giziewicz, J. *Can. J. Chem.* **1982**, *60*, 554.
22. Ziegler, W. *Name Reactions*; Springer: Berlin, 2007; 3rd expanded edn.
23. Miyaura N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. Suzuki, A. *J. Organometallic Chem.* **1999**, *576*, 147.
24. Minato, A.; Suzuki, K.; Tamao, K.; Kumada, M. *J.Chem. Soc., Chem. Commun.* **1984**, 511. Metzger, A.; Piller, F. M.; Knochel, P. *Chem. Commun.* **2008**, 5824.
25. Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 7996.