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An Efficient, Practical Approach to the Synthesis of 2,4-Disubstituted Thiazoles and Oxazoles: Application to the Synthesis of GW475151

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Abstract:

A new method for the synthesis of 2,4-disubstituted oxazoles and thiazoles and 2,4,5-trisubstituted oxazoles from readily available starting materials is described. The methodology has been applied on multigram scale and involves transfer of oxidation state through a molecular framework. In particular the oxazole-containing amino acid fragment of the 5,5-*trans*-fused lactam GW475151, 1, has been prepared in excellent yield and purity.

Introduction

The oxazole and thiazole ring systems are common structural motifs in a number of biologically active molecules.[1]

These five-membered heterocyclic ring systems originate in nature as a consequence of peptide modifications containing serine, threonine, and cysteine side chain residues and are the product of cyclodehydration and redox reactions[2] (Figure 1). All three ring oxidation states (the azoline, azolidine, and azole) are observed and alter peptide backbone connectivity, conformation, and electronic distribution, thus offering opportunity as new recognition elements for intermolecular interactions.

Pyrrolidine 5,5-*trans*-fused ring systems have been of particular interest to us as templates for the inhibition of human neutrophil elastase (HNE).[3,4] In particular we have been interested in the pyrrolidine 5,5-*trans*-fused lactam, GW475151,[5] **1**, containing a 2,4-disubstituted oxazole as a potential therapy for respiratory diseases such as acute respiratory distress syndrome, cystic fibrosis, emphysema, and chronic bronchitis.

Retrosynthetic analysis of GW475151, **1**, (Figure 2) identified two coupling partners, the pyrrolidine 5,5-*trans*-fused lactam, **2**, and the 2,4-disubstituted oxazole acid, **3**.

There have been many synthetic efforts surrounding the preparation of oxazoles[6] including rhodium(II)-catalysed reaction of diazocarbonyl compounds with nitriles,[7] oxidation of oxazolines,[8] Hantzsch-type condensation of amides and α-bromo ketones,[9] acid-catalyzed cyclisation of substituted iminoethers via the Cornforth protocol,[10] cyclodehydration of aldehydoamides using Ph_3PI_2[11] and acid-mediated conversion of amide acetals.[12]

Many of these routes have limitations in terms of yield, operation on kilogram scale, cost of reagents, and robustness. We sought an efficient route into the oxazole acid **3** that would be applicable to routine large-scale manufacture. We surmised that oxazolines could be converted to oxazoles through *transfer of oxidation state through a molecular framework*[13] (Figure 3). To this end we anticipated oxazolines of type **4** (where X is a leaving group) when treated with base would undergo deprotonation α to the ester followed by a subsequent elimination of HX to form intermediates of type **5**. We postulated that the intermediate **5** would either aromatise (pathway A) or be trapped by a nucleophile (pathway B). Should the intermediate **7** be produced, we hoped subsequent elimination of the nucleophile would produce the oxazole **6**. This concept is attractive since environmentally unacceptable and high-cost reagents are circumvented. Indeed, the concept could be applied to the preparation of small-molecule building blocks used in more complex natural product synthesis.

In this report we disclose a novel route to oxazole and thiazole ring systems, with application to the synthesis of the oxazole acid **3** and other oxazole- and thiazole-containing molecules.

Results and Discussion

Preparation of the methyl imidate **9** from dichloroacetonitrile **8** was achieved by the dropwise addition of dichloroacetonitrile to a methanol solution containing sodium meth-

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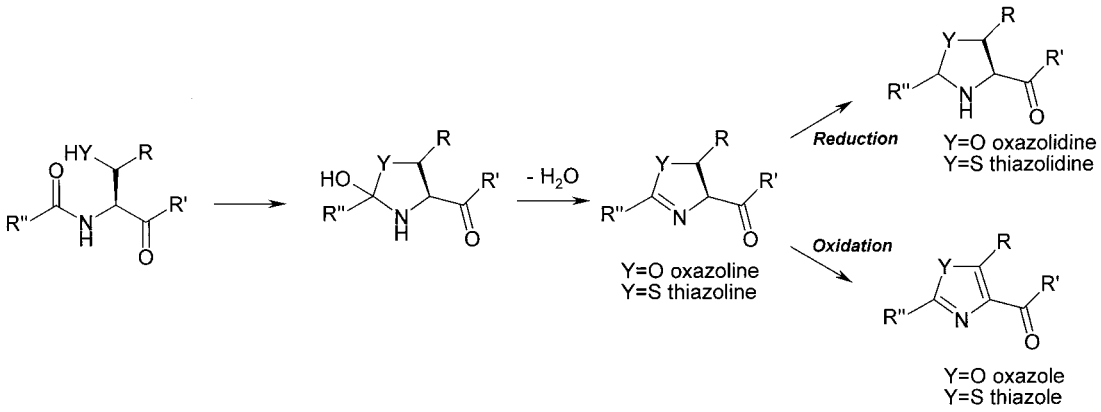


Figure 1.

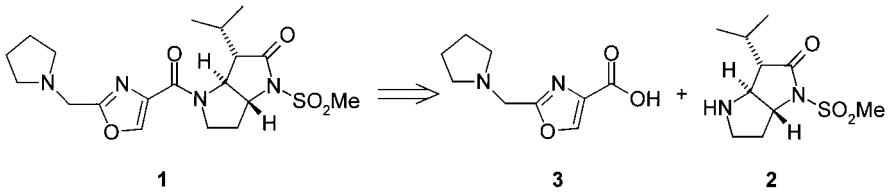


Figure 2.

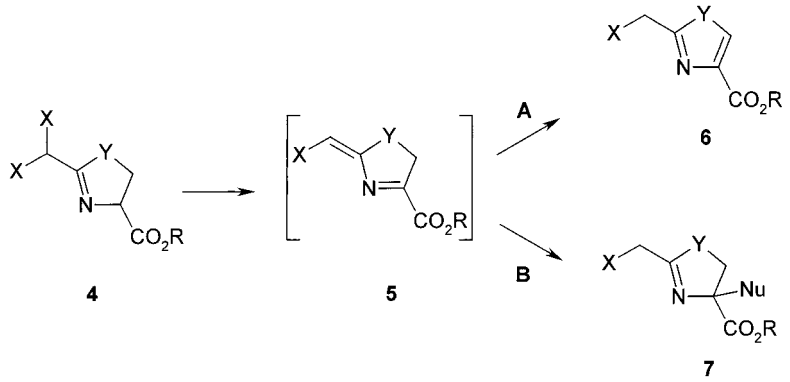


Figure 3.

oxide as catalyst at ~0 °C. Condensation of the methyl imidate **9** with serine methyl ester hydrochloride gave the oxazoline **10** in excellent crude yield. Alternatively, the thiazoline **11** was prepared when **9** reacted with cysteine methyl ester hydrochloride. Upon treatment of **10** and **11** with 1 mol equiv of sodium methoxide in methanol, rearrangement occurred as anticipated in Figure 3. Interestingly, a subtle stereoelectronic effect led to the oxazoline **10** giving rise to the methoxy intermediate **14**, whereas the thiazolidine **11** gave rise to the thiazole **13** directly. Methoxy oxazoline **14** could be converted to oxazole **12** by acid-catalyzed elimination using CSA (camphor sulphonic acid) in toluene at 70 °C. In both cases the oxazole **12** and thiazole **13** were prepared in respectable yield over the synthetic sequence on a multigram scale without intermediate purifications. The structure of oxazole **12** was confirmed by X-ray crystallography as depicted in Figure 4.

In a series of reactions analogous to that depicted in Scheme 1, the more substituted oxazole **17** was prepared in good overall yield of 48% from dichloroacetonitrile **8** and threonine methyl ester hydrochloride (Scheme 2). In the key "transfer of oxidation state" reaction, intermediate methoxy

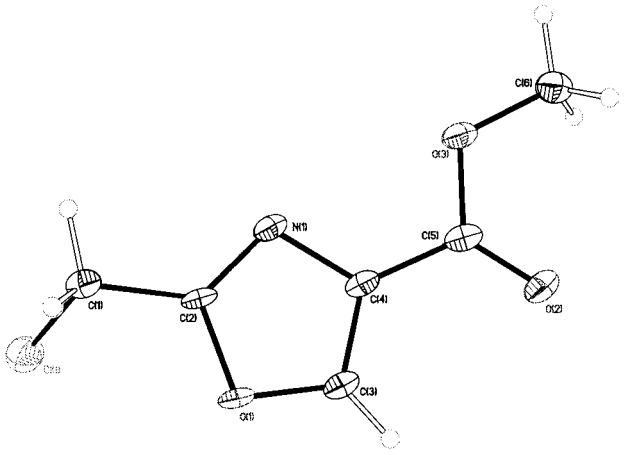
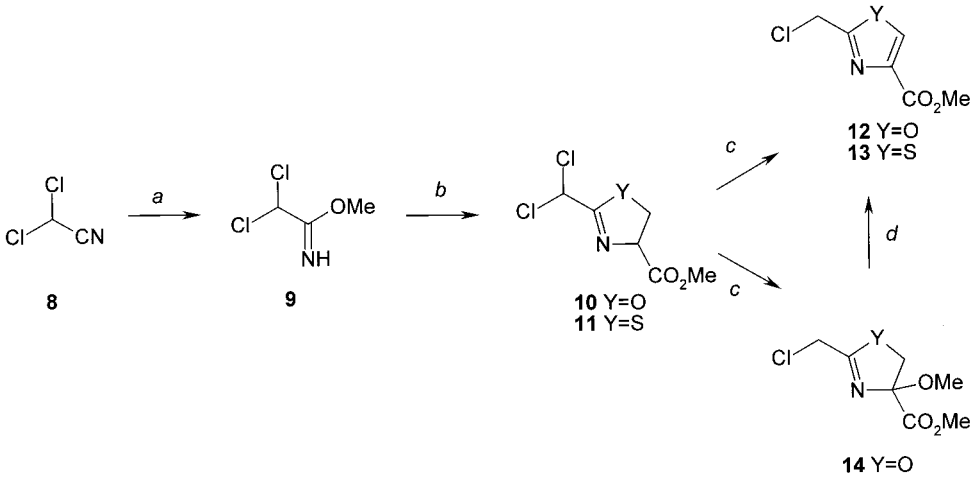


Figure 4. **X-ray structure of 12.**

oxazoline **16** was obtained with little stereoselectivity (3:2 ratio of diastereomers).

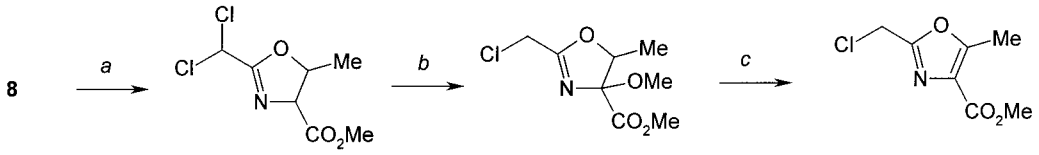
The monochloro derivative **20** was prepared from chloroacetonitrile **18** via the imidate **19**. Transfer of oxidation state was achieved via the methoxyoxazoline **21** to generate **22** (Scheme 3).

Scheme 1[a]



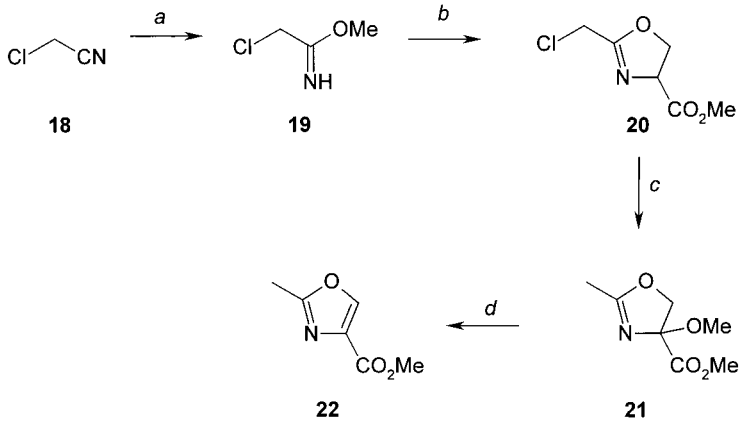
[a] Key: a) NaOMe (10 mol %), MeOH, −10 to 0 °C; b) serine methyl ester hydrochloride, MeOH (**10** 88% crude yield) or cysteine methyl ester hydrochloride, MeOH (**11** 84%, crude yield); c) NaOMe, MeOH, 10 °C (**14** 84% crude from **8**, **13** 66% yield after purification from **8**); d) CSA, toluene, 70 °C (**12** 48% yield after purification from **8**).

Scheme 2 [a]



[a] Key: a) i) NaOMe (10 mol %), MeOH, −10 to 0 °C; ii) threonine methyl ester hydrochloride, MeOH (**15** quantitative crude yield); b) NaOMe, MeOH, 10 °C (**16** 86% crude yield from **8**); c) CSA, toluene, 70 °C (**17** 48% yield after purification from **8**).

Scheme 3 [a]

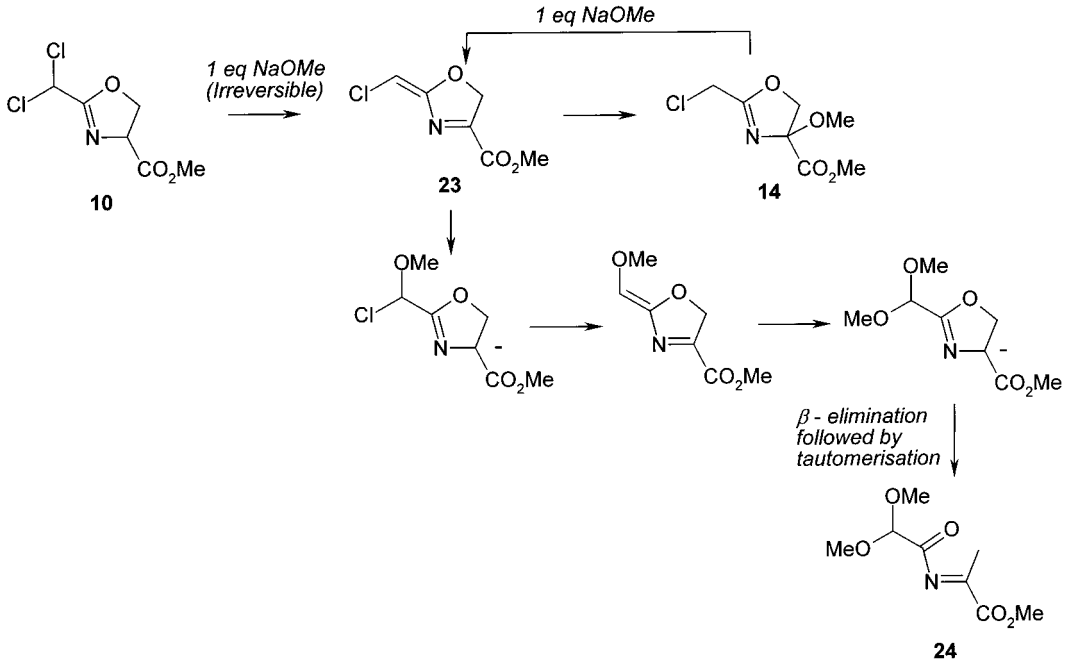


[a] Key: a) i) NaOMe (10 mol %), MeOH, −10 to 0 °C; b) serine methyl ester hydrochloride, MeOH (**20** 70% crude yield from **18**); c) NaOMe, MeOH, 10 °C (**21** 67% crude yield from **18**); d) CSA, toluene, 70 °C (**22** 24% yield after purification from **18**).

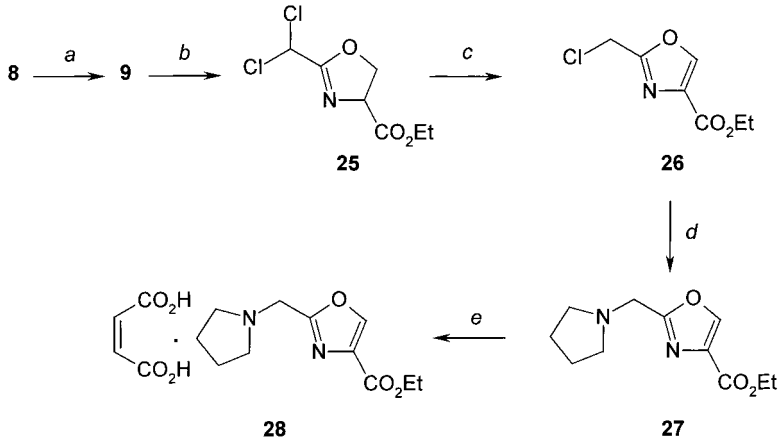
In an effort to establish a reliable process for the manufacture of GW475151, **1**, we investigated the robustness of conversion of **10** to **12** via the intermediate **14**. Our intention was to run a "telescoped process" on pilot plant from dichloroacetonitrile **8** without isolation of any intermediates. Part of our "route robustness testing" was to treat the dichlorooxazoline **10** with 2 equiv of sodium methoxide in methanol to simulate the event of an overcharge of reagent. Interestingly, we observed the conversion of **10** to a mixture of **12** and **24** (1:6). Our proposed mechanism for the formation of this interesting product **24** is outlined in Scheme 4. Reaction calorimetry revealed that the conversion of **10** into **14** is essentially instantaneous and controlled by the rate of addition of sodium methoxide solution. In this process the sodium methoxide is consumed and sodium chloride formed as a by-product. When the second molar equivalent of sodium methoxide is added, we propose that intermediate **23** can be regenerated. This regeneration of **23** from **14** however requires only a catalytic amount of sodium methoxide (since the methoxide anion is renewed as a "leaving group"), allowing the remaining sodium methoxide to act as a nucleophile. Addition of methoxide to **23** followed by elimination of chloride, addition of methanol, and ultimately β-elimination/tautomerisation gives **24**.

Improvements to the Synthetic Route. The observation of dimethoxy derivative **24** led us to examine further our

Scheme 4



Scheme 5 [a]



[a] Key: a) NaOMe (10 mol %), MeOH, CH_2Cl_2 −10 to 0 °C; b) serine ethyl ester hydrochloride, MeOH, CH_2Cl_2; c) $^iPr_2NEt$, CH_2Cl_2; d) pyrrolidine, CH_2Cl_2; e) maleic acid, IPA (**28** 74% yield after purification from **8**).

new methodology for the formation of oxazoles. Our investigations centered around chemical robustness with other considerations such as streamlining of solvents, "work up" requirements, the potential for telescoping stages and "end game" isolations as other key areas. We believed that attaining robustness in our chemical sequence through an understanding of the chemical reactivity and selectivity would increase the overall chemical yield.

Critical examination of the chemistry at each stage led us to optimise the series of reactions depicted in Scheme 5 for the conversion of dichloroacetonitrile **8** through to the pyrrolidinooxazole ethyl ester maleate salt **28**. The conversion of dichloroacetonitrile **8** to the methyl imidate **9** at high concentration (∼2−3 vols in methanol with respect to the dichloroacetonitrile) led to the formation of a dark red solution of the imidate **9** containing unknown impurities. Cleaner conversion of **8** to **9** was observed (monitoring the reaction by ^1H NMR spectroscopy) when a 9:1 dichloromethane:methanol volume solvent mixture was used. Reaction of serine ethyl ester hydrochloride with methyl imidate **9** gave the dichlorooxazoline **25** in excellent crude yield and purity by ^1H NMR spectroscopy. Since the bulk of the solution was dichloromethane at this stage, a simple aqueous work up removed the ammonium chloride by-product leaving the dichlorooxazoline **25** in solution in anticipation for the elimination reaction. A base screen[15] identified Hunig's base ($^iPr_2NEt$) as the best reagent for the smooth conversion of **25** to the oxazole **26**. Evidence of quaternarisation of **26** in the mass spectrum was observed when triethylamine was used as base. The use of dichloromethane instead of methanol as solvent for this reaction circumvented formation of the methoxyoxazoline intermediate **14**. We found it advantageous

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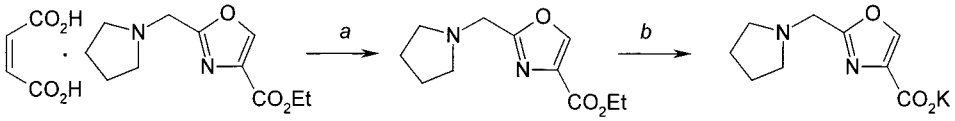
(15) Bases included Et_3N, $^nBu_3N$, $^iPr_2NEt$, *N*-butylpyrrolidine, cyclohexyldiethylamine, *N*-phenyl morpholine, pyridine, dimethyl aniline, picoline.

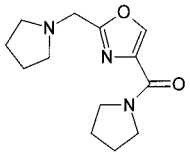
Scheme 6 [a]



28 **27** **29**

[a] Key: a) CH_2Cl_2, aq K_2CO_3; b) KOH, IMS, acetone (**29** 90% yield after purification from **28**)

to remove the Hunig's base at this point with an aqueous acid wash since telescoping the series of reactions with Hunig's base present made for a problematic isolation of maleate salt **28**. When oxazoline **25** and oxazole **26** were independently subjected to prolonged treatment with aqueous acid, the oxazoline hydrolysed to aqueous soluble by-products, whereas the oxazole was recovered in near quantitative yield. This offered purification/rework opportunities should they be required in future batches. Simple pyrrolidine displacement of **26** to give **27** required 2 equiv of pyrrolidine to drive the reaction to completion. This effect has been observed in a similar displacement[16] and is associated with the formation of HCl and protonation of the pyrrolidine during the course of reaction. The use of the ethyl ester **26** offers a significant advantage over the methyl ester counterpart **12**. Treatment of methyl ester **12** with pyrrolidine gave amide **30**[17] as a major by-product, whereas the ethyl



30

ester **26** does not undergo amidation even under forcing conditions using 5 equiv of pyrrolidine at reflux. A screen of acids (CSA, maleic, fumaric, $MeSO_3H$, oxalic) against a series of solvents (acetonitrile, ethanol, isopropylacetate, acetone, dichloromethane, dimethylformamide, isopropyl alcohol) with the pyrrolidinooxazole **27** was examined to determine the best conditions for isolation of **27** as a salt. Our criteria for success was that the salt formed had to be insoluble in the chosen solvent, and the parent acid, soluble. Maleic acid and isopropyl alcohol were chosen, and the maleate salt **28** was isolated in 74% yield in a telescoped process from dichloroacetonitrile **8**. The salt **28** was routinely isolated as a 1:1 stoichiometry of base and acid. In summary, we have significantly improved our original synthetic sequence by carefully considering the choice of solvents (and reaction concentration), the choice of reagents (and their stoichiometry), the ability to telescope reactions, the isolation strategy, and overall robustness of the process.

The target pyrrolidinooxazole potassium salt **29** was prepared in two steps from the maleate salt **28** as outlined in Scheme 6. The free base **27** of **28** was liberated using potassium carbonate solution, extracted into dichloromethane, and subsequently hydrolysed using potassium hydroxide in industrial methylated spirit (IMS). The potassium salt was isolated via precipitation from IMS/acetone in 90% yield from **28**.

(16) Nyce, P. L.; Gala, D.; Steinman, M. *Synthesis* **1991**, 571.
(17) An authentic sample of **30** was prepared from **29** using CSA/CDI activation followed by reaction with pyrrolidine.

Conclusions

This report summarises a novel and efficient route to oxazoles **12**, **17**, **22**, **26**, and the thiazole **13**. The approach uses inexpensive, widely available starting materials and provides another general synthetic approach to this important class of compound. We have applied this chemistry to the synthesis of a key building block, **3**, of GW475151, **1**. This chemistry can be performed on multigram scale and avoids the need for purification by chromatography.

General Experimental Section

Proton and carbon NMR were recorded on a Bruker DPX400 spectrometer. Microanalytical data were performed by Butterworth Laboratories Ltd. Infrared spectra were recorded on a Nicolet 20SXC FTIR spectrophotometer and mass spectra run on Micromass Q-TOF, hybrid quadrupole time-of-flight MS −/+ve ion electrospray instrument. Reagents and solvents were obtained from commercial suppliers.

Experimental Section

Methyl 2-(dichloromethyl)-4,5-dihydro-1,3-oxazole-4-carboxylate, 10. A solution of sodium methoxide in methanol (25% w/w, 5.75 mL, 24.9 mmol) was diluted with methanol (50 mL) and cooled to −10 °C. Dichloroacetonitrile **8** (20 mL, 249 mmol) was added dropwise over 25 min whilst the temperature was maintained below 0 °C. The mixture was stirred for a further 20 min at −5 °C, then DL-serine methyl ester hydrochloride (38.7 g, 249 mmol) was added along with methanol (40 mL). The mixture was stirred overnight, gradually warming to room temperature. CH_2Cl_2 (140 mL) and water (80 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (80 mL) and the combined organic extracts concentrated in vacuo to give dichlorooxazoline **10** (46.7 g, 88%, crude from dichloroacetonitrile) as an orange oil. Spectroscopic data showed dichlorooxazoline **10** to be sufficiently pure to proceed without further purification. R_f 0.30 (20:80 EtOAc: iso-octane); IR (thin film) 1662, 1744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.83 (s, 3H), 4.64−4.69 (m, 1H), 4.73−4.77 (m, 1H), 4.87−4.93 (m, 1H), 6.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 53.01, 60.83, 68.10, 71.25, 164.51, 170.18; MS calcd for $C_6H_8NO_3Cl_2$ (MH^+) 211.9881, found 211.9889.

Methyl 2-(chloromethyl)-4-methoxy-4,5-dihydro-1,3-oxazole-4-carboxylate, 14. To a solution of crude di-

chlorooxazoline **10** (46.2 g, 218 mmol) in methanol (40 mL) was added a solution of sodium methoxide in methanol (25% w/w, 49.9 mL, 218 mmol) dropwise over 50 min, keeping the temperature below 10 °C. The mixture was left to stir overnight, gradually warming to room temperature. CH_2Cl_2 (140 mL) and water (80 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (80 mL), and the combined organic extracts were concentrated in vacuo to give the methoxy intermediate **14** (43.3 g, 84%, crude from dichloroacetonitrile **8** in the previous step) as an oil. R_f 0.25 (25:75 EtOAc:iso-octane); IR (thin film) 1657, 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.42 (s, 3H), 3.85 (s, 3H), 4.19 (d, J = 13, 1H), 4.23 (d, J = 13, 1H), 4.39 (d, J = 10.5, 1H), 4.59 (d, J = 10.5, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 36.03, 51.99, 53.13, 75.48, 101.86, 168.01, 169.28.

Methyl 2-(chloromethyl)-1,3-oxazole-4-carboxylate, 12. To methoxy intermediate **14** (42.9 g, 207 mmol) in toluene (100 mL) was added camphorsulphonic acid (7.21 g, 31.1 mmol) at room temperature, and the mixture was heated to 70 °C. This temperature was maintained for 50 min, and then the mixture was cooled to room temperature and washed with aqueous K_2CO_3 solution (10% w/v, 60 mL) followed by water (80 mL). The combined aqueous extracts were back-extracted with toluene (120 mL) and the combined organic layers concentrated in vacuo to yield the crude chlorooxazole **12** (30.1 g) as a brown solid. A sample of crude chlorooxazole (2.5 g) was purified by flash column chromatography (25:75 EtOAc:iso-octane) to yield the pure chlorooxazole **12** (1.73 g, 48% isolated pure from dichloroacetonitrile **8** in this sequence) as a white solid. IR (Nujol mull) 1578, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.93 (s, 3H), 4.63 (s, 2H), 8.27 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ_C 35.31, 52.35, 133.85, 145.07, 159.91, 161.08; MS calcd for $C_6H_7NO_3Cl$ (MH^+) 176.0114, found 176.0127.

Methyl 2-(dichloromethyl)-4,5-dihydro-1,3-thiazole-4-carboxylate, 11. A solution of sodium methoxide in methanol (25% w/w, 2.67 mL, 11.65 mmol) was diluted with methanol (23.5 mL) and cooled to −10 °C. Dichloroacetonitrile **8** (9.35 mL, 116.5 mmol) was added dropwise over 25 min, keeping the temperature below 0 °C. The mixture was stirred for a further 30 min, and then L-cysteine methyl ester hydrochloride (20.0 g, 116.5 mmol) was added along with methanol (18.7 mL). After the mixture stirred overnight, CH_2Cl_2 (65.5 mL) and water (37.5 mL) were added and the layers separated. The aqueous layer was then extracted with CH_2Cl_2 (37.5 mL), and the combined organic extracts were concentrated in vacuo to yield dichlorothiazoline **11** (22.0 g, 84% crude from dichloroacetonitrile **8**) as an oil. IR (thin film) 1610, 1743, 2850, 2955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.64−3.78 (m, 2H), 3.84 (s, 3H), 5.19 (m, 1H), 6.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 35.81, 53.07, 66.33, 77.46, 170.01, 172.41; MS calcd for $C_6H_8NO_2SCl_2$ (MH^+) 227.9653, found 227.9652.

Methyl 2-(chloromethyl)-1,3-thiazole-4-carboxylate, 13. A solution of dichlorothiazoline **11** (21.3 g, 93.5 mmol) in methanol (20 mL) was treated with a solution of sodium methoxide in methanol (25% w/w, 21.4 mL, 93.5 mmol) dropwise over 50 min, keeping the temperature below 10 °C. The mixture was then stirred for 2 h. CH_2Cl_2 (65.5 mL) and water (37.5 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (37.5 mL) and the sample concentrated in vacuo to yield the crude chlorothiazole **13** (20.3 g) as an orange/brown solid. A sample of the crude product (2.5 g) was removed and purified by flash column chromatography (25:75 increasing to 30:70 EtOAc:iso-octane) to yield the pure chlorothiazole **13** (1.71 g, 66% isolated pure from dichloroacetonitrile **8** used in the synthetic sequence) as a white solid. R_f 0.25 (25:75 EtOAc:iso-octane); IR (Nujol mull) 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.97 (s, 3H), 4.89 (s, 2H), 8.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 41.75, 53.01, 129.59, 147.18, 161.89, 168.00; MS calcd for $C_6H_7NO_2ClS$ (MH^+) 191.9886, found 191.9870.

Methyl 2-(dichloromethyl)- 5-methyl-4,5-dihydro-1,3-oxazole-4-carboxylate, 15. A solution of sodium methoxide in methanol (25% w/w, 0.67 mL, 2.95 mmol) was diluted with methanol (5.9 mL) and cooled to −10 °C. Dichloroacetonitrile **8** (2.37 mL, 29.5 mmol) was added dropwise over 15 min whilst the temperature was maintained below 0 °C. The mixture was stirred for a further 35 min at −5 °C, and then L-threonine methyl ester hydrochloride (5.0 g, 29.5 mmol) was added along with methanol (4.7 mL). The mixture was stirred for 2 h. CH_2Cl_2 (16.5 mL) and water (9.5 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (9.5 mL), and the combined organic extracts were concentrated in vacuo to give the dichlorooxazoline **15** (6.65 g, quantitative) as an orange oil. Spectroscopic data showed dichlorooxazoline **15** to be sufficiently pure to proceed without further purification. IR (thin film) 1658, 1744, 2956 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)_δ_H 1.53 (d, J = 6.3, 3H), 3.81 (s, 3H), 4.39 (d, J = 7.5, 1H), 5.03−5.09 (m, 1H), 6.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 20.96, 53.29, 61.50, 74.79, 81.53, 164.13, 170.51; MS calcd for $C_7H_{10}NO_3Cl_2$ (MH^+) 226.0038, found 226.0027.

Methyl 2-(chloromethyl)-4-methoxy-5-methyl-4,5-dihydro-1,3-oxazole-4-carboxylate, 16. To a solution of dichlorooxazoline **15** (6.39 g, 28.3 mmol) in methanol (4.7 mL) was added a solution of sodium methoxide in methanol (25% w/w, 6.46 mL, 28.3 mmol) dropwise over 20 min, keeping the temperature below 10 °C. After stirring for 90 min, CH_2Cl_2 (16.5 mL) and water (9.5 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (9.5 mL), and the combined organic extracts were concentrated in vacuo to give the methoxy intermediate **16** (5.40 g, 86% crude from dichloroacetonitrile **8**) as an oil. IR (thin film) 1660, 1750, 2954, 2986 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (d, J = 6.8, 1.8H,), 1.44 (d, J = 6.6, 1.2H), 3.43 (s, 1.8H), 3.45 (s, 1.2H), 3.84 (s, 3H), 4.18 (s, 1.2H), 4.20 (s, 1.8H), 4.65 (q, J = 6.8, 0.6H), 4.74 (q, J = 6.6, 0.4H).

Methyl 2-(chloromethyl)-5-methyl-1,3-oxazole-4-carboxylate, 17. To the methoxy intermediate **16** (5.07 g, 22.9 mmol) in toluene (15 mL) was added camphorsulphonic acid (0.80 g, 3.4 mmol) at room temperature and the mixture

heated to 70 °C for 90 min. The solution was cooled to room temperature and washed with aqueous K_2CO_3 solution (10% w/v, 7 mL) followed by water (9.5 mL). The combined aqueous extracts were back-extracted with toluene (14 mL) and the combined organic layers concentrated in vacuo to give the crude chlorooxazole **17** (3.83 g) as an orange solid. A sample of crude chlorooxazole **17** (2.0 g) was purified by flash column chromatography (25:75 EtOAc:iso-octane) to yield the pure chlorooxazole product **17** (1.26 g, 48% from dichloroacetonitrile **8** used in the synthetic sequence) as a white solid. IR (Nujol mull) 1615, 1720, 2961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.66 (s, 3H), 3.92 (s, 3H), 4.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 12.40, 35.85, 52.45, 128.33, 157.41, 158.24, 162.60; MS calcd for $C_7H_9NO_3Cl$ (MH^+) 190.0271, found 190.0256.

Methyl 2-(chloromethyl)-4,5-dihydro-1,3-oxazole-4-carboxylate, 20. A solution of sodium methoxide in methanol (25% w/w, 1.47 mL, 6.43 mmol) was diluted with methanol (10 mL) and cooled to −6 °C. Chloroacetonitrile **18** (4.06 mL, 64.3 mmol) was added dropwise over 15 min keeping the temperature below 2 °C. The mixture was stirred for 45 min, then DL-serine methyl ester hydrochloride (10.0 g, 64.3 mmol) was added along with methanol (8 mL). The reaction mixture was stirred overnight. CH_2Cl_2 (29 mL) and water (16 mL) were then added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (16 mL), and the combined organic extracts were concentrated in vacuo to give the chlorooxazoline **20** (8.02 g, 70% crude from chloroacetonitrile **18**) as an orange oil. Spectroscopic data showed the sample to be sufficiently pure to proceed without further purification. IR (thin film) 1663, 1743, 2957 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.81 (s, 3H), 4.16 (s, 2H), 4.53−4.58 (m, 1H), 4.61−4.66 (m, 1H), 4.81−4.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 36.37, 53.23, 68.60, 70.90, 165.90, 171.21; MS calcd for $C_6H_9NO_3Cl$ (MH^+) 178.0271, found 178.0253.

Methyl 2-methyl-4-methoxy-4,5-dihydro-1,3-oxazole-4-carboxylate, 21. To a solution of chlorooxazoline **20** (7.48 g, 42.1 mmol) in methanol (8 mL) was added a solution of sodium methoxide in methanol (25% w/w, 9.63 mL, 42.1 mmol) dropwise over 20 min, keeping the temperature below 10 °C. The reaction mixture was stirred for 90 min, and then CH_2Cl_2 (29 mL) and water (16 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (16 mL), and the combined organic extracts were concentrated in vacuo to give methyl methoxy intermediate **21** (7.00 g, 40.4 mmol, 67% crude from chloroacetonitrile **18**) as an oil. IR (thin film) 1655, 1750, 2956 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.12 (s, 3H), 3.38 (s, 3H), 3.83 (s, 3H), 4.26 (d, J = 10.3, 1H), 4.47 (d, J = 10.3, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.68, 52.00, 53.32, 74.90, 102.46, 170.33, 171.11; MS calcd for $C_7H_{12}NO_4$ (MH^+) 174.0766, found 174.0758.

Methyl 2-methyl-1,3-oxazole-4-carboxylate, 22. To the methyl methoxy intermediate **21** (6.43 g, 37.1 mmol) in toluene (20 mL) was added camphorsulphonic acid (1.29 g, 5.6 mmol) at room temperature. The mixture was heated to 70 °C for 2 h whereupon a second portion of camphorsulphonic acid (1.29 g, 5.6 mmol) was added. The mixture was stirred for a further 2 h. The solution was cooled to room temperature and washed with aqueous K_2CO_3 solution (10% w/v, 12 mL) followed by water (16 mL). The combined aqueous extracts were back-extracted with toluene (24 mL) and the combined organic layers concentrated in vacuo to yield the methyl oxazole **22** (2.28 g) as a yellow solid. A sample of crude methyl oxazole (1.4 g) was purified by flash column chromatography (25:75 EtOAc:iso-octane) to yield the pure compound **22** (1.14 g, 24% isolated pure from chloroacetonitrile **18**) as a white solid. R_f 0.11 (25:75 EtOAc: iso-octane); IR (Nujol mull) 1734, 2853, 2923 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.52 (s, 3H), 3.91 (s, 3H), 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.21, 52.46, 133.63, 144.14, 162.09, 162.80; MS calcd for $C_6H_8NO_3$ (MH^+) 142.0504, found 142.0487.

Dimethoxy intermediate, 24. To dichlorooxazoline **10** (2 g, 9.43 mmol) in MeOH (10 mL) was added NaOMe in MeOH (4.3 mL, 18.87 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for a further 1 h. CH_2Cl_2 (150 mL) and water (50 mL) were added followed by brine (50 mL). The CH_2Cl_2 layer was separated and concentrated in vacuo to leave an oil (1.66 g). Crude ^1H NMR spectroscopy of the oil indicated a 6:1 ratio of **24**: **12**. Attempts to purify **24** by column chromatography resulted in decomposition. Data on **24**: ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.15 (s, 3H), 3.41 (s, 3H), 3.50 (s, 3H), 3.84 (s, 3H), 5.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.00, 52.56, 52.81, 57.99, 109.87, 145.04, 167.67, 170.37; MS calcd for $C_8H_{14}NO_4$ (MH^+) 204.0872, found 204.0869.

Ethyl 2-(pyrrolidin-1-ylmethyl)-1,3-oxazole-4-carboxylate maleate salt, 28. To CH_2Cl_2 (495 mL) and MeOH (55 mL) was added NaOMe in MeOH (1.61 mL, 0.007 mol, 0.01 equiv, 25% w/w solution) under nitrogen and the mixture cooled to −5 °C. Dichloroacetonitrile **8** (75 g, 0.68 mol) was added dropwise over 45 min, maintaining the temperature below 0 °C, and the mixture stirred for 60 min at 0 °C. Serine ethyl ester HCl was added (115.3 g, 0.68 mol) and the mixture stirred overnight at 20 °C. Water (275 mL) was added and the CH_2Cl_2 layer separated. The aqueous phase was back-extracted with CH_2Cl_2 (275 mL), and the combined CH_2Cl_2 extracts were concentrated at atmospheric pressure to 350 mL. Hunig's base (178 mL, 1.02 mol) was added and the mixture heated to 50 °C for 5 h and then cooled to 20 °C and stirred overnight. CH_2Cl_2 (440 mL) was added, the mixture was cooled to 5 °C, and then HCl (2 M, 500 mL) was added cautiously. The CH_2Cl_2 layer was separated and washed with water (250 mL), and the solution was concentrated to 600 mL at atmospheric pressure and then cooled to 15 °C. Pyrrolidine (113.5 mL, 1.36 mol) was added over 10 min, and the mixture was heated to reflux for 30 min and then chilled to −5 °C and stored overnight. The temperature was adjusted to 20 °C and the CH_2Cl_2 solution washed with aqueous K_2CO_3, (10% w/v, 1000 mL) followed by water (200 mL). The CH_2Cl_2 extracts were concentrated at atmospheric pressure to 350 mL and then IPA (300 mL) was added. The mixture was further concentrated at atmospheric pressure to 350 mL and then cooled to 0 °C. Maleic

acid (78.9 g, 0.68 mol) was added as a solution in IPA (400 mL) over 5 min and the resulting precipitate stirred at 0−4 °C for a further 30 min. The solid was filtered off at suction and washed with chilled (0 °C) isopropyl alcohol (200 mL). The filter cake was dried at 50 °C in vacuo to give maleate salt **28** (1:1 stoichiometry of free base and maleic acid) (170.7 g, 74%) as a pale yellow crystalline solid. IR (Nujol mull) 1724, 2853, 2923 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOH) δ_H 1.35 (t, $J = 7$, 3H), 2.08−2.15 (m, 4H), 3.48−3.51 (m, 4H), 4.35 (q, $J = 7$, 2H), 4.67 (s, 2H), 6.24 (s, 2H), 8.64 (s, 1H); ^{13}C NMR (100 MHz, d_4-MeOH) δ_C 14.47, 24.15, 50.72, 55.90, 62.56, 135.01, 136.52, 147.51, 158.11, 162.16, 170.78; MS calcd for $C_{11}H_{17}N_2O_3$ (MH^+) 225.1239, found 225.1223. Anal. Calcd for $C_{15}H_{20}N_2O_7$: C, 52.94; H, 5.92; N, 8.23. Found: C, 53.30; H, 5.84; N, 8.06.

2-(Pyrrolidin-1-ylmethyl)-oxazole-4-carboxylic acid potassium salt, 29. Maleate salt **28** (20 g, 0.059mol) was slurried in CH_2Cl_2 (100 mL) at 20 °C under nitrogen. Aqueous K_2CO_3 (100 mL, 10% w/v) was added dropwise over ∼20 min. (*Caution!* CO_2 evolution.) The CH_2Cl_2 layer was separated and washed with water (100 mL) and then concentrated at atmospheric pressure to 40 mL. The solution was cooled to ∼30 °C. IMS (100 mL) was added and distillation continued at atmsopheric pressure to ∼40 mL. The solution was cooled to 20 °C. Potassium hydroxide pellets (4.3 g, 0.065 mol, 85% w/w) were dissolved in IMS (40 mL). The potassium hydroxide solution was added to the solution of free base ester over ∼15 min and the solution allowed to stir at ∼20 °C overnight. The solution was concentrated to ∼40 mL. Acetone (60 mL) was added and the slurry stirred at 0 °C for 30 min and then filtered off at suction. The solid was washed with chilled (0 °C) acetone (40 mL) and dried at ∼50 °C in vacuo overnight to give potassium salt **29** (12.41 g, 90%) as a white powder. IR (Nujol mull) 2790, 2853, 2924 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOH) δ_H 1.81−1.84 (m, 4H), 2.64−2.67 (m, 4H), 3.81 (s, 2H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, d_4-MeOH) δ_C 23.23, 51.17, 53.69, 139.34, 141.87, 161.33, 167.48; MS calcd for $C_9H_{13}N_2O_3$ (MH^+) 197.0926, found 197.0914. Anal. Calcd for $C_9H_{11}N_2O_3K$: C, 46.14; H, 4.73; N, 11.96. Found: C, 46.12; H, 4.47; N, 11.68.

Amide impurity, 30. Potassium salt **29** (4 g, 17.1 mmol) was slurried in CH_2Cl_2 (26 mL) under nitrogen and cooled to ∼8 °C. Camphorsulphonic acid (7.9 g, 34.2 mmol) was added in one portion and a suspension of carbonyl diimidazole (CDI) (2.8 g, 17.1 mmol) in CH_2Cl_2 (14 mL) added over ∼25 min. CH_2Cl_2 (7 mL) was used to rinse in excess CDI solid. The mixture was allowed to stir overnight, gradually warming to room temperature and then pyrrolidine (2.2 mL, 25.7 mmol) added in one portion. The mixture was stirred at room temperature for 4 h. Aqueous $NaHCO_3$ (7% w/w solution, 40 mL) was added and the mixture stirred for 15 min. The layers were separated and the aqueous layer back-extracted with CH_2Cl_2 (10 mL). The combined CH_2Cl_2 extracts were washed with aqueous $NaHCO_3$ (7%w/w solution, 20 mL) and brine (20 mL) and then concentrated in vacuo to give the amide **30** as a tan oil (2.04 g, 48%) which solidified upon standing. IR (Nujol mull) 1608, 1633, 2825, 2924 cm^{-1}; ^{1} H NMR (400 MHz, d_4-MeOH) δ_H 1.81−1.86 (m, 2H), 1.90−2.03 (m, 4H), 2.66−2.69 (m, 2H), 3.56−3.59 (m, 2H), 3.85 (s, 2H), 3.88−3.92 (m, 2H), 8.35 (s, 1H); ^{13}C NMR (100 MHz, d_4-MeOH) δ_C 24.33, 24.75, 27.32, 40.03, 49.66, 52.07, 54.78, 137.78, 144.34, 162.04, 162.57; MS calcd for $C_{13}H_{20}N_3O_2$ (MH^+) 250.1556, found 250.1538.

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Supporting Information Available

Crystal structure information for **12**; proton and carbon NMR for compounds **10**−**17**, **20**−**22**, **24**, **28**−**30.** This material is available free of charge via the Internet at http://pubs.acs.org.

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