

Large-Scale Preparation of 2-Methyloxazole-4-carboxaldehyde

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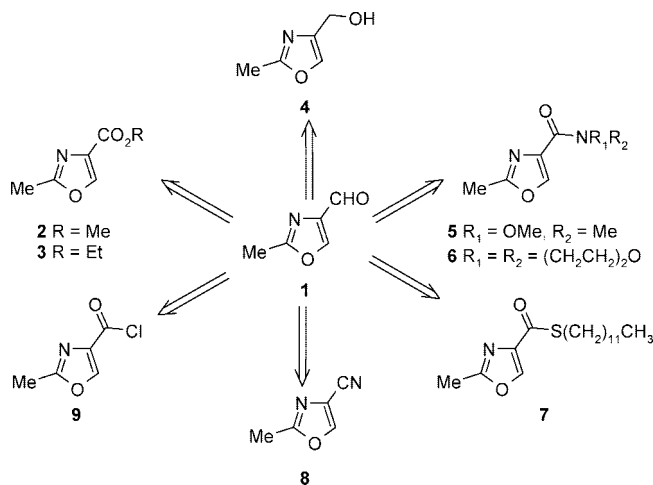
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Abstract:

The large-scale preparation of 2-methyloxazole-4-carboxaldehyde presents a significant challenge due to the physical characteristics of the molecule. A method for the preparation of 10-kg batches of 2-methyloxazole-4-carboxaldehyde is described. The key reaction is the reduction of the corresponding *N*-methoxy-*N*-methyl amide using lithium aluminium hydride, followed by workup and isolation by crystallization.

To support the development of one of our drug candidate molecules, we have had the requirement for many tens of kilograms of 2-methyl-oxazole-4-carboxaldehyde **1** as a starting material. The supply base for electron-rich five-membered heterocyclic starting materials is not as well developed as electron-deficient six-membered ring compounds,¹ and therefore we had to devise our own synthesis that would be amenable to scale-up to a multikilogram scale. The synthesis of oxazole aldehyde **1** has been reported many times; however, the reported scale of preparation is typically only a few grams.^{2,3} The synthesis of oxazole aldehyde **1** on a large scale is a challenging undertaking because the molecule has a low molecular weight, is unstable⁴ to extremes of pH, is very soluble in almost all solvents including water at levels >1g/mL, and has some thermal instability issues; although it is a stable crystalline solid, the melting point is low (58 °C) and it is prone to sublimation.^{2a,5} We report here our preliminary research into and evaluation of synthetic routes⁶ to oxazole aldehyde **1** that would overcome the constraints provided by the molecule and enable the rapid

Scheme 1



initial preparation of multikilogram batches of high quality product in multipurpose pilot plant equipment, without recourse to chromatographic methods of purification.

We envisaged there could be many potential precursors for the aldehyde **1** (Scheme 1). The alcohol **4**, amides **5** and **6**, thioester **7**, and acid chloride **9** would be available by manipulation of the esters **2** or **3**, whereas the nitrile **8** would require an alternative oxazole synthesis.⁷

Our first synthetic method to methyl ester **2** was a modification of a published procedure.⁸ The intermediate oxazoline **12** was readily prepared from ethyl acetimidate **10** and serine methyl ester **11** and required an aqueous workup and then a drying step prior to the oxidation reaction (Scheme 2). Drying by azeotropic distillation was not applicable as partial hydrolysis to form *N*-acetyl serine methyl ester was observed, so we took recourse to drying the solution over MgSO₄. The best conditions we could develop for the oxidation were the addition of 2.0 equiv of DBU to a mixture of oxazoline and bromotrichloromethane (1.5 equiv) over 5 h at 5 °C; however, during the course of the reaction large amounts of dark, unidentified polymeric materials were formed as well. Methyl ester **2** could be isolated by crystallisation from heptane as a white solid once a charcoal treatment had been performed. This procedure was scaled up to 50 kg scale, and ester **2** was isolated as a solvent wet cake containing 34% w/w heptane and in a corrected yield of 56%. Subsequently we developed an alternative process that obviated the need to dry the intermediate oxazoline, avoided

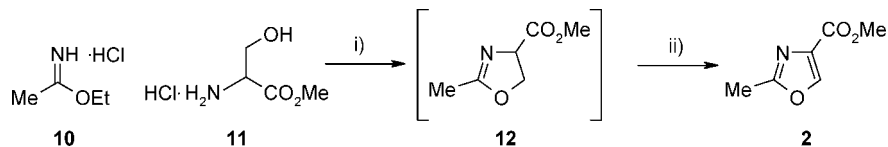
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- (3) Kim, H.-S.; Kim, S. H.; Lee, H. K. *Bull. Korean Chem. Soc.* **1993**, *14*, 524–526.
- (4) Rapid decomposition by hydrolysis to the 1,3-dialdehyde was observed at pH < 3 and pH > 10.
- (5) Some of these physical characteristics are shared by the precursor compounds.
- (6) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. *Chem. Rev.* **2006**, *106*, 3002–3027.

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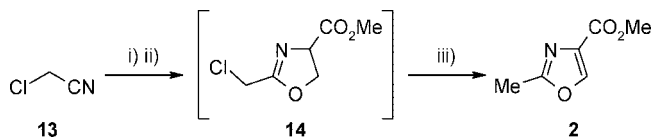
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Scheme 2^a



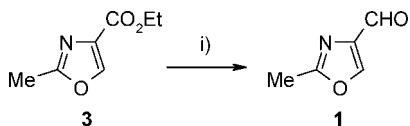
^a Reagents and conditions: (i) NEt₃, CH₂Cl₂; (ii) BrCCl₃, DBU, CH₂Cl₂, 56%.

Scheme 3^a



^a Reagents and conditions: (i) NaOMe, MeOH, CH₂Cl₂; (ii) serine methyl ester hydrochloride, CH₂Cl₂; (iii) DBU, CH₂Cl₂, 69%.

Scheme 4^a

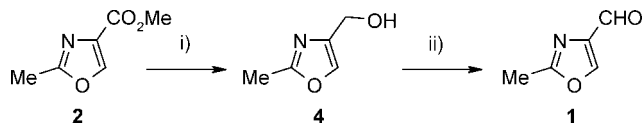


^a Reagents and conditions: (i) DIBALH, CH₂Cl₂, -70 °C, then iPr₂O, 69%.

the use of bromotrichloromethane and therefore the formation of CHCl₃ as a byproduct, and avoided the need to charcoal treat the product stream prior to crystallisation. An imidate was formed from chloroacetonitrile **13**⁹ and MeOH followed by addition of serine methyl ester to form the chloro-oxazoline **14** (Scheme 3). Treatment with DBU resulted in elimination of HCl to form the oxazole ester **2**. This was followed by an acidic wash that furnished an organic stream of essentially pure ester **2**; this could be isolated in 69% yield by crystallisation from heptane if required.

Direct reduction of either ester **2** or **3** to aldehyde **1** has been reported^{2a,b,d,e,10} using either DIBALH or LiAlH₄. The reduction of the closely related ethyl 4-oxazolecarboxylate using DIBALH has been recently reported.¹¹ In our hands, the low temperature reduction of ester **3**¹² using LiAlH₄^{2a,b} resulted in significant over-reduction to alcohol **4** with very little aldehyde **1** observed. Preliminary investigations into the reduction of ester **3** using DIBALH in dichloromethane yielded some promising leads in that only 10% over-reduction to alcohol **4** was observed when the reaction was performed at -70 °C (Scheme 4). It has been suggested that over-reduction in such systems is suppressed because the oxazole function may act as a Weinreb amide

Scheme 5^a



^a Reagents and conditions: (i) LiAlH₄, Et₂O, -5 °C, 70%; (ii) (COCl)₂, DMSO, CH₂Cl₂, NEt₃, -70 °C, 70%.

surrogate.¹³ The crude aldehyde obtained could then be recrystallised to purity from diisopropylether in an overall yield of 69%. Although this was a promising lead, significant challenges were perceived with respect to scaling up this chemistry; in particular the reaction temperature of -70 °C was at the low temperature extreme of our multipurpose pilot plant and we were concerned that a long reagent addition time required to control the reaction exotherm would reduce the chemoselectivity. We were also concerned that the hydrochloric acid quench would be incompatible with the molecule⁴ and that acetal formation, from either the alcohol used in the quench or liberated from the reaction, would occur during the workup or subsequent solvent exchanges via distillation prior to isolation. Because of the very short timelines in which we had to prepare tens of kilograms of material, we did not pursue this approach; however, with further development and greater process understanding it may be possible to use this short, direct route for large-scale preparation.

Reduction of methyl ester **2** to the alcohol **4** was achieved in 70% yield using LiAlH₄ (Scheme 5). Oxidation of alcohol **4** to aldehyde **1** using the procedure of Swern has been published.^{2c,14} This method was used to prepare some very early supplies; however, due to the requirement for cryogenic conditions, the generation of a large amount of gaseous byproduct, and the stench of DMS produced, this method was not considered for further scale-up. Additionally the aldehyde produced using the Swern oxidation was contaminated with some sulfurous residues that had a negative impact on the downstream processing.

Replacement of the oxalyl chloride by SO₃·pyridine complex¹⁵ and running at ambient temperature was not practical; a significant amount (10–15%) of the methyl thioether byproduct **15** was observed (Figure 1). A broad screen of alternative oxidation reagents and conditions was performed.¹⁶ Several sets of conditions that would affect a clean conversion were found,

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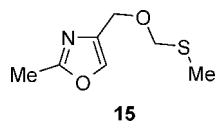
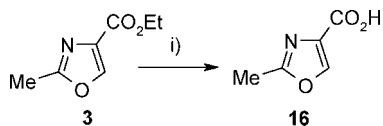


Figure 1

Scheme 6^a



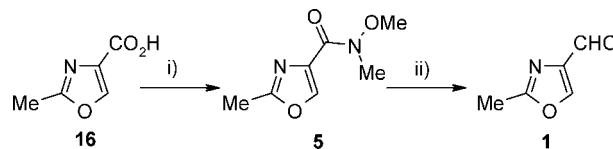
^a Reagents and conditions: (i) NaOH, H₂O, 92%.

such as either TEMPO/[bis(acetoxy)iodo]benzene¹⁷ or pyridinium dichromate (PDC). However, a suitable workup procedure that would enable efficient separation of the product from the reagents could not be found. Oxidation using tetra-*n*-propylammonium perruthenate (TPAP) lacked sufficient chemoselectivity, and overoxidation to carboxylic acid **16** was observed before all of alcohol **4** was consumed. The Dess–Martin periodinane^{2f,g} and 2-iodoxybenzoic acid (IBX) were successful, but the stabilized formulation of IBX, more applicable for scale-up,¹⁸ was not. Alternate TEMPO-based systems using either sodium hypochlorite or Oxone failed to show any significant oxidation, and a similar outcome was observed using MnO₂.

Hydrolysis of ethyl ester **3** to carboxylic acid **16** was carried out in water using aqueous NaOH followed by addition of hydrochloric acid to precipitate the product (Scheme 6). The volume of solvent was reduced to minimise losses to the mother liquors. Acid **16** was shown to be thermally unstable by DSC and ARC, with the onset of an exothermic gas-evolving decomposition detected at 107 °C. Therefore to provide a suitable safety margin we would not subject the material to temperatures above 45 °C on a pilot plant scale. Small-scale laboratory batches could be dried in a vacuum oven; however, we felt that if the chemistry was scaled to multiple kilograms in a pilot plant, vacuum drying of residual water would be very slow. Due to solubility constraints no suitable water-miscible organic solvent could be found that could be used to remove the water by a displacement wash and so ease the drying problem. Any subsequent large-scale chemistry that we developed would need to work using water wet acid **16**. The hydrolysis of ester **3** was scaled up to 100 kg scale, and the acid **16** was obtained as a wet cake containing 19% w/w H₂O and a corrected yield of 92%.

From the survey of methods evaluated on a laboratory scale, preparation and reduction of the Weinreb amide **5** appeared to be the most attractive for rapid scale-up to the pilot plant scale. The Weinreb amide **5** was prepared using the coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) under conditions that were tolerant of significant levels of water (Scheme 7). EDC is a known sensitizer, and we were keen to develop a process that would reduce the exposure to and manual handling of the reagent. To this end we were able

Scheme 7^a



^a Reagents and conditions: (i) NHMe(OMe)·HCl, EDC, NEt₃, CH₂Cl₂, 74%; (ii) LiAlH₄, THF, −35 °C, 50%.

to produce a stable homogeneous solution when we premixed the wet carboxylic acid **16**, dimethylhydroxylamine hydrochloride, and triethylamine in a small volume of the reaction solvent, dichloromethane. This solution was then added to a cooled slurry of EDC in dichloromethane to give clean conversion to the amide. Once the reaction was complete, the solution was washed with minimal amounts of citric acid solution and then water prior to isolating the product by crystallization. In the U.K., dichloromethane is a Class A VOC and its emissions to the environment from our pilot plant facilities are carefully monitored and controlled, so its use is not preferred. Unfortunately dichloromethane was found to be the best solvent with respect to minimizing product losses during the aqueous washes; the use of 2-methyl tetrahydrofuran or *tert*-butylmethylether as solvent lead to significantly decreased yields. Product **5** is very soluble in dichloromethane, so to effect an efficient crystallization it needed to be effectively removed. This was done by several put and take atmospheric distillations with *tert*-butylmethylether until the level of dichloromethane was <30 mol % with respect to amide **5**. At this point a seed could be added followed by the addition of heptane as an antisolvent. This procedure was scaled up to a 75 kg input scale, and the product was obtained in 74% yield.

The Weinreb amide **5** was cleanly reduced to the aldehyde **1** upon reaction with 0.34 equiv of lithium aluminium hydride in THF at −35 °C, and no evidence of over-reduction to the alcohol was observed, even with extended addition or reaction times.¹⁹ Once the reduction was complete, the excess hydride was quenched by the addition of acetic acid. The volume of acetic acid used was optimized to ensure that the pH of the solution post-addition of potassium/sodium tartrate was approximately pH 7. Use of ethanol to quench the excess hydride resulted in the pH rising to pH 14 later in the workup, and considerable decomposition occurred.²⁰ To remove the aluminium salts, a concentrated solution of potassium/sodium tartrate was added, at which point a wet THF layer containing the product separated from the aqueous phase. The solution yield of aldehyde **1** was 85%. A workup was then devised to remove the byproduct dimethylhydroxylamine and then isolate the product by crystallization. The THF solution was diluted with *tert*-butylmethylether and then washed with a minimal volume of 3.5 M aq sodium hydrogen sulfate. This acid was shown to be strong enough to remove the dimethylhydroxylamine, unlike an acetic acid wash, but not cause the same level of decomposition as hydrochloric acid. Failure to remove the dimethylhydroxylamine would lead to the partial formation of amina **17** later in the process (Figure 2). Unfortunately a small but not

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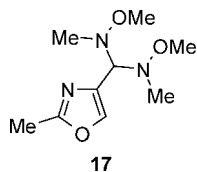


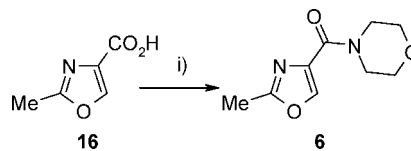
Figure 2

insignificant quantity of aldehyde **1**, approximately 10% as determined by HPLC assay, was lost during the acidic wash. To remove the residual sodium hydrogen sulfate and acetic acid entrained within the organic layer a wash with a minimal amount of sodium carbonate was installed. Again a small but not insignificant quantity of aldehyde **1** was lost during this wash. On a 50 g scale in the laboratory, the solution yield of aldehyde **1** post-workup was 68–70% whereas on a 50 kg scale in the pilot plant the solution yield had slipped to 60–63% due to the increased contact times required for the washes. This product stream was relatively free from any contaminants. To effect an efficient crystallization it was essential to reduce the level of water present to <0.5% w/w, this was achieved by two put and take distillations at atmospheric pressure using *tert*-butylmethylether. Upon cooling slightly, the product would begin to crystallize, and then heptane was added as an antisolvent to maximize recovery. Failure to remove sufficient water would lead to product oiling along with the water when the antisolvent was added. The isolated yield of product on a 50 g scale in the laboratory was 55–57%; however, in the pilot plant the yield had diminished to 42–45%. The solubility of aldehyde **1** in heptane/*tert*-butylmethylether was such that approx 10–12% of yield was lost to the mother liquors, irrespective of scale, and on a pilot plant scale the mother liquors were reconcentrated by distillation under reduced pressure to provide a further 5–7% of yield. Although the product filtered readily, drying was not without difficulty as the product readily sublimes. On a laboratory scale significant losses could be observed when using a Buchner apparatus, and on a pilot scale approximately 0.5–1 kg was lost from each batch during the vacuum drying stage.

Schwartz's reagent, $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$, has been reported as an alternative reagent for the chemoselective reduction of Weinreb's amides to aldehydes.²¹ However, when amide **5** was reacted with the reagent, extensive over-reduction to alcohol **4** was observed as well as the desired aldehyde **1**.

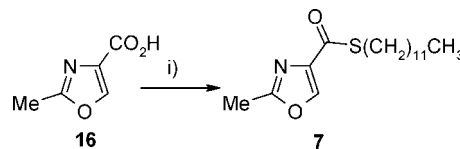
The selective reduction of morpholine amides to aldehydes has been reported to be a cost-effective alternative to the use of the *N,O*-dimethylhydroxylamides.²² An additional attraction to this method would be that an acid weaker than sodium hydrogen sulfate should be able to wash out the morpholine byproduct and therefore potentially reduce the levels of aldehyde decomposition observed during the workup. The morpholine amide **6** was readily prepared from the corresponding acid **16** (Scheme 8). Reaction of morpholine amide **6** with LiAlH_4 in THF at 0 °C proceeded within 1.5 h to produce aldehyde **1** contaminated with 10% of alcohol **4**. The morpholine byproduct

Scheme 8^a



^a Reagents and conditions: (i) morpholine, NEt_3 , EDC, CH_2Cl_2 , 78%.

Scheme 9^a



^a Reagents and conditions: (i) $\text{CH}_3(\text{CH}_2)_{11}\text{SH}$, EDC, DMAP, CH_2Cl_2 , 72%.

could be removed by washing with aqueous acetic acid. However, even on a laboratory scale reaction, the isolated yield of the crude product was no better than that achieved by reduction of the Weinreb amide, and by the time a recrystallisation was performed to improve the quality, the yield had diminished considerably.

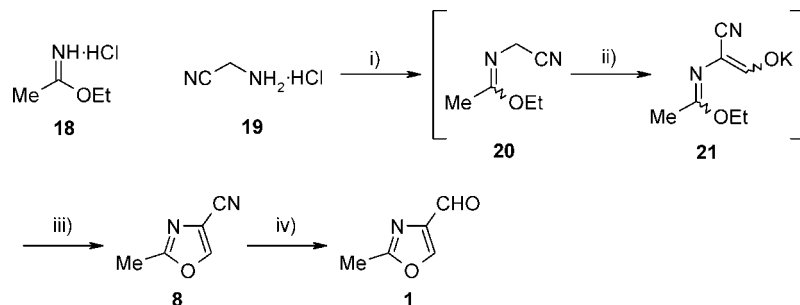
The Fukuyama reduction of a thioester to an aldehyde appeared as an attractive alternative procedure as it would circumvent the use of active metal hydrides such as LiAlH_4 or DIBALH.²³ We chose to prepare the dodecanethiol ester **7** as the required dodecanethiol is odourless²⁴ (Scheme 9). Various solvents, palladium on charcoal catalysts and additives were screened to try and find conditions that would give a chemoselective reduction.²⁵ Under many of the reaction conditions investigated, over-reduction to the alcohol **4** was observed. In a series of control experiments it was shown that the aldehyde **1** could be readily reduced to the corresponding alcohol.

The best conditions we could find for the reduction of thioester **7** to aldehyde **1** were 25% by weight of 5% palladium on charcoal (Engelhard Escat 143), 1.65 equiv of Et_3SiH , 2.0 equiv of MgSO_4 in dichloromethane. After 1 h at ambient temperature the reaction profile showed 5% unreacted thioester **7** and no alcohol **4** present; however, if the reaction time was allowed to increase, then over-reduction occurred faster than consumption of the unreacted thioester. The solids could be removed by filtration to yield a 65% solution yield of aldehyde **1**. Unfortunately an effective practical workup and isolation procedure to remove the excess reagents and byproduct could not be developed.²⁶ This point coupled to the lack of chemoselectivity in the reaction and the sensitivity to reaction time meant that this approach was not deemed suitable for large-scale production.

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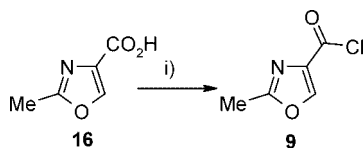
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(26) During the course of the reaction a significant odour of thiol was generated.

Scheme 10^a



^a Reagents and conditions: (i) NEt₃, CH₂Cl₂; (ii) EtOCHO, KO^tBu, CH₂Cl₂; (iii) TMSCl, CH₂Cl₂, Δ, 50%, (iv) DIBALH, CH₂Cl₂, −20 °C 41%.

Scheme 11^a



^a Reagents and conditions: (i) (COCl)₂, DMF, CH₂Cl₂, 61%.

The known cyano-oxazole **8**²⁷ was prepared by a modification of the methods reported by Cornforth^{20,28} (Scheme 10). Imidate **20** was prepared from ethyl acetimidate **18** and aminoacetonitrile **19** and then acylated with ethyl formate in the presence of potassium *tert*-butoxide, to give **21**. Whilst this intermediate could be isolated, it was more convenient to treat it directly with chlorotrimethylsilane to effect cyclisation. This modification of replacing the standard reagent,^{20,28} acetic acid, with chlorotrimethylsilane increased the overall yield for the three-step procedure from 8%^{27a} to 50%.

A brief screen of reduction conditions²⁰ was performed using Red-Al, PtO₂/HCO₂H, and DIBALH. It was found that the use of DIBALH in CH₂Cl₂ at −20 °C afforded the aldehyde in 41% yield. Due to constraints it was not possible to further explore this avenue; however, it may be possible to develop this lead to establish a concise route for large-scale preparation.

The Rosemund reduction of acid chloride **9**, readily prepared from acid **16**, was explored (Scheme 11). A screen of different palladium hydrogenation catalysts (Pd/Ca₂CO₃ + Pb, Pd/Ba₂SO₄, dry Pd/C) and solvents (EtOAc, toluene, NMP) in the presence of a base (Na₂CO₃, K₂CO₃, NEt₃) at various temperatures and pressures was undertaken. Unfortunately, either poor conversion or over-reduction to alcohol **4** was observed, so this avenue was not pursued further.

Conclusions

Tens of kilograms of oxazole aldehyde **1** were prepared to support the early development of a drug candidate molecule. To do this a series of potential precursors were prepared and

then evaluated in the key aldehyde-forming reactions. Reduction of the Weinreb amide **5** was selected as the route to prepare these early supplies as the chemistry required could readily be accommodated in our multipurpose pilot plant equipment and the reaction selectivity was not time-dependent. This chemistry was scaled from 50 g scale in the laboratory to 50 kg scale in the pilot plant. The isolated yield upon scale-up was lower than that achieved in the laboratory, 45% yield versus 55%. The longer contact times for the aqueous washes upon scale-up are partially responsible for the loss in yield, along with some sublimation during the extended distillation and drying stages of the process. Several other shorter approaches, such as reduction of ester **3** or nitrile **8**, showed some promise and may be suitable alternatives for large-scale aldehyde production after further optimization, greater process understanding and use of specific equipment.

Experimental

2-Methyloxazole-4-carboxylic Acid Methyl Ester (**2**).

Procedure 1. Serine methyl ester hydrochloride (50.0 kg, 321 mol) and ethyl acetimidate hydrochloride (47.7 kg, 386 mol) were suspended in dichloromethane (500 L) at 20–25 °C, and triethylamine (32.8 kg, 324 mol) was added. The resulting slurry was stirred at 20–25 °C for 1 h. Water (250 L) was added, the mixture was stirred for 10 min to ensure all solids had dissolved, and then the aqueous and organic layers were separated. The organic layer was washed with water (250 L) and then dried over MgSO₄ (50 kg). The solids were removed by filtration, and the filtercake was washed with dichloromethane (250 L). The filtrate and wash were combined, bromotrichloromethane (95.6 kg, 482 mol) was added, and the solution was cooled to 3–7 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (97.9 kg, 643 mol) was added at 0–5 °C over 5 h. After a further 1 h at 3–7 °C the solution was warmed to 20–25 °C, HCl (250 L; 2 M; aq) was added, and then the organic layer was washed with water (250 L). The organic layer was concentrated by distillation at atmospheric pressure to leave a residual volume of 175 L. Nuchar charcoal (5 kg) was added followed by heptane (500 L). The solution was concentrated by distillation at atmospheric pressure until the distillation temperature reached 98 °C; approx 300 L of distillate was collected. Heptane (375 L) was added, the content temperature was maintained within the range 70–90 °C while the charcoal was removed by filtration and the filterbed was washed with hot heptane (100 L). The solution was cooled to 45 °C and then a seed of methyl ester **2** was added to induce crystallisation. The resulting slurry was cooled to 0–5 °C and

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aged for 6 h. The slurry was then filtered, and the filtercake was washed with cold heptane (2 × 75 L). Methyl ester **2** was isolated as a heptane wet cake, 38.4 kg, which was suitable for onward processing. Loss on drying = 34% w/w. Theoretical dry weight = 25.3 kg (56%).

Procedure 2. Sodium methoxide (25% w/w solution in methanol, 1.65 mL, 7.20 mmol) was added to a solution of methanol (50 mL) in dichloromethane (450 mL) at 0–5 °C. After 5 min, chloroacetonitrile (50 mL, 790 mmol) was added, and the solution was stirred at 0–5 °C for 1.5 h. Serine methyl ester hydrochloride (99.0 g, 636 mmol) was added at 0–5 °C, and the resulting slurry was allowed to warm to room temperature and stirred for 18 h. Water (200 mL) was added, the mixture stirred for 10 min to ensure all solids had dissolved, and then the aqueous and organic layers were separated. The organic layer was washed with water (200 mL) and then concentrated by distillation at atmospheric pressure to leave a residual volume of 150 mL. Fresh dichloromethane (500 mL) was added, and the solution was warmed to 30 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (95 mL, 635 mmol) was added over 2 h while maintaining the internal temperature of the reaction at 30 °C. Upon completion of the addition the reaction mixture was cooled to room temperature, and HCl (200 mL; 2 M; aq) was added. Then the organic layer was washed with water (200 mL). The organic layer was concentrated by distillation at atmospheric pressure to leave a residual volume of 300 mL. Heptane (400 mL) was added, and the solution was concentrated by distillation at atmospheric pressure to leave a residual volume of 300 mL. Heptane (100 mL) was added, the solution was cooled to 45 °C, and then a seed of methyl ester **2** was added to induce crystallisation. The resulting slurry was cooled to 0–5 °C and aged for 2 h. The slurry was filtered, and the filtercake was washed with cold heptane and then dried to give methyl ester **2** (62.11 g, 69%). Mp = 48 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1 H), 3.91 (s, 3 H), 2.52 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 162.2, 161.6, 143.7, 133.1, 51.9, 13.7; IR (neat cm⁻¹) 1732, 1585; LRMS (CI +ve) *m/z* 142 (M⁺ + H).

2-Methyloxazole-4-carboxylic Acid (16). Ethyl ester **3** (100 kg, 645 mol) was dissolved in water (250 L) at 20–25 °C, and NaOH (96 kg; 32% w/w; aq, 768 mol) added over 30 min, while maintaining the temperature in the range 20–25 °C. After 1 h HCl (78 kg; 37% w/w; aq, 770 mol) was added while maintaining temperature in the range 20–25 °C. Upon completion of the addition the resulting slurry was cooled to 0 °C and aged for 1 h. The product was isolated by filtration, and the filtercake was washed with cold water (100 kg). Wet weight of acid = 93 kg, loss on drying = 19% w/w, theoretical weight of dry acid = 75 kg (92%). A small sample was dried for analytical purposes. Mp = 77 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.90 (s, 1 H), 8.57 (s, 1 H), 2.44 (s, 3 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 167.3, 167.0, 150.0, 138.4, 18.5; IR (neat cm⁻¹) 1715, 1585; LRMS (CI – ve) *m/z* 126 (M⁺ – H); water content <0.1% w/w by Karl Fischer titrimetry; residue on ignition = 0.2% w/w.

N-Methoxy-N-methyl-2-methyloxazole-4-carboxamide (5). Carboxylic acid **16** (93 kg, loss on drying = 19% w/w, theoretical weight of dry acid = 75 kg, 591 mol) and *N,O*-

dimethylhydroxylamine hydrochloride (57 kg, 584 mol) were suspended in dichloromethane (225 L) and water (20 L). Triethylamine (60 kg, 593 mol) was added and then stirred at ambient temperature for 1 h to achieve a clear solution that was then cooled to 0–5 °C. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (137 kg, 715 mol) was suspended in dichloromethane (375 L) and then cooled to 0–5 °C. The solution of carboxylic acid was added to the slurry of diimide while maintaining the temperature <10 °C. Once the addition was complete the solution was allowed to warm to ambient temperature and then stirred for 1 h. A solution of citric acid (45 kg) in water (180 L) was added, and the layers were separated. The aqueous solution was re-extracted with dichloromethane (225 L). The organic extracts were combined and then washed with water (112 L). The solution was concentrated by distillation at atmospheric pressure to leave a residual volume = 225 L. *tert*-Butylmethylether (375 L) was added, and the solution was concentrated by distillation at atmospheric pressure to leave a residual volume of 188 L. *tert*-Butylmethylether (375 L) was added, and the solution was concentrated by distillation at atmospheric pressure to leave a residual volume of 188 L. The solution was cooled to 35 °C, and then *tert*-butylmethylether (188 L) was added. The solution was seeded with amide **5** at 35 °C, and heptane (375 L) was added at 35 °C. Once the addition was complete, the slurry was aged at 35 °C prior to being cooled to ambient temperature and aged for a further 2 h. The slurry was cooled to 0–5 °C and aged for 1 h, and the product isolated by filtration. The filtercake was washed with heptane (75 L) and then dried under vacuum to afford the amide **5** as a white solid (74.3 kg, 74%, 68% yield over 2 stages). Mp = 53 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1 H), 3.77 (s, 3 H), 3.37 (s, 3 H), 2.51 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 161.1, 161.0, 142.3, 133.1, 61.2, 33.0, 13.5; IR (neat cm⁻¹) 1639, 1595; LRMS (CI +ve) *m/z* 171 (M⁺ + H).

2-Methyloxazole-4-carboxaldehyde (1). **Procedure 1.** Weinreb amide **5** (50 kg, 294 mol) was dissolved in tetrahydrofuran (300 L) and cooled to –35 °C. Lithium aluminium hydride solution (1 M in tetrahydrofuran, 100 L, 100 mol) was added while maintaining the temperature at –30 to –35 °C. After 30 min a solution of acetic acid (15 L) in tetrahydrofuran (50 L) was added while maintaining the temperature at –30 to –35 °C. The resulting solution was warmed to –15 °C, and a solution of potassium/sodium tartrate (125 kg of K/Na tartrate tetrahydrate in 250 L H₂O) was added while maintaining the temperature <10 °C. Upon completion of the addition the mixture was warmed to 20 °C, and the layers separated. The organic layer was diluted with *tert*-butylmethylether (500 L) and was then washed with sodium hydrogen sulfate (150 L; 3.5 M; aq). The organic layer was then washed with sodium carbonate (125 L; 8% w/v; aq) and then concentrated by distillation at atmospheric pressure to leave a residual volume of 150 L. *tert*-Butylmethylether (250 L) was added and then concentrated by distillation at atmospheric pressure to leave a residual volume of 150 L. *tert*-Butylmethylether (250 L) was added and then concentrated by distillation at atmospheric pressure to leave a residual volume of 150 L. The solution was then sampled for water content (<0.5% w/w by Karl Fischer titrimetry). The resulting solution was cooled to room temper-

ature, during which time crystallization occurred. Heptane (400 L) was added over 2 h, and then the slurry was cooled to 0 °C. The slurry was filtered, and the filtercake washed with cold heptane (50 L) and then dried under vacuum at ambient temperature to afford aldehyde **1** as an off-white solid (14.8 kg, 45%). The mother liquors and wash liquors were combined and then concentrated by distillation under reduced pressure to leave a residual volume of 75 L. The resulting slurry was cooled to -5 to -10 °C and filtered, and the filtercake was washed with cold heptane (7.5 L) and then dried under vacuum at ambient temperature to afford a second crop of aldehyde **1** as an off-white solid (1.78 kg, 5%). Mp = 49 °C; ¹H NMR (400 MHz, CDCl₃) δ 9.92 (s, 1 H), 8.20 (s, 1 H), 2.54 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 183.8, 163.0, 144.6, 140.9, 13.7; IR (neat cm⁻¹) 1674, 1595; LRMS (CI +ve) *m/z* 112 (M⁺ + H).

2-Methyloxazole-4-methanol (4). Methyl ester **2** (500 g, 3.55 mol) was suspended in diethyl ether (7.7 L) and cooled to -5 °C. Lithium aluminium hydride solution (1.0 M in tetrahydrofuran, 2.13 L, 2.13 mol) was added while maintaining the temperature at -5 °C. After 1 h, water (81 mL) was added, followed by NaOH (81 mL; 15% w/v; aq) and further water (242 mL). Sodium sulfate (1.02 kg) was added, and the resulting suspension was allowed to warm to ambient room temperature. The slurry was filtered and the filtercake was washed with dichloromethane (3 × 2.5 L). The filtrate and washes were combined and then concentrated to dryness to afford alcohol **4** as an off-white solid (280 g, 70%). The alcohol could be recrystallised from heptane if required. ¹H NMR (400 MHz, CDCl₃) δ 7.48 (s, 1 H), 5.00 (br s, 1 H), 4.53 (s, 2 H), 2.43 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 162.2, 140.3, 134.9, 55.8, 13.7; IR (neat cm⁻¹) 3212, 1578; LRMS (CI +ve) *m/z* 114 (M⁺ + H).

N-Morpholine-2-methyloxazole-4-carboxamide (6). Carboxylic acid **16** (51.39 g, 405 mmol) was suspended in dichloromethane (515 mL). Triethylamine (59.3 mL, 425 mmol), then morpholine (37.2 mL, 425 mmol) and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (101 g, 527 mmol) were added, and the resulting mixture was stirred at ambient temperature for 70 h. A solution of citric acid (40 g) in water (150 mL) was added, and the layers were separated. The organic layer was washed with water (150 mL), dried over MgSO₄, filtered, and then concentrated to dryness to leave the product **6** as a white solid (62.31 g, 78%). ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1 H), 4.15 (br s, 2 H), 3.74 (br s, 6 H), 2.48 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 160.8, 160.6, 143.4, 136.5, 67.0, 46.9, 42.8, 13.8; IR (neat cm⁻¹) 1738, 1611, 1586; LRMS (CI +ve) *m/z* 197 (M⁺ + H).

2-Methyloxazole-4-carboxylic Acid Dodecanthioester (7). Carboxylic acid **16** (5.00 g, 39.4 mmol) was suspended in dichloromethane (50 mL) and cooled to 0–5 °C. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (9.33 g, 48.7 mmol), *N,N*-dimethylaminopyridine (240 mg, 1.96 mmol), and dodecanthiol (9.42 mL, 39.3 mmol) were added at 0–5 °C, and the resulting mixture was allowed to warm to ambient temperature. After 1 h the reaction was complete, and the dichloromethane was removed on a rotary evaporator. Ethyl acetate (100 mL) was added, and the organic layer was washed

with HCl (50 mL; 2 M; aq), water (50 mL), and then brine (50 mL). The organic solution was dried over MgSO₄, filtered, and then concentrated to dryness to leave the product as a white solid (11.45 g, 93%). This essentially pure product could be recrystallised from methanol (35 mL) to afford thioester **7** as a white solid (8.87 g, 72%). ¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1 H), 3.03 (t, *J* = 7 Hz, 2 H), 2.52 (s, 3 H), 1.65 (quin, *J* = 7 Hz, 2 H), 1.44–1.22 (m, 18 H), 0.88 (t, *J* = 7 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 185.6, 162.0, 139.8, 139.5, 31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 29.1, 28.8, 22.7, 14.1, 13.8; IR (neat cm⁻¹) 2915, 1651, 869; LRMS (CI +ve) *m/z* 312 (M⁺ + H).

2-Methyloxazole-4-carbonitrile (8). Ethyl acetimidate hydrochloride (25.0 g, 202 mmol) and aminoacetonitrile hydrochloride (23.3 g, 252 mmol) were suspended in dichloromethane (500 mL) at room temperature. Triethylamine (28.5 mL, 204 mmol) was added over 1.5 h, and once the addition was complete, the slurry was cooled to 5 °C. Water (125 mL) was added, the mixture was stirred to ensure all solids had dissolved, and then the aqueous and organic layers were separated. The aqueous layer was re-extracted with dichloromethane (50 mL). The organic extracts were combined and then washed with water (125 mL), dried over MgSO₄ (15 g), filtered, and then concentrated by distillation to leave a residual volume of 50 mL. *tert*-Butylmethylether (400 mL) was added, and the solution was cooled to 0 °C. Ethyl formate (14.8 mL, 184 mmol) was added followed by a portionwise addition of potassium *tert*-butoxide (20.6 g, 184 mmol) while maintaining the temperature <10 °C. Once the addition was complete the resulting slurry was stirred at 0 °C for 1.5 h prior to being heated to reflux. Chlorotrimethylsilane (53 mL, 415 mmol) was added at reflux over 1.5 h. Once the addition was complete the mixture was cooled to room temperature, and water (100 mL) was added. Once all of the solids had dissolved, the aqueous and organic layers were separated. The aqueous layer was re-extracted with dichloromethane (100 mL). The organic extracts were combined and then washed with water (100 mL), and the solvent was removed by distillation to leave an oil, which could be purified by short path distillation (oven temperature = 170 °C, 20 mmHg) to give cyano-oxazole **8** as an oil (10.9 g, 50%). ¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1 H), 2.55 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 163.2, 146.2, 114.8, 111.8, 13.7; IR (neat cm⁻¹) 2247, 1589; LRMS (CI +ve) *m/z* 109 (M⁺ + H).

2-Methyloxazole-4-carboxylic Acid Chloride (9). Carboxylic acid **16** (5.00 g, 39.4 mmol) was suspended in dichloromethane (20 mL) and cooled to 0–5 °C. Oxalyl chloride (6.75 mL, 77.4 mmol) and then DMF (50 μL, 0.65 mmol) were added. Once the additions were complete, the mixture was allowed to warm to ambient temperature and then aged for 3 h. The resulting slurry was cooled to 0–5 °C and aged for 1 h, and then heptane (50 mL) was added. The slurry was aged at 0–5 °C for 1.5 h, and then the product was isolated by filtration and dried under vacuum to afford acid chloride **9** as a white solid, which coloured slightly upon standing (3.47 g, 61%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.60 (s, 1 H), 2.46 (s, 3 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 161.2, 161.1, 144.8, 133.1, 133.0; IR (neat cm⁻¹) 1755, 820.

2-Methyloxazole-4-carboxaldehyde (1). *Procedure 2.* Ethyl ester **3** (24.27 g, 156 mmol) was dissolved in dichloromethane (300 mL) and then cooled to -70°C . DIBALH (56 mL, 314 mmol) was added over 45 min while maintaining temperature at -65 to -70°C . After 45 min, methanol (50 mL) was added, and the solution was allowed to warm to ambient temperature, during which period some solids precipitated from solution and stirring became difficult. HCl (150 mL; 2 M; aq) was added, all the solids dissolved, and the layers were separated. The aqueous layer was extracted with dichloromethane (200 mL), and the organic extracts were combined, dried over MgSO_4 , and concentrated to dryness to afford the crude product **1** (15.7 g). Recrystallisation from $i\text{Pr}_2\text{O}$ (60 mL) gave aldehyde **1** as an off-white solid (12.0 g, 69%).

Procedure 3. Dimethylsulphoxide (391 mL, 5.50 mol) in dichloromethane (1.0 L) was added to a solution of oxalyl chloride (236 mL, 2.71 mol) in dichloromethane (3.75 L) while maintaining the temperature at -60 to -55°C . After 5 min a solution of alcohol **4** (289 g, 2.11 mol) in dichloromethane (1.35 L) was added while maintaining the temperature at -60 to -55°C . After 20 min, triethylamine (1.78 L, 12.77 mol) was added while maintaining the temperature at -60 to -55°C . After 45 min the resulting slurry was allowed to warm to ambient room temperature, and water (7.23 L) was added. The layers were separated, and the aqueous layer was re-extracted with dichloromethane (4.34 L). The dichloromethane extracts were com-

bined and dried over MgSO_4 (290 g). The solvent was removed, and the residue purified by column chromatography (Biotage system, eluent petroleum ether/ethyl acetate 3:1) to afford aldehyde **1** as an off-white solid (199 g, 70%).

Procedure 4. Cyano-oxazole **8** (1.45 g, 13.43 mmol) was dissolved in dichloromethane (6 mL) and then cooled to -20°C . DIBALH (1.0 M solution in dichloromethane, 20 mL, 20 mmol) was added over 1 h while maintaining the temperature at -20°C . After 15 h, methanol (5 mL) was added, and the solution was allowed to warm to ambient temperature. Further dichloromethane (20 mL) was added followed by HCl (7.5 mL; 2 M; aq). The layers were separated, and the aqueous layer was re-extracted with dichloromethane (7.5 mL). The organic extracts were combined, dried over MgSO_4 , and concentrated to dryness to afford the product **1** as a light tan solid (612 mg, 41%).

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