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Development of a Fully Telescoped Synthesis of the S1P1 Agonist GSK1842799

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Supporting Information

ABSTRACT: The development of a fully telescoped synthesis of the potent and selective S1P1 agonist GSK1842799 is described. Key features in the synthesis, which has been implemented on a multikilogram scale, include a nucleophilic aromatic substitution to install a lipophilic 1-octyloxy chain, introduction of a chiral quaternary centre, and the use of Lawesson's reagent to form a thiadiazole ring. Due to the lack of crystalline intermediates, workup protocols that took advantage of the lipophilic nature of the compounds were developed. This allowed full combination of the five chemistry stages and a salt formation, with the only isolation being that of the final hemifumarate salt of the drug substance. The synthesis of the *O*-phosphorylated active metabolite is also described.

INTRODUCTION

GSK1842799 (Scheme 1, **1**) is a potent and selective sphingosine-1-phosphate receptor subtype 1 (S1P1) agonist and, as such, has potential utility for the treatment of diseases or conditions associated with inappropriate immune responses, including transplant rejection and autoimmune diseases such as multiple sclerosis and psoriasis.[1,2] Phosphorylation of **1** in vivo generates the active metabolite **2**, which shows structural similarity to naturally occurring S1P (**3**), a bioactive lipid mediator. There are five subtypes of S1P-responsive receptors, and GSK1842799 was designed to be selective for the S1P1 subtype. In order to evaluate the clinical potential of GSK1842799, multikilogram quantities of **1** were required. Additionally, gram-quantities of the phosphate **2** were required to support preclinical activities.

The original synthetic route to GSK1842799, used to prepare the initial gram quantities of **1**, is depicted in Scheme 2.[3] The general synthetic approach for the construction of the drug substance was deemed suitable for the manufacture of multikilogram quantities of **1**, but several issues needed addressing prior to further scale-up. The six-step synthesis provided **1** as the hydrochloride salt in an overall yield of ~20−30%. Although the hydrochloride salt was initially isolated as a crystalline solid, it is hygroscopic and deliquescent; thus, the identification and isolation of a stable, crystalline version of **1** was required. Furthermore, all of the intermediates were isolated by stripping to dryness under vacuum to yield waxy solids, gums, or viscous oils. The greater than 100% uncorrected yields reported at two stages reflect the challenge in isolating these compounds free from residual solvents and impurities. Presumably, the degrees of rotational freedom provided by the octyloxy side chain are in large part responsible for the lack of crystalline intermediates. In addition to handling issues, the lack of solid intermediates meant that purification by crystallisation was not an available option, and so chromatography had been required to control purity at two stages. Although we recognised that the lipophilic side chain would make the isolation of solid intermediates challenging, we reasoned that we might be able to use it to our advantage in designing workup procedures, in a fashion analogous to the use of fluorous tags.[4] Despite the synthetic route to **1** being far from the notion of the 'ideal synthesis',[5] with excess reagents required and byproduct generated at each step, the lipophilic 'tag' might allow us to approach 'ideal purifications', in which the product is separated into a different phase from everything else that is in the reaction mixture.[6] In this manner, we might control the purity during the synthesis through design of workup procedures rather than relying on crystallisations or chromatography.

As well as the challenges posed by the physical properties of the intermediates and drug substance, other issues also required attention. Significant frothing had been reported in the nucleophilic aromatic substitution reaction between 4-fluoro-3-trifluoromethylbenzoic acid **4** and 1-octanol, with the volume of the froth many times that of the reaction mixture. Control of the frothing would be necessary in order to avoid poor throughput in the preparation of **5** due to the requirement for substantial headspace availability above the reaction mixture. We were also concerned about the potential for damage to the reaction vessels due to the fluoride byproduct, particularly upon acidification in order to isolate the benzoic acid product. Conversion of benzoic acid **5** to hydrazide **6** posed safety concerns, since a large excess of hydrazine was employed and upon completion the reaction mixture was concentrated to low volume by distillation prior to extraction into dichloromethane. Although two (*S*)-2-methylserine derivatives, **7a** and **7b**, had been successfully coupled with hydrazide **6** in the gram-scale preparations of **1**, a multikilogram supply would be required. Most of the preparations of **1** had used the dimethyl oxazolidine **7a**, which had been prepared from (*S*)-2-methylserine for which there is not a commercial source on multikilogram scale. The *tert*-butyl oxazolidine **7b** had been prepared from readily available L-serine methyl ester hydrochloride using Seebach's self-regeneration

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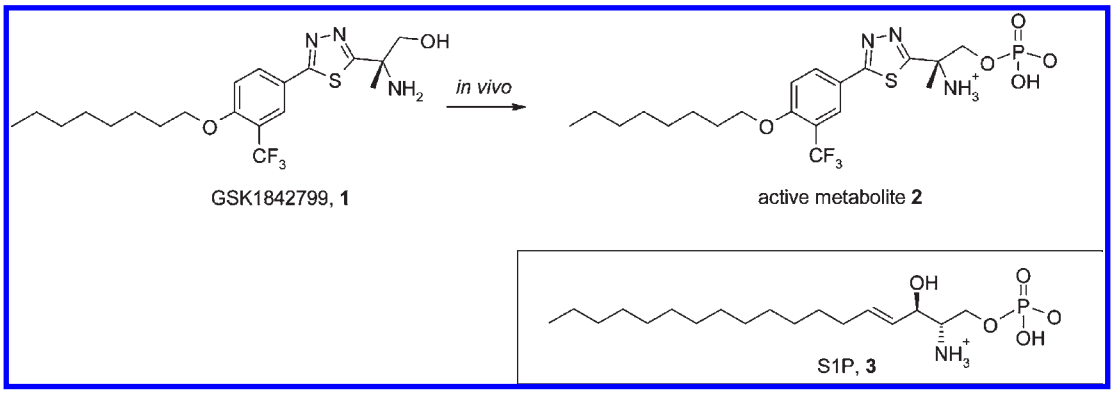
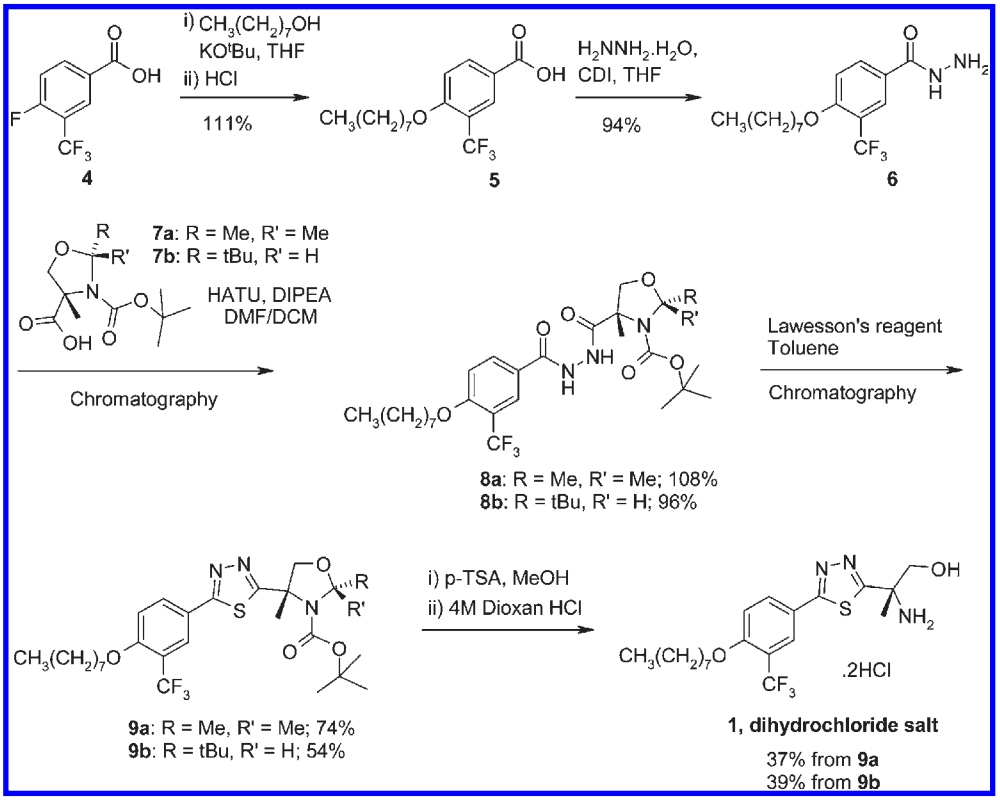
Scheme 1. GSK1842799 (1) and the active metabolite 2, which shows structural similarity to naturally occurring S1P (3)



Scheme 2. Discovery Route to GSK1842799 1[a]



[a] All reported yields are uncorrected for purity.

of stereocentres approach,[7] but when we analysed these samples by chiral GC, they only had a modest purity of ~93% ee and on processing through to drug substance **1** did not produce material with sufficient chiral purity. Furthermore, we had concerns over the ability to successfully scale up the chemistry to **7b**, which includes a diastereoselective alkylation under cryogenic conditions.[8] In completing the synthesis of **1**, the coupling of the (*S*)-2-methylserine derivative with hydrazide **6** used the expensive and thermally unstable coupling reagent HATU; the thiadiazole formation used Lawesson's reagent and so would require the control of the associated stench, and the formation of potentially genotoxic impurities in the deprotection stage would need controlling or avoiding.

The development of the chemistry to address the above issues and allow the manufacture of multikilogram quantities of **1** without recourse to any intermediate isolation is described below. An approach to convert the alcohol **1** to the corresponding phosphate **2** is also described.

RESULTS AND DISCUSSION

Nucleophilic Aromatic Substitution Reaction to Prepare Octyloxy Benzoic Acid 5. The insertion of the octyloxy side chain by a nucleophilic aromatic substitution reaction between 4-fluoro-3-trifluoromethylbenzoic acid **4** and 1-octanol under basic conditions will inevitably generate a soaplike compound,

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Table 1. Nucleophilic aromatic substitution reaction for the preparation of 5

entry[a]	solvent	base	HPLC purity @ 1 h[b] (%)	HPLC purity @ 20 h[b] (%)
1	THF[c]	KO*t*Bu	57	60
2	THF	LiO*t*Bu	0	0
3	THF	NaO*t*Bu	25	75
4	2-MeTHF	NaO*t*Bu	<10	<10
5	toluene	NaO*t*Bu	<10	20
6	1,4-dioxane	NaO*t*Bu	40	60
7	1-octanol[d]	NaO*t*Bu	<10	70
8	THF	NaHMDS[e]	20	85
9[f]	THF	NaHMDS[e]	—	95

[a] Standard conditions: Benzoic acid **4** (1 equiv), 1-octanol (1.2 equiv), and base (2.5 equiv) were heated in solvent (12 vol) to 65 °C for 20 h. [b] Analysis by HPLC at 220 nm. % area product, adjusting for the solvent peak where applicable, is reported. [c] Diluted to 30 vol THF after 2 h. [d] Heated to 130 °C after 2 h. [e] 1 M solution of NaHMDS in THF used. No further THF added. [f] 2.0 equiv 1-octanol, 2.8 equiv NaHMDS (1 M in THF).

with a lipophilic tail and a charged, polar carboxylate headgroup. If this 'soap' is generated under conditions that allow gas ingress into the liquid phase, such as heating under reflux or with vigorous agitation, then it would be expected that a significant generation of froth or foam will occur. The conditions that had been used in the initial gram-scale preparations used 2.5 equiv of base (KO*t*Bu) in refluxing THF, and therefore, it is unsurprising that this led to foam generation. To avoid the formation of a soaplike molecule, we could have considered protecting the carboxylic acid (such as by converting to an ester) or inserting the octyloxy chain later in the synthesis, but for expediency our first choice was to retain the same synthetic route that had already been used by the Discovery Group to produce **1**. As such, we began by screening the reaction conditions in an attempt to identify a process whereby the product **5** could be formed without a foam being generated.

In our hands, the initial conditions gave a rapid initial conversion to **5**, but as the reaction progressed the mixture became gelatinous and did not proceed to completion, presumably due to the very poor mixing (Table 1, entry 1). Since the counterion is known to affect the rate of S_NAr reactions[9] and is also likely to affect the physical properties of the reaction through differing solubilities and potentially different aggregation states, we compared the use of KO*t*Bu with the lithium and sodium salts (entries 2 and 3). No desired reaction was observed with LiO*t*Bu, whereas with NaO*t*Bu the reaction did proceed. The initial rate was slower compared to the that with the use of KO*t*Bu, but the reaction mixture remained a mobile slurry throughout and proceeded further to completion in 24 h. An attempt to change solvent from THF to 2-MeTHF, which would allow a higher reaction temperature and potentially facilitate an easier workup, was unsuccessful, since the reaction became gelatinous and suffered from poor mixing from the start (entry 4). Other solvents screened (entries 5−7) showed no advantage over THF, including the use of 1-octanol as solvent (entry 7), which required a higher reaction temperature to proceed. The reaction in 1-octanol also resulted in significant levels of the phenol, 4-hydroxy-3-(trifluoromethyl)benzoic acid, which was only seen at low levels in the other reactions. However, returning to THF and changing the base from sodium *tert*-butoxide to NaHMDS led to a slightly improved purity profile and higher conversion over 24 h (entry 8). The improvement in the reaction profile might be due to full deprotonation of the 1-octanol with the stronger base or due to changes in aggregation states or enhanced solubility of the reaction components. Following a rapid optimisation study, reaction completion could be achieved within 24 h by using 2.8 equiv of NaHMDS and 2 equiv of 1-octanol (entry 9). Since a 1 M solution of NaHMDS in THF was initially used, the increased base stoichiometry meant that the total solvent volume increased to 13 vol. For the plant campaign we used a more concentrated NaHMDS solution, but diluted with further THF to maintain the same overall reaction dilution. Frothing in the reaction was minimised by running 3−5 °C below the reflux temperature and using minimum agitation to avoid ingress of headspace gas into the reaction mixture. By using this protocol the volume of froth observed was routinely estimated as significantly less than 10% of the reaction volume. No etching of the glassware during the extended reaction time at elevated temperature was observed.

With conditions now identified for the S_NAr reaction, our attention focused on the isolation of **5** from the reaction mixture, which we required in high purity and in a suitable form for onward processing. To do this, we needed to separate the octyloxy benzoic acid product **5** from the reaction solvent, excess reagents (1-octanol and NaHMDS), byproduct (HMDS, NaF), and impurities (including residual starting benzoic acid **4** and the phenol analogue). Since precipitation of the product was not a feasible option, due to its physical properties, and we wanted to avoid the requirement for purification by chromatography, we developed an extractive workup that utilised the lipophilicity of the product imparted by the octyloxy chain (Figure 1). An initial solvent swap into water by distillation was performed to remove the THF. It was important to charge some water prior to commencing the distillation in order to avoid excessive foaming. Upon removal of the THF an aqueous slurry of the sodium carboxylate product was obtained. Due to the high ionic strength of the aqueous phase and the lipophilicity of **5** we were able to extract the sodium carboxylate into an organic solvent, with TBME being chosen for this purpose. The sodium fluoride byproduct together with less lipophilic carboxylate impurities, including unreacted **4**, were removed to the aqueous waste. By removing the fluoride waste whilst the reaction mixture was still basic meant that we were able to avoid the generation of HF in the workup, and no etching of glassware was observed in onward processing. Upon treatment of the organic solution of the sodium carboxylate product with fresh water, the salt preferentially partitioned into the aqueous phase. The choice of TBME as solvent for the initial extraction was important, since very little (<1%) of the product was lost to the organic phase on extraction into water. Organic impurities, including the HMDS and 1-octanol, were removed to the organic waste, and further TBME washes were performed to provide a clean, aqueous solution of the sodium carboxylate. Upon acidification with aqueous HCl, the carboxylic acid **5** could be extracted into an organic solvent. For our first lab-scale batches we extracted into TBME and isolated the product as a waxy solid by removal of the solvent under vacuum. However, we wished to avoid processes involving strips to dryness for transfer to our pilot plant, and thus switched to extracting **5** into 2-MeTHF, since this should be compatible with the downstream processing. The 2-MeTHF solution was washed with water to remove any residual inorganics prior to

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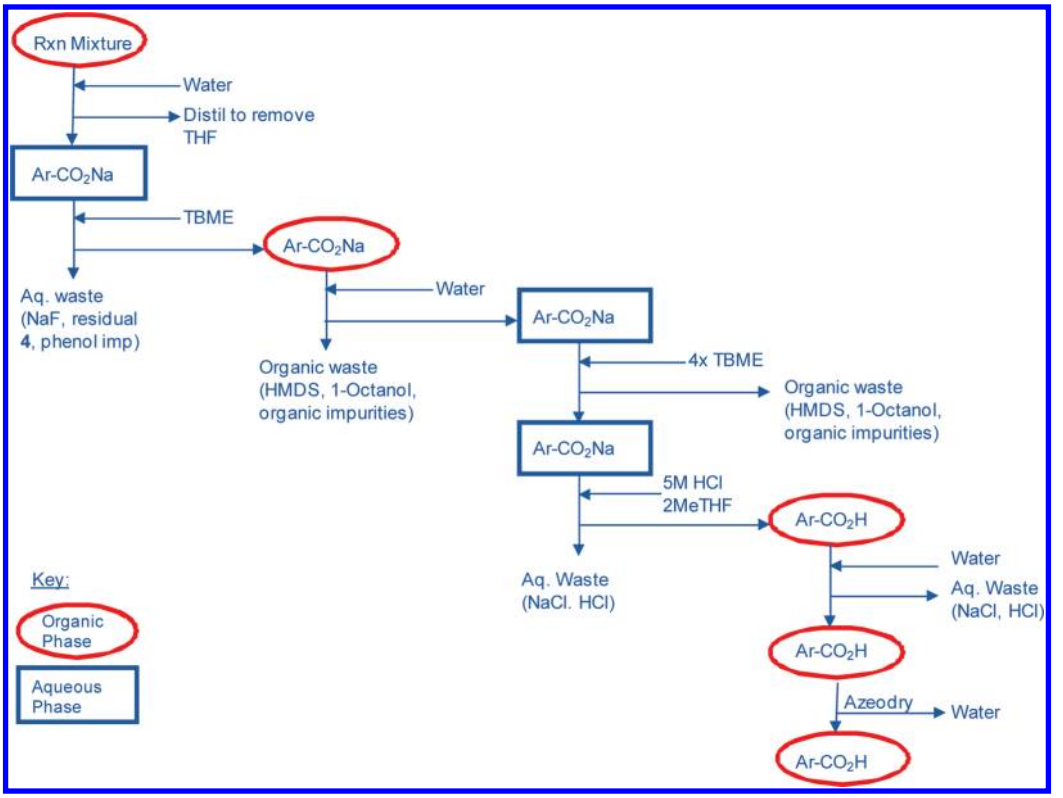

Figure 1. Workup protocol for the isolation of **5** from the S_NAr reaction.

azeotropic distillation to provide a dry solution of **5** in 2-MeTHF with typically ~95% solution yield and >95% area HPLC purity.

In our pilot-plant campaign, using a 7.2 kg input **4** batch size, we achieved a lower than expected yield, with an average of 80% across two batches. The drop in yield was attributed to physical losses during the phase separations, with several litres of the organic phase lost to waste in each phase split. We performed both batches of the nucleophilic aromatic substitution chemistry prior to commencing the next step, and the 2-MeTHF solution of **5** proved chemically and physically stable for more than one week at ambient temperature (no change in HPLC profile and no material out of solution). The ability to split the telescoped process by isolating the intermediate as a solution greatly increased the processing flexibility during the plant campaign.

Preparation of Hydrazide 6. Given the toxicity and safety concerns with the use and handling of hydrazine, a modified procedure was required for the formation of hydrazide **6**. The original process used six equivalents of hydrazine hydrate, and the reaction was concentrated to low volumes upon reaction completion, which gives a safety risk due to the potential to concentrate dry hydrazine. Following dilution with dichloromethane and subsequent aqueous washes, the product **6** was isolated by removal of the solvent under vacuum. Ideally, we wished to isolate **6** without using a strip to dryness procedure and we were also concerned about the compatibility of the hydrazide with dichloromethane. The original process used *N*,*N*′-carbonyldiimidazole (CDI) in THF for the activation of acid **5**, and we found that the activation also proceeded smoothly in 2-MeTHF at ambient temperature. We retained a slight excess (1.3 equiv) of CDI to ensure that the reaction would proceed to completion in the presence of adventitious water. By performing a reverse addition of the activated acid into a solution of hydrazine hydrate in 2-MeTHF we were able to reduce the excess of hydrazine hydrate required to two equivalents. Reducing the equivalents of hydrazine hydrate further led to generation of two impurities, which we assigned as the hydroxyoxadiazole **10** and the *N*,*N*′-carbonyldihydrazide **11** (Figure 2). Both of these impurities would form by reaction of the product hydrazide **6** with CDI, followed by either an intramolecular cyclisation to form **10** or reaction with a further equivalent of **6** to form **11**. With sufficient hydrazine hydrate, the excess CDI remaining after the acid activation step will react to give predominately the acylimidazole hydrazine **12**, and thus, impurities **10** and **11** are not observed. Effective mixing of the reaction and a controlled addition of the activated acid into the hydrazine hydrate solution are also vital in controlling these impurities. Using 2-MeTHF as the reaction solvent, the hydrazine hydrate solution is initially biphasic. If the activated acid is charged too quickly or without effective stirring, then a local excess of hydrazine at the point of addition is not achieved. We set an addition time of at least 20 min which, coupled with modest agitation, allowed full conversion to **6** without formation of impurities **10** and **11**.

Isolation of **6** required the separation of the product from the excess hydrazine, imidazole byproduct, and the acylimidazole hydrazine **12**. We were again able to utilise the lipophilicity of our product to gain the required level of purity control in the workup. Washing the 2-MeTHF solution twice with 5 volumes of 1 M HCl ensured the removal of hydrazine, imidazole, and acylimidazole hydrazine **12** without loss of any hydrazide **6** as the HCl salt. A subsequent wash with aqueous potassium carbonate free-bases the product and removes any residual benzoic acid **5**. A dry solution of **6** in 2-MeTHF was obtained by azeotropic distillation, with typically >95% solution yield and >95% area HPLC purity. The 2-MeTHF solution of **6** is chemically and physically

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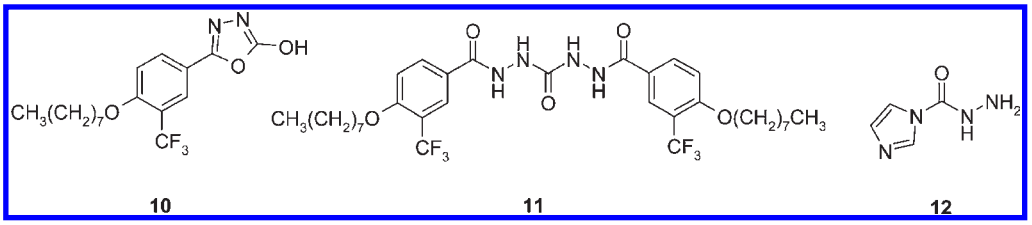
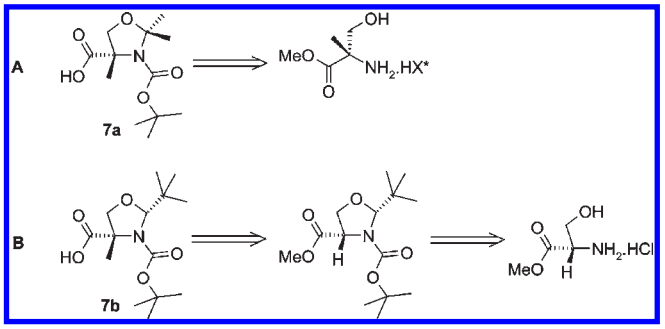


Figure 2. Impurities in the preparation of hydrazide **6**.

Scheme 3. Approaches to (*S*)-(2)-methylserine derivatives 7a and 7b: (A) via diastereoselective salt resolution of racemic 2-methylserine; (B) from L-serine methyl ester via a diastereoselective alkylation



stable, and so we were able to run the hydrazide formation chemistry in plant and hold the output solution at ambient temperature for a month before coupling with the (*S*)-2-methylserine derivative.

Coupling of Hydrazide 6 with a (*S*)-2-Methylserine Derivative. There are many methods available for accessing quaternary α-amino acids,[10] including specific methods for 2-methylserine,[11] but their preparation on a multikilogram scale can remain a challenge. Indeed, we initially contracted a CRO partner to synthesise 4 kg of the dimethyl oxazolidine **7a**, but they were unable to develop a suitable process that could deliver beyond a gram scale. Given the difficulties our initial CRO partner had in identifying a suitable process and in order to reduce supply risk, we chose to explore two complementary methodologies (Scheme 3).[12] These approaches were chosen for investigation on the basis of potential for rapid scale-up and probability of delivering sufficient material of appropriate quality.

The first approach, which involved the diastereomeric salt resolution of racemic 2-methylserine methyl ester,[13] was developed by Chirotech.[14] The six-step synthesis provided over 15 kg of **7a** in >99% ee and about 9% overall yield from hydroxyacetone.[12] The chemistry was simple, robust, and inexpensive and hence suitable for rapid scale-up for large-scale production. The second approach, developed in-house at GSK, involved the diastereoselective alkylation of an L-serine derivative using self-regeneration of stereocentres (SRS) methodology[7,8,15] to access the *tert*-butyl oxazolidine **7b**. The four-step telescoped synthesis was used to prepare over 20 kg of **7b** in 98% ee and about 50% overall yield from L-serine methyl ester hydrochloride.[12] The chemistry required cryogenic conditions for the alkylation, but the route was shorter and higher yielding than the resolution route. Both routes demonstrate a scalable approach to *N*,*O*-protected (*S*)-2-methylserine and allowed us to continue with the manufacture of **1**. The remaining discussion will focus on the use of the dimethyl oxazolidine **7a**, but the *tert*-butyl oxazolidine **7b** can be used analogously.

The original conditions for the coupling of hydrazide **6** with the dimethyl oxazolidine **7a** used the expensive and potentially hazardous coupling agent HATU in dichloromethane and DMF. Since we had isolated hydrazide **6** as a solution in 2-MeTHF, we ideally wished to remain in this solvent for the coupling, and we wanted to move to a safer and less expensive coupling agent. We reasoned that the use of CDI in 2-MeTHF would enable a facile workup to provide a clean solution of the dicarbonyl **8a**, since the imidazole byproduct should be easy to remove with an aqueous acidic wash, and if a small excess of the oxazolidine **7a** was used, then the excess could be removed with an aqueous basic wash. However, the use of CDI had been investigated for the coupling by the Discovery groups, but formation of the *N*,*N*′-carbonyldihydrazide impurity **11**, by reaction of hydrazide **6** with CDI, had proved an issue and would need to be addressed. The activation of acid **7a** with CDI in 2-MeTHF proceeded cleanly, but required gentle warming to 40 °C. Again, we chose to employ a slight excess of CDI to ensure full activation of **7a**. As expected, addition of hydrazide **6** into this reaction mixture produced impurities **10** and **11**, as had been seen in the hydrazide formation reaction. This could be avoided by using a deficit of CDI, but we wanted to avoid the sacrifice of the protected (*S*)-2-methylserine whilst ensuring all hydrazide **6** was consumed, since we considered that **6** would be more challenging to separate away from our desired product. Given the steric hindrance around the activated acid, we reasoned that it should be relatively stable and that it might be possible to destroy the excess CDI without reacting with the activated acid of **7a**. To achieve this, we added one molar equivalent of 2-propanol to the activated acid solution and heated it at 40 °C for 30 min prior to addition of the hydrazide **6**. This resulted in the conversion to dicarbonyl **8a** in 3−4 h at 40 °C, with none of the impurities **10** or **11** detected, indicating that the IPA quench had successfully destroyed the excess CDI. Sequential washes with 1 M HCl, 5% w/w aqueous $NaHCO_3$ solution, and water, followed by azeotropic distillation, resulted in a dry 2-MeTHF solution of **8a**. We assumed 100% yield for this step and used the 2-MeTHF solution directly in the next stage.

Thiadiazole 9 Formation Using Lawesson's Reagent. Despite the often clean conversion of carbonyl compounds to the analogous thiacarbonyl using Lawesson's reagent,[16] the technique often suffers difficulties in product isolation and purification due to the formation of many byproducts. The use of Lawesson's reagent, particularly on an industrial scale, also requires the control of stench, both during the reaction and in associated waste streams. Thermal decomposition of Lawesson's reagent (**13**) generates two equivalents of the dithiophosphine ylide **14**, and it is this that is believed to be the active species (Scheme 4). Carbonyl attack at the electrophilic phosphorous of the dithiophosphine ylide leads to the generation of a thiaoxaphosphetane, which can then collapse to form the thiocarbonyl and an equivalent of the metathiophosphonate byproduct **15**. It is assumed

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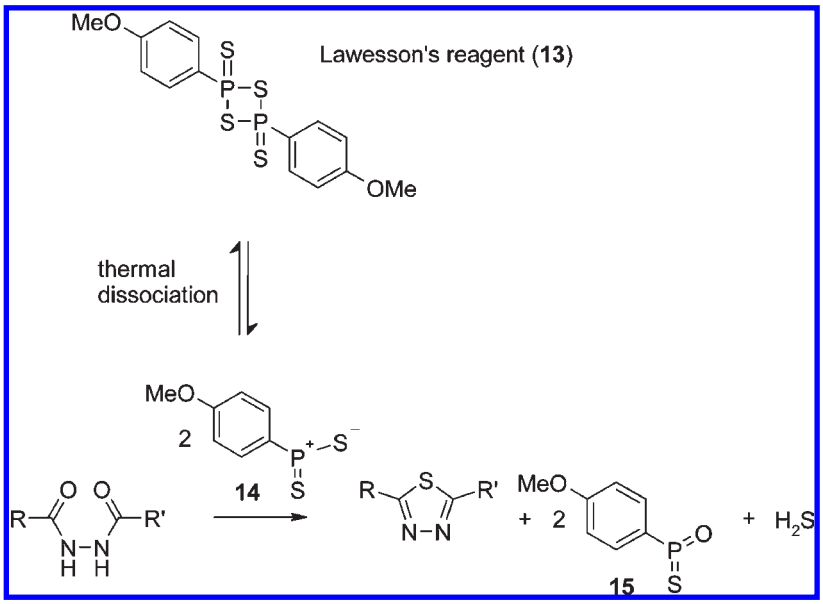
Scheme 4. Thiadiazole formation



that the formation of a thiadiazole ring proceeds via thiation of both carbonyls prior to cyclisation, since one equivalent of Lawesson's reagent (**13**) is required and hydrogen sulfide is generated (Scheme 4).[17]

However, it is not just the hydrogen sulfide and metathiophosphonate **15** that will need to be separated from the thiadiazole product **9**. Both the metathiophosphonate byproduct **15** and any excess dithiophosphine ylide **14** can form various oligomers, and they can also be hydrated, by adventitious water or during an aqueous quench, to give the corresponding thiophosphonic acid and dithiophosphonic acid, respectively. Indeed, when we ran the original conditions for the conversion of the dicarbonyl **8a** to the thiadiazole **9a** - 1.2 equivalents of Lawesson's reagent in toluene at 80 °C for 3−4 h - we saw complete conversion by HPLC to the desired product, but also over twenty other UV active components that we assigned as Lawesson's reagent byproducts. Some of these components were out of solution in toluene and could be removed by filtration, but their removal on scale would be problematic due to the high level of odour associated with the solids. Attempts to perform aqueous washes on the toluene solution led to the formation of emulsions, and whilst clean thiadiazole **9a** could be obtained by column chromatography, this was not a viable option to perform on a multikilogram scale due to the high quantities of odorous waste that would be generated. Gratifyingly, when we treated the input 2-MeTHF solution of **8a** direct from the coupling reaction with 1.1 equiv of Lawesson's reagent at reflux, complete conversion to **9a** was achieved within 3−4 h. A similar HPLC profile was obtained in 2-MeTHF as for the reaction in toluene, but the reaction in 2-MeTHF remained in solution even on cooling at the end of the reaction. We reasoned that treatment of this reaction mixture with aqueous sodium hydroxide would allow removal of some of the polar byproducts to the aqueous waste, such as the metathiophosphonate byproduct **15** by conversion to the corresponding sodium thiophosphonate. Generation of the sodium salts should also reduce the volatility of the compounds and so minimise the issue of stench. Treatment of the 2-MeTHF solution with 5 M NaOH gave clean phase separations and the polar reaction components, which eluted early on the reverse-phase HPLC system, were removed in the aqueous phase. Later running impurities, which might include various oligomeric species, remained in the organic phase. No efforts were made to identify the impurities in the 2-MeTHF solution of **9a**, but if they were oligomers of **14** and **15** then we considered that they might be hydrolysed under acidic conditions to the (di)thiophosphonate species and removed in subsequent basic washes. Given that our final chemistry step in the synthesis of **1** is an acidic deprotection, we chose to proceed with the crude thiadiazole **9a** solution and assumed a 100% yield.

Deprotection of 9 and Isolation of a Crystalline Salt of 1. Conversion of *N*-Boc oxazolidine **9a** to **1** proceeded smoothly upon heating the 2-MeTHF solution with aqueous HCl. We also observed that many of the Lawesson's reagent byproducts were converted to the same polar species that we had removed in the previous step, based on HPLC retention times. Washing the 2-MeTHF solution first with water then with aqueous sodium hydroxide removed these impurities and resulted in a solution of **1** with >90% area purity by HPLC. Using the *t*-butyl oxazolidine analogue **9b** it was required to perform a distillation step after the reaction to remove the pivalaldehyde byproduct, otherwise the oxazolidine ring reformed upon neutralisation. Although 2-MeTHF is more stable than THF to acid-catalysed ring-opening with HCl, we were still concerned about the possibility of forming potentially genotoxic alkyl chloride impurities upon prolonged reaction time at elevated temperature.[18] Use of dilute aqueous sulfuric acid could replace HCl in the deprotection step and so minimise the ring-opening of 2-MeTHF, and, by using aqueous conditions, hydrolysis of any resulting alkyl sulfonate would further minimise the level of any potential genotoxic impurity formed.[19] Alternative solvents, including isopropyl acetate, could also replace 2-MeTHF in the deprotection step.

Attempts to crystallise the free-base of **1** were all unsuccessful, so a salt screen using 16 diverse and pharmaceutically acceptable acids in six different solvent systems was performed. Crystalline solids were obtained with benzoic acid, 2,5-dihydroxybenzoic acid, 1,5-naphthalenedisulfonic acid, and fumaric acid, but only fumaric acid gave a high melting (>100 °C) solid with a single thermal event by DSC. Initially the salt was assigned with 1:1

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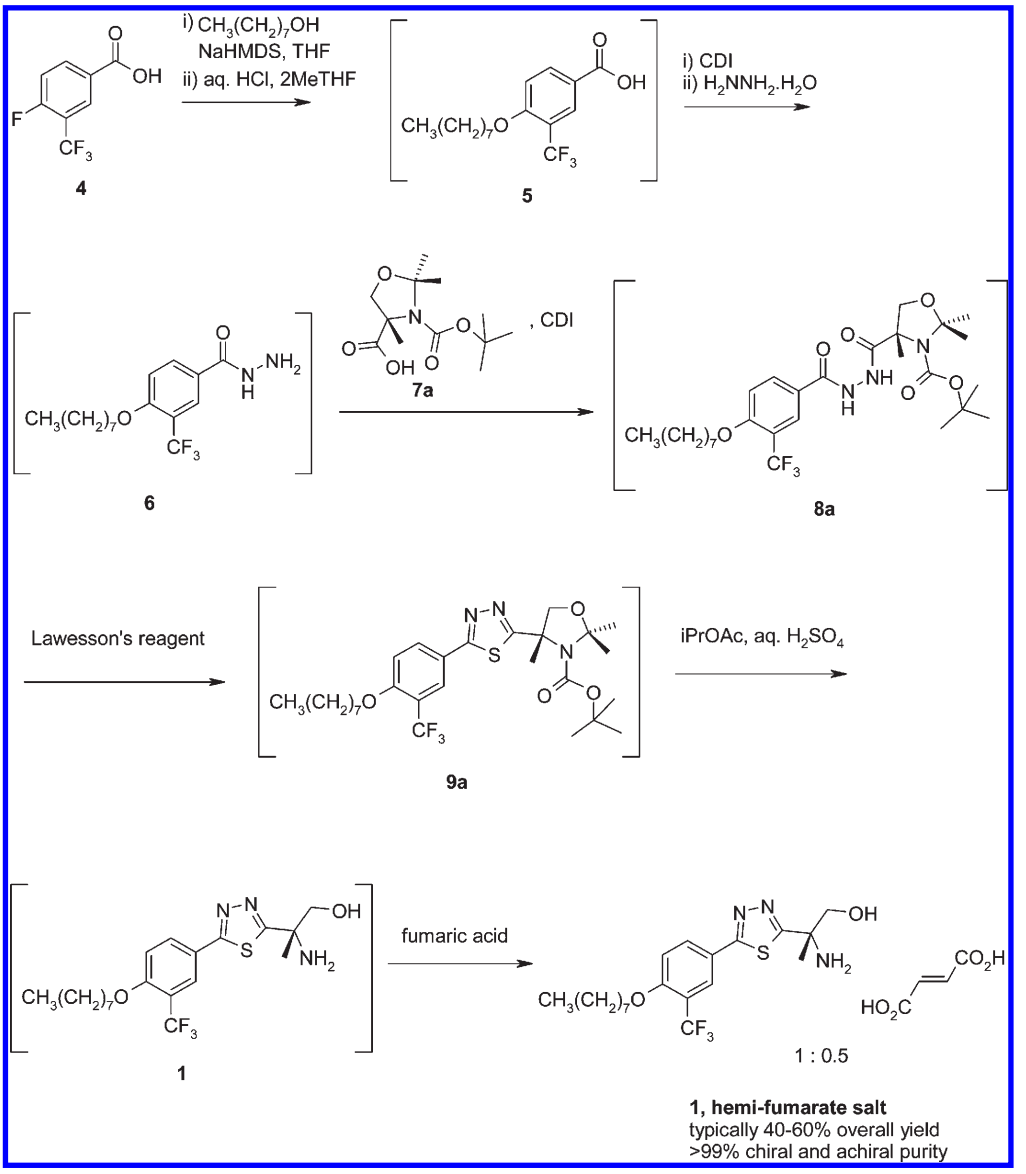
Scheme 5. New six-step telescoped synthesis of the hemifumarate salt of 1



stoichiometry, but later analysis showed it was the hemifumarate salt and initial samples were contaminated with free fumaric acid.

Efforts to crystallise the hemifumarate salt of **1** from a 2-MeTHF solution, with and without cosolvents, resulted in either low recovery or the formation of noncrystalline materials. However, with pure input free-base **1** and 0.5 equiv of fumaric acid a solution was obtained in isopropyl acetate at 70 °C, with the hemifumarate salt of **1** crystallising in good yield upon cooling. To this end, a distillative solvent swap from 2-MeTHF to isopropyl acetate was performed prior to the deprotection step. The deprotection did not occur with fumaric acid but was facile with aqueous sulfuric acid to yield, after aqueous sodium hydroxide washes, a solution of free-base **1** with >90% area purity by HPLC. However, heating this crude solution to 70 °C with fumaric acid gave a hazy, rather than clear, solution, and upon cooling the product **1** was isolated with variable salt stoichiometry (0.6−0.9 equiv of fumaric acid to **1**). We hypothesized that carry-over of base from the aqueous washes in the previous step led to the formation of sodium fumarate, which contaminates the output hemifumarate salt. Performing further water and brine washes prior to the salt formation led to an improved situation, but the stoichiometry of the salt remained >0.5 equiv. However, the hot, hazy solution of the hemifumarate salt of **1** can be washed with water, without loss of product, leading to a clear solution. This solution can be clarified for the preparation of clinical grade material by passing through a ≤5 μm filter, and the product crystallises on cooling to provide the hemifumarate salt of **1** with the correct stoichiometry. This process allowed the direct isolation of the hemifumarate salt of **1** with >99% area HPLC purity and >99.9% ee, in an overall yield of about 50% from 4-fluoro-3-(trifluoromethyl) benzoic acid (**4**) (Scheme 5). The six-step telescoped process was successfully run in the pilot plant to generate 10.4 kg of the hemifumarate salt of **1** across two batches.

Synthesis of Phosphate Metabolite 2. The preparation of 20 g of the phosphate metabolite **2** was required to support preclinical activities. Milligram quantities of **2** had previously been prepared in the Discovery groups, in a four-step process

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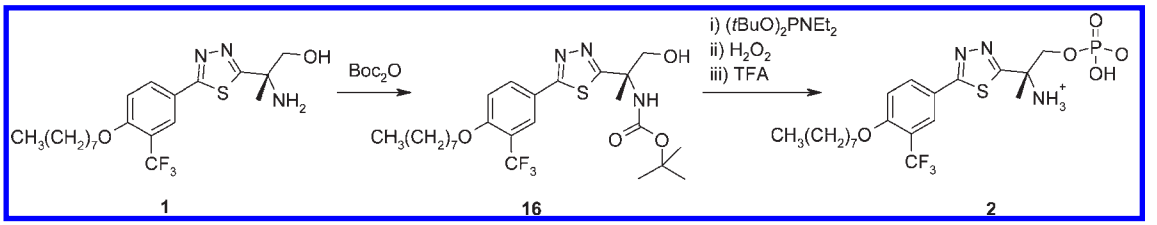
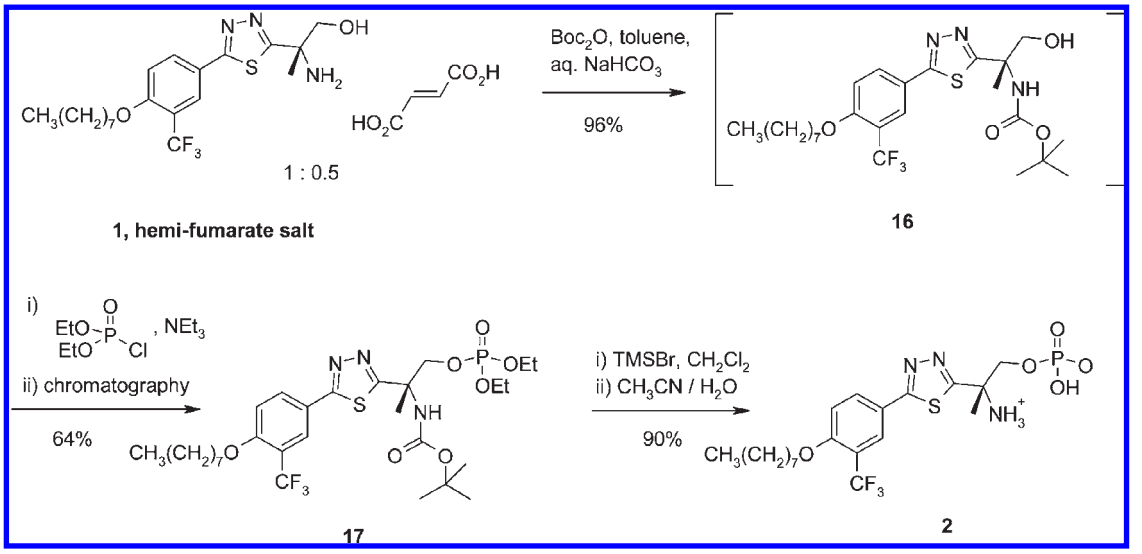
Scheme 6. Initial route to phosphate 2



Scheme 7. New route for the preparation of phosphate 2



from GSK1842799 **1** (Scheme 6).[1a] Protection of the amino group provided the *N*-Boc compound **16**, which was phosphorylated with bis-*tert*-butyldiethylphosphoramidite, oxidised with hydrogen peroxide, and subsequently deprotected with TFA to provide phosphate **2**. This method had been reported to be problematic, and in our hands we found that the oxidation and deprotection steps were low yielding and the product difficult to purify; as a result, we sought an alternative approach. Attempts to directly phosphorylate **1** with $POCl_3$ led to significant decomposition, whereas treatment of the *N*-Boc compound **16** with $POCl_3$ with subsequent hydrolysis by treatment with water did result in the preparation of **2**. However, on scaling this chemistry to the gram-scale the hydrolysis proved slow and generated **2** in low purity, and again purification proved difficult.

Due to the difficulties experienced in purifying **2**, we wished to prepare a stable intermediate that we could purify before performing a final deprotection step to yield **2** directly in high purity (Scheme 7). We found that we could use the hemifumarate salt of **1** directly in the *N*-Boc protection step, by treatment with three equivalents of Boc-anhydride in a biphasic mixture of toluene and aqueous sodium bicarbonate. After removal of the aqueous phase, excess Boc-anhydride was destroyed by the treatment with *N*-methylpiperazine. The resulting *N*-Boc-*N*′-methylpiperazine, together with unreacted *N*-methylpiperazine, was readily removed with a dilute HCl wash, providing a toluene solution of **16** with 96% solution yield and >99% area purity by HPLC on a 90-g scale. The toluene solution of **16** was treated with diethylchlorophosphate and triethylamine at 50 °C, to provide the diethylphosphate **17** with 96% area purity by HPLC. Since we wanted high-purity material to go into the final deprotection step, the crude **17** was purified by column chromatography, with the pure fractions pooled to provide a 64% yield of **17** with >99% area purity by HPLC. Global deprotection of **17** proved quicker and cleaner in dichloromethane rather than continuing in toluene, and the product was isolated by solvent swapping to acetonitrile and crystallising by addition of water to provide 51 g of **2** in 90% yield and 99% area purity by HPLC.

■ CONCLUSIONS

The development of a fully telescoped six-step synthesis allowed the rapid and efficient manufacture of over 10 kg of the hemifumarate salt of GSK1842799 (**1**). Gaining an understanding of the byproducts and impurities at each stage of the chemistry and utilising the lipophilic nature of the compounds allowed the design of efficient workup protocols that gave appropriate control of purity during the synthesis. As well as avoiding all chromatography and intermediate isolations, the new process controls the frothing in the nucleophilic aromatic substitution, demonstrates the safe use of hydrazine, avoids expensive coupling agents, and controls stench issues with the use of Lawesson's reagent. Furthermore, two scaleable approaches to (*S*)-2-methylserine derivatives have been developed,[12] and a multigram-scale preparation of the phosphate active metabolite **2** has been performed.

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EXPERIMENTAL SECTION

4-(Octyloxy)-3-(trifluoromethyl)benzoic Acid (5). A 40% solution of NaHMDS in THF (46 kg, 2.8 equiv) was diluted with THF (51 L), and 1-octanol (9.5 kg, 2.0 equiv) was charged and the reaction warmed to 55−60 °C. A solution of 4-fluoro-3-(trifluoromethyl)benzoic acid (**4**) (7.2 kg, 1 equiv) in THF (15 L) was charged, washing through with further THF (2 L). The reaction mixture was stirred at 55−60 °C until deemed complete by HPLC (~24 h, <4% area **4** remaining). The reaction was then solvent exchanged into water (75 L) by distillation to afford a tan slurry that was extracted into TBME (75 L). Water (75 L) was charged to the organic layer and the product extracted into the aqueous layer. The aqueous layer was washed with TBME (4 × 37 L), then acidified with 5 M HCl (22 L) and extracted into 2-MeTHF (37 L). The 2-MeTHF solution was washed with water (3 × 37 L) and dried azeotropically by put-and-take distillation with 2-MeTHF (3 × 37 L) to provide a dry 2-MeTHF solution of **5** (26.8% w/w; 34.4 kg, 84%) with 95% area purity by HPLC for use directly in the next stage. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 7.0 Hz), 1.18−1.36 (8H, m), 1.37−1.47 (2H, m), 1.69−1.78 (2H, m), 4.18 (2H, t, J = 6.3 Hz), 7.35 (1H, d, J = 8.8 Hz), 8.09 (1H, d, J = 2.0 Hz), 8.16 (1H, dd, J = 8.8, 2.0 Hz).

4-(Octyloxy)-3-(trifluoromethyl)benzohydrazide (6). CDI (5.86 kg, 1.3 equiv) was charged to the 2-MeTHF solution of **5** (26.8% w/w; 34.2 kg, 1 equiv), rinsing in with 2-MeTHF (8 L). The mixture was stirred at 25 ± 5 °C until activation was deemed complete by HPLC (~15 min, ≤2% a/a **5** remaining). The solution was then added over about 20 min to hydrazine hydrate (3.69 kg, 2 equiv) in 2-MeTHF (29 L), rinsing in with further 2-MeTHF (6 L). The resultant reaction mixture was stirred at 25 ± 5 °C until the reaction was deemed complete by HPLC (~30 min, ≤2% a/a activated intermediate remaining). The reaction was washed successively with 1 M HCl (2 × 58 L) and 13% w/w aqueous potassium carbonate solution (35 L), then dried azeotropically by put-and-take distillation with 2-MeTHF (3 × 29 L) to provide a dry 2-MeTHF solution of **6** (16.1% w/w; 55.9 kg, 93%) with 96% area purity by HPLC for use directly in the next stage. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (3H, t, J = 6.8 Hz), 1.18−1.35 (8H, m), 1.36−1.46 (2H, m), 1.66−1.76 (2H, m), 4.14 (2H, t, J = 6.3 Hz), 4.49 (2H, bs) 7.31 (1H, d, J = 9.5 Hz), 8.07−8.12 (2H, m), 9.86 (1H, bs).

1,1-Dimethylethyl-(4*S*)-2,2,4-trimethyl-4-[(2-{[4-(octyloxy)-3-(trifluoromethyl)phenyl]carbonyl}hydrazino)carbonyl]-1,3-oxazolidine-3-carboxylate (8a). Carboxylic acid **7a** (7.31 kg, 1.05 equiv) was dissolved in 2-MeTHF (45 L) and CDI (5.18 kg, 1.2 equiv) was charged, washing in with 2-MeTHF (2 L). The reaction was heated to 40 ± 5 °C and stirred at this temperature for 1 h, when HPLC analysis showed the reaction was complete. 2-Propanol (1.8 L) was charged and the reaction stirred at 40 ± 5 °C for 30 min. The 2-MeTHF solution of **6** (16.1% w/w; 55.4 kg, 1 equiv) was charged, washing in with 2-MeTHF (2 L), and the resulting solution was stirred for 3 h at 40 ± 5 °C, when HPLC analysis showed the reaction was complete. The mixture was cooled to 20 ± 5 °C, and washed successively with 1 M HCl (2 × 27 L), 5% w/w aqueous $NaHCO_3$ solution (36 L) and water (18 L). The organic layer was concentrated to 80 L by distillation and dried azeotropically by put-and-take distillation with 2-MeTHF (3 × 45 L) to provide a dry 2-MeTHF solution of **8a** (assume 100% yield; 92% area purity by HPLC) for use directly in the next stage. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 6.7 Hz), 1.20−1.46 (19H, m), 1.49 (3H, s), 1.54 (3H, s), 1.64 (3H, s), 1.69−1.78 (2H, m), 3.84 (1H, d, J = 8.8 Hz), 4.12 (1H, d, J = 8.8 Hz), 4.19 (2H, t, J = 6.2 Hz), 7.37 (1H, d, J = 9.3 Hz), 8.17 (2H, d, J = 7.6 Hz), 9.52 (1H, d, J = 26.8 Hz), 10.50 (1H, d, J = 58.2 Hz).

1,1-Dimethylethyl-(2*R*,4*S*)-2-(1,1-dimethylethyl)-4-methyl-4-[(2-{[4-(octyloxy)-3-(trifluoromethyl)phenyl]carbonyl}-hydrazino)carbonyl]-1,3-oxazolidine-3-carboxylate (8b). A 2-MeTHF solution of **8b** was prepared in an analogous fashion as above, using carboxylic acid **7b** input. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 6.7 Hz), 0.96 (9H, s), 1.22−1.37 (10H, m), 1.46 (9H, s), 1.63 (3H, s), 1.71−1.86 (2H, m), 3.86 (1H, d, J = 8.6 Hz), 4.18 (2H, t, J = 6.2 Hz), 4.35 (1H, d, J = 8.8 Hz), 5.09 (1H, s), 7.36 (1H, d, J = 8.6 Hz), 8.16−8.22 (2H, m), 9.63 (1H, s), 10.65 (1H, s).

1,1-Dimethylethyl-(4*S*)-2,2,4-trimethyl-4-{5-[4-(octyloxy)-3-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl}-1,3-oxazolidine-3-carboxylate (9a). Lawesson's reagent (11.9 kg, 1.1 equiv) was charged to the above solution of **8a** in 2-MeTHF, washing in with 2-MeTHF (2 L). The reaction was heated to 70 ± 5 °C for 4 h, when HPLC analysis showed the reaction was complete. The reaction was cooled to 20 ± 5 °C and washed with 5 M NaOH (2 × 30 L), and then with 13% w/w brine (20 L). The organic phase was solvent exchanged into isopropyl acetate by vacuum distillation and adjusted to 80 L to provide a solution of **9a** in isopropyl acetate (assume 100% yield; 80% area purity by HPLC) for use directly in the next stage. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 7.1 Hz), 1.15−1.45 (19H, m), 1.57 (3H, s), 1.67 (3H, s), 1.71−1.78 (2H, m), 1.88 (3H, s), 4.08−4.24 (4H, m), 7.41 (1H, d, J = 8.9 Hz), 8.10−8.24 (2H, m).

1,1-Dimethylethyl-(2*R*,4*S*)-2-(1,1-dimethylethyl)-4-methyl-4-{5-[4-(octyloxy)-3-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl}-1,3-oxazolidine-3-carboxylate (9b). An isopropyl acetate solution of **9b** was prepared in a fashion analogous to that above, using **8b** input. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 7.0 Hz), 0.93(9H, s), 1.22−1.37 (17H, m), 1.39−1.48 (2H, m), 1.71−1.78 (2H, m), 1.87 (3H, s), 4.15 (1H, d, J = 8.7 Hz), 4.20 (2H, t, J = 6.2 Hz), 4.37 (1H, bd, J = 8.5 Hz), 5.14 (1H, s), 7.41 (1H, d, J = 8.9 Hz), 8.16 (1H, d, J = 2.1 Hz), 8.23 (1H, dd, J = 8.9, 2.1 Hz).

(2*S*)-2-Amino-2-{5-[4-(octyloxy)-3-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl}-1-propanol Hemifumarate (Hemifumarate Salt of 1). Water (9 L) and conc. sulfuric acid (3.3 kg, 1.2 equiv) were added to the above solution of **9a** in isopropyl acetate and the reaction was warmed to 70 ± 5 °C, until deemed compete by HPLC (~13 h). Water (45 L) was added and the reaction cooled to 20 ± 5 °C. The reaction was washed three times with 2 M NaOH (27 L then 2 × 45 L), then 13% w/w brine (20 L). The solution was adjusted to 80 L by addition of isopropyl acetate (35 L), and fumaric acid (1.51 kg) was charged. The mixture was heated to 70 °C to provide a hazy solution, then cooled to 65 ± 3 °C and washed with water (2 × 18 L). The solution was dried azeotropically by put-take distillation with further isopropyl acetate (45 L), clarified through a 5 μm filter, and the lines were washed through with further isopropyl acetate (45 L). The resulting solution was concentrated to 89 L then cooled to 60 ± 3 °C and seeded with crystals of the hemifumarate salt of **1** (9 g). The resulting slurry was aged at 60 ± 3 °C for 1 h and then allowed to cool to 20 ± 5 °C. The solids were isolated by filtration, washed with isopropyl acetate (3 × 21 L), and dried under vacuum at 50 ± 5 °C to provide a white solid of the hemifumarate salt of **1** (5.3 kg, 41%), with >99.9% ee and >99% area purity by HPLC. Typical differential scanning

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calorimetry (DSC)/thermalgravimetric analysis (TGA) shows melt at ~111−114 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 6.9 Hz), 1.20−1.37 (8H, m), 1.37−1.49 (2H, m), 1.47 (3H, s), 1.70−1.79 (2H, m), 3.52 (1H, d, J = 10.5 Hz), 3.69 (1H, d, J = 10.5 Hz), 4.19 (2H, t, J = 6.2 Hz), 4.90−6.35 (3H, bs), 6.58 (1H, s), 7.41 (1H, d, J = 8.8 Hz), 8.11 (1H, d, J = 2.0 Hz), 8.15 (1H, dd, J = 8.7, 2.1 Hz). HRMS (ES +ve; MH^+) calcd for $C_{20}H_{29}F_3N_3O_2S$ 432.1933, found 432.1935.

The reaction was performed in an analogous fashion using **9b** input, but following addition of water post reaction completion, the trimethyl acetaldehyde byproduct was removed by distillation with further isopropyl acetate (5 vol).

1,1-Dimethylethyl-((1*S*)-2-hydroxy-1-methyl-1-{5-[4-(octyloxy)-3-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl}ethyl) carbamate (16). The hemifumarate salt of **1** (90 g, 1 equiv) was slurried in toluene (1.5 L) and Boc-anhydride (121 g, 3 equiv) was charged, rinsing in with further toluene (0.3 L). A solution of $NaHCO_3$ (77 g, 5 equiv) in water (1 L) was charged and the reaction warmed to ~40 °C for 17 h then at 50 °C for a further 4 h, when the reaction was shown to be complete by HPLC. The reaction was cooled to 20 °C and the lower aqueous phase removed. The aqueous phase was back-extracted with toluene (0.2 L), and the organic phases were combined. 1-Methylpiperazine (61 mL, 3 equiv) was charged and the reaction stirred for 30 min (gas evolution observed for the first 10 min after 1-methylpiperazine addition). The reaction was washed with 1 M HCl (2 × 900 mL) then 6.5% w/w aqueous $NaHCO_3$ solution (0.5 L), and the toluene solution was dried over $MgSO_4$ and concentrated to 0.54 L by distillation to provide a solution of **16** in toluene (19.4% w/w; 484 g; 96%) with >99% area purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3 H, t, J = 7.0 Hz), 1.22−1.39 (8H, m), 1.42 (9H, s), 1.45−1.55 (2H, m), 1.79 (3H, s), 1.79−1.86 (2H, m), 3.82 (1H, bs), 3.92 (1H, t, J = 9.3 Hz), 4.07 (2H, t, J = 6.5 Hz), 4.10 (1H, bs), 5.75 (1H, s), 7.01 (1H, d, J = 8.7 Hz), 8.03 (1H, dd, J = 8.7, 2.1 Hz), 8.09 (1 H, d, J = 2.1 Hz).

1,1-Dimethylethyl ((1*S*)-2-{[bis(ethyloxy)phosphoryl]oxy}-1-methyl-1-{5-[4-(octyloxy)-3-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl}ethyl)carbamate (17). The solution of **16** in toluene (19.4% w/w; 484 g) was treated with triethylamine (123 mL, 5 equiv) and diethylchlorophosphate (64 mL, 2.5 equiv) and warmed to 50 °C for 6 h, when the reaction was shown to be complete by HPLC. The reaction was cooled to 20 °C, and a solution of $NaHCO_3$ (37 g, 2.5 equiv) in water (560 mL) and EtOAc (560 mL) was charged. The lower aqueous phase was removed, and the organics were dried over $MgSO_4$ and concentrated under vacuum to provide crude **17** (147 g) with 96% area purity by HPLC. The crude product was purified in four runs by column chromatography on SiO_2, eluting with EtOAc/heptanes, and the pure fractions were combined and concentrated under vacuum to provide **17** (74.8 g, 64%) as an oil with >99% area purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.0 Hz), 1.22−1.39 (8H, m), 1.34 (6H, t, J = 6.9 Hz), 1.43 (9H, s), 1.43−1.54 (2H, m), 1.80−1.88 (2H, m), 1.89 (3H, s), 4.08 - 4.19 (6H, m), 4.40 (1H, dd, J = 10.3, 6.2 Hz), 4.53 (1H, dd, J = 10.3, 6.2 Hz), 5.90 (1H, s), 7.07 (1H, d, J = 8.9 Hz), 8.05−8.12 (2H, m).

(2*S*)-2-Amino-2-{5-[4-(octyloxy)-3-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl}propyl Dihydrogen Phosphate (2). Bromotrimethylsilane (91.6 g, 5.3 equiv) was charged to a solution of **17** (74.7 g) in dichloromethane (750 mL) and the reaction stirred at 20 °C for 20 h. Further bromotrimethylsilane (8.1 g, 0.5 equiv) was charged and the reaction stirred for a further 3 h. The reaction was solvent exchanged from dichloromethane to acetonitrile by distillation under vacuum at 20 °C, to provide 400 mL of an acetonitrile solution of **2**. A 5% aqueous acetonitrile solution (160 mL) was charged over 1 h and the solids were collected by filtration, washed with acetonitrile (4 × 150 mL) and dried under vacuum at 40 °C to provide **2** (51.4 g, 90%) as a white solid with 99% area purity by HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 0.91 (3H, t, J = 6.8 Hz), 1.25−1.44 (8H, m), 1.48−1.58 (2H, m), 1.80−1.89 (2H, m), 1.90 (3H, s), 4.20 (2H, t, J = 6.2 Hz), 4.32 (1H, dd, J = 11.2, 4.8 Hz), 4.39 (1H, dd, J = 11.2, 5.2 Hz), 7.35 (1H, d, J = 8.7 Hz), 8.18 (1H, dd, J = 8.7, 2.1 Hz), 8.22 (1H, d, J = 2.1 Hz). HRMS (ES +ve; MH^+) calcd for $C_{20}H_{30}F_3N_3O_5PS$ 512.1596, found 512.1593.

■ ASSOCIATED CONTENT

Supporting Information. Methods for in-process monitoring and purity analysis for each reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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