Organic Process Research & Development

ARTICLE

pubs.acs.org/OPRD

Complementary Syntheses of *N*,*O*-Protected-(*S*)-2-methylserine on a Multikilogram Scale

Michael S. Anson,[†] Hugh F. Clark,[†] Paul Evans,[†] Martin E. Fox,[‡] Jonathan P. Graham,*[,†] Natalie N. Griffiths,[†] Graham Meek,[‡] James A. Ramsden,[‡] Alastair J. Roberts,[†] Shaun Simmonds,[‡] Matthew D. Walker,[†] and Matthew Willets[§]

[†]Chemical Development Division, GlaxoSmithKline Research and Development Ltd., Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.

[‡]Chirotech Technology Ltd., A subsidiary of Dr. Reddy's Laboratories (EU) Ltd., Unit 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GH, U.K.

[§]Chirotech Technology Ltd., A subsidiary of Dr. Reddy's Laboratories (EU) Ltd., PO Box 6 Steanard Lane, Mirfield, West Yorkshire WF14 8QB, U.K.

Supporting Information

ABSTRACT: Two complementary and scalable approaches have been used to manufacture multikilogram quantities of *N*,*O*-protected-(*S*)-2-methylserine. The first approach uses a diastereomeric salt resolution of 2-methylserine methyl ester as the (1*S*)-(+)-camphorsulfonate salt, and was used to rapidly access 15 kg of (*S*)-3-*tert*-butoxycarbonyl-2,2,4-trimethyl-1,3-oxazolidine-4-carboxylic acid with >99% ee. The second approach involves a stereoselective enolate methylation of a chiral cyclic L-serine derivative under cryogenic conditions. The four-step telescoped process, starting from L-serine methyl ester, was used to manufacture 20 kg of (2*R*,4*S*)-2-*tert*-butyl-3-*tert*-butoxycarbonyl-4-methyl-1,3-oxazolidine-4-carboxylic acid in 52% overall yield and 98% ee. The advantages and disadvantages for scale-up of both approaches are discussed.

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] A key structural feature of **1** is the chiral quaternary centre. This centre can be derived from (*S*)-2-methylserine, with the dimethyl oxazolidine **2** and the *tert*-butyl oxazolidine **3** both having been used for this purpose in gram-scale preparations of **1** (Scheme 1).[2]

To support the development activities for **1**, we required rapid access to a suitable (*S*)-2-methylserine derivative. There are many methods available for accessing quaternary α-amino acids,[3] including specific methods for 2-methylserine,[4] but their preparation on a multikilogram scale can remain a challenge. Indeed, we initially contracted a CRO partner to synthesise 4 kg of **2**, 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. These approaches were chosen for investigation on the basis of the potential for rapid scale-up and probability of delivering sufficient material of appropriate quality.

The first approach, targeting the manufacture of 15 kg of dimethyl oxazolidine **2**, was conducted by Chirotech.[5] This approach involved the diastereomeric salt resolution of racemic 2-methyl serine methyl ester, with subsequent conversion to the dimethyl oxazolidine **2** (Scheme 2, Route A). Despite the inherent inefficiency of a resolution step, this approach was attractive since a literature method to resolve racemic 2-methylserine methyl ester using an inexpensive resolving agent was available,[6] and the chemistry would be amenable to processing in standard plant equipment.

The second approach, undertaken at GSK, involved the diastereoselective alkylation of an L-serine derivative using self-regeneration of stereocentres (SRS) methodology[7] to access *tert*-butyl oxazolidine **3** (Scheme 2, Route B). This approach would allow rapid access to **3**, and the desired α-methylation of L-serine using SRS chemistry is known.[8] However, we were concerned about the suitability of this chemistry to scale-up due to the propensity of the oxazolidine enolates to undergo β-elimination, even at low temperature.[9] Furthermore, to allow rapid manufacture on a multikilogram scale we wished to avoid purification by chromatography; therefore, the only opportunity to provide an upgrade to the chemical and enantiomeric purity would be by crystallisation of the acid **3**.[10]

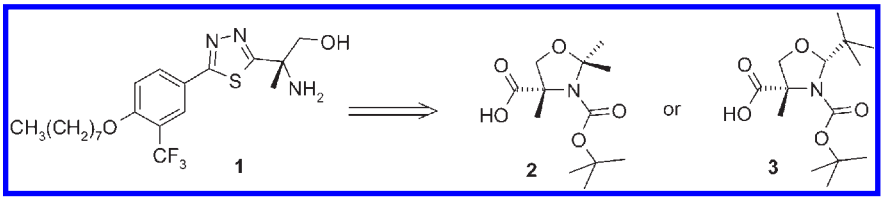
The development of both approaches to enable the multikilogram-scale manufacture of **2** and **3** is discussed below.

RESOLUTION-BASED ROUTE

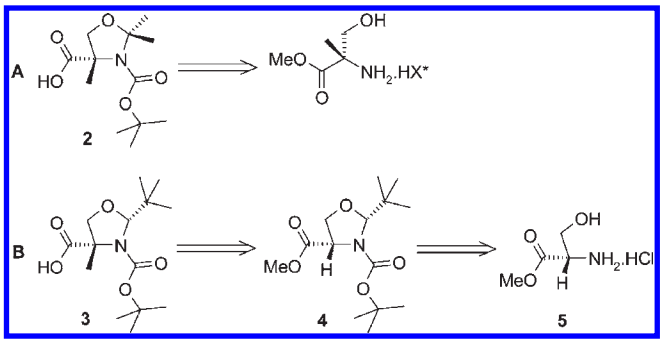
We were attracted to the preparation of oxazolidine **2** via the resolution of 2-methylserine, since the chemistry would all be amenable to processing in standard plant equipment and requires inexpensive and readily available starting materials, including the resolving agent (1*S*)-(+)-camphorsulfonic acid (Scheme 3).[6]

Received: November 9, 2010
Published: January 18, 2011

Scheme 1. Use of dimethyl oxazolidine 2 or *tert*-butyl oxazolidine 3 for the preparation of GSK1842799 (1)



Scheme 2. Approaches to (*S*)-(2)-methylserine derivatives 2 and 3: (A) via diastereoselective salt resolution of racemic 2-methylserine; (B) from L-serine methyl ester via diastereoselective alkylation of 4

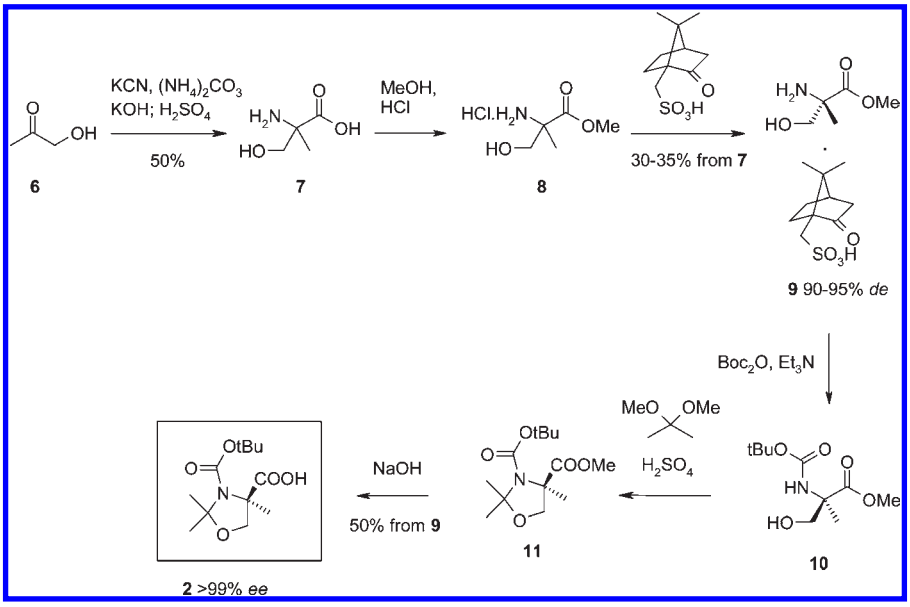


The initial objective was for a 1 kg laboratory-scale make followed by a 15 kg pilot-scale campaign.

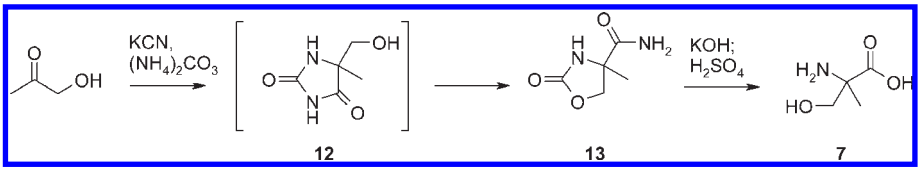
Racemic 2-methylserine **7** was not commercially available on sufficient scale, so an inexpensive synthesis readily scaled to multikg quantities was required. An approach via a Bucherer−Bergs reaction of hydroxyacetone with subsequent hydrolysis was attractive from the points of view of inexpensive raw materials, brevity, and simplicity.[11,12] The amino acid synthesis comprises two steps (Scheme 4), the first being the reaction of hydroxyacetone with ammonium carbonate and cyanide in an aqueous medium to give a hydantoin **12**, and the second, basic hydrolysis to the amino acid **7**. This approach presents the issue of isolation of the highly polar, water-soluble amino acid **7** from an aqueous reaction medium containing inorganic salts. In the literature procedure, this issue was addressed first by isolation of the intermediate hydantoin **12** and second by the use of barium hydroxide for the basic hydrolysis. Neutralisation with sulfuric acid gave insoluble barium sulfate and an aqueous solution of the amino acid **7** free of inorganic salts from which the compound could be isolated. We found that the literature conditions gave the rearranged oxazolidinone **13** rather than the expected hydantoin **12**. Like the amino acid **7**, the intermediate **13** is also highly polar and water soluble, hence, difficult to isolate, and therefore was formed in aqueous solution and hydrolysed in situ without isolation. On the basis of previous experience on another project, we expected the literature barium sulfate procedure to give rise to a finely divided precipitate that is very slow to remove by filtration on large scale. Therefore, this was replaced with a potassium sulfate precipitation, expected to give rise to a more granular solid that is easier to remove by filtration. Thus, potassium cyanide was used as the cyanide source, potassium hydroxide for the hydantoin hydrolysis, and sulfuric acid for the neutralisation. A slight excess of hydroxyacetone was used in the reaction to avoid the presence of cyanide during the neutralisation. Difficulties identified during scale-up of this reaction to a 1-kg scale were sublimation of ammonium carbonate during the initial hydantoin formation, causing blockages in the headspace above the reaction, and outgassing of ammonia during addition of potassium hydroxide. Additional carryover of ammonium carbonate occurred during this outgassing. However, the problems presented by these issues were relatively minor on a 1-kg scale and did not prevent the further scale-up of this chemistry. Potassium sulfate is insoluble in water−alcohol mixtures, and 2-methylserine is soluble in water−methanol, so after the potassium hydroxide hydrolysis and sulfuric acid neutralisation, methanol was added to the aqueous reaction solution to precipitate this salt. After removal of the solid potassium sulfate by filtration, addition of acetone as an antisolvent to the solution of 2-methylserine **7** in water−methanol was used to achieve crystallisation. The amino acid was isolated as the hemihydrate in around 50% yield from hydroxyacetone. The ash content of 1.3−4%, resulting from incomplete removal of inorganics, and water content of 7%, arising from the compound being a hemihydrate, were acceptable for use in the remaining synthetic steps. After transfer of the process to an external contractor, it was found that the anhydrous compound could be prepared from the hemihydrate by heating to 65 °C under vacuum.

The literature method for the esterification employed methanolic hydrochloric acid, generated in situ using thionyl chloride, to give the methyl ester hydrochloride **8**.[13] This was followed by acid exchange with (1*S*)-(+)-camphor-10-sulfonic acid to give the camphorsulfonate salt **9**, where the desired (*S*)-enantiomer of the product crystallised as the less-soluble salt.[6] For the 1-kg campaign, the esterification reaction was run at a higher concentration than the literature procedure, but otherwise with little modification. As with the literature procedure, thionyl chloride was used for in situ generation of a solution of hydrogen chloride in methanol for convenience. The esterification reaction required heating to reflux for 16−24 h to reach a high level of conversion. Acid exchange was achieved by addition of camphorsulfonic acid to the solution of ester hydrochloride **8**, after which the majority of the methanol and hydrogen chloride were removed by distillation. In addition to acid exchange, solvent exchange from methanol to a less polar solvent was required to crystallise the camphorsulfonate salt **9**. Dichloromethane, used in the literature procedure, was too low boiling for adequate removal of methanol, and its use presented difficulties on the pilot plant. However, a facile solvent-swap from methanol into DME was achieved, which allowed the crystallisation of the salt **9** in high yield and in 75−80% diastereomeric excess. This was upgraded to 90−95% diastereomeric excess by heating with acetone to give the salt **9** in 35−40% overall yield from 2-methylserine hydrate. Further upgrade to higher enantiomeric excess was achieved at a later stage in the synthesis. The use of camphorsulfonic acid in the esterification, which would remove the need for acid exchange, was tried, but the reaction was found to be too sluggish in refluxing methanol.

Scheme 3. Resolution-based route



Scheme 4. Bucherer−Bergs reaction of hydroxyacetone



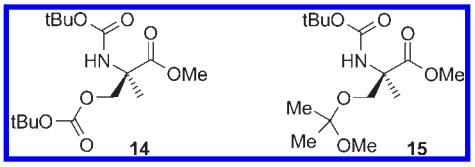


Figure 1. Side product **14** and intermediate **15**.

Boc protection of the salt **9**[6] was readily carried out using Boc-anhydride (1.2 equiv) and triethylamine. THF was used as the reaction solvent instead of the literature chloroform. A side reaction, formation of the *O*-Boc ester **14** (Figure 1), was detected in this reaction, requiring only a modest excess of Boc-anhydride to be used. Aqueous workup with sodium carbonate was used to remove camphorsulfonate salts. Toluene was used as an extraction solvent so that the product **10** could be dried azeotropically before the next stage of chemistry, acetonide formation, which requires anhydrous conditions. We were unable to crystallise the single enantiomer Boc-carbamate **10**, which we were only able to obtain as a liquid. However, the racemate is a crystalline solid, mp 77 °C. These properties allowed an upgrade of the enantiomeric excess by crystallisation of racemic **10**, leaving liquors of high enantiomeric excess, with up to 98% being achieved. However, an efficient, combined upgrade and chemical purification was possible later in the synthesis, and the Boc carbamate **10** was carried through crude to the acetonide formation.

The literature method[14,15] for the formation of acetonide **11** from the *N*-Boc methyl ester **10** used 2,2-dimethoxypropane as a reagent and boron trifluoride etherate as a catalyst. Sulfuric acid was found to be equally effective as a catalyst, while being cheaper and more easily handled on scale. With orthophosphoric acid as the catalyst, the reaction stopped at the 2-methoxypropyl ether intermediate **15** (Figure 1), showing the C−O bond-forming step to occur first, the slower C−N bond-forming step not occurring with the weaker acid catalyst. The reaction required substoichiometric rather than truly catalytic quantities of sulfuric acid. Conditions used for scale-up were slow addition of 0.25 equivalents of sulfuric acid to a solution of the *N*-Boc methyl ester **10** in 5 equivalents of 2, 2-dimethoxypropane, which gave a 95% conversion to the acetonide **11** with the remaining 5% being *N*-Boc methyl ester **10** and intermediate **15**. The reaction was quenched under anhydrous conditions by addition of triethylamine, after which the excess reagent was distilled away from the acetonide **11**, a mobile oil, which was not purified prior to the final deprotection. Cleavage of the methyl ester with sodium hydroxide in methanol was relatively slow but clean, with complete conversion being achieved at 20 °C for 64 h or 2−3 h at reflux. The product was partitioned into water as the sodium salt and base-insoluble material was extracted into toluene. After acidification with orthophosphoric acid, the acid **2** was extracted into toluene. The product was crystallised by addition of heptane anti-solvent to a solution in hot toluene followed by cooling. In this crystallisation, an efficient upgrade to >99.9% ee was achieved, with product in the liquors of around 50% ee being obtained. The chemical

dx.doi.org/10.1021/op100299d |*Org. Process Res. Dev.* 2011, 15, 389–397

purity of the product was also well within the specification of 98%, no single impurity >0.2% by HPLC. On a 500 g to 1 kg scale, the acid **2** was obtained in about 18% overall yield from the racemic 2-methylserine hemihydrate **7**. The only purification steps required were crystallisation of 2-methylserine hemihydrate **7**, the camphorsulfonate salt **9** in the resolution and final product **2**.

For the 15-kg pilot campaign using the resolution process, the racemic 2-methylserine **7** process was transferred to an external contractor, where 80 kg were manufactured. In the esterification step, gaseous hydrogen chloride was used instead of thionyl chloride,[16] but otherwise, the process was run with no significant modification compared to the 1-kg scale. Starting with a 45.4-kg batch of 2-methylserine hemihydrate, a 16.7-kg batch of acid **2** with >99.9% ee was obtained, in an overall yield of 18.2%.

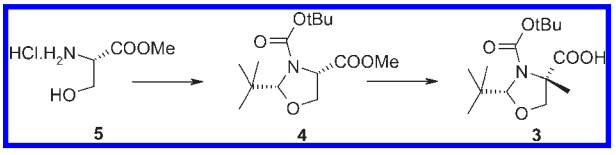
L-SERINE ALKYLATION ROUTE

The route to oxazolidine **3** via the stereoselective alkylation of the L-serine derivative **4** was very attractive, due to the short synthetic sequence and inexpensive and readily available starting materials (Scheme 5). Our main concern prior to commencing work was around the stability of the oxazolidine enolate during the alkylation step,[9] given the inevitable longer processing times at larger scale. We also required the identification of a suitable isolation of **3** that would enable us to control the output purity. We targeted the production of 15 kg of **3** with an ee of >97%.

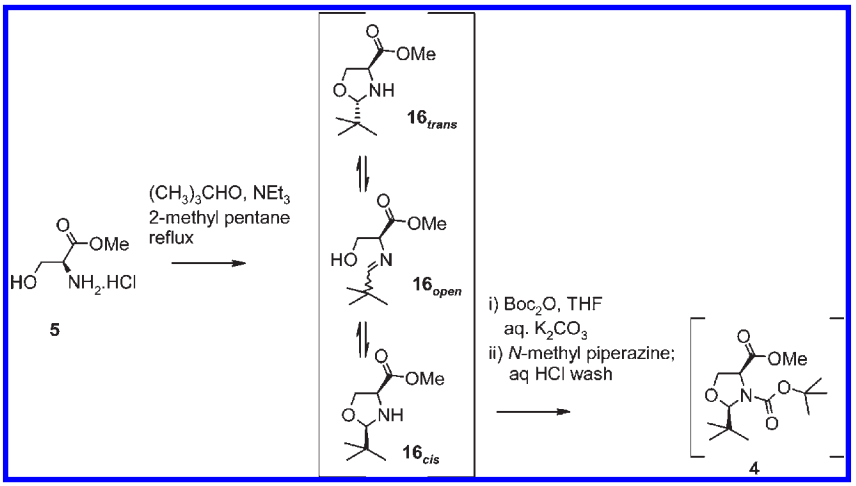
We adapted Seebach's conditions for the condensation of L-serine methyl ester hydrochloride with pivalaldehyde to provide a mixture of the *cis*-, *trans*-, and open-chain oxazolidine diastereomers **16** (Scheme 6).[8b] Analysis of the mixture by ^{1}H NMR in d_4-methanol showed a 47:39:14 mixture of the *cis*-, *trans*-, and open-chain oxazolidine diastereomers **16**. Due to safety concerns and to reduce the risk of emissions of volatile hydrocarbons, we changed solvent from pentane to 2-methylpentane, and we were also able to reduce the excess of pivalaldehyde used from 2 to 1.2 equiv. The reaction was heated under Dean−Stark conditions until no further water was collected (~4 h), with reaction completion confirmed by ^{1}H NMR analysis in d_4-methanol. Upon cooling, the triethylamine hydrochloride was removed by filtration and the filtrate concentrated by distillation. Due to the inefficiency of removing all of the volatiles when at low volume in the reaction vessel, we distilled to a level of ~3 volumes to provide a concentrated solution of **16** for direct use in the next step. This approach saved significant processing time, compared to transferring the reaction mixture to alternative equipment for stripping to dryness, but meant that there was carryover of about two volumes of 2-methyl pentane, as well as the excess pivalaldehyde and triethylamine from the reaction.

Following the literature conditions for the Boc-protection, which involve the reaction of the oxazolidine mixture with 2 equiv of Boc-anhydride in THF,[8c] exclusive formation of the single diastereomer **4** was achieved, since only in the *cis*-oxazolidine is the nitrogen sterically available to react. Using material from the condensation step that had been stripped to dryness under high vacuum, the reaction proceeded smoothly to completion. However, using the concentrated solution following partial distillation, our reaction consistently appeared to stall at about 60% conversion, and would not proceed further even with an additional charge of Boc-anhydride, or by addition of DMAP or triethylamine. ^{1}H NMR analysis of reaction samples in d_4-methanol showed the same ratio of open-chain and oxazolidine ring diastereomers was present when the reaction had stalled as in the initial mixture. To gain insight into why the reaction was not reaching completion, the reaction was investigated in d_8-THF, to allow direct analysis of the reaction mixture by NMR. The equilibrium ratio for the oxazolidine diastereomers is known to be solvent dependent,[17] and in d_8-THF the initial mixture shows a similar ratio of the *cis*- and *trans*-diastereomers, but with considerably less of the open-chain imine (53:44:3 ratio of *cis*-, *trans*-, and open chain). However, at the point when the reaction stalls, only a single component in addition to the desired product **4** is observed by ^{1}H NMR, which was identified as the *trans*-oxazolidine $\mathbf{16}_{trans}$. On adding a drop of D_2O to the NMR sample, the reaction again started to proceed to give the desired Boc-protected *cis*-oxazolidine **4**. It appears that a component in the reaction that is not removed during the partial distillation of **16** inhibits the equilibrium between the oxazolidine diastereomers but addition of a protic source to the reaction reinstates the equilibrium (hence, why the equilibrium mixture was seen when sampling the reaction into d_4-methanol). On spiking individually 2-methyl pentane, pivalaldehyde, and triethylamine into the reaction with a sample of **16** that had been stripped to dryness, only the reaction with added triethylamine stalled, indicating that it is carryover of triethylamine that is preventing the oxazolidine equilibrium. To avoid having to ensure that all triethylamine is removed from the reaction, we investigated the possibility of adding a protic source to allow the equilibration to continue. Since the literature workup involves partitioning of the completed reaction between aqueous sodium bicarbonate and diethyl ether, we charged the aqueous base to a stalled reaction, which then proceeded cleanly to completion on stirring at ambient temperature overnight. Boc-protected oxazolidine **4** could then be directly extracted into a suitable solvent, and we chose to use 2-methylpentane, since it is safer to use on scale than diethyl ether and also minimizes the total number of solvents used in the process. We found that replacing the sodium bicarbonate solution with 1 M potassium carbonate gave a more rapid conversion to **4**, presumably due to the more homogeneous reaction mixture achieved with the lower ionic strength aqueous system. Using this process, we were able to reduce the excess of Boc-anhydride required to 1.1 equiv. Even so, we did not want to carryover any Boc-anhydride into the critical stereoselective alkylation and so sought a method to remove the excess. The literature method removed the excess Boc-anhydride by distillation,[8c] but this was not considered a feasible option on scale. Instead, we treated the 2-methylpentane solution with *N*-methylpiperazine, which rapidly reacted with the remaining Boc-anhydride. The resulting *N*-Boc-*N*′-methylpiperazine, together with unreacted *N*-methylpiperazine, was readily removed with a dilute HCl wash. After further washes with aqueous potassium carbonate and then water, the organic solution was concentrated by distillation to provide **4** as an oil. Due to the thermal properties of **4**, we were restricted in plant to a maximum safe operating temperature of 50 °C, and we ran the distillation at a reduced pressure of ~50 mbar. The concentrate, which contained some residual THF (typically ~20% w/w) and *tert*-butanol (typically ~3% w/w; 15 mol %), a byproduct from the Boc-anhydride, was diluted further with THF for direct use in the next step. An estimation of the yield from the first

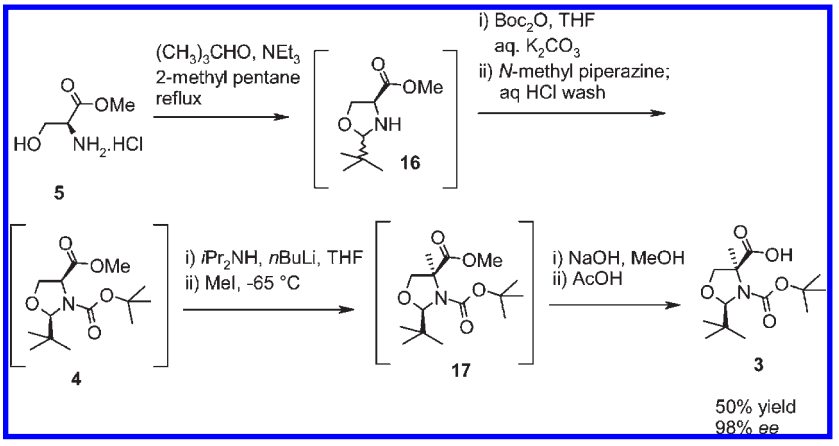
Scheme 5. Diasteoselective alkylation route to 3



Scheme 6. Formation of *N*-Boc *cis*-oxazolidine 4



Scheme 7. Diastereoselective alkylation route to 3



two steps was achieved either by an NMR assay or by loss on drying, with the yield typically in the range 65−75%. Given the timelines we were working to, efforts were not made to improve upon this moderate yield, but it appeared that the majority of the mass balance loss occurred during the filtration of solids in the first step, with unreacted L-serine methyl ester trapped with the triethylamine hydrochloride.

Our main concern with the diastereoselective alkylation was the sensitivity of the chemistry to temperature; thus, a series of experiments were performed using the literature conditions at different temperatures.[8c] When the reaction was run above −50 °C, very little desired product was observed, presumably due to decomposition via a β-elimination pathway. In contrast, our results indicated that the reaction could be performed at up to −50 °C, which we had confidence would be achieved in our cryogenic pilot-plant equipment. Indeed, we rapidly scaled the chemistry into a 10-L jacketed vessel, which performed in a fashion analogous to that of the small-scale reactions. With increased confidence that we would be able to run the chemistry on a pilot-plant scale, we sought to optimise the process for transfer to the pilot-plant and identify conditions to telescope with the hydrolysis step.

To avoid unnecessary cooling, the LDA solution was prepared at 0 ± 5 °C, with reduced quantities of diisopropyl amine (1.5 equiv), *n*BuLi (1.6 M in hexanes, 1.3 equiv), and THF (9 vol) (Scheme 7). The amount of base employed could be further reduced but was maintained at 1.3 equiv of *n*BuLi to ensure that complete conversion to the enolate would still occur in the presence of adventitious water or with higher levels of *tert*-butanol from the Boc-protection step contaminating the input **4**. Robustness studies indicated that the enolate formation could be performed in the temperature range −65 ± 10 °C, which could be maintained by controlled addition of the concentrated THF solution of **4**. Attempts were made to follow the reaction by in situ ReactIR analysis, but the absorbance at cold temperature was too large to decipher any trends. Instead, process monitoring was performed by ^{1}H NMR, with reaction samples immediately quenched into cold d_4-methanol prior to analysis. Complete enolate formation, demonstrated by full deuterium incorporation at the 2-position, was routinely achieved within 30 min of addition of the substrate. Efforts to substitute the volatile methyl iodide for dimethyl sulfate were unsuccessful, but the excess of methyl iodide required could be reduced from 2.7 to 1.7 equiv. Again, a slow addition rate was utilized to maintain the temperature range of −65 ± 10 °C, with ^{1}H NMR

dx.doi.org/10.1021/op100299d |*Org. Process Res. Dev.* 2011, 15, 389–397

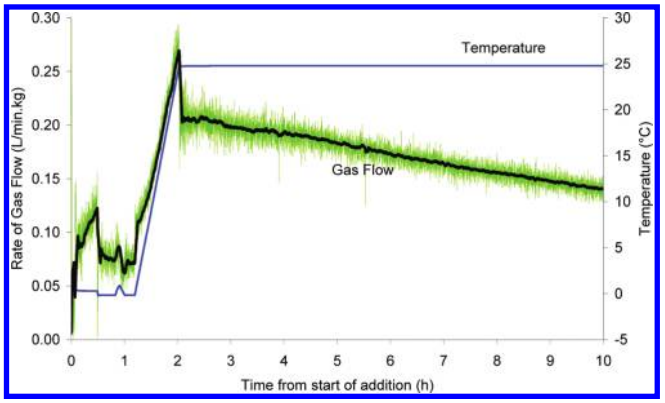


Figure 2. Rate of gas flow during LDA preparation and subsequent warming.

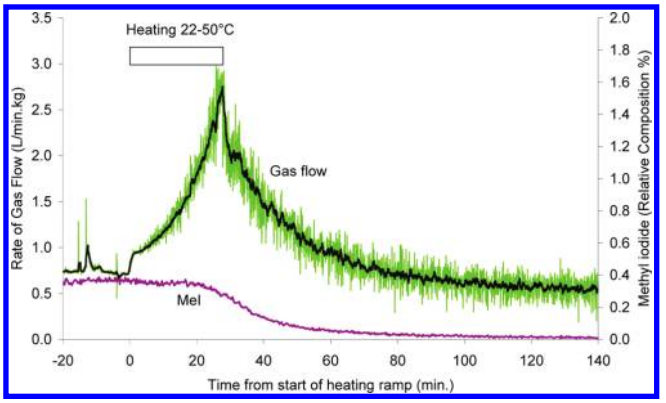


Figure 3. Rate of gas flow and MeI content upon heating reaction after NaOH addition.

analysis showing complete conversion to **17** after ~3 h, with only the single diastereomer observed. We found that a simplified workup was adequate to provide a solution of **17** suitable for direct use in the hydrolysis step. Upon reaction completion, a methanol quench (0.2 vol) was performed at −65 ± 10 °C prior to warming the reaction mixture to 20 °C. A single wash with 22% w/w aqueous ammonium chloride solution removed the inorganics and diisopropylamine, to provide a clear solution of **17** in THF and hexanes.

Hydrolysis of the methyl ester proceeded smoothly upon addition of aqueous sodium hydroxide and methanol, with the reaction typically complete within 90 min at 50 ± 5 °C. Removal of the volatiles (THF, hexanes, and methanol) by distillation and dilution with water provided an aqueous solution of the sodium carboxylate salt, with the acid **3** then crystallised by slow addition of acetic acid. Upon cooling to 0 ± 5 °C, the solids were collected by filtration, washed with water, and dried under vacuum to provide a white solid of **3**, in typically 70−80% yield from **4**, giving an overall yield of ~50% from L-serine methyl ester hydrochloride **5**. The chiral purity of **3** was initially demonstrated to be acceptable by processing a lab-scale sample of **3** through to drug substance **1**, which had an enantiomeric excess of >99%. A chiral GC method was then developed, to allow direct analysis of **3**.

Prior to commencing the pilot-plant campaign, we needed to demonstrate that the maximum rate of emission of the volatile organic compounds was within consented limits. Our main concern was the rate of evolution of butane, and we also needed to demonstrate the fate of excess methyl iodide. Whilst we showed that we could exchange *n*BuLi with *n*HexLi for the enolate formation, thereby replacing the butane byproduct with the less volatile hexane, this change would have led to a delay in commencing the pilot-plant campaign. Investigations using an RC1 and Hiden Gas analyser were performed to understand the rate of butane evolution and to identify a suitable control strategy. Although butane has a boiling point of −1 °C, it has a high solubility in organic solvents and so can be considered under our reaction conditions more like a highly volatile organic solvent than a gas. During the addition of *n*BuLi to diisopropylamine and subsequent stir period at 0 °C very little butane was evolved (see Figure 2). The rate of evolution of butane increased but remained low on warming to 25 °C, meaning that even if the cooling system failed there would not be a sudden increase in the rate of butane emissions.

No gas evolution was detected during the low-temperature chemistry, with low levels of butane and trace levels of methyl iodide detected on warming to 20 °C. ^{1}H NMR analysis showed that the methyl iodide was consumed over a period of about one hour after addition of the sodium hydroxide, and the rate of evolution of methyl iodide fell during the heating period to 50 °C. However, the rate of evolution of butane increased during the reaction heat-up (Figure 3). To minimize the flow of butane, a stepwise temperature ramp was incorporated into the process. Although the rate of evolution of butane still increased during the heat-up, the maximum rate of gas evolution was reduced and meant that we could stay within our consented limits for emission of butane.

In the pilot plant, with 22.5 kg input of L-serine methyl ester hydrochloride, the condensation and Boc-protection chemistry worked as planned, although the calculated solution yield of **4** was at the lower end of what we expected, at 64%. This solution was taken directly into the alkylation and hydrolysis steps, which again performed without issue in 81% yield. A total of 21.5 kg of oxazolidine **3** with 98% ee and >99% chemical purity by HPLC was obtained, with an overall yield of 52% from L-serine methyl ester hydrochloride.

CONCLUSIONS

Two routes to *N*,*O*-protected-(*S*)-2-methylserine have been developed, with the manufacture of >15 kg each of (*S*)-3-*tert*-butoxycarbonyl-2,2,4-trimethyl-1,3-oxazolidine-4-carboxylic acid **2** and (2*R*,4*S*)-2-*tert*-butyl-3-*tert*-butoxycarbonyl-4-methyl-1,3-oxazolidine-4-carboxylic acid **3** achieved. A six-step, resolution-based synthesis was used to prepare **2**, in about 9% overall yield from hydroxyacetone. The chemistry was simple, robust, and inexpensive and hence suitable for rapid scale-up. A four-step telescoped synthesis, involving a diastereoselective alkylation, was used to prepare **3** in about 50% overall yield from L-serine methyl ester. The chemistry required cryogenic conditions for the alkylation, but the route was shorter and higher-yielding than the resolution route. The use of **2** and **3** in the preparation of the S1P1 agonist **1** will be the subject of a future communication.

EXPERIMENTAL SECTION

4-Methyloxazolidine-2-one-4-carboxamide 13.[11,12]. Potassium cyanide (17.6 g, 135 mmol), and ammonium chloride (14.4 g, 270 mmol) were placed in a flask. A solution of hydroxyacetone (10.0 g, 135 mmol) in ethanol (100 mL) and water (100 mL) was added. The suspension was stirred at room temperature for 3 h, then ammonium carbonate (65 g, 675 mmol) was added. The reaction was heated to 60 °C for 7 h, then allowed to cool to room temperature. The solvent was evaporated, ethanol (100 mL) was added, the

dx.doi.org/10.1021/op100299d |*Org. Process Res. Dev.* 2011, 15, 389–397

suspension was filtered, and the solvent was evaporated. The residue was evaporated with methanol (3 × 100 mL) to give the oxazolidinone **13** as a brown foam which solidified slowly on standing (18.8 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 7.48 (br s, 1H), 7.37 (br s, 1H), 4.37 (d, J = 8.8 Hz, 1H), 4.03 (d, J = 8.4 Hz, 1H), 1.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1 (s), 157.9 (s), 73.4 (t), 60.9 (s), and 24.2 (q).

2-Methylserine 7.[11,12]. A 20-L jacketed vessel was charged with ammonium carbonate (2279 g, 23.7 mol) and water (3.0 L). Ammonia solution (S.G. 0.88, 1180 mL, ~17 mol) and potassium cyanide (1000 g, 15.4 mol) were added. The solids were rinsed into the reactor with water (400 mL). Hydroxyacetone (1173 g, 15.8 mol) was added via dropping funnel over 3 h. The temperature of the reaction mixture was kept at 22−24 °C during the addition and then stirred at 20 °C for 30 min. The mixture was heated to 65 °C over 2 h. Above ~60 °C gas evolution (ammonia) became apparent. The mixture was slowly heated to 85 °C over 4 h. The cyanide concentration of the mixture at this point was measured at ~0.25 g/L using a cyanide ion-selective electrode; this represented >99.5% of the cyanide consumed. The reaction mixture was cooled, and potassium hydroxide (4177 g, 85%, 63.3 mol) was added in 100−140 g portions over 90 min. Ammonia was discharged from the reaction during the addition. The mixture was heated to 92 °C overnight. The mixture was cooled to 20 °C and was again checked for free cyanide and contained trace amounts. Methanol (6 L) was added, leading to the crystallization of potassium carbonate. Sulfuric acid was added (50%, 700 mL to pH 13; then 98% 2000 mL to pH 5.8). The head space was monitored for HCN at pH 10.7 (no HCN) and pH 9.3 (3 ppm); below pH 8 carbon dioxide effervescence was significant. The potassium sulfate was removed by filtration (can be very slow), and the cake was washed with aqueous methanol (1:1, 2 × 1 L). The supernatant (10 L) was returned to the 20-L vessel, acetone (5 L) was added, the mixture was seeded and stirred for 1 h, and then acetone (5 L) was added slowly. The product was collected and washed with acetone/water/methanol (2:1:1, 1 L) and acetone (1 L), and was dried in the vacuum oven at 30 °C overnight to give 2-methylserine **7** as the hemihydrate, a slightly off-white solid (1019 g, 52% yield). Karl Fisher Analysis 7.0% water. ^{1}H NMR (400 MHz, DMSO): δ 7 (br s, 4H), 3.43 (d, J = 11.0 Hz), 3.30 (d, J = 11.0 Hz, 1H), and 1.09 (s, 3H). ^{1}H NMR (400 MHz, D_2O): δ 3.91 (d, J = 12.2 Hz, 1H), 3.65 (d, J = 12.2 Hz), and 1.41 (s, 3H). ^{13}C NMR (100 MHz, D_2O): δ 7 175.4 (s), 64.8 (t), 62.6 (s), and 18.5 (q).

2-Methylserine Methyl Ester Hydrochloride 8.[13]. A nitrogen-purged 20-L jacketed vessel with the jacket held at 20 °C was charged with methanol (10 L) and 2-methylserine hemihydrate **7** (1.00 kg, 8.40 mol). Thionyl chloride (1210 mL, 16.8 mol) was added over 3 h and 20 min, during which the maximum temperature reached was 32 °C. The solution was heated to reflux (55−58 °C) for 16 h, then allowed to cool to room temperature to give a solution of 2-methylserine hydrochloride **8** in methanol/HCl. A small aliquot was removed and concentrated to give 2-methylserine methyl ester hydrochloride **8** as a viscous, pale-yellow oil. ^{1}H NMR analysis showed this to be a roughly 20:1 mixture of ester and amino acid hydrochlorides. ^{1}H NMR (400 MHz, DMSO) δ 8.6 (br s, 3H), 3.74 (s, 3H), 3.73 (d, J = 10.8 Hz, 1H), 3.63 (d, J = 10.8 Hz, 1H), and 1.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO): δ 171.0 (s), 64.9 (t), 61.4 (s), 53.3 (q), 18.4 (q). 2-Methylserine hydrochloride: ^{1}H NMR (400 MHz, DMSO) δ 8.4 (br s, 3H), 3.72 (d, J = 11.2 Hz, 1H), 3.59 (d, J = 11.2 Hz, 1H), and 1.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO): δ 172.2 (s), 64.8 (t), 61.0 (s), 18.6 (q).

(*S*)-2-Methylserine Methyl Ester (1*S*)-(+)-Camphor-10-sulfonate 9.[6]. (1*S*)-(+)-Camphor-10-sulfonic acid (1.95 kg, 8.40 mol) was charged to the solution of 2-methylserine methyl ester hydrochloride **8**. An endotherm of 2 °C occurred. The solvent was removed using a rotary evaporator (water bath at 50 °C) to a mass of 4.01 kg. Methanol (5 L) was added, and then the solvent was removed using a rotary evaporator to a mass of 3.49 kg. DME (2.5 L) was added. The solvent was evaporated using a rotary evaporator such that 2 L of distillate was collected. DME (2.5 L) was added to obtain a mobile slurry, then this was transferred to the 20-L vessel, using further DME (2.5 L). The white suspension was stirred at ambient temperature for 65 h, after which the temperature was measured at 10 °C. The suspension was filtered, and the solid was washed with fresh DME (3 × 500 mL) and then dried to give the crude salt **9** as a white, granular solid (1.28 kg). The diastereomeric excess was 78% (*S*), liquors 73% (*R*). The salt, acetone (3.03 L), and methanol (0.54 L) were charged to a 20-L jacketed vessel. The suspension was heated to reflux (55−58 °C) for 2 h, cooled to room temperature over 18 h, and then filtered. The solid was washed with acetone (2 × 500 mL) and dried to give the salt **9** as a white, granular solid (1.12 kg, 36.5%). The diastereomeric excess was 89% (*S*), liquors 23% (*R*). ^{1}H NMR (400 MHz, DMSO): δ 8.4 (br s, 3 H), 5.81 (t, J = 4.8 Hz, 1 H), 3.77 (dd, J = 10.8, 4.8 Hz, 1H), 3.77 (s, 3H), 3.77 (s, 3 H), 3.53 (dd, J = 11.0, 2.6 Hz, 1H), 2.87 (d, J = 14.4 Hz, 1H), 2.70 (quintet, J = 10.2, 1H), 2.37 (d, J = 14.8 Hz, 1H), 2.24 (d, J = 18.3, 3.6 Hz, 1H), 1.94 (t, J = 4.4 Hz, 1H), 1.88−1.82 (m, 1H), 1.80 (d, J = 18.4 Hz, 1H), 1.36 (s, 3 H), 1.27 (q, J = 10.0 Hz, 2H), 1.05 (s, 3 H), and 0.74 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ 216.6 (s), 171.0 (s), 65.0 (t), 61.2 (s), 58.6 (s), 53.5 (q), 47.4 (s), 47.0 (t), 42.6 (t), 42.5 (d), 26.8 (t), 24.5 (t), 20.5 q), 19.9 (q), and 18.6 (t).

(*S*)-*N*-*tert*-Butoxycarbonyl-2-methylserine Methyl Ester 10.[6]. THF (2.0 L) and the camphorsulfonate salt **9** (~90% de, 1.93 kg, 5.29 mol) were charged to a nitrogen-purged 10-L vessel at 20 °C. Triethylamine (884 mL, 6.34 mol) was added. An endotherm of 4 °C occurred. A solution of Boc-anhydride (1384 g, 6.34 mol) and THF (940 mL) was added over 2.5 h. An exotherm to 24 °C and gas evolution were observed. The suspension was stirred at 20 °C for 18 h. A solution of sodium carbonate (585 g, 5.52 mol) in water (6.60 L) was prepared in a 20-L jacketed vessel. The reaction mixture was added into the solution with stirring. Toluene (3.50 L) was added. The mixture was stirred at 17 °C at 160 rpm for 30 min. The phases were separated, and the aqueous phase was extracted with toluene (2 × 2.00 L). The combined organic phases were dried with sodium sulfate (220 g) and filtered. The filtrate was dried in two batches (rotary evaporator, 30 mbar 50 °C bath temp) to give crude (*S*)-*N*-*tert*-butoxycarbonyl-2-methylserine methyl ester **10** (~90% ee) as a viscous, pale-yellow liquid (1.41 kg). The aqueous phase was extracted with toluene and concentrated separately to give ~8 g of product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.29 (br s, 1 H), 3.98 (dd, J = 11.2, 5.6 Hz, 1H), 3.80−3.75 (m, 1H), 3.78 (s, 3H), 3.3 (br s, 1H) 1.47 (s, 3H), and 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3 (s), 155.8 (s), 80.7 (s), 67.3 (t), 61.4 (s), 53.1 (q), 28.6 (q), and 21.2 (q).

(*S*)-Methyl *3*-*tert*-Butoxycarbonyl-2,2,4-trimethyloxazolidine-4-carboxylate 11[13]. (*S*)-Boc-2-methylserine methyl ester **10** (1.41 kg, ~5.2 mmol) and 2,2-dimethoxypropane (3.24 L, 26.4 mol) were charged to a nitrogen-purged 10 L vessel at 20 °C. Concentrated sulfuric acid (70 mL, 1.3 mol) was added over 3 h, then the dark brown solution was stirred at 20 °C for 30 min. GC analysis showed a 96.5:2.5 ratio of starting material and product. The reaction was quenched with triethylamine (368 mL, 2.64 mmol).

An exotherm of 2 °C occurred. The solvent was evaporated using a rotary evaporator to give crude (*S*)-methyl 3-*tert*-butoxycarbonyl-2,2,4-trimethyloxazolidine-4-carboxylate **11** as a biphasic liquid (1649 g). Spectroscopic data for this compound were obtained using a sample purified by flash chromatography on silica eluting with heptane/ethyl acetate (9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10 and 4.08 (d, J = 8.4 Hz and d, J = 8.4 Hz, 1H), 3.81 and 3.79 (d, J = 8.4 Hz and d, J = 8.4 Hz, 1H), 1.62, 1.60, 1.58, and 1.55 (4 s, 12H), and 1.48 and 1.41 (2 s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3 (s), 173.1 (s), 151.8 (s), 151.2 (s), 96.6 (s), 95.7 (s), 80.9 (s), 80.7 (s), 74.1 (t), 73.7 (t), 66.2 (s), 65.7 (s), 52.9 (q), 52.8 (q), 28.7 (q), 28.6 (q), 27.4 (q), 26.7 (q), 25.0 (q), 23.7 (q), 22.3 (q), and 21.2 (q).

(*S*)-3-*tert*-Butoxycarbonyl-2,2,4-trimethyl-1,3-oxazolidine-4-carboxylic Acid 2. Crude (*S*)-methyl 3-*tert*-butoxycarbonyl-2,2,4-trimethyloxazolidine-4-carboxylate **11** (1649 g) and methanol (2.5 L) were placed in a nitrogen-purged 10-L vessel at 20 °C. Sodium hydroxide (423 g, 10.6 mol) was added. An exotherm to 60 °C occurred. The solution was allowed to cool to 20 °C and was stirred at 20 °C for 6 h, then stirred at 30 °C for 16 h. A 20-L jacketed vessel was charged with water (5.8 L), and the crude reaction mixture was added. Toluene (3 L) was added, and the mixture was stirred vigorously for 30 min. The organic phase was removed, and 85% orthophosphoric acid (~920 mL) was added to the aqueous phase over 1.5 h to pH 3.0. The product was extracted into toluene (3 L) with vigorous stirring for 1 h. The solvent was removed on a rotary evaporator to give 925 g of crude product as a pale-yellow solid. The aqueous layer was extracted with a further portion of toluene (1.5 L each), giving a further 40 g of crude product. The crude product and toluene (920 mL) were placed in a nitrogen-purged 10-L jacketed vessel. The suspension was heated to 70 °C at which point a clear, yellow solution resulted. Heptane (2.76 L) was added over 30 min, during which the internal temperature was maintained at 60−70 °C. The clear, yellow solution was seeded with a little of the crude product, then cooled to 50 °C over 1.5 h, stirred at 50 °C for 2 h, cooled to 45 °C over 1.5 h, then 20 °C over 16 h; the suspension was then filtered (the solid tended to stick to the sides of the vessel), and the solid was washed with heptane/toluene (3:1, 2 × 500 mL) and dried under vacuum to give **2** as a white, granular solid (724 g, 53% from the salt). The enantiomeric excess was >99.9%, liquors 48% ee. The liquors were returned to the vessel and cooled to +4 °C for 6 h, then were filtered to give a further 19 g of product of lower purity with 99.7% ee; liquors 42% ee. Mp 124 °C. $^{20}[\alpha]_D$ −27.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.37 and 4.16 (d, J = 8.8 Hz and d, J = 8.8 Hz, 1H), 3.85 and 3.79 (d, J = 8.8 Hz and d, J = 8.8 Hz, 1 H), 1.62, 1.58, and 1.55 (3s, 12 H), and 1.50 and 1.43 (2s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3 (s), 177.7 (s), 152.7 (s), 151.2 (s), 96.9 (s), 96.1 (s), 81.9 (s), 81.3 (s), 74.2 (t), 73.5 (t), 66.2 (s), 65.6 (s), 28.8 (q), 28.7 (q), 27.0 (q), 26.6 (q), 25.3 (q), 23.7 (q), 22.0 (q), and 20.9 (q). HRMS (ES +ve; MH^+) calcd for $C_{12}H_{22}NO_5$ 260.1498, found 260.1500.

(2*R*,4*S*)-2-*tert*-Butyl-3-*tert*-butoxycarbonyl-1,3-oxazolidine-4-carboxylic Acid Methyl Ester 4. L-Serine methyl ester hydrochloride (22.5 kg, 1 equiv), triethylamine (16.0 kg, 1.1 equiv), and pivalaldehyde (15.1 kg, 1.2 equiv) were slurried in 2-methylpentane (225 L). The reaction was heated to reflux under Dean−Stark conditions for 4 h, and reaction completion was confirmed by ^{1}H NMR. The slurry was cooled to 25 °C, and the solids were removed by filtration, washing through with 2-methylpentane (3 × 67 L). The filtrate was concentrated to ~56 L by atmospheric distillation to provide a concentrated solution of **16** in 2-methylpentane. THF (100 L) and Boc anhydride (33.8 kg, 1.1 equiv) were charged, and the reaction was stirred at 20 ± 5 °C for 6 h. A 20% w/w aqueous solution of potassium carbonate (135 kg) was charged, and the resultant biphasic mixture stirred at 20 ± 5 °C for a further 14 h, with reaction completion confirmed by ^{1}H NMR. 2-Methylpentane (113 L) was added, and the phases were separated. The aqueous layer was discarded, and *N*-methyl piperazine (7.2 kg) was charged to the organic solution and stirred for ~1 h. The organic phase was washed with 1 M HCl (2 × 68 kg), 20% w/w aqueous K_2CO_3 (82 kg), and finally with water (67 kg). The volatiles were removed under vacuum by distillation (−0.65 bar, 30−35 °C), and the concentrate was diluted with THF (4.5 L) to afford a 69% w/w solution[18] of **4** (38.6 kg; equivalent to 26.5 kg of **4**, 64%). ^{1}H NMR (400 MHz, d_4-MeOH) 4.99 (s, 1H), 4.72 (dd, J = 8.1, 5.6 Hz, 1H), 4.24 (dd, J = 8.8, 5.6 Hz, 1H), 4.13 (t, J = 8.3 Hz, 1H), 3.74 (s, 3H), 1.48 (s, 9H), 0.93 (s, 9H).

(2*R*,4*S*)-2-*tert*-Butyl-3-*tert*-butoxycarbonyl-4-methyl-1,3-oxazolidine-4-carboxylic Acid 3. A solution of diisopropylamine (14.0 kg, 1.5 equiv) in anhydrous tetrahydrofuran (211 kg) was cooled to 0 ± 5 °C, and 1.6 M *n*-butyl lithium in hexanes (51.0 kg, 1.3 equiv) was charged, maintaining the temperature in the range 0 ± 5 °C. The reaction mixture was cooled to −65 ± 5 °C, and the 69% w/w solution of **4** in THF (38.4 kg; equivalent to 26.4 kg of **4**) was charged and rinsed in with THF (12 kg), maintaining the temperature in the range −65 ± 5 °C. After 45 min, the enolate formation was confirmed to be complete by ^{1}H NMR analysis. Methyl iodide (21.9 kg, 1.7 equiv) was charged and rinsed in with THF (4 kg), maintaining the temperature in the range −65 ± 5 °C. The reaction was stirred at −65 ± 5 °C for 3 h and sampled for reaction completion by ^{1}H NMR. MeOH (4.6 kg) was charged and the reaction warmed to 20 ± 5 °C before washing with 22% w/w aqueous ammonium chloride solution (198 kg). MeOH (127 kg), water (53 kg), and 32% w/w sodium hydroxide (46 kg) were charged, and the reaction was warmed to 50 ± 5 °C over 2.5 h and stirred at this temperature for a further 1.5 h. The reaction was shown to be complete by HPLC analysis. The reaction was concentrated to a level of ~132 L by distillation (~450 L distillate removed), diluted with water (255 kg), and adjusted to 50 ± 5 °C. Glacial acetic acid (41.8 kg) was added over 1 h, rinsing in with water (10 kg), and the resulting slurry was cooled to 0 ± 5 °C over 2 h and aged at this temperature for a further hour. The solids were collected by filtration, washed with 10.5% w/w aqueous glacial acetic acid solution (132 kg) and then water (2 × 132 kg), and dried under reduced pressure at 50 ± 5 °C for 6 h to provide **3** as a white powder (21.5 kg, 81%) with 97.8% ee and >99% area purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (s, 1H), 4.28 (d, J = 8.3 Hz, 1 H), 3.85 (d, J = 8.3 Hz, 1 H), 1.60 (s, 3 H), 1.45 (s, 9 H), and 0.99 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1 (s), 155.6 (s), 98.4 (s), 96.1 (d), 82.3 (s), 78.3 (t), 67.6 (s), 40.3 (s), 28.5 (q), 27.1 (q), and 21.8 (q). HRMS (ES +ve; MH^+) calcd for $C_{14}H_{26}NO_5$ 288.1811, found 288.1817.

■ ASSOCIATED CONTENT

Supporting Information. Methods for the preparation of and spectroscopic data for side product **14** and reaction intermediate **15**; methods of purity analysis for 2-methylserine **7**, (*S*)-3-*tert*-butoxycarbonyl-2,2,4-trimethyl-1,3-oxazolidine-4-carboxylic acid **2** and (2*R*,4*S*)-2-*tert*-butyl-3-*tert*-butoxycarbonyl-4-methyl-1,3-oxazolidine-4-carboxylic acid **3**; methods of chiral analysis for *N*-*tert*-butoxycarbonyl-2-methylserine methyl ester **10**, camphorsulfonate salt **9**, methyl ester **11**, (*S*)-3-*tert*-butoxycarbonyl-2,2,4-trimethyl-1,3-oxazolidine-4-carboxylic acid **2** and (2*R*,4*S*)-2-*tert*-butyl-3-*tert*-butoxycarbonyl-4-methyl-1,3-oxazolidine-4-carboxylic acid **3**; in-process

methods of analysis for preparation of *N*-*tert*-butoxycarbonyl-2-methylserine methyl ester **10**, methyl ester **11** and (2*R*,4*S*)-2-*tert*-butyl-3-*tert*-butoxycarbonyl-4-methyl-1,3-oxazolidine-4-carboxylic acid **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
jonathan.p.graham@gsk.com.

ACKNOWLEDGMENT

We are grateful to Robert Williams at Chirotech and Jamie Russell and Charles Dexter at GSK for assistance with pilot-plant operations, and we thank Kelly Goulston and Fiona King at GSK for key analytical support.

REFERENCES

(1) (a) Evindar, G.; Deng, H.; Bernier, S.; Yao, G.; Coffin, A.; Yang, H. WO 2008016692; (b) Anson, M. S.; Day, C. J.; Graham, J. P.; Kindon, L. J.; Woolham, G. R. WO 2009098193.

(2) Initial discovery and preparation of GSK1842799 was performed by Praecis Pharmaceuticals Inc., and multigram preparations of (2*S*)-2-amino-2-{5-[4-(octyloxy)-3-(trifluoromethyl)phenyl]-1,3,4-thiadiazol-2-yl}-1-propanol **1**, using both **2** and **3**, were performed under contract by Albany Molecular Research, Inc.

(3) For reviews on the synthesis of α,α-disubstituted α-amino acids, see (a) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (b) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127. (c) With, T. In *Organic Synthesis Highlights IV*; Schmalz, H.-G., Ed.; Wiley: Weinheim, 2000; pp 26−33.

(4) For a review on the synthesis of 2-methylserine, see Nakano, K.; Kotsuki, H.; Ichikawa, Y. *Org. Prep. Proced. Int.* **2008**, *40*, 67.

(5) Now Dr. Reddy's Laboratories, Chirotech Technology Ltd.

(6) Jones, M. A.; Hislop, A. D.; Snaith, J. S. *Org. Biomol. Chem.* **2006**, *4*, 3769.

(7) For a review on the concept of self-regeneration of stereocentres, see Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708.

(8) (a) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545. (b) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194. (c) Brunner, M.; Saarenketo, P.; Straub, T.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2004**, 3879–3883. (d) Sankyo Company, Limited. Patent Application EP1806344 A1, 2007.

(9) Seebach notes the decomposition of the lithium enolate of methyl-(2*R*,4*S*)-2-(1,1-dimethylethyl)-3-formyl-1,3-oxazolidine-4-carboxylate even at −78 °C, see ref 8a. In the Sankyo Company patent (see ref 8d) higher temperatures, typically −25 to 10 °C, are used for the alkylation, although only crude yields and no details of stereoselectivity are disclosed.

(10) With the *N*-formyl group employed by Seebach (see ref 8a), it is possible to crystallise the desired oxazolidine diastereomer prior to alkylation. However, the *N*-formyl group would not be compatible with our planned downstream chemistry. When the formyl group is replaced with a Boc group, as used by Koskinen (ref 8c), none of the intermediates to **3** are crystalline.

(11) Abshire, C. J. *Experientia* **1968**, *24*, 778–779.

(12) Abshire, C. J.; Berlinguet, L. *Can. J. Chem.* **1965**, *5*, 1232–1234.

(13) Easton, C. J.; Ivory, A. J.; Smith, C. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 503.

(14) Clemens, J. J.; Davis, M.-D.; Lynch, K. R.; MacDonald, T. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3568–3572.

(15) Lynch, K. R.; MacDonald, T. L. WO 2004/010949, 2004.

(16) Hansen, D.; Webber, R. K.; Pitzele, B. S.; Awasthi, A. K.; Sikorski, J.; Trivedi, M.; Moorman, A. WO 2002/022561, 2002.

(17) Fülöp, F.; Pihlaja, K. *Tetrahedron* **1993**, 6701.

(18) Solution concentration determination: a portion of the THF solution (30.0 g) was concentrated to dryness to provide a clear oil of **4** (20.6 g).