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Synthesis of Akt Inhibitor Ipatasertib. Part I: Route Scouting and Early Process Development of a Challenging Cyclopentylpyrimidine Intermediate

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ABSTRACT: In Part I of this series, the route scouting and early process development of a key cyclopentylpyrimidine ketone intermediate toward the synthesis of Akt inhibitor Ipatasertib are described. Initial supplies of the intermediate were prepared through a method that commenced with the natural product (*R*)-(+)-pulegone and relied on the early construction of a methyl-substituted cyclopentyl ring system. The first process chemistry route, detailed herein, enabled the synthesis of the ketone on hundred gram scale, but was not feasible for the requisite production of multikilogram quantities of this compound and necessitated the exploration of alternative strategies. Several new synthetic approaches were investigated towards the preparation of the cyclopentylpyrimidine ketone, in either racemic or chiral form, which resulted in the discovery of a more practical route that hinged on the initial preparation of a highly-substituted dihydroxypyrimidine (DHP) compound. The cyclopentane ring in the target was then

constructed through a key carbonylative esterification and subsequent tandem Dieckmann-decarboxylation sequence that was demonstrated in a racemic synthesis. This proof-of-concept was later developed into an asymmetric synthesis of the cyclopentylpyrimidine ketone, which is described in Part II of this series in addition to the synthesis of Ipatasertib.

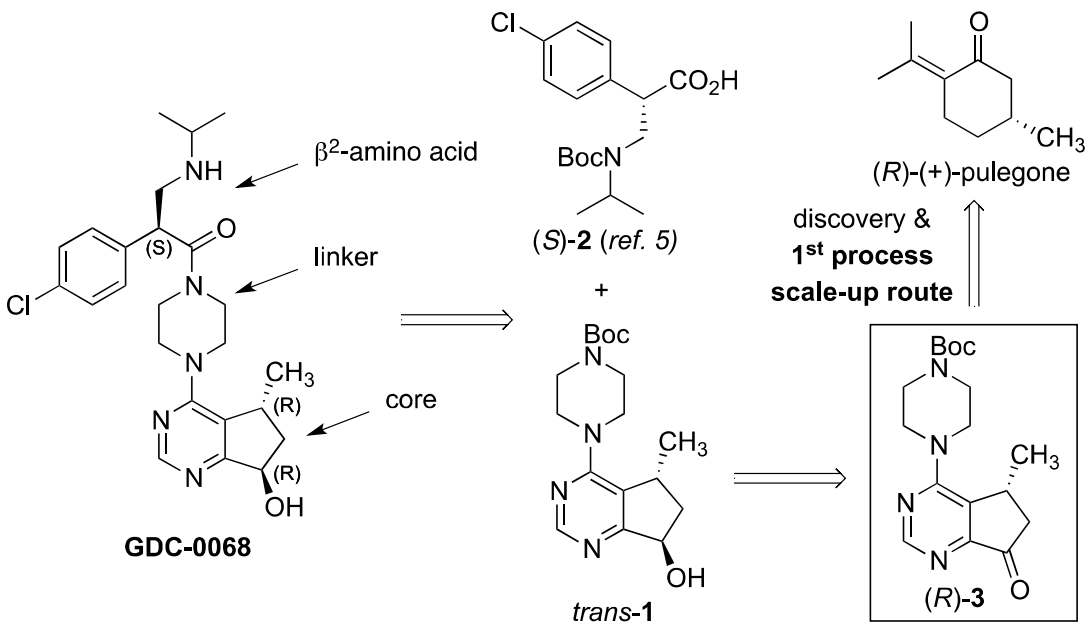
INTRODUCTION

Akt/Protein Kinase B (PKB) is a member of the AGC subfamily and regulates diverse cellular activities including cell growth, proliferation, apoptosis and metabolism.[1] In response to the observation that Akt plays a key role in the survival and progression of various types of cancer cells,[2] the concept of Akt inhibition has generated significant interest in the oncology community.[3] Through an extensive collaboration between the discovery chemistry groups at Array and Genentech (Roche), numerous molecular scaffolds were successfully devised and investigated both *in vitro* and *in vivo* as potential selective inhibitors of Akt, which ultimately resulted in the nomination of Ipatasertib (Figure 1) for clinical development.[4]

Retrosynthetically, Ipatasertib is assembled in a convergent manner from two key components where cyclopentylpyrimidine core *trans*-**1**, which possesses a piperazine linker, is coupled to β^2-amino acid *(S)*-**2** (Figure 1). In the medicinal chemistry synthesis of Ipatasertib, the first coupling partner *(S)*-**2** was prepared from commercially available 4-chlorophenylacetic acid, and two subsequent asymmetric syntheses of this chiral compound have recently been communicated.[5] The second coupling partner *trans*-**1** arose from an asymmetric reduction of ketone *(R)*-**3**, which was originally derived from the natural product (*R*)-(+)-pulegone. Since (*R*)-(+)-pulegone was a starting material from the chiral pool, it was initially attractive from a process point-of-view as it provided a reliable source of chirality for the methyl group in *(R)*-**3**,

and was readily available on kilogram scale.[6] Furthermore, (*R*)-(+)-pulegone has been widely used for the preparation of several natural products containing a methyl stereocenter in a cyclopentyl ring system that was accessed from the well-precedented Favorskii rearrangement.[7] The discovery route to ketone *(R)*-**3** provided a viable basis for further development after addressing several concerns including (1) the ozonolysis reaction[8] that required cryogenic temperatures as well as a facility with an ozone generator, (2) high reaction temperatures (150 °C for 24 h) required to forge the pyrimidine ring system, and (3) the use of undesirable solvents and reagents such as Et_2O (Favorskii rearrangement), $CHCl_3$ (*m*-CPBA oxidation) and PDC (benzylic alcohol oxidation), which were not attractive for scale-up.[4a] Another drawback to the discovery route was the requirement for installation of the benzylic ketone group in *(R)*-**3**, which is eventually reduced to provide *trans*-**1**. Albeit cumbersome, installation of the ketone group was successfully accomplished by a Boekelheide-type oxidation-rearrangement reaction[9] and subsequent Swern oxidation that enabled synthesis of the first hundred-gram quantities of ketone (*R*)-**3**.

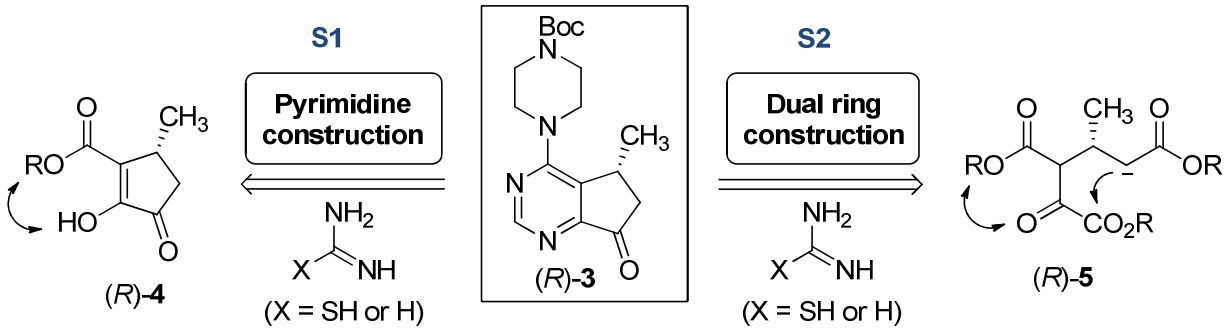
Figure 1. Retrosynthesis of Ipatasertib.



In response to the fact that the (*R*)-(+)-pulegone route was lengthy, low-yielding and employed extensive oxidation chemistry, and concomitant with our initial scale-up efforts,[4a] two new distinct strategies were examined and explored for the preparation of ketone *(R)*-**3** that would potentially better facilitate multikilogram scale production (Figure 2). In the first approach (**S1**), pyrimidine ring construction was envisioned to arise from the condensation of a formamidine equivalent onto a pre-functionalized cyclopentanedione compound such as *(R)*-**4**.[10] In contrast, a second approach (**S2**) would entail sequentially building the pyrimidine ring followed by the cyclopentane ring in *(R)*-**3** from a triester compound *(R)*-**5**. This second strategy was advantageous with respect to enabling the assembly of the key chiral unit in *(R)*-**3** through mild intramolecular annulation approaches with the pyrimidine component already in place. Moreover, the latter approach (**S2**) was the most attractive, because we could employ simple acyclic ester derivatives that would potentially allow for access to chiral products through enzymatic resolution methods. The scale-up of the (*R*)-(+)-pulegone route to *(R)*-**3** and

alternative strategy investigations (**S1**–**S2**) that resulted in the development and *racemic* demonstration of a new lead route to *(R)*-**3** will be discussed herein.

Figure 2. Route scouting strategies for the preparation of ketone *(R)*-**3**.



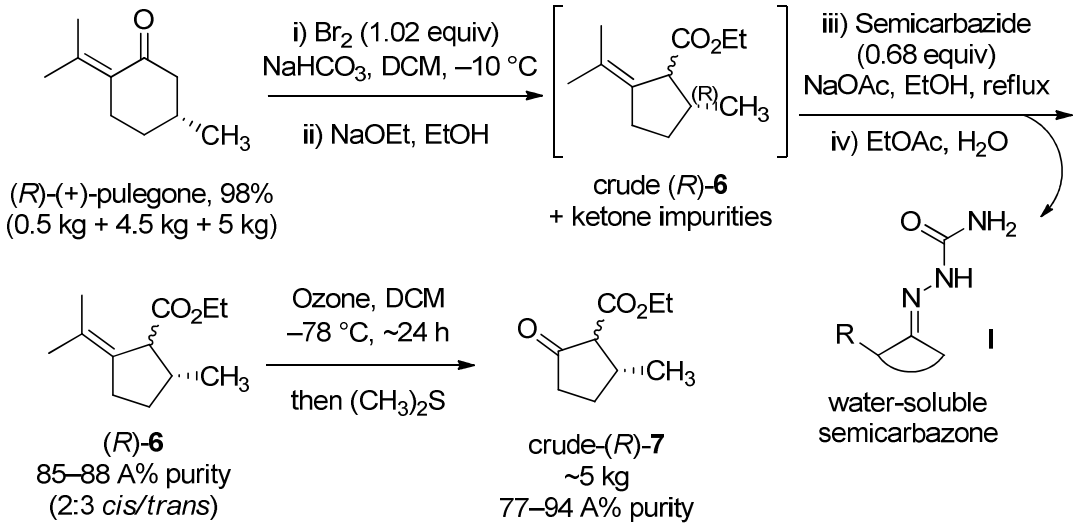
RESULTS AND DISCUSSION

1. Process scale-up of the (+)-pulegone route to ketone *(R)*-3. At the time of this work, the medicinal chemistry group had reported the conversion (*R*)-(+)-pulegone to the Favorskii rearrangement product (*R*)-**6** in 64% isolated yield on 600 g scale (Scheme 1).[11] This procedure was reproducible; however, we sought to eliminate the use of Et_2O for the bromination step prior to further scale-up, and DCM was found to be a suitable and safer alternative. Therefore, starting with a DCM solution of (*R*)-(+)-pulegone[12] and sodium bicarbonate, slow addition of 1.02 equiv Br_2 at –10 °C resulted in near-complete conversion to the corresponding dibromide intermediate (monitored by TLC). Following filtration to remove the inorganic solids, the Favorskii rearrangement was initiated with the addition of NaOEt in EtOH at –40 °C and subsequent warming to ambient temperature. The reaction mixture was then acidified, and the DCM solution was concentrated to a give the crude product (*R*)-**6** following an aqueous work-up. The crude product mixture contained ketone impurities, such as unreacted (*R*)-(+)-pulegone and likely other unidentified reaction intermediates and/or byproducts, which required removal. These impurities

were successfully purged by initial treatment of crude (*R*)-**6** with aqueous semicarbazide to form the corresponding water-soluble semicarbazone[13] derivatives [**I**]. The cyclopentyl ester (*R*)-**6** could then be selectively extracted into EtOAc and isolated as an oil, which was of acceptable quality for further processing. On 5 kg scale, (*R*)-(+)-pulegone was converted to cyclopentyl ester (*R*)-**6** (3.9 kg, 60% yield with ~85 A% GC purity) as a 2:3 mixture of *cis*/*trans* isomers.[14] The next step required cleavage of the exocyclic alkene in (*R*)-**6** in order to unmask the β-ketoester functionality in (*R*)-**7**. Although alternative approaches were examined to replace the existing ozonolysis, none were as efficient.[15] Two modifications were made to the medicinal chemistry procedure where (1) EtOAc was replaced with DCM, and (2) an alternative quench of the ozonide was employed. The use of DCM was driven by the improvement realized in determining the ozone saturation endpoint, which was accomplished by the visual observation of a characteristic blue color. As well, several methods are commonly used for quenching ozonide intermediates including Ph_3P, Zn/AcOH and dimethyl sulfide (DMS), but in our experience DMS was preferred for scale-up and led to a reduction in the exotherm associated with the quench in addition to a more straightforward charging protocol at cryogenic temperatures (–78 °C). In a typical experiment, starting with 500 g cyclopentyl ester (*R*)-**6**, the ozonolysis reaction was complete in ≤24 h. Subsequent quench of the deep blue solution with DMS followed by gradual warming to room temperature and aqueous extraction required an additional ~20 h of processing time before the crude β-ketoester intermediate (*R*)-**7** was isolated as a yellow liquid in ~75% yield. A total of 10 kg (*R*)-(+)-pulegone was processed over the two steps to provide ~6 kg of β-ketoester (*R*)-**7** in multiple batches and variable purity (77–94 A%) by GC. The inconsistent purity was believed to be due to the sensitivity of the ozonolysis work-up on increased scale;

however, the purity of (*R*)-**7** was not critical to the function of the subsequent step to construct the thiopyrimidine.

Scheme 1. Scale-up of the Favorskii rearrangement and ozonolysis reactions.



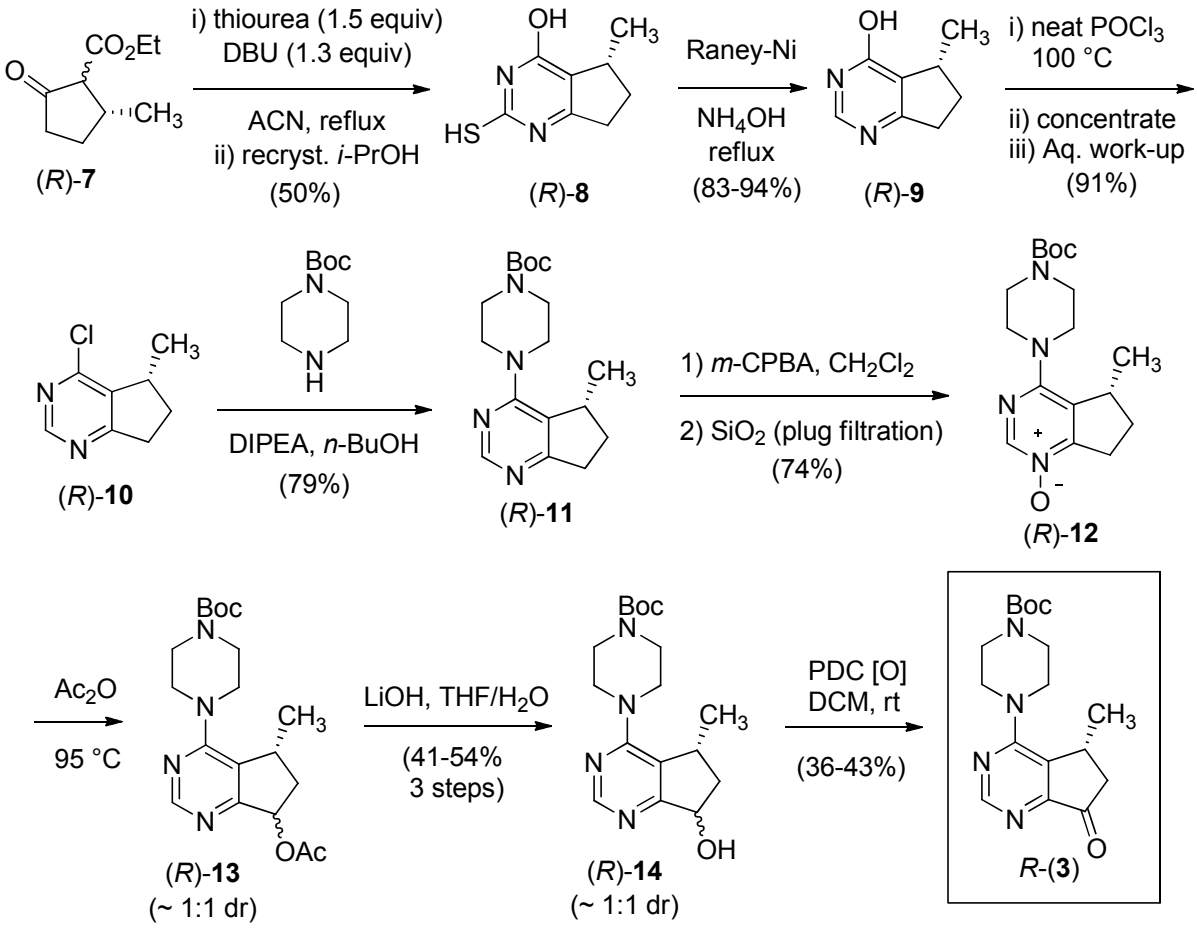
The medicinal chemistry group had previously employed two principle methods to construct the pyrimidine ring associated with Ipatasertib from (*R*)-**7** (Scheme 2). The first method entailed a step-wise condensation whereby β-ketoester (*R*)-**7** was initially treated with NH_4OAc to produce the corresponding enamine derivative, which was then condensed with ammonium formate/formamide at ≤150 °C to give pyrimidine (*R*)-**9** in ~60% yield over the two steps.[4a] In the second method, the more nucleophilic thiourea was initially reacted with β-ketoester (*R*)-**7** under milder reaction conditions (≤85 °C) to produce thiopyrimidine (*R*)-**8** in modest yields (45–55%), after which a subsequent desulfurization step was required to generate pyrimidine (*R*)-**9**.[16] Although the first process afforded improved yields over the thiourea method, the higher reaction temperatures associated with this procedure were unsafe for scale-up as ammonium formate could sublime and plug the reflux condenser.[17] Therefore, the thiourea

approach was ultimately selected for scale-up based on these safety concerns. On scale-up of this process, condensation of the β-ketoester (*R*)-**7** with thiourea was promoted by the slow addition of DBU to the reaction mixture, which resulted in complete consumption of starting material after ~20 h at reflux. The product was precipitated by the addition of aqueous HCl and was then recrystallized from *i*-PrOH to afford thiopyrimidine (*R*)-**8** in ~50% yield with >99 A% HPLC purity on kilogram scale. Subsequent reductive desulfurization of (*R*)-**8** with Raney® Nickel in ammonium hydroxide afforded hydroxypyrimidine (*R*)-**9** in yields ranging from 83–94%.[18] Installation of the piperazine linker in *(R)*-**3** commenced with the chlorination of (*R*)-**9** using neat $POCl_3$ and heating to 100 °C.[19] On scale-up this resulted in clean formation of chloropyrimidine (*R*)-**10** in 91% isolated yield and >99 A% purity.[20] Nucleophilic aromatic substitution of chloropyrimidine (*R*)-**10** with *N*-Boc-piperazine then provided (*R*)-**11** (79%, >99 A% by HPLC) following a silica gel plug filtration and crystallization from EtOAc/heptane.

In order to install the requisite benzylic ketone group in *(R)*-**3**, a Boekelheide-type oxidation-rearrangement sequence was performed. The two-step transformation entailed the initial generation of pyrimidine *N*-oxide (*R*)-**12** through treatment of (*R*)-**11** with *m*-CPBA, followed by subsequent heating of (*R*)-**12** in acetic anhydride to afford rearrangement product (*R*)-**13**. In the original discovery synthesis, $CHCl_3$ was employed for the *m*-CPBA-mediated oxidation; however, DCM was found to be a suitable replacement for this stage of development.[21] On scale-up of this reaction, up to 4 equiv of *m*-CPBA was required in order to achieve complete conversion and gave 74% isolated yield of pyrimidine *N*-oxide (*R*)-**12** after passage of the crude mixture of a plug of silica gel.[22] The resulting brown oil was then heated in neat acetic anhydride to facilitate the desired oxidative transposition, producing the acetate derivative (*R*)-**13** (~ 1:1 *dr*) as a black tar-like residue. Cleavage of the benzylic acetate group in

(*R*)-**13** with aqueous LiOH in THF and purification of the isolated product via a silica gel plug followed by crystallization from ether/heptane afforded the benzylic alcohol (*R*)-**14** in ~99 A% purity and modest yields (41–54%) for the three-step sequence. A Swern oxidation protocol had been previously employed in prior efforts to convert the hydroxyl group in (*R*)-**14** to ketone (*R*)-**3**. However, it was later determined that residual DMSO and dimethylsulfide byproducts associated with (*R*)-**3** produced in this manner were responsible for poisoning the ruthenium catalyst in the subsequent asymmetric ketone reduction to *(R,R)*-**1** (Figure 1). From the examination of alternative oxidation reagents, pyridinium dichromate (PDC) afforded the highest yield of product (*R*)-**3** and circumvented the introduction of any potential impurities that could adversely affect the subsequent asymmetric reduction.[23] In the process, PDC was added portionwise to a solution of (*R*)-**14**, resulting in complete consumption of the alcohol starting material after stirring overnight at ambient temperature. Purification of the crude product over a plug of silica gel, which was required in order to remove several unknown impurities arising from the intrinsic instability of (*R*)-**3** under the reaction conditions, afforded the target ketone in modest yield.

Scheme 2. First generation process route for the preparation of cyclopentyl ketone *(R)*-**3**.



2. (*R*)-(+)-Pulegone route liabilities. Although scale-up of the discovery synthesis successfully facilitated the critical initial delivery of 0.2 kg of ketone *(R)*-**3** in ~2% overall yield from a 5 kg input of (*R*)-(+)-pulegone, this route was not practical for large scale production. The ozonolysis reaction posed significant concerns due to long reaction times, modest yields and the scarce availability of vendors possessing the capabilities necessary to conduct the transformation on multikilogram scale. A suitable replacement to the ozonolysis reaction for cleavage of the exocyclic alkene in *(R)*-**6** was not available. As well, the lengthy and cumbersome benzylic oxidation sequence (Boekelheide reaction) late in the route represented perhaps the most significant challenge for two reasons. First, the initial oxidation to produce *N*-oxide *(R)*-**12**

required the use of *m*-CPBA, which presented safety concerns on scale-up. Second, rearrangement of *(R)*-**12** to *(R)*-**13** was not stereoselective, which necessitated a subsequent low-yielding oxidation to ketone *(R)*-**3** *en route* to an asymmetric reduction to access *trans*-**1** (Figure 1). Indeed, the shortcomings associated with the (*R*)-(+)-pulegone route to *(R)*-**3** highlighted the importance of establishing a new path to this key intermediate. Therefore, several alternative strategies (**S1-S2**, Figure 2) were explored toward the preparation of ketone *(R)*-**3**, initially with racemic inputs in an effort to rapidly assess the feasibility of the key bond-forming steps.

3. Route scouting approach S1: Pyrimidine construction. The first approach (**S1**, Figure 2) was an extension of the original (*R*)-(+)-pulegone route and was initially chosen for investigation in part to avoid the ozonolysis step associated with the preparation of β-ketoester (*R*)-**7** (Scheme 2). We envisioned that use of the alternative cyclopentadione compound *rac*-**4**[10] could also obviate the need for the Boekelheide oxidation/rearrangement used in the scale-up route to install the hydroxyl functionality in (*R*)-**14** that was subsequently oxidized to ketone (*R*)-**3**. Therefore, we prepared gram quantities of cyclopentadione *rac*-**4** as well as the hydroxyl-substituted derivative (*rac*-**16**)[24] according to literature methods and tested these precursors in the key step to forge the corresponding pyrimidine (or thiopyrimidine) ring system (Scheme 3). We adopted reaction conditions similar to those employed in the previous route that entailed treatment of the substrate in various solvents with either thiourea or formamidine in combination with an alkoxide base (entries 1-3, Table 1). Unfortunately, all attempts to react either the cyclopentadione compound *rac*-**4** or the hydroxyl-substituted derivative *rac*-**16** under these conditions failed to provide the desired products, ketone *rac*-**15** or alcohol *rac*-**17**, respectively, in any appreciable quantity as indicated by LCMS analysis. Specifically, at lower reaction temperatures (≤50 °C) only the mono-addition enamine intermediate [**II**] and unreacted starting

material were observed, suggesting that higher temperatures were required to promote the cyclization. Although trace product was observed in some cases by LCMS, the more forcing reaction conditions typically resulted in a complex mixture of products. From these initial results, we concluded that we must develop a route to ketone **3** that either commenced with the pyrimidine ring system in place or, alternatively, employed a more robust substrate that could tolerate the harsh reactions conditions required for pyrimidine ring formation. Our next approach would address this theory.

Scheme 3. Cyclization attempts for oxygen-substituted cyclopentane compounds (**S1**).

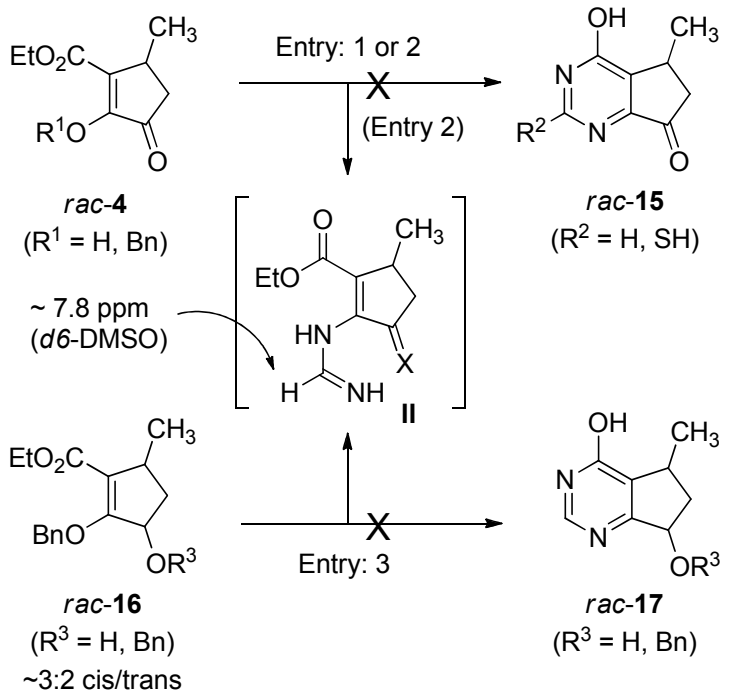


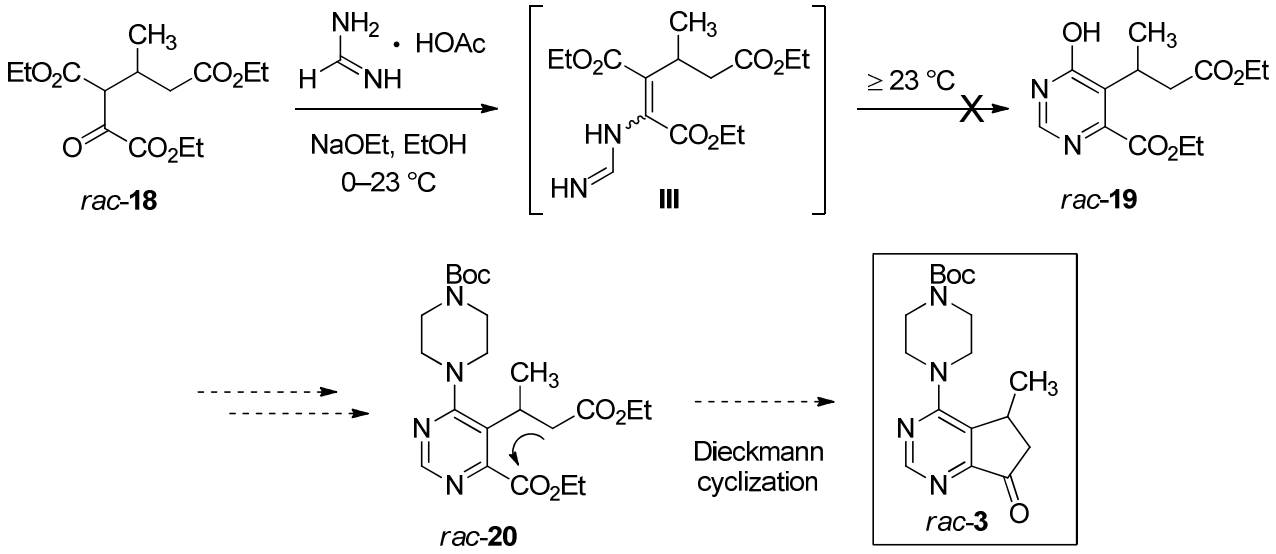
Table 1. Reaction conditions to construct thiopyrimidine and pyrimidine derivatives.

Entry[a]	Experimental Details
1	Thiourea, solvent (MeOH, EtOH, toluene), >100 ˚C.
2	$HN{=}CHNH_2$ (AcOH or HCl salt), NaOMe/MeOH or NaOEt/EtOH, 80 ˚C.
3	$HN{=}CHNH_2$ (AcOH salt), base (none, NaOMe, NaOEt, NaOtBu), solvent (EtOH, DMF, DMSO), 50 ˚C.

[a]All experiments were performed in sealed tubes and analyzed by LCMS (λ = 254 nm) after 8–12 h.

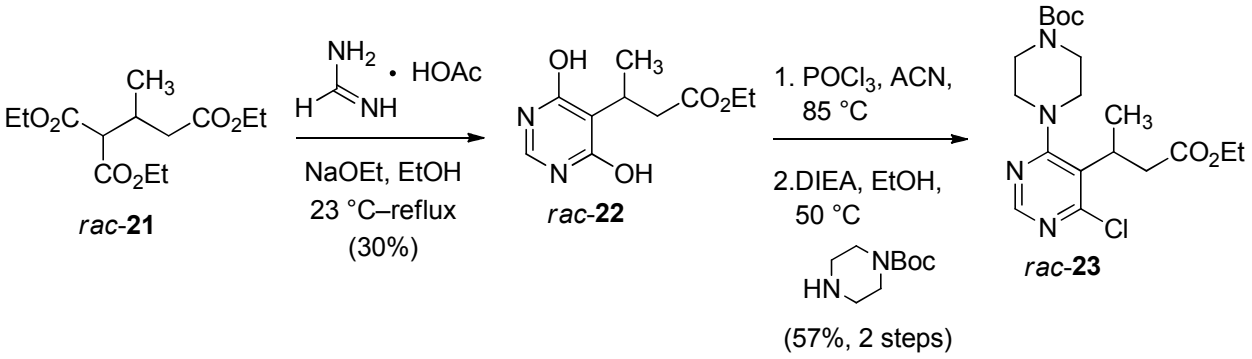
4. Route scouting approach S2: Dual ring construction. Based on our observations from investigations pertaining to **S1**,[25] we proceeded to a second approach (**S2**, Figure 2), which relied on acyclic triester substrates for the construction of both rings comprising the bicyclic core in ketone *(R)*-**3**. Pyrimidine diester *rac*-**19** was a logical target that could arise from keto-triester *rac*-**18** and ultimately provide the desired cyclopentyl ketone ring system in **3** via *rac*-**20** through a Dieckmann cyclization and decarboxylation sequence (Scheme 4).[26] To access *rac*-**19**, we prepared the α-oxalyl methylglutarate substrate *rac*-**18** using known literature methods.[27] Unfortunately, our attempts to cyclize *rac*-**18** in the presence of formamidine acetate and NaOEt/EtOH suffered a similar issue to that which we observed in prior investigations with the cyclopentane-based substrates (Scheme 3). Only the initial condensation product enamine [**III**], in addition to unreacted starting material, were observed at ambient reaction temperatures (≤23 °C). Further heating the reaction mixture resulted in complex product mixtures, and diester *rac*-**19** was not observed.

Scheme 4. Attempted pyrimidine formation with oxalyl methylglutarate *rac*-**18** (**S2**).



Therefore, efforts were refocused on the cyclization of an alternative triester substrate *rac*-**21** that was easily accessed from ethyl crotonate and diethylmalonate through reported methods.[28] To our delight, treatment of *rac*-**21** with formamidine generated dihydroxypyrimidine *rac*-**22** in an unoptimized 30% yield (Scheme 5). Evaluation of the key Dieckmann cyclization strategy toward establishing the cyclopentane unit in *(R)*-**3** next required conversion of *rac*-**22** to the corresponding dichloropyrimidine intermediate through treatment with $POCl_3$, which was then reacted with *N*-Boc piperazine using S_NAr conditions similar to those employed in the (*R*)-(+)-pulegone route (Scheme 2) in order to arrive at Dieckmann substrate precursor chloropyrimidine *rac*-**23**.

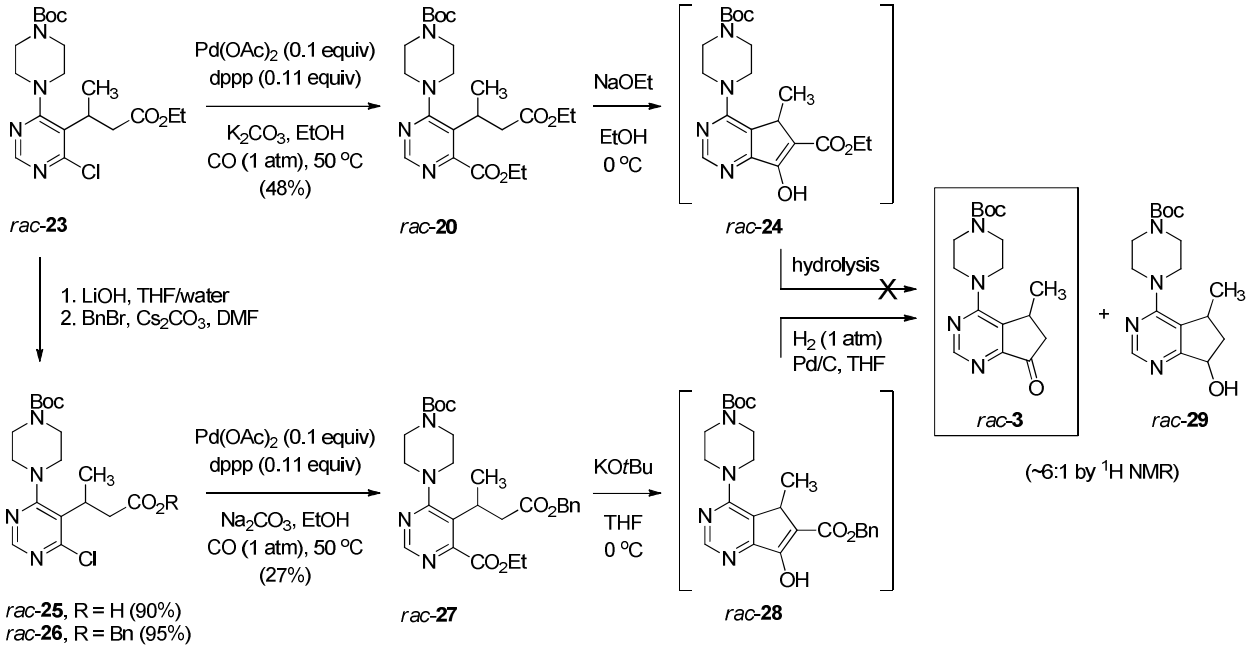
Scheme 5. Successful preparation of chloropyrimidine *rac*-**23** (**S2**).



Having established a path to *rac*-**23**, the next step was to install the requisite aryl ester group in *rac*-**20** that was not directly accessible through *rac*-**18**. The palladium-catalyzed carbonylative esterification of aryl chlorides, including 4-chloropyrimidines, is well-precedented,[29] and a brief survey of the reaction conditions reported by Albaneze-Walker and co-workers[29a] expeditiously revealed that the use of 1,3-bis(diphenylphosphino)propane (dppp) with $Pd(OAc)_2$ was the most effective catalyst system for the conversion of *rac*-**23** to ethyl ester

derivative *rac*-**20** (Scheme 6).[30] In attempts to rapidly validate the Dieckmann approach to *(R)*-**3**, formation of the cyclopentane ring was subsequently effected under mild conditions, generating ketoester *rac*-**24** with complete consumption of starting material and clean reaction profile by LCMS analysis.[31] Unfortunately, removal of the unwanted ethyl ester group in *rac*-**24** proved very challenging. Exposure of *rac*-**24** to a variety of systems typically used to promote this transformation including base (LiOH/THF-H_2O, KOH/MeOH), acid (TsOH/MeOH-H_2O, HCO_2H) and neutral (Krapcho-type: LiCl, DMSO)[32] conditions, all resulted in either recovered starting material or degradation products after heating the reaction mixture. From these studies it was reasoned that the instability associated with *rac*-**24** as well as the product *rac*-**3**,[33] necessitated an alternative ester group that was amenable to decarboalkoxylation under milder reaction conditions.

Scheme 6. Cyclopentane ring formation through a Dieckmann condensation approach.



To this end, *rac*-**27**, the corresponding benzyl ester side-chain derivative of *rac*-**20**, was a logical substrate to investigate in the subsequent Dieckmann-decarboalkoxylation sequence.[34] In practice, we found it more convenient to install the requisite benzyl ester side-chain in *rac*-**27** through the initial hydrolysis of the ethyl ester group of *rac*-**23** followed by the re-esterification of the resulting carboxylic acid intermediate (*rac*-**25**), as opposed to accessing the modified side-chain from the corresponding benzyl triester derivative of *rac*-**21**. Using this method, *rac*-**26** was produced in 86% yield over two steps and employed in the subsequent Pd-mediated carbonylative esterification reaction. Despite the potential for ester group exchange with EtOH, we initially chose to use substantially similar reaction conditions to those employed with the previous substrate *rac*-**23** in order to test our hypothesis, and the carbonylation proceeded to provide mixed diester *rac*-**27** in 27% yield after purification.[35] The Dieckmann cyclization of *rac*-**27** to *rac*-**28** was then successfully promoted through the agency of KO*t*Bu in THF, resulting again in complete conversion for this transformation.[36] Following a simple neutralization with aqueous HCl, benzyl ketoester *rac*-**28** was immediately subjected *in situ* to hydrogenolysis conditions (H_2, Pd/carbon, THF), effectively enabling the desired decarboalkoxylation to *rac*-**3** in excellent conversion (>95% by LCMS) and securing proof-of-concept for the new strategy on milligram scale.[37] However, in this initial demonstration, the over-reduced *rac*-**29** (>10:1 *cis*/*trans*) was also observed as a byproduct and suggested that additional optimization would be required in attempts to suppress this undesired pathway.

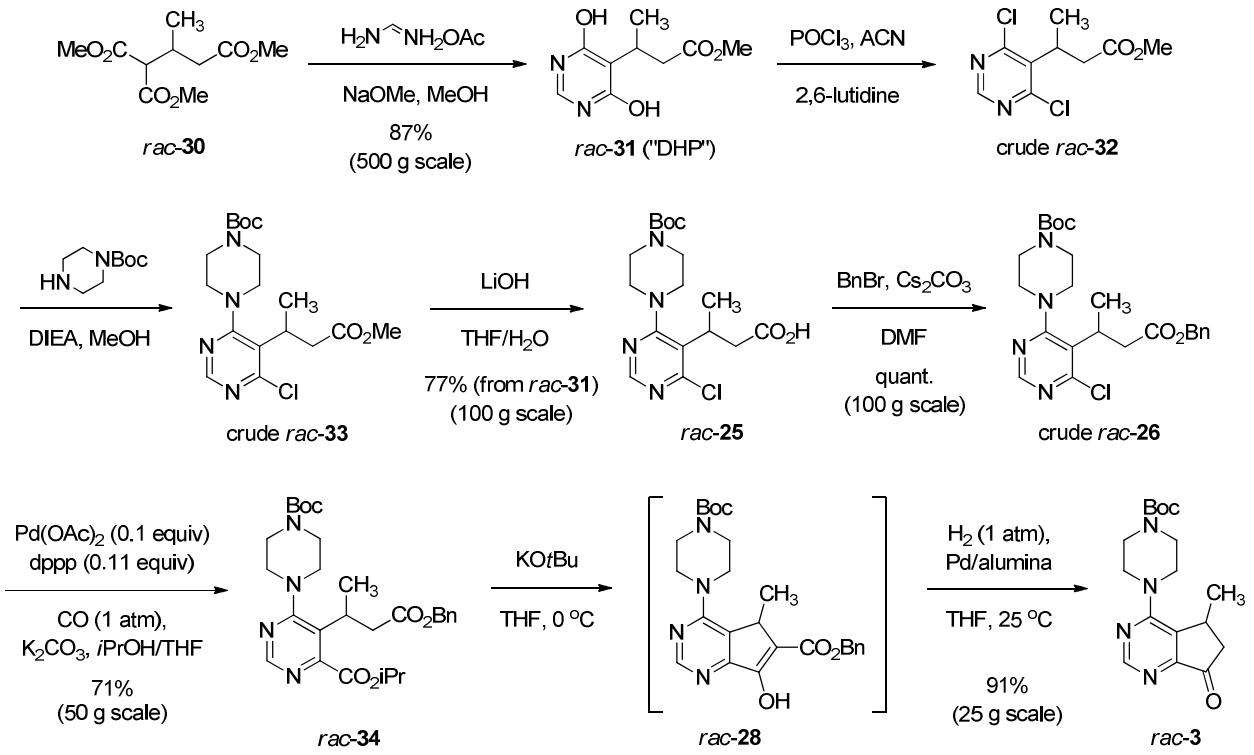
5. Optimized lead route to ketone *rac*-3. Following the initial successful establishment of the Dieckmann-based strategy toward ketone *rac*-**3**, additional optimization was conducted, and scale-up was demonstrated in order to rapidly establish the viability of the new approach. The synthesis commenced from trimethyl ester *rac*-**30** instead of the ethyl ester derivative *rac*-**21**,

and gave dihydroxypyrimidine (DHP) *rac*-**31** in 87% yield (Scheme 7). Improved performance in this reaction was realized with the NaOMe/MeOH based cyclization system due to the enhanced solubility in the reaction mixture, which maintained a homogenous composition. The water-soluble DHP *rac*-**31** product was isolated through filtration following pH adjustment with HCl (g) and solvent exchange to toluene. One notable observation associated with this procedure was the contamination of *rac*-**31** with significant quantities of sodium chloride that had essentially co-precipitated during the isolation. However, the presence of sodium chloride in the product did not adversely impact the subsequent chlorination as the salts were purged in the workup of this transformation.[38]

The conversion of (DHP) *rac*-**31** to dichloropyrimidine intermediate *rac*-**32** through treatment with phosphorous oxychloride ($POCl_3$) initially posed a notable safety concern with respect to the further scale-up of this operation. The source of concern arose from a significant exotherm that was consistently observed upon heating the mixture following the introduction of all reaction components. Fortunately, the exotherm was successfully managed through the use of 2,6-lutidine as a promoter in the context of a controlled charge of $POCl_3$ at elevated temperature (70 ˚C) where the accumulation of reactive intermediates could be avoided.[39] Subsequent introduction of the *N*-Boc-protected piperidine linker through nucleophilic aromatic substitution of *rac*-**32** proceeded in MeOH, circumventing the likelihood of ester group exchange to give intermediate *rac*-**33**. Consistent with prior observations, the corresponding byproduct arising from the addition of two equivalents of *N*-Boc piperidine to *rac*-**32** was not observed by ^{1}H NMR spectroscopy. Hydrolysis of the methyl ester group in *rac*-**33** was accomplished under mild conditions to provide carboxylic acid intermediate *rac*-**25**. In the three-step sequence (*rac*-

31 to *rac*-**25**), intermediates *rac*-**32** and *rac*-**33** were processed without any formal purification, and compound *rac*-**25** was isolated by filtration in 77% overall yield.

Scheme 7. Second-generation process chemistry route to cyclopentylpyrimidine ketone *rac*-3.



Esterification of carboxylic acid *rac*-**25** was accomplished using conditions similar to those employed in our initial studies (Scheme 6), and benzyl ester *rac*-**26** was produced in quantitative yield and used without further purification. Conversely, the subsequent carbonylative esterification of benzyl ester *rac*-**26** had been low-yielding in the context of the reaction conditions employed in our initial demonstration, and conversion as well as exchange of the benzyl ester group with the reaction solvent (EtOH) were identified as key issues. A preliminary survey of ligands, Pd-sources and bases confirmed that our original catalyst system recruited to promote this transformation (dppp, $Pd(OAc)_2$, K_2CO_3) was optimal, and we proceeded to examine alternative solvents. From a screen of various alcohol solvents[40] and co-

solvents, a 3:1 mixture of *i*PrOH and THF was identified as an optimal solvent system whereby the reaction would proceed to completion with near-complete suppression of benzyl ester group exchange,[41] and the resulting aryl isopropyl ester group was competent in the subsequent Dieckmann cyclization. In our final demonstration (50 g scale), the carbonylation proceeded smoothly to give the mixed ester *rac*-**34** in 71% yield after purification over a plug of silica gel and subsequent trituration (heptane/MTBE).[42]

For the key Dieckmann cyclization and decarboxylation sequence, the choice of Pd catalyst was found to be critical. Our initial proof-of-concept demonstration for the hydrogenolysis of intermediate *rac*-**28** (Scheme 6) had employed 10 wt% Pd/carbon as catalyst in the presence of H_2 (1 atm), resulting in complete conversion (>95% by LCMS) to the ketone *rac*-**3** in addition to the formation of *rac*-**29** from further reduction of the ketone group. In order to suppress the observed over-reduction in this step, we found that the use of Pd/alumina (5 wt.%) as catalyst promoted the removal of the benzyl ester group and resulted in <1% of compound *rac*-**29** in our final 25 g demonstration. Using this procedure, ketone *rac*-**3** was produced from *rac*-**34** and then isolated by precipitation (THF/heptane) in 91% yield (>99 A%) wherein alcohol *rac*-**29** was effectively rejected into the filtrate.

CONCLUSION

A new lead route was developed and demonstrated in racemic form toward preparation of the cyclopentylpyrimidine ketone *(R)*-**3** in 8 linear steps and 39% overall yield from triester *rac*-**30**. The new strategy replaced[5a] the less practical first-generation scale-up route to *(R)*-**3** that commenced with (*R*)-(+)-pulegone and only enabled the production of hundred gram quantities of ketone *(R)*-**3** in ~2% overall yield. Two key route scouting approaches were investigated, and

the method based on dual-ring construction (**S2**) proved to be the most successful. In this approach, construction of the pyrimidine ring of DHP *rac*-**31** was accomplished in one step from triester *rac*-**30** in 87% yield. The DHP *rac*-**31** was then readily converted into the diester *rac*-**34** through five additional steps that culminated in a key Pd-catalyzed carbonylation reaction, which was used to install the aryl ester group necessary for the key intramolecular cyclization. In the main event, a telescoped Dieckmann cyclization / decarboxylation sequence of diester *rac*-**34** was used to forge the cyclopentanone ring system of *(R)*-**3** in 91% yield. A salient feature of this route is the ability to introduce chirality through an enzymatic resolution of the triester *rac*-**30**, and this approach is demonstrated in the kilogram synthesis of Ipatasertib in Part II of this series.

EXPERIMENTAL SECTION

Reagents and solvents were purchased from commercial sources and were used as received. ^{1}H and ^{13}C NMR spectra are reported in parts per million (δ) at 400 MHz and 100 MHz, respectively. In cases of ^{1}H NMR spectra where mixtures of compounds are present, the desired product is reported. In cases where weight percent assays were employed to determine product purity, corrected yields were reported. High resolution mass spectra (HRMS) were recorded by Dr. John Greaves at the University of California, Irvine.

Trimethyl 2-methylpropane-1,1,3-tricarboxylate, *rac*-30. A 12 L 4-neck round-bottom flask was charged with THF (3.5 L) followed by 25 wt% NaOMe/MeOH (128 mL, 562 mmol, 0.25 equiv). Dimethylmalonate (259 mL, 2.27 mol, 1.01 equiv) was then added to the cloudy agitated solution at 23 °C over 10 min, which was followed by the addition of *trans*-methyl crotonate (239 mL, 2.25 mol, 1.00 equiv) over 10 min. The resulting pale yellow reaction mixture was heated (45-50 °C) and agitated for 4 h. The reaction was determined to be complete by in-process analysis using ^{1}H NMR spectroscopy (<2% *trans*-methyl crotonate). The reaction was

cooled to ~2 °C (ice bath) over 1 h, after which a solution of AcOH (34.7 mL, 607 mmol, 0.27 equiv) in H_2O (347 mL) was charged over 15 min affording a cloudy, colorless solution. After agitation for 30 min, the reaction was then concentrated *via* rotovap, and the resulting residue was partitioned between EtOAc (2.0 L) and 0.5M aq. $NaHCO_3$ (1.2 L). The layers were separated, and the aqueous phase was extracted with EtOAc (400 mL). The combined organic layers were washed with saturated aq. NaCl (500 mL), dried ($MgSO_4$), filtered and concentrated *via* rotary evaporation to give triester *rac*-**30** as a colorless oil (0.50 kg, 2.17 mol, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) 3.74 (s, 3H), 3.74 (s, 3H), 3.69 (s, 3H), 3.46 (d, J = 7.2 Hz, 1H), 2.75 (m, 1H), 2.55 (1/2 ABX, J_{AB} = 16.0 Hz, 1H), 2.33 (1/2 ABX, J_{AB} = 15.8 Hz, 1H), 1.07 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.6, 169.0, 168.9, 56.0, 52.5 (2), 51.7, 38.5, 30.3, 17.7; HRMS (ESI^+) calculated for $C_{10}H_{16}ONa$ $[M + Na]^+$ (m/z) 255.0845; found (m/z) 255.0844.

Methyl 3-(4,6-dihydroxypyrimidin-5-yl)butanoate (DHP), *rac*-31. A 12 L 4-neck round-bottom flask was charged with MeOH (2.8 L), and the reaction headspace was purged with nitrogen using two evacuation/backfill cycles. The reaction was then charged with NaOMe (25 wt% in MeOH, 1.97 L, 8.61 mol, 4.00 equiv) at 23 °C using MeOH (250 mL) to complete the transfer, after which formamidine acetate (246.6 g, 2.37 mol, 1.10 equiv) was added in one portion. The resulting clear, homogeneous mixture was stirred for 20 min. A solution of *rac*-**30** (500.0 g, 2.15 mol, 1.00 equiv) in MeOH (500 mL) was then added over 5 min, using MeOH (200 mL) to complete the transfer. The intense yellow reaction was stirred at 25 ˚C for 18 h. At this time, the reaction was determined to be complete by in-process analysis using ^{1}H NMR spectroscopy (<2% *rac*-**30**) and was subsequently cooled to ~2 °C (ice bath), after which HCl (g) was bubbled through the mixture for approximately 1 h at a temperature not exceeding 10 °C. At this time pH 2.5 (litmus) had been achieved, and the reaction was warmed to 25 ˚C. The reaction

mixture was concentrated *via* distillation over a period of 7 h (35 °C at 200 Torr) until ~3.3 L of distillate had been collected. The resulting viscous tan slurry was suspended in toluene (3.75 L) and agitated for 30 min at 23 °C, after which the product was collected using a table-top filter device equipped with polypropylene cloth. Toluene (2 × 500 mL) was used to wash and transfer material, and the filter cake was dried under vacuum overnight and subsequently homogenized using a spatula. DHP *rac*-**31** (906.0 g, 43.8 w/w% via HPLC wt% assay, 87% yield) was isolated as a beige solid contaminated with inorganic salts (NaCl). Analysis was conducted on a sample of DHP *rac*-**31** purified through recrystallization in water. ^{1}H NMR (400 MHz, DMSO-d_6) 7.87 (s, 1H), 3.52 (s, 3H), 3.36 (m, 1H), 2.62 (ABX, J_{AB} = 15.0 Hz, 2H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 172.8, 163.8, 147.1, 105.1, 51.1, 37.8, 25.5, 17.6; HRMS (ESI$^+$) calculated for $C_9H_{12}N_2O_4Na$ $[M + Na]^+$ (m/z) 235.0688; found (m/z) 235.0695.

Methyl 3-(4,6-dichloropyrimidin-5-yl)butanoate, *rac*-32. A 3 L 4-neck round-bottom flask was charged with crude DHP *rac*-**31** (220.6 g, 44.3 w/w%, 471 mmol, 1.0 equiv) followed by CH_3CN (600 mL), resulting in a viscous slurry, and the reaction headspace was purged with nitrogen using two evacuation/backfill cycles. The slurry was agitated for ~10 min, after which 2,6-lutidine (54.9 mL, 471 mmol, 1.00 equiv) was added in one portion at 23 °C, leading to an immediate reduction in viscosity. The reaction was then heated to 70 °C, and $POCl_3$ (97.1 mL, 1.06 mol, 2.25 equiv) was added over 12 min. The reaction was further heated to 79 °C over 1 h and was agitated for an additional 18 h, after which the reaction was determined to be complete by in-process analysis using ^{1}H NMR spectroscopy (<2% *rac*-**31**, DMSO-d_6) and was cooled to 25 ˚C over 3 h. At this time, 6N NaOH (78.0 mL, 428 mmol, 1.1 equiv) was added to the mixture at a rate of 1-2 mL/min such that the temperature did not exceed 35 °C. The mixture was concentrated *via* distillation (30 °C at 85-100 Torr) until ~475 mL of distillate had been collected

and the rate of distillation had decreased significantly (1 drop/10 s). The concentration process required ~1.5 h and afforded a viscous solution, which continued to stir efficiently. The reaction was subsequently diluted with *i*PrOAc (1.0 L) followed by H_2O (750 mL), resulting in the dissolution of all solids. The phases were separated, and the organic phase was washed 0.5 M aq. $NaHCO_3$ (250 mL) followed by H_2O (100 mL). The organic phase was concentrated via rotovap affording dichloropyrimidine *rac*-**32** as a light orange oil, which was observed to slowly solidify upon standing. Crude *rac*-**32** was employed in the subsequent S_NAr step without further purification, and quantitative yield (117.4 g, 471 mmol) was assumed. ^{1}H NMR (400 MHz, $CDCl_3$) 8.63 (s, 1H), 4.15 (m, 1H), 3.65 (s, 3H), 3.07 (1/2 ABX, J_{AB} = 16.6 Hz, 1H), 2.86 (1/2 ABX, J_{AB} = 16.6 Hz, 1H), 1.45 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 155.7 (2), 135.1, 52.0, 37.7, 31.8, 17.2.

***Tert*-butyl 4-(6-chloro-5-(4-methoxy-4-oxobutan-2-yl)pyrimidin-4-yl)piperazine-1-carboxylate, *rac*-33**. A 3 L 4-neck round-bottom flask was charged with crude dichloropyrimidine *rac*-**32** (117.4 g, 471 mmol, 1.00 equiv) in MeOH (900 mL), followed by *N*-Boc-piperazine (96.5 g, 518 mmol, 1.10 equiv) and DIEA (90.3 mL, 518 mmol, 1.10 equiv), and the reaction headspace was subsequently purged with nitrogen using two evacuation/backfill cycles. The homogeneous orange mixture was then heated to 60 °C over 45 min and was agitated for an additional 12 h. At this time, the reaction was determined to be complete by in-process analysis using ^{1}H NMR spectroscopy (<2% *rac*-**32**) and was cooled to 30 °C over ~1 h. The mixture was concentrated *via* distillation (~25–30 °C at 80–100 Torr) until the rate of distillation had decreased significantly (1 drop/10 s), and ^{1}H NMR analysis indicated ~5–6 equiv. MeOH remaining in the reaction. The concentration process required ~2 h and afforded a viscous slurry, which was subsequently diluted with EtOAc (1.2 L) followed by 3M aq. NH_4Cl (250 mL),

resulting in the dissolution of all solids after vigorous stirring. The phases were separated, and the organic phase was washed with 3M NH_4Cl (250 mL). The organic phase was then concentrated via rotovap affording S_NAr product *rac*-**33** as a light orange oil, which was observed to slowly solidify upon standing. Crude *rac*-**33** was employed in the subsequent hydrolysis step without further purification, and quantitative yield (188.0 g, 471 mmol) was assumed. ^1H NMR (400 MHz, $CDCl_3$) 8.42 (s, 1H), 3.70-3.55 (m, 5H), 3.66 (s, 3H), 3.28 (m, 4H), 3.04 (1/2 ABX, J_{AB} = 16.2 Hz, 1H), 2.71 (1/2 ABX, J_{AB} = 16.2 Hz, 1H), 1.48 (s, 9H), 1.45 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 168.4, 160.0, 155.2, 154.9, 125.1, 80.3, 52.0, 50.4, 44.0, 38.7, 29.7, 28.6, 17.9; HRMS (ESI^+) calculated for $C_{18}H_{27}ClN_4O_4Na$ $[M + Na]^+$ (m/z) 421.1619; found (m/z) 421.1614.

3-(4-(4-(*Tert*-butoxycarbonyl)piperazin-1-yl)-6-chloropyrimidin-5-yl)butanoic acid, *rac*-25. A 3 L 4-neck round-bottom flask was charged with crude methyl ester *rac*-**33** (188.0 g, 471 mmol, 1.00 equiv) in THF (750 mL), followed by H_2O (250 mL) and LiOH-H_2O (59.3 g, 1.41 mol, 3 equiv). The slightly cloudy, light yellow reaction was stirred for 12 h, after which H_2O (50 mL) was added, and the reaction was agitated for an additional 24 h. At this time, the reaction was determined to be complete by in-process analysis using ^1H NMR spectroscopy (<2% *rac*-**33**), after which the mixture was concentrated *via* distillation (~30 °C at 185 Torr) until the rate of distillation had decreased significantly (1 drop/10 s). The concentration process required ~3 h and afforded a cloudy solution that was subsequently diluted with H_2O (700 mL). The mixture was then cooled to ~2 °C (ice bath), after which 2N aq. HCl (700 mL, 1.4 mol, 3 equiv) was added to the mixture over 3 h. The resulting white slurry (pH 3.5 by litmus) was subsequently warmed to 25 ˚C, after which the product was collected using a Buchner funnel. Additional H_2O (2 × 250 mL) was used to wash and transfer material, and the filter cake was

dried (0.1 Torr, 45 °C) for 60 h during which time the material was homogenized several times using a spatula. Carboxylic acid *rac*-**25** (146.3 g, 95.0 w/w% via HPLC wt% assay, 77% yield from DHP *rac*-**31**) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) 8.44 (s, 1H), 3.72-3.51 (m, 5H), 3.28 (m, 4H), 3.11 (1/2 ABX, J_{AB} = 16.6 Hz, 1H), 2.78 (1/2 ABX, J_{AB} = 16.6 Hz, 1H), 1.49 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.6, 168.4, 159.9, 155.1, 155.0, 125.1, 80.6, 50.3, 44.1, 38.7, 29.6, 28.6, 17.9; HRMS (ESI^+) calculated for $C_{17}H_{25}ClN_4O_4Na$ $[M + Na]^+$ (m/z) 407.1462; found (m/z) 407.1455.

***Tert*-butyl 4-(5-(4-(benzyloxy)-4-oxobutan-2-yl)-6-chloropyrimidin-4-yl)piperazine-1-carboxylate, *rac*-26**. To a solution of carboxylic acid *rac*-**25** (100.0 g, 246.8 mmol, 1.00 equiv) in DMF (600 mL) at 23 °C under a nitrogen atmosphere was added Cs_2CO_3 (84.45 g, 259.2 mmol, 1.05 equiv) followed by benzyl bromide (30.1 mL, 253 mmol, 1.02 equiv). The reaction was agitated for 18 h at 23 °C and was determined to be complete by in-process analysis using ^{1}H NMR spectroscopy (<2% *rac*-**25**). The reaction mixture was then filtered through a plug of celite (washed with EtOAc (200 mL)) to afford a tan solution. The filtrate was subsequently concentrated *via* rotovap to afford a viscous tan residue containing some precipitated salts. [CAUTION: Benzyl bromide is a strong lachrymator and is very irritating to the skin and mucous membranes (see MSDS)]. The residue was partitioned between EtOAc (600 mL) and water (500 mL), after which the aq. layer was extracted with EtOAc (100 mL), and the combined organic layers were washed with H_2O (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *via* rotovap to afford a tan oil, which was further dried under vacuum (0.1 Torr) for 18 h to give benzyl ester *rac*-**26** (119.8 g, 246.8 mmol, *quant*). The product was observed to slowly solidify upon standing. ^{1}H NMR (400 MHz, $CDCl_3$) 8.40 (s, 1H), 7.43-7.24 (m, 5H), 5.09 (s, 2H), 3.66 (m, 1H), 3.54 (m, 4H), 3.22 (m, 4H), 3.06 (1/2 ABX,

J_{AB} = 16.0 Hz, 1H), 2.78 (1/2 ABX, J_{AB} = 16.0 Hz, 1H), 1.49 (s, 9H), 1.45 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.0, 168.4, 160.1, 155.2, 154.9, 135.8, 128.8, 128.6, 128.5, 125.1, 80.3, 66.8, 50.4, 44.0, 39.0, 29.8, 28.6, 18.0; HRMS (ESI^+) calculated for $C_{24}H_{31}ClN_4O_4Na$ $[M + Na]^+$ (m/z) 497.1931; found (m/z) 497.1919.

Isopropyl 5-(4-(benzyloxy)-4-oxobutan-2-yl)-6-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)pyrimidine-4-carboxylate, *rac*-34. A 2 L 3-neck round-bottom flask was charged with benzyl ester *rac*-**26** (50.0 g, 105 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.36 g, 10.5 mmol, 0.10 equiv), dppp (4.78 g, 11.6 mmol, 0.11 equiv) and K_2CO_3 (325 mesh, 8.00 g, 57.9 mmol, 0.55 equiv). The flask was purged with nitrogen using three evacuation/backfill cycles and was then charged with (3:1) *i*PrOH-THF (600 mL) that had been previously degassed by sub-surface sparging with nitrogen for 1 h. The reaction was subsequently stirred for 20 min at 23 °C, which facilitated the dissolution of all solids, except for the K_2CO_3, resulting in a heterogeneous orange solution. The flask was then equipped with a CO source consisting of a double-wall thickness balloon (balloon inside of a balloon, Betallatex™, 11 in. inflated, 0.35 psi CO measured), and the reaction was purged with CO using three evacuation/backfill cycles. [CAUTION: Carbon monoxide is very toxic if inhaled, and a CO detector must be used when handling this gas. It also has a very low flash point (–191 °C) and is considered highly flammable! Refer to the MSDS]. The resulting mixture was stirred at 25 ˚C for 1 h, gradually becoming red in color, after which the reaction was heated to 55 °C and agitated for an additional 40 h. At this time, the reaction was determined to be complete by in-process analysis using ^{1}H NMR spectroscopy (<2% *rac*-**26**), and the temperature was reduced to 45 °C. In a sequence to destroy the catalyst, the CO source was initially removed, and hexanes (600 mL) was charged to the reaction. The resulting mixture was stirred under air atmosphere for 7 h, gradually becoming black in color, after which the reaction

was stirred while sparging with air for an additional 14 h. At this time, the reaction was cooled to 25 ˚C, and additional hexanes (1.2 L) was charged in order to compensate for solvent lost due to evaporation during the sparging process. The reaction was then filtered through a purification plug constructed in a 4 in. diameter fritted glass funnel using (1:1) hexanes-EtOAc (~50 mL) to wash and transfer material from the flask. The plug employed an initial layer of SiO_2 (4.0 in., pre-eluted with hexanes), which was followed by a layer of sand (0.5 in.) and a layer of celite (1.0 in.). Following the initial charge of solution, the plug was subsequently washed with (1:1) hexanes-EtOAc (4 × 400 mL). The dark yellow filtrate was partially concentrated to ~ 300 mL total volume, after which the solution was filtered using a Buchner funnel equipped with Whatman® GF/F paper in order to remove the remaining fine suspension of Pd-black. The filtrate was concentrated *via* rotovap, affording a crude beige solid (45.3 g, 82% crude yield).

A 1 L round-bottom flask was charged with a portion of the crude solid (35.0 g) followed by (15:1) heptane/MTBE (320 mL) at 23 °C under air atmosphere. The suspension was agitated vigorously for 16 h during which time some of the larger product chunks were necessarily homogenized using a spatula. Upon completion of the trituration, the product was collected via Buchner funnel using heptane (150 mL) to wash and transfer material. The product was dried under vacuum (0.1 Torr) for 45 min to give mixed diester *rac*-**34** as a gray solid (30.3 g, 57.5 mmol, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) 8.69 (s, 1H), 7.39-7.27 (m, 5H), 5.31 (sp, J = 6.2 Hz, 1H), 5.10 (s, 2H), 3.63 (m, 1H), 3.54 (m, 4H), 3.22 (m, 4H), 2.91 (1/2 ABX, J_{AB} = 16.4 Hz, 1H), 2.74 (1/2 ABX, J_{AB} = 16.2 Hz, 1H), 1.50 (s, 9H), 1.43 (d, J = 6.2 Hz, 3H), 1.41 (d, J = 6.4 Hz, 3H), 1.34 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.0, 167.8, 166.7, 158.2, 155.7, 154.9, 135.9, 128.8, 128.5, 128.4, 125.4, 80.2, 70.7, 66.6, 50.4, 44.0, 40.8, 29.1, 28.6, 21.8

(2), 19.8; HRMS (ESI^+) calculated for $C_{28}H_{38}N_4O_6Na$ $[M + Na]^+$ (m/z) 549.2689; found (m/z) 549.2690.

***Tert*-butyl 4-(5-methyl-7-oxo-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazine-1-carboxylate, *rac*-3**. A 1 L round-bottom flask was charged with *rac*-**34** (25.0 g, 47.5 mmol, 1.00 equiv), purged with nitrogen using three evacuation/backfill cycles, and then charged with THF (250 mL). The mixture was stirred at 25 ˚C until all solids were dissolved, and the solution was cooled to ~2 ºC (ice bath), after which KO*t*-Bu (1M in THF, 52.2 mL, 52.2 mmol, 1.10 equiv) was added over 5 min, affording a yellow mixture. The reaction was stirred 5 min at ~2 ºC, and was then subsequently warmed to 25 ˚C and stirred for an additional 10 min. At this time, conversion to keto-ester intermediate *rac*-**28** was determined to be complete by in-process analysis using HPLC (<1 A% *rac*-**34**).[37] The pH of the reaction was then adjusted via the addition of 3M aq. HCl solution (16.9 mL, 50.6 mmol, 1.06 equiv), resulting in pH 5.5 (litmus). The reaction was then charged with Pd/alumina (5 wt.%, powder, Aldrich) (1.01 g, 0.475 mmol, 0.01 equiv), after which the mixture was purged with nitrogen using three evacuation/backfill cycles. The reaction flask was then equipped with a hydrogen (H_2) source consisting of a double-wall thickness balloon (balloon inside of a balloon, Betallatex™,11 in. inflated, 0.35 psi H_2 measured). The reaction was then purged with H_2 using three evacuation/backfill cycles and was agitated vigorously for 3 h at 25 ˚C. At this time, the decarboxylation was determined to be complete by in-process analysis using HPLC (<1 A% *rac*-**28**) and the reaction was subsequently sparged with nitrogen (sub-surface) for 10 min in order to eliminate the hydrogen gas present. The mixture was subsequently filtered through a plug of celite (dry, tightly packed) to afford a dark yellow filtrate. Following the initial charge of solution, the plug was washed with THF (300 mL total). The filtrate was concentrated *via* rotovap, after which the residue was re-dissolved in

THF (75 mL) at 25 ˚C, and heptane (225 mL) was charged to the solution over 15 min resulting in precipitation of the product. The slurry was agitated for 18 h, after which the product was isolated via filtration. The product was washed with heptane (100 mL) and allowed to air-dry on the filter. Ketone *rac*-**3** was isolated as a tan solid (14.4 g, 43.2 mmol, 91% yield), with >99 A% purity via HPLC analysis. ^{1}H NMR (400 MHz, $CDCl_3$) 8.73 (s, 1H), 3.88 (m, 2H), 3.72-3.62 (m, 5H), 3.53 (m, 2H), 2.96 (1/2 ABX, J_{AB} = 19.6 Hz, 1H), 2.34 (1/2 ABX, J_{AB} = 19.6 Hz, 1H), 1.50 (s, 9H), 1.32 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 205.3, 161.4, 158.4, 157.5, 153.9, 136.9, 79.2, 45.3, 42.9, 30.7, 28.0, 19.9; HRMS (ESI^+) calculated for $C_{17}H_{24}N_4O_3Na$ $[M + Na]^+$ (m/z) 355.1746; found (m/z) 355.1752.

ASSOCIATED CONTENT

Supporting Information

Additional experimental procedures for the scale-up of the (*R*)-(+)-pulegone route to ketone (*R*)-**3** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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[5] (a) Remarchuk, T. St-Jean, F.; Carrera, D.; Savage, S.; Yajima, H.; Wong, B.; Babu, S.; Deese, A.; Stults, J.; Dong, M. W.; Askin, D.; Lane, J. W.; Spencer, K. L. *Org. Process Res. Dev*. **2014**, *18*, *following manuscript*. (b) Remarchuk, T.; Babu, S.; Stults, J.; Zanotti-Gerosa, A.; Roseblade, S.; Yang, S.; Huang, P.; Sha, C.; Wang, Y. *Org. Process Res. Dev*. **2014**, *18*, 135–141.

[6] Several suppliers of (*R*)-(+)-pulegone, ≥95% [CAS: 89-82-7] report availability on kilogram scale, see: http://www.chemexper.com.

[7] (a) For a review of natural products possessing the same chiral methyl-substituted cyclopentane unit that were derived from (*R*)-(+)-pulegone, see: Silva, L. F. Jr. *Tetrahedron* **2002**, *58*, 9137–9161. (b) Taber, D. F.; Bai, S.; Tian, W. *J. Org. Chem.* **2011**, *76*, 9733–9737.

[8] *Ozonolysis Applications in Drug Synthesis*. Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem Rev*. **2006**, *106*, 2990–3001.

[9] (a) Risatti, C.; Natalie, K. J.; Shi, Z.; Conlon, D. A. *Org. Process Res. Dev*. **2013**, *17*, 257–264. (b) Andreotti, D.; Miserazzi, E.; Nalin, A.; Pozzan, A.; Profeta, R.; Spada, S. *Tetrahedron Lett.* **2010**, *51*, 6526–6530.

[10] Compound *rac*-**4** (Scheme 3, R^1 = H) has been previously reported: Staudinger, H.; Ruzicka, L. *Helv. Chim. Acta*. **1924**, *7*, 377–390. For literature precedent regarding the synthesis and spectroscopic characterization of related compounds, see: Goldsmith, D. J.; Hartman, J. A. *J. Org. Chem*. **1964**, *29*, 3520–3523 and 3524–3527.

[11] The medicinal chemistry procedure for the Favorskii rearrangement in reference 4a was similar to that reported by: Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602–1606.

[12] The 5 kg of (*R*)-(+)-pulegone was supplied with >98 A% purity and had a specific optical rotation [α]20/D: +21.8° (Source: Anthem Biosciences Ltd.).

[13] For an example of the preparation of (*S*)-pulegone semicarbazone followed by crystallization and then regeneration of pure (*S*)-pulegone, see: Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380–381.

[14] (a) *The Favorskii Rearrangement of Pulegone dibromide.* Wolinsky, J.; Chan, D. *J. Org. Chem.* **1965**, *30*, 41–43. The Authors report conversion of (*R*)-(+)-pulegone to (*R*)-**6** in 67% yield as a mixture of isomers (26:74 *cis*/*trans*) after distillation.

[15] An alternative but less effective method examined for the olefin cleavage of (*R*)-**6** on 5 g and 50 g scale used $RuCl_3$ (3.5%), $NaIO_4$ (2 equiv) in CH_3CN/water (48 h, rt) and gave (*R*)-**7** in 35% and 14% isolated yield, respectively. For preparation of β-ketoester (*R*)-**7** *via* ozonolysis at –96 °C, see reference 11.

[16] (a) Nannini, M.; Sampath, D. PCT Int. Appl., 2012135753, 04 Oct 2012. (b) Hoeflich, K.; Merchant, M. PCT Int. Appl., 2012135750, 04 Oct 2012. (c) Lin, K.; Nannini, M.; Punnoose, E.; Sampath, D.; Wallin, J.; Patel, P. PCT Int. Appl., 2012135781, 04 Oct 2012.

[17] In gram scale experiments the direct condensation of β-ketoester (*R*)-**7** with formamidine acetate (1.5 equiv) in the presence of (a) NaOMe/MeOH (2 equiv), or (b) DBU in acetonitrile at reflux for 12 h resulted in an intractable mixture of products and hydroxypyrimidine (*R*)-**9** was not obtained.

[18] See supporting information.

[19] For a recent discussion of chlorination with $POCl_3$, see: Pesti, J. A.; LaPorte, T.; Thornton, J. E.; Spangler, L.; Buono, F.; Crispino, G.; Gibson, F.; Lobben, P.; Papaioannou, C. G. *Org. Process Res. Dev*. **2014**, *18*, 89–102 and references therein.

[20] Alternatively, using 2 equiv of $POCl_3$ in DCM (10 vol) and heating to reflux resulted in a lower yield of chloropyrimidine (*R*)-**10** (71% yield with 98.6 A% purity); See SI.

[21] For a recent discussion on the use of *m*-CPBA in the pilot plant, see: Zhang, X.; Hu, A.; Pan, C.; Zhao, Q.; Wang, X.; Lu, J. *Org. Process Res. Dev*. **2013**, *17*, 1591–1596.

[22] The mono-substituted pyrimidine *N*-oxide product (*R*)-**12** was the only product observed under these reaction conditions. For a study on the synthesis of pyrimidine *N*-oxides, see: Jovanovic, M. V. *Can. J. Chem.* **1984**, *62*, 1176–1180.

[23] Other methods examined to produce ketone (*R*)-**3** from (*R*)-**14** include (1) Swern oxidation (oxalyl chloride, Et_3N, DMSO in DCM); (2) SO_3/pyridine in DCM; (3) Dess-Martin periodinane (1.2 equiv); (4) MnO_2 (5.0 equiv) in DCM; (5) TEMPO (aqueous NaOCl, cat. KBR in DCM). Of these methods, the TEMPO-based protocol resulted in quantitative conversion to product; however, issues were experienced with the stability of ketone (*R*)-**3** in the reaction system.

[24] The benzyl enol ether derivative of *rac*-**4** (R^1 = Bn) was prepared from *rac*-**4** (R^1 = H): BnBr, Cs_2CO_3, DMF, 25 °C. Cyclopentene-ol *rac*-**16** (R^3 = H) was prepared from *rac*-**4** (R^1 = Bn): $NaBH_4$, $CeCl_3$-$7H_2O$, THF:EtOH, 0 °C to 25 °C. The benzyl ether derivative of *rac*-**16** (R^3 = Bn) was prepared from *rac*-**16** (R^3 = H): BnBr, Cs_2CO_3, DMF, 25 °C.

[25] Although extensive research was conducted toward enabling approach **S1**, we have limited our discussion to only the most promising studies. Alternative strategies and results will be published elsewhere.

[26] Schaefer, J. P.; Bloomfield, J. J. In *Organic Reactions*, Dauben, W. G., Ed.; Wiley: New York, 1967; Vol. 15.

[27] For preparation of the analogous triethyl oxalylglutarate (des-methyl) substrate, see: Yamashita, M. *J. Org. Chem.* **1958**, *23*, 835–837. We prepared triethyl oxalyl-methylgluatarate *rac*-**18** from commercially available 1-ethyl hydrogen 3-methylglutarate (Aurora Fine Chemicals, LLC) and diethyloxalate in 2 steps: (1) acylation via LDA (2.3 equiv), diethyloxalate

(1.10 equiv), DMPU (4.0 equiv), THF, –78 °C gave 89% yield of 5-ethoxy-4-(ethoxycarbonyl)-3-methyl-5-oxopentanoic acid; (2) esterification using EtI (1.2 equiv), Cs_2CO_3 (1.1 equiv), DMF, 25 °C resulted in 33% yield of *rac*-**18**.

[28] (a) Cason, J. In *Organic Syntheses*; Wiley: New York, 1958; 38, 52–54. (b) For a report of using an asymmetric Michael reaction to access (*R*)-**21**, see: Park, S.-Y.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 2815–2818. (c) See Part II of this series (reference 5a) for two additional methods to prepare triester (*R*)-**21**.

[29] (a) Albaneze-Walker, J; Bazaral, C.; Leavey, T.; Dormer, P. G.; Murray, J. A. *Org. Lett.* **2004**, *6*, 2097–2100. (b) Crettaz, R.; Waser, J.; Bessard, Y. *Org. Process Res. Dev*. **2001**, *5*, 572–574.

[30] The conversion of *rac*-**23** to *rac*-**20** did not proceed to completion under these unoptimized reaction conditions, and *rac*-**20** was isolated by flash chromatography.

[31] The structure of *rac*-**24** was confirmed by 2D NMR analysis (see Figures 1.17–1.19 of supporting information). Compound *rac*-**24** was observed to slowly oxidize under air atmosphere to form the proposed α-hydroxyketoester, which was supported by LCMS and 2D NMR analysis data acquired from a related derivative. Therefore, no efforts were made to purify *rac*-**24**, and investigations directed toward promoting decarboethoxylation to *rac*-**3** were conducted using crude material following an aqueous workup.

[32] (a) Krapcho, A. P. *Synthesis* **1982**, 805–822. (b) Krapcho, A. P. *Synthesis* **1982**, 893–914.

[33] Compound *rac*-**3** decomposed upon heating to 90 ˚C in DMSO.

[34] The *tert*-butyl and methyl derivatives of *rac*-**20** as well as the *p*-methoxy benzyl (PMB) derivative of *rac*-**34** (Scheme 7, *vide infra*) were also prepared and tested in the subsequent Dieckmann cyclization/decarboxylation reaction, but were not superior to the benzyl ester substrate.

[35] The poor yield for this unoptimized transformation was primarily attributed to the incomplete conversion of starting material *rac*-**26**, which was difficult to separate from product *rac*-**27** by chromatography, in addition to the generation of byproducts arising from exchange at the benzyl ester group with EtOH as observed by LCMS.

[36] The benzyl ketoester derivative *rac*-**28** was confirmed to exist as the enol tautomer through corroboration with data acquired for the corresponding chiral derivative (see the supporting information in reference 5a).

[37] The successful production of *rac*-**3** from *rac*-**28** was verified by ^{1}H NMR and LCMS analysis in the crude reaction mixture, and product was not formally isolated.

[38] The precipitation of NaCl in pyrimidine formation has been reported. See (a) Connolly, T. J.; Matchett, M.; Sarma, K. *Org. Process Res. Dev*. **2005**, *9*, 80–87. (b) Anderson, N. G.; Ary, T. D.; Berg, J. L.; Bernot, P. J.; Chan, Y. Y.; Chen, C.-K.; Davies, M. L.; DiMarco, J. D.; Dennis, R. D.; Deshpande, R. P.; Do, H. D.; Droghini, R.; Early, W. A.; Gougoutas, J. Z.; Grosso, J. A.; Harris, J. C.; Hass, O. W.; Jass, P. A.; Kim, D. H.; Kodersha, G. A.; Kotnis, A. S.; LaJeunesse, J.; Lust, D. A.; Madding, G. D.; Modi, S. P.; Moniot, J. L.; Nguyen, A.; Palaniswamy, V.; Phillipson, D. W.; Simpson, J. H.; Thoraval, D.; Thurston, D. A.; Tse, K.; Polomski, R. E.; Wedding, D. L.; Winter, W. J. *Org. Process Res. Dev.* **1997**, *1*, 300−310.

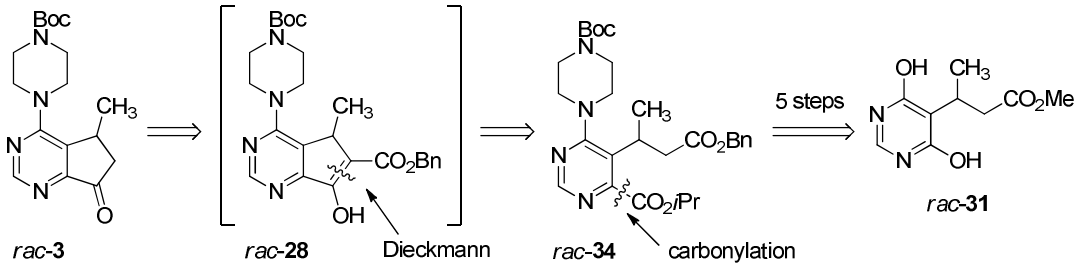
[39] See references 19 and 38b and references therein for a good discussion of the chlorination of pyrimidines using $POCl_3$.

[40] In addition to *i*-PrOH, other hindered alcohol solvents explored for the carbonylative esterification included *tert*-AmOH, *i*-BuOH and *n*-BuOH, all of which led to very poor conversion when used as the exclusive reaction medium.

[41] A variety of minor byproducts arising from solvent exchange with the benzyl ester group as well as displacement at the aryl chloride position through nucleophilic aromatic substitution were routinely observed, but none of these impurities exceeded 1% by ^{1}H NMR analysis.

[42] Residual palladium and/or phosphine ligand from the cabonylative esterification reaction resulted in poisoning of the benzyl ester hydrogenolysis, and removal of these impurities through purification of diester *rac*-**34** was determined to be critical to the performance of this transformation.

TOC Graphic


Boc
N
CH3
CO2Bn
OH
rac-3
rac-28
Dieckmann
CO2iPr
rac-34
carbonylation
5 steps
OH
CO2Me
rac-31
Process chemistry lead route
Medicinal chemistry scale-up route
4 steps
7 steps
(R)
O
(R)-3
(R)-11
(R)-(+)-
Pulegone