ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Full Paper

Decoration of an #-Resorcylate Nucleus as part of the Manufacture of a Glucokinase Activator

Phillip Hopes, Thomas Langer, Kirsty Millard, and Alan Steven

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.8b00175 • Publication Date (Web): 13 Jul 2018

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Decoration of an α-Resorcylate Nucleus as part of the Manufacture of a Glucokinase Activator

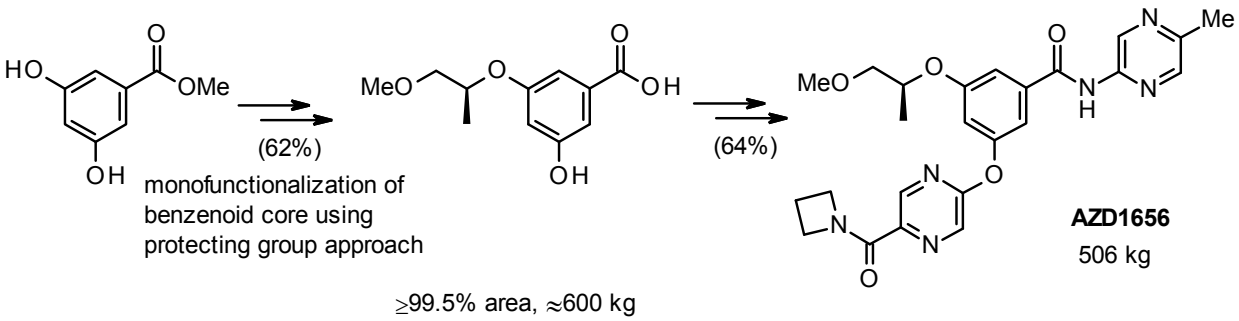
Phillip Hopes,[†] Thomas Langer,[‡] Kirsty Millard,[‡] and Alan Steven[*,‡]

[†] Cyton Biosciences Ltd, 68 Macrae Road, Bristol, BS20 0DD, United Kingdom

[‡] Pharmaceutical Technology & Development, AstraZeneca, Charter Way, Macclesfield, SK10 2NA, United Kingdom

Alan.Steven@astrazeneca.com

TOC graphic goes here



≥99.5% area, ≈600 kg

ABSTRACT

The need to define a set of processes for the manufacture of a glucokinase activator called for an evaluation of different strategies to differentiate the hydroxyls of an α-resorcylic acid derivative. Whilst direct functionalization proved possible, it did not allow access to crystalline intermediates that offered control over the rejection of process impurities. The strategy taken forward involved the installation of a benzoyl protecting group using careful control of pH in order to achieve useful levels of selectivity. This allowed the remaining α-resorcylate hydroxyl to be functionalized using a Mitsunobu reaction, with liquid-liquid partitioning being used to separate downstream intermediates of interest away from the redox byproducts of this reaction. Downstream challenges that were overcome in order to deliver a commercially viable means of manufacturing the API included developing an amidation reaction with a poorly reactive aminopyrazine coupling partner.

KEY WORDS

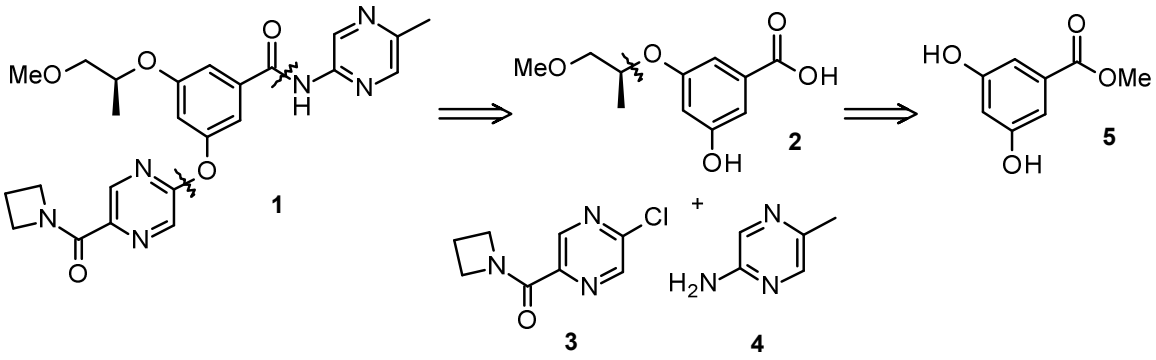
resorcylate, monobenzoylation, Mitsunobu, glucokinase activator, S_NAr, amidation

INTRODUCTION

AZD1656 (**1**), a compound containing two pyrazine units, has been under development by AstraZeneca as a glucokinase activator for the treatment of type 2 diabetes.[1-4] Investigations around synthetic route design for **AZD1656** (**1**) led to the decision to route via acid **2**, and to elaborate it to the API through couplings with chloropyrazine **3**[5] and aminopyrazine **4** (Scheme 1),[6] compounds whose development activities have been disclosed recently. Access to acid **2**, an α-resorcylate derivative bearing a side-chain with a stereogenic center, required a means of differentiating between the hydroxyl groups of methyl α-resorcylate (**5**), our starting material of choice. This article will discuss how this challenge was overcome, as part of a wider discussion around the selection of the synthetic route, the development

of manufacturable processes and learning gained from the commercial-scale manufacture of **AZD1656** (**1**).

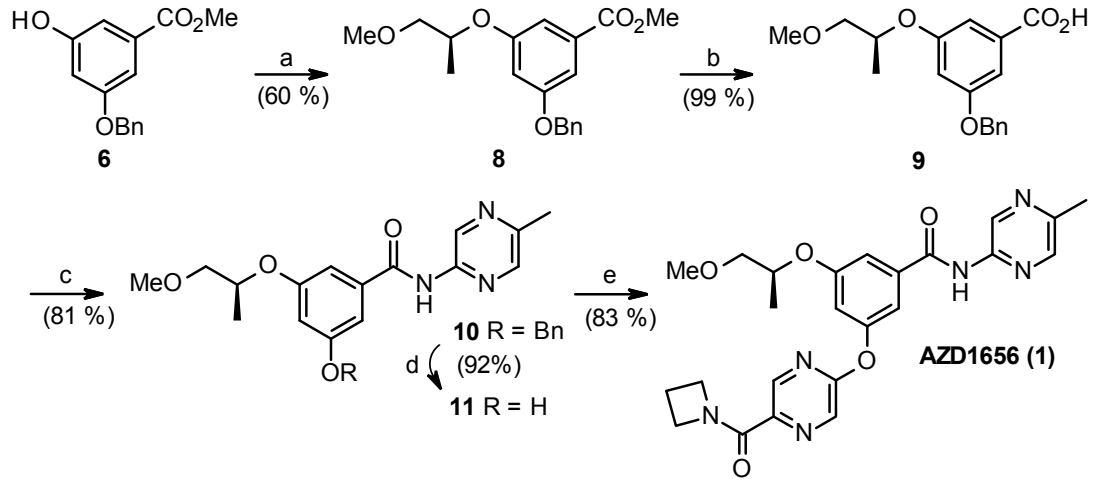
Scheme 1. Disconnections of **AZD1656** (**1**)



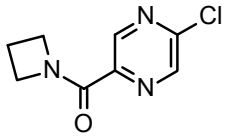
MEDICINAL CHEMISTRY APPROACH

The chemistry utilized in order to achieve the selection of a candidate drug by the project is outlined in Scheme 2. It differentiated the hydroxyl groups of the α-resorcylate core by dibenzylating methyl α-resorcylate (**5**) before hydrogenolyzing this material using exactly one equivalent of hydrogen gas. This protocol produced ether **6** contaminated by methyl α-resorcylate (**5)** and residual dibenzylated material, both of which were removed by chromatographic purification. The chiral side-chain was incorporated by engaging phenol **6** in a Mitsunobu etherification with (*R*)-1-methoxypropan-2-ol (**7**) so as to afford ether **8**. The API was duly accessed, after the required protecting group removals, through the sequential appendage of aminopyrazine **4** to acid **9** so as to afford amide **10**, and chloropyrazine **3** to phenol **11**. As well as being step-heavy, a consequence of the use of protecting groups to differentiate between the α-resorcylate hydroxyls, the intermediates associated with the medicinal chemistry route included a number of oils and low-melting solids whose purification required chromatography.

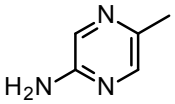
Scheme 2 Medicinal Chemistry Approach to **AZD1656** (**1**)



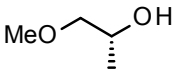
a) **7**, PPh_3, DIAD, THF; b) 2 M NaOH, MeOH; c) $(COCl)_2$, DMF, CH_2Cl_2 then **4**, C_5H_5N, 0 °C to RT; d) H_2, 10 %wt/wt, Pd-C, ethanol, THF; e) **3**, Cs_2CO_3, MeCN, 120 °C (microwave)



3



4



7

SYNTHESIS STRATEGY

When the project entered development, the retention of the α-resorcylate core, two pyrazines and a chiral side-chain as the building blocks of the synthesis was appealing. The use of acid **12** (Figure 1) as the synthetic precursor to the API held attraction on the grounds that it was known to be a highly crystalline material whose isolation could be used as a late-stage control point. Regardless, in the spirit of building up knowledge around alternative route options in early chemical development, exploratory studies that involved the early introduction of aminopyrazine **4** were undertaken. Its amidation with an α-resorcylate unit with at least one unprotected hydroxyl quickly floundered. The activated carbonyl functionality of the α-resorcylate preferred to react with another such unit to form ester impurities, rather than with the poorly nucleophilic amine of aminopyrazine **4**.

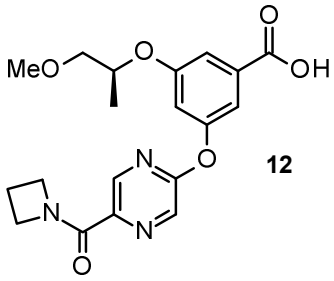
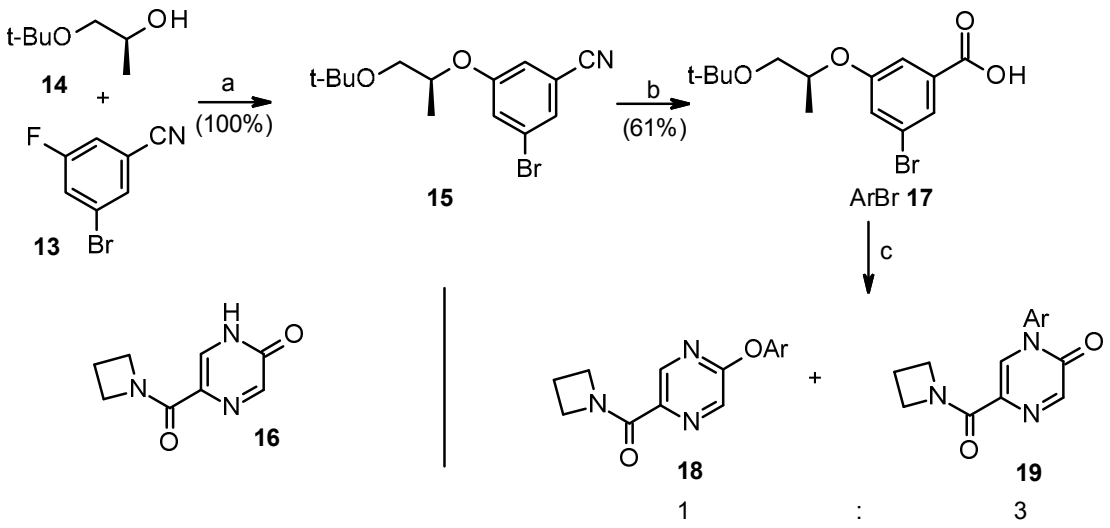


Figure 1 Synthetic precursor to API

INITIAL α-RESORCYLATE FUNCTIONALIZATION STUDIES

Given the intent to use the amidation of aminopyrazine **4** with acid **12** for the API bond-forming step, efforts turned to the identification of an efficient synthesis of the latter. The use of a 3,5-dihalobenzonitrile starting material, as an alternative to methyl α-resorcylate (**5**), was briefly considered. Successive nucleophilic displacements on a compound such as **13** should differ greatly in their respective rates, allowing the 3- and 5- positions to be successfully differentiated. This approach was tested on material that was associated with a structurally-related drug candidate, alcohol **14** (Scheme 3).[7] Whilst the initial S_NAr to give ether **15** was successful, the attempted union of pyrazinone **16** and aryl bromide **17** afforded a mixture of ethers **18** and **19** in which the ambidentate nucleophile had preferentially reacted through nitrogen, rather than the pyrazinone oxygen atom.

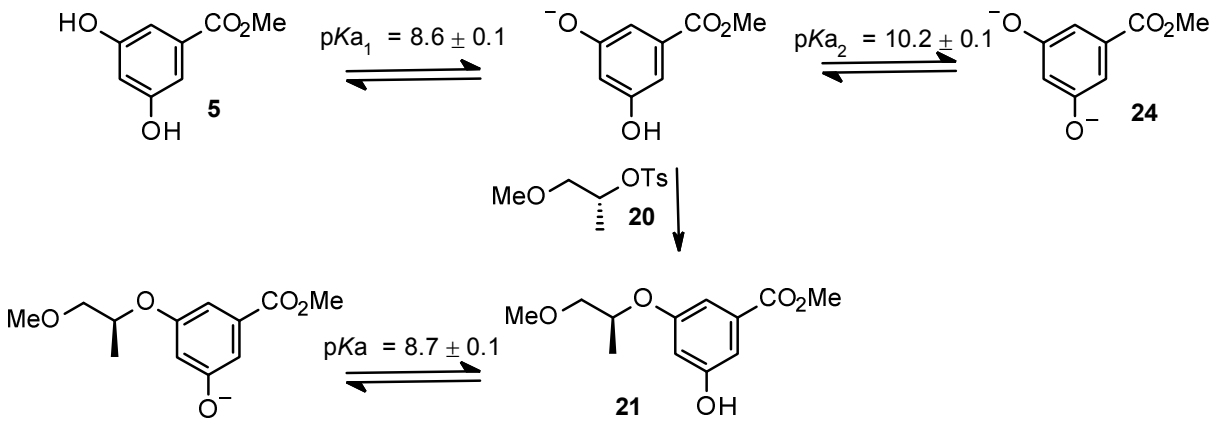
Scheme 3 Attempted derivatization of a 3,5-dihalobenzonitrile **13**



a) NaHMDS, DMF, 23 ◦C; b) NaOH (aq.), EtOH, Δ then HCl (aq.); c) **16**, Cs_2CO_3, CuI, 2,2,6,6-tetramethylheptane-3,5-dione, NMP, 125 ◦C then HCl (aq.)

Attention returned to methyl α-resorcylate (**5**) as a starting material and the search for a selective monoalkylation that would allow the chiral side-chain to be introduced.[8-9] In spite of the screening of different bases and solvents, alkylations with tosylate **20** (prepared from alcohol **7**[3a,10]) suffered from poor conversions or selectivity (monoalkylation vs bisalkylation).[11] The same problem was observed with an assessment of a Mitsunobu etherification option. The propensity for a monoalkylated derivative like ether **21** to react again, before all of the methyl α-resorcylate (**5**) has been consumed may be explained by the similarity in the pK_a values of the latter and ether **21** (Scheme 4).

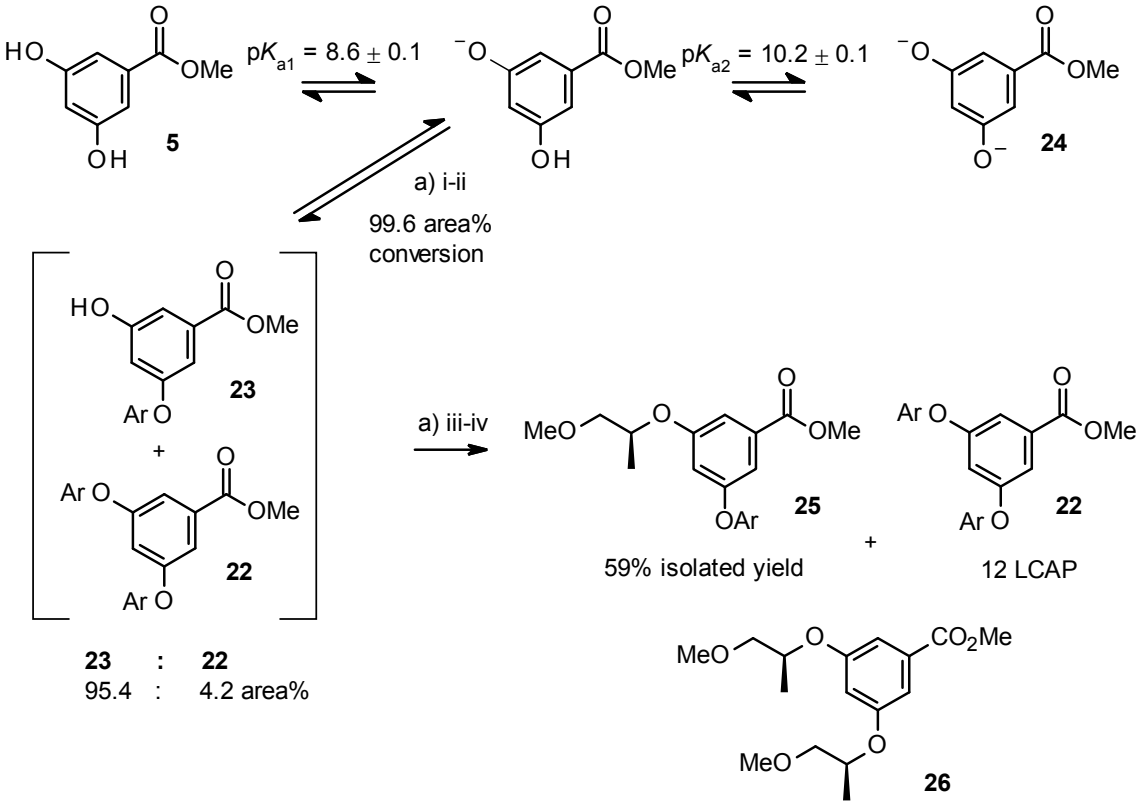
Scheme 4 Calculated pK_a values (aqueous, T=25 °C, zero ionic strength)[12] relevant to monoalkylation approach



A monoarylation approach was studied in parallel with the alkylation studies described above, and started with the use of potassium carbonate as base and chloropyrazine **3** as electrophile. In addition to the risk of overarylation to form bisether **22** (Scheme 5), in an analogous fashion to that described above, these efforts were soon found to be complicated by the ability of the newly-installed pyrazine of ether **23** to intermolecularly migrate under the basic conditions of the reaction. This led to the regeneration of a quantity of bisether **22** (now via a mechanism distinct from overreaction) and methyl α-resorcylate (**5**).[3c] Gratifyingly, prestirring the methyl α-resorcylate (**5**) with excess carbonate base, prior to the addition of the electrophile led to useful selectivities, by allowing access to the more basic (and presumably more nucleophilic) α-resorcylate dianion **24** (Scheme 5). After some optimization which included switching to the use of cesium carbonate as base, the dosed addition of a slight subcess (0.97 molar equivalents) of chloropyrazine **3** to a solution of methyl α-resorcylate (**5**) in dimethyl sulfoxide led to a useful level of selectivity for ether **23** versus bisether **22** (Scheme 5). The intention was then to alkylate the remaining α-resorcylate hydroxyl through a Williamson etherification with tosylate **20**, so as to form ether **25**. The screening of solvents, carbonate bases and strong organic bases led to the selection of the use of cesium carbonate in DMSO for the etherification. A drawback of the telescoped use of these basic conditions was disruption of the equilibrium shown in Scheme 5, resulting in scrambling of the recently installed pyrazine moiety. This migration led to an increase in the amount

of bisether **22** in the mixture (to 12% area by HPLC (LCAP)). The migration also liberated methyl α-resorcylate (**5**), opening the door to the formation of another bisether **26**.[13]

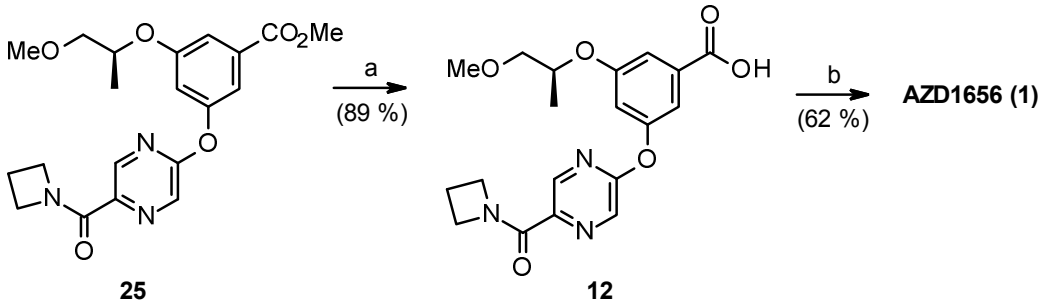
Scheme 5 Derivatization of methyl α-resorcylate (**5**) using an initial monoarylation.



a) i) Cs_2CO_3 (2.5 eq.), DMSO, 50 °C, ii) **3** (0.97 eq.), dosed addition, iii) **20**, 80 °C, iv) chromatography

Even when pure, ether **25** was an oil preventing its purification through crystallization. After it had been chromatographically purified from the mixture of compounds shown in Scheme 5, ether **25** was successfully hydrolyzed to acid **12**, using careful control of the reaction temperature and time to minimize hydrolysis of the base-labile azetidine amide and pyrazine-ether bonds. The sequences shown in Schemes 5 and 6 were leveraged in order to deliver 3.4 kg of **AZD1656** (**1**).

Scheme 6 Completion of the first development delivery of **AZD1656** (**1**)



a) i) NaOH (aq), NMP, –10 °C, ii) AcOH (aq); b) **4**, T3P, *N*-methylmorpholine, 2-MeTHF, reflux

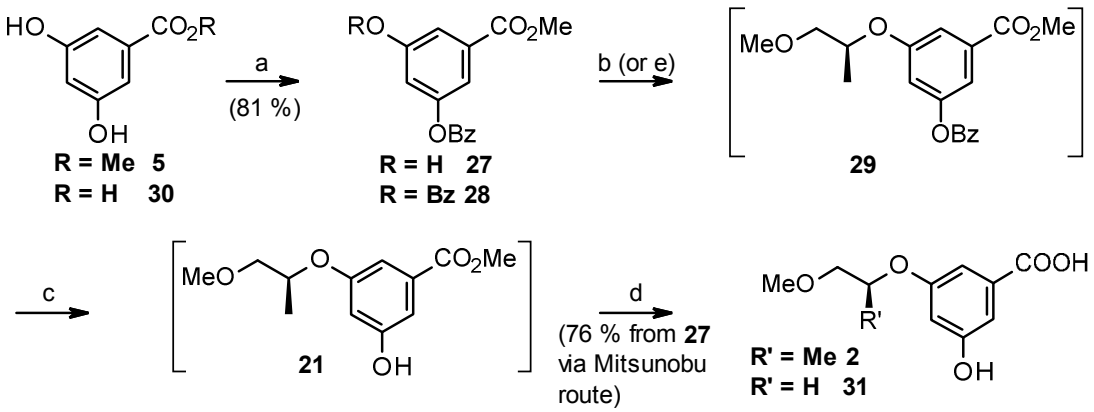
LATER α-RESORCYLATE FUNCTIONALIZATION STUDIES

The attractiveness of compound **25** as an intermediate for the commercial route used to supply **AZD1656** (**1**) was diminished by its being an oil. Thus, our investigation of competing route options was restarted and focused on the identification of possible crystalline intermediates. The α-resorcylate studies detailed above were already known to generate materials that were mostly oils and so attention turned to the generation of a crystalline material through the monoprotection of methyl α-resorcylate (**5**). Such a material would be primed for the introduction of the chiral side-chain through alkylation before deprotection steps would reveal acid **2** (Scheme 1), a solid that was known to be isolable in spite of its modest melting point (42 °C). Whilst a synthetic strategy which uses protecting groups has inherent inefficiencies associated with it, it was hoped these could be mitigated by using a group that could be removed alongside the hydrolysis of the methyl ester functionality of the α-resorcylate ring.

These considerations led to the targeting of the monobenzoylation of methyl α-resorcylate (**5**),[9,14] a known transformation and one that was reported to generate a solid product,[15] ester **27** (Scheme 7), whose crystallization could further enhance the impurity control strategy for the API. Gratifyingly, the transformation was successful in our hands. The insolubility of ester **27** in the aqueous reaction medium was no doubt responsible for the limited levels of the bisbenzoyl byproduct **28** observed. Maintaining

the pH within a range of 7.8–8.2 was found to be critical. This was initially achieved by codosing benzoyl chloride with a separate addition of sodium hydroxide buffered with sodium dihydrogenphosphate, and restricted bisbenzoylation to ca. 6 LCAP. The use of aqueous solutions of lithium hydroxide or potassium carbonate offered improvements, and their use in combination produced a superior result still. Buffering with this mixture allowed ester **27** to be isolated with levels of methyl α-resorcylate (**5**) and the overreaction product **28** that were both below 2 LCAP.

Scheme 7 Synthesis of acid **2** using a benzoyl protecting group strategy



a) BzCl, PhMe, LiOH (aq), K_2CO_3 (aq); b) (*R*)-1-methoxypropan-2-ol (**7**), PPh_3, DIAD, PhMe, 0 °C; c) NaOMe, MeOH; d) KOH (aq); e) **20**, Cs_2CO_3, DMSO

With the α-resorcylate 3- and 5-substituents successfully differentiated, through either monoarylation or monobenzoylation, there was now the need to etherify the remaining hydroxyl with the chiral side-chain. Whilst the retention of the Williamson ether synthesis remained an option, drawbacks included the relative expense of cesium carbonate, concerns over its suspension given its high density, and the negative impact on process mass intensity and throughput of washing out DMSO using multiple water washes. Further caveats included its use of a potential genotoxic impurity, in the form of tosylate **20**, albeit one whose downstream purging meant that it did not affect the API quality, and benzoyl group migration under the basic conditions of the reaction. Attention thus returned to the consideration of a Mitsunobu reaction as a possible means of installing the side-chain. This reaction has found limited

uses in large-scale production due to the challenge of separating the reaction product from its redox byproducts, a phosphine oxide and dialkyl azodicarboxylate.[16-21] In our case, we were attracted by the option of telescoping the product of the etherification into a step that would remove the benzoyl protecting group. In unveiling the α-resorcylate hydroxyl, it was hoped that liquid-liquid partitioning could then be used to draw it into an alkaline phase, away from the Mitsunobu byproducts.

After some experimentation with the solvent and the order of addition of the reagents, it was found the addition of diisopropyl azodicarboxylate to a toluene solution of the other components led to the rapid and clean conversion of phenol **27** to ether **29** (Scheme 7). The reaction proved to be a faster and higher-yielding than the Williamson etherification conditions against which it was being compared (reaction condition *e* in Scheme 7), and proceeded without any scrambling of the benzoyl group. DSC analysis showed there were no thermal stability issues with any of the process or waste streams associated with the Mitsunobu reaction.[22]

Using a benzoyl protecting group to access acid **2** potentially posed the challenge of cleanly separating benzoic acid from the compounds of interest arising from the removal of the two ester groupings of compound **29** using aqueous base. With this in mind, a transesterification approach was instead targeted for the debenzoylation. Gratifyingly, the addition of methanolic sodium methoxide, once the redox byproducts of the Mitsunobu reaction had been filtered off, smoothly converted ester **29** to phenol **21** (Scheme 7). Curiously, any lingering compound **28**, an impurity which would reform α-resorcylic acid (**30**) on downstream processing, transesterified at a slower rate than ester **29**. Thus, once the transesterification was complete, careful extraction with dilute (0.25 M) potassium hydroxide solution left the methyl esters of the α-resorcylate components intact, allowing the potassium salt of phenol **21** to be partitioned away from compound **28**, together with the methyl benzoate coproduct of the transesterification, residual organic-soluble redox byproducts from the Mitsunobu reaction, and bisether **26**, a compound which arose from the reaction of the residual methyl α-resorcylate (**5**) in phenol **27**.

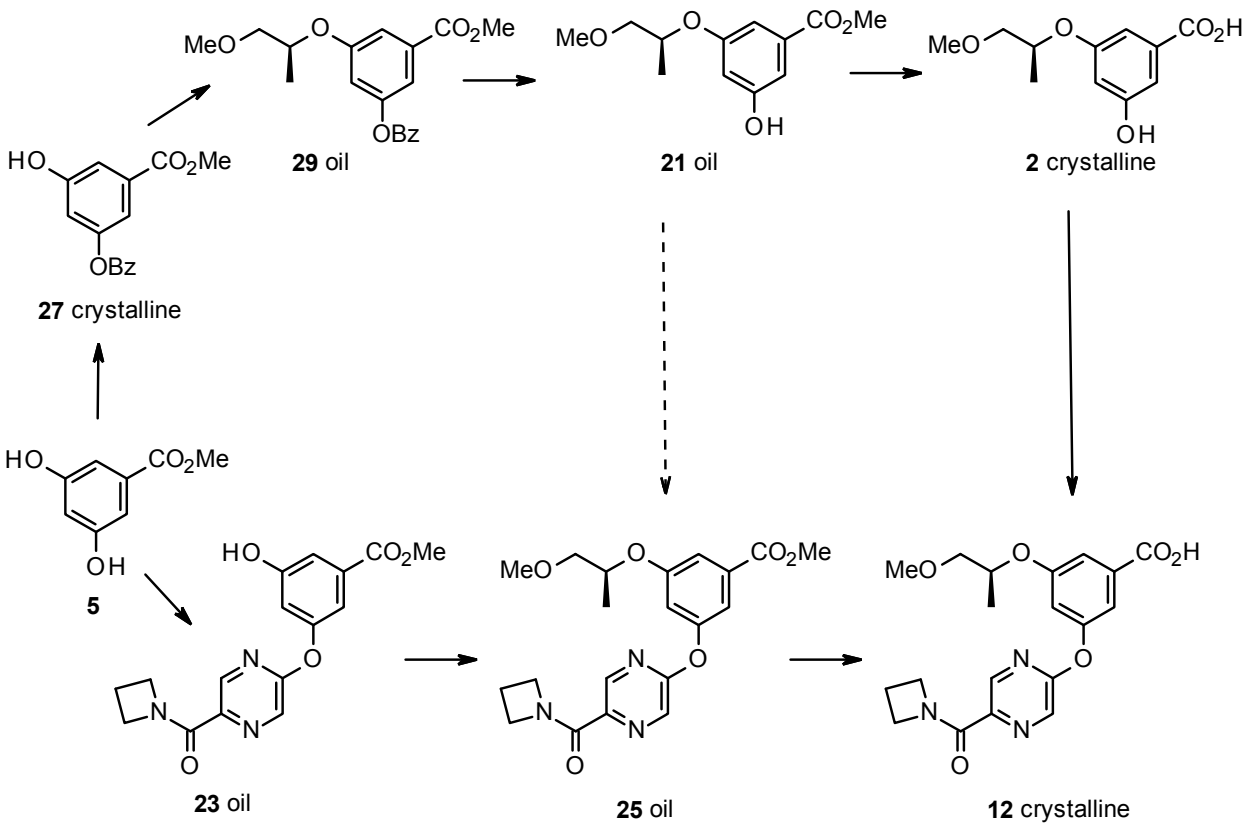
The addition of more potassium hydroxide basified the phase containing the phenol **21**, allowing the hydrolysis of its methyl ester so as to give acid **2** (Scheme 7). Trace levels of upstream impurities were still present alongside acid **2**, though they could be purged by pH-controlled liquid-liquid extractions, ahead of the crystallization of **2**. Thus, after a pH adjustment to 9.5–10.0, washing the aqueous phase with *tert*-butyl methyl ether removed any residual triphenylphosphine oxide and diisopropyl azodicarboxylate. After further acidification to pH 1.3–1.5, the extraction of acid **2** with *tert*-butyl methyl ether reduced accompanying levels of α-resorcylic acid **30** (arising from the presence of compound **28** in ester **29**) to ≤0.2 LCAP.

The coupling of acid **2** and chloropyrazine **3** was assessed using a variety of solvents and bases. The reaction proved high-yielding using cesium carbonate in DMSO. Whilst this combination of materials brought with it the drawbacks outlined above for the Williamson etherification, we were confident that these could be overcome with future process design studies. Consequently, the route that had been initiated with the monobenzoylation of methyl α-resorcylate (**5**) had yielded a means of accessing acid **12**, the precursor to the API.

ROUTE SELECTION

The existence of both the monobenzoylation approach and that which was initiated by the monoarylation of methyl α-resorcylate (**5**) meant one option had to be discarded prior to initiating development for commercial-scale production of the API. The route options are outlined in Scheme 8. In spite of the monobenzoylation approach involving two more transformations (5) than the monoarylation option that routed via ether **23**, the selection of the former was straightforward. The monobenzoylation approach featured a crystalline precursor (acid **2**) to acid **12**, high-yielding transformations, the ability to partition away related substances and reaction byproducts through liquid-liquid extractions and the opportunity to telescope the steps associated with the conversion of ester **27** to acid **2**.

Scheme 8 Summary of approaches to acid **2**



Whilst the monoarylation approach featured fewer chemical transformations than the monobenzoylation approach, this came at the expense of routing via oils. Another consideration was that the hydrolysis of the ester functionality of compound **25**, so as to afford acid **12**, was still going to be challenging to achieve whilst avoiding significant levels of hydrolysis of the azetidine amide and $C_{pyrazine}$–O bonds. This also ruled out converting compound **21** of the monobenzoylation approach to acid **12** via ether **25** (dotted arrow in Scheme 8).

SCALEUP OF MANUFACTURE OF ACID 2

Not unexpectedly, given the presence of multiple phases, and the potential for bisbenzoylation, the successful scaleup of the monobenzoylation reaction was envisaged as being challenging.[23] Indeed, initial pilot plant batches produced ester **27** with up to 20 LCAP of overreaction product **28**. This was

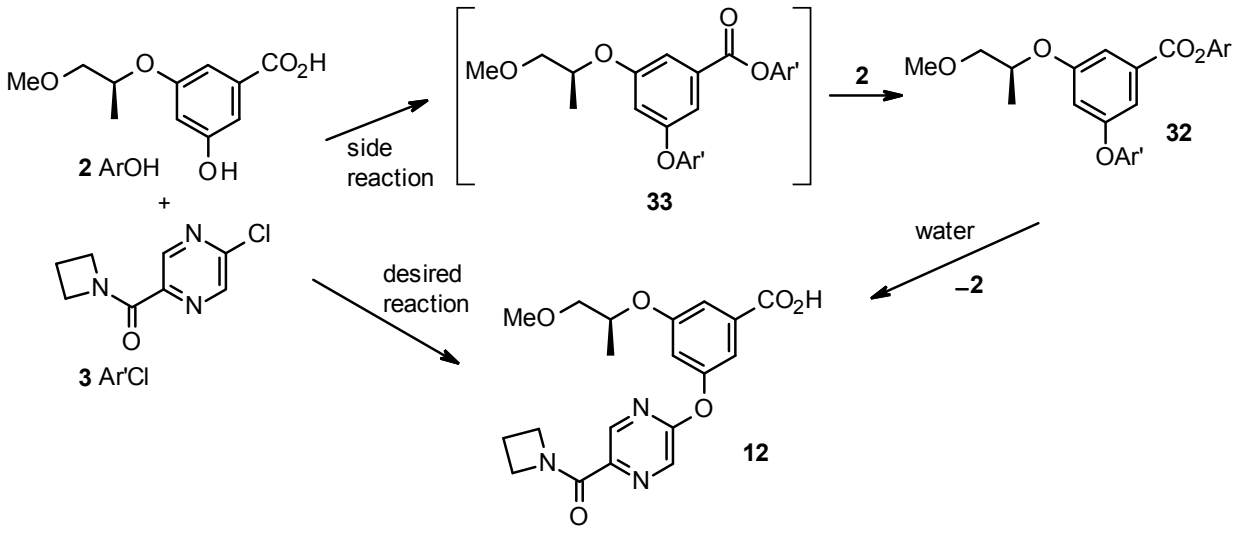
partly attributed to pH measurements used to control the reagent additions, not aligning with the local pH at the site of the reaction. After assessing different locations of the reactor pH probe in an attempt to achieve a correlation with at line measurements, the attachment of the pH probe to the reactor's sampling device was selected and used to control the rate of reagent addition. Dosing the benzoyl chloride as a solution in toluene was found to attenuate its background hydrolysis to benzoic acid and to make the control of pH easier. This had to be balanced against the increasing tendency of ester **27** to coalesce from fine particles into a thick, unstirrable mixture as the amount of toluene used was increased. A path forward was achieved by limiting the amount of toluene (54% wt/wt) used to dilute the benzoyl chloride and the length of time after the end of the addition before the product was filtered off. With these modifications in place, a normalized conversion of methyl α-resorcylate (**5**) to ester **27** of 96 LCAP could be typically achieved whilst restricting the amount of overreaction product **28** to about 2 LCAP. Prolonged vacuum drying failed to reduce the water content of the initially isolated ester **27** below ~0.5% wt/wt. This level required better control to ensure ester **27** was reproducibly consumed in the ensuing Mitsunobu reaction, thus limiting the amount of α-resorcylic acid equivalent that could potentially track through the rest of the synthesis. This control was achieved and the purity improved by treating a solution of the initially isolated ester **27** with powdered cellulose before it was crystallized from a mixture of toluene and isopropyl acetate. In this way, 1.02 metric tons of ester **27** with a water content of <0.1% wt/wt were manufactured over four batches, and in an overall yield of 81%. At the end of the Mitsunobu reaction, the addition of 0.07% mol/mol seed induced the crystallization of 75% of the theoretical amount of both triphenylphosphine oxide and diisopropyl hydrazine-1,2-dicarboxylate as a readily filtered complex (1:1 mol/mol). The further elaboration of the toluene solution of ether **29** proved straightforward, using the chemistry shown in Scheme 7. In this way, 619 kg of acid **2** were made with an α-resorcylic acid (**30**) content of only 0.1 LCAP and in an overall yield of 62% from methyl α-resorcylate (**5**). The purity across four batches was 99.5–99.7 LCAP with the largest impurity

(ca. 0.20 LCAP) being the analog **31** arising from the presence of 2-methoxyethanol in the (*R*)-1-methoxy-2-propanol (**7**) starting material (Scheme 7). Despite its reputation of generating a lot of waste, it should be noted that, in spite of development efforts, the sequence that utilized a Williamson etherification (reaction condition *e* in Scheme 7) had a much less favourable process mass intensity (207.4 kg/(kg **2**)) at the point where it was supplanted by the Mitsunobu route (69.6 kg/(kg **2**)).

S_NAr REACTION DEVELOPMENT

A large amount of process development was performed on the stages associated with the conversion of methyl α-resorcylate (**5**) to acid **2** in the period leading up to route selection. By contrast, the development of the conversion of acid **2** to **AZD1656** (**1**) had been developed only enough to derisk the continual manufacture of clinical supplies. With the route selected, there was the opportunity to consider more wide-ranging improvements to these latter stages. The assessment of 325 mesh potassium carbonate as a cheaper and more easily suspended alternative to the cesium carbonate used to date was initially characterized by excessive reaction times. This was addressed through the addition of 1 relative volume of water which presumably helped to solubilize the base (Scheme 9). More basic systems, accessed by adding more water or replacing too much of the potassium carbonate charge with potassium hydroxide liquor, gave rise to byproducts arising from the hydrolysis (not shown) of the amide or $C_{pyrazine}$–O bonds of ether **12**. As with all heterogeneous reactions, there was the risk of the offline analysis of the reaction being performed with a sample that was not representative of the whole batch. With this in mind, a model based on in-line Raman data was built to allow the conversion of acid **2** to ether **12** to be followed during production.[24] A small amount (0.1-0.2 LCAP) of impurity **32** always formed in the reaction, presumably through the intermediacy of an activated carbonyl species **33** (Scheme 9). Impurity **32** could be conveniently degraded to acid **12** by adding more water at the end of the reaction to basify the system.

Scheme 9 Transformations associated with S_NAr reaction



Conditions: DMSO-water (6:1, v/v), K_2CO_3, 57 ◦C then water

The acidification of the batch at the reaction close with dilute aqueous hydrochloric acid resulted in the uncontrolled precipitation of acid **12**. After gathering solubility data for this material as a function of temperature and solvent (DMSO-water mixtures), a final solvent composition of 56% v/v dimethyl sulfoxide was targeted. This was achieved by acidifying with hydrochloric acid, whilst taking care to ensure the final pH was above 2.5 so as to avoid the acid-mediated degradation of acid **12**. The potassium chloride generated by the neutralization of the potassium carbonate base was screened off in order to control the sulfated ash content of the product. After subsequent cooling and seeding, a slurry of acid **12** formed which filtered rapidly and gave low losses to liquors (1.8% yield loss). After drying, the material isolated contained low amounts of dimethyl sulfoxide (<0.05% wt/wt), inorganics (0.35% wt/wt), water (0.16% wt/wt) and related substances (0.56 LCAP). Despite the volumetric efficiency of this processing option, to date there has not been the opportunity to test it in anything other than a laboratory setting. Instead, as part of plant manufactures, the acid **12** content of the slurry arising from the acidification of the batch was dissolved in warm isopropyl acetate by way of liquid-liquid extractions. A water wash rid the extracts of adventitiously extracted dimethyl sulfoxide before

azeodrying and cooling crystallized acid **12** that was readily filtered, washed and dried. This protocol allowed 742 kg of acid **12** to be produced in an overall yield of 93%.

AMIDATION

The elaboration of acid **12** to **AZD1656** (**1**) requires its union with aminopyrazine **4**. The poor nucleophilicity displayed by aminopyrazine **4** led to limited success when a slew of different amidation conditions were screened. Whilst conversions were in general aided by increasing the reaction temperature, this was often at the expense of competing S_NAr reactions at the pyrazine rings of **AZD1656** (Figure 2).[25] Activating acid **12** as an acid chloride generated hydrogen chloride which, without scavenging, was found to open the azetidine ring so as to form alkyl chloride **34** as a byproduct (Figure 2). The limited delocalization of the azetidine nitrogen lone pair into the amide carbonyl can be used to rationalize the comparative basicity of the azetidine nitrogen and hence the susceptibility of the azetidine amide towards this side-reaction. It is notable that this ring-opening of azetidine amides has found preparative use.[26]

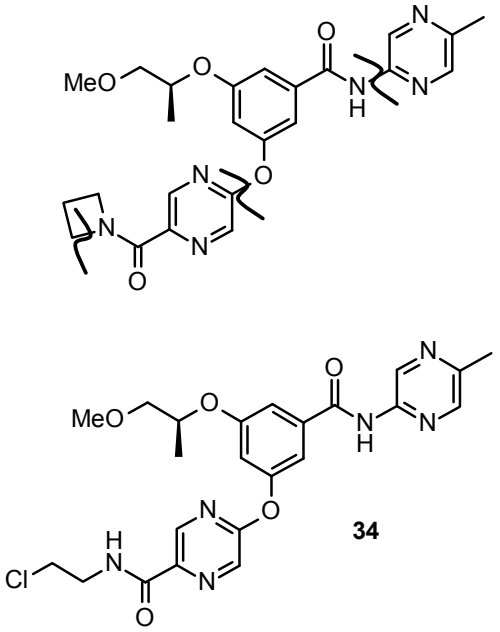


Figure 2 Sites of side reactions when screening conditions for conversion of acid **12** to **AZD1656** (**1**) and structure of alkyl chloride **34**

A successful reagent combination used *n*-propylphosphonic anhydride (T3P) and *N*-methylmorpholine in 2-methyltetrahydrofuran. Whilst this enabled early development deliveries of **AZD1656** (**1**) (Scheme 6), the continued use of T3P posed a number of drawbacks. These included the need and expense associated with the use of a ~70% mol/mol excess of the reagent to completely consume acid **12**.[27] As a listed chemical weapons precursor,[28] the storage, use and disposal of T3P needs to be fully documented, whilst the *n*-propylphosphonic acid waste generated by its use requires treatment prior to discharge into watercourses. Finally, impurities formed in a process using T3P retarded the rate of crystallization of the desired polymorph (vide infra), necessitating its later recrystallization.

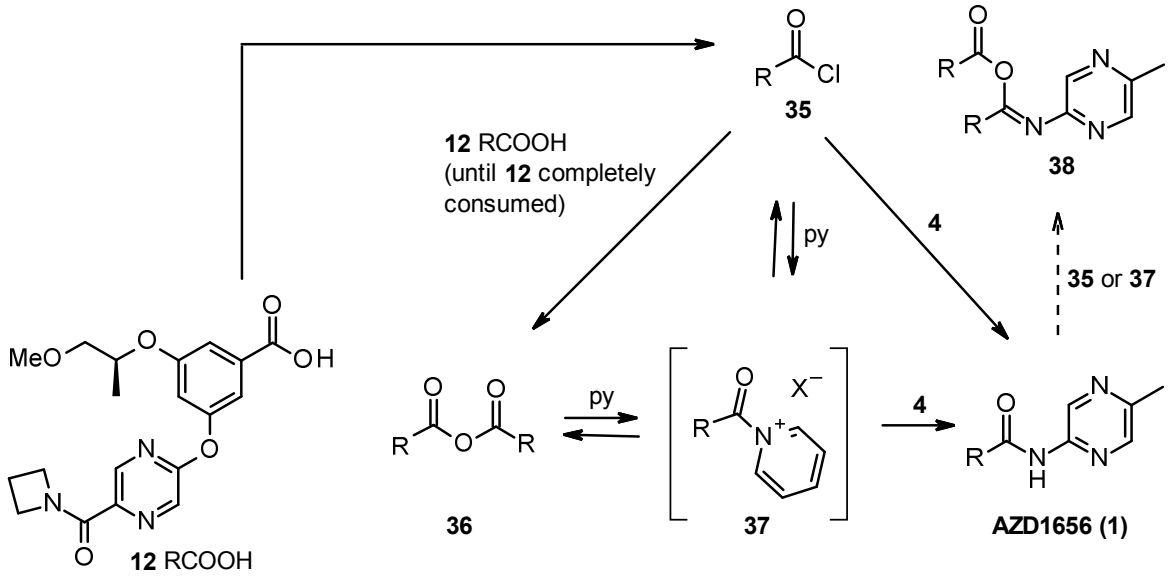
With the need to development a long-term solution for the amidation step, attention turned to the activation of acid **12** as an acid chloride **35** (Scheme 10). Whilst the use of thionyl chloride in this regard was one of the better performers in the initial screen of conditions, the conversion was still only

modest due to the formation of significant quantities of the acid anhydride intermediate **36** (Scheme 10), a material that showed limited reactivity towards aminopyrazine **4**. The generation of hydrogen chloride as a byproduct also brought the need to scavenge it adequately so as to avoid the formation of alkyl chloride **34** (Figure 2).

In spite of these challenges, the economics of using thionyl chloride as a reagent were persuasive. It was recognized from the outset that the presence of even small amounts of an acyl pyridinium species **37** could provide a valuable conduit for improving the conversion of acid **12** to acid chloride **35** (at the expense of acid anhydride **36**), as shown in Scheme 10, and accelerating the conversion of acid chloride **35** to **AZD1656** (**1**).[29] It was also appreciated that through the judicious choice of solvent, (super)stoichiometric amounts of pyridine itself could simultaneously be used to scavenge the hydrogen chloride generated as a byproduct of the acid chloride formation, limiting its ability to open up the azetidine ring. The examination of literature pK_a data immediately drew us to the potential use of acetonitrile as the reaction solvent (p$K_{a\ HCl}$ = 10.3,[30] p$K_{a\ pyH^+}$ = 12.5[31]). Gratifyingly, this combination of pyridine additive (3 eq.) and solvent met with immediate success and a readily stirred reaction mixture. Raman monitoring revealed the rapid consumption of acid **12** to give an intermediate, presumably anhydride **36**. Levels of the latter then fell away to low levels at the expense of growth in levels of another material, presumably acid chloride **35**, which was now able to persist given the ever decreasing levels of acid **12**. The addition of aminopyrazine **4** at this point led to a high reaction conversion to **AZD1656** (**1**) in under 30 min and the material isolated contained only ca. 200 ppm of alkyl chloride **34**. Process optimization involved the addition of the activated species to a solution of aminopyrazine **4**. This controlled overreaction to form *O*-acyl impurity **38** (Scheme 10), and allowed a reaction conversion of 99 LCAP to be reliably achieved. Interestingly, the reaction conversion was found to be adversely affected when particularly dry acetonitrile (20 ppm) was used. This water had a role in hydrolysing the excess thionyl chloride (20% mol/mol) present at the end of the activation stage of the reaction,

preventing the excess reagent from transforming aminopyrazine **4** into an *N*-sulfinyl imine **39** (Scheme 10).[32] Gratifyingly, the reactions went to completion with a 10% molar excess of aminopyrazine **4** and plant-grade acetonitrile (water content 100-200 ppm). Workup development included washing out the pyridine at the end of the reaction using sulfuric acid, rather than hydrochloric acid, in order to mitigate the risk of azetidine ring-opening.

Scheme 10 Working mechanism summarizing key transformations consistent with conversion of acid **12** to **AZD1656** (**1**)



CRYSTALLIZATION OF AZD1656 (1)

Screening had unearthed five polymorphs (including hydrates) on top of Form VI, the thermodynamically most stable polymorph that had been requested by drug product colleagues. Form VI could be accessed by slowly cooling a methyl isobutyl ketone (MIBK) solution of the API in the

presence of micronized Form VI seed (>55 m^2/kg input) such that the batch was kept supersaturated with respect to Form VI but undersaturated with respect to a metastable (but kinetically more accessible) form.[33] When levels of chloropyrazine **3** and compound **40** (Figure 3), the latter arising from the presence of α-resorcylic acid (**30**) in acid **2** were below levels that slowed the rate of crystallization of Form VI, this polymorph could be crystallized in an isolated yield of 86%. Slow cooling was also important in that it reduced the entrainment of MIBK in the crystals. The enantiomeric excess of the **AZD1656** (**1**) prepared (97.6 LCAP), prior to the crystallization of Form VI was in accord with that of the (*R*)-1-methoxy-2-propanol (**7**) input (97.5 LCAP), consistent with a complete inversion of stereochemistry during the Mitsunobu reaction. The crystallization of Form VI reduced the amount of the undesired enantiomer to 1.3-1.4 LCAP. As the initial crystallization was performed in a facility that was not fully certified for the isolation of API destined for clinical trials, it was necessary to redissolve the material in MIBK, screen it and to crystallize it again in just such a facility. When the amidation process was not capable of producing Form VI directly (as was the case with the T3P-mediated amidation), such a recrystallization was required anyway. Whilst it may not be a necessity for any future manufactures performed in an appropriately certified facility, in this case it allowed the isolation of the API in a yield of 86%.

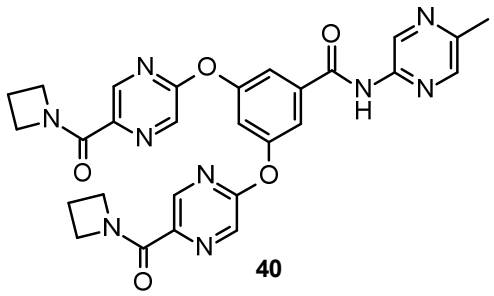


Figure 3 Structure of API impurity **40**

CONCLUSIONS

Various strategies were investigated in order to differentiate between the hydroxyl groups of an α-resorcylate derivative. The option pursued involved the monobenzoylation of methyl α-resorcylate (**5**), a slurry-to-slurry reaction that relied on the insolubility of the monobenzoyl ester product **27** in the reaction medium and maintaining accurate pH control on changing scale and equipment in order to limit bisbenzoylation. The chiral side-chain was emplaced using the Mitsunobu reaction: the solubility of a downstream intermediate in alkali allowed it to be partitioned away from the organic-soluble byproducts. These reaction conditions generated significantly less waste than a Williamson etherification variant. Thionyl chloride and pyridine in acetonitrile were used to achieve the successful amidation of an aminopyrazine **4** displaying low reactivity. These conditions offered a substantial cost-saving over the use of T3P. They also allowed access to the desired polymorph of the drug substance, a form that was thermodynamically preferred but slow-growing and disfavored by the presence of impurities, such that the recrystallization of the API was no longer a necessity. The processes described herein allowed the production of 506 kg of **AZD1656** (**1**).

Experimental Section

General. NMR spectra were recorded on a Bruker instrument with tetramethylsilane (TMS) as internal reference. Chemical shifts are expressed in ppm (δ) relative to TMS, coupling constants (*J*) are in Hz. Infrared spectra were recorded with diamond ATR sampling on an FTIR spectrometer using powdered samples or oils. Melting points were recorded using a Q2000 differential scanning calorimeter from TA Instruments. High resolution mass spectra were recorded on a Waters Synapt UPLC-MS instrument. Unless stated otherwise, commercial grade materials were used and stated temperatures refer to the temperature of the batch.

Preparation of ester 27[34]

A solution of benzoyl chloride (479 kg, 3.41 kmol) in toluene (658 L) was added over no more than 2 h to a slurry of methyl α-resorcylate (**5**) (259 kg, 1.54 kmol) in water (2,600 L), which was being stirred at 20 °C. The pH was adjusted to 8.0±0.2 prior to the start of (ca. 55 L) and during (ca. 1525 L) the addition by dosing a freshly-prepared aqueous solution containing both lithium hydroxide (3.8% wt/wt) and potassium carbonate (4.8% wt/wt). At the end of the addition of the benzoyl chloride solution, the batch was maintained for a further 30 min using the addition of the alkali (ca. 65 L) to maintain the same pH. The slurry was then filtered and the cake was washed with water (640 L). The material was dissolved in isopropyl acetate (1755 L) and stirred at 55 °C with Vitacel FAC 200 (21 kg) and activated charcoal (8 kg of 2CW CECA). After 15 min., the slurry was filtered and washed through with isopropyl acetate (275 L). The batch volume was then reduced by vacuum distillation (275 mBarA). Once 800 kg of distillate had been collected, toluene was added continuously (1155 L) whilst a further 800 kg of distillate were collected. The batch was cooled to 12 °C over at least 2 h. After a further 1 h, the slurry was isolated by filtration and the cake washed with toluene (555 L). Vacuum drying (50 mBarA) at 60 °C afforded ester **27** as a white solid (340 kg, 81%). Mp 139 °C. IR 3431, 1706, 1599, 1331, 1272, 1246, 1144, 1106, 1086, 1071, 1009, 998, 764, 706 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 10.26 (1H, s), 8.12 (2H, dd, *J*=8.2, 1.3 Hz), 7.74 (1H, tt, *J*=7.5, 1.3 Hz), 7.60 (2H, dd, *J*=8.2, 7.5 Hz), 7.32 (1H, dd, *J*=2.2, 1.4 Hz), 7.28 (1H, dd, *J*=2.2, 1.4 Hz), 6.98 (1H, dd, *J*=2.2, 2.2 Hz), 3.84 (3H, s). ^{13}C NMR (DMSO-d_6, 126 MHz) δ (ppm) 165.5, 164.4, 158.6, 151.6, 134.1, 131.6, 129.9 (2C), 129.0 (2C), 128.8, 114.0, 113.6, 113.2, 52.3. HRMS elemental calculated for $C_{15}H_{11}O_5$ $(M–H)^-$: 271.0606; found: 271.0615.

Preparation of phenol 2. (*R*)-1-Methoxy-2-propanol (**7**) (102 kg, 1.13 kmol) was added to a solution of phenol **27** (245 kg, 900 mol) and triphenylphosphine (295 kg, 1.12 kmol) in toluene (2087 kg), and washed through with toluene (20 kg). Diisopropyl azodicarboxylate (228 kg, 1.13 kmol) was added over at least 1 h whilst maintaining the batch temperature at 2 °C. After stirring for 30 min at this

temperature, and warming to 20 °C, the batch was seeded with the 1:1 mol/mol complex of triphenylphosphine oxide and diisopropyl hydrazinedicarboxylate (0.6 kg, 0.2% wt/wt). After stirring for 2 h, the slurry was filtered and the cake washed with toluene (210 kg). A chromatographically-purified sample of the filtrate gave ether **29** as a colorless oil. IR 1721, 1589, 1446, 1300, 1242, 1136, 1101, 1079, 1060, 1022, 996, 765, 705 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 8.13 (2H, dd, *J*=8.3, 1.3 Hz), 7.71 (1H, tt, *J*=7.1, 1.3 Hz), 7.58 (2H, dd, *J*=8.3, 7.1 Hz), 7.40 (1H, app d, *J*=2.3 Hz), 7.40 (1H, app d, *J*=2.2 Hz), 7.22 (1H, dd, *J*=2.3, 2.2 Hz), 4.68 (1H, qdd, *J*=6.3, 6.1, 4.0 Hz), 3.84 (3H, s), 3.49 (1H, dd, *J*=10.6, 6.1 Hz), 3.45 (1H, dd, *J*=10.6, 4.0 Hz), 3.29 (3H, s), 1.24 (3H, d, *J*=6.3 Hz). ^{13}C NMR (DMSO-d_6, 126 MHz) δ (ppm) 165.4, 164.4, 158.7, 151.7, 134.1, 131.7, 129.9 (2C), 128.9 (2C), 128.7, 114.8, 114.4, 113.8, 74.9, 73.3, 58.5, 52.4, 16.3. HRMS elemental calculated for $C_{19}H_{19}O_6$ $(M–H)^-$: 343.1182; found: 343.1202.

The filtrate was treated with methanolic sodium methylate (130 kg of 30.0% wt/wt, 722 mol) and stirred at 25 °C for 60 min. After cooling to 2 °C, the solution was extracted with dilute potassium hydroxide solution (1547 kg of 0.25 M, 387 mol, split over two extractions). A chromatographically-purified sample of the extracts gave phenol **21** as a colorless oil. IR (cm^{-1}) 3353, 1721, 1593, 1236, 1148, 1096, 1025, 1001, 765. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 9.82 (1H, s), 6.99 (1H, dd, *J*=2.2, 1.5 Hz), 6.94 (1H, dd, *J*=2.4, 1.5 Hz), 6.61 (1H, dd, *J*=2.4, 2.2 Hz), 4.55 (1H, qdd, *J*=6.3, 6.0, 4.1 Hz), 3.80 (3H, s), 3.45 (1H, dd, *J*=10.5, 6.0 Hz), 3.38 (1H, dd, *J*=10.5, 4.1 Hz), 3.26 (3H, s), 1.18 (3H, d, *J*=6.3 Hz). ^{13}C NMR (DMSO-d_6, 126 MHz) δ (ppm) 166.2, 159.0, 158.9, 131.6, 108.9, 107.8, 107.1, 75.1, 72.8, 58.5, 52.1, 16.5. HRMS elemental calculated for $C_{12}H_{15}O_5$ $(M–H)^-$: 239.0919; found: 239.0926.

The extracts were combined and diluted with potassium hydroxide liquor (100 kg of 50% wt/wt, 891 mol). The solution was stirred at 24 °C for 60 min. The pH was adjusted to 9.5–10.0 using hydrochloric

acid solution (approximately 57 kg of 33% wt/wt, 516 mol), before it was washed at 23 °C with *tert*-butyl methyl ether (927 kg, split over 2 washes). The pH was then adjusted to 1.5 at 23 °C using concentrated hydrochloric acid (approximately 160 kg of 33% wt/wt, 1.45 kmol) before extractions were performed with *tert*-butyl methyl ether (927 kg, split over two extractions). The organic extracts were combined and stirred for 30 min with activated charcoal (17 kg, 25W CECA). The slurry was filtered and the charcoal washed with *tert*-butyl methyl ether (89 kg). The batch volume was reduced by 670 kg using vacuum distillation at 300 mBarA, before it was diluted with toluene (632 kg). The solution was washed with water (735 kg) at 50 °C before being diluted with toluene (253 kg) and heptane (300 kg). Solvent (315 kg) was removed by vacuum distillation at 350 mBarA. The batch was cooled to 38 °C and seeded with acid **2** (0.2 kg). It was then cooled to 2 °C over at least 1 h and left to desupersaturate for a further 30 min. The slurry was filtered and the cake washed with toluene (211 kg). The cake was vacuum dried below 50 °C and 100 mBarA. This afforded acid **2** as a white solid (155 kg, 76%). Mp 42 °C. IR (cm^{-1}) 2933, 1687, 1592, 1448, 1296, 1203, 1147, 1082, 1022, 846, 770, 730, 704, 674. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 6.94 (1H, dd, *J*=2.2, 1.4 Hz), 6.91 (1H, dd, *J*=2.4, 1.4 Hz), 6.55 (1H, dd, *J*=2.4, 2.2 Hz), 4.54 (1H, qdd, *J*=6.3, 6.0, 4.1 Hz), 3.46 (1H, dd, *J*=10.5, 6.0 Hz), 3.44 (1H, br s), 3.44 (1H, br s), 3.41 (1H, dd, *J*=10.5, 4.1 Hz), 3.27 (3H, s), 1.19 (3H, d, *J*=6.3 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 167.2, 158.7, 158.6, 132.8, 108.9, 107.4, 107.0, 74.9, 72.6, 58.5, 16.5. HRMS elemental calculated for $C_{11}H_{13}O_5$ $(M–H)^-$: 225.0763; found: 225.0759.

Preparation of ether 12. A slurry of acid **2** (150.0 kg at 98.5% wt/wt, 653.1 mol), chloropyrazine **3** (136.4 kg at 98.4% wt/wt, 679.2 mol) and potassium carbonate (226 kg, 1.63 kmol) in dimethyl sulfoxide (886 L) and water (148 L) was stirred with a jacket temperature of 57 °C overnight (16 h). Water (1240 L) was added and the batch maintained with the same jacket temperature for a further 60 min before being cooled to 21 °C.[35] Concentrated hydrochloric acid (203 L of 11.60 M, 2.35 kmol) was added over 60 min. Dilute hydrochloric acid (approx. 261 L of 1 M, 261 kmol, CARE: offgassing of

carbon dioxide) was then added so that the final measured pH was in the range of 3.0–4.5. The batch was then warmed and isopropyl acetate (1480 L) charged so that the batch temperature did not drop below 40 °C. The batch was allowed to equilibrate with a 75 °C jacket and the phases cut. The aqueous phase was extracted once again at 75 °C with more isopropyl acetate (1480 L) before being discarded. The two isopropyl acetate extracts were combined and washed at 63 °C with water (739 L), seeded (738 g of acid **12**). The jacket temperature was linearly ramped to 60 °C over 6 h. The batch was then distilled to 900–1200 L using a –450 mbarG vacuum. The jacket temperature was then ramped to 21 °C at –12 °C/h. After stirring out at this temperature for a further 6 h, the slurry was filtered and the damp cake washed with isopropyl acetate (591 L). Vacuum oven drying (–250 mBarG) at 50 °C afforded acid **12** as a white solid (227.2 kg, 89.8%). Mp 157 °C. IR (cm^{-1}) 1701, 1609, 1565, 1438, 1274, 1112, 1028, 771, 704. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 8.65 (1H, d, *J*=1.3 Hz), 8.50 (1H, d, *J*=1.3 Hz), 7.36 (1H, dd, *J*=2.3, 1.3 Hz), 7.31 (1H, dd, *J*=2.1, 1.3 Hz), 7.14 (1H, dd, *J*=2.3, 2.1 Hz), 4.66 (1H, qdd, *J*=6.3, 6.1, 3.9 Hz), 4.53 (2H, t, *J*=7.7 Hz), 4.07 (2H, t, *J*=7.8 Hz), 3.49 (1H, dd, *J*=10.6, 6.1 Hz), 3.44 (1H, br s), 3.44 (1H, dd, *J*=10.6, 3.9 Hz), 3.27 (3H, s), 2.27 (2H, tt, *J*=7.8, 7.7 Hz), 1.21 (3H, d, *J*=6.3 Hz). ^{13}C NMR (DMSO-d_6, 126 MHz) δ (ppm) 166.4, 162.7, 159.9, 158.9, 153.6, 142.1, 141.4, 133.6, 133.4, 114.4, 113.5, 113.4, 74.9, 73.2, 58.5, 54.2, 48.8, 16.3, 16.2. HRMS elemental calculated for $C_{19}H_{22}N_3O_6$ ($M+H^+$): 388.1509; found: 388.1511.

Preparation of Form VI of AZD1656 (1). A mixture of acid **12** (100 kg, 258 mol) and pyridine (61.3 kg, 774 mol) in dry acetonitrile (500 L) was prepared. Thionyl chloride (36.9 kg, 310 mol) was added rapidly (CARE: exotherm, off-gassing of sulfur dioxide) and washed through with dry acetonitrile (100 L), whilst maintaining the batch temperature below 20 °C. The yellow solution so formed was added without undue delays to a pre-prepared solution of aminopyrazine **4** (31.0 kg, 284 mol) in dry acetonitrile (500 L),[36] whilst maintaining the batch temperatures of both solutions below 20 °C. After washing through with dry acetonitrile (100 L) and a further 1 h at 20 °C, the batch was washed (CARE:

off-gassing) twice with sodium bicarbonate solution (150 L total of 7% wt/wt, split over 2 washes). The organic phase (solution A) was retained, whilst the aqueous washes were back-extracted at 20 °C with MIBK (250 L). The back-extract and solution A were combined and distilled to 450 L at 250 mBarA. MIBK (1000 L) was charged and the batch redistilled to 400 L at 300 mBarA. MIBK (600 L) was added and the solution washed at 45 °C with dilute sulfuric acid solution (1000 L of 1 M). The organic phase (solution B) was retained, whilst the aqueous washes were back-extracted at 45 °C with MIBK (250 L).[37] The back-extract and solution B were combined and washed at 45 °C with sodium bicarbonate solution (500 L, 7% wt/wt) then water (500 L). The organic phase was distilled to 400 L before being diluted with more MIBK (420 L). Seeding at 45 °C with **AZD1656** (**1**) (Form VI, 4.0 kg, 4.0% wt/wt) was followed by aging at this temperature for 4 h. The batch was cooled at 6 °C/h to 20 °C where it was held for a further 4 h before heptane (1200 L) was added in 6 equal portions at 1 h intervals. The batch was isolated by filtration and the cake washed with a mixture of heptane and MIBK (500 L of 2:1 v/v) before being vacuum dried at 45 °C. This yielded **AZD1656** (**1**) as a white solid (107 kg, 85% corrected for 98% wt/wt). Mp 108 °C. IR (cm^{-1}) 3249, 1632, 1549, 1435, 1344, 1307, 1291, 1273, 1264, 1248, 1225, 1175, 1132, 1113, 1090, 1027, 843, 752, 699. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 11.03 (1H, s), 9.26 (1H, d, *J*=1.4 Hz), 8.67 (1H, d, *J*=1.3 Hz), 8.55 (1H, d, *J*=1.3 Hz), 8.34 (1H, d, *J*=1.4 Hz), 7.57 (1H, dd, *J*=2.2, 1.6 Hz), 7.47 (1H, dd, *J*=2.1, 1.6 Hz), 7.12 (1H, dd, *J*=2.2, 2.1 Hz), 4.78 (1H, qdd, *J*=6.3, 6.0, 3.9 Hz), 4.55 (2H, t, *J*=7.4 Hz), 4.08 (2H, t, *J*=7.8 Hz), 3.52 (1H, dd, *J*=10.7, 6.0 Hz), 3.47 (1H, dd, *J*=10.7, 3.9 Hz), 3.29 (1H, s), 3.26-3.31 (2H, m), 2.47 (3H, s), 2.28 (2H, tt, *J*=7.8, 7.4 Hz), 1.25 (3H, d, *J*=6.3 Hz). ^{13}C NMR (DMSO-d_6, 126 MHz) δ (ppm) 164.6, 162.7, 159.9, 158.8, 153.6, 148.7, 146.5, 142.2, 141.7, 141.4, 136.3, 135.9, 133.5, 113.3, 113.0, 111.9, 74.9, 73.0, 58.5, 54.1, 48.7, 20.4, 16.4, 16.1. HRMS elemental calculated for $C_{24}H_{27}N_6O_5$ ($M+H^+$): 479.2043; found: 479.2051.

Recrystallization of AZD1656 (1). A supersaturated solution of **AZD1656 (1)** (100 kg, 1 eq.) and MIBK (670 L), that had been pre-screened at 70 °C, was seeded at 45 °C with a micronized (surface area = 3.3 m^2/g) sample of **AZD1656 (1)** (Form VI, 1.75 kg, 1.75% wt/wt). After being aged for 3 h, the batch was cooled at 0.1 °C/min to 0 °C,[38] where it was isolated by filtration after being held for a further 3 h.[39] The cake was sequentially washed with a chilled (0 °C) mixture of MIBK and heptane (200 L of 1:2 v/v) and then heptane (200 L), before being dried under vacuum at 60 °C. This yielded **AZD1656** (**1**) (Form VI, 83.3 kg, 83.3%) as a white solid.

ASSOCIATED CONTENT

Supporting information available: ^{1}H NMR spectra, ^{13}C NMR spectra, infrared spectra and DSC traces for ester **27**, ether **29**, phenol **21**, acid **12** and **AZD1656** (**1**).

AUTHOR INFORMATION

Corresponding Author

E-mail: Alan.Steven@astrazeneca.com

ORCID Alan Steven: 0000-0002-0134-0918

Notes

The authors declare no competing financial interest.

Acknowledgement

We are grateful to Dottikon Exclusive Synthesis for performing the manufacture of acid **2**.

REFERENCES

1. McKerrecher, D.; Waring, M. J., Chapter One - Property-Based Design in the Optimisation of Benzamide Glucokinase Activators: From Hit to Clinic. In *Progress in Medicinal Chemistry*, Lawton, G.; Witty, D. R., Eds. Elsevier: 2013; Vol. 52, pp 1-43.

2. Waring, M. J.; Clarke, D. S.; Fenwick, M. D.; Godfrey, L.; Groombridge, S. D.; Johnstone, C.; McKerrecher, D.; Pike, K. G.; Rayner, J. W.; Robb, G. R.; Wilson, I., Property based optimisation of glucokinase activators - discovery of the phase IIb clinical candidate AZD1656. *MedChemComm* **2012,** *3* (9), 1077-1081.

3. Processes for making **AZD1656** (**1**) are covered in the following patents. a) Butters, M.; Crabb, J.; Hopes, P.; Patel, B. Process for preparation of benzoyl amino heterocyclic compounds. WO 2010092387, August 19, 2010. b) Bowden, S. A.; Hoile, D. P.; Lövqvist, K. Crystalline polymorphic form 631. WO 2010092386, August 19, 2010. c) Briggner, L.-E.; Lindfors, L.; Smith, C. M. Pharmaceutical formulations. WO 2012007758, January 19, 2012.

4. World Health Organization *Global Report on Diabetes*; 2016 http://www.who.int/diabetes/global-report/en/ (accessed May 24, 2018).

5. Hose, D. R. J.; Hopes, P.; Steven, A.; Herber, C., Redesign of the Synthesis and Manufacture of an Azetidine-Bearing Pyrazine. *Org. Process Res. Dev.* **2018,** *22* (2), 241-246.

6. Steven, A.; Hopes, P., Use of a Curtius Rearrangement as Part of the Multikilogram Manufacture of a Pyrazine Building Block. *Org. Process Res. Dev.* **2018,** *22* (1), 77-81.

7. Hopes, P. A.; Parker, J. S.; Patel, B.; Welham, M. J. Chemical process for the preparation of an amido-phenoxybenzoic acid compound. U.S. Patent 7,973,178 B2, July 5, 2011.

8. For a study that featured differentiating between the two hydroxyl groups of resorcinol, see: Prasad, K.; Xu, D. D.; Tempkin, O.; Villhauer, E. B.; Repič, O. *Org. Process Res. Dev.* **2003**, *7*, 743-749.

9. For a desymmetrization of resorcinol that routes via its monobenzoate, see: Boxhall, J.Y.; Bulman Page, P.C.B.; Chan, Y., Hayman, C.M.; Heaney, H.; McGrath, M.J. *Synlett* **2003**, *7*, 997–1001.

10. 3-Dimethylaminopropylamine was used to quench the excess tosyl chloride and formed a water-soluble derivative, which could be partitioned away from **20** in an aqueous workup.

11. A two step tosylation-etherification sequence proceeded with complete inversion of stereochemistry with a variety of α-resorcylate derivatives over the course of the project, with no detectable erosion in the integrity of the stereogenic center.

12. pK_a DB in ACD/Spectrus software, ACD Labs, 2015 Pack 2.

13. Whilst the amount of bisether **26** present in the batch generated as part of the first development manufacture was not recorded, a laboratory run where it was present at 6.5 LCAP at the end of the reaction provides some idea of the level likely to have been present.

14. Brief attempts to monofunctionalize using a biotransformation were also made. A range of hydrolases were screened using vinyl acetate, butanoate, laurate, stearate and benzoate as acyl donors for 3,5-dihydroxybenzonitrile. Monoacylation was selectively observed, though the reactions never went to completion.

15. Schwender, C. F.; Pike, R. E.; Shavel, J.; Kaplan, H. R., β-Adrenergic blockade by 3-[3-(substituted amino)-2-hydroxypropoxy]-5-hydroxybenzyl alcohols. *J. Med. Chem.* **1975,** *18* (2), 211-213.

16. Wallace, M. D.; McGuire, M. A.; Yu, M. S.; Goldfinger, L.; Liu, L.; Dai, W.; Shilcrat, S., Multi-Kiloscale Enantioselective Synthesis of a Vitronectin Receptor Antagonist. *Org. Process Res. Dev.* **2004,** *8* (5), 738-743.

17. Sharma, P. K.; Shah, R. N.; Carver, J. P., Scale-Up Synthesis of Swainsonine: A Potent α-Mannosidase II Inhibitor. *Org. Process Res. Dev.* **2008,** *12* (5), 831-836.

18. Connolly, T. J.; Auguscinski, W.; Fung, P.; Galante, R.; Liu, W.; McGovern, L.; Sebastian, A.; Shen, X.; Shi, X.; Wilk, B.; Varsalona, R.; Zhong, H., Development of a Pilot-Plant-Scale Synthesis of an Alkylated Dihydrobenzothiadiazole *S*,*S*-Dioxide: Incorporation of a Late-Stage Mitsunobu Reaction. *Org. Process Res. Dev.* **2010,** *14* (4), 868-877.

19. de Koning, P. D.; McAndrew, D.; Moore, R.; Moses, I. B.; Boyles, D. C.; Kissick, K.; Stanchina, C. L.; Cuthbertson, T.; Kamatani, A.; Rahman, L.; Rodriguez, R.; Urbina, A.; Sandoval, A.; Rose, P. R., Fit-for-Purpose Development of the Enabling Route to Crizotinib (PF-02341066). *Org. Process Res. Dev.* **2011,** *15* (5), 1018-1026.

20. Ford, J. G.; Pointon, S. M.; Powell, L.; Siedlecki, P. S.; Baum, J.; Chubb, R.; Fieldhouse, R.; Muxworthy, J.; Nivlet, A.; Stenson, R.; Warwick, E., Process Research and Development for the Kilogram Manufacture of the SRC Kinase Inhibitor AZD0530. *Org. Process Res. Dev.* **2010,** *14* (5), 1078-1087.

21. Scott, J. P.; Alam, M.; Bremeyer, N.; Goodyear, A.; Lam, T.; Wilson, R. D.; Zhou, G., Mitsunobu Inversion of a Secondary Alcohol with Diphenylphosphoryl azide. Application to the Enantioselective Multikilogram Synthesis of a HCV Polymerase Inhibitor. *Org. Process Res. Dev.* **2011,** *15* (5), 1116-1123.

22. A tracking investigation revealed no residual diisopropyl azodicarboxylate tracked through into the workup.

23. The monobenzoylation of resorcinol on an industrial scale is precedented: Gearhart, W. M.; Hill, R. O., Jr.; Broyles, M. H. US 2571703, 1951.

24. Hart, R. J.; Pedge, N. I.; Steven, A. R.; Sutcliffe, K., *In situ* Monitoring of a Heterogeneous Etherification Reaction Using Quantitative Raman Spectroscopy. *Org. Process Res. Dev.* **2015,** *19* (1), 196-202.

25. The installation of the aminopyrazine using the palladium-catalyzed coupling of the primary amide with 2-halo-5-methylpyrazine, the reverse of one of these degradation pathways, was considered as a means of synthesizing the API. However, the primary amide starting material associated with this transformation was known to be difficult to purge from the drug substance through crystallization and the use of a palladium-catalyzed process in the API step was unappealing.

26. Bailey, J. M.; Bruton, G.; Huxley, A.; Milner, P. H.; Orlek, B. S. Preparation of substituted piperidines as histamine H3 receptor ligands. WO2005014571A1, February 17, 2005.

27. Unpublished process development studies with benzoic acid indicated that the need for excess reagent was consistent with the propensity of the activated intermediate to intermolecularly react with another molecule of T3P prior to the activation of all of the acid substrate.

28. Chemical Weapons Convention Implementation Assistance Programme webpage. http://iap.cwc.gov/ (accessed May 27, 2018).

29. Bender, M. L., Mechanisms of Catalysis of Nucleophilic Reactions of Carboxylic Acid Derivatives. *Chem. Rev.* **1960,** *60* (1), 53-113.

30. Raamat, E.; Kaupmees, K.; Ovsjannikov, G.; Trummal, A.; Kütt, A.; Saame, J.; Koppel, I.; Kaljurand, I.; Lipping, L.; Rodima, T.; Pihl, V.; Koppel, I. A.; Leito, I., Acidities of strong neutral Brønsted acids in different media. *J. Phys. Org. Chem.* **2013,** *26* (2), 162-170.

31. Lõkov, M.; Tshepelevitsh, S.; Heering, A.; Plieger, P. G.; Vianello, R.; Leito, I., On the Basicity of Conjugated Nitrogen Heterocycles in Different Media. *Eur. J. Org. Chem.* **2017,** *2017* (30), 4475-4489.

32. Kresze, G.; Maschke, A.; Albrecht, R.; Bederke, K.; Patzschke, H. P.; Smalla, H.; Trede, A., Organic N-sulfinyl compounds. *Angew. Chem.* **1962,** *74*, 135-44.

33. A low equilibrium concentration of molecules displaying the conformation of Form VI was provisionally used to explain why its crystals grew much more slowly than the metastable polymorph ('Form I').

34. In order to afford a homogeneous solution and to mitigate the risk of precipitation of insoluble lithium carbonate, the alkaline solutions used in this benzoylation reaction were prepared by mixing separate aqueous solutions of lithium hydroxide and potassium carbonate, shortly before their use, in order to give a solution with the solute concentrations indicated.

35. This step serves to hydrolyse an ester impurity **32**.

36. This reverse addition limits the formation of impurity **38** formed by the *O*-acylation of the newly-installed amide of **AZD1656** (**1**).

37. Unnecessary delay should be avoided during the preceding wash and this back-extraction in order to avoid the acid-mediated degradation of **AZD1656** (**1**).

38. The entrainment of MIBK in occlusions was a problem with this crystallization. Although temperature cycling could be used such that the MIBK content could be reduced to below 0.5% wt/wt after drying, it damaged the agglomerates of API and hindered their filtration and was superceded by carefully controlled cooling.

39. The polymorph was checked by XRPD prior to isolation. In the event that the undesired Form I was present, the slurry was recrystallized after heating to 50 °C.