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Development and Scale-Up of a Manufacturing Route for the Non-nucleoside Reverse Transcriptase Inhibitor GSK2248761A (IDX-899): Synthesis of an Advanced Key Chiral Intermediate

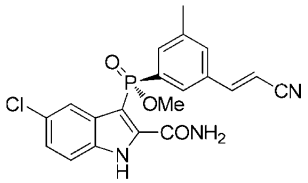
Richard Bellingham,[†,§] Gary Borrett,[†] Guillaume Bret,[†,§] Bernadette Choudary,[†,§] David Colclough,[†,§] Jerome Hayes,[†] John Hayler,[†] Neil Hodnett,[†] Alan Ironmonger,[*,†] Augustine Ochen,[†] David Pascoe,[†] John Richardson,[†,§] Erica Vit,[†,§] François-René Alexandre,[‡] Catherine Caillet,[‡,∥] Agnès Amador,[‡,∥] Stéphanie Bot,[‡] Séverine Bonaric,[‡,∥] Daniel da Costa,[‡] Marie-Pierre Lioure,[‡] Arlène Roland,[‡,∥] Elodie Rosinovsky,[‡,∥] Christophe Parsy,[‡,∥] and Cyril B. Dousson[‡]

[†]GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.
[‡]Merck & Co., Inc.,126 East Lincoln Avenue, Rahway, New Jersey 07065, United States

ABSTRACT: A new and improved synthetic route to an intermediate in the synthesis of the phosphinate ester GSK2248761A is described. In the key step, we describe the first process-scale example of a palladium-catalyzed phosphorus−carbon coupling to give the entire backbone of GSK2248761A in one telescoped stage in 65% average yield on a 68 kg scale. This unusual chemistry enabled the route to be reduced from six chemistry stages to four and eliminated a number of environmentally unfriendly reagents and solvents.

INTRODUCTION

GSK2248761A (fosdevirine, IDX-899, **1**) (Figure 1) is an experimental non-nucleoside reverse transcriptase inhibitor (NNRTI) discovered by Idenix Pharmaceuticals that was in development for the treatment of HIV.[1] The unusual structure is *P*-stereogenic and was required as a single *S* enantiomer. Interestingly, the *R* enantiomer has been shown to be 1800-fold less active against the wild-type virus and inactive against NNRTI-resistant viruses.[2] Multikilogram quantities were required to support the clinical development program, and a more efficient manufacturing route was sought for long-term commercial production. Herein we describe the development of an alternative route to compound **10**, a key intermediate in the synthesis of GSK2248761A.



GSK2248761A, 1

Figure 1. Chemical structure of GSK2248761A (IDX-899).

FIRST-GENERATION SYNTHESIS OF GSK2248761A

The first-generation chemistry route is outlined in Scheme 1 and was used by an outsource partner to prepare supplies for early-phase clinical and preclinical development.[3] The synthesis commenced with Mg−Br exchange on *N*-benzenesulfonyl-protected bromoindole **2** using the tributylmagnesate method described by Oshima under cryogenic conditions.[4] The resulting arylmagnesium species **3** was then quenched with diethyl chlorophosphite to give intermediate **4**, which rearranged to ethyl *H*-phosphinate **5** upon workup with dilute hydrochloric acid. A toluene solution of **5** then underwent palladium-catalyzed phosphonylation with the iodocinnamonitrile **6** starting material to produce ethyl phosphinate ester **7**.[5] This ethyl phosphinate **7** was then cleaved with bromotrimethylsilane and subsequently chlorinated using oxalyl chloride in the presence of a catalytic amount of *N*,*N*-dimethylformamide (DMF). The resulting phosphinyl chloride was then quenched in situ with methanol to deliver the backbone of GSK2248761A containing the required methyl phosphinate moiety. Ester **8** was saponified with lithium hydroxide in aqueous acetonitrile with the concomitant removal of the *N*-benzenesulfonyl protecting group, which provided a carboxylic acid handle for resolution. A classical resolution was performed using cinchonidine as the resolving agent, followed by salt dissociation to give the enantiomerically pure acid **10**, a key intermediate in the synthesis. The final amide bond formation was performed via activation with 1,1′-carbonyldiimidazole (CDI) followed by treatment with gaseous ammonia, and the product was crystallized from aqueous methanol to give GSK2248761A (**1**).

A number of issues were identified within the first-generation route. Although the synthesis of the Grignard reagent proceeded smoothly, there were safety and environmental concerns over the use of superstoichiometric amounts of *n*-butyllithium and *n*-butylmagnesium chloride, which were needed to generate the active "ate" complex **3** under cryogenic conditions. A slight excess of *n*-butyllithium was required for

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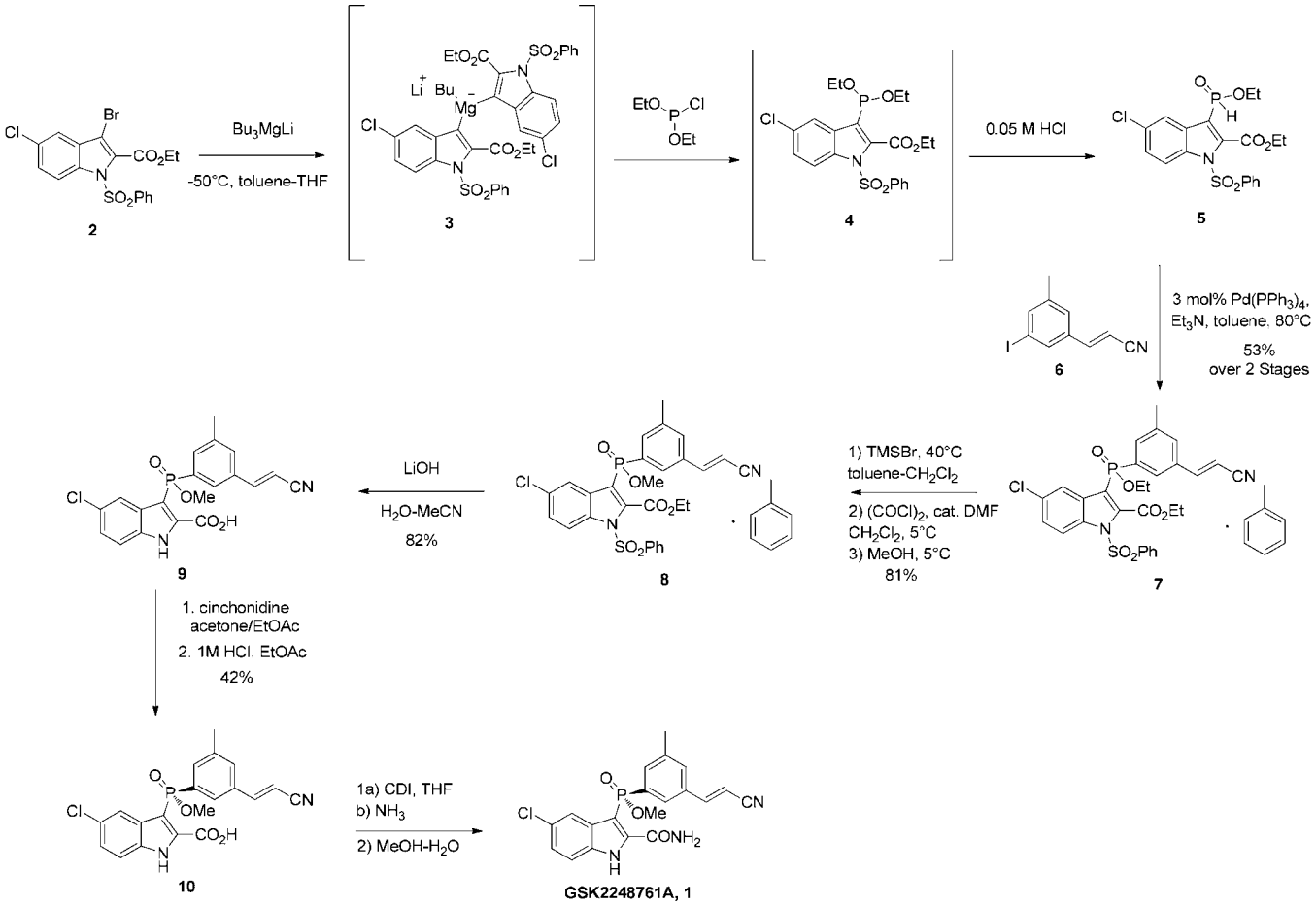
Scheme 1. First-Generation Route to GSK2248761A



this reaction to proceed robustly, as it was observed that only the "ate" complex was active in the reaction and the corresponding dibutylmagnesium species was completely inactive toward Br−Mg exchange. Moreover, when the reaction was performed under noncryogenic conditions, impurity **11** resulting from addition of a butyl group at the 3-position of the indole (Figure 2) was poorly controlled. The use of alternative

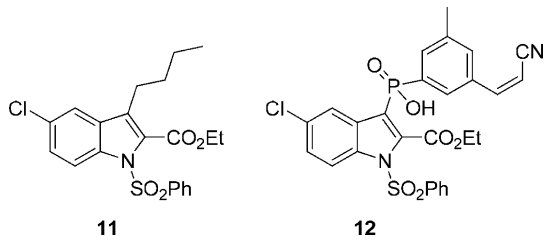


Figure 2. Two process impurities formed.

Grignard technologies, such as the isopropylmagnesium chloride−lithium chloride reagent developed by Knochel,[6] was unsuccessful. The diethyl chlorophosphite electrophile used in the process is highly toxic and moisture-sensitive, representing potential handling/quality issues, and the resulting toluene solution of the ethyl *H*-phosphinate product **5** had to be stored in a cold room because of concerns over its stability. The palladium-catalyzed P−C coupling performed well, but the product **7** was isolated in only 53% yield over the two stages. However, this chemistry installed the ethyl phosphinate **7** rather than the required methyl phosphinate **8**, which required later modification in the synthesis. These steps involved the use of dichloromethane, a nonpreferred solvent, and the combination of oxalyl chloride and DMF, which is known to generate dimethylcarbamoyl chloride (DMCC) as a byproduct, as well as the gaseous byproducts generated during processing, which presented potential engineering/safety issues. DMCC is reasonably anticipated to be a human carcinogen,[7] and its generation is strictly governed by COMAH regulations in the U.K.[8] Some of the batches of bromotrimethylsilane had been shown in the laboratory to partially isomerize the cinnamonitrile double bond, forming impurity **12** (Figure 2), which was difficult to purge in the downstream chemistry. This impurity is probably formed as a result of the presence of small quantities of HBr present in the bromotrimethylsilane. Finally, although the yield of the classical resolution was reasonable, such a late resolution in the synthesis severely impeded the efficiency of the overall route. Herein we report our progress in developing new chemistry to obtain the key late-stage intermediate **10** that largely circumvents some of the above issues.

NEW ROUTE DEVELOPMENT

We were keen to avoid the necessity of correcting the ethyl group in **7** to a methyl group in **8** during the synthesis, as this would eliminate much of the problematic chemistry and greatly improve the efficiency. The corresponding dimethyl chlorophosphite electrophile had limited commercial availability and had previously been reported to have limited stability on

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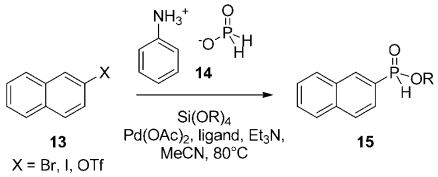
storage.[9] Our limited attempts to prepare a pure sample of dimethyl chlorophosphite were unsuccessful. We became interested in the palladium-catalyzed formation of *H*-phosphinate esters reported by Montchamp and others (Scheme 2).[5a,10] This chemistry would allow the direct

Scheme 2. Palladium-Catalyzed P−C Coupling Utilizing Anilinium Hypophosphite



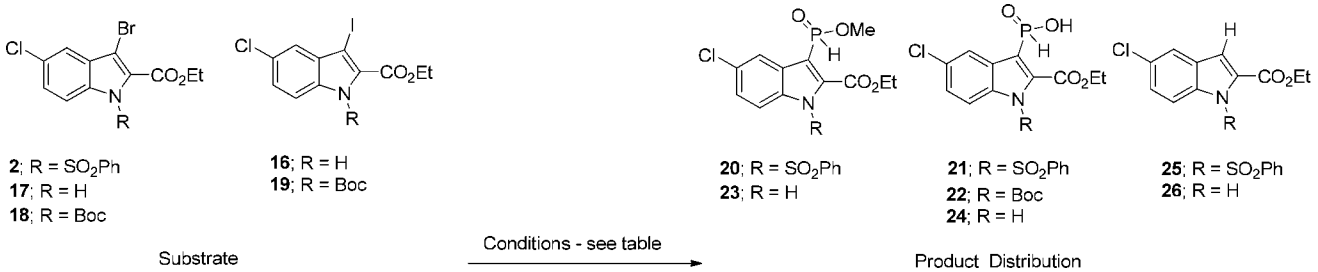
formation of the *H*-phosphinate methyl ester, which could then be followed by a second palladium-catalyzed reaction to construct the complete framework of GSK2248761A.

Idenix also noted this chemistry before the project was in-licensed to GSK and had instructed Johnson-Matthey to perform a catalyst screen, which demonstrated that in principle this transformation should be possible.[11] Building on the $Pd(dppf)Cl_2$ catalyst conditions identified by Johnson-Matthey, we investigated many alternative coupling conditions/substrates to establish the most feasible direction and reaction conditions for the coupling (Table 1).

The coupling was investigated starting initially with a haloindole derivative to produce a phosphinic ester that could then be coupled onward. Three major impurity pathways were apparent in the reaction profile depending on the coupling conditions and the reaction partner. Direct reduction of the haloindole can occur to give the parent indole (e.g., **25** and **26**), hydrolysis of the methyl phosphinate intermediate can occur upon prolonged heating (e.g., **21**, **22**, and **24**), and the protecting group could also be cleaved during the reaction (e.g., **23**, **24**, and **26**). We found that the reductive dehalogenation could be controlled by judicious choice of the catalyst, methyl source, and phosphinate salt. Our best results were obtained when we used $Pd(dppf)Cl_2$ and 3-aminopropyltrimethoxysilane in conjunction with anilinium hypophosphite at reflux in ethyl acetate (entry 6). Attempts to avoid the use of aniline by screening other salts of hypophosphorous acid such as ammonium hypophosphite and sodium hypophosphite resulted in reduction as the major pathway, with a <5% yield of the desired product observed and concomitant precipitation of palladium black. The methylating agent also proved to be important: when 3-aminopropyltrimethoxysilane was replaced with tetramethyl orthosilicate or with trimethoxyphenylsilane and an organic base, the reaction stalled. Interestingly, when the methyl phosphinate ester of hypophosphoric acid (prepared either from trimethyl orthoformate[5a] or tetramethyl orthosilicate,[10b] isolated, and characterized by ^{31}P NMR spectroscopy) was used as a source of phosphorus, the reaction stalled at less than 10% conversion. The most efficient coupling partner was *N*-benzenesulfonyl bromoindole derivative **2**, and we believe that the protecting group increased the rate of reaction because of withdrawal of electron density from the indole ring, facilitating oxidative addition of the palladium species. Our deconstruction of the reaction suggested that the mechanism involved the coupling of hypophosphorous acid followed by methylation of the coupled derivative, releasing the product from the catalyst.

We also investigated the coupling in the alternative synthetic direction starting from cinnamonitrile derivative **6** and found that methyl phosphinate **27** could be synthesized in 80% yield but was unstable and readily underwent demethylation to form **28**, followed by oxidation to the phosphonate **29** in air upon storage (Scheme 3). Our optimized reaction conditions for the reaction giving **30** involved performing the reaction in *N*-methyl-2-pyrrolidinone (NMP) spiked with a small quantity of water, and it was necessary to add trimethyl orthoformate to retard demethylation during coupling. These issues could be partially circumvented by telescoping the second coupling to iodoindole derivative **16**, but we chose to pursue the other reaction direction, as it seemed more amenable to process development.

Table 1. Summary of P−C Coupling Reactions



entry	substrate	conditions[a]	product distribution[b]
1	**17**	A	**17**, 59%; **23**, 0%; **26**, 36%
2	**16**	A	**2**, 26%; **23**, 35%; **26**, 34%
3	**16**	B	**2**, 4%; **23**, 55%; **26**, 24%
4	**19**	C	**19**, 8%; **22**, 34%; **23**, 13%
5	**18**	C	**18**, 10%; **22**, 64%; **23**, 8%
6	**2**	C	**2**, 5%; **20**, 82%; **23**, 2%

[a]Conditions A: 2 mol % $Pd(OAc)_2$, 2 mol % dppp, 1.2 equiv of anilinium hypophosphite, 1.2 equiv of (3-aminopropyl)trimethoxysilane, MeCN, 82 °C. Conditions B: 2 mol % $Pd(dppf)Cl_2$, 1.2 equiv of anilinium hypophosphite, 1.2 equiv of (3-aminopropyl)trimethoxysilane, MeCN, 82 °C. Conditions C: 2 mol % $Pd(dppf)Cl_2$, 1.2 equiv of anilinium hypophosphite, 1.2 equiv of (3-aminopropyl)trimethoxysilane, EtOAc, 77 °C. [b]Determined as HPLC % a/a of species detected at 220 nm.

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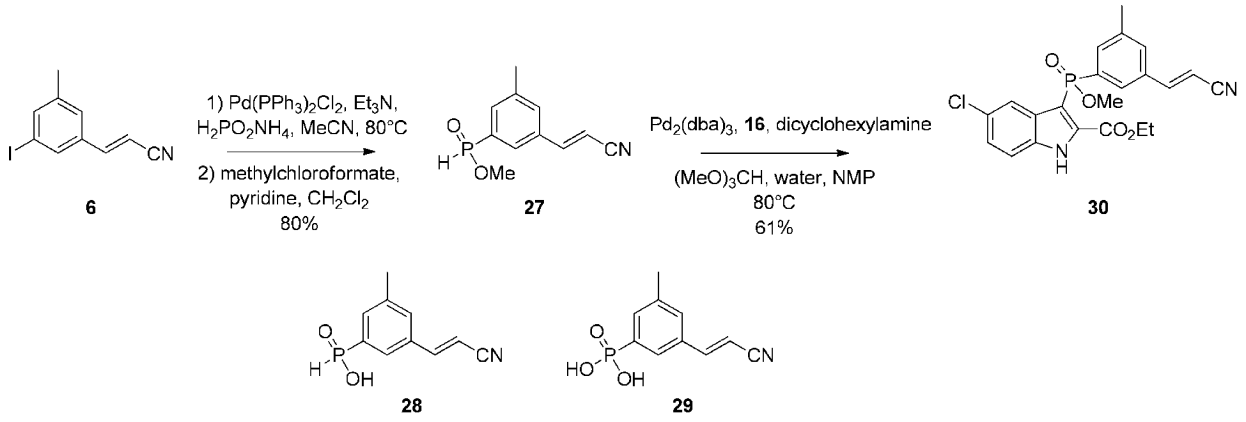
Scheme 3. Palladium-Catalyzed Coupling Starting with Aryl Iodide 6



Scheme 4. Telescoped Pd-Catalyzed P−C Coupling

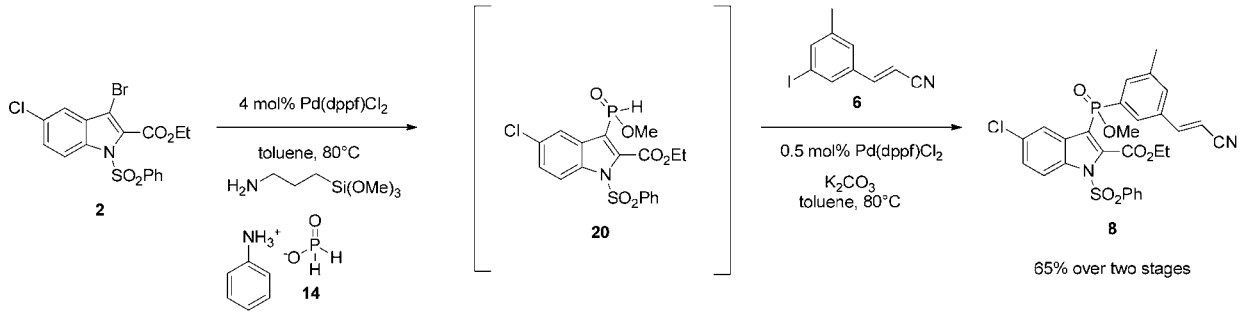
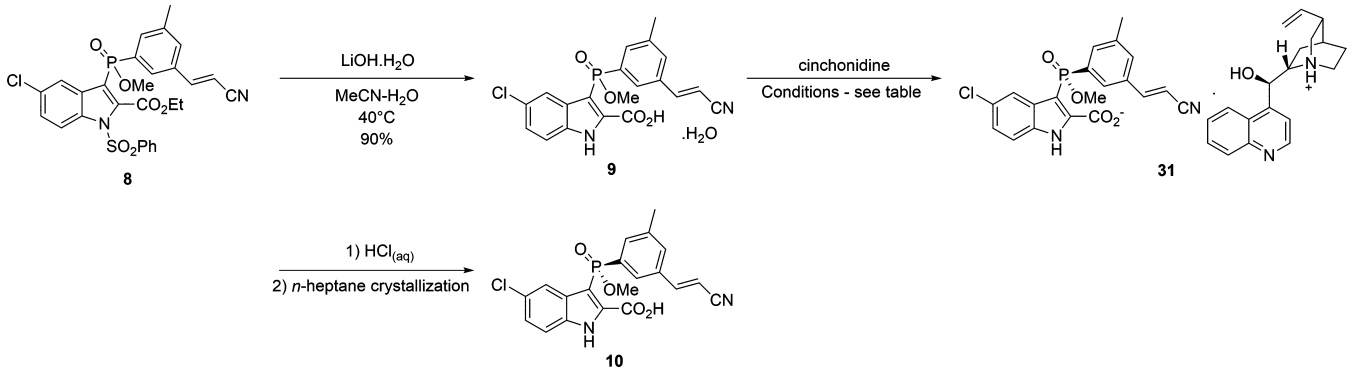


Table 2. Summary of Resolution Experiments



entry	conditions[a]	first % *d.r.* of salt[b]	second % *d.r.* of salt[b]	% *e.r.* of **10**[b]	% yield
1	A	97.0	99.3	99.3	42
2	B	96.5	99.8	99.8	40
3	C	96.2	99.8	99.8	40

[a]Conditions A: 1 equiv of cinchonidine in acetone at 50 °C, then cool to 20 °C, solvent swap to EtOAc, filter, wash, reslurry in EtOAc at 50 °C, then cool to 20 °C, filter. Suspend in EtOAc, wash with 0.1 M HCl(aq), water, and brine, solvent swap to *n*-heptane to crystallize. Conditions B: 1 equiv of cinchonidine in EtOAc at 50 °C, then cool to 20 °C, filter, wash. Suspend in EtOAc, wash with 0.1 M HCl(aq), water, and brine, azeotrope dry, charge with 1 equiv of cinchonidine in EtOAc at 50 °C, then cool to 20 °C, filter, wash. Suspend in EtOAc, wash with 0.1 M HCl(aq), water, and brine, solvent swap to *n*-heptane to crystallize. Conditions C: 1 equiv of cinchonidine in EtOAc at 50 °C, then cool to 20 °C, filter, wash, reslurry in acetone at 50 °C, then cool to 20 °C, filter. Suspend in EtOAc, wash with 0.1 M HCl(aq), water, and brine, solvent swap to methylcyclohexane to crystallize. [b]ChiralPak AD-H column (0.46 cm × 25 cm), isocratic elution with 75:25:0.04 isopropanol/methanol/TFA, detection at 270 nm.

We attempted to perform a one-pot reaction where a solution of intermediate **20** was treated with 1 equiv of aryl iodide **6** and triethylamine in ethyl acetate to form methyl phosphinate ester **8** directly (Scheme 4). A large amount of demethylation of **8** occurred during the reaction, and we hypothesized that the iodide liberated as the reaction proceeded was responsible via S_N2 attack onto the methyl group. The demethylation pathway was shut down when triethylamine was replaced with dicyclohexylamine in order to generate an insoluble iodide salt that would not participate in this side reaction. More detailed studies revealed that ethyl acetate was not completely inert in the coupling reaction and caused methyl to ethyl phosphinate ester exchange to give the undesired ethyl phosphinate ester **7** at low but unacceptable

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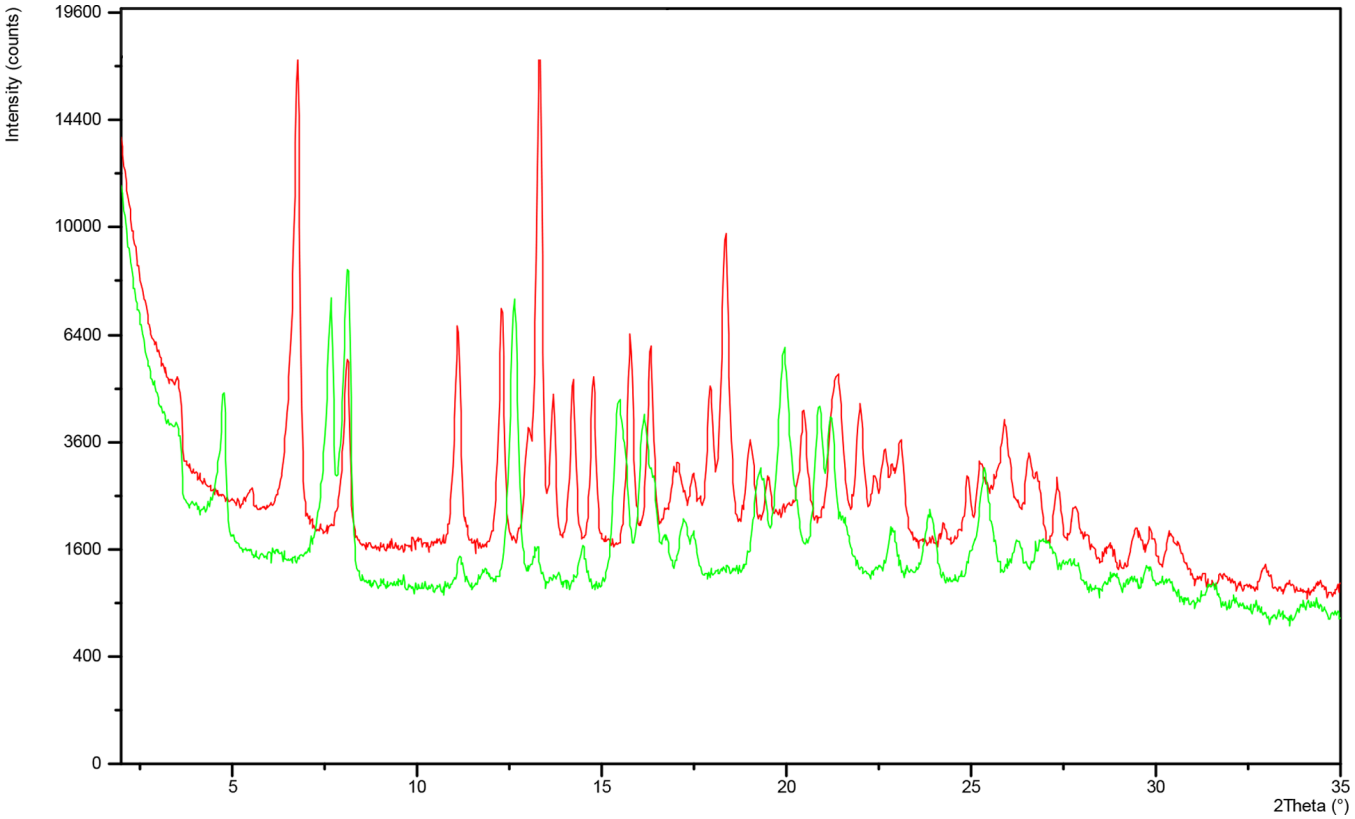

Figure 3. Representative PXRD traces of cinchonidine salt **31** slurried in (a) ethyl acetate (red trace) and acetone (green trace).

levels that were not purged downstream. The solvent was switched to isopropyl acetate to retard this pathway, and the reaction was performed in a 2 L controlled lab reactor (CLR) to evaluate the potential scale-up. The first coupling performed as desired, but the dicyclohexylamine hydrogen iodide produced as the second reaction progressed, in combination with polymeric silane byproducts, produced large hard balls that we anticipated would cause damage to our vessels as well as engineering challenges upon scale-up. We elected to perform a weakly acidic workup of **20** followed by a filtration to remove the problematic silane byproducts, and we changed the solvent to toluene to facilitate this. The toluene solution of methyl *H*-phosphinate ester **20** was azeotropically dried, and we found that solid potassium carbonate was an excellent base in the second coupling, as no demethylation occurred and the rate of reaction was significantly increased. Indeed, only an additional charge of 0.5 mol % $Pd(dppf)Cl_2$ catalyst was required to robustly perform the reaction within 2 h. After hot aqueous workup and azeotropic distillation, methyl phosphinate ester **8** crystallized as a toluene solvate, which provided excellent purification to give >98% a/a HPLC purity. The new telescoped process was successfully performed in the pilot plant in four batches, affording the product in 65% average yield, with some initial minor processing issues associated with the filtration of the silane polymer that were overcome with the addition of Celite to the vessel.

Ester **8** was saponified and deprotected using lithium hydroxide in aqueous acetonitrile at 40 °C on a 125 kg scale. The product **9** crystallized directly from the reaction mixture as the hydrate upon adjustment of the pH using aqueous hydrochloric acid in 90% yield with excellent purity. The acid provided a handle for a classical resolution in which the alkaloid cinchonidine had previously been shown to be a very efficient resolving agent.[3] The addition of 1 equiv of cinchonidine (based on assay) to an acetone solution caused the desired diastereomeric salt **31** to crystallize out. The solvent was exchanged to ethyl acetate to increase the yield, and **31** was filtered to provide material with 96−97% *d.r.*, which was immediately reslurried in ethyl acetate at 50 °C, followed by a cooling ramp to room temperature and filtration. The salt was washed with ethyl acetate to give material with >99.1% *d.r.* that was subsequently converted into chirally enriched *S* enantiomer **10** in an excellent yield of 42% for the whole process (Table 2). However, in our hands we were unable to robustly obtain the chiral upgrade upon reslurrying in ethyl acetate under a variety of conditions, including various seeding and temperature cycling regimes. In order to meet our timelines, we chose to regenerate the free acid and reform the salt with cinchonidine to generate the required *d.r.* Upon scale-up to 93 kg, the first salt formation was performed in ethyl acetate at 50 °C, followed by cooling to 20 °C, filtration, and washing to give 96.5% *d.r.* The second salt formation, filtration, and washing provided material with 99.8% *d.r.*, which was dissociated again, and the product **10** was obtained upon crystallization from *n*-heptane in an overall yield of 40% with 99.8%*e.r.* As the use of two cinchonidine salt formations was wasteful and potentially unnecessary, we revisited the reslurry conditions to upgrade the chiral purity.

During our investigations, comparison of the powder X-ray diffraction (PXRD) traces of cinchonidine salt **31** formed in different solvents (Figure 3) revealed that a form change upon reslurrying was a potential source of the irreproducibility. The initial salt formation performed in ethyl acetate gave form I (red trace), which when dried and reslurried in acetone at 50

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°C and then aged at 20 °C gave form II (green trace). Interestingly, when the reslurrying was performed in this order a chiral upgrade from 96.2% *d.r.* to >99.5% *d.r.* was observed. Conversely, when the crystallization was performed in acetone and the salt was subsequently reslurried in either fresh acetone or ethyl acetate, there was no change in form or upgrade in *d.r.*, suggesting that the change in form was in part responsible for the chiral upgrade upon reslurrying. The new process was scaled up to a 5 L CLR scale to demonstrate that this new reslurrying process was not scale-dependent. Gratifyingly, the reslurry protocol performed as expected to give acid **10** with 99.8% *e.r.* in 39% overall yield with excellent purity.

In summary, we have demonstrated the first pilot-plant-scale palladium-catalyzed *H*-phosphinate ester coupling to produce the entire backbone of GSK2248761A. Compared with the previous route, the new route is two stages shorter, eliminates most of the materials of concern for production, controls the impurities identified as problematic, and improves the overall yield from 15% to 23%. The key intermediate produced in this synthesis was successfully converted into GSK2248761A active pharmaceutical ingredient that met clinical specifications, and the procedure will be reported in a subsequent publication.

EXPERIMENTAL SECTION

General Experimental. Reactions were monitored using HPLC on a Luna C18(2) column (50 mm × 2 mm, 3 μm), eluting with a gradient of 0 to 95% (0.05% v/v TFA in water to 0.05% v/v TFA in acetonitrile) over 8 min at 40 °C with detection at 220 nm. Chiral HPLC was performed on a ChiralPac AD-H column (250 mm × 4.6 mm) with isocratic elution (70:30 *n*-heptane/ethanol) at 1 mL/min over 20 min with detection at 270 nm. NMR spectra were recorded on a Bruker 400 MHz Ultrashield or Bruker AV500 spectrometer. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = doublet of doublets, dt = doublet of triplets. Mass spectra were recorded on a Waters ZQ mass spectrometer, and high-resolution mass spectrometry (HRMS) was performed on an LQT Orbitrap spectrometer.

Syntheses. *1-Benzenesulfonyl-5-chloro-3-[methyl-3-((E)-2-cyanovinyl)-5-methylphenyl]phosphinoyl-1H-indole-2-carboxylic Acid Ethyl Ester (**8**).* Anilinium hypophosphite (27.5 kg, 173 mol) was suspended in toluene (232 L), and 3-aminopropyltrimethoxysilane (31 kg, 173 mol) was added while the temperature was maintained at 25 ± 5 °C. After 30 min, the resulting solution was transferred to another vessel containing bromoindole **2** (51 kg, 115 mol) and Pd(dppf)Cl_2·acetone (3.6 kg, 4.6 mol) in toluene (385 L) over approximately 1.5 h while the temperature was maintained at 77−82 °C. After 30 min, the reaction mixture was cooled to 20 °C, and aqueous hydrochloric acid (0.1 M, 306 kg) was added, followed by the addition of Celite (6 kg). The suspension was stirred for 30 min and filtered, and the Celite was washed with toluene (103 L). The phases were separated, and the organic phase was washed with aqueous sodium chloride (153 kg of a 20% w/w solution), after which ∼95 L was distilled off under reduced pressure. The reaction solution was transferred to another vessel containing iodocinnamonitrile **6** (29.2 kg, 109 mol), potassium carbonate (20.9 kg, 151 mol), and Pd(dppf)-Cl_2·acetone (0.5 kg, 0.63 mol). The reaction mixture was heated to 75 °C for 2 h and then cooled to 35 °C, and a solution of sodium hydrogen carbonate (153 kg of a 7% w/w solution) was added, followed by THF (409 L). The phases were separated, and the organic phase was washed with aqueous sodium chloride (153 kg of a 20% w/w solution) and distilled down to ∼200 L under reduced pressure. Toluene (153 L) was charged into the vessel, and the crystallization mixture was heated to 70 °C, cooled to 20 °C over ∼2.5 h, and stirred for 4 h. The protected indole phosphinate **8** (56.3 kg, 72%) was isolated by filtration, washed with toluene (3 × 103 L), and dried at 60 °C under vacuum in an agitated drier. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (t, *J* = 7.1 Hz, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 3.79 (d, *J* = 11.7 Hz, 3H), 4.53 (q, *J* = 7.1 Hz, 2H), 5.92 (d, *J* = 16.7 Hz, 1H), 7.13−7.19 (m, 3H), 7.23−7.27 (m, 2H), 7.32−7.39 (m, 3H), 7.52 (t, *J* = 7.9 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.75 (dd, *J* = 13.4, 8.0 Hz, 2H), 7.85 (d, *J* = 1.9 Hz, 1H), 7.94 (dd, *J* = 8.8, 1.3 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 12.1, 19.5, 19.7, 50.3, 50.4, 61.8, 96.2, 113.5, 115.9, 120.0, 123.5, 125.3, 125.4, 125.9, 126.4, 127.3, 127.7, 127.8, 129.2, 130.3, 132.2, 132.3, 133.2, 135.3, 136.1, 138.0, 147.5, 159.9.

*(E)-5-Chloro-3-((3-(2-cyanovinyl)-5-methylphenyl)-(methoxy)phosphoryl)-1H-indole-2-carboxylic Acid Hydrate (**9**).* Lithium hydroxide monohydrate (5.3 kg, 126 mol) was added to a stirred solution of protected indole phosphinate **8** (42.6 kg, 63.1 mol) in acetonitrile (202 kg) and water (128 L), and the resulting mixture was stirred at 22 °C for 2 h. The reaction mixture was heated to 40 °C for 12 h and then cooled back to 25 °C, and the pH was adjusted to pH 1−1.5 using aqueous hydrochloric acid (2 M solution). Water (149 L) was added over 30 min and the resulting slurry was aged at 40 °C for 30 min, cooled to 25 °C over 2 h, and then stirred at this temperature for a further 2 h. Acid **9** (23.1 kg, 85%) was isolated by filtration, washed with 1:2 acetonitrile/water (86 L), water (85 L), and 9:1 acetone/water (86 L), and dried at 70 °C under vacuum in an agitated drier. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.35 (s, 3H), 3.72 (d, *J* = 11.7 Hz, 3H), 6.51 (d, *J* = 16.7 Hz, 1H), 7.38 (dd, *J* = 8.9, 1.3 Hz, 1H), 7.65−7.73 (m, 3H), 7.85 (d, *J* = 13.6, 1H), 7.99 (d, *J* = 1.9 Hz, 1H), 12.97 (br s, 1H), 14.38 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.7, 51.7, 98.1, 115.0, 118.5, 120.9, 125.4, 126.7, 127.8, 127.9, 131.2, 133.5, 133.9, 134.0, 134.6, 134.7, 138.8, 138.9, 149.6, 160.4.

*(R,E)-5-Chloro-3-((3-(2-cyanovinyl)-5-methylphenyl)-(methoxy)phosphoryl)-1H-indole-2-carboxylic Acid (**10**).* Cinchonidine (64.7 kg, 220 mol) was added to a stirred solution of carboxylic acid **9** (93.2 kg, 225 mol) in ethyl acetate (1126 L) at 50 °C. The suspension was stirred at 50 °C for 2 h, cooled to 22 °C for 2 h, and then filtered, washing with ethyl acetate (300 L). The damp cake was reloaded into the reaction vessel and suspended in ethyl acetate (1180 L) and aqueous hydrochloric acid (0.5 M, 465 kg) until dissolved. The solution was then filtered through an R55SP Cuno cartridge, and the layers were separated. The organic phase washed with water (298 L) and aqueous sodium chloride solution (10% w/w, 2 × 199 kg) and then azeotroped dry, adjusting to a final volume of approximately 930 L. The solution was heated to 50 °C, and cinchonidine (32.4 kg, 110 mol) was added. The resulting slurry was stirred for 2 h, cooled to 22 °C for 2 h, filtered, and washed with ethyl acetate (300 L). The damp cake was reloaded into the reaction vessel and suspended in ethyl acetate (940 L) and aqueous hydrochloric acid (0.5 M, 466 kg) until dissolved. The layers were separated, and the organic phase was washed with water (279 L) and aqueous sodium chloride solution (10% w/w, 2 × 199 kg), after which the solvent was swapped to *n*-heptane (745 L) via distillation. The crystal-

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lization mixture was cooled to 10 °C and stirred for 2 h, and the crystals were filtered off, washed with *n*-heptane (185 L), and dried in a vacuum oven at 58 °C to give chiral acid **10** (34.4 kg, 39.7%, 99.8% *e.r.*).

*Alternative Process for **10**.* Cinchonidine (204.1 g, 693 mmol) was added to a stirred solution of carboxylic acid **9** (300 g, 693 mmol) in ethyl acetate (3.6 L) at 50 °C. The suspension was stirred at 50 °C for 2 h, cooled to 22 °C over 1 h, held for 2 h, and then filtered off, washing with ethyl acetate (900 mL). The damp cake was reloaded into the reaction vessel, stirred in acetone (3 L) at 50 °C for 1.5 h, cooled to 22 °C, stirred for 1 h, filtered off, and washed with acetone (600 mL) and ethyl acetate (600 mL). The damp cake was reloaded into the reaction vessel and stirred in ethyl acetate (3.3 L). Aqueous hydrochloric acid (0.5 M, 1 L) was added, and the were layers separated. The organic phase washed with water (600 mL) and aqueous sodium chloride solution (10% w/w, 2 × 400 mL) and then azeotroped dry, adjusting to a final volume of 900 mL. The solvent was swapped to dry methylcyclohexane (900 mL) via distillation under reduced pressure. The crystallization mixture was cooled to 20 °C and held overnight. The crystals were filtered off, washed with methylcyclohexane (600 mL), and dried in a vacuum oven at 60 °C to give **10** (113 g, 39%, 99.8% *e.r.*).

AUTHOR INFORMATION

Corresponding Author

*E-mail: Alan.2.Ironmonger@gsk.com.

ORCID

Jerome Hayes: 0000-0001-9875-0464
John Hayler: 0000-0003-3685-3139
François-René Alexandre: 0000-0003-1396-3757

Notes

The authors declare no competing financial interest.
[§]R.B., G.B., B.C., D.C., J.R., and E.V. are former GSK employees.
[‖]C.C., A.A., S.B., A.R., E.R., and C.P. are former Idenix employees.

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