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Development of a Kilogram-Scale Asymmetric Synthesis of a Potent DP Receptor Antagonist

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Abstract:

An efficient asymmetric synthesis of a unique sulfenylated prostaglandin DP receptor antagonist candidate is described. The synthesis is characterized by a novel intramolecular Friedel−Crafts cyclization of an imino-pyrrole to prepare the azaindole core. Other key steps include a highly selective Horner−Wadsworth−Emmons olefination of a tricyclic ketone intermediate and subsequent catalytic asymmetric hydrogenation of a trisubstituted α,β-unsaturated ester to install the chirogenic center. Finally, a new indole sulfenylation protocol was developed to install the aromatic thioether functionality in good yield.

Introduction

Prostaglandin D_2 (DP) receptor antagonists, indicated for the treatment of allergic rhinitis, have recently been shown to mitigate the unpleasant side effects of niacin, a prophylactic medication with proven cardio-protective benefits that patients often abandon due to the uncomfortable flushing side effects. MK-0524 (Tredaptive) an indole derivative, was previously identified as a potent (K_i = 0.57 nM) and selective DP antagonist.[1a−d] Efforts within the medicinal chemistry at Merck group subsequently identified azaindole **1** as a strong back-up candidate.[2a,b] In order to support preclinical toxicity and phase I studies we required a multikilogram synthesis of **1**.

Discussion and Results

Our efforts were focused on designing a safe, scalable, and efficient asymmetric synthesis of the azaindole core. The medicinal chemistry synthesis of **1** (Scheme 1),[2c] was not amenable to scale-up due to a potentially explosive high-temperature cyclization of **2** to afford indole **3**[3a] and the Stille coupling of aryl-chloride **4** with a toxic propenyl-stannane reagent[3b] to introduce the isopropyl substituent of ketone **5**. Other areas of concern were the use of sodium hydride in the Horner−Wadsworth−Emmons (HWE) olefination to prepare enoate **6**, and the sulfenylation reaction of racemic ester **7** that generated penultimate intermediate **8** together with significant levels of a 3-chloroindole byproduct **9** which was removed via chromatography. Since the first-generation synthesis was racemic, a late-stage chiral HPLC purification was employed to separate the undesired enantiomer of penultimate intermediate **8** from the desired one. Following this, a final hydrolysis of the ester moiety of **8** provided **1**.

With these issues driving our synthetic planning, we targeted several improvements to the existing route. Our main concern was identifying a safe and scalable route to the azaindole core which circumvented the use of azide intermediate **2** and the propenylstannane reagent. Enoate **6** was an attractive intermediate since either **6** or its corresponding acid were potential substrates for asymmetric hydrogenation to provide enantioenriched **7**.[4] Alternatively, racemic hydrogenation of **6** followed by enzymatic resolution of **7**[5] could also afford enantiomerically enriched **1** without the need for chiral chromatography.

Since the assembly of the azaindole core of **1** was critical to the evaluation of the downstream chemistry, our preliminary synthetic efforts focused on the rapid construction of **10** where the isopropyl group was installed earlier. Our strategy involved formation of the pyridine ring via Friedel−Crafts cyclization of imine **11** which should be readily available from pyrrole **12** (Scheme 2). Installation of the C-ring would be achieved using the same chemistry outlined in Scheme 1, viz. *N*-alkylation of azaindole **10** with methylacrylate followed by Dieckmann cyclization to provide ketone **5**. To install the chiral acid motif of **1**, we planned to olefinate the ketone **5** via a HWE reaction and then set the stereogenic center by asymmetric hydrogenation. A less desirable sequence involving racemic hydrogenation followed by biocatalytic resolution of the methyl ester was also considered. Finally, we planned to identify suitable leaving groups for sulfenyl derivative **13** to avoid the use of strong

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(1) (a) Cheng, K.; Wu, T. J.; Wu, K. K.; Sturino, C.; Metters, K.; Gottesdiener, K.; Wright, S. D.; Wang, Z.; O'Neill, G.; Lai, E.; Waters, M. G. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 6682. (b) Lai, E.; Wenning, L. A.; Crumley, T. M.; De Lepeleire, I.; Liu, F.; de Hoon, J. N.; Van Hecken, A.; Depré, M.; Hilliard, D.; Greenberg, H.; O'Neill, G.; Metters, K.; Gottesdiener, K. G.; Wagner, J. A. *Clin. Pharmacol. Ther.* **2008**, *83*, 840. (c) Paolini, J. F.; Bays, H. E.; Ballantyne, C. M.; Davidson, M.; Pasternak, R.; Maccubbin, D.; Norquist, J. M.; Lai, E.; Waters, M. G.; Kuznetsova, O.; Sisk, C. M.; Mitchel, Y. B. *Cardiol. Clin.* **2008**, *26*, 547. (d) Sturino, C. F.; O'Neill, G.; Lachance, N.; Boyd, M.; Berthelette, C.; Labelle, M.; Li, L.; Roy, B.; Scheigetz, J.; Tsou, N.; Aubin, Y.; Bateman, K. P.; Chauret, N.; Day, S. H.; Levesque, J. F.; Seto, C.; Silva, J. H.; Trimble, L. A.; Carriere, M. C.; Denis, D.; Greig, G.; Kargman, S.; Lamontagne, S.; Mathieu, M.-C.; Sawyer, N.; Slipetz, D.; Abraham, W. M.; Jones, T.; McAuliffe, M.; Piechuta, H.; Nicoll-Griffith, D. A.; Wang, Z.; Zamboni, R.; Young, R. N.; Metters, K. M. *J. Med. Chem.* **2007**, *50*, 794.

(2) (a) Paolini, J. F.; Lai, E.; Mitchel, Y. B. WO/2008/097535, 2008. (b) Kamanna, V. S.; Ganji, S. H.; Kashyap, M. L. *Int. J. Clin. Pract.* **2009**, *63*, 1369. (c) Leblanc, Y.; Roy, P.; Dufresne, C.; Lachance, N.; Wang, Z.; O'Neill, G.; Greig, G.; Denis, D.; Mathieu, M.-C.; Slipetz, D.; Sawyer, N.; Tsou, N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2125.

(3) (a) Dynamic scanning calorimetry revealed unsafe exotherms at operating temperatures. (b) For review of toxicological effects of organotin compounds see: Appel, K. E. *Drug Metab. Rev.* **2004**, *36*, 3−4763.

(4) For review of hydrogenation of α,β-unsaturated acids and esters see: Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(5) For review of enzymatic resolutions see: Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071.

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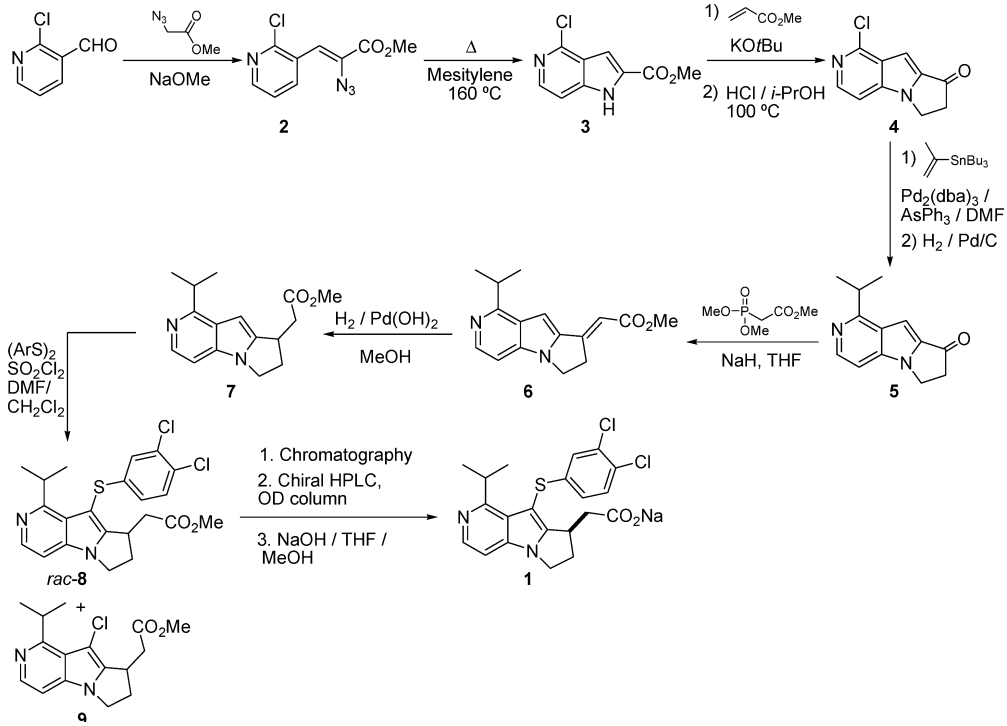
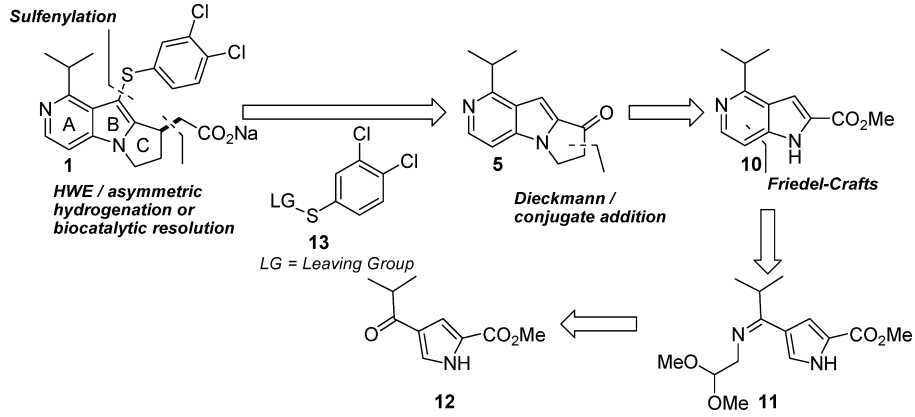
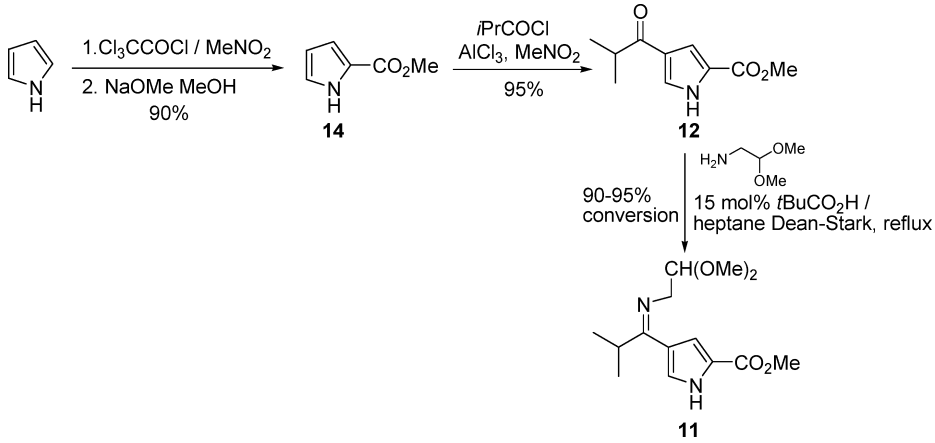
Scheme 1. **First-generation synthesis**



Scheme 2. **Retrosynthetic analysis to the azaindole core**



Scheme 3. **Preparation of cyclization precursor 10**



chlorinating agents during the penultimate sulfenylation step which led to the formation of the 3-chloroindole impurity.

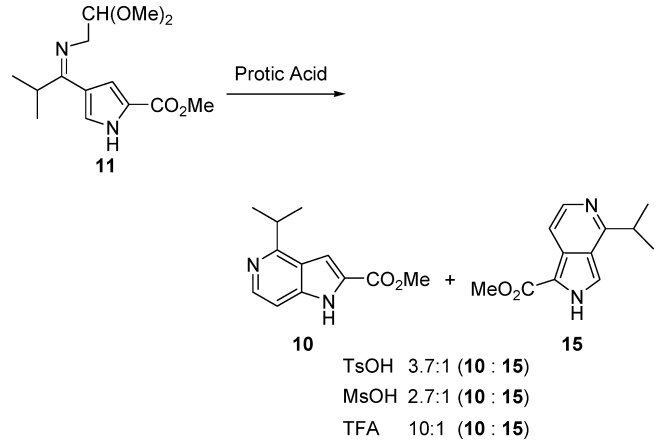
Preparation of The Azaindole Core. Our synthetic studies began by quickly developing a scalable preparation of pyrrole **12** (Scheme 3). Pyrrole **12** could be prepared in a highly regioselective manner via a sequence involving Friedel−Crafts acylation of pyrrole with trichloroacetyl chloride followed by basic methanolysis of the trichloromethyl group to give methyl

ester **14**.[6] Aluminum trichloride-promoted Friedel−Crafts acylation with isobutyryl chloride in nitromethane at 0 °C afforded pyrrole **12**[7] which was readily isolated via crystallization from toluene/heptane. Several attempts were made to form imine **11** from **12** using aminoacetaldehyde dimethyl acetal under a variety of dehydrating conditions (Dean−Stark, $Ti(OEt)_4$, $P(OEt)_3$, 4 Å molecular sieves, $MgSO_4$, P_2O_5, or $ZnCl_2$) with varying results. Complete conversion to imine **11** by GC and ^1H NMR was observed using stoichiometric quantities of $Ti(OEt)_4$ and excess amino acetal in toluene at 70 °C. Unfortunately, the downstream isolations proved difficult to optimize due to the mixture of transesterification products that resulted from the $Ti(OEt)_4$-promoted imine formation.[8] Furthermore, many of the workup protocols we investigated resulted in precipitation of titanium salts which were difficult to remove on-scale.[9] After exhausting many of the condensation procedures, a simple Dean−Stark protocol, employing 15 mol % pivalic acid, 1.7 equiv of aminoacetaldehyde dimethylacetal, in 4−6 volumes (V) of heptane, at reflux for 40 h, provided 90−95% conversion to the desired imine **11** favoring the *Z*-isomer. This protocol was therefore selected for our subsequent kilogram-scale operations due to its operational simplicity and simple incorporation into the subsequent cyclization.

With the desired imine **11** in hand, we began to investigate the acid-promoted cyclization to generate azaindole **10** (Scheme 4).[10] A limited screen of protic acids identified TFA (10−20 equiv. at 60−70 °C) as a competent promoter of the Friedel−Crafts annulation providing the desired azaindole **10** in ∼70% assay yield (10:1 ratio of **10**:**15**, respectively). The residual ketone **12** was easily rejected by extraction of **10** into aqueous acid, followed by pH adjustment to ∼10 and extraction into IPAc. The product was then crystallized from MeOH/H_2O or EtOAc/heptane to give azaindole **10** in 65% isolated yield with ∼5% liquor losses.

Having successfully performed the reaction on 1−2 g, we increased the scale to 50 g of ketone **12** to refine the workup and isolation protocols. Formation of imine **11** using the Dean−Stark protocol proceeded smoothly (92% conversion by GC). At this point we opted to remove the excess aminoacetalehyde dimethylacetal via azeotropic distillation with xylene as this impurity hindered the downstream isolation of the

Scheme 4. **Screen of protic acids for Friedel−Crafts annulation**



azaindole **10**. To promote cyclization, the concentrated xylene solution of imine **11** was added to hot TFA (20 equiv, 45 °C) and aged at 65 °C for 6 h before cooling to ambient temperature over 18 h. Removal of excess TFA via distillation and solvent switching into IPAc provided crystalline azaindole **10** as its TFA salt. Although this salt could be isolated by filtration, high hygroscopicity and high mother liquor losses prompted investigation of an alternative salt for isolation. After performing a small number of slurry experiments and quantitatively analyzing the supernatant, *p*-toluenesulfonic acid (*p*-TSA) was found to be ideal. Turnover to the *p*-TSA salt was easily achieved by diluting the TFA salt slurry with water (1.2 V) and then adding a solution of 2.7 equiv of *p*-TSA acid in 2:1 IPAc/water (15 V). After aging the reaction for 30 min at 30 °C, the triphasic mixture was cooled to ambient temperature and the *p*-TSA salt of **10** isolated in 72% overall yield from the pyrrole **12**. With our streamlined process in place, we began our initial front runs prior to our kilogram-scale operations. Unfortunately, when the imine formation was scaled to 150 g, only 72% conversion was obtained. Further studies revealed that the rate of heptane distillation, and thus the rate of dehydration in the reaction, was directly correlated to the conversion of ketone **12** to imine **11**. At lower distillation rates insufficient drying resulted in <80% conversion and significant depreciation in the rate towards the end of the reaction. To mitigate this problem on-scale, we reduced our planned 8−10 kg batch size and ran multiple 2.5 kg batches so that a steady heptane distillation rate of 500 mL/min could be accommodated.[11]

Imine Formation and Cyclization. Using the process outlined previously, three batches of ketone **12** were condensed with aminoacetaldehyde dimethylacetal in the presence of 15 mol % of pivalic acid in heptane at reflux; in all cases a distillation rate of ∼500 mL/min was maintained. Each batch proceeded to 85−90% conversion, at which point they were combined and the solvent switched to xylene to afford a concentrated solution of imine **11** (∼32.7 mols) after continued distillation. After splitting the xylene solution into two batches, the concentrated solution of imine **11** was added to warm TFA (45 °C, 20 V) over 40 min and then heated to 65 °C for 5 h to

(6) For previous syntheses of pyrrole ester **14** see: (a) Wasley, J. W. F. U.S. Patent 4,596,799, 1986. (b) Bailey, D. M.; Johnson, R. E.; Albertson, N. F. *Org. Synth.* **1971**, 100. (c) Harbuck, J. W.; Rapoport, H. *J. Org. Chem.* **1972**, *37*, 3618. (d) Bailey, D. M.; Johnson, R. E.; Albertson, N. F. *Org. Synth.* **1988**, *VI*, 618. (e) Schmuck, C.; Bickert, B.; Merschky, M.; Geiger, L.; Rupprecht, D.; Dudaczek, J.; Wich, P.; Rehm, T.; Machon, U. *Eur. J. Org. Chem.* **2008**, *2*, 324.

(7) For similar synthesis of pyrrole **12** see: Bhuniya, D.; Kapkoti, S. G.; Warrier, S. J.; Kukrejka, G.; Mavinahalli, N. J.; Palle, P. V.; Mookhtiar, A. K. WO/2008/149382, 2008. CAN 150:35222.

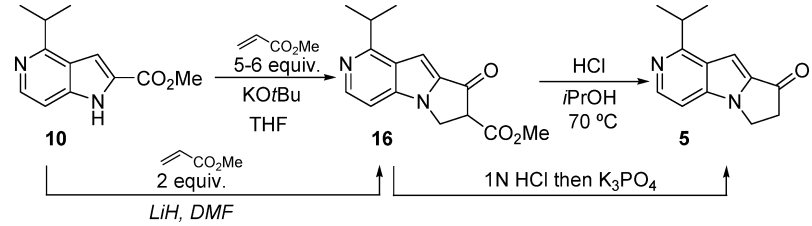
(8) Commercial $Ti(OEt)_4$ is received as a 4:1 mixture of $Ti(OEt)_4$/$Ti(OiPr)_4$. Imine formation using this reagent gave mixtures of methyl, ethyl, and isopropyl esters of imine **11**.

(9) Although most aqueous systems gave emulsions, titanium salts could be removed by washing the IPAc extract with 40% aqueous glycolic acid.

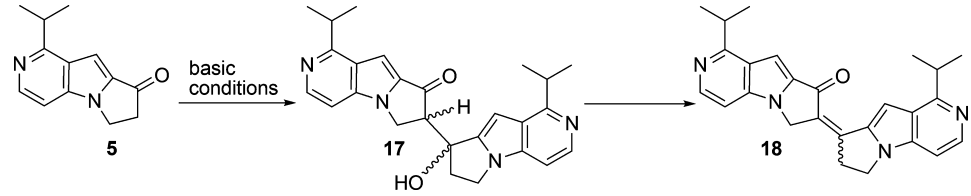
(10) For examples of azaindole syntheses, including Friedel−Crafts cyclization protocols see: (a) Dekhane, M.; Potier, P.; Dodd, R. H. *Tetrahedron* **1993***49*, 36, 8139. (b) Willette, R. E.; *Adv. Heterocycl. Chem.*: Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1968; Vol. 9, p 27. (c) Yakhontov, L. N. *Russ. Chem. Rev.* **1968**, *37*, 551. (d) Yakhontov, L. N.; Prokopov, A. A. *Russ. Chem. Rev.* **1980**, *49*, 428. (e) Dumas, D. J. *J. Org. Chem.* **1988**, *53*, 4650.

(11) Further engineering studies to address the distillation rate issue would need to be conducted prior to scale-up beyond 2.5 kg. Since this project was discontinued, no further work in this area has been conducted.

Scheme 5. **Formation of the C ring**



Scheme 6. **Basic stability of tricyclic ketone 5**



complete the cyclization. Distillation followed by azetropic removal of the residual TFA using the previously discussed protocol generated an IPAc slurry of the TFA salt of azaindole **10**, which was smoothly converted to desired *p*-TSA salt via the protocol *vide supra*. The first batch provided 7.6 kg (3.44 kg free base equiv) and the second 10.85 kg (5.13 kg free base equiv), respectively. The batches were combined to provide 18.5 kg of the *p*-TSA salt of **10** in 72% overall yield from ketone **12**. The *p*-TSA salt of **10** was converted to the free base using aqueous triethylamine to minimize potential ester hydrolosis or transesterification. Crystallization from ethyl acetate-heptane gave 8.3 kg (95%) of indole ester **10** as its free base.

Conjugate Addition/Dieckmann Cyclization. Our approach to forming the C ring of **1** closely mirrored that of the original medicinal chemistry route *viz* azaindole **10** was reacted with methyl acrylate in the presence of potassium *tert*-butoxide in THF, followed by decarboxylation under acidic conditions (concd HCl/*i*PrOH, 70 °C) to generate ketone **5** in ~80% yield after workup and isolation (Scheme 5).[12]

On scale-up, the initial conjugate addition proved problematic due to complications with reaction workup and the isolation of keto-ester **16**. The likely problem was polymeric byproduct derived from the 5−6 equiv of methyl acrylate which was required to drive the reaction to completion. A simple screen of bases and solvents showed that LiO*t*Bu or the more economical LiH[13] in DMF gave a clean reaction requiring only two equivalents of methyl acrylate for a complete reaction. On scale up, portion wise addition of LiH (1.5 equiv.) to a cooled (~10 °C) solution of azaindole **9** in DMF (2 volumes) resulted in an exothermic deprotonation event where the internal temperature of the reaction was allowed to reach 65 °C. Gradual addition of two equivalents of methyl acrylate over 1 h followed by a 1 h age resulted in >99.5% conversion to the desired keto-ester **16**. Direct crystallization from the reaction mixture via addition of acetic acid (1.5 equiv.) and water (9 volumes) provided the keto-ester **16** in 87% isolated yield after filtration and drying. Two equal sized batches of azaindole **10** were processed affording a total of 8.7 kg of keto-ester **16** (87% and 86% yields respectively).

A slightly modified decarboxylation protocol was also developed for the keto-ester **16** employing 1.5 equiv. of 1 M aq HCl at 91−95 °C for 3 h. Scale-up of the decarboxylation step was largely uneventful, except for the foamy evolution of CO_2 which was easily controlled by addition of a small amount of toluene and MeOH. Upon completion of the reaction, careful control of the pH was required to prevent the formation of dimeric biproducts during the crystallization (Scheme 6). Adjustment of the pH with bases such as NaOH, resulted in formation of the dimeric aldol products **17** which dehydrated to give a mixture of enones **18** in (10−20%) conversion. A screen of bases revealed that quenching the reaction with 1.5 equivalents *N*-methylmorpholine or tribasic potassium phosphate minimized the formation of **18** to <1%.

On kilogram scale, basification with K_3PO_4 (1.5 equiv.) to pH = 7 proceeded smoothly, resulting in crystallization of the tricyclic ketone in 93−94% yield. Two kilogram scale batches of the keto-ester **16** were processed to provide a total of 6.2 kg (89% yield) of tricyclic ketone **5**.

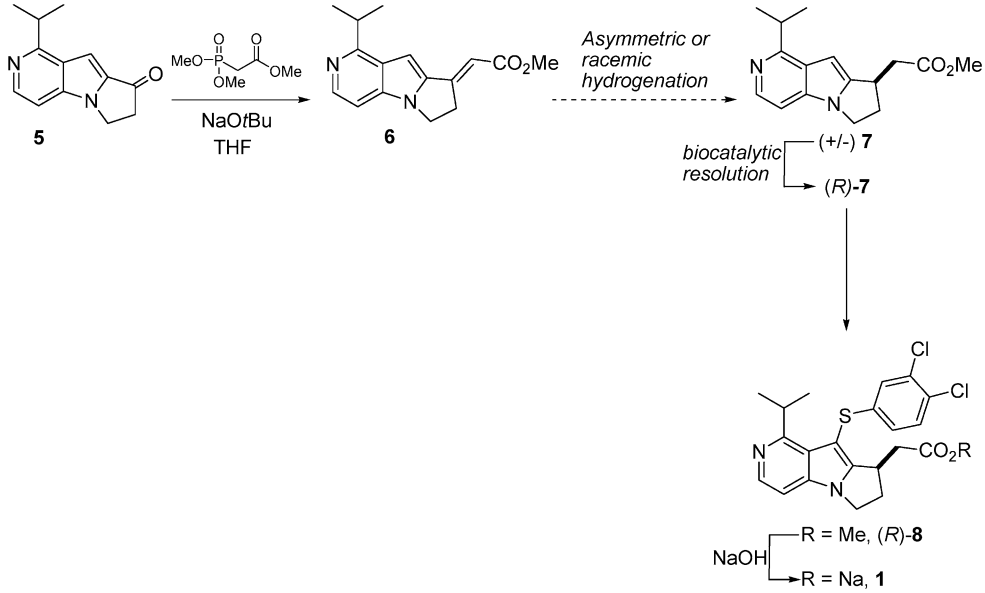
Horner-Wadsworth-Emmons (HWE)/Hydrogenation/Sulfenylation/Hydrolysis. With a scalable synthesis of ketone **5** in hand, we focused our investigations on the endgame process (Scheme 7). Since ketone **5** was an actual intermediate in the medicinal chemistry route, we believed that the HWE step would be amenable to scale-up with minimal process development.

To circumvent the use of sodium hydride, a screen of bases and solvents was run. Ethereal solvents such as THF and MTBE gave superior results, although the solubility of the trimethylphosphonoacetate anion and ketone starting material limited the concentration and rate of the reaction. Of all the bases screened, sodium amylate in THF (15 V) provided the cleanest reaction profile. In methanol, significant formation the aldol byproduct **17** (Scheme 6) was observed; however, in polar solvents such as acetonitrile and dimethylformamide, or in the

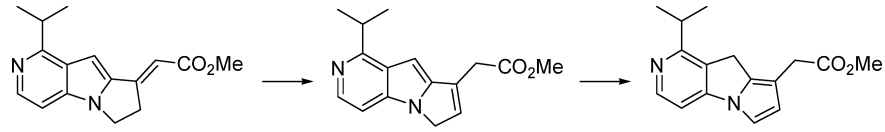
(12) For other conjugate addition/Dieckmann cyclization protocols see: (a) Allen, G. R., Jr.; Poletto, J. F.; Weiss, M. J. *J. Org. Chem.* **1965**, *30*, 2897. (b) Bailey, A. S.; Scott, P. W.; Vandrevala, M. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, *1*, 97. (c) Casner, M. L.; Remers, W. A.; Bradner, W. T. *J. Med. Chem* **1985**, *28*, 921. (d) Perzyna, A.; Klupsch, F.; Houssin, R.; Pommery, N.; Lemoine, A.; Henichart, J.-P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2363. (e) Khdour, O.; Skibo, E. B. *J. Org. Chem.* **2007**, *72*, 8636.

(13) In-house data generated over several years has demonstrated clear safety advantages for the use of LiH over NaH. For computational calculations of the bond lengths of LiH versus NaH see: Wenthold, P. G. *Int. J. Mass Spectrom.* **2000**, *195/196*, 319.

Scheme 7. **The end-game**



Scheme 8. **Isomerization to pyrrole 20**



presence of excess base, ester **19** was formed which was then converted to pyrrole **20** (Scheme 8).[14]

Addition of sodium amylate to a THF solution of trimethylphophonoacetate provided a thick slurry; however, after aging for 2 h the slurry became much lighter and could be readily stirred. A screen of alkylphosphonoacetates (Me, Et, *t*Bu) was performed to see if the volume efficiency could be improved. Although similar *E*/*Z* ratios (~14:1 respectively) were obtained, the ethyl- and *tert*-butyl- phosphonoacetates generated significantly more of the aldol byproduct **17** than the methylphophonoacetate. Following workup, pure *E*-enoate **6** could be obtained by crystallization from MeOH/H_2O (70% isolated yield - >10 g batches, 50:1, *E*/*Z*). While this isolation allowed us to prepare enough of enoate **6** to investigate the downstream chemistry, high liquor losses (about 10% loss of the *E*-isomer) prompted us to seek an alternate isolation. Several acids (MsOH, $PhSO_3H$, CSA, TsOH, citric acid) were shown to precipitate salts enriched in the *E*-isomer with *p*-TSA and citric acid showing the most promise. This initial lead was quickly incorporated into the process. After completion of the HWE reaction (trimethylphosphonoacetate, 2 equiv; sodium amylate, 1.5 equiv; THF, 15 V), we opted to quench the reaction with the more economical 85% phosphoric acid (1.5 equiv), thus minimizing the theoretical charge of *p*-TSA by 50%. Addition of an aqueous solution of *p*-TSA to the slurry of the phosphate salt afforded a highly crystalline salt which could be isolated with minimal liquor losses (44-g scale, 77% isolated yield, 79% crude assay yield). The salt was then converted to the free base of **6** via treatment with triethylamine in 2.5:1 methanol/water to give the desired *E*-enoate **6** in good yield and high purity (*E*/*Z* ratio, 1000:1, 98% isolated yield, 99% LCAP). With our optimized conditions in hand, two batches of enoate **6** were prepared on kilogram scale. In each case, the reactions proceeded as expected providing 2.2 and 3.1 kg of the free base of **6** (76% and 75% yield, respectively).

Hydrogenation of α,β-Unsaturated Methyl Ester 6. As outlined in Scheme 7, we envisioned two approaches to install the chirogenic center of **1**. First, we planned to utilize the existing racemic hydrogenation of **6** and then resolve the enantiomers of **7** biocatalytically. Our second approach relied on asymmetric hydrogenation of **6** to install the chirality directly. Since the racemic ester **7** had already been prepared, we initially evaluated the biocatalytic option. A screen of hydrolases quickly revealed that the two enantiomers of **7** could be easily resolved using *P. cepacia* lipase[15] or immobilized CALB[16] to afford the desired enantiomer of **7** in ~48% yield and 95−97% ee. Although this strategy gave the desired ester **7** in high enantiomeric excess, the low yield (maximum 50%) so late in the synthesis was inefficient and costly. Consequently, we focused our efforts on the more challenging asymmetric hydrogenation.

It is well documented that hydrogenations of an enoate such as **6**, typically proceed with low enantioselectivity, require high catalyst loadings (>1 mol %), and necessitate the use of high hydrogen pressures (>500 psig).[4] This is attributed to the lack of a coordinating group to chelate the catalyst and "direct" the

(14) Studies to expand the scope of this reaction will be reported in due course.

(15) Guieysse, D.; Salagnad, C.; Monsan, P.; Remaud-Simeon, M. *Tetrahedron: Asymmetry* **2003**, *14*, 317.

(16) Velonia, K.; Flomenbom, O.; Loos, D.; Masuo, S.; Cotlet, M.; Engelborghs, Y.; Hofkens, J.; Rowan, A. E.; Klafter, J.; Nolte, R. J. M.; de Schryver, F. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 560.

Table 1. **Screen of metal precursors and ligands for aymmetric hydrogenation of enoate 6**

entry	metal	ligand[a]	A% conversion	% ee
1[b]	Rh	Et-BoPhoz	53	71
2[b]	Rh	C1-TunaPhos	36	11
3[b]	Rh	CTH-P-Phos	89	28
4[b]	Rh	xyl-BINAP	45	54
5[b]	Rh	xyl-P-Phos	25	40
6[b]	Rh	Walphos Ph_2P-Ph-Fc-C-P(3,5-Me_2Ph)$_2$ (W006−1)	95	25
7[b]	Ir	Phanephos	13	56
8[b]	Ir	Xyl-PhanePHOS	49	−49
9[b]	Ir	Taniaphos Ph_2P-Fc-C-Ph-PPh_2 (SLT001-1)	35	69
10[b]	**Ir**	**Walphos (3,5-Me_2-4-MeO-Ph)$_2$P-Ph-Fc-C-P(3,5-$(CF_3)_2$Ph)$_2$ (SLW005-1)**	**100**	**−77**
11[b]	**Ir**	**Walphos Ph_2P-Ph-Fc-C-P-(3,5-$(CF_3)_2$Ph)$_2$ (W001-1)**	**77**	**−83**

[a] All ligands are commercially available from Strem Chemicals Inc. or Solvias. [b] Conditions: 10 mol % catalyst, 18 h, 40 °C, 90 psig. Metal precursors: $Rh(COD)_2BF_4$ and $Ir(COD)_2BF_4$.

hydrogenation.[17] Given the limited precedence for this transformation, we opted to perform a broad screen of chiral ligands and metal precursors (Ru, Rh, Ir) at a constant hydrogen pressure (90 psig) in dichloroethane. A subset of ligands from each ligand family (planar chiral, BINAP, P,N-ligand, monodentate) was studied as opposed to screening every ligand within a particular family which is typical for traditional hydrogenations; e.g., ene acid, enamide, ketone.[18] Selected results from this screen are shown in Table 1. Good reactivity was observed with rhodium catalysts, albeit, with poor to moderate enantioselectivity. Ruthenium catalysts exhibited very little reactivity. We were pleased to find that iridium with the Walphos family of ligands gave the best reactivity and enantioselectivity (Table 1, entries 10 and 11).[19] We opted to focus on the Walphos ligand used in entry 10 as it was found to be more reactive than Walphos ligand W001-1 (entry 11).

A solvent screen was performed in order to find a more environmentally friendly solvent than 1,2-dichloroethane. The results from this solvent screen are highlighted in Figure 1. Surprisingly, the iridium−Walphos catalyst exhibited nearly identical performance regardless of solvent (Figure 1). This lack of dependence on solvent is not observed in most hydrogenations. For example, DMF and DMAc, solvents typically not used in asymmetric homogeneous hydrogenations, gave good reactivity *and* enantioselectivity. Ultimately, we opted to use

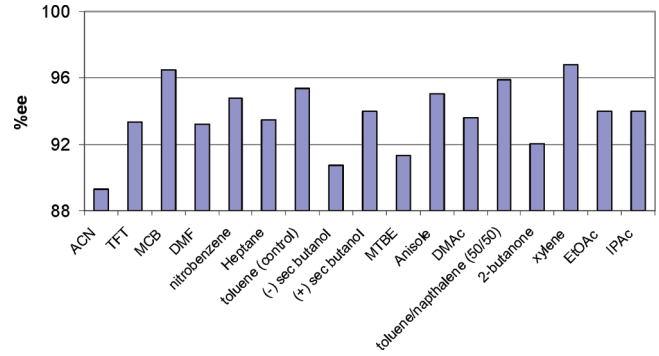


Figure 1. **Percent ee as a function of solvent. Conditions: 0.5 mol % catalyst loading and 90 psig H_2. All solvents gave >85% conversion.**

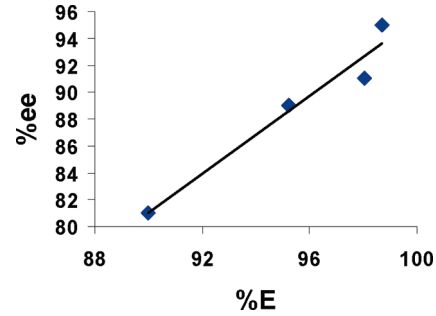


Figure 2. **Reaction % ee plotted as a function of % *E* isomer in 6 (0.5 mol % catalyst loading and 90 psig H_2).**

toluene as the hydrogenation solvent, allowing efficient telescoping of the process stream into the sulfenylation step.[20]

Having identified a suitable catalyst lead, subsequent efforts focused on developing a robust and scaleable process while minimizing catalyst loading. Hydrogenation optimization was done in parallel with route optimization. Not surprisingly, reactivity and enantioselectivity varied substantially with purity of starting material. In order to circumvent this, a highly pure sample of **6** was prepared by chromatography, providing material to facilitate hydrogenation optimization. With purified starting material, the reaction performance improved markedly where catalyst loadings down to 0.1% could be obtained without sacrificing ee or conversion. During the optimization process, we also examined the impact of the *E*/*Z* ratio of enoate **6** on enantioselectivity. Indeed, under the optimized conditions, batches of enoate **6** containing ∼9% of the *Z*-isomer afforded **7** in only 81% ee, whereas batches of **6** containing 1% of the *Z*-isomer gave **6** in 96% ee (Figure 2).

The low catalyst loading and high enantioselectivity obtained from the chromatographically pure material further reinforced the need for an efficient isolation of **6** in high purity (*vide supra*). Gratifyingly, we found that the optimized HWE reaction coupled with the newly developed isolation and purity upgrade provided material that behaved optimally in the hydrogenation. Small-scale demonstration reactions (5−10 g) proceeded in excellent yield and enantioselectivity, as did the multiple

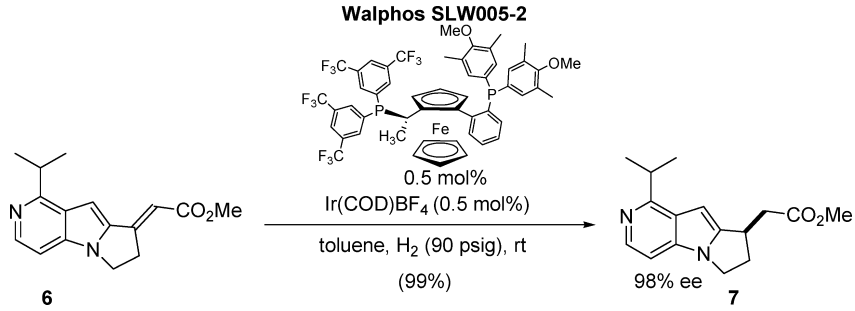
(17) (a) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6* (12), 2023. (b) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160. (c) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789. (d) Pugin, B.; Studer, M.; Kuesters, E.; Sedelmeier, G.; Feng, X. *Adv. Synth. Catal.* **2004**, *346*, 1481. (e) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513. (f) Guimet, E.; Dieguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2247. (g) Reetz, M. T.; Kayser, F. *Tetrahedron: Asymmetry* **1992**, *3* (11), 1377. (h) Ponikwar, W.; Mayer, P.; Beck, W. *Eur. J. Inorg. Chem.* **2002**, 1932.

(18) Shultz, C. S.; Krska, S. W. *Acc. Chem. Res.* **2007**, *40*, 1320.

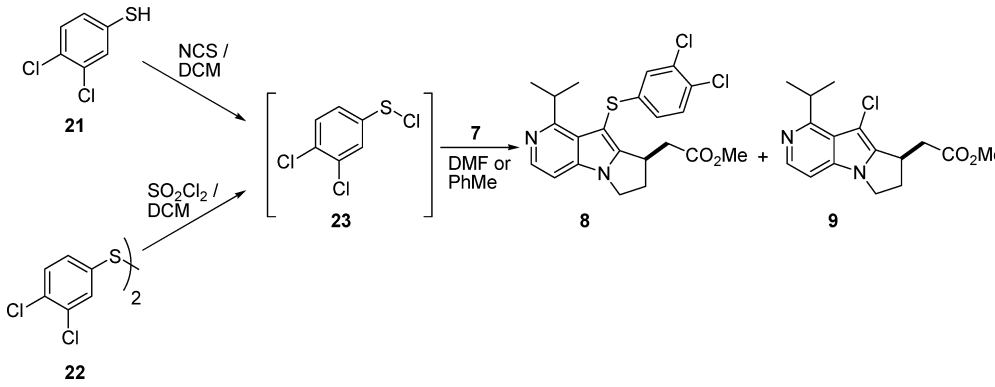
(19) For an example of an asymmetric hydrogenation of β,β-substituted enoates at higher pressure, see: Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 943.

(20) Care should be taken when handling toluene on scale, given that it has a high potential for static build-up. Hydrogenation vessels should be properly grounded when transferring toluene solutions.

Scheme 9. **Optimized asymmetric hydrogenation of enoate 6**



Scheme 10. **Optimized medicinal chemistry sulfenylation**



kilogram scale-up.[21] The optimized process is shown in Scheme 9. A total of 5.2 kg of **6** were subjected to the hydrogenation conditions. The hydrogenations were performed in three batches and yielded **7** in 99% assay yield and 98% ee. Compound **7** was carried on directly into the sulfenylation step as the high yield and purity obviated the need for purification since the residual iron and iridium could be removed via a combination of activated carbon treatment and crystallization.

Introduction of the Arylsulfide Moiety. Our initial strategy for introducing the aryl sulfide motif centered around two protocols. Both involved stoichiometric oxidation of thiophenol **21**[22] (NCS, DCM) or disulfide **22**[23] (SO_2Cl_2, DCM) to the requisite sulfenyl chloride moiety **23** which, in turn, was reacted with azaindole **7** to afford the penultimate intermediate **8** (Scheme 10). In both cases, appreciable amounts of chlorinated indole **9** were observed by HPLC, LC/MS, and ^{1}H NMR. Further ^{1}H NMR studies showed that the NCS oxidation generated both sulfenyl chloride and disulfide in a 1:2.5 ratio. This ratio could be improved to ~20:1 by slow addition of the thiol to an excess of NCS over 3 h. Unfortunately, upon addition of azaindole **7** to the reaction, concomitant chlorination of the indole resulted in the generation of significant quantities of chloro-indole **9**. For the first small-scale delivery of **1**, we decided to optimize the medicinal chemistry protocol to suit our needs. Formation of the chlorosulfide proceeded smoothly (**22**, SO_2Cl_2, CH_2Cl_2); however, when this solution was treated with azaindole **7**, significant quantities of chloroindole **9** were observed.

A survey of the literature revealed that sulfuryl chloride was known to chlorinate the 3-position of indoles,[24] prompting us to remove the residual reagent via distillation prior to addition of azaindole **7**. The methylene chloride was therefore removed *in vacuo* and replaced with toluene. This solution was then treated with a toluene solution of azaindole **7** and heated to 70 °C for 24 h to afford sulfenylated azaindole **8** as its HCl salt 90−98% yield (92−95% LCAP). While this protocol was suitable for delivering 30−40 g of penultimate intermediate **8**, instability of the sulfenyl chloride intermediate prompted us to seek alternate sulfenylating agents for our kilogram-scale operations.

A search of the literature revealed that thiosuccinimide and thiophthalimide reagents were crystalline, bench-stable compounds.[25] On this basis, we elected to prepare the 3,4-dichlorophenylthio analogues and assess them as electrophilic sulfenylating agents. Both the thiophthalimide **24** and the thiosuccinimide **25** reagents were easily prepared (**21** 1 equiv, pyr. 3 equiv, Br_2 1.14 equiv, succinimide 1.1 equiv, MeCN 7 V) on a multigram scale (Scheme 11). In each case, the desired products crystallized directly from the reaction mixture with the thiophthalimide reagent **24** being isolated in near quantitative yield.

In an initial screen, both thiophthalimide **24** and thiosuccinimide **25** (1.5 equiv) reacted smoothly with the azaindole **7** to afford the penultimate intermediate **8** in 80−86% assay yield. Under the optimized reaction conditions (DMAc, 100 °C), the thiophthalimide reagent **24** was found to be more stable than

(21) *Nota bene*: The iridium precursor is thermally stable, and the quality of those from different vendors varies dramatically (e.g., reaction vs nonreaction). Pure iridium precursor is deep purple and yields a homogeneous dark-red solution.

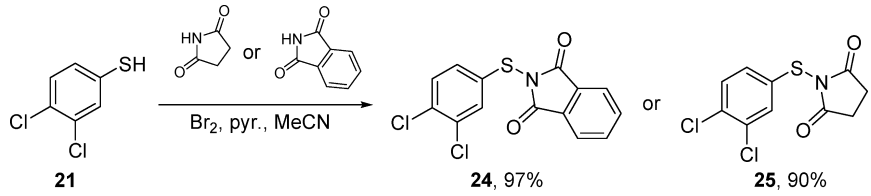
(22) Schlosser, K. M.; Krasutsky, A. P.; Hamilton, H. W.; Reed, J. E.; Sexton, K. *Org. Lett.* **2004**, *6* (5), 819.

(23) Anzai, K. *J. Heterocycl. Chem.* **1979**, *16*, 567.

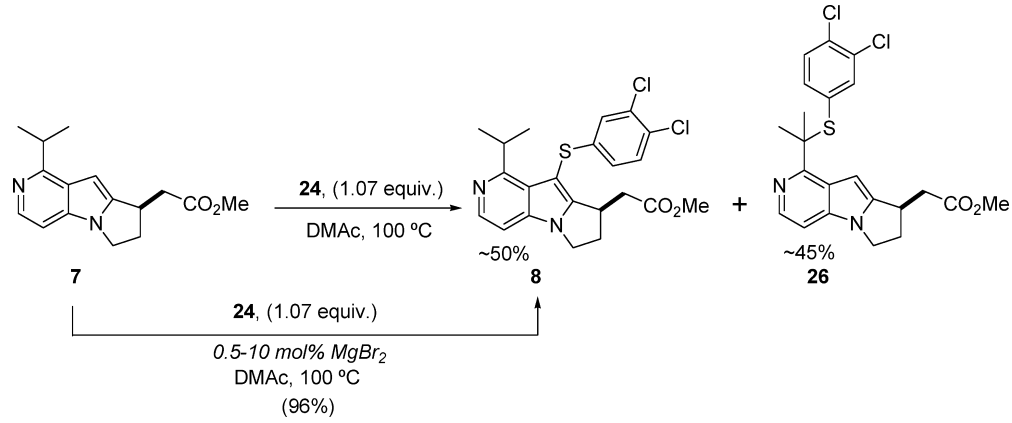
(24) For examples of the synthesis of 3-chloroindoles with sulfuryl chloride see: (a) De Rosa, M.; Carbognani, L.; Febres, A. *J. Org. Chem.* **1981**, *46*, 2054. (b) Erickson, K. L.; Brennan, M. R.; Namnum, P. A. *Synth. Commun.* **1981**, *11*, 253. (c) Brennan, M. R.; Erickson, K. L.; Szmalc, F. S.; Tansey, M. J.; Thornton, J. M. *Heterocycles* **1986**, *24*, 2879.

(25) For a scalable synthesis of thiophthalimide reagents see: Klose, J.; Reese, C. B.; Song, Q. *Tetrahedron* **1997**, *53*, 14411.

Scheme 11. **Preparation of thiosuccinamide and thiophthalimide reagents**



Scheme 12. **Generation of an unexpected byproduct**



25 to thermal and oxidative decomposition to the disulfide **22**. This decomposition pathway could be further minimized by the efficient degassing of the reaction solvent, allowing the charge of the thiophthalimide reagent to be dropped to 1.07 equiv.

One batch of thiophthalimide **24** was prepared by treating thiol **21** and phthalimide with bromine (1.1 equiv) in CH_3CN in the presence of pyridine to give **24** (8.13 kg, 103 wt %, 97% isolated yield). Surprisingly, a small-scale (~100 g) use test of the bulk thiophthalimide reagent **24** with the previously prepared hydrogenation product **7** only gave ~50% yield of the desired product with the remainder converted to thio-ether **26** in 45% yield (Scheme 12).

After further investigating the reaction using previously prepared batches of thiophthalimide **24**, it quickly became apparent that the kilogram-scale batch of this reagent was the problem. Detailed analysis by NMR and LC/MS revealed no difference between the kilogram-scale and the gram-scale batches. After discounting the theory that residual transition metals were involved in the reaction, we hypothesized that residual bromide might be the culprit. Indeed, this was confirmed when the bromide content of the two batches was determined. The gram-scale batches contained as much as 1000 ppm of bromide contamination, whereas on kilogram scale a more controlled crystallization had reduced this to ~40 ppm. This hypothesis was further supported when additive screening identified 10 mol % $MgBr_2$ as being an effective catalyst, most likely by generating small concentrations of the highly reactive sulfenyl bromide in the reaction.[26] Following further optimization studies to reduce the catalyst loading, two batches the crude hydrogenated product were submitted to the sulfenylation conditions (1.1 equiv of thiophthalimide **23**, 0.5 mol % $MgBr_2$ in DMAc, 90 °C). The kilogram-scale batches proceeded smoothly, providing 3.7 and 4.0 kg of sulfenylated ester **8** in 97% assay yield, which after isolation gave 3.5 kg, 95 wt %, 96% isolated yield, 97% ee, Ir 101 ppm, and 3.76 kg, 95 wt %, 91% isolated yield, 98.5% ee, Ir 148 ppm. To reduce the Ir content to an acceptable level, the methyl ester was treated with Ecosorb C-905 (89% recovery) in EtOAc at 40 °C for 2.5 h and crystallized from EtOAc/heptane: 6.8 kg, 95 wt %, 89% isolated yield (Ir 37 ppm).

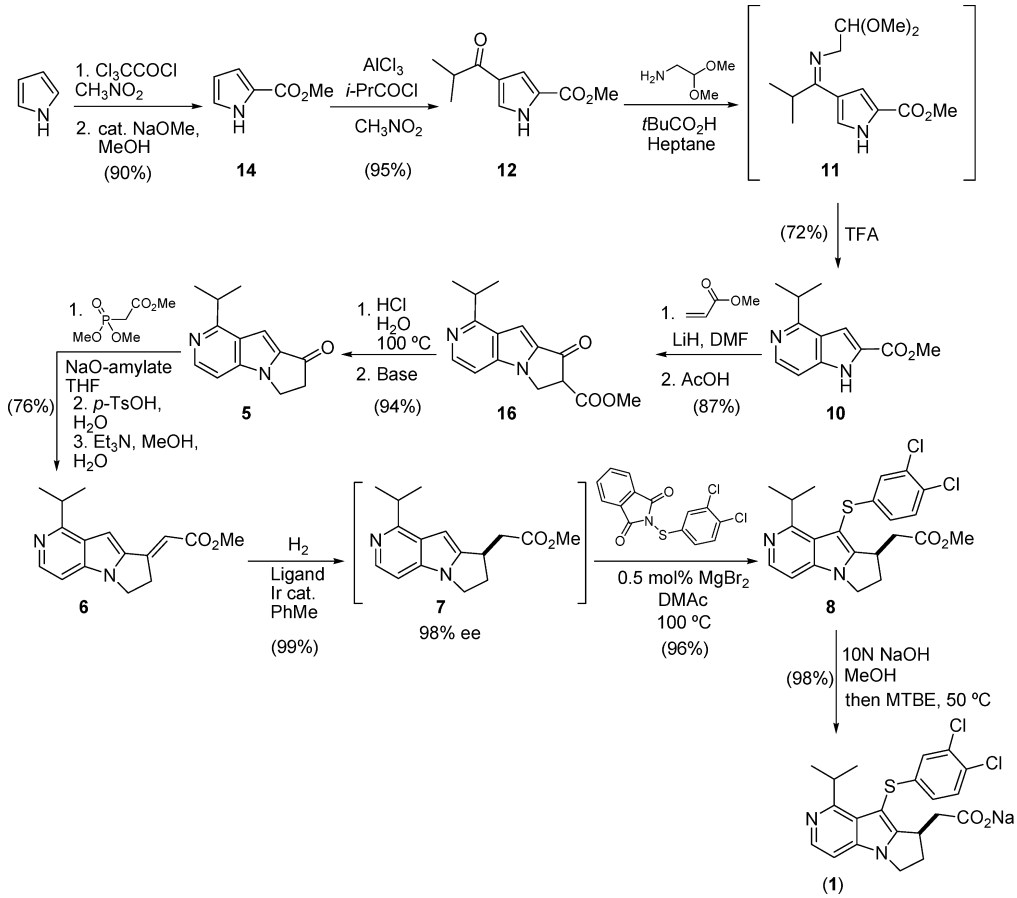
Ester Saponification and Isolation of 1. With the sulfenylation complete, all that remained to complete the synthesis was saponification of the methyl ester to the acid. Treatment of the methyl ester **8** in MeOH with aq NaOH (10 M; 1.3 equiv) at 50−60 °C resulted in complete conversion to **1** in essentially quantitative assay yield. Addition of water to the methanolic solution resulted in crystallization the Na salt of **1** as a hydrate (6.8 kg, 89 wt %) in 99% yield. Finally, the hydrated Na salt was treated with MTBE (11 V) at 50 °C for 1.5 h to convert the API to the required anhydrous crystal form. The slurry was filtered and dried to afford pure **1** (6.3 kg, 95 wt %) in 99% isolated yield.

Conclusions and Summary

In summary, we have developed a scalable and efficient synthesis of a DP receptor anatomist **1**. Key steps include a novel intramolecular Friedel−Crafts cyclization to form the aza indole core, a highly selective Horner−Wadsworth−Emmons olefination to install the *E*-enoate, and a novel iridium−Walphos-catalyzed enantioselective hydrogenation to set the lone chiral center. Finally, a robust sulfenylation of the azaindole was developed. The 11-step synthesis (Scheme 13) was used to prepare 6.3 kg of **1** as its monohydrate Na salt in 35% overall yield from pyrrole. Studies to expand the substrate scope of the azaindole synthesis and the asymmetric hydrogenation are underway and will be communicated in due course.

(26) Tudge, M.; Tamiya, M.; Savarin, C.; Humphrey, G. *Org. Lett.* **2006**, *4*, 565.

Scheme 13. **Final route to the drug candidate**



Experimental Section

General. Assay yields were obtained using analytical standards prepared by recrystallization, distillation or preparative chromatography. All isolated yields reflect correction for purity based on HPLC assays.

HPLC Methods. *Method A.* Zorbax Eclipse XDB-C8 4.6 mm × 150 mm column, gradient elution from 40:60 to 90:10 ACN/0.1% aqueous H_3PO_4, over 15 min,1.0 mL/min at 35 °C with UV detection at 210 and 254 nm.

Method B. Zorbax SB C-18, 25 cm ×4.6 mm column, isocratic 50:50 ACN/0.1% H_3PO_4, 1.0 mL/min at 30 °C with UV detection at 210 nm.

Method C. Zorbax Eclipse RX-C18; 4.6 mm × 150 mm column, gradient elution from 10:90 to 90:10 ACN/0.1% H_3PO_4 over 14 min, then hold at 90:10 CAN/0.1% H_3PO_4 for 2 min, 1.0 mL/min at 35 °C with UV detection at 210 nm.

Method D. Ace C8 3.0 mm ×150 mm, gradient elution from 20:80 to 80:20 ACN:0.1% H_3PO_4 over 10 min, 0.75 mL/min, at 30 °C with UV detection at 215 nm.

Method E. Chiralpak IA, 250 mm × 4.6 mm, isocratic 17% MeOH (25 mM iBuNH$_2$ in MeOH) in scCO_2 (200 bar), 35 °C, 1.5 mL/min with UV detection at 215 nm.

Method F. Zorbax Eclipse XDB-C8 4.6 × 150 mm column, gradient elution from 10:90 to 90:10 ACN/0.1% aqueous H_3PO_4, over 15 min, 1.25 mL/min at 35 °C, with UV detection at 210 nm.

Method G. Chiralpak AD-H, 250 mm × 4.6 mm, isocratic 10:90:0.1 EtOH/heptane/diisopropylamine, 1.5 mL/min, at 22 °C, with UV detection at 210 nm.

1*H*-Pyrrole-2-carboxylic Acid Methyl Ester (14).[6] A solution of *N*-methylmorpholine (6.0 kg, 52.3 mol) in MTBE (16 L) was cooled to 10 °C, and pyrrole (3.25 kg, 47.5 mol) was added in one portion. Trichloroacetylchloride (9.1 kg, 49.9 mol) was added over 1 h, maintaining the reaction temperature 10−30 °C. The slurry was aged at 20−25 °C for 1 h. The addition was exothermic, and a slurry of NMM·HCl formed during addition. The reaction was typically complete (>99 mol % conversion) after 1 h at 20−25 °C (HPLC). Upon complete reaction, methanol (1.0 L) was added, and the slurry was added to 25 wt % NaOMe in methanol (11.3 kg, 52.3 mol) at 20−35 °C over 1 h using methanol (1.0 L) to rinse the flask into the quench vessel. The slurry was stirred at 20−30 °C for 30 min until complete conversion to the ester by HPLC. Water (15 L) was added, and the lower aqueous layer was separated. The aqueous layer was extracted with MTBE (8 L), and the organics were combined. Aqueous citric acid (2.0 M, 15 L) was added to adjust pH to 4−4.5. The aqueous layer was cut and extracted with MTBE (8.0 L). The combined organics were washed with brine (15 wt %, 8.0 L). The crude organic mixture was treated with heptane (20 L) to crystallize the desired product as brown needles (5.93 kg, 100% isolated yield).

HPLC (Method A) retention times: pyrrole 2.84 min; trichloroester 7.03 min; methyl ester 2.84 min.

4-Isobutyryl-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (12).[7] Aluminum chloride (7.0 kg, 52.8 mol) was added in three portions to cold (0 °C) nitromethane (9.0 L). The addition of aluminum chloride was exothermic and temperature was maintained <40 °C. The solution was cooled to ambient and

iso-butyrylchloride (5.7 kg, 52.8 mol) added in one portion. The solution was cooled to −5 °C and solid pyrrole ester (6.0 kg, 48.0 mol) added over 1 h in 5 portions, maintaining the reaction temperature <15 °C. The solution was aged at 15−20 °C for 30 min. The reaction was followed by HPLC and was complete (>99.9 mol % conversion) 5−10 min post addition of pyrrole. A 50 L separator was charged with toluene (30 L) and water (30 L). The two-phase mixture was cooled to 5 °C and the keto-ester reaction mixture added to the aqueous toluene over about 30 min maintaining the quench temperature <40 °C. On complete addition the mixture was stirred for 30 min at 30−35 °C. The aqueous layer was removed and the organic layer washed with water (15 L). The organics were concentrated at 10−25 °C under reduced pressure to remove water and nitromethane and to crystallize the product. Toluene (20 L) was added and the distillation continued until the nitromethane level was <4 mg/mL and the final batch volume was approx 30 L. Heptane (40.0 L) was added and the slurry stirred at 5 °C for 1 h. The slurry was filtered and washed with heptane (1 L) to afford **12** (8.7 kg, 93% yield): mp 117−118 °C; H^1 NMR (DMSO, 400 MHz): δ 12.54 (br s, 1H), 7.73 (s, 1H), 7.14 (s, 1H), 3.78 (s, 3H), 3.30 (sept., J = 6.8 Hz, 1H), 1.04 (d, J = 6.8 Hz, 6H); C^{13} NMR (DMSO, 100.6 MHz): 199.2, 160.9, 128.4, 125.2, 123.8, 114.9, 51.8, 36.3, 19.6. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.49; H, 6.68; N, 7.10. *HPLC Assay (method B) retention times*: nitromethane 3.1 min; pyrrole ester 3.8 min; keto-ester 4.2 min.

4-Isopropyl-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic Acid Methyl Ester (10). A slurry of heptane (10 L), keto-ester **12** (2.5 kg, 12.8 mol), aminoacetaldehyde dimethylacetal (2.0 kg, 19.0 mol), and pivalic acid (19.6 g) was warmed to reflux (99−100 °C) and aged under Dean−Stark conditions for 40 h. A total of 500 mL of aqueous distillate was collected. Heating mantles were used to heat the flask to obtain a condensation rate of at least 500 mL/min. The conversion was monitored by GC analysis as follows:

GC Assay. Column HP-1 30 m, 0.32 mm × 0.25 μm. T (inj) = 250 °C, T (det) = 300 °C; split 50:1; flow 80 mL/min. Temperature ramp 50 °C (4 min), 25 °C/min to 250 °C (18 min). Retention times: aminoacetal, 4.6 min; keto-ester, 11.1 min; imine-ester, 12.6 min; keto-amide, 13.5 min; imine-amide, 15.8 min.

Upon completion of the reaction by GC, the mixture was cooled and concentrated under reduced pressure at 40−50 °C with concomitant addition of xylenes (40 L) to remove the excess of amino acetal. The final volume was adjusted to about 18 L and the product imine solution cooled to rt. The crude imine **11** was used in cyclization step.

A xylene solution of imine **11** (~38.4 mol) was added to TFA (50 L) held at 45 °C over 40 min. Upon complete addition the batch was aged at 60 °C for 5 h and then cooled to rt. The solution was concentrated under reduced pressure (10−25 °C) to remove excess TFA (~45 L). The solution was then flushed with MeOH (40 L), IPAc (40 L), and the volume was finally adjusted to 60 L with IPAc (40 L) to afford a slurry of the azaindole trifluoroacetate salt. A separate 50-L round-bottom flask was charged with *p*-TsOH (6.5 kg, 34.1 mol), IPAc (25 L), and H_2O (12.5 L) and stirred to obtain a homogeneous biphasic solution. Water (3 L) was added to the TFA salt slurry followed by the *p*-TsOH solution at 30 °C over 40 min. The resulting thick slurry was aged at 30 °C for 30 min and then cooled to rt. The slurry was filtered, and the cake was washed with IPAc/MeOH/H_2O (100:5:2.5; 10 L) and IPAc (20 L) and dried. The desired product **10·*p*-TSA** salt was obtained as beige needles (10.8 kg, 72%).

To a solution of NEt_3 (3.7 L, 26.5 mol) in EtOAc (20 L) was added **10·*p*-TSA** salt (9.4 kg, 24.05 mol). The resulting mixture was stirred at ambient for 30 min. Water (13 L) was then added and the solution stirred for 1 h. The aqueous layer was separated and extracted twice with EtOAc (2 × 6 L). The combined organic layer was washed with water (3 × 6 L), concentrated, and flushed with EtOAc (20 L) to reach a final volume of 20 L. Heptane (60 L) was then added slowly with further concentration to reach a final volume of 40 L (EtOAc < 5%). The slurry was filtered and washed with heptane (20 L). The solid was dried under nitrogen to afford azaindole **10** as needles (5.0 kg, 95%): mp 140−141 °C; ^{1}H NMR (DMSO, 400 MHz): δ 12.27 (br s, 1H), 8.18 (d, J = 5.8 Hz, 1H), 7.37 (s, 1H), 7.20 (d, J = 5.8 Hz, 1H), 3.88 (s, 3H), 3.51 (sept, J = 6.8 Hz, 1H), 1.29 (d, J = 6.8 Hz, 6H); ^{13}C NMR (DMSO, 100.6 MHz): 162.4, 161.8, 142.4, 140.9, 127.8, 121.8, 107.1, 105.9, 52.4, 33.1, 22.3. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.74; H, 6.40; N, 12.77.

HPLC (method C) retention times: pyrrole ketone methyl ester 6.9 min; pyrrole ketone ethyl ester 7.9 min; pyrrole ketone isopropyl ester 8.8 min; desired indole methyl ester 4.1 min; desired indole ethyl ester 4.7 min; desired indole isopropyl ester 5.6 min; undesired indole methyl ester 3.5 min; undesired indole ethyl ester 4.2 min; undesired indole isopropyl ester 4.8 min.

2-(4-Isopropyl-1*H*-pyrrolo[3,2-*c*]pyridine-2-carbonyl)-butyric Acid Methyl Ester (16).[11] To a cooled (~10 °C) solution of azaindole **10** (4.8 kg, 22.2 mol) in DMF (10.0 L) was added LiH (264.6 g, 33.3 mol) in portions to maintain batch temperature at 60−65 °C. Upon complete addition, the reaction was aged for 30 min before adding methyl acrylate (3.8 kg, 44.4 mol) over 45 min while maintaining the internal temperature at 60−65 °C. After aging for 2 h at 60 °C, the mixture was cooled to 30 °C. Acetic acid (2.0 kg, 33.3 mol) was added followed by water (44.4 L) over 1 h and the resulting mixture cooled to 5−10 °C for 1 h. The beige crystalline solid was filtered, washed with cold water (15−20 L) and dried under N_2 stream in a filter pot to afford keto-ester **16** as a yellow crystalline solid (5.2 kg, 86%): mp 203−205 °C (free base); H^1 NMR (CD_3COOD, 400 MHz): δ 8.54 (d, J = 6.9 Hz, 0.35 H), 8.43 (d, J = 6.8 Hz, 0.65 H), 8.05 (d, J = 6.9 Hz, 0.35 H), 7.89 (d, J = 6.8 Hz, 0.65H), 7.71 (s, 0.35 H), 7.28 (s, 0.65H), 5.08−5.02 (m, 2 H), 3.92−3.80 (m, 4 H), 1.62−1.59 (m, 6H); C^{13} NMR (CD_3COOD, 100.6 MHz): 186.0, 167.0, 166.1, 161.9, 158.0, 157.8, 144.1, 139.6, 138.4, 132.9, 131.7, 125.7, 107.6, 106.0, 105.7, 101.7, 95.6, 52.7, 51.5, 47.1, 44.6, 32.5, 32.2, 20.3, 20.2. HRMS $C_{15}H_{16}N_2O_3$ [M + H] calcd, 273.1239, found 273.1238 (−0.4 error). Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.21; H, 5.91; N, 10.05.

HPLC Assay (method C) retention times: pyrrole ketone methyl ester 6.9 min; desired indole methyl ester 4.1 min; methyl keto-ester 4.3 min.

1-(4-Isopropyl-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-butan-1-one (5).[12] Keto-ester **16** (5.1 kg, 18.7 mol), toluene (187 mL) and methanol (187 mL) were added to 1 M HCl (28 L, 28.0 mol) and the mixture heated to 95 °C for 3 h. Approximately 1 L of distillate was collected and the mixture cooled to 50 °C. K_3PO_4 (5.96 kg, 28.0 mol) in water (9.4 L) was added over 1 h and the resultant slurry cooled to 5−20 °C for 1 h. The yellow crystalline solid was filtered and washed with cold water (15−20 L). The solid was dried overnight in the filter pot and then in a vacuum oven at 45 °C to afford ketone **5** as yellow crystalline needles (3.7 kg, 91 wt %, 84% yield): mp 129−132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.39 (d, J = 5.9 Hz, 1H), 7.17 (dd, J = 6.0, 0.7 Hz, 1H), 7.14 (d, J = 0.8 Hz, 1H), 4.45 (t, J = 6.4 Hz, 2H), 3.34 (sept, J = 6.9 Hz, 1H), 3.23 (t, J = 6.4 Hz, 2H), 1.41 (d, J = 6.9, 6H), ^{13}C NMR ($CDCl_3$, 100.6 MHz): 192.5, 165.4, 142.1, 138.1, 135.3, 126.5, 103.3, 98.1, 40.1, 39.3, 33.7, 21.7; HRMS $C_{13}H_{14}N_2O$ [M + H] calcd, 215.1184; found, 215.1184 (0 error).

HPLC (method C) retention times: pyrrole ketone methyl ester 6.9 min; desired indole methyl ester 4.1 min; methyl keto-ester 4.3 min; tricyclic ketone 3.2 min; dimeric byproducts (unsaturated ketone isomers) 4.4 and 4.5 min.

(*E*)-3-(4-Isopropyl-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-hex-2-enoic Acid Methyl Ester (6). To a solution of trimethyl phosphonoacetate (3.9 kg, 21.4 mol) in THF (30 L) was added sodium amylate (1.8 kg, 16.1 mol) in one portion (exotherm from 17 to 32 °C). The thick, white slurry was aged for 2 h. The mixture was cooled to −2 °C and ketone **5** (2.3 kg, 10.7 mol) added in 2 equal portions. The mixture was aged for 23 h under nitrogen between −3 and 2 °C and reaction progress monitored by HPLC assay until <3% ketone remained. 85% H_3PO_4 (1.1 L, 16.2 mol) in water (9.3 L) was added to the reaction mixture (exothermic; yellow solid precipitates). An aqueous solution of *p*-TSA monohydrate (2.1 kg, 10.9 mol) in H_2O (1.2 L) was added in one portion. The mixture was aged for 1 h and concentrated under reduced pressure to approximately 27 L. Water (23 L) was added and the slurry aged at 20 °C for 2 h. The fine, pale-yellow crystals were filtered and washed with water (15 L). The product was dried *in vacuo* for 48 h to afford unsaturated ester **6** as yellow needles (3.7 kg, 77%).

To a solution of triethylamine (1.5 L, 10.8 mol) in MeOH (8 L) was added tosylate ester **6** (3.66 kg, 8.26 mol) in one portion and stirred to obtain complete dissolution. Water (0.8 L) was added, and the solution was seeded with product (1 g) and aged for 30 min. Water (22.2 L) was added over 20 min, maintaining the temperature between 20 and 26 °C. The slurry was filtered and washed with water (20 L). The product was dried *in vacuo* to afford unsaturated ester **6** as a fine, yellow crystalline solid (2.19 kg, >99 wt %, 98% yield): mp 137−140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, J = 5.9 Hz, 1H), 7.08 (d, J = 5.7 Hz, 1H), 6.86 (br s, 1H), 6.42 (t, J = 2.6 Hz, 1H), 4.27 (t, J = 6.5 Hz, 2H), 3.84 (dt, J = 6.9 Hz, 2.6, 2H), 3.81 (s, 3 H), 3.52 (sept, J = 6.9 Hz, 1H), 1.44 (d, J = 6.9 Hz, 6H),; ^{13}C NMR ($CDCl_3$, 100.6 MHz): 167.2, 162.4, 148.2, 141.5, 140.8, 137.2, 126.9, 110.0, 103.2, 93.6, 51.3, 42.7, 34.1, 33.6, 21.7. HRMS $C_{16}H_{18}N_2O_2$ [M + Na] calcd, found. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.03; H, 6.70; N, 10.31.

(*R*)-3-(4-Isopropyl-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)hexanoic Acid Methyl Ester (7). A 5-gal autoclave was charged with ene ester **6** (2.2 kg, 8.0 mol) and toluene (8.5 L). The orange slurry was stirring and was degassed using vacuum/nitrogen purges.

[Catalyst preparation: In an inert atmosphere glovebox, degassed 1,2-dichloroethane (166 mL) was charged to a vessel containing $Ir(COD)_2BF_4$ (10.7 g, 21.6 mmol) and SLW005-2 (24.96 g, 23.8 mmol). The solution was stirred for 1.5 h at room temperature after which time the resulting deep-red homogeneous solution was charged into a stainless steel bomb to enable direct, inert charging to the hydrogenation vessel].

Confirmation of the activity/selectivity of the catalyst solution was obtained by use test and vessel conditioning runs.

The iridium catalyst solution [(SLW005-2) $Ir(COD)BF_4$] previously prepared was charged to the autoclave.

Safety Warning: introduction of hydrogen produces an exotherm which must be carefully controlled to avoid temperature run away.

The solution was hydrogenated under hydrogen gas (90 psig) **at 15 °C** for 1 h then at 22 °C for 23 h.

After the resulting orange homogeneous solution aged overnight (~24 h), the pressure vessel was vented to atmospheric pressure (assay yield **7**, 99%, 98.0% ee). This solution of **7** was used without further purification or processing in the next step. A small amount of the solution was evaporated to dryness for analytical data: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, J = 5.5 Hz, 1H), 6.98 (d, J = 5.5 Hz, 1H), 6.28 (s, 1H), 4.12 (ddd, J = 10.2, 8.6, 4.2 Hz, 1H), 4.01 (app. ddd, J = 10.2 Hz, 1H), 3.79 − 3.74 (m, 1H), 3.76 (s, 3H), 3.44 (app. p, J = 6.9, 1H), 2.88 (ddd submerged, J = 12.3, 7.8, 4.2, 1H), 2.85 (dd, J = 16.2, 6.5 Hz, 1H), 2.63 (dd, J = 16.2, 8.3 Hz, 1H), 2.34 − 2.29 (m, 1H), 1.42 (d, J = 2.1 Hz, 3H), 1.40 (d, J = 2.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.23, 160.31, 146.43, 139.78, 136.19, 129.17, 127.04, 103.13, 91.8, 52.0, 43.1, 38.9, 34.9, 33.8, 22.0, 21.9. HRMS $C_{16}H_{20}N_2O_2$ [M + H] calcd, 273.1603, found 273.1602 (−0.4 error).

HPLC (method D) retention times: chiral ester 3.7 min; ene ester (*E* isomer) 4.0 min; ene ester (*Z* isomer) 4.2 min; toluene 7.5 min.

Chiral HPLC (method E) retention times: toluene 2.0 min; ene ester (*Z* isomer) 7.4 min; chiral ester (desired enantiomer) 8.2 min; ene ester (*E* isomer) 9.1 min; chiral ester (undesired enantiomer) 11.2 min.

2-(3,4-Dichlorophenylsulfanyl)isoindole-1,3-dione (24).[23] 3,4-Dichlorothiophenol (4.46 kg, 24.9 mol), phthalimide (4.03 kg, 27.4 mol), and pyridine (10.9 kg, 79.1 mol) were added to acetonitrile (35.2 L). The slurry was stirred, and bromine (725 mL, 2.34 kg, 14.6 mol) was added over 30 min. The temperature was allowed to reach 40 °C before adding product seed (330 g, 1.02 mol) and additional bromine (100 mL, 311.9 g, 1.95 mol) over 15 min. The temperature was held at 38 °C and the remainder of the bromine added dropwise over 25 min. After 45 min, the reaction was treated with 10% water in methanol (34.5 L), cooled to 25 °C and filtered (typical mother liquor loss 1.5%). The filter cake was washed with MeOH (20 L) and

dried to afford the title compound **24** as a pink solid (8.13 kg, 97% isolated yield, ~100 wt %): mp 165−169 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (app dd, J = 5.5, 3.1 Hz, 2H), 7.81 (app dd, J = 5.5, 3.1 Hz, 2H), 7.65 (d, J = 1.9 Hz, 1H), 7.42 (dd, J = 1.9, 8.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.2, 134.9, 134.8, 133.8, 133.3, 132.1, 131.7, 131.0, 129.8, 124.2. HRMS $C_{14}H_7NO_2SCl_2$ [M + H] calcd, 323.9653, found 323.9650 (−0.9 error).

(*R*)-Methyl-3-[3-(3,4-dichlorophenylsulfanyl)-4-isopropyl-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]-hexanoate (8).[24] A toluene solution of azaindole ester **7** (2.2 kg in a total of 10.32 kg toluene solution, 8.02 mol) and dimethylacetamide (12.6 kg, 13.4 L) was concentrated under reduced pressure (60 mmHg) to remove most of the toluene. Distillation was continued until the assay of toluene was <12 wt % by HPLC. The reaction solution was treated with thiophthalimide (2.79 kg, 8.6 mol) followed by magnesium bromide (7.5 g, 0.04 mol). The batch was heated to 90 °C for 4 h. On complete reaction the batch was cooled to room temperature before being treated with 85% H_3PO_4 (610 mL, 8.9 mol) and stirred for 10 min. Water (8.6 L) and phthalimide (30 g) were added, followed by additional water (20 L over 50 min) and Solka-Floc (1 kg). The slurry was cooled to 10 °C and filtered, and the cake washed with 17 wt % H_3PO_4 (2 × 2.8 L). The combined filtrates were treated with NEt_3 (1.2 L, solution pH ~ 4) and then seeded with product (20 g) while stirring vigorously. Additional NEt_3 (3.5 L) was added over 45 min until the pH reached ~8. The resulting slurry was cooled to 10 °C and filtered (typical losses 0.3%). The filter cake was washed with 2:1 methanol/water (18 L, typical losses, 0.44%) before being dried to afford the title compound **8** as a pink solid (3.66 kg, 95 wt %, 96% isolated yield).

A solution of the isolated solid (7.25 kg, 16.18 mol) was dissolved in EtOAc (73 L) and treated with Ecosorb-C905 (7.3 kg). The reaction was heated to 40 °C for 2.5 h and then filtered through a pad of solka-floc (3 kg). The cake was washed with EtOAc (14 L) and the combined organics concentrated under reduced pressure (~50 mmHg) to ~15 L. At this point, heptane (80 L) was added to the slurry and the distillation continued until the volume was approximately 50 L and the solution concentration of the product was <2 mg/mL. The solid was collected by filtration and the cake washed with heptane (2 × 10 L). The cake was dried via pulling N_2 through the cake for 48 h to afford the desired product as an light pink solid: mp. = 155 − 157 °C; H^1 NMR ($CDCl_3$, 400 MHz): δ 8.33 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.06 − 7.04 (m, 2H), 6.80 (dd, J = 8.5, 2.1 Hz, 1H), 4.25−4.20 (m, 1H), 4.08−4.05 (m, 2H), 3.81−3.79 (m, 1H), 3.62 (s, 3H), 3.17 (dd, J = 16.7, 3.7 Hz, 1H), 2.96 − 2.92 (m, 1H), 2.58 (dd, J = 16.7, 9.6 Hz, 1H), 2.43 − 2.36 (m, 1H), 1.20 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.8 Hz, 3H). C^{13} NMR ($CDCl_3$, 100.6 MHz): δ 171.7, 161.6, 152.6, 141.0, 140.8, 137.5, 133.0, 130.5, 128.6, 126.3, 126.0, 124.2, 103.5, 90.3, 51.8, 43.8, 36.9, 34.1, 33.5, 30.2, 22.6, 22.1. Anal. Calcd for $C_{22}H_{22}Cl_2N_2O_2S$: C, 58.80; H, 4.93; Cl, 15.78; N, 6.23; S, 7.14. Found: C, 58.69; H, 4.77; Cl, 15.98; N, 6.13; S, 7.16.

HPLC (method F) retention times: SM 5.16 min; product 9.18 min.

Chiral HPLC (method G) retention times: minor 9.66 min; major 13.37 min; ee = 97%.

(*R*)-Sodium 3-[3-(3,4-Dichlorophenylsulfanyl)-4-isopropyl-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]hexanoate) (1). Methyl ester **8** (6.7 kg, 95 wt %, 14.2 mol) was suspended in MeOH (15 L) and treated with aq 10 N NaOH (1.9 L, 19.0 mol) (*exotherm to 30 °C*). The slurry was warmed to 50 °C and aged for 2 h (>99.5% conversion). Upon completion of the reaction, the solution was filtered at 50 °C, via a 1 μm filter, into another vessel. Water (60 L) was added to the MeOH solution at 50 °C. The solution was allowed to cool slowly (seeding at saturation point T = 37−40 °C). The slurry was cooled to 0−5 °C and aged 1 h. The slurry was filtered, the cake washed with cold MeOH/H_2O, 1:4 (typical loss: <1%), and dried at rt under vacuum/N_2 to afford the sodium salt of **1**·H_2O (6.8 kg, 99% yield, >98% ee).

HPLC (method A) retention times: Starting material methyl ester 10.0 min; Final API 8.7 min.

The amorphous sodium salt of **1**·H_2O (6.8 kg) and MTBE (75 L) was stirred at 50 °C for 1.5 h to achieve polymorph conversion to the crystalline anhydrous Na salt. The slurry was cooled to ambient, filtered, and washed with MTBE (7 L). The product was dried *in vacuo* to afford crystalline **1**·Na·H_2O (6.3 kg, 95 wt % based on free base, >99 LCAP, 99% isolated yield, 98% ee): mp 389.06 °C; ^{1}H NMR (DMSO, 400 MHz): δ 8.16 (d, J = 5.5 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.25 − 7.21 (m, 2H), 6.95 (dd, J = 8.4, 1.7 Hz, 1H), 4.23−4.06 (m, 1H), 4.13−4.07 (m, 2H), 3.66−3.62 (m, 1H), 2.80−2.75 (m, 1H), 2.55 (dd, J = 15.1, 2.8 Hz, 1H), 2.34 − 2.26 (m, 1H), 2.06 (dd, J = 15.0, 10.9 Hz, 1H), 1.09 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO, 100.6 MHz): 174.6, 159.7, 157.2, 142.2, 140.1, 137.4, 132.0, 131.2, 127.4, 126.2, 125.5, 125.2, 104.5, 87.2, 44.2, 41.9, 36.1, 34.0, 30.1, 23.0, 22.7. Anal. Calcd for $C_{21}H_{20}$ Cl_2 N_2O_2S: C, 57.93; H, 4.63; Cl, 16.29; N, 6.43; S, 7.37. Found: C, 57.75; H, 4.49; Cl, 16.17; N, 6.33; S, 7.45.

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