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Asymmetric Synthesis of a Glucagon Receptor Antagonist via Friedel–Crafts Alkylation of Indole with Chiral α-Phenyl Benzyl Cation

John Y. L. Chung,*[,†] Dietrich Steinhuebel,[†] Shane W. Krska,[†] Fred W. Hartner,[†] Chaoxian Cai,[†] Jonathan Rosen,[†] Danny E. Mancheno,[†] Tao Pei,[†] Lisa DiMichele,[†] Richard G. Ball,[†] Cheng-yi Chen,[†] Lushi Tan,[†] Antony D. Alorati,[‡] Sarah E. Brewer,[‡] and Jeremy P. Scott[‡]

[†]Process Chemistry, Merck Research Laboratories, Rahway, New Jersey 07065, United States

[‡]Process Research Preparative Laboratory, Merck Sharp & Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, United Kingdom

Supporting Information

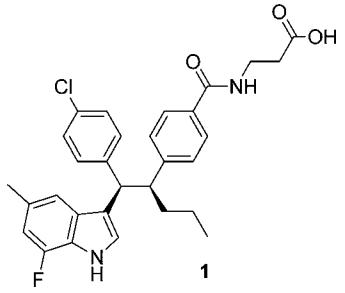
ABSTRACT: Development of a practical asymmetric synthesis of a glucagon receptor antagonist drug candidate for the treatment of type 2 diabetes is described. The antagonist consists of a 1,1,2,2-tetrasubstituted ethane core substituted with a propyl and three aryl groups including a fluoro-indole. The key steps to construct the ethane core and the two stereogenic centers involved a ketone arylation, an asymmetric hydrogenation via dynamic kinetic resolution, and an *anti*-selective Friedel–Crafts alkylation of a fluoro-indole with a chiral α-phenyl benzyl cation. We also developed two new efficient syntheses of the fluoro-indole, including an unusual Larock-type indole synthesis and a Sugasawa-heteroannulation route. The described convergent synthesis was used to prepare drug substance in 52% overall yield and 99% ee on multikilogram scales.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) worldwide is a fast growing, progressive disease with multiple unmet needs.[1] Despite existing therapies, glycemic lowering efficacy remains sub-optimal, with less than 50% of patients achieving stated glycemic goals. Existing products, such as biguanides (metformin), sulfonylureas, and PPAR γ agonists, are considered to be effective in lowering glucose, and yet all have room for improvement with respect to their efficacy, safety, and tolerability profiles.[2] Newer agents recently launched, such as GLP-1 analogues and DPP-4 inhibitors (JANUVIA), offer additional treatment options for patients.[3] As part of a program at Merck directed toward this goal, new mechanisms such as antagonism of the glucagon receptor (GRA) have been targeted, and **1** was identified as a candidate for further development.[4]

Drug candidate **1**, containing a tetrasubstituted ethane core, poses a number of challenges with regard to development of a concise and practical synthesis. Most notably, construction of the two adjacent tertiary asymmetric carbon centers in a highly efficient manner is expected to be highly demanding. In addition, this endeavor requires the regio- and chemoselective introduction of 1,1,2,2-triaryl monoalkyl moieties, where one of the aryls is a fluoro-indole, which by itself is a challenging target. Herein we describe the development of a concise synthesis of **1**, which leverages the enantioselective Friedel–Crafts (F.-C.) indole alkylation with benzylic cations previously disclosed.[5]

Convergent Asymmetric Synthesis Strategy. We envisaged a new route that brings together the four substituents, namely the fluoro-indole, *n*-propyl, and two para-substituted phenyl moieties, on to the ethane core in a convergent and stereoselective fashion (Scheme 1). Retrosynthetically, the indole moiety in **1** could be installed in a diastereoselective manner via addition of fluoro-indole **2** to chiral α-phenyl benzylic cation **3**. We hoped the diastereoselectivity would be improved with sterically bulky indole **2** relative to the small allylsilane nucleophile[6] employed in the previous synthesis,[4] and the sense of relative stereochemical induction should be the same. Although Bach et al.'s studies on arene addition to chiral α-alkyl benzyl cations afforded *syn*-selective products,[7] our initial efforts demonstrated a reversal of stereochemistry with the proposed substrates, affording moderate *anti*-selectivity (Scheme 2).[5]



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Optically active benzyl alcohol **4** could serve as precursor to chiral benzyl cation **3** and should be accessible from racemic ketone **5** through an asymmetric reduction via a kinetic dynamic resolution (DKR) process.[8,9] Ketone **5**, in turn, could be prepared in one step via palladium catalyzed α-arylation[10] of ketone **7** with aryl bromide **6**.

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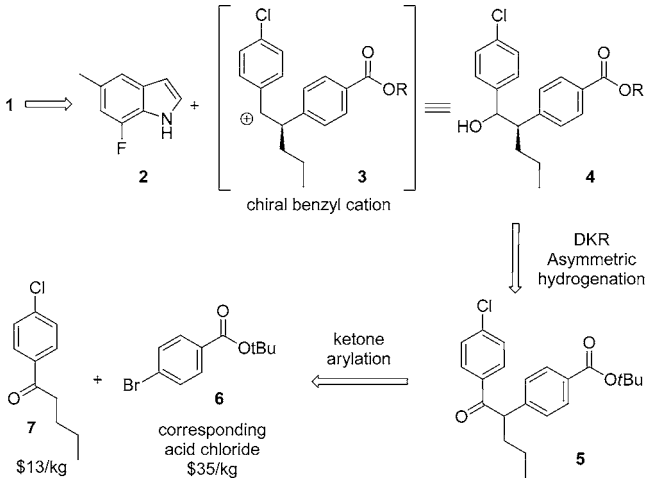
Scheme 1. Retrosynthetic Analysis of Drug Candidate 1



RESULTS AND DISCUSSION

Preparation of Benzyl Alcohol 4. *Step 1—Ketone Arylation.* Two routes to ketone **5** were examined: (1) a two-step synthesis involving a Pd-catalyzed α-arylation of 4′-chloroacetophenone (**14**) with bromide **6** followed by *n*-propylation of the resulting **15**; and (2) a one-step preparation via Pd-catalyzed α-arylation of ketone **7** with bromide **6** (Scheme 3). Both routes afforded ketone **5** in similar efficiency. Initially, the 2-step synthesis of ketone **5**, having one additional step for purification, appeared to have the advantage with respect to lower residual Pd and phosphine, which we presumed to be detrimental for the subsequent DKR step.

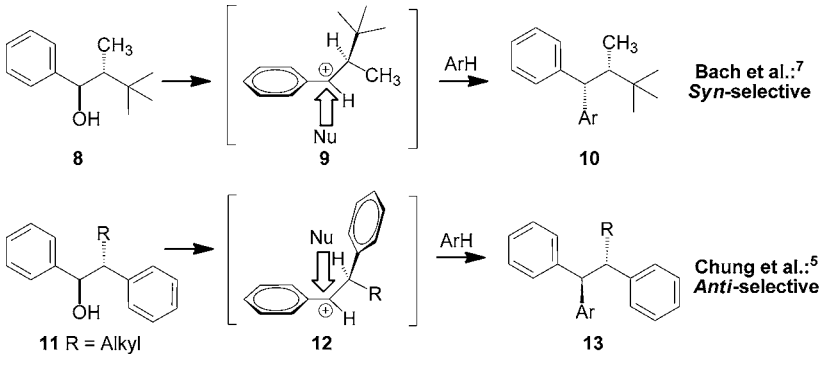
Subsequent studies showed the one step preparation of **5** from **6** and **7** did not pose a problem for the DKR step, since a simple filtration of the product stream through a silica pad provided material of adequate purity for the DKR reaction. The yields for the one step cross coupling were 86−92% using 1.5 mol % $Pd_2(dba)_3$ and 3 mol % (*S*)-tol-BINAP at optimum temperatures of 55−60 °C. Although there was no asymmetric induction in the arylation reaction to **5**, optically active (*S*)-tol-BINAP was preferred over racemic tol-BINAP due to better solubility and reaction kinetics. Early development of cross coupling between **6** and **7** at 80 °C saw significant debromination of **6**, and byproduct **16** as a result of further cross-coupling between product **5** with starting **7** (Scheme 3). These side reactions were suppressed by lowering the reaction temperatures to 55−60 °C. In the reaction, bromide **6** was consumed faster than **7**, so a slight overcharge of **6** (1.1 equiv) was advantageous. Further optimization identified $Pd(OAc)_2$ as a suitable replacement for $Pd_2(dba)_3$.

Due to the high cost of (*S*)-tol-BINAP, we undertook a ligand screen for a more cost-effective catalyst system. The studies identified two viable catalyst systems: $(dtBuPF)PdCl_2$ and DPEphos/$Pd(OAc)_2$.[11] DPEphos was selected for further development based on its lower cost and was optimized at a loading of 0.5 mol %. This new catalyst system achieved a 10× cost reduction, while maintaining similar reaction yields and impurity profile. The optimized reaction conditions also used less solvent (6.5 vol vs 13 vol), which led to a shorter reaction time (6 h/60 °C vs 16 h/60 °C for tol-BINAP). The assay yield of product **5** after aqueous work up was ∼90%. After crystallization from IPA:water, ketone **5** was isolated in 86% corrected yield as a 99 wt % pure off-white solid. The residual Pd was ∼150 ppm, which is excellent considering the simplified workup. However, on larger lab scales, aqueous $NaHCO_3$ workup did not adequately remove residual Pd and led to lower % ee (97.5−97.8% ee) in the subsequent Ru-catalyzed reaction. A work up involving washing with aqueous sodium thiosalicylate followed by a silica pad filtration restored the excellent % ee in the next step.

Step 2—Asymmetric Hydrogenation via Kinetic Dynamic Resolution. With ketone **5** in hand, we proceeded to screen the DKR asymmetric hydrogenation condition. Based on the experience from this lab,[9] we quickly found excellent results with several catalysts and chose $RuCl_2$[(*S*)-Xyl-SEGPHOS]-[(*S*)-DAIPEN] for further development. With this catalyst, DKR asymmetric hydrogenation of ketone **5** produced the desired enantiomer **17** required for drug candidate **1** with *anti*-selectivity (Scheme 4). The reaction was typically carried out at 20−25 °C, 90−100 psi H_2, 20 mol % KOtBu in IPA with 0.08−0.1 mol of catalyst for 4 h. The reaction mixture after filtration was diluted with water, which directly crystallized alcohol **17** in >90% yield, > 99% dr, and ≥98.5% ee.[12] As low as 0.02 mol % catalyst has been successfully run from fairly clean starting material. The corresponding (*R*,*R*)-catalyst produced the enantiomer of **17** with similar efficiency. Although the alcohol chiral center is inconsequential in the subsequent Friedel−Crafts reaction, we did not find catalyst that affords the *syn*-product.

Preparation of 7-Fluoro-5-methyl-1*H*-indole (2). The only prior synthesis of fluoro-indole **2** was a Bartoli indole synthesis[15,16] from 2-fluoro-4-methyl-1-nitrobenzene and vinyl-magnesium bromide; although the one step synthesis was convenient, yields of several experiments in our hands were only 12−16%, which are consistent with the literature reports.

Scheme 2. Differential Diastereofacial Addition of α-Chiral Benzylic Cation



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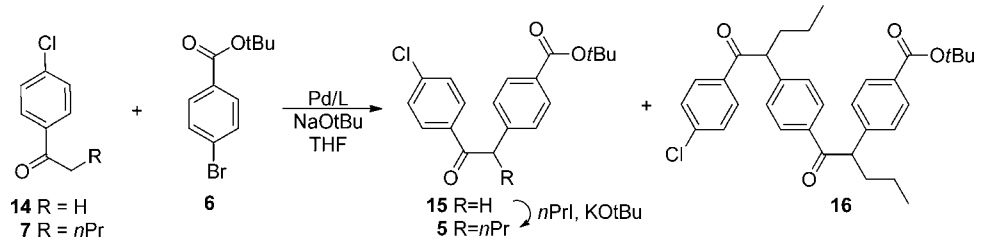
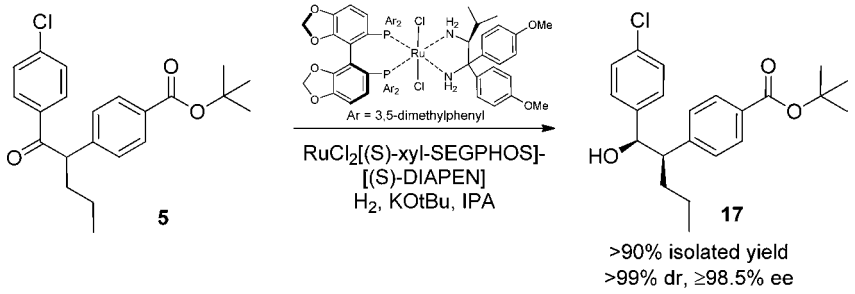
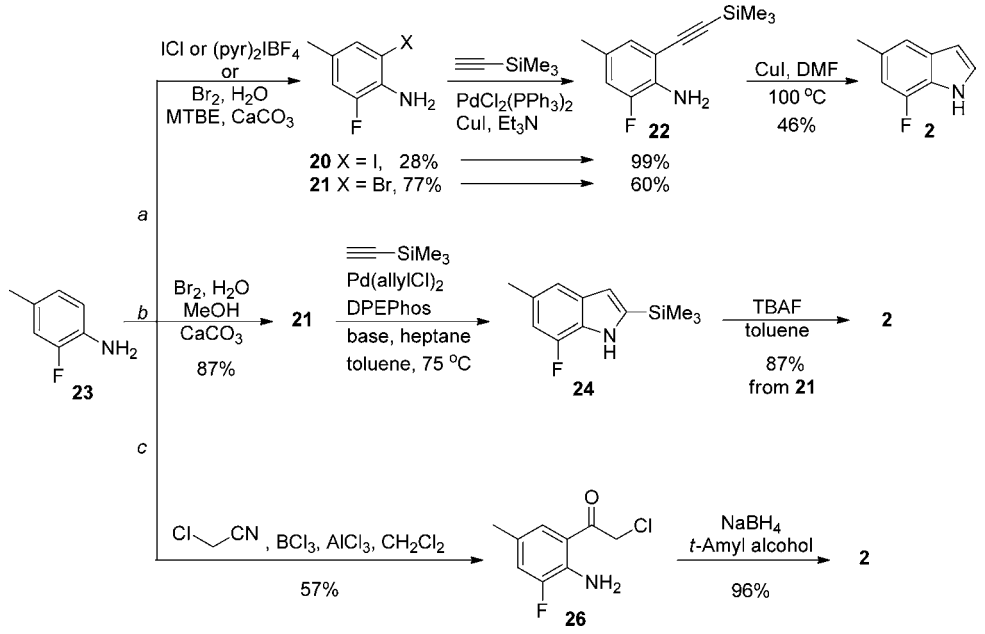
Scheme 3. Ketone α-Arylation



Scheme 4. DKR Asymmetric Hydrogenation of Ketone 5 to Alcohol 17



Scheme 5. Synthetic Routes to Indoles 2



Thus, alternate syntheses were investigated. We identified two syntheses that are amendable for large scale preparation: an unusual Larock-type indole synthesis,[17] which was successfully run on multikilogram scales, and a Sugasawa sequence as an alternate long-term manufacturing route.

(1). Larock Heteroannulation Route. Our initial plan to prepare fluoro-indole **2** adapted a Sonogashira heteroannulation strategy, i.e., a Sonogashira coupling of 2-halo-6-fluoro-4-methylaniline **20** or **21** with TMS-acetylene to form **22**, followed by a Cu catalyzed cyclization to indole **2** (Scheme 5). We decided to use bromoaniline **21** rather than iodoaniline **20** based on atom economy. Thus, bromination of aniline **23** using Br_2 and $CaCO_3$ in MTBE afforded **21**[18] in 77% yield. Because of literature reports of instability with bromine/MTBE systems,[19] subsequent optimization was carried out using bromine in methanol with aqueous calcium carbonate as a buffer, which offered good conversion and yield. Care was taken to prevent a build-up of bromine by slow addition of 1 equiv of bromine. On a 100 kg scale run, bromine was added over 6 h and aged until >96% conversion. Bromoaniline **21** was isolated in 87% yield after purification by distillation.

Because of low reactivity of bromoaniline **21** relative to the iodoaniline with TMS-acetylene in the Sonogashira reaction, a screen of the catalyst/ligand/base/solvent was carried out. We were pleasantly surprised to find conditions where the reaction directly afforded 2-TMS-indole **24**[20,21] as the major product with only minor Sonogashira product **22**. The transformation did not appear to be consecutive reactions of Sonogashira followed by cyclization, because with extended reaction time the ratio of cyclized **24** vs noncyclized **22** did not change. Exposing the isolated Sonogashira product **22** to the same reaction conditions also did not result in cyclization: neither did

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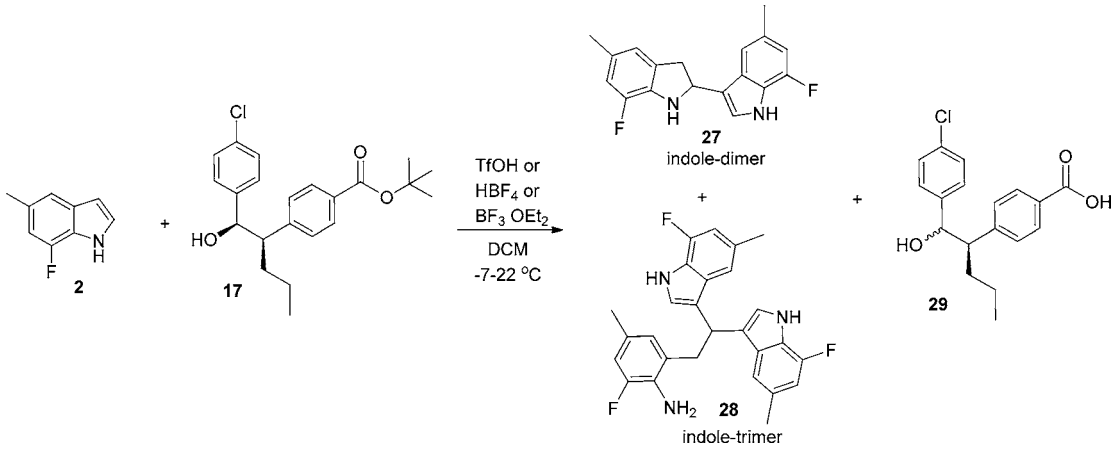
Scheme 6. Attempted Friedel–Crafts Alkylation of Unprotected Indoles 2



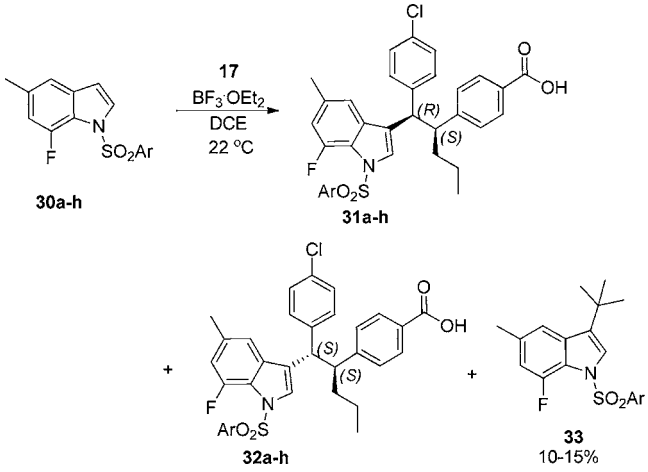
deprotonation (LiHMDS) and heating. Further optimization found allylpalladium(II) chloride dimer, DPEphos, and *N*-methyldicyclohexylamine in toluene/heptane afforded a ratio of ~30:1 indole **24**:Sonogashira product **22**, in ~90–95% assay yield from distilled **21**. With crude **21**, the ratio deteriorated to as low as 7:1. Key parameters identified included running the reaction under pressure to prevent evaporation of TMS–acetylene and selecting base (dicyclohexylmethylamine) and solvent (toluene/heptane). Following workup, the toluene stream of **24** was treated with TBAF at 80–90 °C to remove the TMS group. Crude fluoro-indole **2** was purified by distillation. It was found that residual TBAF decomposed under the Kugelrohr conditions (0.1–0.4 mmHg at 140–160 °C), resulting in tributylamine and butyl chloride contaminating the next step product. Although use-tests showed that these two impurities did not impact the subsequent sulfonylation, for long-term robustness and also to develop a process that could be scaled, the Kugelrohr distillation was eventually replaced by a milder steam-distillation where crude indole **2** was distilled using a 58 to 1 ratio of water to substrate in 96% recovery and >99% purity. The distillation also removed the excess palladium catalyst generated in the second step and eliminated issues with layer cuts (emulsion) and product quality in the subsequent step.

2. Sugasawa Reductive Heteroannulation. In an effort to further improve cost, we explored a second route to **2** (Scheme 5). Thus, the Sugasawa reaction[22,23] of 2-fluoro-4-methylaniline (**23**) with 2 equiv of chloroacetonitrile mediated by 1.1 equiv each of BCl_3 and $AlCl_3$ in refluxing dichloromethane afforded a 57% isolated yield of chloroacetophenone **26**. After work up, about 18% of starting aniline could be recovered from the acidic aqueous phase and recycled. Treatment of **26** with $NaBH_4$ in refluxing aqueous 2-methyl-2-butanol afforded indole **2** in 96% yield. With further optimization, this 2-step route has the potential to be the long-term route because of its overall low cost based on the fact that all the reagents used are inexpensive commodity chemicals. Obviously, other factors, such as safety, throughput, scale, IP, etc., will also need to be weighed.

Friedel–Crafts Alkylation of Indoles with Chiral Benzylic Cation. With both chiral benzyl alcohol **17** and fluoro-indole **2** in hand, we proceeded to study the key Friedel–Crafts reaction. Initial attempts to affect the Friedel–Crafts alkylation of unprotected indole **2** with benzylic cation generated from chiral alcohol **17** by triflic acid, HBF_4, or BF_3 etherate did not afford any desired product; instead the main products were indole-dimer **27**, trimer **28**,[24] and carboxylic acid **29** (Scheme 6).

To suppress the reactivity of **2**, a series of arylsulfonyl-protected indoles **30a–h** were prepared using a biphasic condition and investigated under a set condition of 3 equiv of BF_3 etherate added to indole and benzyl alcohol **17** in dichloroethane starting at 5–22 °C. As shown in Table 1, all

Table 1. Electronic Effect of Indole Protecting Group



entry	indole	Ar	σ-para	1*R*,2*S*:1*S*,2*S*
1	**30a**	4-Me-Ph	−0.17	3.3:1 (**31a:32a**)
2	**30b**	4-H-Ph	0	3.6:1 (**31b:32b**)
3	**30c**	Ms		4.4:1 (**31c:32c**)
4	**30d**	4-Cl-Ph	0.23	4.4:1 (**31d:32d**)
5	**30e**	4-NO_2-Ph	0.78	6.0:1 (**31e:32e**)
6	**30f**	2,4,6-tri-Cl-Ph		6.2:1 (**31f:32f**)
7	**30g**	penta-F-Ph		7.9:1 (**31g:32g**)
8	**30h**	CF_3		low reactivity

protected indoles produced the desired C–C bond forming products but as a mixture of desired *anti* (**31a–h**) and undesired *syn* (**32a-h**) diastereomers.[25] There is a clear trend that the diastereoselectivity improved with increasing electron-withdrawing ability of the sulfonyl groups.[26] Based on cost and availability, we decided to take nosyl indole **30e** forward for further development. Scale up preparation of **30e** involved reaction of distilled indole **2** with nosyl chloride in a toluene–50% aqueous NaOH biphasic system in the presence of

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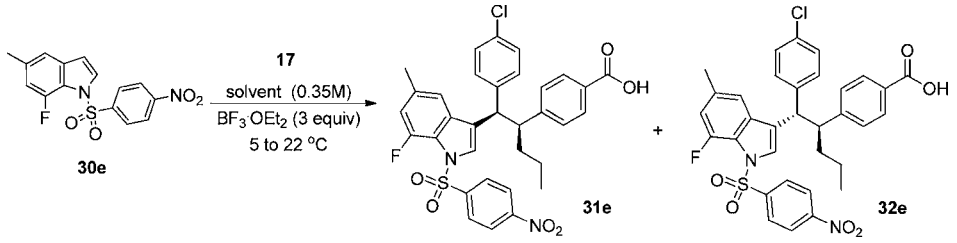
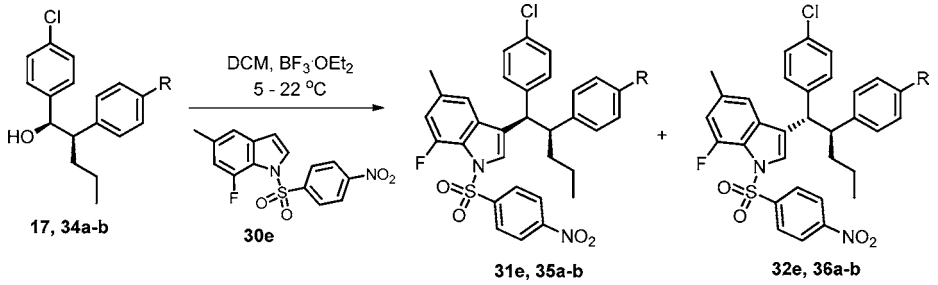
Table 2. Solvent Effect



	solvent	31e:32e[a]
1	1,2-dichloroethane	86:14
2	dichloromethane	85:15
3	trifluorotoluene	82:18
4	1,2-dichlorobenzene	82:18
5	chlorobenzene	81:19
6	trichloroethylene	81:19
7	toluene	55:45 (20% conv)
8	isopropyl acetate	76:24 (10% conv)
9	cyclopropyl methyl ether	77:23 (5% conv)
10	2-Me-THF	no product
11	dioxane	no product
12	DME	no product
13	acetonitrile	no product
14	nitromethane	86:14

[a]>90% conversion unless specified otherwise.

Table 3. Electronic Effect of α-Phenyl Substituents



	R	σ-para	syn:anti	$t_{95\%}$
1	-Br (**34a**)	0.23	82:18 (**35a:36a**)	<1 h
2	-CO_2tBu (**17**)	0.45	86:14 (**31e:32e**)	12 h
3	-CN (**34b**)	0.66	86:14 (**35b:35b**)	3 d
			Reaction rate: **34a** > **17** > **34b**	

catalytic nBu$_4$HSO$_4$. After workup, product **30e** was crystallized from cold 2-propanol in 87% yield for the step or in an overall yield of 65−70% for the four-step process from aniline **23**. This route was successfully run on one hundred kilogram scale with little deviation from the lab, producing excellent quality material (100 wt %, 7 ppm Pd, and 2 ppm Cl).

A solvent screen was performed for the Friedel−Crafts reaction as shown in Table 2. DCM was chosen for further development. A Hammet effect was also observed with the *para*-substituents in the remote phenyl moiety of the substrate (Table 3). The reaction time to reach 95% conversion increased from 1 to 12 h to 3 d as the electron-withdrawing ability increased with R = −Br, −CO_2tBu, and −CN, respectively. Thus, ionization of the benzylic alcohol is sensitive to the β phenyl group, in which the electron-withdrawing groups appeared to raise the ionization barrier. Although phenolium participation is a possible explanation, it is inconsistent with the *anti*-selectivity.

In all the Friedel−Crafts reactions with *tert*-butyl ester **17**, we observed formation of 10−15% of 3-*tert*-butyl indoles **33** as a result of the indole reacting with the *tert*-butyl cation. This lowered the assay yields of desired diastereomer **31e** from **30e** and **17** to a moderate ∼60−65%. We, therefore, decided to deprotected the *tert*-butyl ester prior to the Friedel−Crafts reaction. An attempt to develop a through process from **17** was sought. Treatment of **17** with TFA in DCM followed by several cycles of concentration and evaporations and then performing the BF_3·OEt_2 reaction gave <1% **33**. But this could not be reproduced on scale. Simple distillation of DCM did not completely remove the *tert*-butyl cation precursor (possibly *tert*-butyl trifluoroacetate), and **33** was generated at elevated levels. A discrete isolation of benzoic acid **37** was therefore sought. Phosphoric acid in acetonitrile[27] at 65 °C was found to affect the cleavage in near quantitative yield. Subsequent addition of water crystallized benzoic acid **37** as a monohydrate in 91% isolated yield (Scheme 7).[28]

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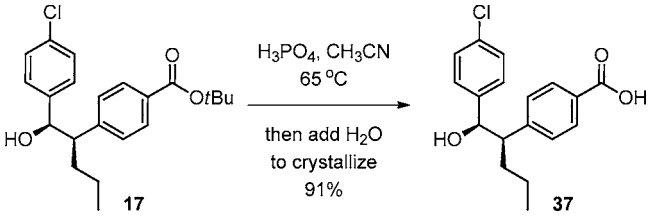
Scheme 7. Hydrolysis of *tert*-Butyl Ester 17



Under the best Friedel–Crafts condition identified from above, screens with nosyl indole **2** and acid **37**, using dichloromethane as solvent and 3 equiv of BF_3 etherate at room temperature, the reaction reliably afforded a diastereomeric ratio (dr) of 86:14 in favor of the desired diastereomer **31e** in ~75% assay yield, which was only minimally affected by temperature, concentration, and stoichiometry. Following an aqueous workup, the product could be crystallized from IPAC/heptane with good rejection of diastereomer **32e** and other impurities in 67–70% isolated yield with 99% dr.

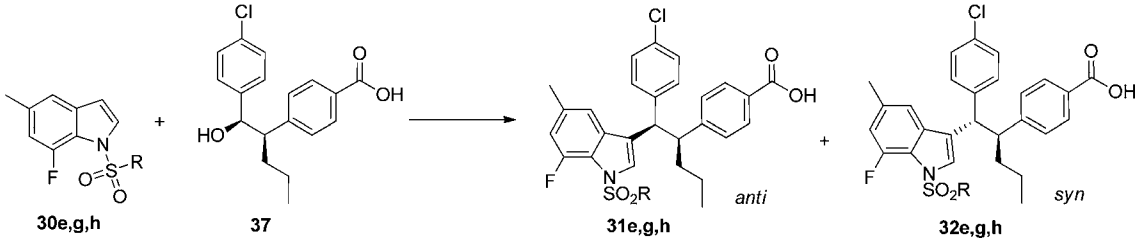
Unsatisfied with the 86:14 diastereoselectivity, we proceeded to screen a variety of Lewis/Brønsted acids. Most of the acids examined afforded similar or poorer selectivity.[29] In general, conditions that afforded improved dr usually are low yielding. Finally, a significant improvement was observed with trifluoroacetic acid as solvent, where as high as 12:1 (92:8) was observed, but the reaction stalled at 75% conversion after 20 h (Table 4, entries 2 and 3). Heating the reaction did improve conversion but at the expense of impurity formation and slightly lower dr. The reason for the stall was that trifluoroacetylation is competitive with the ionization of the benzyl alcohol and the trifluoroacetylated product was slow to ionize. We reasoned that TFA is not acidic enough to protonate and ionize trifluoroacetoxy product; therefore, usage of additional stronger acids was examined. Methanesulfonic acid emerged to be optimum compared to $BF_3{\cdot}OEt_2$, $HBF_4{\cdot}OEt_2$, and TfOH, affording **31e**/**32e** in 99% assay yield and 11:1 dr (entry 10).

Initial development to upgrade the dr by crystallization of the mixture found variable results. In some runs the crystallization supernatant saw a 60:40 ratio of undesired **32e** to desired **31e** diastereomers and 80% isolated yield with >99:1 dr. In the others, we observed a 30:70 ratio in the supernatant and 65% isolated yield. After some detective work, it was discovered that the observed variation was due to seeding of different crystal forms of **31e** which have different solubilities relative to the undesired diastereomer. To date, five different crystal forms and solvates have been identified, and a mono-IPAC solvate of the desired diastereomer exhibited the least solubility and the largest differential solubility between the desired and the undesired, thus affording the best recovery and purity upgrade. The optimum crystallization condition involved seeding the crude mixture in IPAC/heptane. Product **31e** was isolated in 83% yield with >99:1 dr.

Endgame. Attachment of the β-alanine amide side chain to acid **31e** using 1,1′-carbonyldiimidazole (CDI) was facile. Stirring **31e** with 1.2 equiv of CDI in THF led to complete conversion to the imidazolide intermediate. Subsequent addition of 1.2 equiv of β-alanine methyl or ethyl ester hydrochloride led to a quantitative yield of amide **38** or **39**, respectively (Scheme 8).

The above reaction mixture containing **38** was directly treated with 1.7 N NaOH to affect the concomitant hydrolysis of methyl ester and N-nosyl moieties. HPLC analysis showed that the rates of hydrolysis between the two groups are competitive, where a mixture of two intermediates, presumably the partially hydrolyzed or deprotected intermediates, was observed, before hydrolysis was complete.

Table 4. Friedel-Crafts Alkylation in TFA



entry	R	solvent	additive	temp/time	assay yield	*anti*:*syn*
1	4-NO_2Ph (**30e**)	DCM	BF_3 OEt_2	22 °C/20 h	92%	6:1
2		TFA	none	22 °C/4 h	52%	12:1
3		TFA	none	50 °C/24 h	92%	11:1
4		TFA	BF_3 OEt_2	22 °C/20 h	95%	9:1
5		TFA	HBF_4 OEt_2	22 °C/20 h	94%	9:1
6		TFA	TfOH (1equiv)	0 °C/1 h	90%	10:1
7		TFA	TfOH (1 equiv)	22 °C/5 h	93%	10:1
8		TFA	TfOH (0.5 equiv)	−12–20 °C/18 h	94%	10:1
9		AcOH	TfOH (1equiv)	50 °C/2 d	14%	4:1
10		TFA	MsOH (1equiv)	22 °C/20 h	**99%**	**11:1**
11		TFA	MsOH (1equiv)	22 °C/20 h	96%	12:1[a]
12	F_5-Ph (**30g**)	TFA	none	22 °C/1 h	25%	13:1
13		TFA	TfOH (1equiv)	22 °C/2 h	95%	12:1
14	CF_3 (**30h**)	TFA	none	22 °C/1 h	<2%	
15		TFA	TfOH (1equiv)	22 °C/2 h	80%	10:1

[a]Slow addition of **30e**/TFA/MsOH to **37**.

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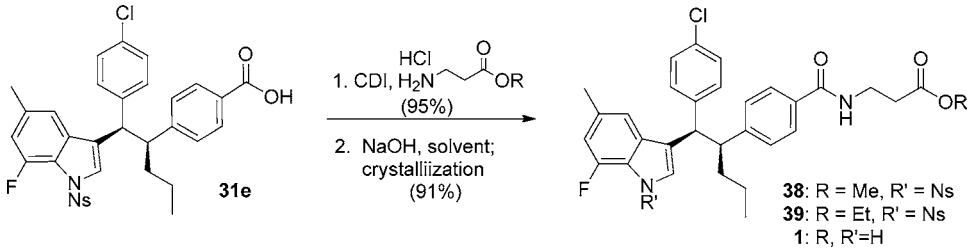
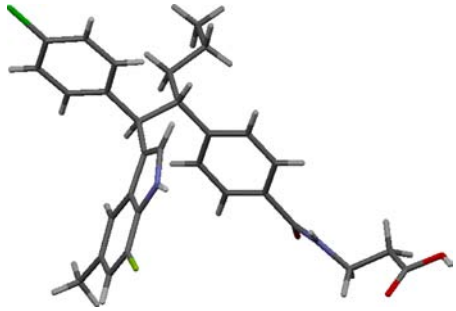
Scheme 8. Endgame



The reaction was neutralized with 3 N HCl, salted, and extracted with MTBE. After a solvent switch to IPA, compound **1** was crystallized by the addition of water. Compound **1** was isolated as a hemihydrate in 87% yield and ≥99% ee. A single crystal X-ray structure of **1** was obtained, which confirmed the identity and absolute stereochemistries.



CONCLUSION

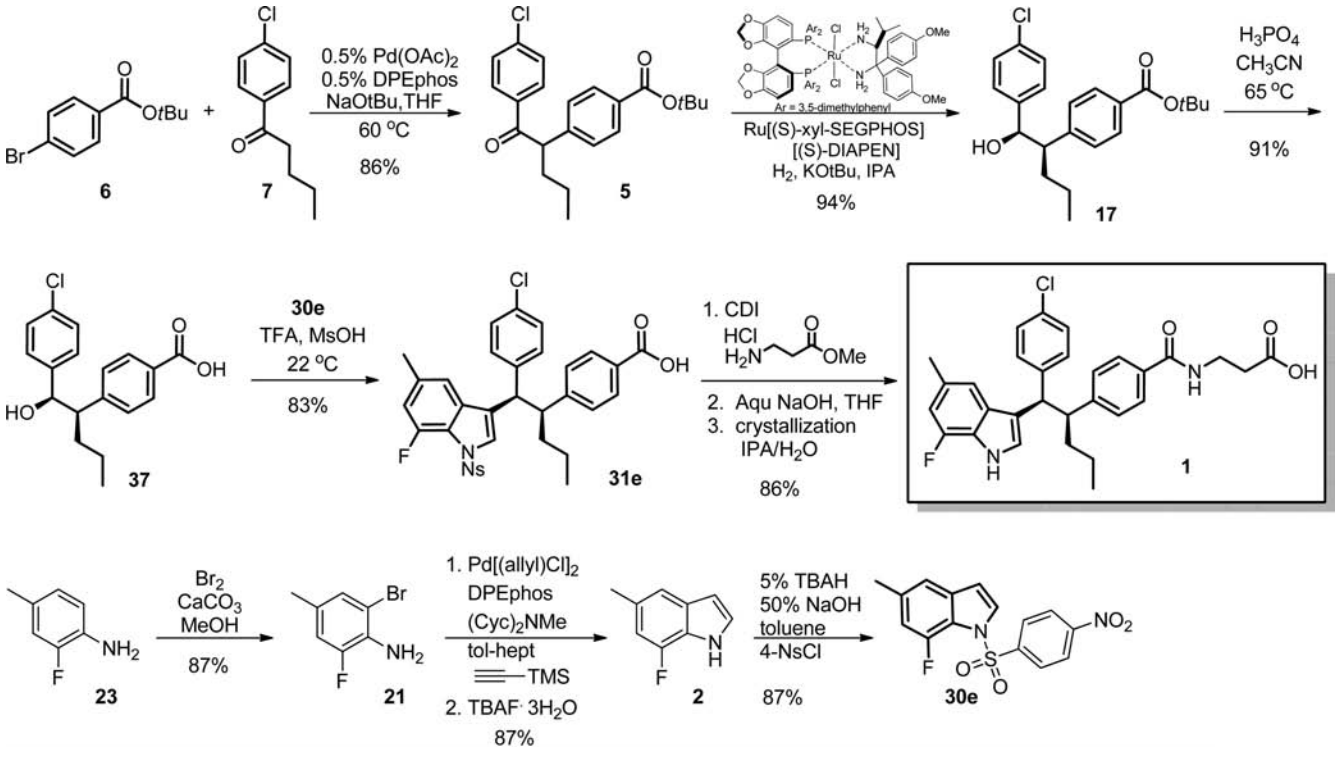
In conclusion, an efficient asymmetric synthesis of glucagon receptor antagonist **1** was developed (Scheme 9).[20] The ethane core was constructed in a highly regio-, diastereo-, and enantioselective manner via a Buchwald ketone arylation, a DKR asymmetric hydrogenation, and an *anti*-selective Friedel–Crafts indole alkylation with a chiral α-phenyl benzyl cation. Optimal Friedel–Crafts diastereoselectivity and yield were achieved with nosyl protected indole using TFA as solvent and catalytic MsOH. A highly efficient Larock-type fluoro-indole synthesis from 2-bromoaniline was also developed. The described convergent synthesis was used to prepare 20 kg of drug substance **1** in 52% overall yield with >99% ee.

EXPERIMENTAL SECTION

General. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by HPLC. Assay yields were obtained using analytical standards prepared by recrystallization or preparative chromatography. All isolated yields reflect correction for purity based on HPLC assays. HPLC analyses were performed using one of the following methods:

HPLC Methods. (A) Zorbax Eclipse XDB-C8 150 mm × 4.6 mm, 5 μm, gradient elution from 45:55 to 95:5 MeCN/0.1% aqueous H_3PO_4 over 15 min, then isocratic elution with 95:5 MeCN/0.1% aqueous H_3PO_4 over 2 min, 1.0 mL/min

Scheme 9. Final Process of Asymmetric Synthesis of 1 via DKR and Indole Addition to Chiral Benzyl Cation



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flow at 35 °C with detection at 254 nm. **23**, 2.4 min; **21**, 6.5 min.

(B) Zorbax Eclipse XDB-C8 150 mm × 4.6 mm, 5 μm, gradient elution from 50:50 to 90:10 MeCN/0.1% aqueous H_3PO_4 over 10 min, then isocratic elution with 90:10 MeCN/0.1% aqueous H_3PO_4 over 6 min, then gradient elution from 90:10 to 50:50 over 2 min, then hold isocratic for 2 min, 1.0 mL/min flow at 25 °C with detection at 215 nm. **24**, 12.3 min; **2**, 7.4 min; **30e**, 9.8 min.

(C) Zorbax Eclipse XDB-C8 150 mm × 4.6 mm, 5 μm, gradient elution from 10:90 to 90:10 MeCN/0.1% aqueous H_3PO_4 over 10 min, then isocratic elution with 90:10 MeCN/0.1% aqueous H_3PO_4 over 3 min, 1.0 mL/min flow at 35 °C with detection at 220 nm. 4-Bromobenzoic acid, 10.27 min; 4-bromobenzoyl chloride, 12.95 min; **6**, 14.04 min.

(D) Zorbax Eclipse XDB-C8 150 mm × 4.6 mm, 5 μm, gradient elution from 70:30 to 95:5 MeCN/0.1% aqueous H_3PO_4 over 15 min, then isocratic elution with 95:5 MeCN/0.1% aqueous H_3PO_4 over 2 min, then gradient elution from 95:5 to 70:30 over 1 min, then hold isocratic for 5 min, 1.0 mL/min flow at 30 °C with detection at 210 nm. **7**, 4.25 min; **5**, 9.6 min; 4-bromobenzoic acid, 1.94 min; **16**, 13.9 min; 17, 7.4 min; **31e**, 7.32 min; **32e**, 5.66 min; **33e**, 6.69 min; imidazolide of **31e**, 6.80 min; imidazolide of **32e**, 5.82 min; **39**, 8.00 min; **40**, 6.36 min; **1**, 3.65 min.

(E) Zorbax Eclipse XDB-C8 150 mm × 4.6 mm, 5 μm, gradient elution from 75:25 to 95:5 MeCN/0.1% aqueous H_3PO_4 over 4 min, then isocratic elution with 95:5 MeCN/0.1% aqueous H_3PO_4 over 2 min, then gradient elution from 95:5 to 75:25 over 0.1 min, then hold isocratic for 2 min, 1.0 mL/min flow at 22 °C with detection at 210 nm. **7**, 1.24 min; **6**, 1.68 min; **5**, 3.31 min; **16**, 4.97 min; carboxlyic acid of **5**, 0.68 min,

(F) Chiralcel AD-H 250 mm × 4.6 mm, 5 μm, isocratic elution at 95:5 hexane/ethanol, 1.0 mL/mL flow at 5 °C with detection at 238 nm. **17**, 25 min; enantiomer of **17**, 15 min.

(G) Zorbax Eclipse XDB-C8 150 mm × 4.6 mm, 5 μm, gradient elution from 70:30 to 90:10 MeCN/0.1% aqueous H_3PO_4 over 15 min, then isocratic elution with 90:10 MeCN/0.1% aqueous H_3PO_4 over 2 min, then gradient elution from 90:10 to 70:30 over 0.1 min, then hold isocratic for 5 min, 1.0 mL/min flow at 30 °C with detection at 210 nm. **17**, 8 min; diastereomer of **17**, 7 min.

(H) Phenomenex Luna C18 150 mm × 4.6 mm, 3 μm, gradient elution from 30:70 to 90:10 MeCN/0.02% aqueous TFA, then isocratic elution with 90:10 MeCN/0.02% aqueous TFA for 6 min, 1.0 mL/min flow at 45 °C with detection at 210 nm. **17**, 14.7 min; **37**, 9.7 min.

(I) Zorbax Eclipse XDB-C8 50 mm × 4.6 mm, 1.8 μm, gradient elution from 30:70 to 95:5 MeCN/0.1% aqueous H_3PO_4 over 5 min, then isocratic elution with 95:5 MeCN/0.1% aqueous H_3PO_4 over 3 min, then gradient elution from 95:5 to 30:70 over 0.1 min, then hold isocratic for 2 min, 2.0 mL/min flow at 40 °C with detection at 210 nm. **17**, 4.7 min; **37**, 2.8 min.

(J) ChiralPak IB, 250 mm × 4.6 mm, isocratic elution at 6:94 0.1% TFA in 50/50 EtOH/MeOH/0.1% TFA in heptane, 1 mL/min flow at 25 °C with detection at 254 nm. **37**, 17.1 min; enantiomer of **37**, 21.1 min.

(K) Thermo Gold PFP 4.6 mm × 50 mm, 1.9 μm; A, 0.1% H_3PO_4 aqueous; B, acetonitrile; 60% to 95% B over 2 min, hold 1 min, post time 2 min; 0.75 mL/min, 3 μL, 210 nm, 22 °C column temperature. **22**, 1.6 min; **24**, 1.8 min.

(L) Zorbax Eclipse XDB-C8, 50 mm × 4.6 mm, 1.8 μm, gradient elution from 50:50 to 90:10 MeCN/0.1% aqueous H_3PO_4 over 5 min, then isocratic elution with 90:10 MeCN/0.1% aqueous H_3PO_4 over 3 min, then gradient elution from 90:10 to 50:50 over 0.1 min, then hold isocratic for 2 min, 2.0 mL/min flow at 40 °C with detection at 210 nm. **37**, 1.33 min; **30e**, 2.24 min; **31e**, 4.16 min; **32e**, 3.71 min.

(M) Chiral SFC method: ChiralPak IB column (250 mm × 4.6 mm), isocratic 25% MeOH with 0.1% TFA/CO_2 over 35 min, 1.5 mL/min flow at 200 bar, 35 °C with detection at 210 nm. **31e**, 18.11 min; enantiomer of **31e**, 17.28 min; **32e**, 19.85 min; enantiomer of **32e**, 24.15 min.

(N) XBridge C18, 4.6 mm × 150 mm, 3.5 μm, A, 10 mM ammonium bicarbonate pH 8.0; B, acetonitrile; 30% to 95% B over 13 min, 95% to 90% B over 4 min, then to 30% B over 0.1 min, post time 4 min. 1.00 mL/min flow, 5 μL, detection at 210 nm, 30 °C column temperature. **31e**, 9.7 min; **1**, 7.9 min; **38**, 13.9 min; pyrrolidine amide of **31e**, 14.79 min.

(O) Chiral SFC method: ChiralPak AD-H column (250 mm × 4.6 mm), isocratic 15% MeOH with 25 mM isobutylamine/CO_2 over 30 min, 1.5 mL/min flow at 200 bar, 35 °C with detection at 210 nm. **1**, 18.9 min; enantiomer of **1**, 15.7 min.

*tert-Butyl 4-Bromobenzoate (**6**).* 4-Bromobenzoyl chloride (106 kg, 483 mol) was dissolved in THF (484 L) and cooled to −5 °C. Potassium *tert*-butoxide (75.8 kg, 677 mol) was dissolved in THF (572 L), cooled to −5 °C, and added to the acid chloride solution via an inline filter over ∼3 h at ≤5 °C. After stirring at −5 to 5 °C for 30 min, the reaction was assayed for completion by HPLC (0.5% vs specification of <2% 4-bromobenzoyl chloride). In a separate vessel, NaCl (40 kg) was dissolved in water (736 mL), then heptane (878 L) was charged, and the mixture was cooled to −5 °C. The reaction mixture was added to the aqueous mixture at ≤5 °C. The layers were separated, and the aqueous layer was extracted with heptane (291 L). The combined organic layer was filtered through a pad of anhydrous $MgSO_4$ (15.9 kg). The filtrate was concentrated to ∼212 L under vacuum at 30−40 °C, THF was (692 L) charged, and the resulting mixture was concentrated to ∼212 L. This was repeated, and heptane was 4.2 wt % (vs specification of ≤12%) and KF was ∼0% (vs specification of <0.05%). The organics was concentrated in vacuum (10−15 Torr) under 50 °C to afford 170 kg of *tert*-butyl 4-bromobenzoate as a 69.9 wt % mobile oil in 95.7% corrected yield with 99.6 LCAP. **6**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 1.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 131.7, 131.2, 131.1, 127.6, 81.7, 28.4. Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.10; Br, 31.08. Found: C, 51.61; H, 5.09; Br, 31.35.

*tert-Butyl 4-[1-(4-Chlorobenzoyl)butyl]benzoate (**5**).* Sodium *tert*-butoxide (53 kg, 552 mol) in THF (460 L) was degassed via three N_2/vacuum purge cycles and agitated for 30 min to dissolve the solids. Palladium acetate (454 g, 2 mol) was charged via a nitrogen-inerted glovebag, followed by (oxidi-2,1-phenylene)bis(diphenyl-phosphine) (DPEphos) (1.08 kg, 1.59 mol) in the same manner. The batch was degassed again via three N_2/vacuum purge cycles and aged for 30 min. 4-Chlorovalerophenone (**7**) (79 kg, 98.4%, 395 mol) and *tert*-butyl-4-bromobenzoate (**6**) (160.7 kg as a 71.3 wt % solution in THF, 446 mol) were then charged, rinsing with THF (75 L) and taking care to exclude air throughout the operation. The mixture was degassed again via three N_2/vacuum purge cycles. The batch was heated gradually to 58−64 °C, stirred for 8 h, and checked by HPLC for completion. After cooling to 15−25

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°C, the batch was quenched into a 0−5 °C mixture of heptane (1059 L) and $NaHCO_3$ solution (prepared by dissolving 42.8 kg of $NaHCO_3$ and 808 kg of water) at <10 °C. The vessel was rinsed with heptane (49 L) and added to the quenched mixture. The mixture was warmed to 15−25 °C, and the layers were separated. The aqueous layer was extracted with heptane (558 L). The combined organics were treated with aqueous sodium 2-mercaptobenzoate (prepared from 32 kg of 2-mercaptobenzoic acid, 354 kg of water, and 159 kg of 10% NaOH solution, pH 8−9). After stirring at 25−30 °C for 6−8 h, the layers were separated. The organic layer was washed with 3% aqueous $NaHCO_3$ solution (2 × 549 kg). The analysis of the organic layer showed that the residual 2-mercaptobenzoic acid was below the detection limit (vs expectation of <0.05%). The organic layer was washed with water (2 × 426 kg) until pH 7 and then was further washed with 20% NaCl solution (2 × 476 kg). A silica plug was prepared in a large filter using 50 kg of silica gel topped with 40 kg of Na_2SO_4 and marinated with heptane (117 L). The batch was then filtered through the silica, washing with heptane (115 L). The filtrates were combined and concentrated to 160 L under vacuum at batch temperature <40 °C. Isopropyl alcohol (1185 L) was added and concentrated to 160 L under vacuum at <40 °C. This was repeated with 791 L of isopropyl alcohol, and then diluted with 294 L of isopropyl alcohol. The mixture was warmed to 45−60 °C and stirred for 15 min until solid dissolved. Water (93 L) was added at 40−60 °C, and the mixture was allowed to cool slowly to 20−25 °C. The mixture was further cooled to −5−5 °C and stirred for 2 h. The solid was collected by centrifugation and washing with 2:1 *i*PrOH/H_2O (50 kg). The wet cake was dried under vacuum at 38−40 °C for 22 h to afford 129.4 kg of product **5** as a yellow solid having 98.4 wt %, 98.2 LCAP, and 0.03% H_2O. The corrected yield was 86.4%. **5**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.92 (m, 2H), 7.87 (m, 2H), 7.36 (m, 2H), 7.33 (m, 2H), 4.54 (t, *J* = 7.2 Hz, 1H), 2.16 (m, 1H), 1.83 (m, 1H), 1.57 (s, 9H), 1.37−1.17 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 198.4, 165.6, 144.3, 139.6, 135.2, 131.2, 130.3, 130.2, 129.1, 128.3, 81.2, 53.7, 36.0, 28.4, 20.9, 14.2. Anal. Calcd for $C_{22}H_{25}ClO_3$: C, 70.86; H, 6.76; Cl, 9.51. Found: C, 70.73; H, 6.98; Cl, 9.21.

*tert-Butyl 4-{(1R)-1-[(R)-(4-Chlorophenyl)(hydroxyl)-methyl]butyl}benzoate (**17**).* Ketone **5** (110 kg, 293 mol) and IPA (869 L) were charged to a hydrogenation vessel. The solution was thoroughly degassed using N_2/vacuum purge cycles. The catalyst solution was prepared in a separate vessel. Potassium *tert*-butoxide (7.0 kg, 62.3 mol) was dissolved in IPA (84 L) and thoroughly purged with N_2. The catalyst, $RuCl_2$[(*S*)-xyl-SEGPHOS][(*S*)-DIAPEN] (551 g, 455 mmol) was added, and the catalyst mixture aged for 1 h whilst purging with N_2. This catalyst preparation was then added to the ketone IPA solution, taking care to exclude air during this operation, and degassing using N_2/vacuum purge cycles after the addition. The batch was then hydrogenated for 4 h at 20−25 °C with 95−100 psi H_2 pressure. HPLC assay after this time showed no starting material remaining (0.04% starting ketone). The batch was filtered through a silica gel pad (22 kg, marinated with IPA) twice. The clarified solution was concentrated to ∼880 L by distillation at <40 °C. The solution was heated to 55−58 °C; then H_2O (780 L) was slowly added over 1.5 h, while maintaining the temperature at 55−58 °C. The batch, crystallized during this addition, was aged at 55−58 °C for a further 1 h, then cooled to 20−25 °C over 2 h, then cooled to 0−5 °C over 2 h. After stirring for 1.5 h at 0−5 °C, the slurry was filtered, washing with cold 2:1 IPA/water (2 × 120 L). The product was dried under vacuum for 30 h at 40−45 °C to afford 106 kg of product **17** as an off-white solid (97.6 wt %, 98.5% ee, and 99.5% de) in 94.1% corrected yield. **17**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.96 (m, 2H), 7.32 (m, 2H), 7.26 (m, 2H), 7.22 (m, 2H), 4.76 (dd, *J* = 7.7, 2.9 Hz, 1H), 2.89 (ddd, *J* = 11.5, 7.7, 4.2 Hz, 1H), 1.84 (d, *J* = 2.9 Hz, −OH), 1.62 (s, 9H), 1.61 (m, 1H), 1.41 (m, 1H), 1.05 (m, 2H), 0.76 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 165.9, 146.3, 141.4, 133.7, 131.0, 129.8, 128.9, 128.7, 128.4, 81.1, 78.01, 54.2, 34.2, 28.4, 20.6, 14.1. FTIR (thin film) ν_{max} 3502, 2959, 2868, 1684, 1316, 1299, 1158, 1125, 1011, 847, 828, 712 cm^{-1}. Anal. Calcd for $C_{22}H_{27}ClO_3$: C, 70.48; H, 7.26; Cl, 9.46. Found, C, 70.45, H, 7.40, Cl, 9.24. The *syn* diastereomer was prepared from $NaBH_4$ reduction of ketone **5**, followed by flash chromatography purification: ^{1}H NMR (400 MHz, $CDCl_3$) partial: δ 7.83 (m, 2H), 7.18 (m, 2H), 7.06 (m, 2H), 7.04 (m, 2H), 2.95 (ddd, *J* = 11.1, 7.3, 3.9 Hz, 1H), 1.93 (m, 1H), 0.83 (t, *J* = 7.3 Hz, 3H).

*4-{(1R)-1-[(R)-(4-Chlorophenyl)(hydroxyl)methyl]butyl}-benzoic Acid Monohydrate (**37**).* Alcohol **17** (90 kg, 240 mol) was slurried in acetonitrile (840 L), and 85% phosphoric acid (1136 kg) was charged in one portion. The slurry was made inert with N_2 and slowly heated to 62−68 °C. Isobutylene gas was evolved as the reaction progressed. After 3.5 h, the solution was cooled to 30−40 °C, and the reaction was deemed to be completed by HPLC analysis (starting material = 0.4%). The solution was heated to 55−65 °C, and water (98 kg) was charged over 45 min. The mixture was cooled to 45−50 °C, and seeded with 430 g of **37** to effect the crystallization. Once a seedbed was established after 20 min, further water (861 kg) was slowly charged over 1.5 h at 45−50 °C. The mixture was cooled slowly to 20−25 °C and then aged for 2−3 h. The slurry was then filtered, washing with 1:3 acetonitrile/water (88 kg), and the product was dried in a vacuum oven at 40 °C for 16 h to give 73.3 kg of acid **37** monohydrate as a yellow solid (100 wt %, 99.5 LCAP, KF 5.7% H_2O, 98.6% ee) in 90.7% corrected yield. **37**: ^{1}H NMR (400 MHz, DMSO-d_6) 12.71 (br s, −CO_2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.19−7.25 (m, 4H), 5.32 (br s, −OH), 4.76 (d, *J* = 6.3 Hz, 1H), 2.85 (dt, *J* = 10.7, 5.4 Hz, 1H), 1.61 (m, 1H), 1.44 (m, 1H), 1.00 (m, 2H), 0.73 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) 167.4, 147.7, 143.7, 131.0, 129.1, 128.6, 128.4, 128.3, 127.6, 75.1, 52.7, 34.0, 20.0, 13.8. Anal. Calcd for $C_{18}H_{19}ClO_3{\cdot}H_2O$: C, 64.19; H, 6.28; Cl, 10.53. Found: C, 64.43; H, 6.06; Cl, 10.30.

*2-Bromo-6-fluoro-4-methylaniline (**21**).* A reactor equipped with a condenser, stirrer, and thermometer was charged with calcium carbonate (91.5 kg, 914 mol) and methanol (554 L), and the mixture was stirred until it formed a white slurry. 2-Fluoro-4-methylaniline (**23**) (100 kg, 799 mmol) was charged to the reactor at 20−25 °C. The resulting slurry was cooled to −5 to 0 °C. Bromine (128 kg, 799 mol) was added over 6 h at −3 to 2 °C. After stirring for 2 h, the reaction was checked by GC analysis to be 96.6% relative to starting material. An additional amount of bromine (0.5 kg, 3 mol) was charged to the reaction mixture and stirred for an additional 1 h to achieve 96.8% conversion. The pH of the reaction mixture was tested with a wetted pH paper to be ∼pH 3−4. A water/methanol mixture (200 + 200 L) was slowly added to the reaction mixture, and the material was allowed to warm to 20 °C. If a solid layer formed, more methanol could be added to dissolve the solid. The pH of the reaction mixture was adjusted to 10−11 with 20 wt % NaOH (16.5 L). The methanol was vacuum

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distilled, and MTBE (207 L) was added to the product/water mixture. The mixture was then filtered and washed with MTBE (3 × 145 L), and the layers were allowed to separate. The aqueous layer was extracted with MTBE (3 × 145 L). The combined organic layer was dried over sodium carbonate (15.3 kg), filtered, and washed with MTBE (138 L). The organic layer was concentrated to an oil. The oil was flash distilled using a wipe-film distillation (156 ± 4 °C at 0.1−0.5 mmHg) to give **21** in 99+% purity and 87% corrected yield (141 kg based on NMR). Compound **21** is a known commercial compound, and its spectroscopic data is consistent with the reported literature.[15,16]

7-Fluoro-5-methyl-1H-indole (2). Distilled bromoaniline **21** (167 kg, 818 mol), toluene (778 L), *N*-methyldicyclohexylamine (352 kg, 1804 mol), and trimethylsilylacetylene (145 kg, 1481 mol) were charged to a vessel. This mixture was then deoxygenated by bubbling nitrogen through the solution for 2 h. The exhaust of the vessel was vented into a dry ice/acetone trap to trap any escaping trimethylsilylacetylene. The recovered trimethylsilylacetylene in the trap was transferred with N_2 pressure back into the vessel. In a separate vessel, allylpalladium(II) chloride dimer (6.8 kg, 18.5 mol) and (oxidi-2,1-phenylene)bis(diphenylphosphine) (20.2 kg, 37.5 mol) were charged and deoxygenated via vacuum/nitrogen pressure (5 cycles). Deoxygenated heptane (1675 L) (by bubbling nitrogen) was added to the catalyst. The catalyst slurry was charged to a N_2-pressurized reactor followed by the bromo-aniline/toluene/amine/TMS-acetylene mixture. The reactor was sealed and heated to 72−75 °C. The reactor built up 5−7 psig pressure during this heating period. After 16 h, the reaction was checked by GC (0.04% bromoaniline **21**, 99.96% TMS-indole **24** with a TMS-indole to Sonogashira product **22** ratio of 30:1). The reaction mixture was cooled to room temperature and vented, the material was filtered, and the residue was rinsed with heptane (470 L). The filtrate was worked up by gently washing the organic layer with dilute hydrochloric acid (130 L of 37% HCl diluted with 760 L water) with an exotherm from 21 to 30 °C and then water (810 L) (each stirred at 60 rpm for 1 h). A second same size batch run afforded similar results. The washed organic layers from both batches were combined and concentrated using vacuum and up to a pot temperature of 50−64 °C to remove any excess trimethylsilylacetylene to around 300 mL. Toluene (952 L) was added and concentrated to 940 kg. At this stage no trimethylsilylacetylene was detected by GC, and the product was filtered, diluted to 1140 kg, and used as is for the next step. HPLC assayed 355 kg of TMS-indole **24** (98%). ^{1}H NMR (400 MHz, $CDCl_3$) 8.15 (br s, -NH), 7.18 (s, 1H), 6.74 (d, J = 12.0 Hz, 1H), 6.67 (dd, J = 3.6, 2.2 Hz, 1H), 2.44 (s, 3H), 0.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) 149.2 (d, J_{CF} = 243.3 Hz), 139.6, 132.8 (d, J_{CF} = 5.0 Hz), 130.0 (d, J_{CF} = 6.0 Hz), 125.6 (d, J_{CF} = 14.1 Hz), 115.8 (d, J_{CF} = 3.0 Hz), 111.5 (d, J_{CF} = 2.0 Hz), 108.7 (d, J_{CF} = 15.0 Hz), 21.6, −0.91.

Solutions of tetrabutylammonium fluoride trihydrate (282 kg, 895 mmol), methanol (41 L), and THF (878 L) were charged to 7-fluoro-5-methyl-2-(trimethylsilyl)-1H-indole (**24**) (177.5 kg, 801.9 mol) as a 24.7 wt % solution in toluene over 2 h while the internal temperature was kept below 30 °C. The mixture was heated to 80−85 °C for 3 h and then checked for completion. There was 0.003% starting material to product, and the reaction was deemed complete. THF was distilled at reduced pressure up to a jacket temperature of 50−55 °C. The amount of THF remaining in the reaction mixture was less than 1.6%. The reaction mixture was washed with 10% aqueous sodium chloride (2 × 3600 kg), and layers were separated. The combined aqueous layer was extracted with toluene (513 L). The combined organic layers were filtered through a carbon impregnated filter and washed with toluene (90 L). A second desilylation reaction run was done just like the first run. There was no detectable starting material after the 3 h hold at 80−85 °C. The combined work up mixture was steam-distilled using a ratio of 58 L DI water to 1 kg expected final product. The distillate, containing a mixture of desired product, toluene, and water, was salted with NaCl (68 kg), and the layers were separated. The aqueous layer was extracted with toluene (92 L), and the combined organic layer was used as is for the next step. The toluene solution was determined by HPLC assay to contain 207.2 kg of desired product **2**, which was 87% yield. **2**: ^{1}H NMR (400 MHz, $CDCl_3$) 8.20 (br s, -NH), 7.22 (d, J = 0.6 Hz, 1H), 7.20 (dd, J = 2.9, 2.7 Hz, 1H), 6.78 (dd, J = 12.0, 0.7 Hz, 1H), 6.52 (ddd, J = 3.3, 3.3, 2.2 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 149.4 (d, J = 242.9 Hz), 131.8 (d, J = 5.5 Hz), 130.2 (d, J = 5.7 Hz), 125.0, 122.6 (d, J = 13.2 Hz), 116.1 (d, J = 3.1 Hz), 108.6 (d, J = 15.7 Hz), 103.0 (d, J = 2.3 Hz), 21.6. ^{19}F NMR (376 MHz, $CDCl_3$) −136.5. Anal. Calcd for C_9H_8FN: C, 72.47; H, 5.41; F, 12.74; N, 9.39. Found: C, 72.15; H, 5.34; F, 12.74; N, 9.28.

1-(2-Amino-3-fluoro-5-methylphenyl)-2-chloroethanone (26). A round-bottom flask was cooled in ice bath and charged with $AlCl_3$ pellets (117.2 g, 880 mmol), dichloromethane (200 mL), and 1 M BCl_3/CH_2Cl_2 solution (880 mL, 880 mmol) under N_2 with an outlet into an aqueous NaOH solution bath. The suspension was cooled in ice bath, and a mixture of 2-fluoro-4-methylaniline (**23**) (102.0 g, 800 mmol) and chloroacetonitrile (120.8 g, 1600 mmol) was then added dropwise with caution to keep the internal temperature < 20 °C. An extra 120 mL of dichloromethane was used to rinse the flask upon complete addition. The ice bath was removed, and the reaction was aged at room temperature for 10 min before it was heated to reflux. After 14 h of reflux, the brown mixture was cooled in an ice bath, quenched with 2 N HCl (1040 mL), and heated to reflux for 15 min. The mixture turned into two homogeneous layers and was extracted with dichloromethane twice (total 1000 mL). The organic was washed with 1 N HCl (400 mL) and then a mixture of brine/saturated Na_2CO_3/water (1:1:1, 600 mL). The combined HCl layers were washed again with dichloromethane (500 mL). The assay yield of product **26** in the combined organics was 61.4%, with 98.6 LCAP purity. The organic solution was filtered through a silica pad (104 g), washed with extra dichloromethane, and concentrated to obtain a dark yellow solid. The solid was stirred with hexanes (200 mL), cooled in an ice bath, filtered, and washed with a solution of MTBE/hexanes (1:4, 160 mL), and the collected solid was dried under vacuum at 40 °C to obtain **26** as a bright yellow solid (93.7 g, 98.8 wt %, LC 100%AP, 57.4% corrected yield based on starting aniline). Total loss of product in filtrate was ∼6.68 g by assay, 65.8 LCAP. The combined HCl wash was treated with 50 wt % NaOH/water (280 mL) to pH = 4−5, extracted with MTBE/heptane (1:1, 800 mL), and concentrated to recover starting aniline as a dark brown liquid (18.8 g, 95.2% assay pure, 100 LCAP, 17.9% recovery). An analytical standard **26** was prepared by flash chromatography: Yellow solid, mp 98−91 °C. ^{1}H NMR (500 MHz, $CDCl_3$): *d* 7.21 (s, 1H), 7.01 (dd, J = 11.9, 1.9 Hz, 1H), 5.99 (br s, 2H), 4.67 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2 (d, J = 2.4 Hz), 152.4, 150.5, 138.2 (d, J = 14.2 Hz), 125.2 (d, J = 3.0

Hz), 124.3 (d, J = 6.7 Hz), 120.5 (d, J = 7.8 Hz), 116.7 (d, J = 4.3 Hz), 46.6, 20.5 (d, J = 1.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): d −136.4. Anal. Calcd for C_9H_9ClFNO: C, 53.61; H, 4.50; N, 6.95. Found: C, 53.80; H, 4.37; N, 6.83.

*7-Fluoro-5-methyl-1H-indole (**2**)—Method 2.* To a round-bottom flask was charged chloroacetophenone **26** (92.2 g, 98.8%, 452 mmol), 2-methyl-2-butanol (1028 mL), $NaBH_4$ (21.1 g, 542 mmol), and water (92 mL) at room temperature. The yellow cloudy mixture was aged at room temperature for 25 min. The reaction temperature slowly rose up to 38 °C while the mixture turned to a yellow solution. The reaction was then heated to reflux for 2 h, cooled to room temperature, worked up with MTBE (1000 mL) and water (240 mL), washed with brine/water (1:1, 600 mL), dried over $MgSO_4$, and concentrated to obtain indole **2** as a dark yellow clear liquid (70.8 g), which solidified to become an off-white wax at room temperature (96% assay yield, 64.7 g, 97.4 LCAP). The crude product contains 2-methyl-2-butanol. Loss of indole product in the distillate was <0.5 g by assay.

*7-Fluoro-5-methyl-1-[(4-nitrophenyl)sulfonyl]-1H-indole (**30e**).* 7-Fluoro-5-methylindole (**2**) (63.9 kg, 428.4 mol) in toluene was charged to a reactor and adjusted to 10 L of toluene/gram of **2**. 50 wt % NaOH (191 L) followed by tetrabutylammonium hydrogen sulfate (7.5 kg, 22.1 mol) were charged to the reactor and cooled to 15 °C. A mixture of 4-nosyl chloride (118 kg, 533.3 mol) in toluene (320 L) was added over 1−2 h, while maintaining the temperature at <20 °C. The reaction was checked for completion by HPLC. After stirring for 30 min, there was <0.07% starting material relative to desired product, and the reaction was carefully quenched by adding water (1354 L). The layers were separated. The aqueous layer was back extracted with toluene (480 L). The combined organic layer was washed with 0.5 M HCl (200 L) and then water (1354 L). The toluene was vacuum distilled from the organic solution to ∼2 vol, and isopropyl alcohol (715 L) was added to crash out the solids. The resulting slurry was cooled to 5 °C, and isopropyl alcohol (715 L) was charged to complete crystallization. After aging for 1.5 h at 5 °C, the solids are collected on a filter and washed with 5−10 °C isopropyl alcohol (640 L). The wet solids were dried at <1 mmHg/50 °C to afford 125 kg nosyl indole **30e**. The solid was found to have 2 ppm chloride, 7 ppm palladium, 0.05% water, and ∼100 wt % purity (87% yield). **30e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.8 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 3.7 Hz, 1H), 7.13 (s, 1H), 6.81 (d, J = 13.1 Hz, 1H), 6.66 (dd, J = 3.5, 2.4 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 149.2 (d, J = 249.2 Hz), 144.1, 135.5 (d, J = 6.5 Hz), 135.3 (d, J = 3.8 Hz), 129.2 (d, J = 2.8 Hz), 128.7, 128.6, 120.0 (d, J = 11.2 Hz), 117.6 (J = 3.4 Hz), 113.1 (d, J = 19.4 Hz), 109.1 (d, J = 2.1 Hz). Anal. Calcd for $C_{15}H_{11}FN_2O_4S$: C, 53.89; H, 3.32; F, 5.68; N, 8.38; O, 19.14; S, 9.59. Found: C, 53.68; H, 3.16; F, 5.58; N, 8.30; S, 9.64.

*4-[(1R,2S)-1-(4-Chlorophenyl)-1-{7-fluoro-5-methyl-1-[(4-nitrophenyl)sulfonyl]-1H-indol-3-yl}pentan-2-yl]benzoic Acid Propan-2-yl Acetate (1:1) (**31e**).* To acid **37** (42.7 kg of 93.7 wt %, 125.5 mol) and nosyl indole **30e** (41.3 kg of 99.5 wt %, 122.9 mol) were added trifluoroacetic acid (943 kg) and methanesulfonic acid (6.0 kg), while maintaining the temperature at 20−25 °C. The vessel was vented to a 1% NaOH scrubber solution. The solution was aged at 20 °C for 18 h and then sampled to check for reaction completion. HPLC assay determined 0.4% unreacted nosyl indole, and the reaction was deemed completed. During the age, solids precipitated out of solution. The batch was cooled to ∼8 °C, and then isopropyl acetate (1070 kg), ∼0 °C 20% NaOH solution (1200 kg), and 15% K_2HPO_4 solution (908 kg) were added over 4.5 h, while maintaining the temperature between 8 and 16 °C. The layers were separated, and the organic layer was washed with 15% K_2HPO_4 solution (908 kg). The layers were separated. The pH of the final aqueous layer was ∼5.7. The organic was adjusted to pH ∼2 by washing with 0.1 N HCl (136 kg) and then washed with water (1207 kg). The ratio of desired to undesired diastereomeric was ∼11:1, and the estimated yield of the desired product in the organic layer was 71.5 kg. [Seed preparation: 6.1 kg (containing ∼0.42 kg product) of the organic postextraction was distilled to 2 L and flushed with 4 × 2 L IPAC. IPAC was charged to bring the volume to 2 L. Solids had precipitated out of solution during distillation. The crystalline solids were confirmed to be "Form D" by xRPD. The crystallization was completed with the addition of 1 volume of heptane (1.12 kg) and 3 vol of heptane (3.36 kg)]. The organic solution was passed through a carbon filtration system, with washing with IPAC (182 kg). No loss was observed to the carbon. The filtrate was reduced in vacuo at 20−25 °C to a volume of ∼325 L, and flushed with IPAC until <0.02% H_2O. The batch was heated up to 55−60 °C and seeded with the slurry prepared as described above. The batch was aged for 30 min and then cooled to 18−25 °C over 2 h. Heptane (190 kg) was charged over 3 h, followed by heptane (575 kg) charged over 2 h, and then aged over a weekend. The final heptane/IPAC ratio was 4:1. The supernatant assay showed 1.9 g/L desired diastereomer, and 1:2.3 desired/undesired ratio. The batch was filtered and washed with a total of 430 kg of 4:1 heptane/IPAC, and then it was blown dry with nitrogen overnight to afford 74.9 kg of **31e** mono-IPAC solvate as a tan solid (86.4 LCWP) in 82.9% corrected yield. **31e**: ^{1}H NMR (400 MHz, $CDCl_3$) 8.13 (d, J = 8.9 Hz, 2H), 8.05 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 7.45 (s, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.38−7.31 (m, 4H), 6.89 (s, 1H), 6.68 (d, J = 12.8 Hz, 1H), 4.32 (d, J = 11.5 Hz, 1H), 3.43 (dt, J = 10.8, 3.5 Hz, 1H), 3.29 (s, 3H), 1.55 (m, 1H), 1.47 (m, 1H), 1.06 (m, 2H), 0.76 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 171.4, 151.0, 150.7, 149.1 (d, J = 250.6 Hz), 143.4, 140.1, 135.4 (d, J = 6.4 Hz), 134.9 (d, J = 3.2 Hz), 133.1, 130.7, 129.9, 129.3, 128.6, 128.5, 127.7, 127.7, 126.4 (d, J = 3.2 Hz), 124.5, 124.4, 119.8 (d, J = 11.1 Hz), 115.5, 113.5 (d, J = 19.3 Hz), 50.5, 47.7, 37.4, 21.4, 20.4, 14.1. ^{1}H NMR (400 MHz, DMSO-d_6) 8.23 (d, J = 8.8 Hz, 2H), 7.95 (s, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.70−7.60 (m, 4H), 7.57 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.27 (s, 1H), 6.83 (d, J = 13.2 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 3.80 (dt, J = 11.6, 3.2 Hz, 1H), 2.25 (s, 3H), 1.45 (m, 1H), 1.29 (m, 1H), 0.93 (m, 2H), 0.68 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) 171.8, 167.2, 150.4, 149.9, 148.2 (d, J = 250.0 Hz), 141.7 (d, J = 30.3 Hz), 135.0 (d, J = 6.5 Hz), 134.8 (d, J = 3.2 Hz), 131.1, 130.2, 129.1, 128.5, 128.4, 128.3, 128.1, 126.8, 125.5 (d, J = 1.6 Hz), 124.7, 118.5 (d, J = 10.3 Hz), 115.7, 112.7 (d, J = 19.5 Hz), 47.9, 45.8, 36.7, 20.6, 19.7, 13.6. ^{19}F NMR (376 MHz, $CDCl_3$) −122.8; Anal. Calcd for $C_{38}H_{38}ClFN_2O_8S$: C, 61.91; H, 5.20; Cl, 4.81; F, 2.58; N, 3.80; S, 4.35. Found: C, 62.04; H, 5.09; N, 3.79; Cl, 4.82; F, 2.63; S, 4.47. **Syn diastereomer 32e**: Selective NMR signals: ^{1}H NMR (400 MHz, $CDCl_3$) 8.32 (d, J = 8.9 Hz, 2H), 8.08 (d, J = 8.9 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 7.72 (s, 1H), 7.16 (d, J = 8.2 Hz, 2H), 7.07 (s, 1H), 7.05 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 12.8 Hz, 1H), 4.27 (d, J = 10.8 Hz, 1H), 3.47 (m, 1H), 2.37 (s, 3H), 1.85 (m, 1H), 1.20 (m, 1H), 1.15

(m, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) −122.3. Anal. Calcd for $C_{33}H_{28}ClFN_2O_6S$·0.5MTBE·0.2heptane: C, 63.38; H, 5.36; N, 4.01; Cl, 5.07; F, 2.72; S, 4.59. Found: C, 63.59; H, 5.36; N, 3.84; Cl, 4.94; F, 2.75; S, 4.61.

N-({4-[(1R,2S)-1-(4-Chlorophenyl)-1-(7-fluoro-5-methyl-1H-indol-3-yl)pentan-2-yl]phenyl}carbonyl)-β-alanine Hemihydrate (1). Penultimate **31e** (30.0 kg of 99.4 wt %, 47.0 mol) was dissolved in THF (169 L) and degassed using N_2/vacuum purge cycles. *N,N*-Carbonyldiimidazole (13.1 kg, 98.2%, 79.2 mol) was charged, and degassed using N_2/vacuum purge cycles. The mixture was heated over 60 min to 40 °C and aged for 1 h. Conversion was determined by a quench of 50 μL of reaction mixture into 50 μL of pyrrolidine followed by dilution to 25 mL with acetonitrile to give the pyrrolidine amide, and the ratio of acid to pyrrolidine amide was determined by HPLC. After 99.5% conversion to the imidazolide, the batch was cooled to 25 °C and β-alanine methyl ester HCl (12.4 kg, 86.8 mol) and THF (17 L) were charged. After a repurge of the vessel, the batch was then heated over 1.4 h to 60 °C and aged for 6 h. After cooling to ambient, HPLC analysis showed 99.6% conversion to **38**. 1.7 N NaOH (198 L, 337 mol) was charged over 1 h, and the batch was allowed to warm during the charge. The batch was aged at 40 °C for 9 h (99.6% conversion), cooled to 25 °C, and MTBE (196 L) charged, followed by 5 wt % NaCl (200 kg). After agitation and settling, the phases were separated and the organics washed with 5 wt % NaCl (200 kg), 3 N HCl (50 kg), and finally water (208 kg). The pH of the final aqueous layer was 6. The organics were concentrated to ∼182 L and solvent switched to IPA using a total of 833 L IPA via vacuum distillation with a maximum batch temperature of 30 °C. The organic was assayed by HPLC and diluted to ∼110 g/L by charging the appropriate volume of IPA. Water (150 kg) was then slowly added over 45 min followed by seed (20 g). The vessel was repurged and 160 kg water was charged over 1.25 h. After aging for 4.5 h, the batch was filtered, and washed with 190 kg 2/1 (v/v) IPA/water. The cake was blown dry for 4 h and then dried in the tray dryer for 39 h at 60 °C to give 21.8 kg of **1** (98.6 LCWP, 99% ee) in 87.3% corrected yield. **1**: ^{1}H NMR (400 MHz, $CDCl_3$) 8.20 (br s, NH), 7.46 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.94 (s, 1H), 6.83 (d, J = 2.1 Hz, 1H), 6.72 (t, J = 6.0 Hz, -CONH), 6.60 (d, J = 11.9 Hz, 1H), 4.37 (d, J = 10.7 Hz, 1H), 3.58 (m, 2H), 3.37 (dt, J = 10.7, 3.2 Hz, 1H), 2.57 (m, 2H), 2.35 (s, 3H), 1.50 (m, 1H), 1.40 (m, 1H), 0.98 (m, 2H), 0.71 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 176.6, 168.2, 149.2 (d, J_{CF} = 243.8 Hz), 149.0, 142.6, 132.1, 131.7, 130.9 (d, J_{CF} = 5.5 Hz), 130.0, 129.6 (d, J_{CF} = 5.6 Hz), 128.8, 128.5, 127.1, 122.8, 122.6 (d, J_{CF} = 13.3 Hz), 118.6 (d, J_{CF} = 1.2 Hz), 114.3 (d, J_{CF} = 2.5 Hz), 108.6 (d, J_{CF} = 15.7 Hz), 50.3, 48.2, 37.3, 35.5, 34.0, 21.8, 20.5, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) −136.3. Anal. Calcd for $C_{30}H_{31}ClFN_2O_{3.5}$: C, 67.98; H, 5.90; Cl, 6.69; F, 3.58; N, 5.29. Found: C, 68.11; H, 5.84; Cl, 6.70; F, 3.54; N, 5.33.

Ethyl *N*-({4-[(1*R*,2*S*)-1-(4-chlorophenyl)-1-{7-fluoro-5-methyl-1-[(4-nitrophenyl)sulfonyl]-1*H*-indol-3-yl}pentan-2-yl]phenyl}carbonyl)-β-alaninate hemihydrate (**39**). Compound **39** was prepared similarly as for **38** except that the β-alanine ethyl ester was used instead of the β-alanine methyl ester and the product was not hydrolyzed but isolated and purified. **39**: ^{1}H NMR (400 MHz, $CDCl_3$) 8.16 (m, 2H), 7.72 (m, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.44 (s, 1H), 7.36−7.31 (m, 6H), 6.94 (t, J = 5.9 Hz, -NH), 6.87 (s, 1H), 6.67 (d, J = 12.8 Hz, 1H), 4.30 (d, J = 11.5 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.77 (dd, J = 11.7, 6.0 Hz, 2H), 3.82 (dt, J = 10.9, 3.5 Hz, 1H), 2.67 (t, J = 5.8 Hz, 2H), 2.28 (s, 3H), 1.68 (brs, H_2O), 1.53 (m, 1H), 1.45 (m, 1H), 1.25 (t. J = 7.1 Hz, 3H), 1.10−0.97 (m, 2H), 0.74 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 173.4, 166.8, 150.8, 149.1 (d, J = 250.6 Hz), 148.4, 143.2, 140.2, 135.4 (d, J = 6.4 Hz), 135.0 (d, J = 3.4 Hz), 133.0, 132.9, 129.9, 129.2, 128.6 (d, J = 1.9 Hz), 128.4, 127.5, 126.5, 124.6, 124.4 (d, J = 1.6 Hz), 119.8 (d, J = 11.1 Hz), 115.5 (d, J = 3.2 Hz), 113.3 (d, J = 19.8 Hz), 61.0, 50.2, 47.7, 37.5, 35.6, 34.0, 21.4, 20.4, 14.3, 14.0. Anal. Calcd for $C_{38}H_{37}ClFN_3O_7S$·0.5 H_2O: C, 61.41; H, 5.15; Cl, 4.77; F, 2.56; N, 5.65; O, 16.14; S, 4.31. Found: C, 61.10, H, 5.54, N, 5.29. Syn diastereomer **40**: ^{1}H NMR (400 MHz, $CDCl_3$) 8.31 (m, 2H), 8.07 (m, 2H), 7.71 (s, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.3 Hz, 2H), 7.06 (s, 1H), 7.03 (m, 2H), 6.97 (m, 2H), 6.81 (d, 13.7 Hz, 1H), 6.79 (t, J = 5.9 Hz, -NH), 4.25 (d, J = 10.9 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.71 (dd, J = 11.8, 6.0 Hz, 2H), 3.41 (dt, J = 10.9, 3.0 Hz, 1H), 2.64 (t, J = 5.9 Hz, 2H), 2.37 (s, 3H), 1.85 (m, 1H), 1.62 (m, 1H), 1.61 (br s, H_2O), 1.28 (t, J = 7.1 Hz, 3H), 1.12 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 173.2, 167.2, 150.8, 149.4 (d, J = 250.1 Hz), 146.5, 143.9, 140.1, 135.6 (d, J = 6.3 Hz), 135.3 (d, J = 3.8 Hz), 132.7, 132.4, 129.7, 129.5 (d, J = 1.3 Hz), 128.8, 128.6, 127.2, 125.2, 124.9, 124.7, 120.5 (d, J = 10.1 Hz), 115.8 (d, J = 2.5 Hz), 113.6 (d, J = 18.9 Hz), 61.0, 50.7, 48.6, 37.1, 35.5, 34.2, 21.5, 20.8, 14.4, 14.2.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Alternative synthesis of **2**, crystallographic information files for **1**, and NMR NOE for **39** and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: john_chung@merck.com.

Notes

The authors declare no competing financial interest.

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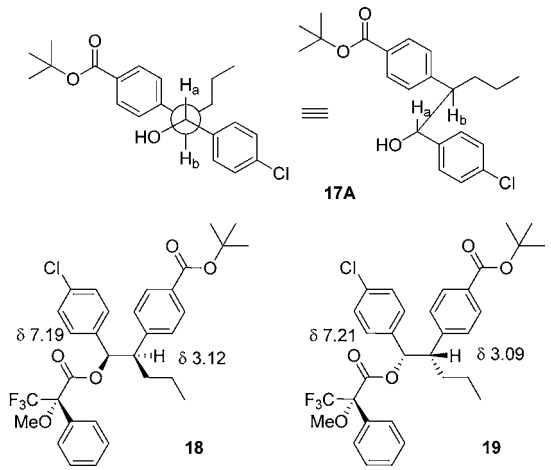
(11) (dtBuPF)$PdCl_2$ is dichloro[1,1′-bis(di-*tert*-butylphosphino) ferrocene]palladium(II). DPEphos is bis(2-diphenylphosphinophenyl)ether.

(12) The relative stereochemistry of the two stereogenic centers in **17** was determined by NMR based on the coupling constants, chemical shifts, and shielding effect of the phenyls of a low energy conformer **17A**. The absolute configuration of the secondary alcohol center was determined via the corresponding Mosher's esters.[13,14] The chemical shift differences between **18** and **19**, although small, shown below, did support the absolute stereochemistry as drawn in **17**. This was ultimately unambiguously established by the single crystal X-ray structure of **1**.



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(28) It is interesting to note that the monohydrate form of **37** offered better impurity rejection and better isolated yield than the anhydrate form.

(29) Brønsted and Lewis acids screened in DCM included $HBF_4{\cdot}OEt_2$ (2 equiv, dr 5:1, 80% yield), $BF_3{\cdot}OEt_2$ (3 equiv, dr 6:1, 90% yield), $B(PhF_5)_3$ (2 equiv, dr 6:1, 50% conv), BCl_3 (2 equiv, dr 8:1, 14%), BBr_3 (2 equiv, dr 4:1, 7% yield), $ZnCl_2$ (3 equiv, no reaction (NR)), $ZnBr_2$ (3 equiv, NR), $EtAlCl_2$ (3.3 equiv, dr 4:1, 60% conv), $TiCl_4$ (1.1 equiv, dr 6:1, 62%), $Y(OTf)_3$ (1.2 equiv, NR), $Eu(OTf)_3$ (1.2 equiv, NR), $Yb(OTf)_3$ (0.5 equiv, NR), $Dy(OTf)_3$ (0.5 equiv, NR), $Sc(OTf)_3$ (0.1 equiv, NR; 1.2 equiv, dr 10:1, 50% yield), $Sc(OTf)_3/CH_3NO_2$ (0.2 equiv, 50 °C, dr 7:1, 56% yield), $Sc(OTf)_3/CH_3NO_2$/trifluoroethanol (0.2 equiv, dr 8:1, 76% yield), $Hf(OTf)_4/CH_3NO_2$ (0.2 equiv, 50 °C, dr 7:1, 61% yield), $InBr_3$ (2.1 equiv, dr 8:1, 80% yield; 0.1 equiv, NR), $HClO_4$ (1 equiv, NR), HNO_3 (1.1 equiv, dr 6:1, 25% conv), 30% HBr/AcOH (1.1 equiv, NR), BsOH (1.1 equiv, NR), MsOH (1.1 equiv, dr 6:1, 56% yield), H_2SO_4 (1.1 equiv, dr 6:1, 60% yield), TfOH (2 equiv, dr 8:1, 68% yield; −70 °C to r.t., dr 6:1, 36% yield; 0.1 equiv, dr 7:1, 25% yield), $TfOSiMe_3$ (2 equiv, dr 6:1, 58% yield), Tf_2O (1.2 equiv, dr 7:1, 66% yield), Nafion SAC-13 (100 wt%, NR), Nafion NR 50 (100 wt%, NR), and 0.5 M dodecylbenzenesulfonic acid (DBSA) (60 °C, NR), DBSA + 1 equiv $Sc(OTf)_3$ (100 °C, NR). Improved dr values were observed with $Sc(OTf)_3$ and $InBr_3$ in DCM, affording 10:1 and 8:1 ratios, respectively, but they required more than a stoichiometric amount to achieve full conversion and reasonable yield. Catalytic $Sc(OTf)_3$ was

achieved in nitromethane, but at the expenses of lower dr (8:1) and low yield. Two equivalents of TfOH in DCM gave a fast reaction and afforded 8:1 dr but poor yield due to impurities formation. Nafion[30] and aqueous DBSA micellar conditions[31] gave no reaction.

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