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Practical, Highly Convergent, Asymmetric Synthesis of a Selective PPARγ Modulator

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Abstract:

A practical, highly convergent, asymmetric synthesis of a selective PPARγ modulator 1 is described. The inhibitor contains two key components, a 6-trifluoromethoxy-3-acylindole (6) and (*R*)-α-aryloxybutanoic acid derivative (10). Two methods were developed to overcome the regioselectivity issues encountered in the preparation of the 6-substituted indole. The first involved an intramolecular Heck reaction of an iodoaryl enamine. The second involved application of a catalytic Meerwein arylation reaction between 2-nitro-4-trifluoromethoxyaniline and isopropenyl acetate and subsequent reductive cyclization. The α-aryloxybutanoic acid was prepared via an asymmetric hydrogenation of the corresponding α-aryloxy-α,β-unsaturated acid. Tetrabutylammonium iodide-catalyzed coupling of the two fragments and ester hydrolysis completed the convergent synthesis. The described convergent synthesis was used to prepare >3 kg of drug substance 1 in 50% overall yield and with >99.5% ee.

Introduction

Noninsulin-dependent or type 2 diabetes mellitus (T2DM) is a major medical concern, and incidence worldwide is expected to grow significantly over the next decade.[1] Although the onset of T2DM predominantly occurs in middle age, an increasing number of younger adults are diagnosed each year. Contributing factors in the increased incidence of T2DM in the industrialized world are high caloric intake, sedentary lifestyles, and lack of exercise. Symptoms of T2DM may include hyperglycemia, hyperlipidemia, atherosclerosis, and obesity. Peroxisome proliferator-activated receptors (PPARs) are a large family of ligand-activated nuclear transcription factors involved in nutrient storage and catabolism.[2] Rosiglitazone[3] and pioglitazone[4] are synthetic, full agonists that specifically activate PPARγ and are used to treat T2DM. However, in humans, mechanism-based adverse events (AEs) such as weight gain, edema, and anemia, limit their use as front-line therapy in T2DM. Consequently, in recent years, the search for PPAR ligands without the unwanted AEs has been intense. Selective PPAR modulators (SPPARMs) have attracted much interest recently with evidence that selective modulation of the PPARγ and PPARα receptors could provide antidiabetic activity with reduced side-effects such as adipogenesis.[5,6] Several of these SPPARMs have been reported from our own research laboratories in recent years.[7] As part of an ongoing drug discovery program in our laboratories, the chiral *N*-benzylated-3-acylindole **1** was identified as a potent, selective PPARγ modulator.[8] In order to evaluate the pharmacological and safety properties of **1**, we required an efficient, chromatography-free, asymmetric synthesis. In this paper we disclose a highly convergent synthesis of **1**, suitable for the preparation of multikilogram quantities for safety assessment and clinical investigation.

Medicinal Chemistry Synthesis. The medicinal chemistry synthesis of **1** was carried out starting from 3-trifluoromethoxyaniline **2** in 7 steps in approximately 13% overall yield (Scheme 1).[9] Gassman reaction of aniline **2** with (ethylthio)acetone afforded a 2:1 mixture of desired **4** and the undesired 4-isomer **3**, respectively, in 87% combined yield.[10] Treatment of the crude mixture with Raney-Ni in ethanol, followed by chromatography, furnished the desired 6-trifluoromethoxyindole **5**[11] in 49% yield. Acylation of **5** using $ZnCl_2$/EtMgBr and *p*-chlorobenzoyl

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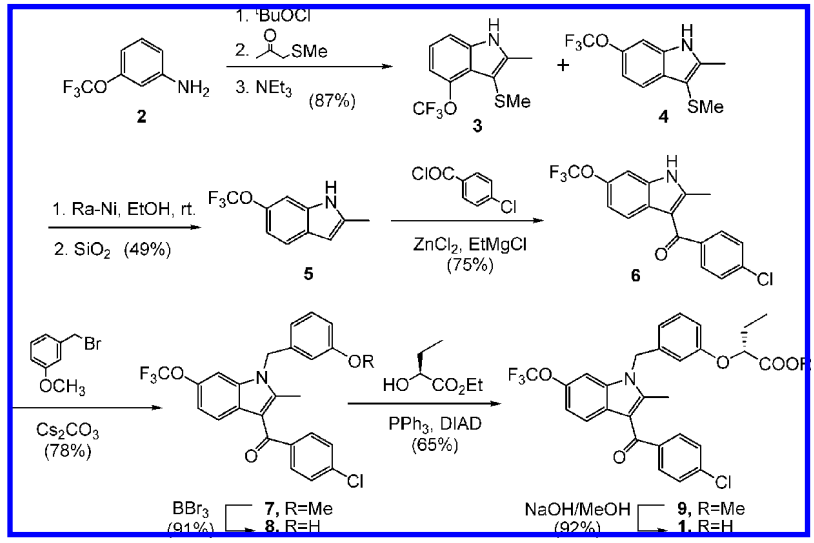
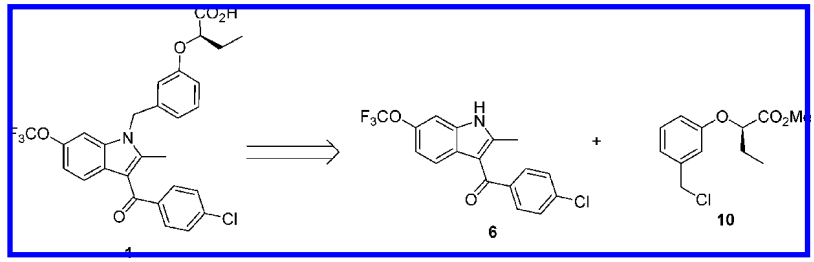
Scheme 1. **Medicinal chemistry synthesis of 1**



Scheme 2. **Proposed convergent synthesis**



chloride gave the acylindole **6** in 75% yield. Benzylation at the indole nitrogen with *m*-methoxybenzyl chloride followed by BBr_3-mediated demethylation provided a 71% yield of the phenolic intermediate **8**. Mitsunobu reaction of **8** with (*S*)-ethyl butyrate, chromatogaphy, and subsequent hydrolysis gave the desired acid **1** in 60% yield. While this route was aptly suitable for the preparation of several grams of **1**, the low overall yield, multiple chromatographic purifications, as well as high cost and low volume availability of several raw materials, prompted us to rapidly investigate an alternative scaleable synthesis.[12] The details of that investigation are outlined in the following discussion.

Convergent Synthesis Strategy. At the outset we envisioned that compound **1** could be prepared in a highly convergent manner via the direct coupling of the acylated indole **6** with the complete optically enriched side chain **10** (Scheme 2). The key synthetic challenges would be regioselective formation of the 6-substituted indole **5**, introduction of the stereogenic center in the 2-aryloxy-butanoate **10**, and an efficient coupling protocol wherein the asymmetric center would not be compromised.

Results and Discussion

Preparation of Indole 6. Although there are many methods for the preparation of substituted indoles, the selective preparation of 6-substituted indoles poses significant regiochemical challenges.[13,14] Our initial approaches to the 6-trifluoromethoxy indole core utilized either commercially available **2** or *m*-trifluoromethoxyphenyl hydrazine (**11**)[15] as starting materials. The preparation of 6-substituted indoles directly from *m*-anilines or *m*-arylhydrazines is known to suffer from poor regioselectivity with respect to the 4- vs 6-isomers.[13] Attempts to improve the regioselectivity of the Gassman synthesis by altering the substituent on the sulfur from the commonly used methyl to either Ph or *t*-Bu resulted in sluggish reactions, byproduct formation, and no improvement in selectivity.

In order to circumvent the regioselectivity issues commonly encountered with the use of *m*-trifluoromethoxy derivatives, our attention was focused on the more readily available and less expensive *p*-trifluoromethoxybenzene analogues. It was envisioned that ortho-nitration followed by installation of a 3-carbon unit would provide substrates suitable for subsequent cyclization to the desired 6-substituted indole (Scheme 3). While nitration of *p*-bromotrifluoromethoxybenzene (**12**) gave a 1:1 mixture of the regioisomers **13**, and **14**, *p*-trifluoromethoxyphenol (**15**) could be cleanly nitrated as expected to give **16** in high yield. Nitrophenol **16** was converted to triflate **17**, but attempted

(12) Hydrazine **11** and (*S*)-ethyl butyrate were not readily available in bulk quantities at the time of this work.

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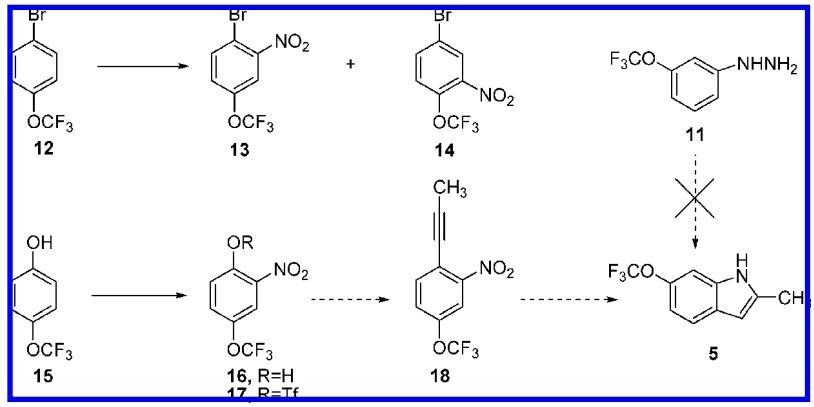
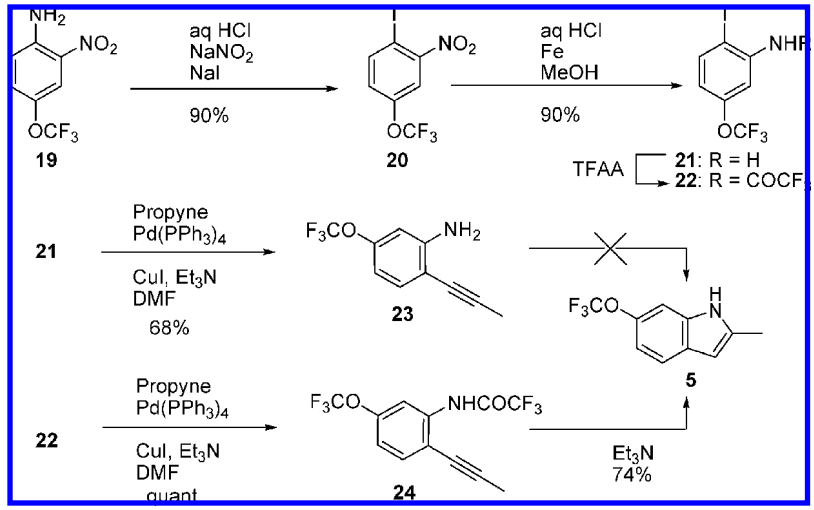
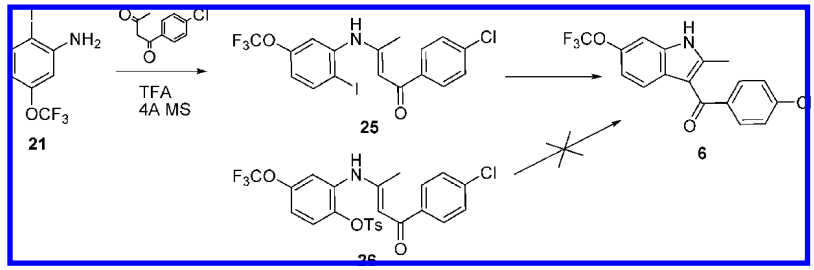
Scheme 3. **Attempted use of 12 or 15 to prepare indole 5**



Scheme 4. **Alkyne cyclization approach to indole 5**



Scheme 5. **Intramolecular Heck approach to 6**



Sonogashira coupling of the triflate with propyne gave complex mixtures of products.

Nitro-aniline **19**[16] was readily diazotized and converted to the iodide **20** in 81% isolated yield (Scheme 4). Reduction of the nitro functionality in the presence of the aryl iodide using hydrazine, catalytic $FeCl_3$, and carbon provided iodoaniline **21** in 90% yield.[17] This reduction could also be accomplished in similar yield with iron and aq HCl in MeOH. Sonogashira coupling of **21** with propyne gave the aryl propyne **23** in 68% yield. Spontaneous cyclization to the desired indole **5** did not occur under these conditions. However, conversion of **21** to the trifluoroacetamide **22** followed by coupling with propyne gave the arylpropyne **24** in virtually quantitative yield. Treatment of the more acidic trifluoroacetamide **24** with excess Et_3N provided indole **5** in 74% yield.[18]

With iodoaniline **21** on hand, a potentially more convergent intramolecular Heck approach[19] (Scheme 5) was examined. The enamine **25** was formed by an acid-catalyzed reaction of **21** with 4-chlorobenzoyl acetone.[20] A screen of acids and dehydrating agents revealed the best conditions to be reaction in the

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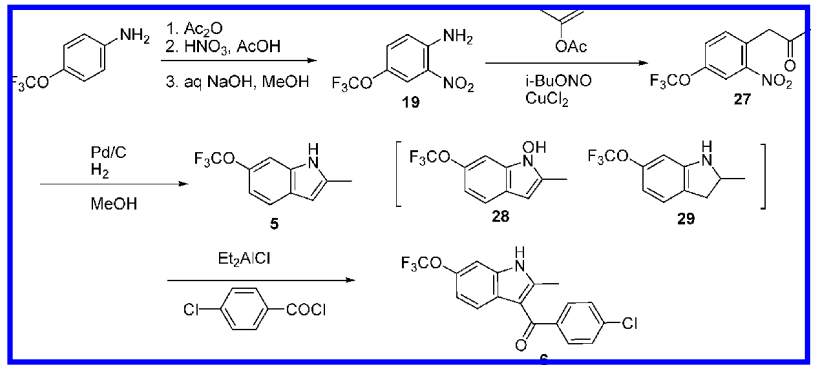
(20) Popic, V. V.; Korneev, S. M.; Nikolaev, V. A.; Korobitsyna, I. K. *Synthesis* **1991**, 195–198.

Scheme 6. **Meerwein arylation approach to 6**



presence of TFA and 4 Å molecular sieves in 1,2-dichloroethane. Interestingly, the reaction was found to be difficult to drive to completion (75−80% conversion at 80 °C), while allowing the reaction mixture to slowly cool to 20 °C overnight provided >95% conversion. Presumably, the higher temperature allows a reasonable reaction rate up to 80% completion but the equilibrium at the lower temperature favors the absorption of more water by the molecular sieves. Enamine **25** was isolated in 81% yield after crystallization from heptane. The intramolecular Heck reaction of **25** was successfully performed with DABCO or $NaHCO_3$ in the presence of $Pd(OAc)_2$ or Pd on charcoal in DMF at 90 °C to provide the benzoyl indole **6** directly, in 70−74% yield, after crystallization from heptane/EtOAc. The more easily prepared 2-tosyloxy-5-trifluoromethyoxyaniline was converted to the analogous enamine **26**, but this enamine did not undergo the intramolecular Heck cyclization.[21]

While the intramolecular Heck approach (Scheme 5) provided the desired acyl-indole **6** in a convergent manner, the cumbersome, multistep synthesis of iodo-aniline **21** prompted further investigation into an alternative, more efficient synthesis of the indole core.

We ultimately focused our attention on the readily synthesized nitro-aniline **19** and envisioned that a Meerwein arylation of isopropenyl acetate with diazotized **19** followed by Leimgruber−Batcho-type cyclization[22] of the resulting aryl acetone **27** would provide access to indole **5** (Scheme 6). A Meerwein arylation strategy has been reported for the construction of 6-substituted indoles, but a three-step sequence was required for the preparation of the nitroaryl ketone starting from methacrylic acid.[23]

Since nitroaniline **19** was unavailable in bulk quantity, an optimized procedure was developed for large-scale preparation. Acetylation of 4-trifluoromethoxyaniline was followed by nitration of the acetanilide with 90% nitric acid in HOAc to provide 2-nitro-4-trifluoromethoxyacetanilide in 92−95% yield after crystallization. The use of a catalytic amount of H_2SO_4, with one equivalent of HNO_3 was required to drive the nitration to completion. Hydrolysis of the acetanilide with aq NaOH in MeOH furnished nitroaniline **19** in 95% yield after crystallization. Rapid optimization of the arylation reaction with respect to a number of variables (solvent, temperature, concentration, copper and nitrite source) was performed. The original conditions used $CuCl_2$ (1.2 equiv), isoamylnitrite (1.5 equiv) and isopropenyl acetate (18 equiv) in acetonitrile (0.25M) at ambient temperature. Under these conditions, HPLC assay yields varied between 50−65%. Under semioptimized conditions, the reaction was carried out in neat isopropenyl acetate (0.5M) with $CuCl_2$ (1.2 equiv) and isobutyl nitrite (1.25 equiv) at 25−40 °C to afford >98% conversion and 85% assay yield. Aryl acetone **27** was isolated in up to 80% yield, at several kilogram scale, after crystallization from MeOH/H_2O (5:3 v/v) or toluene/heptane (1:3 v/v) at −20 °C.[24]

Hydrogenation of the arylketone **27** was carried out using Pd/C, under 60 psi H_2, at 65 °C for 6 h, to give **5** directly in 90% yield after isolation. On scale-up, cooling of the reaction mixture was required in order to circumvent a temperature spike that occurred upon introduction of hydrogen. Detailed calorimetric monitoring of the reaction revealed that 2 equiv of hydrogen were taken up in the initial stages of the reaction at temperatures below 25 °C. Subsequent heating to 65 °C was then required to convert the *N*-hydroxy intermediate **28**[25] to the desired product with uptake of one equivalent of hydrogen. Decreasing the catalyst load or lowering the reaction temperature or pressure resulted in under-reduction and the presence of *N*-OH indole **28** in the isolated product. Similar problems were encountered when using Raney nickel catalyst or toluene instead of MeOH as solvent. On the other hand, extended reaction times and higher temperatures (>80 °C) and pressures (100 psi) led to over-reduction of the indole and increased amounts of the indolene side product **29**. Use of a two-stage heat-up protocol at large scale smoothly provided indole **5** in 93% assay yield after catalyst filtration. This material was of suitable quality to be carried into the acylation step without purification.

Acylation of indole **5** was accomplished using a slightly modified procedure from Okauchi and co-workers.[26] Treatment of indole **5** with Et_2AlCl (1.2 equiv) and *p*-chlorobenzoyl chloride (1.2 equiv) in a mixture of toluene and heptane afforded

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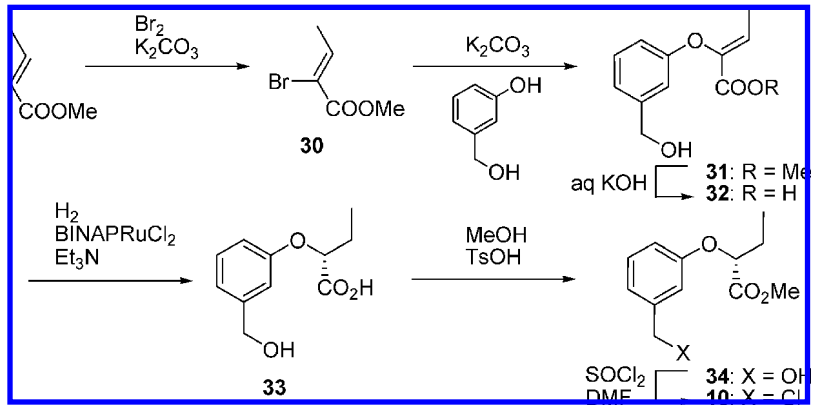
(24) The low temperature for crystallization was required due to the low melting point of **27**.

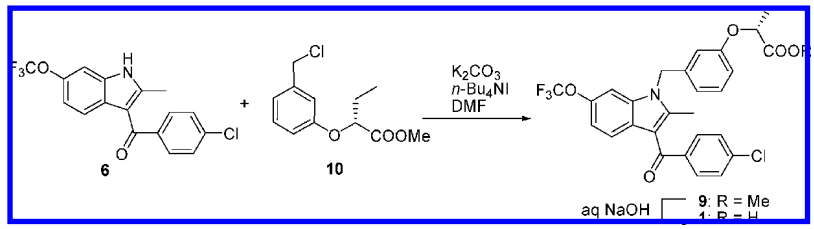
(25) Wong, A.; Kuethe, J. T.; Davies, I. W. *J. Org. Chem.* **2003**, *68*, 9865–9866.

(26) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485–1487.

Scheme 7. **Asymmetric synthesis of benzyl chloride 10**



Scheme 8. **Final coupling and hydrolysis to form 1**



the desired acylindole in high HPLC assay yield. Due to the high crystallinity and low solubility of the desired product **6**, a standard aqueous wet workup was not viable. It was discovered that direct addition of MeOH (5 equiv) to the crude reaction mixture gave a filterable crude solid. The isolated solids contained the product **6** as well as the majority of the aluminum salts. Recrystallization of the crude solids from boiling MeOH/H_2O (4:1) gave **6** in 91% yield isolated yield and 99.8 wt % purity. Metals analysis of isolated **6** after recrystallization showed <30 ppm Al and <3 ppm Cu.

Preparation of α-Aryloxybutanoate 10. We have recently reported a novel asymmetric hydrogenation of α-aryloxy-α,β-unsaturated acids, using a number of chiral ruthenium catalysts, to provide saturated α-aryloxy acids in high optical purity.[27] We hoped to apply this methodology to the asymmetric synthesis of coupling partner **10** (Scheme 7). Methyl 2-bromobuteneoate (**30**) was obtained as a mixture of isomers from methyl crotonate and bromine, using a modification of a literature procedure.[28] Alkylation of commercially available 3-hydroxybenzyl alcohol using **30** followed by hydrolysis gave the α-aryloxybut-2-enoic acid **32** in 80% isolated yield as a crystalline solid.[29] With a highly efficient route to the hydrogenation precursor in hand, we investigated the asymmetric hydrogenation. To our delight, a screen of hydrogenation catalysts revealed that hydrogenation (25 °C, 90 psig) of **32** in the presence of 0.5 mol % [(*R*)-BINAP]$RuCl_2$ gave **33** in virtually quantitative yield (HPLC assay) with 94% ee. The reaction required the addition of one equivalent of base (Et_3N) in order to proceed at an acceptable rate. The enantioselectivity was found to exhibit a slight negative pressure dependence (92% ee was obtained at 500 psig) as well as a negative dependence on temperature (96% ee at 10 °C; 92% ee at 40 °C). Decreasing the catalyst loading to 0.2 mol % had no impact on the enantioselectivity but approximately doubled the reaction time (from 20 to 39 h). In general, the reaction rate was found to be proportional to the substrate/catalyst ratio rather than to the absolute concentrations of substrate and catalyst. These results were in accord with reported mechanistic studies by Ashby and Halpern on the asymmetric hydrogenation of tiglic acid catalyzed by (BINAP)$Ru(OAc)_2$.[30]

Ruthenium Removal and Enantiomeric Purity Upgrade. Residual ruthenium was removed using a Darco G-60 treatment during workup. The acid **33** could be crystallized from toluene or heptane/i-PrOAc to upgrade the optical purity up to >99% ee with excellent recovery. Since the optical purity of the final product **1** could also be upgraded very easily, acid **33** was used without purification.

Preparation of benzyl chloride 10. Conversion of **33** to methyl ester **34** was performed with catalytic TsOH in MeOH. Complications due to intermolecular transesterification of the methyl ester by the benzylic alcohol were avoided by running the esterification at <0.5 M concentration and neutralization of the toluenesulfonic acid, with Et_3N, prior to concentration and workup.[31] Benzylic alcohol **34** was converted to benzylic chloride **10** using $SOCl_2$ in DMF in 96% yield from **33** without any loss of optical purity.

Coupling of 6 and 10. Indole **6** underwent smooth coupling with **10** in the presence of K_2CO_3 in DMF at 45−50 °C for 24 h to give **9** in 96% yield (Scheme 8). HPLC analysis of the crude product showed partial degradation of the optical purity to 93% ee. Fortunately, activation of the benzyl chloride by

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(30) Ashby, M. T.; Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589–594.
(31) The use of higher concentrations of substrates **33** and **34** in the presence of acid resulted in substantial polymerization to polyester-type products.

the addition of 5 mol % n-Bu_4NI allowed the reaction to reach completion in 22 h at 30−35 °C with minimal loss of optical purity.[32] Hydrolysis of **9** with aq NaOH in MeOH gave **1** with >99.7% ee in 96% yield after crystallization.

Conclusion

A practical, highly convergent, asymmetric synthesis of the selective PPARγ modulator **1** was developed. The synthesis addressed the key scale-up issues of the medicinal route and provided a practical solution to the regioselective indole formation as well as the efficient introduction of the stereogenic center. The described convergent synthesis was used to prepare >3 kg of drug substance **1**, in 50% overall yield and with >99.5% ee, and this was used to support early safety and clinical development studies.

Experimental Section

General. Melting points were determined on an open capillary apparatus and are uncorrected. 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. Solka-floc was obtained from Seidler Chemical Co., Newark, NJ. All reagents and solvents were used as received without further purification.

HPLC Methods. (A) Zorbax extend C18 4.6 mm × 150 mm column, gradient elution from 10:90 to 80:20 MeCN/0.1% aqueous H_3PO_4 over 10 min, then isocratic elution with 80:20 MeCN/0.1% aqueous H_3PO_4 over 5 min, 1.0 mL/min flow at 30 °C with detection at 210 nm.

(B) Zorbax RX-C18 4.6 × 150 mm column, gradient elution from 50:50 to 60:40 MeCN/0.1% aqueous H_3PO_4 and from 1.0 to 1.5 mL/min flow over 5 min, then isocratic elution with 60:40 MeCN/0.1% aqueous H_3PO_4 over 1 min, 1.5 mL/min flow at 30 °C with detection at 210 nm.

(C) Chiral HPLC method. Chiracel OD-H 4.6 mm × 250 mm column, isocratic elution with 85:15 n-heptane/i-PrOH containing 0.15% TFA over 10 min, 1.5 mL/min flow at 25 °C with detection at 275 nm.

(D) ThermoHypersil-Keystone 5 μm HS C18 4.6 mm × 250 mm column, gradient elution from 5:95 to 45:55 MeCN/0.1% aqueous $HClO_4$ over 5 min, then gradient elution from 45:55 to 75:25 MeCN/0.1% aqueous $HClO_4$ over 5 min, then gradient elution from 75:25 to 90:10 MeCN/0.1% aqueous $HClO_4$ over 5 min, 1.0 mL/min flow at 30 °C with detection at 210 nm.

(E) Water SymmetryShield RP8 C18 4.6 mm × 250 mm column, gradient elution from 5:95 to 45:55 MeCN/0.1% aqueous $HClO_4$ over 5 min, then gradient elution from 45:55 to 75:25 MeCN/0.1% aqueous $HClO_4$ over 5 min, then gradient elution from 75:25 to 90:10 MeCN/0.1% aqueous $HClO_4$ over 5 min, 1.0 mL/min flow at 30 °C with detection at 210 nm.

(F) HPLC conditions: 5 μm Zorbax RX-C18 4.6 mm × 150 mm column, gradient elution from 80:20 to 90:10 MeCN/0.1% aqueous H_3PO_4 and from 1.0 to 1.5 mL/min flow over 5 min, then isocratic elution with 90:10 MeCN/0.1% aqueous H_3PO_4 over 1 min, 1.5 mL/min flow at 30 °C with detection at 210 nm.

(32) Optical purity of **9** was 93% starting from **10** at 94% ee.

(G) Chiral HPLC method: Chiracel OD-H 4.6 mm × 250 mm column, isocratic elution with 70:30 n-heptane/i-PrOH containing 0.15% TFA over 15 min, 1.5 mL/min flow at 25 °C with detection at 275 nm. HPLC retention time: **(*R*)-9** = 11.1 min, **(*S*)-9** = 5.0 min. Chiral SFC conditions: Chiracel OJ 4. mm × 250 mm column, isocratic elution with 40% MeOH in CO_2 over 12 min, 1.5 mL/min flow at 35 °C and 200 bar with detection at 215 nm. HPLC retention time: **(*R*)-9** = 4.1 min, **(*S*)-9** = 9.8 min.

Methyl 2-Bromobut-2-enoate (30). Bromine (1.55 L, 30.3 mol) was added to a mixture of heptane (9.0 L) and methyl crotonate (3.00 kg, 29.4 mol) at 25 to 35 °C over 20−30 min. The reaction mixture was stirred at 30 °C for 1 h. Acetonitrile (18 L) was added, followed by powdered potassium carbonate (6.08 kg, 44.0 mol) in one portion. The reaction slurry was warmed and stirred at gentle reflux. The heptane/MeCN azeotrope (bp 69 °C) was distilled to remove a total of 15 L of solvent. Acetonitrile (6 L) was added during the atmospheric distillation. After completion of distillation the slurry was aged at 80 °C for 3−4 h to complete the dehydrobromination. The slurry was cooled to 20 °C and filtered. The cake was washed with acetonitrile (2 × 6 L). The combined filtrates were assayed by quantitative HPLC and were found to contain 22−23 wt % bromobutenoate **30** (95% yield). The solution was used without further purification in the subsequent reaction. HPLC retention times (Method A): methyl crotonate = 4.7 min, dibromo ester intermediate = 8.1 min, bromobutenoate **30** = 6.9 min.

(2*Z*)-2-[3-(Hydroxymethyl)phenoxy)but-2-enoic Acid (32). Powdered potassium carbonate (6.54 kg, 47.4 mol) was added to a mixture of the crude acetonitrile solution of **30** (20.9 kg, 22.4 wt % by assay, 26.1 mol) and 3-hydroxybenzyl alcohol (3.00 kg, 23.7 mol) at 20−25 °C. The slurry was warmed to 80−82 °C over 1 h and aged for 2 h. Acetonitrile (10 L) was distilled off over 2 h at atmospheric pressure. The reaction mixture was cooled to 50 °C and toluene (20 L) added. The slurry was concentrated at 30−40 °C under reduced pressure to remove a total of 25 L distillate. Toluene (10 L) was added and the slurry cooled to 15 °C. The mixture was washed with water (20 L). Water (7.5 L) and 50% w/v aq KOH (5.31 L, 47.4 mol) were added to the mixture containing methyl ester **31**. The two-phase mixture was stirred at 35 °C for 5−10 h. The mixture was cooled to 20 °C, and the lower aqueous layer (18.5 L) was separated. The aqueous phase was acidified to pH = 8−9 with concd HCl (2.25 L, 30.6 mol) at <25 °C. i-PrOAc (25 L) was added, and the pH was adjusted to 1.5 (± 0.2) with concd HCl (2.25 L, 30.6 mol). The organic phase was washed with water (2 × 3.0 L). The organic layer was concentrated under reduced pressure and solvent switched to obtain a final toluene/i-PrOAc ratio of about 4:1 by wt. The slurry was aged at 20 °C for 30 min and filtered. The cake was washed with toluene (20 L) and dried to provide unsaturated acid **32** (4.00 kg, 80% yield from **30**). HPLC retention times (Method A): 3-hydroxybenzyl alcohol = 2.1 min, unsaturated ester **31** = 5.9 min, unsaturated acid **32** = 4.5 min. **32**: mp = 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 2 active H), 7.26 (t, J = 7.9, 1 H), 6.97 (dq, J = 7.6, 0.7, 1 H), 6.89 (m, 1 H), 6.79 (m, 1 H), 6.74 (q, J = 7.2, 1 H), 4.55 (s, 2 H), 1.73 (d, J = 7.2, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 157.4,

144.0, 141.3, 129.6, 128.5, 120.4, 113.4, 112.9, 63.5, 10.9; FTIR (thin film) ν_{max} 3346, 1700, 1658, 1447, 1251 cm^{-1}; ES HRMS *m/z* calcd for $C_{11}H_{11}O_4$ ($M - H^+$) 207.0657, found 207.0659; Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.56; H, 5.83.

(2*R*)-2-[3-(Hydroxymethyl)phenoxy]butanoic Acid (33). A mixture of the unsaturated acid **32** (3.92 kg, 18.8 mol), Et_3N (1.91 kg, 18.9 mol), [(*R*)-BINAP]$RuCl_2$ (76.4 g, 0.096 mol), and MeOH (13.4 L) was hydrogenated at 100 psi hydrogen and 20 °C for 20 h. Quantitative HPLC assay indicated a 99% yield and 94% ee. The hydrogenation mixture was filtered through a 5 μm in-line filter and concentrated in a 50 L vessel to 12 L volume. The residue was evaporated (29.5″ Hg, 13−18 °C), maintaining a constant volume (12 L) while feeding in 12 L of toluene. Toluene (8 L), water (8 L), and 5 M aq NaOH (4 L, 20.0 mol) were added to the mixture. The phases were separated, and the organic phase was washed with water (4 L). The organic phase contained 450 ppm ruthenium and 386 ppm phosphorus. The combined aqueous phases were treated with Darco G-60 carbon (400 g, Sigma-Aldrich, Inc.) for 1 h at 60 °C in a 22-L flask. The pH of the mixture was adjusted to pH = 7 by addition of concd aq HCl (300 mL, 3.6 mol), and the mixture was allowed to cool to 22 °C overnight (16 h). Solka-floc (200 g) was added, and the mixture was filtered through a pad of solka-floc, washing with water (4 L). The dried carbon filter cake contained 1800 ppm ruthenium and 174 ppm phosphorus. The filtrates were cooled to 13 °C in the 50-L vessel and acidified to pH = 1 with concd 12 M HCl (3.7 L, 44.4 mol), maintaining the temperature at 13−18 °C with cooling. The mixture was extracted with *i*-PrOAc (20 L then 10 L). The *i*-PrOAc extracts were washed with brine (2 × 4 L). The combined *i*-PrOAc extracts were treated with $MgSO_4$ (400 g, 10 wt %) and Darco G-60 carbon (400 g, 10 wt %) for 1 h at 20−25 °C in a 50-L flask. The mixture was filtered through solka-floc, washing with *i*-PrOAc (4 L, 1 vol). The dried carbon filter cake contained 28 ppm ruthenium and 108 ppm phosphorus. The filtrates were concentrated (29.5″ Hg, 3−18 °C) to 13 L in the 50-L vessel, and the temperature was raised to 28 °C. Quantitative HPLC analysis indicated the solution contained 3.75 kg of **33** (both antipodes) (30.4 wt % solution). Heptane (30 L) was added to the mixture over 2 h while the temperature fell to 24 °C, and the mixture was aged for 2 h while the temperature was lowered to 15 °C. The mixture was filtered, and the solid was washed with 4:1 heptane-*i*-PrOAc (10 L) and heptane (10 L). The crystalline solid was dried under a stream of nitrogen to provide saturated acid **33** (3.32 kg, 86%, 97.3% ee by chiral HPLC). The crystalline solid **33** contained 4 ppm ruthenium and 7 ppm phosphorus. HPLC retention time (Method B): saturated acid **33** = 1.53 min. Chiral HPLC retention times (Method C): **(*R*)-33** = 4.2 min, **(*S*)-33** = 5.7 min, unsaturated acid **32** = 4.9 min, 3-hydroxybenzyl alcohol = 5.0 min. **33**: mp = 83−84 °C (99.5% ee); mp = 87−89 °C (racemic); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J = 7.9, 1 H), 6.97 (br s, 2 active H), 6.89 (m, 2 H), 6.81 (dd, J = 8.2, 2.3, 1 H), 4.59 (dd, J = 6.8, 5.4, 1 H), 4.57 (s, 2 H), 2.00 (m, 2 H), 1.09 (t, J = 7.4, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 158.0, 142.2, 129.7, 120.3, 114.6, 113.6, 77.3, 64.7, 26.0, 9.6; FTIR (thin film) ν_{max} 3408, 2929, 1728, 1587, 1258 cm^{-1}; ES HRMS *m/z* calcd for $C_{11}H_{13}O_4$ ($M - H^+$) 209.0814, found 209.0813; Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.61; H, 6.72.

Methyl (2*R*)-2-[3-(Hydroxymethyl)phenoxy]butanoate (34). The saturated acid **33** (3.27 kg, 15.5 mol, 97.3% ee), $TsOH \cdot H_2O$ (58.1 g, 0.31 mol), and MeOH (46 L) were heated to 60 °C for 14−18 h. Then Et_3N (62.9 g, 0.62 mol) was added, and the mixture was concentrated to ∼6.5−9.8 L at 26−29.5″ Hg and 0−30 °C and evaporated, maintaining a constant residue volume of ∼6.5−9.8 L with the gradual addition of *i*-PrOAc (46 L). The mixture was concentrated to 7.5 L. This crude solution was used in the next step without further purification. HPLC retention times (Method B): methyl ester **34** = 2.2 min, intermolecular esterification dimeric byproduct = 5.4 min, TsOH = 1.24 min. Chiral HPLC retention times (Method C): **(*R*)-34** = 4.2 min, **(*S*)-34** = 5.7 min. An analytical standard of **34** was prepared as a colorless, viscous oil by evaporation of this solution and bulb-to-bulb distillation at 0.055 Torr: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, J = 7.9, 1 H), 7.96 (dd, J = 7.6, 0.6, 1 H), 6.91 (s, 1 H), 6.78 (dd, J = 2.5, 8.2, 1 H), 4.64 (s, 2 H), 4.59 (t, J = 6.2, 1 H), 3.74 (s, 3 H), 2.02 (br s, 1 H), 6.98 (m, 2 H), 1.07 (t, J = 7.4, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 158.2, 142.9, 129.7, 120.1, 114.1, 113.8, 77.7, 65.0, 52.2, 26.2, 9.7; FTIR (thin film) ν_{max} 3418, 2934, 1738, 1586, 1454 cm^{-1}; ES HRMS *m/z* calcd for $C_{12}H_{16}O_4Li$ ($M + Li^+$) 230.1200, found 230.1197; Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.42; H, 7.37.

Methyl (2*R*)-2-[3-(Chloromethyl)phenoxy]butanoate (10). The crude solution containing methyl ester **34** (3.43 kg, 15.3 mol, 97.3% ee) and *i*-PrOAc (3.07 kg) was transferred to a 50-L extractor. DMF (7.6 L) was added, and the mixture was cooled to −15 °C. $SOCl_2$ (2.0 kg, 16.8 mol) was added to the homogeneous pale-amber mixture over 45 min while the temperature rose to 12 °C. The mixture was warmed to 20 °C over 30 min aged for 90 min at 20 °C. The mixture was then cooled 0 °C, and *n*-heptane (7.6 L) was added. Water (15.3 L) was added over 5 min during which the temperature rose to 18−20 °C. The aqueous phase was cut and discarded. The organic phase was washed with water (2 × 15 L). The organic phase was concentrated to ∼4 L. Quantitative HPLC analysis indicated this solution contained 3.56 kg of the benzylic chloride **10** (96% yield from **33**) (89.7 wt % solution). Chiral HPLC indicated the optical purity to be 97.5% ee. This solution was used in the next step without further purification. HPLC retention times (Method B): benzylic chloride **10** = 5.5 min, *p*-TsCl = 5.1 min. Chiral HPLC retention times (Method C): **(*R*)-10** = 5.2 min, **(*S*)-10** = 3.5 min. An analytical sample of the benzylic chloride was obtained as a colorless mobile oil by vacuum distillation of a sample at 0.055 Torr (bp = 113−120 °C): d = 1.158 g/mL; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J = 7.8, 1 H), 7.00 (d, J = 7.9, 1 H), 6.94 (t, J = 4.0, 1 H), 6.83 (m, 1 H), 4.60 (t, J = 6.2, 1 H), 4.54 (s, 2 H), 4.76 (s, 3 H), 2.00 (m, 2 H), 1.09 (t, J = 7.5, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 158.1, 139.1, 129.9, 121.7, 115.4, 114.8, 77.7, 52.2, 46.0, 26.6, 9.6; FTIR (thin film) ν_{max} 2972, 1756, 1586, 1451, 1274 cm^{-1}; ES HRMS *m/z* calcd for $C_{12}H_{15}ClO_3Li$ ($M + Li^+$) 248.0861, found 248.0869.

2-Nitro-4-(trifluoromethoxy)acetanilide. Acetic anhydride (18.1 kg, 177 mol) was added to a mixture of 4-trifluoromethoxyaniline (8.00 kg, 44.3 mol) and HOAc (8.8 L) over 20 min, maintaining temperature 20−35 °C. Concentrated H_2SO_4 (320 mL, 5.76 mol) followed by 90% HNO_3 (2.08 L, 44.3 mol) was added (exothermic) to the mixture over 1 h at 25−30 °C. The mixture was stirred at 20−25 °C for 1 h, and water (60 L) was added to the mixture over 1.5 h at 15−25 °C, during which the product crystallized from the mixture. The slurry was stirred for 1 h and filtered. The yellow solid was washed with water (3 × 20 L) and dried to provide 2-nitro-4-(trifluoromethoxy)acetanilide (11.0 kg, 92%, 97−98 wt % purity by quantitative HPLC analysis). HPLC retention times (Method D): 4-trifluoromethoxyaniline = 9.2 min, 4-trifluoromethoxyacetanilide = 11.7 min, 2-nitro-4-(trifluoromethoxy)acetanilide = 12.1 min, *N*-nitro-4-trifluoromethoxyacetanilide = 13.1 min, 2, *N*-dinitro-4-trifluoromethoxyacetanilide = 13.6 min.

2-Nitro-4-(trifluoromethoxy)aniline (19). NaOH (5 N aq, 10.4 L, 52.0 mol) was added to a slurry of 2-nitro-4-(trifluoromethoxy)acetanilide (11.0 kg, 41.6 mol) in MeOH (42 L), and the resulting homogeneous brown solution was stirred at 20−30 °C for 1 h. Water (63 L) was added over 1 h at 15−25 °C, and the mixture was stirred for 3 h. The slurry was filtered, and the yellow solid was washed with 3:2 MeOH/water. The solid was dried to give nitroaniline **19** (8.79 kg, 95%, 99 wt % by quantitative HPLC analysis). HPLC retention time (Method D): nitroaniline **19** = 12.9 min.

1-[2-Nitro-4-(trifluoromethoxy)phenyl]acetone (27). A 100-L jacketed flask equipped with two addition funnels was charged with isopropenyl acetate (40 L) and $CuCl_2$ (3.08 kg, 22.7 mol). One addition funnel was charged with a solution of nitroaniline **19** (4.3 kg, 19.2 mol) in isopropenyl acetate (3 L), and the second addition funnel was charged with isobutyl nitrite (2.61 kg, 24.0 mol). The contents of both addition funnels were gradually added simultaneously to the stirred mixture of isopropenyl acetate and $CuCl_2$ over 1 h, maintaining the temperature at 40−55 °C, during which nitrogen was slowly evolved. The simultaneous addition of aniline and nitrite minimizes the unproductive decomposition of nitrite at higher temperature and the formation of 2-nitro-4-trifluoromethoxyacetanilide byproduct. The mixture was stirred at 45−50 °C for 2 h. The mixture was cooled to 20 °C, diluted with toluene (21.5 L), and quenched with 1 N aq HCl (21.5 L). The organic phase was concentrated *in vacuo* at 20 °C to a volume of 9.5 L. Toluene (20 L) was added, and the mixture was concentrated as before to 9.5 L. Heptane (41 L) was added over 1 h while the mixture was cooled to −10 °C. The slurry was cooled to −25 °C for 1 h and filtered. The yellow solid was washed with 6:1 heptane/toluene (10.8 L) and then with heptane (4.3 L) at −25 °C. The solid was dried to provide nitroaryl ketone **27** (3.90 kg, 79%, 94−98 wt % by quantitative HPLC analysis). HPLC retention times (Method E): nitroaryl ketone **27** = 12.2 min, nitroaniline **19** = 12.7 min, 2-nitro-4-(trifluoromethoxy)-acetanilide = 11.6 min. **27**: Mp = 42−44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 1.6, 1 H), 7.47 (d, J = 8.4, 1 H), 7.33 (d, J = 8.4, 1 H), 4.16 (s, 2 H), 2.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 149.0, 148.4, 134.9, 129.0, 125.8, 120.3 (q, J = 256), 118.0, 48.1, 30.0; ES HRMS *m*/*z* calcd for $C_{10}H_8F_3NO_4Li$ (M + Li^+) 269.0557, found 269.0562; Anal. Calcd for $C_{10}H_8F_5NO_4$: C, 45.64; H, 3.06. Found: C, 45.47; H, 3.07.

2-Methyl-6-(trifluoromethoxy)-1H-indole (5). A solution of nitroaryl ketone **27** (3.60 kg, 93.5 wt %, 12.8 mol) in MeOH (13 L) containing 5% Pd/C (0.83 kg, 0.39 mol) was hydrogenated under an atmosphere of H_2 at 60 psi at 0 °C for 1 h and at 60 °C for 6 h. The reaction was cooled to 22 °C and filtered through solka-floc (1.3 kg), and the collected solids were washed with MeOH (12 L). The filtrate which contained <5 ppm palladium was found to contain 2.56 kg (93%) of product according to quantitative HPLC assay, and was taken on to the next step without further purification. Alternatively, the product can be obtained via concentration of the filtrate *in vacuo* to 1/3 the original volume and dilution with the original volume of water to promote crystallization of the indole product (90% recovery). After filtration **5** was isolated as an off-white solid. HPLC retention times (Method D): indole **5** = 14.6 min, ketone **27** = 12.7 min, *N*-hydroxyindole **28** = 13.9 min, indoline **29** = 11.9 min. **5**: mp 87−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (br s, 1 H), 7.50 (d, J = 8.6, 1 H), 7.15 (s, 1 H), 7.01 (d, J = 8.6, 1 H), 6.27 (s, 1 H), 2.44 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.2, 136.7, 135.5, 127.7, 120.8 (q, J_{CF} = 108.8 Hz), 119.9, 113.6, 103.4, 100.3, 13.5; IR ($CDCl_3$) 3399, 2361, 2338, 1457, 1299, 1205, 1147 cm^{-1}; Anal. Calcd. for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; N, 6.51. Found: C, 55.73; H, 3.52; N, 6.45.

(4-Chlorophenyl)[2-methyl-6-(trifluoromethoxy)-1H-indol-3-yl]methanone (6). To a crude solution of indole **5** (2.56 kg, 11.9 mol) in MeOH (26 L) obtained from the previous reaction was added toluene (36 L), and the solution was concentrated to a volume of 13 L via distillation under reduced pressure. ^{1}H NMR of a reaction aliquot showed no residual MeOH remaining. This mixture was cooled to 0 °C, and 1.8 M Et_2AlCl (7.9 L, 14.3 mol) in toluene was added over 20 min during which time the reaction temperature rose to a maximum of 5 °C. A solution of *p*-chlorobenzoyl chloride (2.50 kg, 14.28 mol) in heptane (3.7 L) was then added over 1.5 h over a temperature range of 0−13 °C, and the reaction was stirred to rt over 16 h. The reaction was recooled to 0 °C and MeOH (2.3 L, 57.12 mol) was added to quench (*Caution: exothermic, gas evolution*). Heptane (22 L) was added, and the resultant slurry was filtered. The collected precipitate was washed with additional heptane (28 L) and recrystallized from boiling MeOH/H_2O (4:1, 90 L) to give **6** (3.84 kg, 91%, 99.8 wt % by HPLC assay) as a white solid. HPLC retention times (Method D): acylindole **6** = 15.9 min. **6**: mp 234−236 °C; ^{1}H NMR (DMSO-d_6) δ 12.19 (br s, 1 H), 7.63 (dd, J = 1.1, 7.3 Hz, 2 H), 7.54 (dd, J = 1.8, 7.3 Hz, 2 H), 7.34 (d, J = 8.7 Hz, 1 H), 7.37 (s, 1 H), 7.02 (d, J = 8.7 Hz, 1 H), 2.39 (d, 3 H); ^{13}C NMR (DMSO-d_6) δ 190.5, 146.6, 144.2, 140.1, 136.5, 135.1, 130.4, 128.9, 126.6, 122.0, 121.8 (q, J_{CF} = 255.3 Hz), 114.9, 112.6, 104.6, 14.6; IR (MeOH) 3107, 2361, 2336, 1587, 1455, 1213, 1164 cm^{-1}; ES HRMS *m*/*z* calcd for $C_{17}H_{11}ClF_3NO_2Li$ (M + Li^+) 359.0582, found 359.0584; Anal. Calcd for $C_{17}H_{11}ClF_3NO_2$: C, 57.72; H, 3.13; N, 3.96. Found: C, 57.63; H, 2.78; N, 3.86.

4-Iodo-2-nitro(trifluoromethoxy)benzene (20). Concentrated HCl (12.5 mL, 150 mmol) was added to a solution of

nitroaniline **19** (11.1 g, 50.0 mmol) in HOAc (50 mL) at 20 °C. Water (10 mL) was added, and the mixture was cooled to −5 °C. A solution of $NaNO_2$ (3.62 g, 52.5 mmol) in water (15 mL) was added over 10 min, maintaining the temperature at −10 to −5 °C. The mixture was warmed to 3 °C for 10 min and cooled back down to −5 °C. A solution of urea (0.45 g, 7.5 mmol) in water (5 mL) was added to scavenge excess nitrous acid. A solution of NaI (15.0 g, 100 mmol) was added over 20 min, maintaining the temperature at 0 °C. The mixture was warmed to 15 °C for 30 min after which the gas evolution had subsided. The mixture was cooled to −10 °C, and a solution of K_2SO_3 (4.0 g, 25 mmol) in water (10 mL) was added. The yellow solid was filtered off, washed with 1:1 MeOH/water (100 mL), and dried under a stream of nitrogen to provide 15.0 g of crude aryl iodide. The solid was dissolved in hexanes (100 mL) and was filtered through silica (10 g). The filtrate was evaporated to give iodide **20** (14.5 g, 87%) as a mobile yellow oil which solidified on standing. Mp = 30−32 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.6, 1 H), 7.77 (dd, J = 2.8, 0.7, 1 H), 7.19 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 149.3, 143.2, 125.8, 120.2 (q, J = 260), 118.4, 83.4; FTIR (thin film) ν_{max} 1575,1541, 1468, 1349, 1262 cm^{-1}; Anal. Calcd for $C_7H_3F_3INO_3$: C, 25.25; H, 0.91. Found: C, 25.12; H, 0.89.

2-Iodo-5-(trifluoromethoxy)aniline (21). Concentrated HCl (5.50 mL, 66 mmol) was added to a mixture of nitroaryl iodide **20** (3.33 g, 10.0 mmol), MeOH (10 mL), and electrolytic iron powder (2.23 g, 40.0 mmol) over 15 min with cooling to maintain gentle reflux (exothermic). The mixture was stirred at 60 °C for 10 min and was filtered through 0.1 g silica gel on a cotton plug, using hot MeOH (5 mL) to rinse the plug. The filtrate was cooled to 22 °C, diluted with water (10 mL), and extracted with 2:1 hexanes/MTBE (15 mL). The organic extract was washed with 10% aq *N*-(2-hydroxyethyl)ethylenediamine triacetic acid trisodium salt. The aqueous phases were back extracted with 2:1 hexanes/MTBE (15 mL). The combined organic phases were dried ($MgSO_4$) and filtered through silica gel (0.5 g). The filtrate was evaporated to give crude iodoaniline **21** (2.90 g, 96%) which can be used without further purification in the next step. This batch of crude product was converted to its HCl salt by dissolving the crude residue in *i*-PrOAc (20 mL), adding 1.68 M HCl in *i*-PrOAc (6.25 mL, 10.5 mmol) over 10 min at 40 °C, cooling to 20 °C for 10 min, and filtering to provide **21** (3.02 g, 89%) as the HCl salt after drying under a stream of nitrogen. Mp = 194−204 dec °C (HCl salt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.6, 1 H), 6.60 (m, 1 H), 6.39 (m, 1 H), 4.25 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 148.1, 139.8, 120.4 (q, J = 257), 112.1, 106.8, 80.7; FTIR (thin film) ν_{max} 1620, 1483, 1258, 1219, 1171 cm^{-1}; ES HRMS m/z calcd for $C_7H_6F_3INO$ (M + H$^+$) 303.9446, found 303.9453; Anal. Calcd for HCl salt $C_7H_6ClF_3INO$: C, 24.77; H, 1.78. Found: C, 24.64; H, 1.82.

(2*E*)-1-(4-Chlorophenyl)-3-{[2-iodo-5-(trifluoromethoxy)phenyl]amino}but-2-en-1-one (25). A solution of iodoaniline **21** (2.42 g, 8.00 mmol), 4-chlorobenzoylacetone (1.65 g, 8.40 mmol), TFA (0.91 g, 8.0 mmol) and 1,2-dichloroethane (32 mL) was slowly distilled at 80−85 °C over 1 h to a volume of 10 mL. Powdered 4 Å molecular sieves (2.5 g) were added, and the mixture was stirred at 80 °C for 2 h. The mixture was allowed to cool to 22 °C over 2 h and stirred at 22 °C for 16 h. The mixture was filtered using 1,2-dichloroethane (8 mL) and the heptane (32 mL) to wash the filter cake. The filtrate was washed with water (24 mL) and 1 M K_2HPO_4 (2 × 24 mL). The organic phase was dried ($MgSO_4$) and filtered through silica gel (0.5 g). The filtrate was evaporated to 5 mL, and the residue was dissolved in heptane (32 mL) at 50 °C. The solution was evaporated *in vacuo* at 50 °C to a volume of 12 mL. The mixture was cooled gradually over 1 h to −40 °C. The enamine was filtered off and washed with heptane (10 mL) at −40 °C. The filter cake was dried under a stream of nitrogen to provide 3.12 g (81%) of enamine **25** as a pale-yellow crystalline solid. **25**: mp = 69−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.92 (br s, 1 H), 8.00 (d, J = 8.7, 1 H), 7.92 (dt, J = 8.8, 2.2, 2 H), 7.46 (dt, J = 8.8, 2.2, 2 H), 7.29 (d, J = 2.5, 1 H), 6.99 (m, 1 H), 6.07 (s, 1 H), 2.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 162.2, 149.3, 142.5, 140.5, 137.9, 136.9, 128.8, 128.5, 120.3 (q, J = 257), 120.2, 119.8, 94.5, 94.0, 19.4; FTIR (thin film) ν_{max} 1588, 1308, 1258, 1218, 1173 cm^{-1}; ES HRMS m/z calcd for $C_{17}H_{13}ClF_3INO_2$ (M + H$^+$) 481.9632, found 481.9627; Anal. Calcd for $C_{17}H_{12}ClF_3INO_2$: C, 42.39; H, 2.51. Found: C, 42.58; H, 2.60.

3-Acylindole 6. A mixture of enamine **25** (2.41 g, 5.00 mmol), DABCO (1.12 g, 10.0 mmol), 10% Pd on carbon (0.480 g), and DMF (10 mL) was degassed under a stream of nitrogen and was stirred at 100 °C for 36 h. The mixture was filtered at 40 °C, and the filter cake was washed with DMF (10 mL) and then MeOH (10 mL). Water (15 mL) was added over 1 h at 20 °C, and the mixture was filtered. The filter cake was washed with 1:1 MeOH/water (20 mL) and dried under a stream of nitrogen. The crude, brown filter cake was dissolved in EtOAc (25 mL) at reflux, and the solution was treated with Darco G-60 for 1 h at 75 °C. The mixture was filtered hot through silica gel (1 g), washing with 10 mL of EtOAc, and the filtrate was concentrated to ∼10 mL volume at 80 °C. Heptane (30 mL) was added, and the mixture was concentrated to 20 mL volume at 80−100 °C. The mixture was cooled to 20 °C over 1 h and filtered. The filter cake was washed with heptane (20 mL) and dried under a stream of nitrogen to give acyl indole **6** (1.31 g, 74%).

Methyl (2*R*)-2-(3-{[3-(4-Chlorobenzoyl)-2-methyl-6-(trifluoromethoxy)-1H-indol-1-yl]methyl}phenoxy)butanoate (9). The acyl indole **6** (2.52 kg, 7.13 mol), benzylic chloride **10** (1.97 kg of 90.0 wt % solution in heptane, 7.27 mol, 97.3% ee), K_2CO_3 (1.92 kg, 13.9 mol), nBu_4NI (263 g, 0.713 mol), and DMF (5.70 L) were charged to a 50-L jacketed extractor and were maintained at 35 °C for 22 h. The mixture was cooled to 20 °C, and MTBE (4 L) and then HOAc (0.43 kg, 7.13 mol) were added during which the temperature rose to 24 °C. Then MTBE (17.4 L) and water (14.3 L) were added over 5 min during which the temperature rose to 27 °C. The aqueous phase was cut at 28 °C and discarded. The organic phase was washed with water (21.4 L) at 27 °C and 1 wt % brine (21.4 L) at 32 °C. The organic phase was diluted with MTBE (4 L). Quantitative HPLC analysis indicated this solution contained 3.84 kg of **9** (96% yield from the benzoyl indole). This solution was used in the next step without further purification. HPLC retention times (Method F): benzylic chloride **10** = 1.99, indole

6 = 2.5 min, methyl ester **9** = 4.2 min, indole **6** (*N*-tosylated) = 5.1 min, benzylic iodide derived from **10** = 2.24 min. Chiral HPLC retention times (Method G): **(*R*)-9** = 11.1 min, **(*S*)-9** = 5.0 min. An analytical standard of **9** was prepared by crystallization from MeOH: mp = 119.5−120.0 °C (99.5% ee); mp = 120−121 °C (racemate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 2 H), 7.46 (m, 2 H), 7.36 (m, 1 H), 7.24 (m, 1 H), 7.13 (m, 1 H), 7.00 (m, 1 H), 6.79 (dd, J = 8.0, 2.4, 1 H), 6.65 (d, J = 7.5, 1 H), 6.55 (m, 1 H), 5.33 (s, 2 H), 4.47 (m, 1 H), 3.66 (s, 3 H), 3.53 (s, 3 H), 1.96 (m, 2 H), 1.05 (t, J = 7.5, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 171.8, 158.7, 145.7, 145.3, 139.2, 138.2, 137.3, 136.3, 130.7, 130.5, 128.8, 125.7, 121.7, 120.7 (q, J = 256), 119.1, 115.5, 114.3, 113.9, 113.1, 103.0, 77.8, 52.2, 46.9, 26.2, 12.7, 9.6; FTIR (thin film) ν_{max} 1755, 1588, 1409, 1258, 1220 cm^{-1}; ES HRMS *m/z* calcd for $C_{29}H_{25}ClF_3NO_5Li$ ($M + Li^+$) 565.1525, found 565.1539; Anal. Calcd for $C_{29}H_{25}ClF_3NO_5$: C, 61.60; H, 4.50. Found: C, 61.81; H, 4.67.

(2*R*)-2-(3-{[3-(4-Chlorobenzoyl)-2-methyl-6-(trifluoromethoxy)-1H-indol-1-yl]methyl}phenoxy)butanoic Acid (1). NaOH (1 M aq, 13.3 L, 13.3 mol) was added to a solution of **9** (3.71 kg, 6.63 mol) in MTBE (20 L) and MeOH (11 L) at 20 °C. The biphasic mixture was heated to 40 °C for 4 h. The mixture was cooled to 20 °C, and 5 M aq HCl (2.91 L, 14.6 mol) was added. The organic phase was washed with water (3 × 9 L) at 30−35 °C. The organic phase was filtered and distilled under reduced pressure at 15−30 °C while toluene (32 L) was added. Distillation was continued until the mixture contained <5% by volume of MTBE by ^{1}H NMR and the final volume was 24 L. Heptane (24 L) was added to the mixture over 30 min at 20 °C. The mixture was stirred for 12 h at 20 °C. The crystalline solid was filtered from the mixture and washed with 2:1 heptane/toluene (12 L) and then with heptane (8 L). The solid was dried under a stream of nitrogen to provide **1** (3.47 kg, 96%, 99.5 area %, 99.1 wt % by HPLC assay, 99.7% ee by chiral HPLC). HPLC retention time (Method F): **1** = 2.98 min. **1**: mp = 172−173 °C (99.5% ee); mp = 148−149 °C (racemate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.5, 2 H), 7.45 (d, J = 8.5, 2 H), 7.33 (d, J = 8.7, 1 H), 7.26 (d, J = 12.7, 1 H), 7.24 (d, J = 15.9, 1 H), 7.14 (s, 1 H), 7.00 (dm, J = 8.7, 1 H), 6.81 (dd, J = 8.2, 2.4, 1 H), 6.67 (d, J = 7.6, 1 H), 6.66 (br s, 1 H), 6.49 (s, 1 H), 5.33 (AB q, J = 23.0, 17.1, 2 H), 4.46 (t, J = 6.1, 1 H), 2.49 (s, 3 H), 1.97 (m, 2 H), 1.06 (t, J = 7.4, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 176.0, 158.5, 146.2, 145.4, 139.0, 138.4, 137.4, 136.4, 130.8, 128.8, 125.7, 124.5, 121.7, 120.7 (q, J = 256), 119.2, 115.7, 114.2, 113.9, 113.4, 103.1, 77.3, 46.9, 26.0, 12.7, 9.5; FTIR (thin film) ν_{max} 1745, 1587, 1487, 1412, 1260 cm^{-1}; ES HRMS *m/z* calcd for $C_{28}H_{22}F_3NO_5$ ($M - H^+$) 544.1138, found 544.1141; Anal. Calcd for $C_{28}H_{23}ClF_3NO_5$: C, 61.60; H, 4.25. Found: C, 61.50; H, 4.47.

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