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Synthesis of A-9758, an Inverse Agonist of Retinoic Acid-Related Orphan Receptor γt

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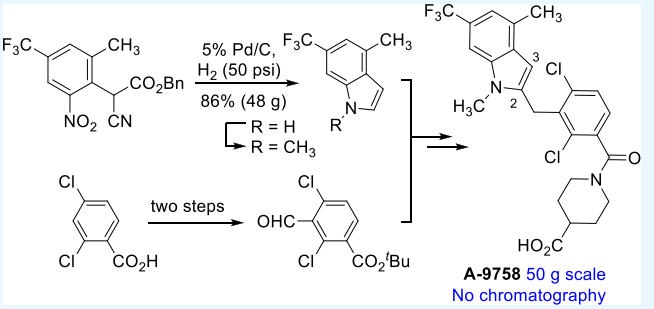
ABSTRACT: A-9758 is an inverse agonist of retinoic acid-related orphan receptor γt with well-characterized in vitro and in vivo anti-inflammatory activity. A chromatography-free decagram-scale synthesis of this compound was developed to support pre-clinical research activities. This route was designed to enable late-stage structure−activity relationship studies of the amide moiety and convergently uses a reductive alkylation sequence between indole and benzaldehyde intermediates. A key advantage of this strategy is the fact that the indole precursor can be alkylated at C2, as required for A-9758, or at C3 to provide access to an isomeric chemical series. Access to the critical indole fragment was expedited via an underutilized SnAr/reductive cyclization cascade sequence, and the benzaldehyde fragment was prepared in two steps from inexpensive 2,4-dichlorobenzoic acid.



INTRODUCTION

Dysregulation of IL-17 producing T helper cells (Th17) is associated with the pathology of many autoimmune diseases. Two strategies to dampen Th17-related inflammation have focused on biologics-based approaches. Sequestration of pro-inflammatory cytokine IL-17 is achieved by antibodies such as secukinumab and ixekizumab.[1,2] Antibodies ustekinumab, guselkumab, and tildrakizumab represent another approach by targeting IL-23, another pro-inflammatory cytokine that is involved in the activation and expansion of the Th17 cell population. Retinoic acid-related orphan receptor (ROR) γt has emerged as a compelling target for a complimentary small molecule-based approach to quell Th17 driven inflammation.[3−9] ROR is a member of the superfamily of steroid nuclear receptor transcription factors and is involved in diverse biological processes.[10−12] The γt isoform of ROR is expressed exclusively in immune cells and thymus-derived lymphocytes. It serves as a master regulator for the differentiation of Th17 cells and subsequent production of IL-17A as well as other pro-inflammatory cytokines. RORγt has an intrinsic level of basal activity. Therefore, programs targeting it as a potential treatment for chronic inflammation have prioritized inverse agonists over standard inhibitors with the goal of suppressing RORγt's baseline activity.

Early discovery work by medicinal chemistry colleagues identified a series of quinoline sulfonamide compounds with RORγt inverse agonist activity.[13] Continued exploration of other heterocyclic series resulted in the identification of A-9758 as an inverse agonist with high selectivity for RORγt versus other ROR family members (Figure 1).[14] This compound inhibits release of IL-17A both in vitro and in multiple animal models of inflammation. Due to increased compound demands that accompanied late-stage preclinical research activities, a new synthetic route was needed to accelerate access to decagram quantities of A-9758 (**1**).[15]

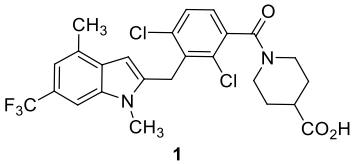


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Figure 1. Structure of A-9758.

The original medicinal chemistry route to A-9758 involved 14 total synthetic steps (11 steps longest linear sequence). It was designed around a Larock indole synthesis strategy where **5** could be replaced with other *o*-iodoanilines for the diversification of indole substituents at carbons 4−7 (Scheme 1).[16,17] While this route was well suited for the preparation of indole analogues during early medicinal chemistry work, it presented several disadvantages for the larger-scale synthesis of A-9758. The cost of highly substituted benzene starting materials **2** and **4** was a concern. At the time of this work, the expense of carboxylic acid **2** necessitated its preparation from

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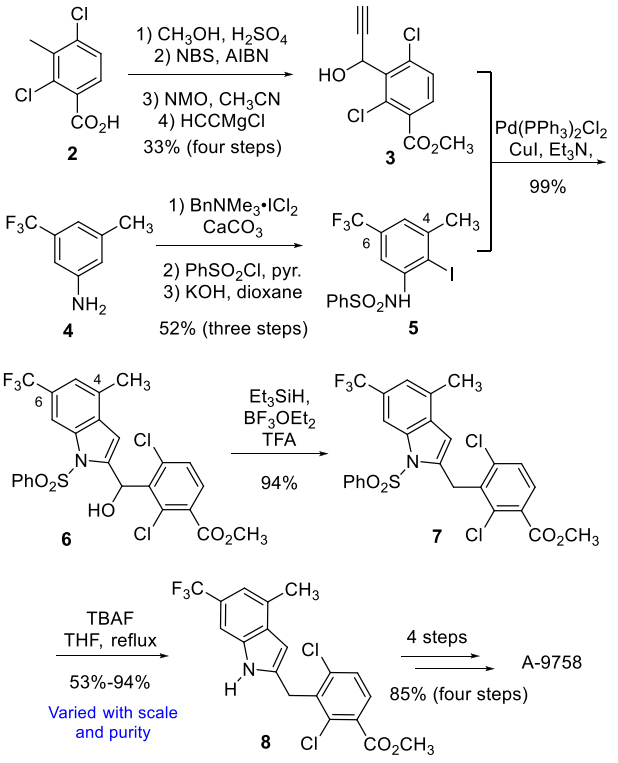
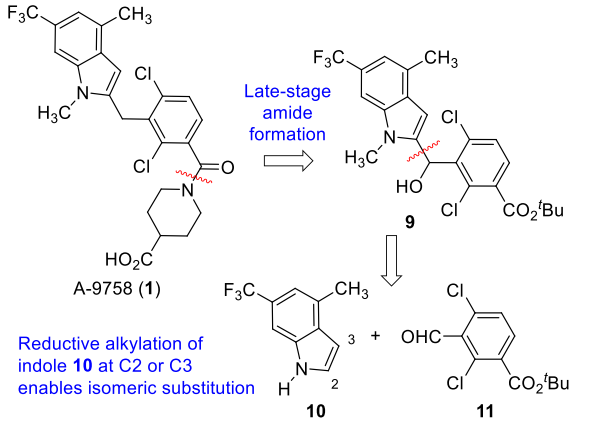
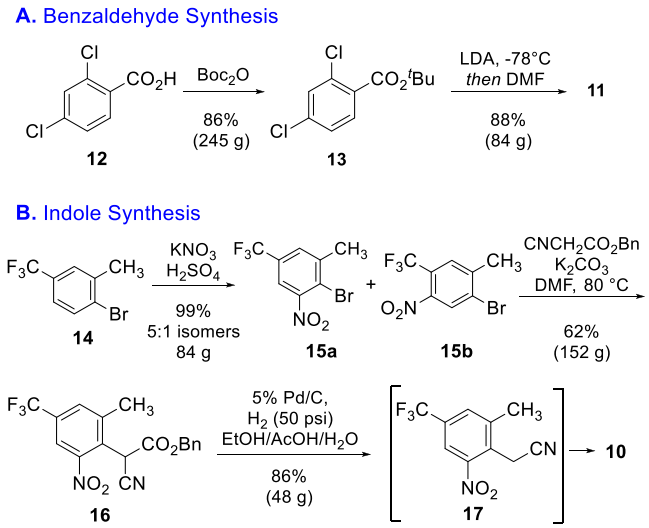
Scheme 1. Early Discovery Route to A-9758[16,17]



Scheme 2. Retrosynthetic Analysis for the Second-Generation Discovery Route



Scheme 3. Synthesis of (A) Key Benzaldehyde and (B) Indole Intermediates



1,3-dichlorotoluene for early scale-ups (not shown). Exploratory attempts at modified Larock indole synthesis without the phenylsulfonyl group were unsuccessful, providing only uncyclized Sonogashira-coupling products. While the phenylsulfonyl group appeared to be optimal for the Larock synthesis of indole **6**, this group was undesirable from the perspective of non-productive steps involved with its introduction and removal. Deprotection of the sulfonamide group itself became problematic on scales of >10 g due to variability with respect to both yield and reaction purity profile. Reproducibility in the deprotection step was only achieved in yields of >65% upon rigorous chromatographic purification of precursors, and the full synthetic route to A-9758 ultimately required more than five chromatography steps.

RESULTS AND DISCUSSION

Key considerations that informed the development of a decagram route were goals to minimize the number of synthetic steps, eliminate chromatography, and support ongoing medicinal chemistry structure−activity relationship (SAR) studies. Therefore, the retrosynthesis shown in Scheme 2 was prioritized since it would provide access to A-9758 as well as other amide analogues through the diversion of compound **9** at a late stage of the synthesis. Secondary alcohol **9** would be prepared by lithiation of indole **10** at C2 and subsequent addition to benzaldehyde **11**, a disconnect involving two fragments of comparable molecular weight and complexity. This disconnection also would allow access to isomeric unions where the fragments also could be joined at C3 of the indole by reductive alkylation. Thus, efforts focused on the identification of the rapid and chromatography-free syntheses of key intermediates **10** and **11**.

Preparations of aldehyde **11** and key indole intermediate **10** are shown in Scheme 3. Commercial 2,4-dichlorobenzoic acid was converted to *t*-butyl ester **13** followed by LDA-mediated deprotonation and formylation with DMF to give benzaldehyde **11** (Scheme 3A). High yields in the formylation step required careful control of the reaction temperature, staying below −70 °C for deprotonation and maintaining low temperatures during the addition of DMF and quenching of the tetrahedral intermediate. While aldehyde **11** was prepared in this manner via a batch process on an 84 g scale, synthesis on a kilogram scale was more efficiently achieved by flow chemistry.[18]

Indole **10** was prepared in four steps from commercially available 1-bromo-2-methyl-4-(trifluoromethyl)benzene (**14**; Scheme 3B). Nitration gave **15a** as the major component of a 5:1 mixture of regioisomeric products that were advanced without separation. Of the many methods available for indole synthesis,[19] we were inspired by an underutilized SnAr/reductive cyclization sequence that was reported by Walkington and co-workers for the kilogram scale-synthesis of C6-substituted indoles.[20] Gram-scale experiments demonstrated that elevated temperature was necessary for the SnAr reaction between benzyl cyanoacetate and bromobenzene **15a**, most likely due to its sterically hindered nature. Careful monitoring of the reaction temperature revealed that this SnAr

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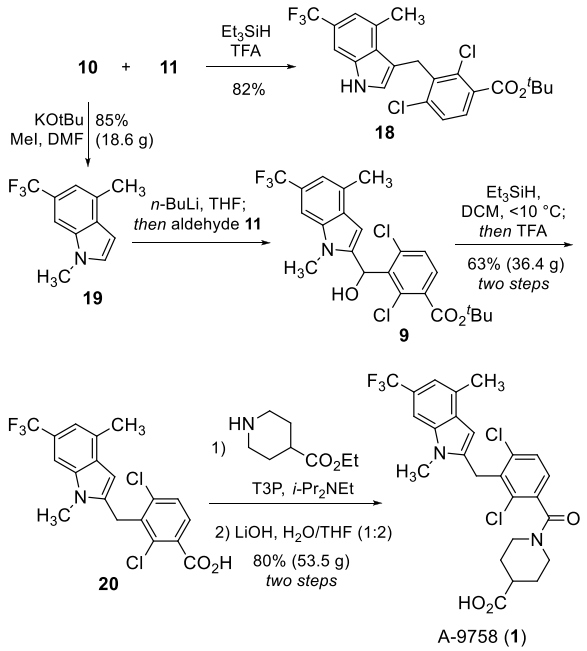
reaction does not initiate until reaching a temperature of 80 °C at which point it then becomes exothermic. Due to this observation, this reaction was profiled by differential scanning calorimetry (DSC). DSC confirmed that the initiation of the SnAr reaction was exothermic and revealed the onset of an additional undesired exothermic event at 107 °C. Mindful of the DSC results, reaction temperature was internally monitored and regulated by controlled addition of nitrobromide **15a** to an 80 °C solution of benzyl cyanoacetate and base so as to maintain a reaction temperature of 80−90 °C. This protocol enabled execution of this reaction on a scale of 150 g.[21] Nitrophenylacetonitrile **16** was isolated after simple aqueous work-up and precipitation from MTBE and heptanes. Hydrogenation of **16** drives a cascade of reactions that ultimately results in reductive cyclization to indole **10**. Despite the number of distinct reactions occurring in this transformation—debenzylation, decarboxylation, reduction of the nitro group, and reductive cyclization of the resulting aniline to form the indole—this was a remarkably clean process. Impurities and by-products were rejected by aqueous work-up, affording 86% isolated yield of **10**. The precise sequencing of this indole-forming cascade is uncertain and remains an opportunity for mechanistic studies. A related step-wise sequence has been reported, which suggests involvement of intermediate **17** or a related structure.[22]

Indole **10** was considered a key intermediate for both SAR studies and scale-up efforts since it offered access to both C2 and C3 substitution patterns (*vide supra*) (Scheme 4).

Scheme 4. Alkylation of Indoles at C2 versus C3 and Conversion to A-9758



Reductive alkylation of **10** with aldehyde **11** in the presence of triethylsilane and TFA gave C3 regioisomer **18**.[23] To access the C2 connectivity required for A-9758, **10** was *N*-methylated to **19**, which was precipitated in high purity from the reaction mixture after dilution with water. Lithiation at C2 of *N*-methyl indole **19** was achieved with *n*-butyllithium at −10 °C, which was transferred to a −50 °C solution of aldehyde **11** for electrophilic trapping to give secondary alcohol **9**. Crude **9** was reduced with triethylsilane in the presence of excess TFA to provide concomitant deprotection of the *tert*-butyl ester to carboxylic acid **20**. Cyclopentyl methyl ether (CPME) and heptanes (1:1) were identified as effective recrystallization solvents to provide **20** in high purity on a 36 g scale. Ethyl 4-piperidinecarboxylate was coupled to carboxylic acid **20** with propanephosphonic acid anhydride (T3P) followed by ester saponification to give A-9758. T3P conditions were selected for this late amide coupling due to the fact that its by-products are water-soluble and are readily rejected by aqueous work-up, resulting in high purity amide products. Indeed, A-9758 precipitated from the reaction mixture after acidification. Its purity was further enhanced to >97.7% HPLC purity via hot acetonitrile reslurry, delivering A-9758 in 22.6% overall yield from trifluorometylbenzene **14**.

CONCLUSIONS

A second-generation synthesis of A-9758 was developed to deliver this RORγt inverse agonist in high purity on a 50 g scale. This second-generation synthesis begins from less expensive starting materials and offers improved step efficiency over the early discovery route: 8- versus 11-step longest linear sequence and 10 versus 14 steps overall. More significantly, while the previous route required five chromatographic purifications, the second-generation route is chromatography-free. The efficient synthesis of benzaldehyde **11** and indole **10** drove much of the improvements in step economy. Benzaldehyde **11** was prepared rapidly in two steps from inexpensive 2,4-dichlorobenzoic acid. The key indole intermediate **10** was prepared efficiently through SnAr addition of benzyl cyanoacetate to sterically hindered bromonitrobenzene **15a** followed by a reductive cyclization cascade. The route described herein enabled advanced pre-clinical characterization of A-9758. Furthermore, it supported medicinal chemistry with access to C2 and C3 indole substitution patterns and a means for late-stage diversification of the amide moiety for additional SAR exploration. Thorough in vitro and in vivo characterization of A-9758 has made it a valuable tool compound for the interrogation of RORγt biology. Additional findings regarding the medicinal chemistry of this and related series as well as the enabling syntheses of other indole series will be reported in due course.

EXPERIMENTAL SECTION

***tert*-Butyl 2,4-dichlorobenzoate (13).** Di-*tert*-butyl dicarbonate (571 g, 2.618 mol) and 4-dimethylaminopyridine (32.0 g, 0.262 mol) were added to a stirred solution of 2,4-dichlorobenzoic acid (500.0 g, 2.618 mol) in anhydrous THF (2.6 L), which was immersed in an ice bath to maintain a temperature <30 °C. Once the addition was complete, the reaction was heated to 40 °C for 12 h. Removal of solvent under reduced pressure gave an oil that was partitioned between water (300 mL) and EtOAc (500 mL). The phases were separated, and the aqueous layer was back-extracted with EtOAc (2 × 100 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (3 × 200 mL), 1 N aq. HCl (3 × 150 mL), water (2 × 200 mL), brine (2 × 100 mL), and dried ($MgSO_4$). Removal of solvent under reduced pressure gave product **13** as a pale yellow oil (245.8 g, 995 mmol, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 2.1 Hz, 1H), 7.27 (dd, J = 8.4, 2.0 Hz, 1H), 1.60 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4 (C), 137.7 (C),

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134.4 (C), 132.3 (CH), 130.9 (CH), 130.6 (C), 127.0 (CH), 82.9 (C), 28.3 ($CH_3 \times 3$). HRMS-ESI (positive ionization) m/z $[M + H]^+$ calcd for $C_{11}H_{13}Cl_2O_2$, 247.0287; found, 247.0286.

***tert*-Butyl 2,4-dichloro-3-formylbenzoate (11).** Lithium diisopropylamide (180 mL, 2.0 M in THF, 0.360 mol) was added dropwise over 40 min via a syringe pump to a solution of *tert*-butyl 2,4-dichlorobenzoate (**13**) (75.01 g, 0.304 mol) in THF (300 mL), maintaining a temperature of less than −70 °C (internally monitored). The reaction immediately became dark red upon addition of LDA. After 3.5 h, a second portion of lithium diisopropylamide (40 mL, 80 mmol) was added and stirring continued for 1 h, whereupon the dark red solution was transferred dropwise over 40 min via cannula to a −64 °C solution of *N*,*N*-dimethylformamide (29.4 mL, 0.379 mol) in THF (50 mL). After 45 min, the reaction mixture was quenched below 64 °C with sat. aq. NH_4Cl (225 mL) and 1 M aq. HCl (300 mL). It was then warmed to room temperature and extracted with MTBE (750 mL). The organic phase was washed with 2 M aq. HCl (2 × 200 mL × 2), sat. aq. $NaHCO_3$ (2 × 300 mL), brine (100 mL), and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give product **11** as a light-yellow oil [84.07 g, 88% yield after 87.2% adjusted purity due to the presence of 0.38 mol equiv of ethylbenzene (from commercial LDA) by ^1H NMR], which was used without further purification. A portion was purified by chromatography (silica) eluting with a gradient of 0−15% MTBE/heptanes for characterization. ^1H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.8 (C), 164.1 (C), 137.8 (C), 135.0 (C), 133.8 (CH), 133.4 (C), 132.4 (C), 129.5 (CH), 83.8 (C), 28.3 ($CH_3 \times 3$). HRMS data was not obtained due to poor ionization.

2-Bromo-1-methyl-3-nitro-5-(trifluoromethyl)-benzene (15a).[24] A three-neck flask equipped with a mechanical stirrer, addition funnel, and thermocouple was immersed in an ice water cooling bath. The flask was charged with 1-bromo-2-methyl-4-(trifluoromethyl)benzene (**14**) (69.29 g, 0.290 mol) followed by dropwise addition of concentrated sulfuric acid (355 mL, 6.660 mmol), which was added via the addition funnel at a rate that maintained an internally monitored temperature of less than 6 °C. Next, potassium nitrate (33 g, 0.327 mol) was added portion-wise over 18 min to maintain a temperature of <19 °C (CAUTION: Exothermic!). The reaction was complete after 30 min, where it was poured slowly over 5 min into an externally cooled and mechanically stirred mixture of crushed ice (800 g) and *t*-butyl methyl ether (200 mL) (CAUTION: Exothermic!). The reaction flask was rinsed with two portions of MTBE (2 × 100 mL), which were added to the aqueous work-up. The layers were separated, and the aqueous phase was extracted with MTBE (3 × 200 mL). The combined organics were washed with brine (200 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure to give an oil. Storage of this oil in the freezer overnight induced crystallization of the product, 2-bromo-1-methyl-3-nitro-5-(trifluoromethyl)benzene (**15a**) with the 4-nitro regioisomer (**15b**) as a minor by-product (5:1 ratio, light yellow needles, 84.8 g, 99% yield), which was used without further purification. The minor isomer can be rejected by chromatography (silica) eluting with a gradient of 0−10% MTBE/heptanes to give the title compound as a single regioisomer. Melting point: 50.9−52.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 2.2 Hz, 1H), 7.71−7.66 (m, 1H), 2.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (C), 143.0 (C), 130.4 (C, q, J_{C-F} = 34.4 Hz), 129.7 (CH, q, J_{C-F} = 3.4 Hz), 122.6 (C, q, J_{C-F} = 272.9 Hz), 120.2 (C), 119.5 (CH, q, J = 3.9 Hz), 24.0 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.54. HRMS-ESI (negative ionization) m/z $[M-H]^-$ calcd for $C_8H_5BrF_3NO_2$, 281.93830; found, 281.93832.

Benzyl 2-Cyano-2-(2-methyl-6-nitro-4-(trifluoromethyl)phenyl)acetate (16). This procedure should be conducted with extreme caution due to its exothermic nature. An appropriate cooling bath should be kept on-hand for emergency cooling. A three-neck flask equipped with a mechanical stirrer, thermocouple, and addition funnel was charged with potassium carbonate (210.06 g, 1.520 mol) and DMF (200 mL). A solution of benzyl cyanoacetate (120 mL, 0.760 mol) in DMF (50 mL) was added dropwise to this room temperature suspension over 15 min (mild exotherm to 26 °C). Once the addition was complete, this stirred suspension was heated to 80 °C, whereupon a solution of 2-bromo-1-methyl-3-nitro-5-(trifluoromethyl)benzene (**15a**) (185.92 g, 0.655 mol) in DMF (200 mL) was added dropwise over >60 min via an addition funnel so as to maintain an internally monitored temperature of 80−90 °C (CAUTION: Exothermic!). It is critical to maintain a reaction temperature below 90 °C due to a subsequent, undesired, exothermic event initiating at 107 °C that can result in a thermal runaway. The reaction was stirred for an additional 45 min at 80 °C, it was then cooled to 20 °C, diluted with MTBE (1800 mL), and quenched by slow addition of 2 M aq. HCl (1227 mL, 2.455 mol) (CAUTION: Effervescence!). The layers were separated, and the aqueous phase was extracted with MTBE (1000 mL, then 3 × 500 mL). The combined organics were washed with brine (500 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a slurry (ca. 100 mL volume). Treating this stirred slurry with a 3:2 mixture of MTBE/heptanes (950 mL total) precipitated the product, which was filtered through a medium porosity frit and rinsed with an additional portion of 3:2 MTBE/heptanes (180 mL). Drying in the vacuum oven at 50 °C overnight gave product **16** as a tan crystalline solid (152.4 g, 62% yield), which was used without further purification. For characterization, a portion was purified by chromatography (silica) eluting with a gradient of 0−50% EtOAc/heptanes to give the product as a white solid. Melting point: 112.6−114.8 °C (decomp at 134.2 °C). ^1H NMR (500 MHz, DMSO-d_6) δ 8.35−8.31 (m, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.44−7.32 (m, 5H), 6.33 (s, 1H), 5.27 (ABq, J_{AB} = 12.3 Hz, 2H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.5 (C), 149.0 (C), 143.1 (C), 134.8 (C), 132.7 (CH, q, J_{C-F} = 3.1 Hz), 130.4 (C, q, J_{C-F} = 33.5 Hz), 128.54 (CH × 2), 128.53 (CH), 128.1 (CH × 2), 127.8 (C), 122.7 (C, q, J_{C-F} = 273.0 Hz), 120.6 (CH, q, J_{C-F} = 3.8 Hz), 114.3 (C), 68.3 (CH_2), 37.67 (CH), 19.8 (CH_3). ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.35. HRMS-ESI (negative ionization) m/z $[M-H]^-$ calcd for $C_{18}H_{12}F_3N_2O_4$, 377.0755; found, 377.0749.

4-Methyl-6-(trifluoromethyl)-1*H*-indole (10). A 500 mL stainless steel pressure bottle was charged with benzyl 2-cyano-2-(2-methyl-6-nitro-4-(trifluoromethyl)phenyl)acetate (**16**) (21.43 g, 56.64 mmol), 5% Pd/C (Johnson Matthey #9, wet) (4.4 g, 2.067 mmol), and solvent: EtOH (200 mL), water (20 mL), and acetic acid (20 mL). The reaction mixture was shaken for 16 h at 50 psi of H_2 and 50 °C. Five batches were reacted at this scale (total amount of benzyl 2-cyano-2-(2-

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methyl-6-nitro-4-(trifluoromethyl)phenyl)acetate (**16**) = 107.15 g, 0.283 mol), which were combined for work-up. The combined crude reaction mixtures were filtered through Celite, and the solvent was removed under reduced pressure. The resulting brown syrup was dissolved in EtOAc (500 mL), washed with 2 M aq. HCl (260 mL), 1 M aq. $Na_2S_2O_3$ (260 mL), sat. aq. $NaHCO_3$ (3 × 260 mL), brine (80 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the product as a dark oil that solidified to a tan solid upon standing at room temperature (48.42 g, 0.243 mol, 86% yield). Product **10** was used in the next step without further purification. Melting point: 45.3−53.7 °C. Broad range; amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (s, 1H), 7.58 (t, J = 1.4 Hz, 1H), 7.54 (t, J = 2.8 Hz, 1H), 7.09−7.04 (m, 1H), 6.57 (ddd, J = 3.1, 2.0, 1.0 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 134.4 (C), 130.4 (C), 130.3 (C), 128.1 (CH), 125.6 (C, q, $J_{C\text{-}F}$ = 271.1 Hz), 121.6 (C, q, $J_{C\text{-}F}$ = 30.8 Hz), 114.9 (CH, q, $J_{C\text{-}F}$ = 3.4 Hz), 106.7 (CH, q, $J_{C\text{-}F}$ = 4.6 Hz), 100.3 (CH), 18.5 (CH_3). ^{19}F NMR (376 MHz, DMSO-d_6) δ −58.35. HRMS-ESI (negative ionization) m/z [M-H]$^-$ calcd for $C_{10}H_7F_3N$, 198.0536; found, 198.0534.

2,4-Dichloro-3-((4-methyl-6-(trifluoromethyl)-1*H*-indol-3-yl)methyl)benzoic Acid (18). A solution of 4-methyl-6-(trifluoromethyl)-1*H*-indole (**10**) (0.2253 g, 1.131 mmol) in DCM (1.0 mL) was cooled to <5 °C, and *tert*-butyl 2,4-dichloro-3-formylbenzoate (**11**) (0.380 g, 1.382 mmol), triethylsilane (0.6 mL, 3.76 mmol), and TFA (0.15 mL, 1.947 mmol) were added at a rate so as to maintain a temperature of <5 °C. After 30 min, a saturated solution of aq. $NaHCO_3$ (10 mL) was added and extracted with MTBE (15 mL). The organic phase was washed with brine (10 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by chromatography (silica) eluting with a gradient of 0−30% MTBE/heptanes gave product **18** as a white solid (0.424 g, 0.925 mmol, 82% yield). ROESY and HMBC experiments confirmed the regiochemical outcome of the reductive alkylation. Melting point: 138.8−141.6 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.18 (d, J = 2.7 Hz, 1H), 7.63 (s, 2H), 7.52 (d, J = 1.6 Hz, 1H), 7.04 (s, 1H), 6.51−6.47 (m, 1H), 4.62 (d, J = 1.3 Hz, 2H), 2.82 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.5 (C), 137.6 (C), 137.1 (C), 135.6 (C), 132.7 (C), 132.5 (C), 131.3 (C), 128.9 (CH), 128.4 (CH), 127.8 (C), 125.4 (C, q, $J_{C\text{-}F}$ = 271.2 Hz), 124.9 (CH), 121.7 (C, q, $J_{C\text{-}F}$ = 31.0 Hz), 115.8 (CH, q, $J_{C\text{-}F}$ = 3.6 Hz), 111.8 (C), 107.1 (CH, q, $J_{C\text{-}F}$ = 4.5 Hz), 82.7 (C), 29.4 (CH_2), 27.7 (CH_3 × 3), 20.1 (CH_3). ^{19}F NMR (376 MHz, DMSO-d_6) δ −58.61. HRMS-ESI (positive ionization) m/z [M + H]$^+$ calcd for $C_{22}H_{21}Cl_2F_3NO_2$, 458.0896; found, 458.08954.

1,4-Dimethyl-6-(trifluoromethyl)-1*H*-indole (19). A three-neck flask was equipped with a mechanical stirrer and then charged with a solution of 4-methyl-6-(trifluoromethyl)-1*H*-indole (**10**) (20.42 g, 103 mmol) in DMF (80 mL), which was cooled to <5 °C (internally monitored). Sodium *t*-butoxide (12.81 g, 133 mmol) was added portion-wise to maintain a temperature of <16 °C (mildly exothermic). Upon completion of the addition, the reaction was cooled back to <5 °C, whereupon iodomethane (9.49 mL, 152 mmol) was added dropwise over 10 min via a syringe to maintain a temperature of <30 °C. Methylation was complete within 15 min. Addition of water (200 mL) precipitated the product, which was filtered and washed with additional portions of water (2 × 100 mL). Drying in the vacuum oven overnight at 50 °C gave product **19** as an off-white solid (18.64 g, 85% yield). Melting point: 90.5−96.0 °C (suggests amorphous solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (t, J = 1.3 Hz, 1H), 7.50 (d, J = 3.1 Hz, 1H), 7.10 (d, J = 1.5 Hz, 1H), 6.55 (dd, J = 3.0, 0.9 Hz, 1H), 3.84 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 135.0 (C), 132.3 (CH), 130.7 (C), 130.6 (C), 127.02 (C, $J_{C\text{-}F}$ = 271.3 Hz), 121.8 (C, q, $J_{C\text{-}F}$ = 31.0 Hz), 115.1 (CH, q, $J_{C\text{-}F}$ = 3.4 Hz), 105.2 (CH, q, $J_{C\text{-}F}$ = 4.6 Hz), 99.5 (CH), 32.9 (CH_3), 18.3 (CH_3). ^{19}F NMR (376 MHz, DMSO-d_6) δ −58.19. HRMS-ESI (positive ionization) m/z [M + H]$^+$ calcd for $C_{11}H_{11}F_3N$, 214.0838; found, 214.0840.

2,4-Dichloro-3-((1,4-dimethyl-6-(trifluoromethyl)-1*H*-indol-2-yl)methyl)benzoic Acid (20). Step 1: *n*-Butyllithium (100 mL, 1.6 M in hexanes, 160 mmol) was added dropwise over 30 min to a −10 °C solution of 1,4-dimethyl-6-(trifluoromethyl)-1*H*-indole (**19**) (29.56 g, 139 mmol) in THF (280 mL), maintaining an internally monitored temperature of <0 °C. After 45 min, the lithiated indole was transferred via cannula to a solution of crude *tert*-butyl 2,4-dichloro-3-formylbenzoate (**11**) (48.48 g, 153 mmol) in THF (150 mL) at less than −50 °C. After 40 min, the reaction was warmed to −5 °C and quenched by addition of 10% aq. citric acid (150 mL), extracted with toluene (150 mL), washed with 1 M aq. $Na_2S_2O_3$ (100 mL), brine (60 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was redissolved in MTBE (2 × 150 mL), which was removed under reduced pressure to give the product, secondary alcohol **9**, as a dark foam that was used without further purification. A portion was purified for characterization by reverse phase HPLC. White solid (amorphous). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 1.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.11 (s, 1H), 6.79 (s, 1H), 6.08 (t, J = 0.9 Hz, 1H), 3.98 (s, 3H), 3.18 (s, 1H), 2.47 (s, 3H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9 (C), 139.1 (C), 137.3 (C), 137.1 (C), 136.7 (C), 133.8 (C), 133.3 (C), 131.5 (C), 130.4 (CH), 129.5 (CH), 129.2 (C), 125.4 (C, q, $J_{C\text{-}F}$ = 271.6 Hz), 124.6 (C, q, $J_{C\text{-}F}$ = 31.5 Hz), 116.6 (CH, q, $J_{C\text{-}F}$ = 3.4 Hz), 104.8 (CH, q, $J_{C\text{-}F}$ = 4.6 Hz), 101.1 (CH), 83.7 (C), 67.9 (CH), 31.0 (CH_3), 28.3 (CH_3 × 3), 18.8 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.14. HRMS-ESI (positive ionization) m/z [M + H]$^+$ calcd for $C_{23}H_{23}Cl_2F_3NO_3$, 488.1002; found, 488.1007.

Step 2: A solution of *tert*-butyl 2,4-dichloro-3-((1,4-dimethyl-6-(trifluoromethyl)-1*H*-indol-2-yl)(hydroxy)methyl)-benzoate (**9**) (67.9 g, 139 mmol) in DCM (200 mL) was cooled to <5 °C, where triethylsilane (24 mL, 150 mmol) and then TFA (200 mL) were added dropwise over 20 min, maintaining a temperature of <10 °C. The cooling bath was removed once the addition was complete, and the reaction was stirred at room temperature for 6 h. The solvent was removed under reduced pressure, and the resulting dark residue was redissolved in CPME (70 mL) and concentrated twice to drive off as much residual TFA as possible. The residue was then treated with CPME (130 mL), sonicated, and stirred vigorously. Slow addition of heptanes (130 mL) precipitated the product, which was filtered and washed with 1:1 CPME/heptanes (70 mL). Vacuum drying overnight at 50 °C gave product **20** as a gray solid (30 g, 72 mmol, 52% yield). A second crop of the product was obtained from the mother liquor after removal of solvent under reduced pressure, treatment with CPME (60 mL) followed by heptanes (60 mL), filtration, and vacuum drying. The second crop of the

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product (6.42 g, 11% yield) brought the total isolated product to 36.42 g [63% yield, two steps from 1,4-dimethyl-6-(trifluoromethyl)-indole]. Melting point: 230.6−234.4 °C (decomp at 234.4 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 5.67 (s, 1H), 4.48 (s, 2H), 3.92 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6 (C), 139.7 (C), 137.4 (C), 135.8 (C), 135.2 (C), 133.2 (C), 132.3 (C), 129.8 (CH), 129.5 (C), 129.5 (C), 128.5 (CH), 125.6 (C, q, $J_{C\text{-}F}$ = 271.5 Hz), 121.2 (C, q, $J_{C\text{-}F}$ = 30.9 Hz), 115.4 (CH, q, $J_{C\text{-}F}$ = 3.7 Hz), 104.9 (CH, q, $J_{C\text{-}F}$ = 4.6 Hz), 97.1 (CH), 30.0 (CH_3), 29.4 (CH_2), 18.2 (CH_3). ^{19}F NMR (376 MHz, DMSO-d_6) δ −58.08. HRMS-ESI (positive ionization) m/z [M + H]$^+$ calcd for $C_{19}H_{15}Cl_2F_3NO_2$, 416.0426; found, 416.0428.

1-(2,4-Dichloro-3-((1,4-dimethyl-6-(trifluoromethyl)-1*H*-indol-2-yl)methyl)benzoyl)piperidine-4-carboxylic Acid (1, A-9758). Step 1: *N*,*N*-Diisopropylethylamine (42 mL, 240 mmol) and ethyl piperidine-4-carboxylate (27 mL, 172 mmol) were added sequentially to a 0−5 °C stirred suspension of 2,4-dichloro-3-((1,4-dimethyl-6-(trifluoromethyl)-1*H*-indol-2-yl)methyl)benzoic acid (**20**) (48.86 g, 117 mmol) in ethyl acetate (995 mL). Propylphosphonic anhydride (108 mL, >50 wt % in ethyl acetate, 182 mmol) then was added dropwise over 20 min. After 45 min, the reaction was quenched by addition of water (250 mL). The phases were separated, and the organic layer was washed with water (500 mL), 1 M aq. NaOH (500 mL), 1 M aq. $Na_2S_2O_3$ (250 mL), 1 M aq. HCl (250 mL × 2), brine (125 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting gum was redissolved in a minimal volume of 10% MeOH/DCM and filtered through a plug of silica gel eluting with a gradient of 0−10% MeOH/DCM. Removal of solvent under reduced pressure gave the amide-coupling product as an off-white solid (70.2 g). NMR indicated a 1:1 ratio of rotamers at room temperature: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.70 (s, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.46 (d, J = 8.3 Hz, 0.5H), 7.39 (d, J = 8.2 Hz, 0.5H), 7.06 (s, 1H), 5.67 (d, J = 11.1 Hz, 1H), 4.56−4.32 (m, 4H), 4.07 (q, J = 7.0 Hz, 1H), 4.03 (q, J = 7.1 Hz, 1H), 3.91 (s, 3H), 3.34−3.26 (m, 1H), 3.08 (dddd, J = 13.9, 11.4, 6.3, 2.9 Hz, 1H), 2.96 (dddt, J = 13.1, 10.6, 7.4, 3.0 Hz, 1H), 2.63 (dtd, J = 11.2, 7.2, 3.6 Hz, 1H), 2.35 (s, 3H), 1.93 (dt, J = 9.0, 4.2 Hz, 1H), 1.78 (dt, J = 13.7, 8.5 Hz, 1H), 1.64−1.41 (m, 2H), 1.18 (t, J = 7.1 Hz, 1.5H), 1.13 (t, J = 7.1 Hz, 1.5H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.8 (C), 173.7 (C), 164.9 (C), 164.8 (C), 139.7 (C), 139.7 (C, q, $J_{C\text{-}F}$ = 2.2 Hz), 136.1 (C), 136.0 (C), 135.8 (C), 135.3 (C), 135.2 (C), 134.7 (C), 134.6 (C), 131.5 (C), 131.3 (C), 129.6 (C, q, $J_{C\text{-}F}$ = 2.9 Hz), 129.5 (C, q, $J_{C\text{-}F}$ = 2.9 Hz), 129.49 (C), 129.43 (C), 129.1 (CH), 129.0 (CH), 127.4 (CH), 127.2 (CH), 125.6 (C, q, $J_{C\text{-}F}$ = 271.4 Hz), 121.3 (C, q, $J_{C\text{-}F}$ = 30.7 Hz), 115.4 (q, $J_{C\text{-}F}$ = 3.1 Hz), 105.1−104.9 (m), 97.2 (C), 97.1 (C), 60.1 (CH_2), 60.08 (CH_2), 45.9 (CH_2), 45.2 (CH_2), 40.23 (CH_2), 40.2 (CH_2), 40.0 (CH), 39.9 (CH), 30.0 (CH_3), 29.2 (CH_2), 28.2 (CH_2), 28.0 (CH_2), 27.5 (CH_2), 27.5 (CH_2), 18.2 (CH_3), 18.1 (CH_3), 14.1 (CH_3), 14.0 (CH_3). Rotamers collapsed to one signal at 120 °C: ^{1}H NMR (500 MHz, DMSO-d_6, 120 °C) δ 7.62−7.57 (m, 2H), 7.36 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 5.81 (s, 1H), 4.64−4.37 (m, 4H), 4.11 (q, J = 7.0 Hz, 2H), 3.90 (s, 3H), 3.12 (ddd, J = 13.8, 10.8, 3.3 Hz, 2H), 2.65 (td, J = 10.3, 5.1 Hz, 1H), 2.39 (s, 3H), 2.04−1.77 (m, 2H), 1.68−1.60 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6, 120 °C) δ 172.8 (C), 164.5 (C), 139.2 (C), 135.9 (C), 135.5 (C), 134.7 (C), 134.4 (C), 131.0 (C), 129.2 (C), 128.8 (C), 128.2 (CH), 126.6 (CH), 121.2 (C, q, $J_{C\text{-}F}$ = 31.5 Hz), 114.8 (CH, q, $J_{C\text{-}F}$ = 4.6, 3.8 Hz), 104.0 (CH, q, $J_{C\text{-}F}$ = 4.7 Hz), 97.1 (CH), 59.3 (CH_2), 44.6 (CH_2), 39.4 (CH), 29.2 (CH_3), 28.5 (CH_2), 27.0 (CH_2), 17.2 (CH_3), 13.2 (CH_3). Note: One carbon (C-CF_3) was not observed at 120 °C due to decreased signal to noise. ^{19}F NMR (471 MHz, DMSO-d_6) δ −58.07. HRMS-ESI (positive ionization) m/z [M + H]$^+$ calcd for $C_{27}H_{28}Cl_2F_3N_2O_3$, 555.1424; found, 555.1428.

Step 2: Water (225 mL) and lithium hydroxide (5.75 g, 240 mmol) were added to a solution of ethyl 1-(2,4-dichloro-3-((1,4-dimethyl-6-(trifluoromethyl)-1*H*-indol-2-yl)methyl)-benzoyl)piperidine-4-carboxylate (70.2 g, 126 mmol) in THF (450 mL), which then was heated to 60 °C. Saponification was complete within 75 min. The reaction mixture then was acidified with 1 M HCl (250 mL) and stirred rapidly with magnetic stirring at room temperature for 30 min. Solids slowly formed, and then, the dark color of the solution dissipated to give an off-white supernatant and yellow-tan solid, which was filtered, resuspended in acetonitrile (300 mL), and heated to 80 °C for 2 h. The slurry was cooled slowly to room temperature and filtered to give the product (**1**, A-9758) (46.62 g, 70% yield, 97.7% peak area by HPLC at 210 nm). A second crop of the product (6.92 g, 10% yield) was obtained by processing the mother liquor [concentration, suspension in acetonitrile (75 mL) at 80 °C for 4 h, cooling, and filtration]. NMR indicated rotamers at room temperature: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (s, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.44 (d, J = 8.2 Hz, 0.5H), 7.37 (d, J = 8.2 Hz, 0.5H), 7.06 (s, 1H), 5.69 (d, J = 10.1 Hz, 1H), 4.53−4.31 (m, 3H), 3.89 (s, 3H), 3.35−3.26 (m, 1H), 3.07 (tt, J = 13.8, 3.3 Hz, 1H), 3.01−2.87 (m, 1H), 2.59−2.46 (m, 1H), 2.34 (s, 3H), 1.98−1.88 (m, 1H), 1.83−1.72 (m, 1H), 1.64−1.41 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.6 (C), 175.5 (C), 165.0 (C), 164.9 (C), 139.8 (C), 136.2 (C), 136.1 (C), 135.9 (C), 135.8 (C), 135.4 (C), 135.3 (C), 134.8 (C), 134.7 (C), 131.6 (C), 131.4 (C), 129.6 (C), 129.6 (C), 129.5 (C), 129.2 (CH), 129.1 (CH), 127.4 (CH), 127.3 (CH), 125.7 (C, q, $J_{C\text{-}F}$ = 271.4 Hz), 121.4 (C, q, $J_{C\text{-}F}$ = 31.0 Hz), 115.5 (CH), 105.2−104.8 (CH, m, q split by rotamers), 97.3 (CH), 97.2 (CH), 46.1 (CH_2), 45.4 (CH_2), 40.5 (CH_2), 40.4 (CH_2), 40.1 (CH), 40.1 (CH), 30.0 (CH_3), 29.3 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 27.7 (CH_2), 18.2 (CH_3), 18.2 (CH_3). Rotamers collapsed to one signal at 130 °C: ^{1}H NMR (400 MHz, DMSO-d_6, 130 °C) δ 7.60 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.06 (s, 1H), 5.81 (t, J = 1.1 Hz, 1H), 4.49 (s, 2H), 4.39−4.17 (m, 2H), 3.90 (d, J = 1.3 Hz, 3H), 3.37 (s, 1H), 3.11 (ddd, J = 13.9, 10.8, 3.3 Hz, 2H), 2.57 (tt, J = 10.3, 4.2 Hz, 1H), 2.39 (s, 3H), 1.89 (s, 2H), 1.70−1.56 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6, 130 °C) δ 174.9 (C), 165.1 (C), 139.8 (C), 136.4 (C), 136.1 (C), 135.3 (C), 135.0 (C), 131.7 (C), 129.9 (C), 129.4 (C), 128.8 (CH), 127.2 (CH), 125.57 (C, q, $J_{C\text{-}F}$ = 271.5 Hz), 121.8 (C, q, $J_{C\text{-}F}$ = 31.0 Hz), 115.4 (CH, q, $J_{C\text{-}F}$ = 3.6 Hz), 104.6 (CH, q, $J_{C\text{-}F}$ = 4.6 Hz), 97.7 (CH), 45.5 (CH_2), 40.0 (CH), 29.8 (CH_3), 29.1 (CH_2), 27.7 (CH_2), 17.8 (CH_3). ^{19}F NMR (376 MHz, DMSO-d_6, 130 °C) δ −59.13. HRMS-ESI (positive ionization) m/z [M + H]$^+$ calcd for $C_{25}H_{24}Cl_2F_3N_2O_3$, 527.1111; found, 527.1113.

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■ ASSOCIATED CONTENT

Supporting Information

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General experimental procedures, DSC results for the reaction between **15a** and benzyl cyanoacetate, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

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■ REFERENCES

(1) Campa, M.; Mansouri, B.; Warren, R.; Menter, A. A Review of Biologic Therapies Targeting IL-23 and IL-17 for Use in Moderate-to-Severe Plaque Psoriasis. *Dermatol. Ther.* **2016**, *6*, 1−12.

(2) Schön, M. P.; Erpenbeck, L. The Interleukin-23/Interleukin-17 Axis Links Adaptive and Innate Immunity in Psoriasis. *Front. Immunol.* **2018**, *9*, 1323.

(3) Gege, C. Retinoic acid-related orphan receptor gamma t (RORγt) inverse agonists/antagonists for the treatment of inflammatory diseases − where are we presently? *Expert Opin. Drug Discovery* **2021**, *16*, 1517−1535.

(4) Jetten, A. M.; Cook, D. N. (Inverse) Agonists of Retinoic Acid−Related Orphan Receptor γ: Regulation of Immune Responses, Inflammation, and Autoimmune Disease. *Annu. Rev. Pharmacol. Toxicol.* **2020**, *60*, 371−390.

(5) Sun, N.; Guo, H.; Wang, Y. Retinoic acid receptor-related orphan receptor gamma-t (RORγt) inhibitors in clinical development for the treatment of autoimmune diseases: a patent review (2016-present). *Expert Opin. Ther. Pat.* **2019**, *29*, 663−674.

(6) Pandya, V. B.; Kumar, S.; Sachchidanand; Sharma, R.; Desai, R. C. Combating Autoimmune Diseases With Retinoic Acid Receptor-Related Orphan Receptor-γ (RORγ or RORc) Inhibitors: Hits and Misses. *J. Med. Chem.* **2018**, *61*, 10976−10995.

(7) Bronner, S. M.; Zbieg, J. R.; Crawford, J. J. RORγ antagonists and inverse agonists: a patent review. *Expert Opin. Ther. Pat.* **2017**, *27*, 101−112.

(8) Cyr, P.; Bronner, S. M.; Crawford, J. J. Recent progress on nuclear receptor RORγ modulators. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4387−4393.

(9) Fauber, B. P.; Magnuson, S. Modulators of the Nuclear Receptor Retinoic Acid Receptor-Related Orphan Receptor-γ (RORγ or RORc). *J. Med. Chem.* **2014**, *57*, 5871−5892.

(10) Dhar, T. G. M.; Zhao, Q.; Markby, D. W. In *Annual Reports in Medicinal Chemistry*; Desai, M. C., Ed.; Academic Press: 2013; Vol. *48*, p 169−182.

(11) Solt, L. A.; Burris, T. P. Action of RORs and their ligands in (patho)physiology. *Trends Endocrinol. Metab.* **2012**, *23*, 619−627.

(12) Jetten, A. M. Retinoid-Related Orphan Receptors (RORs): Critical Roles in Development, Immunity, Circadian Rhythm, and Cellular Metabolism. *Nucl. Recept. Signaling* **2009**, *7*, nrs.07003.

(13) Amaudrut, J.; Argiriadi, M. A.; Barth, M.; Breinlinger, E. C.; Bressac, D.; Broqua, P.; Calderwood, D. J.; Chatar, M.; Cusack, K. P.; Gauld, S. B.; Jacquet, S.; Kamath, R. V.; Kort, M. E.; Lepais, V.; Luccarini, J.-M.; Masson, P.; Montalbetti, C.; Mounier, L.; Potin, D.; Poupardin, O.; Rouaud, S.; Spitzer, L.; Wallace, C. D. Discovery of novel quinoline sulphonamide derivatives as potent, selective and orally active RORγ inverse agonists. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1799−1806.

(14) Gauld, S. B.; Jacquet, S.; Gauvin, D.; Wallace, C.; Wang, Y.; McCarthy, R.; Goess, C.; Leys, L.; Huang, S.; Su, Z.; Edelmayer, R.; Wetter, J.; Salte, K.; McGaraughty, S. P.; Argiriadi, M. A.; Honore, P.; Luccarini, J.-M.; Bressac, D.; Desino, K.; Breinlinger, E.; Cusack, K.; Potin, D.; Kort, M. E.; Masson, P. J. Inhibition of Interleukin-23−Mediated Inflammation with a Novel Small Molecule Inverse Agonist of RORγt. *J. Pharmacol. Exp. Ther.* **2019**, *371*, 208−218.

(15) Voight, E. A.; Greszler, S. N.; Kym, P. R. Fueling the Pipeline via Innovations in Organic Synthesis. *ACS Med. Chem. Lett.* **2021**, *12*, 1365−1373.

(16) Argiriadi, M. A.; Breinlinger, E.; Cusack, K. P.; Hobson, A. D.; Potin, D.; Barth, M.; Amaudrut, J.; Poupardin, O.; Mounier, L.; Kort, M. E. ROR Nuclear Receptor Modulators. WO 2016/198908 A1, 2016

(17) Argiriadi, M. A.; Breinlinger, E. C.; Cusack, K. P.; Hobson, A. D.; Potin, D.; Barth, M.; Amaudrut, J.; Poupardin, O.; Mounier, L.; Kort, M. E. Nuclear Receptor Modulators. WO2016/200851 A1, 2016

(18) Cardinal-David, B.; Harper, K. C.; Verma, A.; Hanna, D.; Caspi, D. D.; Vitale, C.; Bien, J. T.; Wang, Z.; Diwan, M. Continuous Multiphase Flow Nitration and Cryogenic Flow Formylation: Enabling Process Development and Manufacturing of Pharmaceutical Intermediates. *Org. Process Res. Dev.* **2021**, *25*, 2473−2481.

(19) Humphrey, G. R.; Kuethe, J. T. Practical Methodologies for the Synthesis of Indoles. *Chem. Rev.* **2006**, *106*, 2875−2911.

(20) Walkington, A.; Gray, M.; Hossner, F.; Kitteringham, J.; Voyle, M. A Simple Two-Step Synthesis of Indoles. *Synth. Commun.* **2003**, *33*, 2229−2233.

(21) This SnAr reaction was conducted with extreme caution due to the DSC analysis. The undesired exothermal event at 107 °C had potential for thermal runaway. An appropriate cooling bath was kept on-hand for emergency cooling. For a detailed report, see the Experimental Section and Supporting Information.

(22) Belley, M.; Scheigetz, J.; Dubé, P.; Dolman, S. Synthesis of *N*-Aminoindole Ureas from Ethyl 1-Amino-6-(trifluoromethyl)-1*H*-indole-3-carboxylate. *Synlett* **2001**, *2001*, 222−225.

(23) Mahadevan, A.; Sard, H.; Gonzalez, M.; McKew, J. C. A general method for C3 reductive alkylation of indoles. *Tetrahedron Lett.* **2003**, *44*, 4589−4591.

(24) Newton, C. G.; Braconi, E.; Kuziola, J.; Wodrich, M. D.; Cramer, N. Axially Chiral Dibenzazepinones by a Palladium(0)-Catalyzed Atropo-enantioselective C−H Arylation. *Angew. Chem., Int. Ed.* **2018**, *57*, 11040−11044.