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An Efficient Large-Scale Synthesis of a Naphthylacetic Acid CRTH2 Receptor Antagonist

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Supporting Information

ABSTRACT: An efficient and practical synthesis of a naphthylacetic acid CRTH2 receptor antagonist is reported. Michael addition of ethyl *t*-butyl malonate to an allenoate afforded a triester, which was selectively hydrolyzed and decarboxylated to give a benzylidenepentanedioic acid monoester. Treatment of this compound with potassium acetate and acetic anhydride produced the naphthylacetate core. The triflate of the key building block was coupled with a zinc reagent of the side chain under improved Negishi coupling conditions to afford the target product. The process was successfully scaled up to produce over 2 kg of the API.

INTRODUCTION

CRTH2, chemoattractant receptor-homologous molecule expressed on T-helper-type cells, is one of the prostaglandin D_2 receptors that is expressed on effector cells involved in allergic inflammation such as T-helper type 2 (Th2) cells, eosinophils, and basophils.[1] Studies suggest that CRTH2 plays a proinflammatory role in inflammation diseases. Thus, a CRTH2 receptor antagonist could be therapeutically useful for the treatment of asthma, allergic inflammation, COPD, allergic rhinitis, and atopic dermatitis.[2] Over the past few years, a number of distinct CRTH2 antagonists have been reported that gave encouraging proof-of-concept results in clinical trials.[2] At Roche, compound **14**, a naphthylacetic acid, was identified as a potent CRTH2 receptor antagonist with good pharmacologic properties. In order to support further preclinical/clinical development, process research was initiated to develop a practical synthesis of this molecule in bulk quantities.

The original synthesis of **14** (Scheme 1)[3] was not suitable for large-scale production due to several issues: (1) chromatographic purification were required for seven steps; (2) environmentally unfriendly or safety hazardous reagents, such as carbon tetrachloride and lithium aluminum hydride were used; (3) the formation of the zincate **12** for the Negishi coupling step was highly exothermic under the original conditions; and (4) the high catalyst loading in the penultimate step for the Negishi coupling could result in problems with palladium removal. Herein, we describe the development of a practical synthesis of **14**, which has been successfully scaled up to produce >2 kg of active pharmaceutical ingredient (API).

RESULTS AND DISCUSSION

Synthesis of the Naphthylacetate Core. In the original synthesis, the naphthylacetate **9** was prepared in seven steps from **1**. Five of the seven steps were, however, for the homologation of **4**, which was considered poor atom economy, despite good yields obtained for each individual step. The most problematic step was the condensation of **1** with **2**, which was poorly selective and produced many byproducts. As a result, the product isolation was tedious, and the yield was low. Therefore, it was decided to abandon this approach and explore alternative syntheses.

Retro-synthetic analysis revealed several potential approaches to **18**. Of these, three disconnection strategies (Scheme 2) were selected for investigation.

Route (a) was initially considered the most promising since a highly selective annulation process of a related compound has been previously described in the literature.[4] The synthesis of the precursor of **16**, however, was found to be a challenge. Though the Heck reaction of a close analogue of **17** is known in the literature,[5] no reaction between **17** and **23** was detected under similar conditions (Scheme 3). Friedel–Crafts reactions of analogues of **25**, an alternative approach, have also been reported.[6] However, with compound **25**, the reactions were poor under all conditions examined (Scheme 3). The lack of reactivity for **25** is likely due to the deactivating effect of fluorine.

The preparation of precursors for route (b) was also problematic. The coupling of **26** with **27** was studied under a variety of conditions described in the literature.[7] Unfortunately, none afforded a clean reaction that had the potential for scale-up (Scheme 4). This result was somewhat consistent with the observation of Davies et al.,[7a] that reactions of methyl propiolate with 2-fluorobenzyl chloride or 4-trifluoromethylbenzyl chloride gave complex mixtures.

On the other hand, route (c) intermediate allenoate **32** was easily prepared via reaction of **31** with acid chloride **30** under typical Wittig reaction conditions.[8] The subsequent Michael addition with a Meldrum's acid proceeded cleanly to give **34** in 97% yield. With **34** in hand, we envisioned that an intramolecular Friedel–Crafts reaction would directly provide **35** with elimination of acetone and carbon dioxide (Scheme 5). Though catalytic intramolecular Friedel–Crafts reactions of Meldrum's acids have been utilized for the synthesis of 1-tetralones,[9] compound **34** was found to be stable under neutral or weak acidic (e.g., boric acid) conditions; no cyclization was

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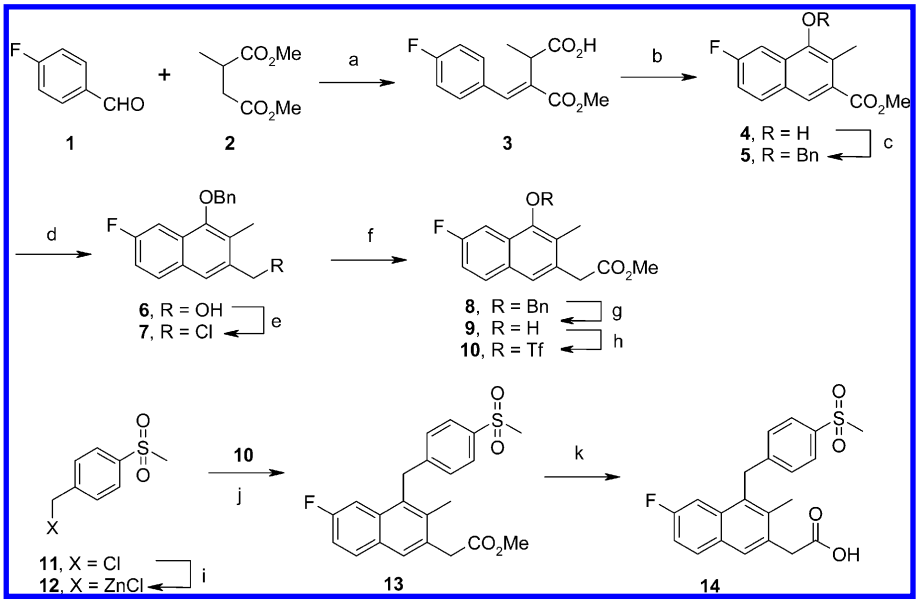
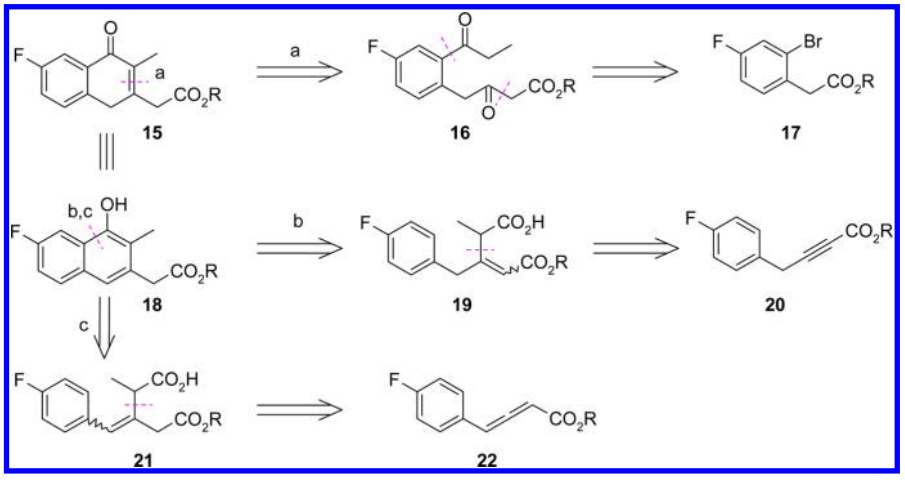
Scheme 1. Original synthesis of 14[a]

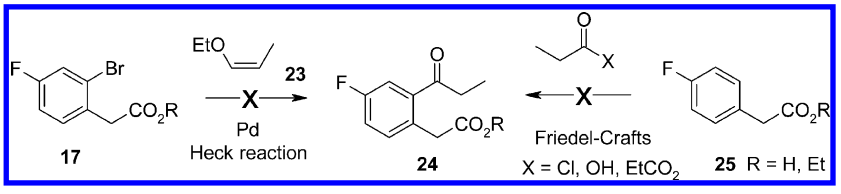


[a]Reagents and conditions: a) NaH, rt, chromatography, 33%; b) (i) $(CF_3CO)_2O$, TEA, (ii) $NaBH_4$, MeOH, chromatography, 80%; c) BnBr, K_2CO_3, chromatography, 94%; d) $LiAlH_4$, 92%; e) PPh_3, CCl_4, chromatography, 83%; f) $Pd(PPh_3)_2Cl_2$, CO, MeOH, chromatography, 97%; g) H_2, 10% Pd/C, 98%; h) Tf_2O, pyridine, CH_2Cl_2, chromatography, 84%; i) Zn, LiCl, $BrCH_2Cl_2Br$, TMSCl, THF; j) $Pd(OAc)_2$ (0.1 equiv), S-Phos (0.2 equiv), chromatography, 98% from **10**; k) aq LiOH, THF, 92%.

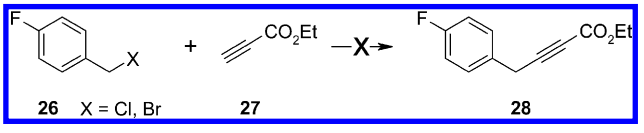
Scheme 2. Retro-synthetic analysis of naphthylacetate 18



Scheme 3. Attempted preparation of precursor 24



Scheme 4. Attempted preparation of 28



observed after stirring in xylene at reflux overnight. With stronger acids, such as acetic acid, decarboxylation occurred, and monoacid **36** was obtained. Treatment of **36** with potassium acetate in acetic anhydride resulted in the formation of a mixed anhydride intermediate which, upon stirring at 80 °C overnight, was converted to a new compound with a molecular weight matching that of **35**. Attempts to isolate this major component in the pure form were not successful as it decomposed during the work-up. ^{1}H NMR spectrum of the crude product showed the coupling pattern of a para-substituted aromatic ring, and LC−MS analysis did not give the expected [M − 1] peak in the negative mode. The lack of

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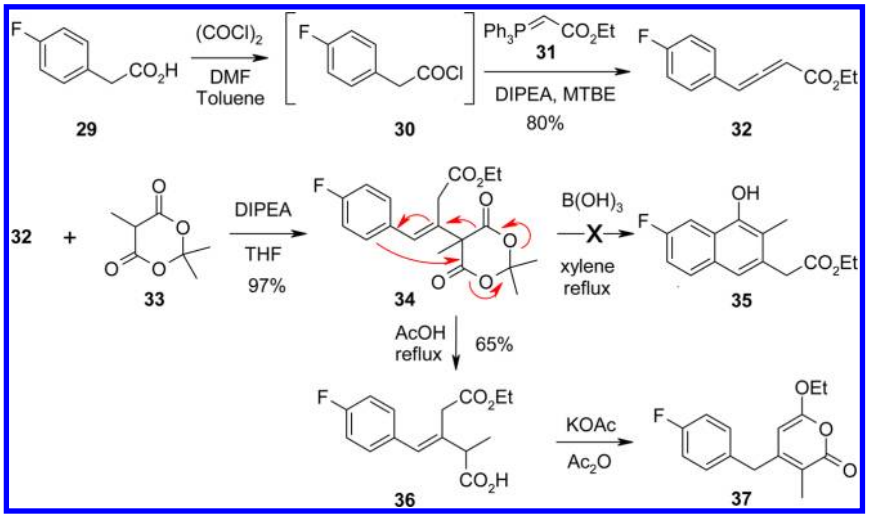
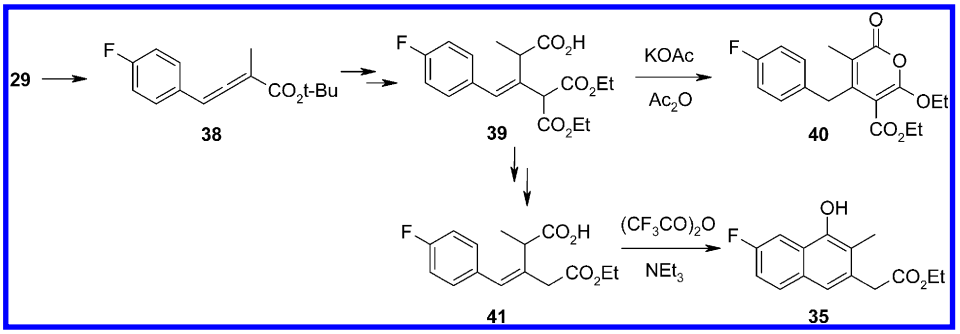
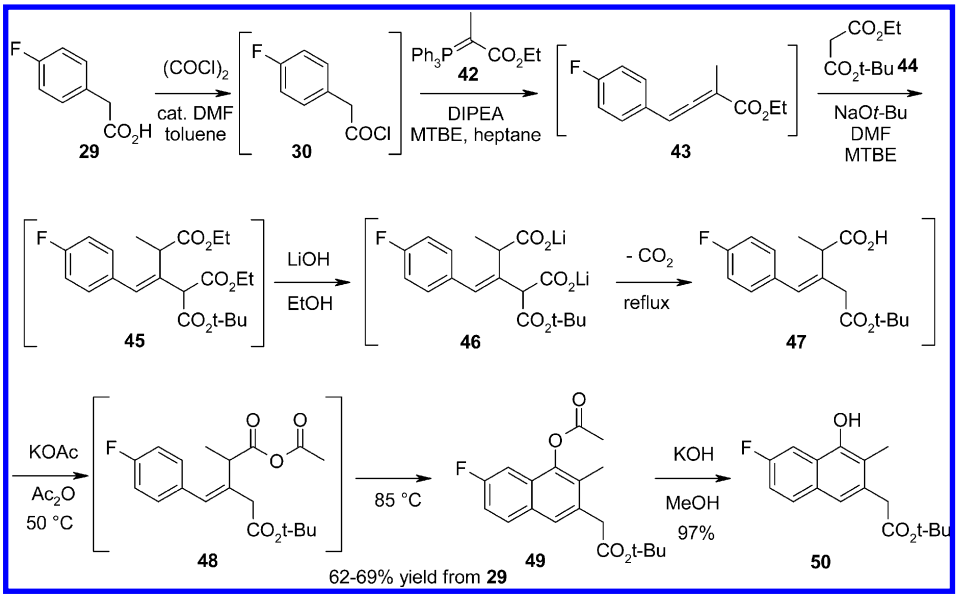
Scheme 5. Attempted preparation of 35 via 34



Scheme 6. Preparation of 35 via 41



Scheme 7. New synthesis of naphthylacetic acid core 50



stability combined with the spectral result suggested that a competing cyclization occurred, and **37** was likely the major product.

Initially, we presumed that the double bond in **36** would migrate or isomerize under the reaction conditions. Therefore, the configuration of this double bond would not be important. The formation of **37** prompted us that a substrate with a *Z*-double bond may be required to suppress this detrimental cyclization pathway. Thus, the *Z*-isomer **41** was prepared in several steps from **29** for evaluation. Although compound **39**, an analogue of **41**, also underwent a similar cyclization pathway as **36** to give **40**, treatment of **41** with trifluoroacetic anhydride and triethylamine indeed afforded the desired cyclization product, presumably via a ketene intermediate. After hydrolysis

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and aqueous work-up, a few milligrams of **35** was obtained after purification by chromatography followed by crystallization (Scheme 6), and its structure was confirmed by NMR analysis.

With the encouraging result of **41**, the synthetic plan was revised, as the preparation of **41** was poorly selective and low yielding. Instead of **38**, allenoate **43** was produced via the Wittig reaction of **30** with phosphorane **42**. Subsequent Michael addition with *tert*-butyl ethyl malonate (**44**) afforded triester **45**, in which the ethyl esters could be selectively hydrolyzed to give the *tert*-butyl ester **46**. Upon heating to reflux, **46** was decarboxylated to give the monoacid monoester **47** containing the desired *Z*-double bond (Scheme 7).

A solution of **30** in toluene and methyl *tert*-butyl ether (MTBE) was added to a suspension of **42** and DIPEA in a mixture of MTBE and *n*-heptane at around 5 °C. The solid byproduct, triphenylphosphine oxide, was removed by filtration, and **43** was obtained as a solution in >97% HPLC purity after aqueous work-up. Compound **43** was not stable at room temperature; HPLC analysis indicated formation of a new broad peak at the level of ∼50% after **43** was stored as a neat oil at room temperature for a week. LC−MS showed a molecular weight of 440, suggesting a dimerization product, presumably **51** (Figure 1). In order to slow this dimerization process, **43**

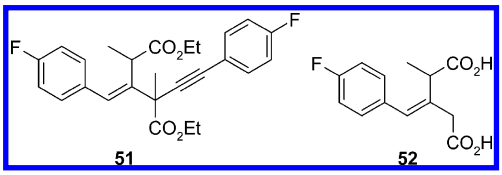


Figure 1. Dimerization product **51** and over-hydrolysis product **52**.

was stored as an MTBE solution at 0 °C prior to further processing. Under these storage conditions, the degradation over one week was <1.5%.

In the Michael addition step, the solution of **43** in MTBE was added to the enolate prepared by addition of **44** to a suspension of sodium *tert*-butoxide in DMF. Triester **45** was obtained as an oil in ∼95% HPLC purity and was directly used in the next step.

The conversion of **45** to **47** was carried out in ethanol by treatment with 3 equiv of lithium hydroxide. Once the hydrolysis was complete, the reaction mixture was heated to reflux to promote the decarboxylation. After careful aqueous work-up, **47** was obtained as an oil in 92−93 area% HPLC purity, which was directly used in the next step without purification. The major byproduct **52** (Figure 1) was removed by washing with aqueous sodium carbonate.

Monoacid **47** was added to a suspension of potassium acetate in acetic anhydride and *n*-heptane. The mixture was warmed to 50 °C to induce the formation of mixed anhydride intermediate **48** (Scheme 7). The reaction temperature was then raised to 85 °C, and the cyclization was complete within 17 h. Upon aqueous work-up, compound **49**, the first crystalline intermediate in the reaction sequence, precipitated from *n*-heptane and was isolated in 99% HPLC purity and 62−69% overall yield from **29**. The acetyl group was then easily hydrolyzed by treatment with aqueous potassium hydroxide. The resulting naphthol **50** was obtained in 97% yield.

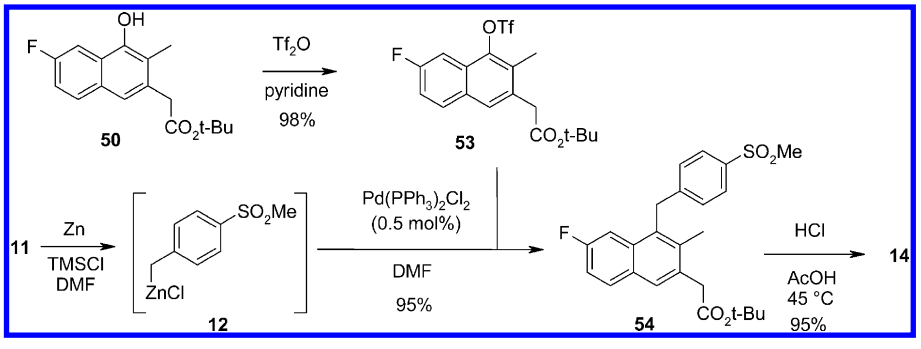
Since the hydrolysis of **45** was carried out in ethanol, the Michael addition to **43** was examined in this solvent using sodium ethoxide as the base. The resulting solution of **45** in ethanol was treated with NaOH (2 equiv), and decarboxylated to afford **47** as the major product. While this process eliminated the isolation of **45**, the downstream steps using this material, however, gave **49** in lower yield and quality.[10]

Final Coupling and Hydrolysis. Triflate **53** was prepared by the reaction of **50** with triflic anhydride using pyridine as the base. After aqueous work-up, **53** was crystallized from DMF−water and collected by filtration in 98% yield (Scheme 8).

The Negishi coupling of triflate **53** with **12** was very problematic. In the original synthesis, this step was carried out under typical conditions (Scheme 2).[11] A mixture of predried zinc dust and lithium chloride was dried under high vacuum at 170 °C and then suspended in anhydrous THF and treated three times with 1,2-dibromoethane at reflux, followed by further treatment with trimethylchlorosilane. This zinc activation process is highly exothermic with vigorous foaming that clearly cannot be run on a large scale. In the absence of lithium chloride, the zinc activation was slightly less exothermic, but the subsequent Negishi coupling was found to be inconsistent. Since compound **11** is a benzyl chloride, which should be relatively reactive to zinc, such a harsh zinc activation process may not be necessary. A traditional zinc activation method[12] was thus investigated. Zinc dust was suspended in DMF and treated with trimethylchlorosilane (0.1 equiv to **53**). This activation process was only mildly exothermic; with 237 g of zinc, only a 5 °C temperature increase was observed over a period of 30 min. Hydrogen chloride, which was generated from trimethylchlorosilane and residual water in DMF, was the actual reagent for the zinc surface cleaning. On scale-up, when the water level in the DMF was lower, it was compensated by the addition of isopropanol.

After activation of the zinc, a portion (20−50%) of a DMF solution of **11** was added, and the temperature was raised to 30−45 °C. Once the zinc insertion was initiated, the remaining

Scheme 8. Improved Negishi coupling of 53



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solution of **11** was added slowly to maintain the temperature at ~45 °C. The reaction was typically complete within 1 h. An excess of zinc (3 equiv to **53**) was required to suppress the formation of the homocoupling product **55** (Figure 2).

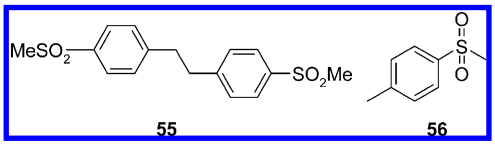

Figure 2. Byproducts from the Negishi coupling step.

The loadings of the palladium acetate and S-Phos were also reduced to 0.5 and 1.0 mol %, respectively. However, even at this level, the cost of the S-Phos was still considered too high for large-scale production. Therefore, a readily available and inexpensive palladium complex, bis(triphenylphosphino)palladium chloride, was tested, and the reaction worked equally well using a 0.5 mol % loading.

Due to safety concerns with transferring a zinc reagent from one vessel to another in the lab setting, the coupling step was carried out in one pot. Thus, to the zinc reagent, prepared as described above, was added $Pd(PPh_3)_2Cl_2$ (0.5 mmol %), followed by **53** as a solid in one portion. Since no reaction occurred below 50 °C, the reaction mixture was warmed to ~60 °C. The coupling was initiated at this temperature and was complete within 30 min to 1 h as indicated by HPLC analysis. The reaction mixture was quenched with water and diluted with isopropyl acetate. The resulting mixture was treated with *N*-acetyl-L-cysteine to assist in removal of the palladium catalyst. After crystallization from isopropyl acetate−*n*-heptane, compound **54** was collected by filtration in 95% yield and >99% purity as a white solid. The two major byproducts, **55** and **56** (Figure 2), were easily removed as they remained in the filtrate.

The reaction has been successfully and consistently carried out multiple times on a 500-g scale. However, once the reaction was initiated at 60−65 °C, a 30 °C temperature increase over 10 min was observed, while the external heating was removed. Attempts to control the exotherm by a slow addition of **53** in DMF to a preheated mixture of **12** in the presence of the catalyst resulted in inconsistent reactions. In addition, once the reaction stalled, it could not be resumed unless fresh zinc reagent **12** was added, indicating that the zinc reagent may lose reactivity in the reaction media. Therefore, for further scale-up, adding a solution of **12** to the mixture of **53** and the catalyst might be still required,[13] or alternatively, the reaction could be run in a continuous manner.[14]

The hydrolysis of **54** to **14** was carried out in acetic acid with HCl at ~45 °C. The reaction was complete within 30 min to give a thick slurry. After aqueous work-up, **14** was isolated by filtration in 95% yield and >99.5% purity as a white solid. The residual metal level was well controlled: 6 ppm of palladium and 20 ppm of zinc.

CONCLUSION

In summary, we have developed a new synthesis of a potent CRTH2 antagonist in eight linear steps and 53% overall yield from readily available **29**. A novel telescoped process for the preparation of naphthylacetate **49** from allenoate **43** has been successfully carried out in the pilot-plant scale. Negishi coupling between **53** and **12** under improved conditions was successfully carried out at 500-g scale to produce >2 kg of the API. Additional development work would be required for further scale-up.

EXPERIMENTAL SECTION

General. HPLC analyses were performed using an Agilent 1100 system with a HALO C8 (100 mm × 3 mm, 2.7 μm) column, 30−100% CH_3CN−water (+0.1% TFA) as mobile phase at flow rate of 0.5 mL/min over 10 min, and UV detection at 260 nm. HRMS (ESI, positive mode) was obtained by an orbit-trap mass analyzer. Zinc dust (≤10 μm) was purchased from Sigma-Aldrich and used as received.

4-(4-Fluorophenyl)-2-methylbuta-2,3-dienoic Acid Ethyl Ester (43). A reactor was sequentially charged with 4-fluorophenylacetic acid **29** (8.24 kg, 53.4 mol), DMF (0.95 kg, 1.30 mol), and toluene (34 kg). While agitating at 21−26 °C, oxalyl chloride (7.6 kg, 59.9 mol) was added via a metering pump. The resulting mixture was agitated at 18−20 °C for 33 min, then concentrated under reduced pressure to ~20 L. The resulting concentrate was diluted with MTBE (16 kg) to give a solution of **30** in MTBE−toluene.

A reactor was charged with (carboethoxyethylidene)-triphenylphosphorane **42** (20.0 kg, 55.2 mol) and MTBE (45 kg). The resulting suspension was agitated at ~20 °C for 12 h,[15] and then DIPEA (8.5 kg, 65.8 mol) and MTBE (30 kg) were added. After the mixture was cooled to 7 °C, the solution of **30** from above was added over 2.3 h, and the empty reactor was rinsed with MTBE (8 kg). The resulting suspension was agitated at 5−6 °C for 30 min and then dropped into a centrifuge. The collected solid was washed with MTBE−*n*-heptane (1:1 mixture, three times, total 79 kg). The combined filtrate and wash were charged back to the reactor. Then a mixture of citric acid (50%, 15 kg) in water (28 kg) was cautiously added over 41 min at ~9 °C. The organic layer was separated and washed with water (2 × 41 kg) and then concentrated and diluted with MTBE (7.4 kg) to give a solution of **43** in MTBE (~40 kg, 53.4 mol in theory). ^{1}H NMR (300 MHz, DMSO-d_6) 7.35 (m, 2H), 7.20 (m, 2H), 6.82 (q, J = 2.9 Hz, 1H), 4.14 (m, 2H), 1.92 (d, J = 2.9 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)[16] 211.35, 129.09, 129.01, 128.50, 116.01, 115.79, 98.68, 96.02, 60.78, 14.89, 14.12; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_2F$ $[M + H]^+$ 221.0978, found 221.0976.

2-Ethoxycarbonyl-3-[1-(4-fluorophenyl)meth-(*E*)-ylidene]-4-methylpentanedioic Acid 1-*tert*-Butyl Ester 5-Ethyl Ester (45). A 400 L reactor was charged with NaO*t*Bu (5.34 kg, 55.6 mol) and DMF (77 kg). *t*-Butyl ethyl malonate **44** (11.5 kg, 61.1 mol) was added over 1 h at ~20 °C, followed by the solution of **43** (~40 kg, 53.4 mol in theory) from above over 100 min. The empty drum was rinsed with MTBE (7 kg), which was added to the reactor. The resulting solution was agitated at ~20 °C for 70 min, after which HPLC analysis indicated an acceptable level of 0.31 area % of **43**. The reaction mixture was then diluted with MTBE (45 kg). After the mixture was cooled to 15 °C, AcOH (4.0 kg, 66.6 mol) was cautiously added over 20 min at ~15 °C, followed by water (66 L) over 40 min at 18 ± 3 °C. The organic phase was separated, washed with water (2 × 50 kg), and concentrated to dryness at 16−34 °C/5−100 mmHg vacuum (85.5 L of solvent was removed) to give **45** (~21.8 kg, 53.4 mol in theory) as an oil. The resulting material was used directly in the next step without further purification. ^{1}H NMR analysis showed a mixture of triester and its enol forms. HRMS (ESI) m/z calcd for $C_{22}H_{29}FO_6Na$ $[M + Na]^+$ 431.1846, found 431.1833.

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3-[1-(4-Fluorophenyl)meth-(*Z*)-ylidene]-2-methylpentanedioic Acid 5-*tert*-Butyl Ester (47). The 400 L reactor, containing **45** (~21.8 kg, 53.4 mol in theory) from above, was charged with ethanol (88 kg). The mixture was cooled to 15 °C, and a solution of LiOH (6.9 kg, 164 mol) in water (157 L) was added over 80 min at ~15 °C. The resulting mixture was agitated at ~18 °C for three days[17] and then heated to 82 °C for 4.5 h and concentrated to remove 125 L of solvents at 23−35 °C/10−60 mmHg. The concentrate was diluted with MTBE (80 kg) and cooled to <8 °C. The pH was then cautiously adjusted to 3.0 with conc. HCl (16.0 kg) at ~8 °C. The organic phase was separated and successively washed with water (61 L), a mixture of water (61 L), and 15 wt % aq Na_2CO_3 (5.3 kg), and a 2 wt % aq NaCl (60 kg). Then it was transferred to a drum with a MTBE rinse (7.5 kg). The resulting solution of **47** in MTBE (~83.3 kg, 53.4 mol in theory) was charged to a 200 L reactor and then concentrated by vacuum distillation at 15−17 °C/130−165 mmHg until 70 L of solvent had been removed. The concentrate was diluted with MTBE (40 kg), and the distillation was resumed at 23 °C/60 mmHg until no distillate was collected (62.5 L of solvent was removed) to give **47** (16.5 kg, 53.4 mol in theory) as an oil. Karl Fischer analysis indicated the presence of 0.82 wt % water. This material was used directly in the next step without further purification.

***tert*-Butyl-(4-acetoxy-6-fluoro-3-methylnaphthalen-2-yl)acetate (49).** The 200 L reactor, containing **47** (16.5 kg, 53.4 mol in theory) from above, was charged with Ac_2O (42.3 kg), *n*-heptane (27 kg), and KOAc (7.74 kg, 79.0 mol). The mixture was heated to 50 °C for 1.1 h and at 85−86 °C for 17 h; HPLC analysis indicated the presence of 0.12 area % of **48**. While the mixture was maintained at 19−25 °C, water (3 L) was added in three portions over a period of 1.5 h. Then, additional water (73 L) was added over 70 min. The resulting suspension was agitated at 22−23 °C for 4.3 h and then dropped into a centrifuge. The collected solids were washed with potable water (5 L) and *n*-heptane (28 kg) and then dried to give **49** (11.0 kg, 62% overall yield from **29**, 98.8% HPLC purity) as an off-white solid. Mp 150−151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.78 (dd, J = 9.1, 5.6 Hz, 1H), 7.61 (s, 1H), 7.31 (dd, J = 10.1, 2.6 Hz, 1H), 7.21 (td, J = 8.6, 2.6 Hz, 1H), 3.73 (s, 2H), 2.50 (s, 3H), 2.26 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6)[16] 170.09, 169.00, 161.77, 159.34, 143.75, 143.69, 132.62, 132.59, 130.58, 130.49, 129.07, 127.95, 126.69, 126.60, 116.23, 115.97, 104.91, 104.69, 80.42, 27.63, 20.41, 12.68; HRMS (ESI) m/z calcd for $C_{19}H_{21}FO_4Na$ $[M + Na]^+$ 355.1322, found 355.1311.

***tert*-Butyl-(6-fluoro-4-hydroxy-3-methylnaphthalen-2-yl)acetate (50).** To a mixture of **49** (1.45 kg, 4.36 mol) and methanol (8.7 L) was added potassium hydroxide (303 g, 5.40 mol) portionwise over 10 min. The reaction mixture was stirred at 20−28 °C for 30 min, and then water (5.8 L) was added, followed by the dropwise addition of conc. HCl (405 mL, 4.93 mol). The resulting suspension was filtered, and the filter cake was washed successively with MeOH−water (1:1, 2 × 3.6 L) and water (4.2 L), and dried to give **50** (1.23 kg, 97% yield) as a white solid. Mp 131−132 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 9.09 (s, 1H), 7.86−7.76 (m, 2H), 7.35−7.26 (m, 2H), 3.71 (s, 2H), 2.24 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6)[16] 170.47, 160.74, 158.33, 149.21, 149.16, 132.87, 132.85, 130.05, 129.96, 129.21, 125.10, 125.01, 120.66, 120.64, 119.90, 115.36, 115.10, 105.35, 105.13, 80.15, 40.67, 27.68, 12.40; HRMS (ESI) m/z calcd for $C_{17}H_{18}FO_3Na$ $[M + Na - H]^+$ 312.1138, found 312.1128.

***tert*-Butyl-(6-fluoro-3-methyl-4-trifluoromethanesulfonyloxynaphthalen-2-yl)acetate (53).** A 22 L flask was charged with **50** (1.23 kg, 4.24 mol), CH_2Cl_2 (7.1 L), and pyridine (686 mL, 8.48 mol). After the solution was cooled to 2 °C, Tf_2O (857 mL, 5.09 mol) was added over 40 min at 7 ± 5 °C. The resulting red solution was warmed to 18 °C, and quenched with 1 M citric acid (5.1 L, 5.10 mol). The organic layer was separated, washed with water (2 × 6.5 L), and concentrated at 25 °C/100 mmHg to remove most of the solvent. The residue was diluted with DMF (4.9 L) and further concentrated. The remaining solution was warmed to 33 °C, and water (4.9 L) was added over 1 h. The resulting suspension was stirred at room temperature for 2.5 h and then filtered. The filter cake was washed with DMF−water (1:1, v/v, 2 × 1.9 L) and water (2 × 2.8 L) and dried to give **53** (1.76 kg, 98% yield) as an off-white solid. Mp 87−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.81 (dd, J = 8.8, 5.3 Hz, 1H), 7.72 (s, 1H), 7.64 (dd, J = 10.4, 2.6 Hz, 1H), 7.29 (td, J = 8.8, 2.6 Hz, 1H), 3.75 (s, 2H), 2.50 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$)[16] 169.87, 162.82, 160.35, 142.50, 142.45, 132.47, 132.44, 130.24, 130.15, 130.10, 129.78, 129.27, 129.25, 127.27, 127.17, 123.43, 120.25, 117.26, 117.07, 117.00, 113.89, 105.40, 105.17, 81.85, 40.95, 27.91, 14.13; HRMS (ESI) m/z calcd for $C_{18}H_{18}O_5F_4NaS$ $[M + Na]^+$ 445.0709, found 445.0704.

***tert*-Butyl-[6-fluoro-4-(4-methanesulfonylbenzyl)-3-methylnaphthalen-2-yl]acetate (54).** A 12 L flask was charged with zinc dust (237 g, 3.63 mol), DMF (750 mL), and *i*PrOH (8 mL, 0.10 mol). TMSCl (15.2 mL, 0.12 mol) was added, and the suspension was stirred at room temperature for 30 min. Then, a solution of **11** (173 g, 0.84 mol) in DMF (375 mL) was added. The mixture was warmed to 30 °C to initiate the reaction. Once the internal temperature reached 45 °C, the remaining solution of **11** (173 g, 0.84 mol) in DMF (375 mL) was added dropwise over 20 min at ~45 °C. $PdCl_2(PPh_3)_2$ (4.24 g, 6.04 mmol) was added, followed by **53** (500 g, 1.18 mol), and the mixture was warmed to 60 °C to initiate the reaction. Without further heating, the internal temperature increased to 86−95 °C over 10−15 min and then started to decrease. After stirring at 65−85 °C for 2.5 h, the reaction mixture was quenched with water (75 mL).

This reaction was repeated five times as described above, and the reaction mixtures from all six runs were combined, diluted with *i*PrOAc (15 L), and filtered through a pad of Celite (2.5 kg). The pad was washed with *i*PrOAc (3 × 5 L), and the combined filtrates were transferred to an extractor. *N*-Acetyl-L-cysteine (54.0 g, 0.33 mol) was added, and the mixture was stirred at room temperature for 2 h, and then diluted with water (7 L) and *i*PrOAc (2 L). The organic layer was separated and washed successively with a mixture of DMF (8 L), 5 wt % aqueous NaCl (8 L), and water (16 L), and then diluted with *n*-heptane (15 L). The resulting suspension was filtered, and the filter cake was washed with *n*-heptane (2 × 4 L) and dried to give **54** (2.10 kg, 67% yield, 99.3% HPLC purity) as a white solid. Additional **54** (865 g, 28% yield, 99.3% HPLC purity) with identical purity was recovered from the filtrate after additional aqueous washes followed by crystallization. Mp 148−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.82−7.78 (m, 3H), 7.68 (s, 1H), 7.38 (dd, J = 11.8, 2.6 Hz, 1H), 7.24 (m, 2H), 7.20 (td, J = 8.8, 2.6 Hz, 1H), 4.54 (s, 2H), 3.78 (s, 2H), 3.03 (s, 3H), 2.36 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$)[16] 170.83, 162.36, 159.93, 146.41, 138.40, 135.52, 132.95, 132.86, 131.94, 131.91, 131.66, 131.61, 130.83, 130.74, 129.32, 129.00, 128.88, 127.73, 115.57, 115.32, 107.59, 107.38,

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81.20, 44.56, 41.83, 34.70, 28.04, 16.52; HRMS (ESI) m/z calcd for $C_{25}H_{27}O_4FNaS$ $[M + Na]^+$ 465.1512, found 465.1508.

[6-Fluoro-4-(4-methanesulfonylbenzyl)-3-methylnaphthalen-2-yl]acetic Acid (14). Three 22 L flasks were each charged with **54** (989 g, 2.23 mol), water (495 mL), AcOH (6.9 L), and conc. HCl (989 mL, 12.0 mol). Each mixture was stirred at ~47 °C for 90 min, and then water (8 L) was added. The contents of the three flasks were poured into a table-top funnel, and the collected solid cake was washed with water (2 × 6 L) and dried to give **14** (2.47 kg, 95% yield, 99.5% HPLC purity) as a white solid. Mp 209−210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 12.46 (s, 1H), 7.94 (dd, J = 9.0, 6.2 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.79 (s, 1H), 7.68 (dd, J = 12.1, 2.3 Hz, 1H), 7.35 (td, J = 8.6, 2.3 Hz, 1H), 7.30 (d, J = 8.4, 2H), 4.60 (s, 2H), 3.84 (s, 2H), 3.16 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)[16] 172.71, 161.63, 159.22, 146.41, 138.54, 135.85, 132.66, 132.63, 132.41, 132.33, 132.28, 132.22, 130.98, 130.89, 129.01, 128.65, 127.22, 115.25, 115.00, 107.76, 107.55, 43.56, 39.99, 33.67, 16.23; HRMS (ESI) m/z calcd for $C_{21}H_{19}FO_4NaS$ $[M + Na]^+$ 409.0880, found 409.0880.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra of compounds **14**, **40**, **43**, **45**, **47**, **49**, **50**, **53**, and **54**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) ^{13}C NMR showed more peaks than the number of inequivalent carbons due to F−C coupling.

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