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Development of an Early Enabling Synthesis for PF-03052334-02: A Novel Hepatoselective HMG-CoA Reductase Inhibitor

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Abstract:

Early process development work toward a promising pyrazole-based HMG-CoA reductase inhibitor is described. PF-03052334-02 (1) was prepared in 14 synthetic steps with a 21% overall yield, highlighted by a modified three-step hydroxypyrazole formation in which the yield was improved from 37% to 73%, a Suzuki/ozonolysis pathway that streamlined the downstream chemistry, and a reversed Wittig olefination strategy that improved the key coupling step from 50% to 95% yield. Multiple process hazards and most chromatography steps were removed, and a highly effective active pharmaceutical ingredient (API) salt formation, purification, and isolation protocol was also developed.

Introduction

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors,[1] are regularly prescribed in the battle against coronary heart disease (CHD).[2,3] While statins are generally well tolerated, musculoskeletal side effects such as myalgia can limit compliance with treatment regimens; moreover, in rare cases these musculoskeletal effects can progress to a serious and life-threatening condition known as rhabdomyolysis.[4] During ongoing studies, our Discovery Chemistry colleagues became interested in pyrazole **PF-03052334-02** (**1**, Figure 1), an HMG-CoA reductase inhibitor[5] characterized by promising efficacy and high hepatoselectivity that may lead to reduced risk of musculoskeletal effects.[6]

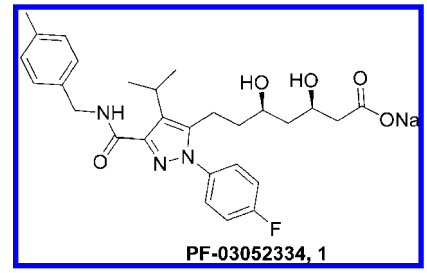

Figure 1. **HMG-CoA reductase inhibitor candidate PF-03052334 (1).**

First-Generation Route. While the original medicinal chemistry route (Scheme 1)[5] was effective at generating a variety of analogues, it was relatively linear, and as a result the throughput was somewhat low (5.6% yield over 15 linear steps).[7] The synthesis also contained several nonprocess-friendly steps by using diazonium chemistry, a nitrilimine formation, a 1,3-dipolar cycloaddition reaction that afforded a regioisomeric mixture, ceric ammonium nitrate oxidation, and a tedious borane/Dess−Martin reduction/oxidation sequence all in order to reach intermediate pyrazole aldehyde **11**.

In addition, the downstream conversion of aldehyde **11** to **1**, while capable of supporting the manufacture of subgram active pharmaceutical ingredient (API) quantities, was not convenient for further scale-up (Scheme 2). $NaBH_4$ reduction of amide **14** was followed by treatment with Ph_3P•HBr, and resulting ylide **16** was treated with costly and unstable aldehyde **17**[8] to afford only a 50% yield of **18** as a mixture of cis/trans isomers.[9] The mixture was deprotected, reduced, and saponified to produce **1** as an amorphous foam that was contaminated with inorganic impurities.

Further complicating the early route, nearly every step required cleanup by silica gel chromatography. As a result, the original route totaled >25 operational steps when considering scale up into our kilo-lab facility. With an increasing demand for API in support of early toxicological and clinical studies, it became critical to develop a second generation route capable of delivering hundred-gram quantities of **1**. In designing such

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(1) McKenney, J. M. *Clin. Cardiol. (Suppl. III).* **2003**, *26*, 32–38.
(2) Grundy, S. M. *J. Intern. Med.* **1997**, *241*, 295–306.
(3) Jones, P.; Kafonek, S.; Laurora, I.; Hunninghake, D. *Am. J. Cardiol.* **1998**, *81*, 582–587.
(4) Cerivastatin was withdrawn from the world market because of its potential for severe myotoxic effects. For reviews, see: (a) Rosenson, R. *Am. J. Med.* **2004**, *116*, 408–416. (b) Tiwari, A.; Bansal, V.; Chugh, A.; Mookhtiar, K. *Expert Opin. Drug Saf.* **2006**, *5*, 651–666. For related information see: (c) Graham, D. J.; Staffa, J. A.; Shatin, D.; Andrade, S. E.; Schech, S. D.; La Grenade, L.; Gurwitz, J. H.; Chan, K. A.; Goodman, M. J.; Platt, R. *JAMA* **2004**, *292*, 2585–2590.
(5) Pfefferkorn, J. A.; Choi, C.; Larsen, S. D.; Auerbach, B.; Hutchings, R.; Park, W.; Askew, V.; Dillon, L.; Hanselman, J. C.; Lin, Z.; Lu, G. H.; Robertson, A.; Sekerke, C.; Harris, M. S.; Pavlovsky, A.; Bainbridge, G.; Caspers, N.; Kowala, M.; Tait, B. D. *J. Med. Chem.* **2008**, *51*, 31–45.
(6) For a review of other recent hepatoselective statins, see: Pfefferkorn, J. A. *Curr. Opin. Invest. Drugs* **2009**, *10*, 245–252.
(7) Total step count does not include additional operations necessary for silica gel chromatography cleanup and for the synthesis of Konoike ylide **32**.
(8) Rádl, S. *Synth. Commun.* **2003**, *33*, 2275–2283.
(9) The mixture of cis/trans isomers was not considered an issue because the olefin is reduced downstream.

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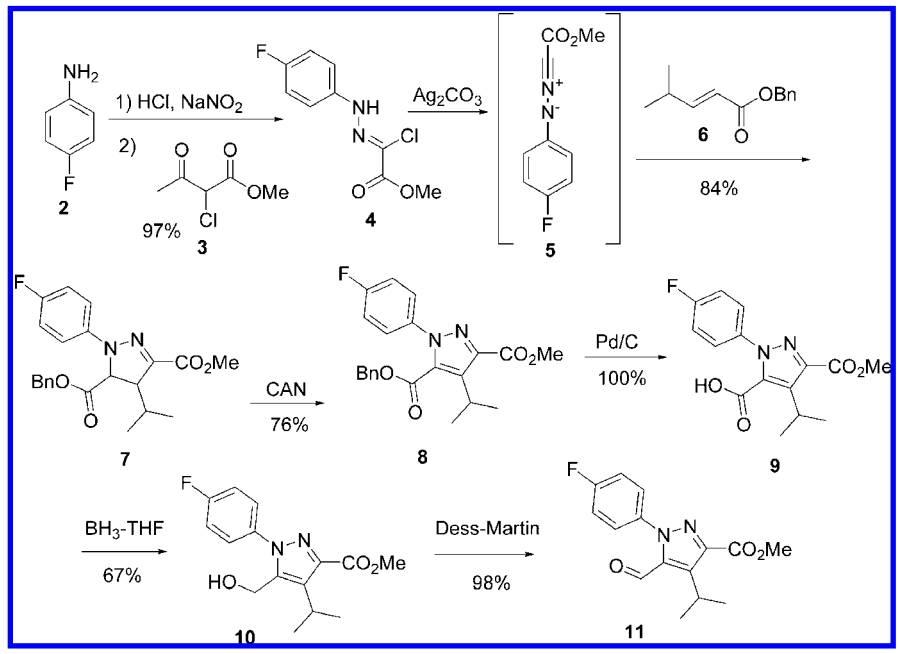
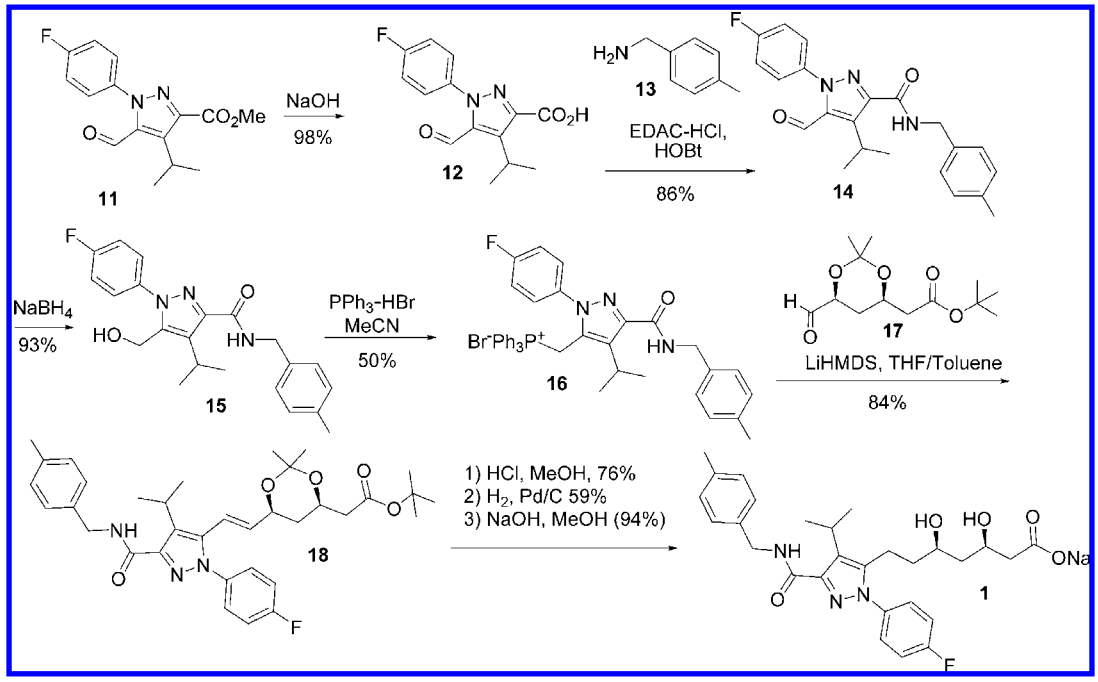
Scheme 1. **First-generation route to pyrazole aldehyde 11**



Scheme 2. **First-generation endgame**



a route, we sought to remove the most hazardous and nonscalable steps while eliminating the need for silica gel chromatography.

Results and Discussion

Hydroxypyrazole Synthesis. Based on a route previously developed by our medicinal chemistry colleagues toward a related oxypyrazole series,[10] we were able to readily synthesize hydroxypyrazole **24b** as a key intermediate for the second generation synthesis of **1** (Scheme 3).

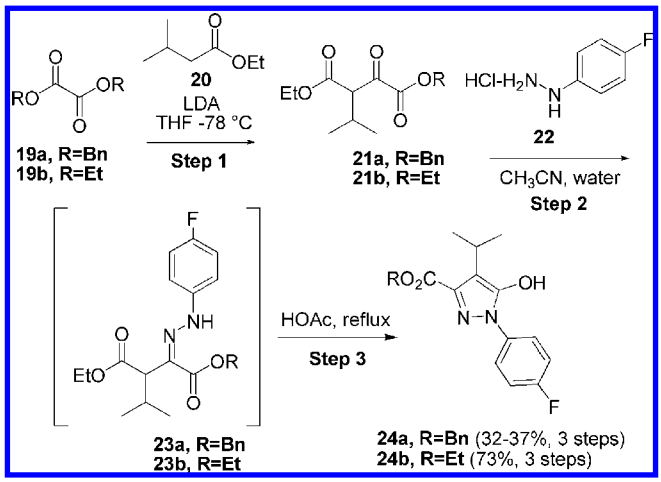
While the original medicinal chemistry synthesis afforded only a 32−37% yield of corresponding benzyl ester **24a**, we were able to improve the three step yield of **24b** to 73% by using diethyl oxalate instead of dibenzyl oxalate.[11] Cryogenic treatment of a THF solution of ethyl isovalerate **20** with LDA followed by slow addition of **19b** afforded oxalate-ester **21b**, which after aqueous workup was treated with 4-fluorophenylhydrazine hydrochloride **22** in aqueous acetonitrile to produce hydrazone **23b** (not isolated). Acetonitrile was exchanged with refluxing acetic acid, during which time ring closure resulted in smooth conversion to **24b**. The crude product was isolated by crystallization from toluene/heptane in 73% yield (99% regioselectivity,[12] >99% HPLC purity) in over three steps on

(10) Larsen, S. D.; Poel, T. J.; Filipski, K. J.; Kohrt, J. T.; Pfefferkorn, J. A.; Sorenson, R. J.; Tait, B. D.; Askew, V.; Dillon, L.; Hanselman, J. C.; Lu, G. H.; Robertson, A.; Sekerke, C.; Kowala, M. C.; Auerbach, B. J. Bioorg. Med. Chem. Lett. **2007**, *17*, 5567–5572.

(11) Yield improvement is attributed to enhanced stability of the oxalate to reaction conditions and ease of purification by crystallization.

(12) The >99% regioselectivity was determined by chiral HPLC vs chiral standards and verified by ^{1}H NMR.

Scheme 3. **Synthesis of hydroxypyrazole 24**



21 kg scale. In one pilot batch, cooling was lost during the oxalate addition, and the reaction temperature reached −30 °C. As a result, the three step process afforded **24b** of poor quality (<50% purity).

Pyrazole Activation. With a steady supply of **24b** in hand, we focused our effort toward conversion of the hydroxyl functionality into a more suitable handle for dihydroxyester side-chain attachment.[13] A retrosynthetic analysis (Scheme 4) based on a wealth of literature examples[14] highlighted several potential alternatives to the medicinal chemistry approach (*Wittig Route 1*) including direct pyrazole alkylation, metal-mediated coupling, or reversing the Wittig partners (*Wittig Route 2*). Unfortunately, the most convergent of these options met with the most difficulty. In particular, a general lack of activity toward pyrazole lithiation ruled out a direct alkylation approach,[15] and attempts toward halogenation (formation of **25**) followed by metal−halogen exchange were also not successful (Scheme 5). In addition, we observed that coupling unsaturated dihydroxyester side-chain moieties to an activated pyrazole core (Suzuki, Sonagashira, Heck coupling) were not feasible in our hands toward substrates such as **28**.[16] Instead, we converted the hydroxyl group in **24b** to its corresponding triflate by treatment with trifluoromethanesulfonic anhydride and triethylamine in dichloromethane. Following aqueous workup, the crude product mixture was crystallized from aqueous 2-propanol to provide **26** in 95% yield with >99% HPLC purity on 4.5 kg scale.

Activation and Coupling. As illustrated in Scheme 6, we found it difficult to couple triflate **26** with complex dihydroxyester boronic acid moieties such as **27**; however, we observed that styrenylboronic acid **29** was an effective coupling partner. Thus, we investigated a Suzuki/ozonolysis route to pyrazole aldehyde **11b**. Unfortunately, we initially observed that the Suzuki coupling was not robust upon scale-up.[17] However, after reaction optimization screening we observed that dichlorobis-(triphenylphosphine)palladium(II) with a 4:1:1 ratio of toluene/isopropyl alcohol/water was quite effective for this transformation. A series of bases and additives were also screened, and the combined use of potassium carbonate with either potassium bromide or benzyltriethylammmonium chloride significantly improved conversion to pyrazole **30**, which was conveniently crystallized and filtered from the crude reaction mixture in 91% yield (>98% purity) on 3.5 kg scale.

Ozonolysis and Amide Formation. The styrene functionality in **30** (Scheme 6) was readily cleaved in batch mode on 750 g scale by bubbling ozone gas through a cryogenic solution in dichloromethane and methanol followed by quenching with dimethylsulfide. Crude workup resulted in isolation of aldehyde **11b** in 76% yield.

The resulting crude ester was saponified with sodium hydroxide in aqueous methanol and was extracted into DCM to afford **31** in good yield (75%). Activation with EDAC·HCl/HOBt followed by treatment with 4-methylbenzylamine in DMF/DCM at 0 °C formed amide **14**, which was isolated by aqueous workup followed by crystallization from acetonitrile in 89% yield with >97% HPLC purity on 400 g scale.

Considering the hazardous potential with batch ozonolysis on scale, we also sought to investigate a flow-ozonolysis approach to conversion of **30** to **14**. Over 1 kg of **30** was treated with ozone in a flow-manner using a relatively simple home-made reactor,[18] in which a steady stream of ozone was bubbled through a flowing countercurrent of olefin solution in a mixing tube. The resulting ozonide solution was directed into a stirring quench tank with dimethylsulfide in methanol to afford what was thought to be aldehyde **11b**. Unfortunately, the batch of **30** used in this case was isolated differently than previous batches and was likely contaminated with residual HCl,[19] and as a result dimethylacetal **11c**[20] was the major ozonolysis product (Scheme 7) in our flow campaign. Fortunately, the flow-ozonolysis batch was recovered by saponification followed by hydrolysis of the acetal with aqueous TFA in DCM to afford **31** in 60% yield on 500 g scale.

(13) For a recent review article related to the synthesis of statins, see: Èasar, Z. *Curr. Org. Chem.* **2010**, *14*, 816–845.

(14) Additional references from a retrosynthetic approach include: (a) Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Seo, S.; Hirai, K. *Bioorg. Med. Chem.* **1997**, *5*, 437–444. (b) Easar, Z.; Tramšek, M.; Goršek, A. *Acta Chim. Slov.* **2010**, *57*, 66–76. (c) Kim, H. S.; Kim, H.; Sim, J. Y.; Cho, S. M.; Kim, W. J.; Suh, K. H.; Lee, G. S. PCT Int. Appl. 41, 2010. (d) Wu, X.; Wang, L.; Wang, S.; Chen, Y. *Amino Acids* **2010**, *39*, 305–308. (e) Hobson, L. A.; Akiti, O.; Deshmukh, S. S.; Harper, S.; Katipally, K.; Chiajen, J.; Livingston, R. C.; Lo, E.; Miller, M. M.; Ramakrishnan, S.; Shen, L.; Spink, J.; Tummala, S.; Wei, C.; Yamamoto, K.; Young, J.; Parsons, R. L. *Org. Process Res. Dev.* **2010**, *14*, 441–458. (f) Liljeblad, A.; Kallinen, A.; Kanerva, L. T. *Curr. Org. Synth.* **2009**, *6*, 362–379. (g) Job, A.; Stolle, A. *Asymmetric Synth.* **2007**, *1*, 326–330. (h) Bergeron, S.; Chaplin, D. A.; Edwards, J. H.; Ellis, B. S. W.; Hill, C. L.; Holt-Tiffin, K.; Knight, J. R.; Mahoney, T.; Osborne, A. P.; Ruecroft, G. *Org. Process Res. Dev.* **2006**, *10*, 661–665.

(15) A wide variety of pyrazole esters and amides were found to be either unreactive or unstable when treated with alkyllithium bases in our hands. It is unknown whether alkyllithium bases deprotonated the methine proton, possibly leading to further decomposition pathways.

(16) We were unsuccessful in converting the hydroxyl functionality to its halogen counterpart. We continue to study alternate methods for hydroxypyrazole activation and intend to publish related work in a future manuscript. In particular, failed attempts toward forming substrate **28** via Suzuki with activated pyrazoles seemed to result more from relatively poor stability of a variety of coupling partners similar to **27** in our hands.

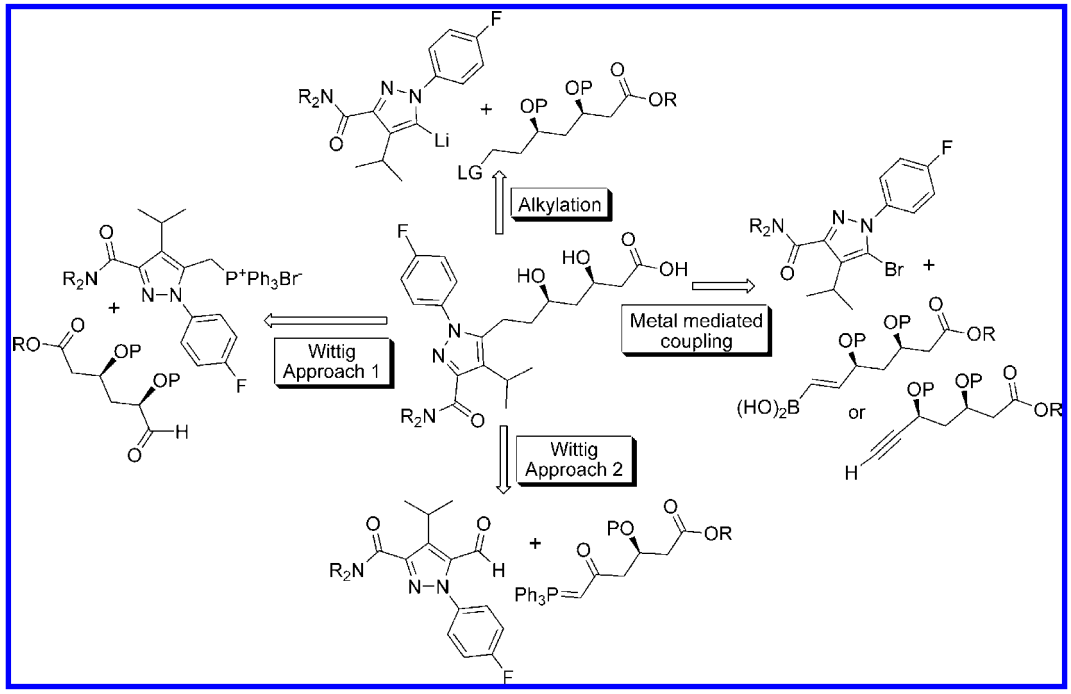
(17) In early Suzuki trials we observed significant decomposition (30−50%) of the triflate. Optimization of the catalyst, solvent system, base, and additives reduced decomposition to the corresponding hydroxy-pyrazole almost entirely.

(18) A similar setup was described by Pelletier and coworkers: Pelletier, M. J.; Fabiilli, M. L.; Moon, B. *Appl. Spectrosc.* **2007**, *61*, 1107–1115. Flow ozonolysis can readily be outsourced to Bridge Organics, http://www.bridgeorganics.com.

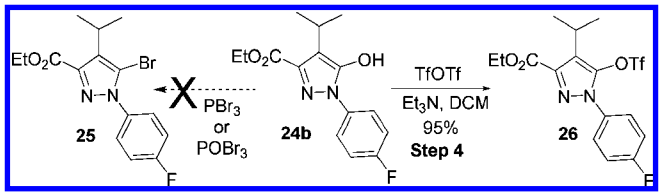
(19) The batch of olefin used in the flow ozonolysis campaign, unlike the material for one-pot ozonolysis, was isolated after a dilute HCl wash.

(20) As determined by ^{1}H NMR and MS analysis.

Scheme 4. **Retrosynthetic analysis of dihydroxyester side-chain attachment**



Scheme 5. **Activation of the hydroxypyrazole core via formation of triflate 26**



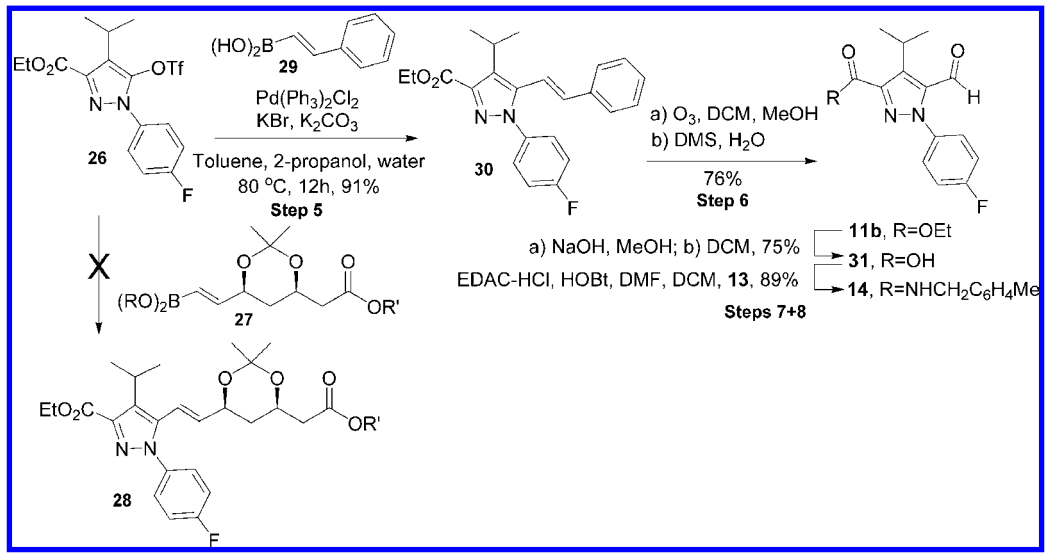
Side-Chain Coupling and Reduction. In a significant improvement over the original Wittig strategy (Scheme 2), aldehyde **14** was readily coupled with stabilized Konoiki ylide **32**[21] in refluxing toluene to afford **33** a 95% yield of a mixture of cis/trans olefins with excellent retention of stereochemistry (Scheme 8, >99.5% ee).[22] Unfortunately we observed that the triphenylphosphine oxide byproduct had a deleterious effect on downstream chemistry if not sufficiently purged. As we were unable to isolate the desired product by crystallization, we were forced to purify the crude reaction mixture on a silica gel pad to afford **33** in 95% yield on 660 g scale. We were also met with some difficulty in isolating downstream intermediates, as most steps leading up to API crystallization resulted in crude oils.[23]

Deprotection with aqueous HF in acetonitrile afforded β-hydroxy ketone **34** in 93% yield. Reduction with sodium borohydride[24] afforded very high stereoselectivity for the desired olefin syn-diol diastereomer **35** (>99% de), which was hydrogenated with 10% Pd/C in a Parr reactor to afford **36** in 91% yield over 2 steps.[25]

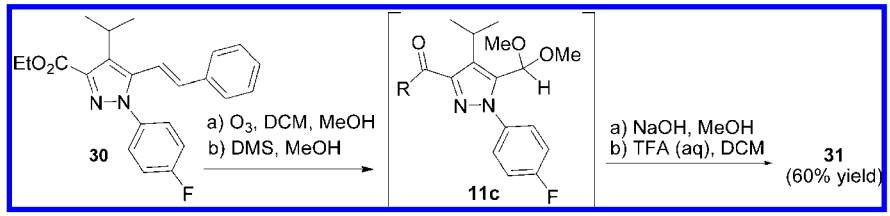
API Isolation. In the original second generation process, the palladium catalyst was filtered off and the crude product mixture was treated with 50% NaOH to afford crude carboxylate salt **1**, which was acidified, purified using chromatography, treated with caustic, and concentrated to dryness to afford small quantities of API contaminated with residual NaOH. A more practical salt formation based on a method previously developed in our laboratories[26] was applied upon scale-up. The crude sodium salt was first adjusted to pH 5 with acetic acid and then extracted into ethyl acetate as free acid **37**. Removal of ethyl acetate for2-propanol by distillation at reflux afforded a mixture of **37** and lactone **38**. As a result, a 1:1 sodium salt was easily formed in a stoichiometric manner by slowly charging aqueous NaOH until the level of **38** fell to below 0.5% by HPLC analysis.[27] Residual water was removed via azeotropic distillation until a 97:3 ratio of 2-propanol to water was obtained,[28] and crude sodium salt **1** was isolated by filtration. Recrystallization, filtration, and drying afforded >160 g of the desired API in an 81% yield with excellent chemical (>99%) and stereochemical purity (>99.5% de) with the desired physical properties.[29,30]

(21) Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849–7854.
(22) The relative ratio of *E*/*Z* isomers was estimated at 60:40 *E*/*Z* by ^{1}H NMR analysis, although this result is effectively inconsequential due to downstream olefin reduction.
(23) Oil intermediates were typically isolated by concentration to dryness or were carried forward as crude solutions. Any attempts to further scale this chemistry would benefit greatly from identification of more solid isolation points after the Wittig chemistry. For one potential alternative to dealing with late-stage non-crystalline intermediates, see: Klajic, A.; Zupet, R. PCT Int. Appl. 39, 2010.
(24) Standard syn-reduction conditions: diethylmethoxyborane and sodium borohydride in 3:1 THF/MeOH at <−70 °C.
(25) With excellent retention of stereochemistry (>99% de).
(26) Bowles, D. M.; Bolton, G. L.; Boyles, D. C.; Curran, T. T.; Hutchings, R. H.; Larsen, S. D.; Miller, J. M.; Park, W. K. C.; Ritsema, K. G.; Schineman, D. C. *Org. Process Res. Dev.* **2008**, *12*, 1183–1187.
(27) Sodium hydroxide selectively consumes free acid **37**, followed by reaction with lactone **38**, in that order. This phenomenon allowed careful titration to the desired addition endpoint.
(28) As indicated by ^{1}H NMR analysis.
(29) Crystalline form A with rodlike 10−20 μm particle size.
(30) Small pilot batches with varying amounts of isomeric impurities were found to be upgraded from ∼95−97% de to >99.5% de using this recrystallization protocol.

Scheme 6. **Sukuki/Ozonolysis route to amide-aldehyde 14**



Scheme 7. **Recovery of the flow-ozonolysis batch**



Conclusion

A relatively low-yielding first-generation synthetic route[31] that was heavily dependent on nonprocess-friendly chemistry and silica gel chromatography was replaced with a more scalable synthesis enabling manufacture of several hundred grams of **1** in a matter of weeks. Utilization of hydroxypyrazole **24b** as a core starting material enabled a rapid synthesis of amide aldehyde **14**, which allowed downstream conversion to 166 g of sodium salt **1** in support of phase I clinical studies. The synthesis was completed in 14 steps[32] with a 21% overall yield, including removal of all but one silica gel chromatography step. Although further process development will be needed before larger-scale plant campaigns may be realized, the enabling work presented herein has resulted in rapid advancement of this promising cardiovascular candidate into early clinical trials.

Experimental Section

HPLC analyses of chemical purity were carried out using an Agilent 1100 HPLC using a YMC Pack Pro C-18 column (150 mm × 4.6 mm, 3 μm) with two mobile phases: 0.2% $HClO_4$ in 95:5 water/acetonitrile (mobile phase A) and acetonitrile (mobile phase B); and a gradient method: 20% eluent B linearly increased to 95% eluent B over 20 min, 1.0 mL/min, 235 nm. HPLC chiral purity analyses were carried out using an Agilent 1100 HPLC using a Diacel Chiralpak AD column (250 mm × 4.6 mm, 10 μm) with an isocratic mobile phase of hexanes/2-propanol 85:15, 1.0 mL/min, 210 nm.

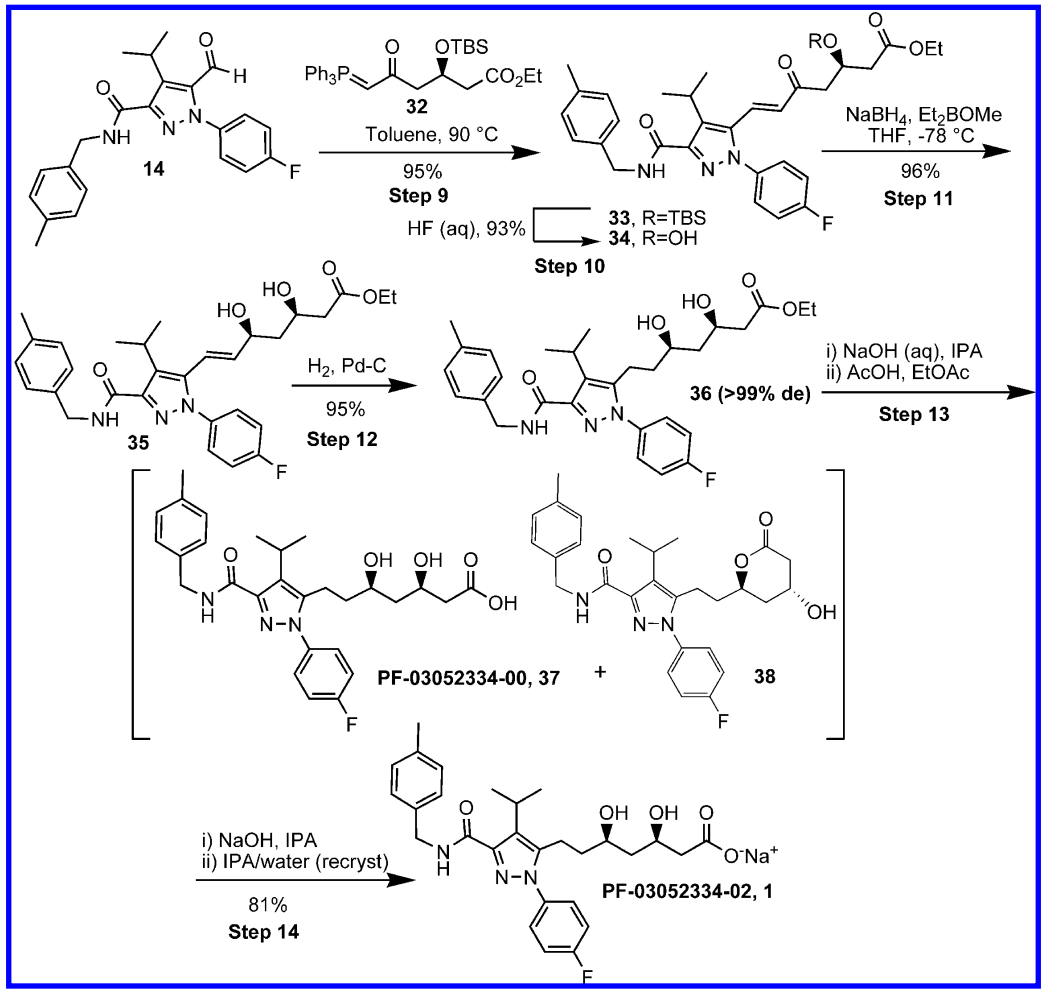
2-Isopropyl-3-oxo-succinic Acid Diethyl Ester (21b). *Laboratory Procedure.* To a solution of diisopropylamine (1.13 L, 816 g, 8.02 mol) in THF (1.0 L) held below −70 °C was charged *n*-butyllithium (2.5 M solution in hexanes, 3.20 L, 512 g, 8.00 mol, 1.0 equiv) at a rate to maintain the pot temperature below −60 °C. After stirring for 30 min, ethyl isovalerate **20** (1.06 kg, 8.15 mol, 1.0 equiv) was added dropwise via addition funnel, maintaining the pot temperature between −75 to −60 °C. The mixture was stirred at this temperature for 1 h, after which time diethyl oxalate **19b** (1.2 kg, 8.21 mol, 1.02 equiv) was charged via addition funnel, holding the reaction between −70 to −60 °C. The cold bath was removed, and the pot mixture was warmed to −20 °C over 2 h, after which time HPLC analysis indicated >99.5% consumption of **20**. The reaction mixture was charged with glacial acetic acid (814 g, 13.6 mol, 2.26 equiv) followed by water (1.5 L), and the mixture was allowed to warm to 20 °C over 2 h. After phase separation, the organic layer was washed with water (1.5 L), saturated sodium bicarbonate solution (1.5 L), and saturated sodium chloride solution (1.5 L), and was concentrated at <50 Torr to produce an oil that was held under vacuum for 2 h to afford 1.79 kg (97% yield, >98% HPLC purity, RRT 13.6 min) of **21b** as an orange oil that was carried forward without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36−4.29 (m, 2H), 4.21−4.15 (m, 2H), 3.84 (d, J = 6.8 Hz, 1H), 2.52−2.43 (sept, J = 6.8 Hz, 1H), 1.36 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), and 1.03−0.99 (m, 6H). MS (APCI$^+$): 231 [M + H].

Kilogram-Laboratory Procedure (Not Isolated). To a solution of diisopropylamine (13.7 L, 9.9 kg, 97.8 mol) in THF (16 L) held between −75 to −70 °C was charged *n*-butyllithium

(31) A 5.6% yield over 15 linear steps (23 steps overall including ylide synthesis) without including multiple silica gel chromatography operations.

(32) Excluding the synthesis of side-chain ylide **32**, which remained virtually unchanged from the original first-generation route.

Scheme 8. **Side-chain attachment and deprotection**



(2.5 M solution in hexanes, 39.1 L, 27.1 kg, 97.8 mol, 1.0 equiv), holding the pot temperature < −60 °C.[33] After stirring for 30 min, ethyl isovalerate **20** (12.9 kg, 99.1 mol, 1.0 equiv) was charged via transfer pump at < −60 °C during the addition. The mixture was stirred between −75 to −65 °C for 1 h, after which time diethyl oxalate **19b** (14.5 kg, 99.3 mol, 1.01 equiv) was charged via transfer pump at < −60 °C. The reactor jacket temperature was raised to warm the pot mixture to −20 °C over 2 h, after which time HPLC analysis indicated >99.5% consumption of **20**. The reaction mixture was transferred into a 10 °C solution of glacial acetic acid (13.2 kg, 12.6 L, 220 mol, 2.26 equiv) and water (80 L), and the mixture was warmed to 20 °C after addition was complete. The phases were separated, and the organic layer was washed with water (25 L), saturated sodium bicarbonate solution (20 L), and 5 wt % sodium chloride solution (20 L). The resulting mixture was concentrated by distillation at 40 °C under vacuum to 20 L. Acetonitrile (30 L) was charged, and the resulting mixture was distilled at 40 °C and 40 Torr to isolate crude **21b** as a solution in acetonitrile, final volume 30 L, that was carried forward into the second step without further purification (assumed yield 100%). A small aliquot was concentrated and was found to exhibit the desired representative spectral properties listed above.

(33) Approximately 30 min.

2-[(4-Fluorophenyl)-hydrazono]-3-isopropyl-succinic Acid Diethyl Ester (23b). *Laboratory Procedure.* To a slurry of 4-fluorophenylhydrazine hydrochloride **22** (565 g, 3.48 mol, 1.12 equiv) in water (800 mL) was charged a solution of **21b** (714 g, 3.10 mol, 1.0 equiv) in acetonitrile (1.0 L). The biphasic suspension was heated to between 45−50 °C for 24 h and the reaction mixture was separated. The aqueous layer was diluted with water (2 L) and extracted with MTBE (2 × 2 L). The combined organic layers were washed with saturated brine solution (2 × 2 L), concentrated to dryness at <50 Torr, and the resulting oil was dried at 20 °C and 10 Torr for 16 h to afford hydrazone **23b** (1.02 kg, 99% yield, 96% HPLC purity, RRT 7.8 min), as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.10 (m, 2H), 7.00−6.96 (m, 2H), 4.25 (q, J = 7.2 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.45 (d, J = 8.2 Hz, 1H), 2.50 (sept, J = 6.8 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), and 0.98 (d, J = 6.7 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.40. MS ($APCI^+$): 339 [M + H]

Kilogram-Laboratory Procedure. To a slurry of 4-fluorophenylhydrazine hydrochloride **22** (18.4 kg, 113 mol, 1.16 equiv) in water (26.0 L) was charged a crude solution of **21b** in acetonitrile (carried forward without isolation from step 1; assumed 100% yield, 97.8 mol) in acetonitrile, total volume 30 L. The biphasic suspension was stirred

at between 45−50 °C for 24 h and the reaction layers were separated. The aqueous layer was diluted with water (65 L) and extracted with MTBE (2 × 65 L). The combined organic layers were washed with 10 wt % brine solution (2 × 65 L) and concentrated by vacuum distillation at 30 °C and 60 Torr to a final volume of 30 L to afford hydrazone **23b** as a crude solution in MTBE (yield assumed to be 100%) that was carried forward without further purification. A small aliquot was found to exhibit the desired representative spectral properties listed above.

1-(4-Fluorophenyl)-5-hydroxy-4-isopropyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (24b). *Laboratory Procedure.* A solution of hydrazone **23b** (1.27 kg, 3.75 mol, 1.0 equiv) in glacial acetic acid (2.0 L) was heated to reflux for 16 h, cooled to 80 °C, and concentrated to dryness at <30 Torr. The resulting solids were reconcentrated from toluene (3 × 750 mL) on the rotary evaporator to remove residual acetic acid. The resulting brown solids were recrystallized from a mixture of toluene (1.8 L) and n-heptane (3.6 L), rinsed with n-heptane (1 × 2 L), and dried for 16 h at 50 °C to provide hydroxypyrazole **24b** (0.88 kg, 80% yield, >99% HPLC purity, RRT 8.9 min) as a white to off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.65 (m, 2H), 7.34−7.30 (m, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.27 (sept, J = 7.0 Hz, 1H), 1.41 (t, 3H), 1.28−1.22 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.31, 22.15, 23.98, 60.54, 116.11, 116.26, 125.54, 135.18, 139.99, 149.83, 160.12, 163.79. ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.28. MS (APCI$^+$): 293 [M + H]. Anal. Calcd for $C_{15}H_{17}FN_2O_3$: C, 61.63; H, 5.86; N, 9.58; Obs: C, 61.60; H, 5.89; N, 9.52.

Kilogram-Laboratory Procedure. To a solution of hydrazone **23b** in MTBE (total volume 30 L, assumed to be 100% yield from steps 1−2, 97.8 mol **23b**) was charged glacial acetic acid (52 L), and the mixture was distilled at 30 Torr and 50 °C until MTBE had been fully displaced. The resulting solution was heated to reflux for 20 h until **23b** had been fully consumed (less than 0.5% **23b** by HPLC analysis). The pot mixture was distilled at 30 Torr and 60 °C to a total volume of 35 L. Toluene (20 L) was added, and the pot was redistilled to 35 L. The toluene charge and distill cycle was repeated twice more to afford a crude solution of **24b** in toluene (35 L total volume). The pot mixture was charged with toluene (40 L), heated to 50 °C, and charged with *n*-heptane (94 L). The resulting slurry was heated to 80 °C to fully dissolve any solids and then cooled at a rate of 1 °C/min to 10 °C. The resulting solids were collected by filtration, washed with n-heptane (2 × 50 L), and dried at ∼5 Torr and 50 °C 24 h to afford hydroxypyrazole **24b** (20.9 kg, 73%) as a white solid that was carried forward without further purification. The spectral data for this batch was found to be identical to the laboratory lot described above.

1-(4-Fluorophenyl)-4-isopropyl-5-trifluoromethanesulfonyloxy-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (26). To a solution of hydroxypyrazole **24b** (3.2 kg, 10.8 mol) in dichloromethane (10.4 L)[34] was charged triethylamine (1.7 L, 12.2 mol, 1.1 equiv) in one portion, and the solution was cooled to between −30−20 °C. Trifluoromethanesulfonic anhydride (3.28 kg, 11.8 mol, 1.1 equiv) was added via addition funnel over 1.5 h at < −20 °C. The reaction mixture was warmed to 18−25 °C and was stirred for 8 h, until less than 0.5% **24b** was observed by HPLC. The reaction mixture was quenched with water (2 L) and the layers were separated. The lower organic layer was extracted with HCl (1N, 2 L) followed by water (2 L). The resulting dichloromethane solution was charged with 2-propanol (7 L) and concentrated on the rotary evaporator to remove dichloromethane. The resulting solution was heated to 60 °C, charged with water (6 L) at >50 °C, then cooled at a rate of 0.5 °C/min to 5 °C. The resulting solids were filtered, washed with aqueous 2-propanol (3:1 water/IPA, 2 × 1.6 L), and dried for 48 h at 45 °C to afford **26** (4.4 kg, 95% yield, >99% HPLC purity, RRT 11.3 min) as a white granular solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.45 (m, 2H), 7.21−7.17 (m, 2H), 4.49−4.40 (q, 2H), 3.32−3.21 (m, 1H), 1.43−1.38 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.90, 21.14, 24.11, 61.48, 101.15, 117.37, 117.45, 120.30, 128.01, 137.29, 140.52, 160.92, 164.91. MS (APCI$^+$): 425 [M + H]. Anal. Calcd for $C_{16}H_{16}F_4N_2O_5S$: C, 45.28; H, 3.80; N, 6.60; Obs: C, 45.26; H, 3.91; N, 6.59.

1-(4-Fluorophenyl)-4-isopropyl-5-styryl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (30). To a nitrogen-purged slurry of triflate **26** (3.5 kg, 8.25 mol), styrenylboronic acid **29** (1.31 kg, 8.8 mol, 1.07 equiv), potassium bromide (196 g, 1.65 mol, 0.20 equiv), and potassium carbonate (3.4 kg, 24.7 mol, 3.0 equiv) was charged a mixture of toluene (24 L), water (7 L), and 2-propanol (7 L), and the resulting slurry was treated with dichloro-bis(triphenylphosphine)palladium(II) (145 g, 207 mmol, 2.5 mol %), and heated to reflux for 12 h. The phases were separated, and the product containing organic layer was extracted in succession with potassium carbonate (2 N, 2.5 L), water (2.5 L), and HCl (3 N, 2.5 L).[35] The solvent mixture was switched to 2-propanol via continual distillation at ambient pressure, affording a crude solution of **30** in 2-propanol (5 L). The solution was cooled to 50 °C, clarified by filtration through a 0.2 μm cartridge, and was charged with water (1 L). The resulting solution was cooled at a rate of 1 °C/min to 5 °C with stirring over 1 h and the resulting solids were filtered, washed with 2-propanol/water (2:1, 3 L) and dried at 45 °C and 20 Torr for 12 h to afford **30** (2.8 kg, 91% yield, >99.5% HPLC purity, RRT 12.9 min) as a crystalline white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.45 (m, 2H), 7.38−7.25 (m, 5H), 7.19−7.12 (m, 2H), 6.80 (d, J = 4.2, 1H), 6.58 (d, J = 4.1, 1H), 4.49−4.40 (q, 2H), 3.51−3.43 (m, 1H), 1.48−1.40 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.17, 22.33, 24.17, 60.90, 115.73, 116.12, 116.26, 127.55, 127.70, 129.05, 129.14, 128.08, 129.98, 136.41, 138.13, 141.87, 161.32, 163.56. MS (APCI$^+$): 378 [M]. Anal. Calcd for $C_{23}H_{23}FN_2O_2$: C, 73.00; H, 6.13; N, 7.40; Obs: C, 73.13; H, 6.10; N, 7.45.

1-(4-Fluorophenyl)-5-formyl-4-isopropyl-1*H*-pyrazole-3-carboxylic Acid (31). *Laboratory Procedure.* To a solution of styrene**30** (789 g, 2.09 mol) in dichloromethane (8.0 L) was charged methanol (2.0 L), and the solution was cooled with

(34) General attempts toward replacing dichloromethane with alternate solvents were met with significantly lower yields and new impurities.

(35) It should be noted that residual HCl in the Suzuki product likely led to the formation of the corresponding dimethylacetal in the Bridge Organics ozonolysis campaign, requiring additional rework.

stirring to between −70−60 °C. Ozone[36] was charged at a rate of 10 mL/min < −60 °C. The reaction mixture was monitored by periodically quenching samples into DCM/DMS for HPLC analysis. After 1.5 h, there was no more **30** remaining. The reaction mixture was sparged with nitrogen for 1 h and was then transferred into a stirred mixture of dimethylsulfide (260 g, 4.18 mol, 2.00 equiv) in dichloromethane (1 L) and stirred for 1 h at 0 °C. The quenched mixture was concentrated to dryness at 30 °C and 50 Torr to afford a brown oil (900 g of crude **11b**) that was redissolved in methanol (7.2 L), diluted with water (360 mL), charged with sodium hydroxide pellets (432 g, 10.8 mol, 5.17 equiv), and heated to reflux for 4 h. The resulting solution was concentrated to 2 L at 50 °C and 30 Torr, diluted with water (12 L), adjusted to pH 6 with concentrated HCl, and extracted with dichloromethane (3 × 5 L). The organic extracts were concentrated to 2 L, then charged with toluene (2 L). The remaining dichloromethane was removed by distillation at 50 °C and <40 Torr, and the resulting toluene solution was cooled to 0 °C. The solids were collected by filtration, washed with chilled toluene (2 × 100 mL) and dried for 12 h at 50 °C and <20 Torr to afford aldehyde **31** (433 g, 75% yield, >97% HPLC purity, RRT 10.7 min) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.50−7.43 (m, 2H), 7.25−7.18 (m, 2H), 4.10−3.98 (m, 1H), 1.51−1.40 (m, 6H). HRMS calcd for $C_{14}H_{13}FN_2O_3$: 276.0910, obs: 276.0922.

Flow Ozonolysis Procedure.[37] To a solution of styrene **30** (1125 g, 3.0 mol) in dichloromethane (11.4 L) was charged methanol (2.9 L), and the solution was cooled to −60 °C. The stock solution was pumped into the top of jacketed (−60 °C)[38] continuous flow ozonolysis tube reactor[39] at a rate of ca. 15 mL/minute while infusing ozone gas at a rate of 0.4 mol/h. The rate of ozone infusion was regulated to maintain an excess of ozone near the bottom of the reactor.[40] The reactor output was transferred into a quench solution containing 4:1 dichloromethane/methanol (2 L) and dimethyl sulfide (252 mL), and regular TLC analysis (1:1 heptane/EtOAc) of quench solution aliquots indicated full consumption of **30** (R_f = 0.3). The quench solution was concentrated at 30 °C and <50 Torr to 2 L, diluted with 12 L of water, and extracted with dichloromethane (3 × 7 L). The organic extracts were concentrated to dryness at 30 °C and <20 Torr to afford 1.63 kg of crude product, which was identified as the corresponding dimethyl acetal **11c** by ^{1}H NMR. The crude product was treated with methanol (10.5 L) and water (0.5 L) followed by sodium hydroxide pellets (630 g), and the mixture was heated to reflux for 4 h. The solution was cooled, concentrated to 6 L at 50 °C and 50 Torr, charged with water (17.4 L) and was extracted with dichloromethane (3 × 10 L) to remove impurities. The resulting aqueous phase was cooled to 0 °C, acidified with conc HCl (1.6 L), and extracted with dichloromethane (3× 10 L). The organic layer was concentrated to 8.5 L and was treated with aqueous TFA (50 wt %, 3.63 L) at 20 °C for 3 h. The resulting mixture was washed with water (17.5 L), and the aqueous layer was back-extracted with dichloromethane (3.5 L). The combined organic layers were washed with aqueous NaCl (10 wt %, 2 × 1.5 L), dried over magnesium sulfate, filtered, and concentrated to dryness at 30 °C and >20 Torr to afford a crude solid that was recrystallized from toluene[41] (5.5 L) to afford 493 g (1.78 mol, 60% yield) of **31** as a pale-yellow solid with spectral properties identical to those above.

Preparation of 1-(4-Fluorophenyl)-5-formyl-4-isopropyl-1*H*-pyrazole-3-carboxylic Acid 4-Methylbenzylamide (14). To a solution of **31** (400 g, 1.45 mol) in dichloromethane (4 L) was charged *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDAC-HCl, 411 g, 2.14 mol, 1.5 equiv) at 22 °C, and the mixture was stirred for 25 min. Solid 1-hydroxybenzotriazole hydrate (HOBT hydrate, 332.5 g, 2.17 mol, 1.5 equiv), was charged in one portion, and the resulting slurry was cooled to −5 °C. 4-Methylbenzylamine **13** (240.7 g, 1.99 mol, 1.37 equiv) was added via addition funnel over 30 min at <0 °C. The reaction mixture was warmed to 20 °C for 16 h and was poured cautiously into sodium bicarbonate (saturated, 2.7 L), taking care to stir well until bubbling subsided. Agitation was stopped, and the mixture was separated. The organic layer was washed with additional sodium bicarbonate solution (5 wt %, 3 L) and sodium chloride (10 wt %, 3 L). The resulting mixture was charged with acetonitrile (2 L) and was distilled at 30 °C and 50 Torr to remove dichloromethane. The acetonitrile solution was distilled at 50 °C and 30 Torr to a final pot volume of ∼1.6 L, then cooled to 0 °C. The resulting solids were collected by filtration and dried in a vacuum oven at 65 °C for 18 h to provide amide **14** (490 g, 89% yield, 97% HPLC purity, RRT 12.1 min) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.38−7.35 (m, 2H), 7.23−7.18 (m, 3H), 7.15−7.11 (m, 3H), 4.54 (d, J = 5.9 Hz, 2H), 4.16 (sept, J = 7.0 Hz, 1H), 2.31 (s, 3H), 1.43 (d, J = 7.2 Hz, 6 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.19. MS (APCI$^+$): 380 [M + H]. Anal. Calcd for $C_{22}H_{22}FN_3O_2$: C, 69.64; H, 5.84; N, 11.07. Obs: C, 69.71; H, 5.89; N, 11.17.

3-(*tert*-Butyl-dimethyl-silanyloxy)-7-[2-(4-fluorophenyl)-4-isopropyl-5-(4-methyl-benzylcarbamoyl)-2*H*-pyrazol-3-yl]-5-oxo-hept-6-enoic Acid Ethyl Ester (33). A mixture of **14** (405 g, 1.07 mol) and ylide **32** (604 g, 1.1 mol, 1.03 eq, >99.5% ee) in toluene (5 L) was heated to reflux for 36 h until HPLC analysis indicated full consumption of **14**. The pot mixture was cooled to 20 °C and was concentrated by rotary evaporation to produce a brown/yellow oil (∼1.1 kg) that was absorbed onto silica gel (1.1 kg) by concentration from dichloromethane (1.5 L) at 40 °C and 20 Torr. The solids were poured onto a silica gel pad (1.5 kg),[42] and the desired product was eluted with 20% ethyl acetate/heptane.[43] The desired fractions (analyzed by HPLC to be >97% **33** by area %) were concentrated at 50 °C and <20 Torr to afford olefin **33** (661 g, 95%, 98.5% HPLC purity, RRT 16.0 min, >99.5% ee by chiral HPLC) as a pale-orange oil that was carried forward without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 16.4 Hz, 1H),

(36) Benchtop ozone generator. Pacific Ozone, Lab Series L23. Pacific Ozone, 6160 Egret Court, Benicia, CA 94510, United States. E-mail: support@pacificozone.com.
(37) Performed at Bridge Organics, 311 W. Washington St., Vicksburg, MI 49097; http://www.bridgeorganics.com.
(38) Temperature of inner cooling coil.
(39) Ozone was introduced 2 in. from the bottom of the tube reactor.
(40) As indicated by a blue solution.
(41) Cooled to −20 °C to increase recovery of the crystallized product.
(42) Crystallization efforts were cut short due to demands on project timelines, necessitating silica gel chromatography.
(43) There was 30 L collected in 2.5 L fractions. Fractions with less than 1.5 area % triphenylphosphine oxide contaminant were included.

7.35−7.33 (m, 2H), 7.25−7.23 (m, 3H), 7.18−7.12 (m, 3H), 6.12 (d, J = 16.3 Hz, 1 H), 4.56 (m, 4H), 4.11 (q, J = 7.2 Hz, 2H), 3.57 (sept, J = 7.2 Hz, 1H), 2.74 (m, 2H), 2.48 (m, 1H), 2.32 (s, 3H), 1.45 (d, J = 7.0 Hz, 6H), 1.30−1.23 (m, 12H), 0.05 (s, 3H), and −0.01 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.61. HRMS calcd for $C_{36}H_{48}FN_3O_5Si$: 649.3347, found 649.3340.

7-[2-(4-Fluorophenyl)-4-isopropyl-5-(4-methyl-benzylcarbamoyl)-2*H*-pyrazol-3-yl]-3-hydroxy-5-oxo-hept-6-enoic Acid Ethyl Ester (34). To a solution of TBS-olefin **33** (242 g, 373 mmol, 1.0 equiv) in acetonitrile (2.0 L) held between 0−5 °C and was added aqueous HF [(**CAUTION: use of HF requires knowledge of handling and disposal information specific to this material. Do not run this chemistry before reviewing relevant safety information, including verification of the proper PPE with a qualified scientist)** 48 wt %, 120 mL, 3.31 mol, 8.80 eq] via transfer pump over 30 min. The pot mixture was warmed to 20 °C and was stirred for 19 h until HPLC analysis confirmed desilylation was complete (<0.5% of **33** remaining). The reaction mixture was charged with ethyl acetate (1 L) and saturated sodium chloride solution (1 L), and stirred for 10 min. The layers were separated, and the organic layer was carefully washed with saturated sodium bicarbonate solution (1.5 L, aqueous layer pH = 8) followed by sodium chloride (5 wt %, 1.5 L) and was concentrated to dryness at 60 °C and <20 Torr to afford 186 g (93% yield, 98.5% HPLC purity, RRT 11.9 min, >99% ee) of β-hydroxy ketone **34** as an orange oil that was stored at 0 °C under nitrogen until further use. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 16.3 Hz, 1H), 7.36−7.32 (m, 2H), 7.25−7.20 (m, 3H), 7.17−7.12 (m, 3H), 6.10 (d, J = 16.3 Hz, 1H), 4.56 (d, J = 6.0 Hz, 2H), 4.47 (pent., J = 7.1 Hz, 1H), 4.19−4.15 (m, 2H), 3.59 (sept, J = 7.1 Hz, 1H), 3.38 (br s, OH, 1H), 2.74−2.71 (m, 2H), 2.52 (d, J = 6.3 Hz, 2H), 2.32 (s, 3H), 1.45 (d, J = 7.0 Hz, 6H), and 1.26 (t, J = 7.0 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.40. MS ($APCI^+$): 535 [M]. Anal. Calcd for $C_{30}H_{34}FN_3O_5$: C, 67.27; H, 6.40; N, 7.85. Obs: C, 67.10; H, 6.44; N, 7.80.

7-[2-(4-Fluorophenyl)-4-isopropyl-5-(4-methylbenzylcarbamoyl)-2*H*-pyrazol-3-yl]-3-hydroxy-5-oxo-hept-6-enoic Acid Ethyl Ester (35). To a solution of crude β-hydroxy ketone **34** (183 g, 341 mmol, 1.0 equiv) in THF (1.8 L) in MeOH (600 mL) at between −78−72 °C was charged diethylmethoxyborane (1.0 M in THF, 444 mL, 444 mmol, 1.3 equiv) in one portion. The mixture was stirred for 1 h and then treated with sodium borohydride (15.1 g, 0.4 mol, 1.17 equiv) in four portions over 45 min while maintaining the pot temperature below −72 °C. The reaction mixture was stirred for 2 h until HPLC analysis confirmed full consumption of **34**. The reaction mixture was warmed to −30 °C and was quenched with glacial acetic acid (68 mL) in one portion, allowing the pot mixture to warm to 20 °C. The resulting thick solution was charged with ethyl acetate (1.5 L) and water (1 L), and the phases were separated. The organic layer was extracted with saturated sodium bicarbonate (1.5 L) and sodium chloride (5 wt %, 1 L) and concentrated to dryness at 60 °C and <20 Torr to afford an oil that was reconcentrated twice from methanol (2 × 500 mL) to afford 177 g (96% yield, 98.1% HPLC purity, RRT 11.2 min, >99% de) of *syn*-diol **35** as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.33 (m, 2H), 7.26−7.21 (m, 3H), 7.13−7.08 (m, 3H), 6.46 (d, J = 16.2 Hz, 1H), 5.64 (d, J = 16.2 Hz, 1H), 4.53 (d, J = 5.8 Hz, 2H), 4.48−4.46 (m, 1H), 4.23−4.21 (m, 1H), (q, J = 7.1 Hz, 2H), 3.63 (br s, OH, 1H), 3.49 (sept, J = 7.0 Hz, 1H), 2.45 (d, J = 6.0 Hz, 2H), 2.30 (s, 3H), 1.61−1.51 (m, 2H), 1.38 (d, J = 7.0 Hz, 6H), and 1.26 (t, J = 7.0 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.18. HRMS calcd for $C_{30}H_{36}FN_3O_5$ [M]: 537.2639, found 537.2641.

7-[2-(4-Fluorophenyl)-4-isopropyl-5-(4-methyl-benzylcarbamoyl)-2*H*-pyrazol-3-yl]-3,5-dihydroxy-heptanoic Acid Ethyl Ester (36). To a stainless steel Parr shaker containing *syn*-diol **35** (159 g, 296 mmol) and absolute ethanol (1.5 L) under nitrogen was charged with Pd/C (10 wt %, 15 g, 50% water). The reactor was purged with nitrogen followed by pressurization to 50 psi with hydrogen gas at between 20 and 25 °C, and the reaction mixture was stirred until hydrogen gas uptake ceased (4 h). The reaction was purged with nitrogen gas and filtered through a pad of Celite. The filter cake was rinsed with ethanol (500 mL), and the filtrates were concentrated to dryness at 50 °C and <20 Torr to afford 151.6 g (95% yield, 98.1% HPLC purity, RRT 11.1 min, >99% de) of diol **36** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.33 (m, 2H), 7.23−7.21 (m, 2H), 7.16−7.10 (m, 4H), 4.52 (d, J = 6.1 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.74−3.70 (m, 1H), 3.39 (sept, J = 7.0 Hz, 1H), 2.83−2.78 (m, 1H), 2.68−2.63 (m, 1H), 2.42−2.40 (m, 2H), 2.30 (s, 3H), 1.49−1.41 (m, 3H), 1.39 (d, J = 7.0 Hz, 6H), and 1.27−1.20 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.47. HRMS calcd for $C_{30}H_{38}FN_3O_5$: 539.2795, obs: 539.2801.

7-[2-(4-Fluorophenyl)-4-isopropyl-5-(4-methyl-benzylcarbamoyl)-2*H*-pyrazol-3-yl]-3,5-dihydroxy-heptanoic Acid Sodium Salt (1). To a solution of ester **36** (204 g 378 mmol) in absolute ethanol (500 mL) at 15−25 °C was charged aqueous NaOH (50 wt %, 37.7 g, 471 mmol, 1.25 equiv) in one portion, and the resulting solution was stirred for 2 h until HPLC analysis confirmed complete consumption of **36** (less than 0.2% **36** by HPLC). The reaction mixture was concentrated to remove ethanol at 50 °C and <20 Torr to produce a light-brown foam that was redissolved in water (750 mL), warmed to 65 °C, and treated with a solution of acetic acid (31.1 g, 0.52 mol, 1.38 equiv) in water (100 mL). The resulting mixture was extracted with ethyl acetate (750 mL, warmed to 65 °C to improve solubility), and the product-containing organic layer was separated and set aside. The aqueous layer (pH 6.5) was readjusted to pH 5 with glacial acetic acid (5 g) and extracted a second time with ethyl acetate (200 mL). The combined organic layers were washed with sodium chloride (5%, 200 mL) and water (200 mL) and concentrated to dryness at 60 °C and 30 Torr to afford a mixture of **37** and **38** as a crude orange paste that was reconcentrated twice from 2-propanol (2 L) to dryness (60 °C and 30 Torr) and then dissolved in 2-propanol (1.12 L) and deionized water (50 mL) at 60 °C. The resulting solution was held at this temperature and treated dropwise with NaOH (50 wt %) with stirring over 3 h via transfer pump until HPLC analysis indicated less than 0.25% lactone **38** remaining (24.0 g, 300 mmol 50% NaOH solution charged).[43] The reaction mixture was distilled by reflux at ambient pressure to remove water while backfilling, as necessary, with anhydrous 2-pro-

panol, until the batch reached 2 wt % water by KF analysis.[44] The pot mixture was cooled at a rate of 0.5 °C/min to 15 °C and was held with stirring for 1 h. The resulting solids were filtered, washed with 2-propanol (2 × 250 mL), and dried under vacuum at 40 °C for 22 h to afford 194 g (96%) of **1** as a granular white solid (96% HPLC purity). The crude product was recrystallized using a similar procedure from 98:2 IPA/water to afford 163.3 g (81% yield; >99% HPLC purity, RRT 10.0 min; 99.5% de) of **1** as a crystalline white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (t, J = 6.3 Hz, NH), 7.54−7.49 (m, 3H), 7.34−7.30 (m, 1H), 7.15−7.13 (m, 2H), 7.07−7.05 (m, 2H), 4.72 (br s, OH), 4.31 (d, J = 6.1, 2H), 3.63−3.59 (m, 1H), 3.46−3.43 (m, 1H), 3.21 (sept, J = 7.0 Hz, 1H), 2.73−2.67 (m, 1H), 2.59−2.53 (m, 1H), 2.22 (s, 3H), 1.94−1.90 (m, 1H), 1.74−1.68 (m, 1H), 1.38−1.29 (m, 3H), 1.26 (d, J = 7.0 Hz, 6H), and 1.16−1.10 (m, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ −113.41. ^{13}C NMR (100 MHz, CD_3OD) δ 19.94, 20.10, 21.98, 24.10, 42.99, 43.71, 44.11, 67.03, 68.86, 115.97, 115.99, 126.18, 127.91, 128.11, 129.88, 134.29, 136.50, 142.09, 143.98, 161.15, 163.93, 164.05, 178.91. MS (APCI$^+$): 533 [M − H + 23]. Anal. Calcd for $C_{28}H_{33}F_1N_3NaO_5$: C, 63.03; H, 6.24; N, 7.86; Na, 4.30. Found: C, 62.62; H, 5.97; N, 7.67; Na, 4.19. Karl Fischer: 0.14% water.

(44) The first 95 mol % of hydroxide was added over 10 min with stirring, and the final amount was titrated in on the basis of HPLC monitoring. A total of 104 mol % NaOH was required in this campaign to reach the endpoint, likely due to residual acetic acid.

(45) If necessary, the pot can be distilled until all water is removed at reflux and then adjusted back to 2 wt % water.

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