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Development of a Scalable Process for CI-1034, an Endothelin Antagonist

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Abstract:

A concise, convergent multikilogram synthesis of CI-1034 (1), a potent endothelin receptor antagonist, is described. A 15-step preparation from commercially available *o*-vanillin and benzenesulfonyl chloride employs a remarkably robust Suzuki coupling between a boronic acid and an aromatic sulfonate ester as the key synthetic step. A scalable route capable of producing multikilogram quantities of CI-1034 with no chromatographic steps is described in this contribution. Improvements to the process included using a 4-fluorobenzenesulfonate ester as a suitable substitute for the triflate group in the Suzuki reaction and the use of $MgCl_2$ as a substitute for $TiCl_4$ in a Dieckmann condensation to provide the benzothiazine dioxide core.

Introduction

In support of our endothelin receptor antagonist program[1] for the treatment of primary pulmonary hypertension and congestive heart failure, we required multikilogram quantities of CI-1034 (**1**), a novel ET_A receptor antagonist. This molecule, although achiral, possesses a complex structure due to a highly functionalized aryl moiety. To meet the needs of the project, a scalable route to CI-1034 was required to quickly deliver kilograms of material in support of toxicology research and clinical trials. As the discovery route[2] appeared, overall, to be a fairly workable synthetic approach, we used this route as a solid starting point for the preparation of CI-1034.

A retrosynthetic analysis of **1** (Scheme 1) reveals an obvious disconnection to give a "northern half" coupling partner, an aryl moiety activated as a boronic acid **2a** or zincate **2b**, for coupling via Suzuki or Negeshi protocol. The other entity, a triflate **3** or other similarly activated structure, can be seen as the "southern half" section of the molecule. The northern half can be further disconnected to aldehyde **4**, which is easily derived from commercially available *o*-vanillin (**5**). The southern half activated ester can be obtained from heterocycle **6** which can be synthesized in three steps from commercially available benzenesulfonyl chloride and 2-(trifluoromethyl)aniline.

Results and Discussion

Northern Half Strategy. The desired aryl boronic acid **2a** was prepared from commercially available *o*-vanillin in a seven-step synthetic sequence. Bromination of *o*-vanillin (**5**) via a modification of a literature preparation[3] provided bromide **7** in 92% yield with only minor amounts of dibromination and isomeric impurities (Scheme 2). Cleavage of the aryl-methyl ether to the required bromocatechol **8**, however, presented a challenge due to the harsh conditions usually required for this deprotection. Typical lab-scale deprotection using BBr_3 in CH_2Cl_2 was fast and efficient, and we used this reagent in the pilot plant twice on fairly large scale to move the project forward quickly. It was clear from the start that this method was not a solution in the long term due to the high cost of the reagent, the cryogenic reaction conditions required, and concern with the energetics of the quench on a manufacturing scale. Other methods examined to perform this cleavage included $AlCl_3$/pyridine,[4] LiCl/DMF,[5] and TMSCl/NaI[6] and met with various levels of success (Table 1). The method that proved most efficient was the use of HBr in acetic acid at 90−100 °C.[7] Although this method required a large excess of HBr (typically 4 mol equiv) under fairly harsh conditions, catechol **8** was isolated in 81.9% yield after purification by recrystallization. Alkylation of the relatively unstable catechol **8** to aldehyde **4** was conducted immediately and accomplished via treatment with CH_2Br_2/K_2CO_3 in DMF.[8] Although a number of other alkylation methods were examined (CH_2I_2, K_2CO_3, DMF;[9]

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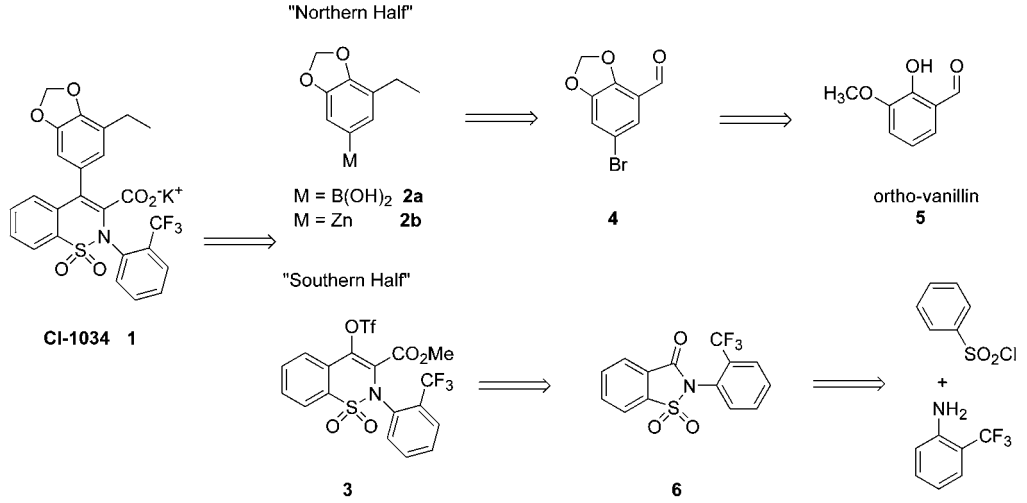
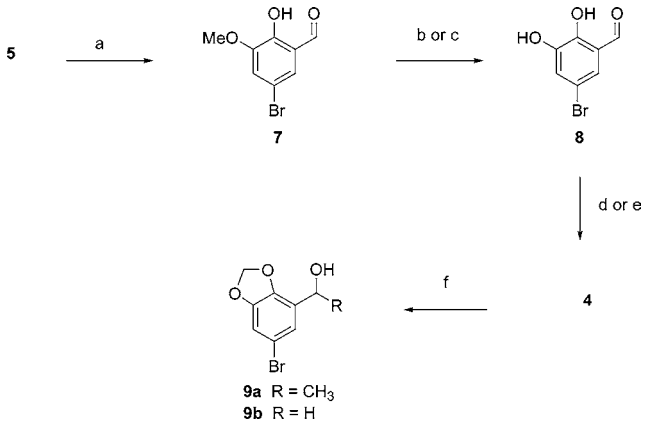
Scheme 1



Scheme 2 [a]



[a] *Reagents:* a) Br_2, KBr, HOAc, H_2O, 92% b) BBr_3, CH_2Cl_2, 85% c) HBr, HOAc, 82% d)CH_2ClBr, Cs_2CO_3, DMF, 75% e) CH_2Br_2, K_2CO_3, DMF, 68% f) MeMgCl, 91%.

Table 1. **Cleavage conditions for aryl methyl ether 7**

method	yield (%)	comment
BBr_3/CH_2Cl_2	85[a]	98.6% purity
$AlCl_3$/pyr./MeCN	86.9[a]	10% SM remains
LiCl/DMF	41.4[b]	sig. decomposition
TMSCl/NaI/MeCN	trace[b]	decomposition
HBr/HOAc	81.9[a]	98.4% purity

[a] Isolated yield. [b] HPLC yield.

and CH_2ClBr, Cs_2CO_3, DMF[10]) the CH_2Br_2/K_2CO_3 in DMF method consistently proved superior on scale in the pilot plant (Table 2). The crude aldehyde was recrystallized from heptane/ethyl acetate to provide **4** in a modest 68.4% isolated yield.

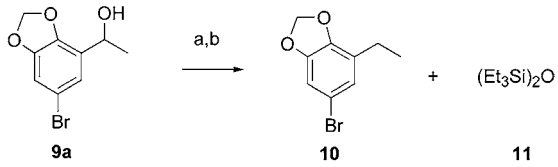
With **4** in hand, the crucial one-carbon homologation/reduction sequence was explored. Surprisingly, employing a typical procedure where the MeMgCl solution (3 M in THF) was added directly to a solution of **4** provided the required alcohol **9a**, but with 6−8% of the reduction product, alcohol **9b**![11] While looking into alternatives ($TiMeCl_3$,[12] MeLi) it was discovered that the order of reagent introduction was crucial to the success of this transformation. Thus, addition of a solution of aldehyde **4** in THF to a cold solution of MeMgCl in THF provided alcohol **9a** in 91.1% isolated yield with no detectable amount of **9b**.

Table 2. **Alkylation of catechol 8**

method	scale	yield (%)
CH_2I_2/K_2CO_3/DMF	lab scale[a]	70
CH_2ClBr/Cs_2CO_3/DMF	lab scale[a]	75
CH_2Br_2/K_2CO_3/DMF	222 kg	68.4

[a] Lab-scale yields reported, as scale-up yields were poor.

Scheme 3 [a]



[a] *Reagents*: a) Et_3SiH, CF_3CO_2H, b) distillation, 55% overall yield.

The reduction of alcohol **9a** to furnish the desired bromide **10** proved to be the most challenging transformation in the entire synthesis. The original route used a silane reduction sequence (Et_3SiH/CF_3CO_2H)[13] and our first pilot campaign employed this method. However, a full equivalent of the triethylsilyl ether **11** is produced in this reaction, which cannot be separated from the desired product by distillation (Scheme 3). Because of the high cost of this approach, this method was not considered suitable for the long term, and a number of other methods were investigated (Scheme 4). A one-step method using excess TMS−Cl/NaI in MeCN[14] was effective on a small scale, but not with multigram quantities.

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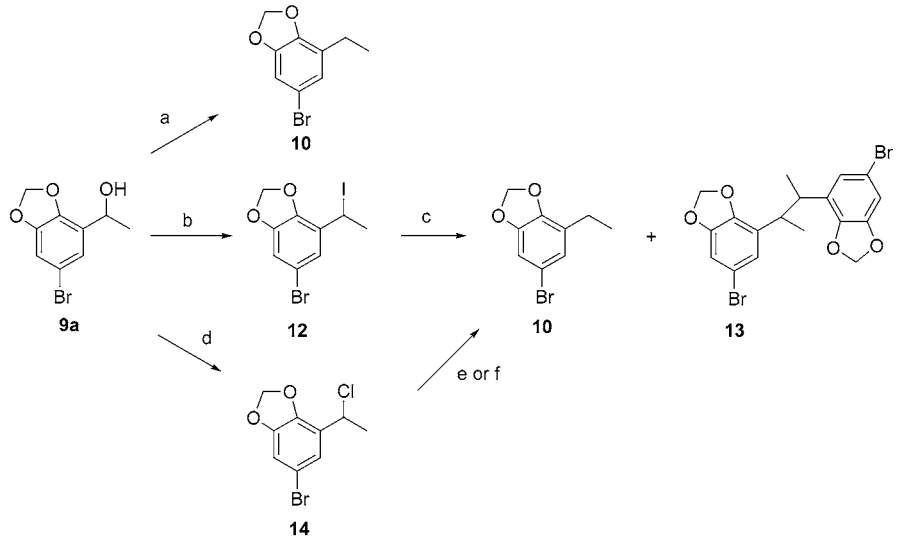
Scheme 4 [a]



[a] *Reagents and conditions:* a) excess TMS-Cl, NaI, MeCN, 65%; b) TMS-Cl, NaI, MeCN; c) Zn, HOAc, 52% (for b and c); d) $SOCl_2$, heptane, 93%; e) $ZnCl_2$, $NaBH_3CN$, 76%; f) $ZnCl_2$, $NaBH_4$, 70% from **9a**.

A more reliable and scalable approach was to prepare iodide **12** and reduce to **10** with Zn/HOAc.[15] However, this approach resulted in a significant amount of dimer **13**. To avoid this problem, the alcohol was instead converted to the chloride **14** using a variety of known conditions ($SOCl_2$,[16] MsCl/Et_3N,[17] HCl (g),[18] TMSCl/LiCl[19]). We settled on the $SOCl_2$ for cost and ease of processing reasons and reduced with Zn/HOAc[15] to provide excellent yields of the desired bromide **10** without Wurtz-coupled products. Although this method was fine on a laboratory scale, we were concerned about using a Zn metal reduction on pilot-plant scale and decided not to pursue this approach further.

We turned our attention to metal hydride reducing agents to accomplish the desired reduction. A modification of a literature method using $NaCNBH_3/ZnCl_2$[20] worked quite well on a laboratory scale, and we were able to successfully scale up this chemistry in the pilot plant, preparing bromide **10** in 70% yield (from alcohol **9a** via chloride **14**) after isolation by distillation. We were, however, concerned about the cyanide waste stream produced with this chemistry. Fortunately, we discovered that the less expensive and cyanide-free $NaBH_4$ reducing agent in tandem with $ZnCl_2$ gave similar results. Using the $ZnCl_2/NaBH_4$ system in heptane/THF we were able to produce bromide **10** in 70% yield in two steps from alcohol **9a** on 60−70-kg scale in the pilot plant. The entire six-step sequence from *o*-vanillin provided bromide **10** in a modest 32.7% overall yield.

Although the route to bromide **10** just described proved to be scalable, several different approaches were examined to prepare this compound. One approach used *o*-vanillin as the starting material but employed a different sequence of assembly (see Scheme 5). Treating **5** with 2 equiv of MeMgCl gave an alcohol as a complex mixture, that was reduced with H_2 and Pd/C and brominated with NBS/H_2SO_4 (cat.) in THF[21] to provide crude **15** in 91% yield. Ether cleavage to catechol **16** and alkylation completed this sequence to the desired bromide **10** in an overall yield of 35−55% for the crude bromide **10**. However, because the yield in the last two steps was inconsistent, we were reluctant to take this process to the pilot plant.

In a similar strategy, 2-ethylphenol **17** was used as a starting material, establishing the ethyl group from the outset. Bromination with either Br_2 in heptane or NBS/H_2SO_4(cat.) in THF[21] provided the desired bromophenol **18**. Formylation with hexamethylenetetramine/$(CH_2O)_x/H_2SO_4$/HOAc[22] or $MgCl_2/(CH_2O)_x/Et_3N$[23] provided the required aldehyde **19** in modest yield (60−70%), depending on the exact conditions. Dakin oxidation[24] with H_2O_2/NaOH provided catechol **16** which could be alkylated as described above. However, once again the yields varied wildly in the alkylation step regardless of the method of preparation. This was likely due to the instability of the electron-rich catechol **16** in base, where significant evidence of decomposition was usually observed and alkylation of the ring was likely. Also, all alternate routes to **10** outlined in Scheme 5 provided intermediates that were either oils or low-melting solids, making purification of intermediates difficult. Because of the harsh formylation conditions and the low or unpredictable yield in several of the steps, these alternate routes offered no real cost advantage and were dropped from further consideration. Although we were not completely satisfied with the described route to bromide **10**, we had shown that this chemistry was feasible on-scale and were confident that processing improvements could be made over time.

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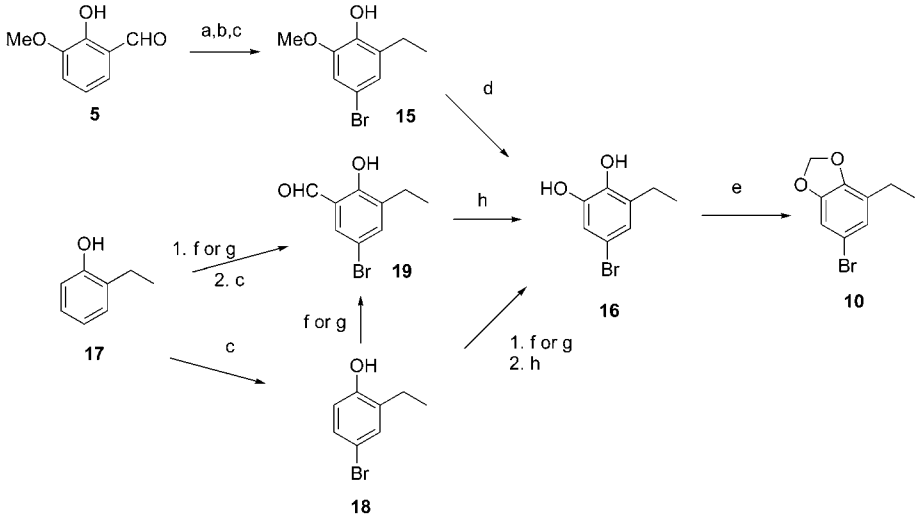
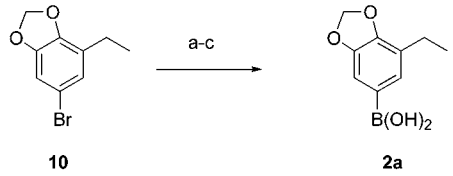
Scheme 5 [a]



[a] *Reagents:* a) MeMgCl; b) H_2, Pd/C, 96% for steps a and b; c) NBS, THF, H_2SO_4(cat.), 95%; d) $AlCl_3$, pyr., NaI, MeCN, 84% e) CH_2Br_2, K_2CO_3, DMF, 76% crude yield; f) $C_6H_{12}N_4$, $(CH_2O)_x$, H_2SO_4, 60%; g) $MgCl_2$, $(CH_2O)_x$, Et_3N, MeCN, 70%; h) NaOH, H_2O_2, 90% (crude yield).

Scheme 6 [a]



[a] *Reagents and conditions:* a) *n*-BuLi, −70 °C; b) $B(OC_3H_7)_3$; c) HOAc(aq), 95% for a−c.

The final step in the northern half sequence was preparation of a suitably activated species for coupling with the southern half moiety. In the original synthesis, bromide **10** was activated for coupling by preparing the zincate **2b** and using it directly in the Negishi coupling step. We chose to examine the preparation of boronic acid **2a** (Scheme 6). Boronic acids are generally stable and can be prepared and isolated (and purified, if necessary) or used in situ as a solution.[25] Thus, a THF solution of bromide **10** at −60 to −70 °C was treated sequentially with *n*-BuLi and triisopropyl borate to provide, after quenching with aqueous acid, the desired boronic acid, but in a modest 70−80% yield and contaminated with a number of impurities. Although we could purify the boronic acid via recrystallization, we examined this key reaction to see if we could improve the impurity profile. It was found that better results could be realized if the bromide was lithiated using an inverse addition method. Thus, to a cold (−60 to −70 °C) solution of *n*-BuLi in THF/hexanes was slowly added bromide **10**, neat. After stirring for 30 min, the mixture was treated with triisopropyl borate. Warming to 0 °C and quenching with an aqueous solution of acetic acid provided boronic acid **2a** in excellent yield (>95%) and purity. The boronic acid could then be isolated or, preferably, used directly in the Suzuki coupling step. From *o*-vanillin, the required northern half boronic acid **2a** was prepared in seven steps with an overall yield of 31.6%.

Southern Half Strategy. Heterocycle **6** was envisioned as a key intermediate in construction of the benzothiazine dioxide core structure of CI-1034. Starting from readily available benzenesulfonyl chloride and 2-(trifluoromethyl)-aniline, sulfonamide **20** was prepared in 97% yield with 99% purity on large scale (Scheme 7).

The sulfonamide was metalated with 2 mol equiv of *n*-BuLi at 0 to −10 °C and the resulting dianion **21** trapped by reaction with CO_2(g). This key step required the slow addition of the dianion reaction mixture as a slurry in THF to a separate vessel of THF where CO_2 was constantly being introduced. This procedure was carried out by bubbling CO_2 into the mixture below surface level via a sparging tube throughout the dianion addition. Whereas quenching **21** by direct introduction of CO_2 into the dianion slurry resulted in up to 15% of ketone **22**, by using this procedure no detectable levels of **22** were produced. The ensuing lithium carboxylate was converted directly to the desired cyclic sulfonamide **6** by treatment with acetic anhydride and catalytic methanesulfonic acid and isolated in an overall yield of 89.6% for the two steps.

Because sulfonamide **6** is a saccharin derivative, we explored its preparation via commercially available sodium saccharin (**23**) (Scheme 8). Reaction of sodium saccharin with HCl(aq) and removal of water provided salt **24** (containing approximately 17% NaCl).[26] Activation with thionyl chloride, amide formation with 2-(trifluoromethyl)-aniline, and finally activation/cyclization provided the desired sulfonamide **6** in 70−75% isolated yield. In a similar fashion, mixed anhydride **25**[27] (commercially available or easily prepared) could be treated with thionyl chloride and 2-(trifluoromethyl)aniline to provide **6** in 73% yield from sodium saccharin in >98% purity. Although these yields were slightly lower than the benzenesulfonyl chloride approach, this attractive route avoided *n*-BuLi and the problems

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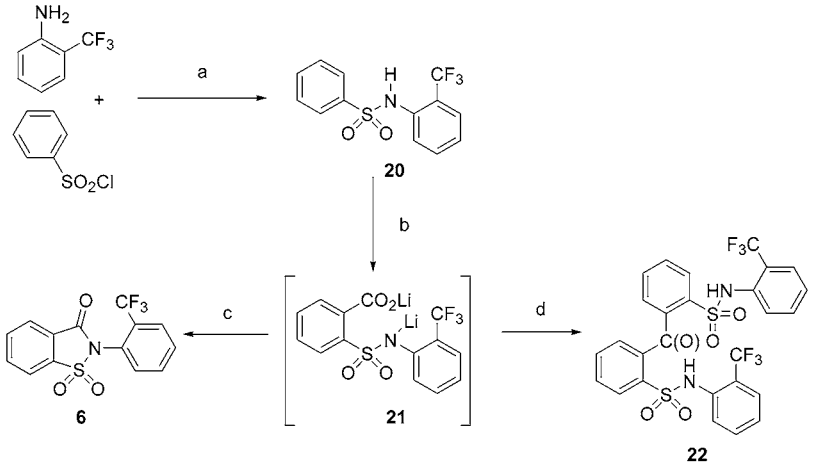
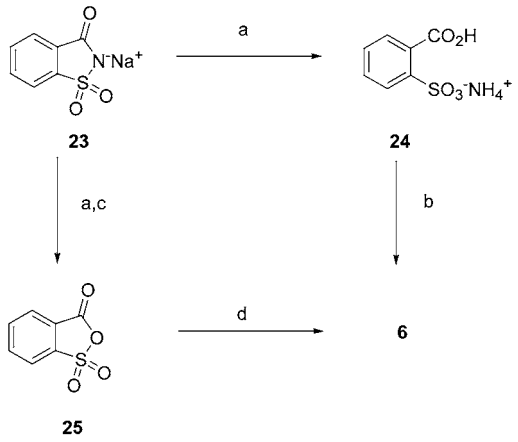
Scheme 7 [a]



[a] *Reagents and conditions:* a) pyridine, MeCN, then HCl(aq), 96.8%; b) i *n*-BuLi, ii CO_2(g); c) Ac_2O, CH_3SO_3H, 89.6% for b and c; d) CO_2(g) added directly to **21**.

Scheme 8 [a]



[a] *Reagents and conditions:* a) HCl(aq), b) i $SOCl_2$, ii $C_7H_6F_3N$, iii $SOCl_2$, 70−75% for a−b; c) i distill, ii $SOCl_2$; d) i $SOCl_2$, ii $C_7H_6F_3N$, 70−75%.

associated with dianion **21.** However, unpredictable gas evolution plagued this procedure regardless of the conditions examined. Due to the large scale that would be required and the severe time constraints of the project, these routes to **6** were dropped from further development.

Preparation of diester **26** was accomplished in a straightforward manner by treatment of **6** with methyl bromoacetate in a solution of 25% sodium methoxide in methanol. The product precipitated from the reaction mixture upon cooling in 80−85% yield and >99% purity. This chemistry was performed a number of times in our pilot plant on a large scale. However, this reaction resisted going to completion, even upon addition of additional reagents or in different solvent systems. Monoester **27** is observed in the course of the reaction and is easily isolated, and thus we explored a two-step procedure to **26**. Reaction of sulfonamide **6** with NaOMe in MeOH and quenching with HCl(aq) provided monoester **27** in 91% isolated yield. Treatment of the monoester with methyl bromoacetate in MeCN with Na_2CO_3 as base and catalytic sodium iodide provided diester **26** in 90% yield (for the two steps) and >98% purity. Alternatively, instead of employing two isolations, after reaction to form monoester **27** a solvent exchange with MeCN could be performed. Reaction with methyl bromoacetate in MeCN with Na_2CO_3 as base provided diester **26** in 89% yield with slightly lower product purity (97%). Thus, by tolerating slightly lower product purity a substantial gain in ease of processing was realized (Scheme 9).

On the basis of this encouraging result, we briefly explored a more direct preparation of monoester **27**. Reaction of sulfonamide **20** with *n*-BuLi, trapping with CO_2, and Fischer esterification in MeOH gave monoester **27** but in modest yield. Using a different approach, treatment of sulfonamide **20** with 2 equiv of *n*-BuLi and trapping with methyl chloroformate provided direct access to the desired monoester, but with 15−20% starting material, presumably due to HCl in the methyl chloroformate. Both approaches provided straightforward access to diester **26**, and we felt both approaches were viable and worthy of further investigation. Time restraints, however, prevented further development.

With **26** in hand, we proceeded to the key Dieckmann condensation[28] that would provide the benzothiazine dioxide core of CI-1034 (Scheme 10). The original route employed a Lewis acid-catalyzed approach to ketoester **28**. Using 2.2 mol equiv of $TiCl_4$ in CH_2Cl_2 with Et_3N as base at −55 °C, ketoester **28** (shown as the enol form) was cleanly and efficiently prepared in 98% yield.[29] However, the use of less base, elevated temperatures, or different solvents resulted in drastically reduced yield and purity. Typically, we did not isolate **28** but used it directly in the next step as a solution in CH_2Cl_2 after an aqueous work up and drying over $MgSO_4$.

The yield of the $TiCl_4$-catalyzed Dieckmann condensation was superb, but there are a number of drawbacks to employing this reagent on a large scale. Although not expensive, $TiCl_4$ requires special handling, low-temperature conditions in CH_2Cl_2, and produced significant waste that we had to treat before disposal.

Unfortunately, a Lewis acid-catalyzed approach to ketoester **28** seemed a certainty. When treated with strong bases such as LDA, HMDSLi, NaH, etc., diester **26** undergoes a

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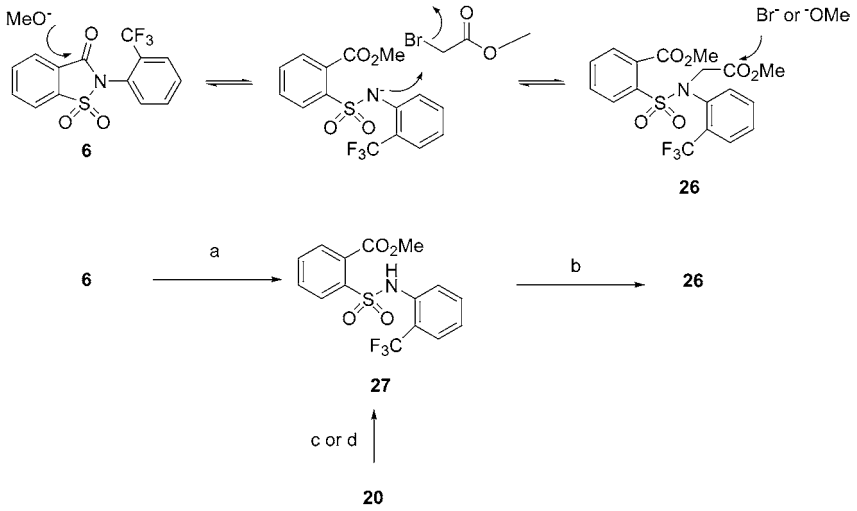
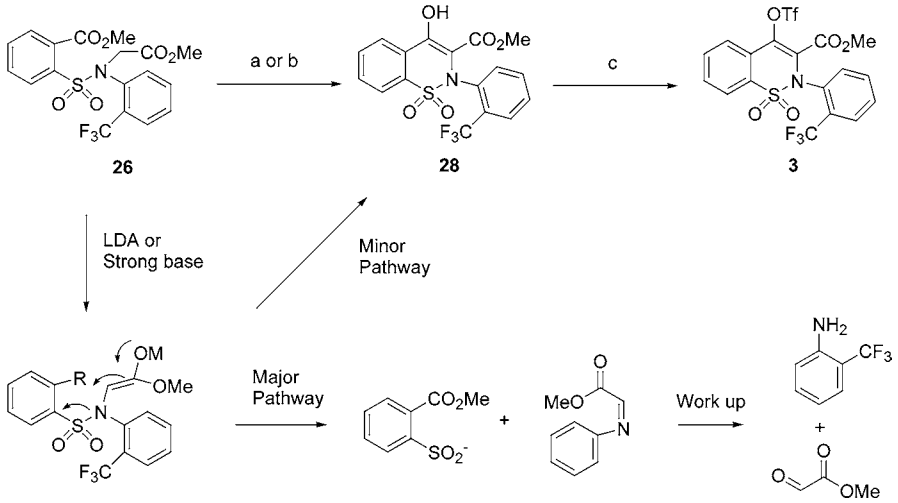
Scheme 9 [a]



[a] *Reagents and conditions:* a) NaOMe, isolate or solvent exchange with MeCN, 91%; b) $C_3H_5O_2Br$, Na_2CO_3, NaI, MeCN, 99%; c) i *n*-BuLi, ii CO_2,H^+ iii MeOH, H^+, 55% d) i *n*-BuLi, ii $ClCO_2Me$, 75%.

Scheme 10 [a]



[a] *Reagents and conditions:* a) $TiCl_4$, Et_3N, CH_2Cl_2, −55 °C, 98.5%; b) $MgCl_2$, DBU, MeCN, 89.7%; c) Tf_2O, pyridine, CH_2Cl_2, 93.2%.

rapid decomposition, even at very low temperatures, with only minor amounts of **28** produced (Scheme 10). The use of methoxide in selected solvents (such as toluene) worked to some degree, but the yields were not attractive and this approach was deemed unacceptable. The use of inexpensive and easy-to-handle $MgCl_2$ as a Lewis acid catalyst in carbon−carbon bond forming reactions has been reported.[30] Much to our delight, this salt, in conjunction with many standard organic bases (using 3 mol equiv), was very effective and provided an attractive alternative to $TiCl_4$ (Table 3). Using $MgCl_2$ and DBU in MeCN ketoester **28** was obtained in 89.7% isolated yield with excellent purity. Although the yield and purity of ketoester **28** was slightly lower, $MgCl_2$ was demonstrated as a viable alternative that eliminated the low-temperature chemistry, CH_2Cl_2 solvent, and special handling and waste stream problems associated with $TiCl_4$.

Preparation of triflate **3** from a CH_2Cl_2 solution of ketoester **28** was straightforward,[31] providing **3** in 93.2% yield (for the two steps) with >99% purity. Overall, the yield of triflate **3** was a very respectable 68% starting from benzenesulfonyl chloride.

Table 3. **Dieckmann condensation to prepare ketoester 28 using $MgCl_2$ as Lewis acid catalyst with various bases and solvents**

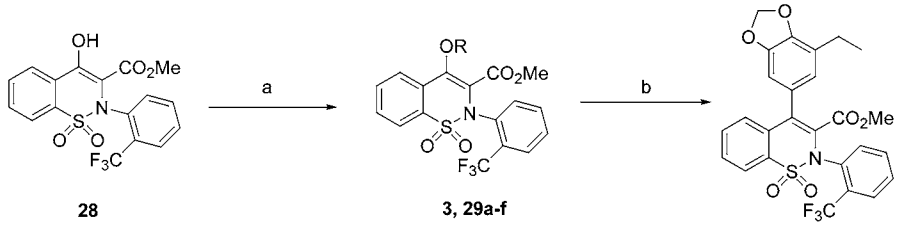
solvent	base	base (mol equiv)	yield (%)	product purity (HPLC area %)
MeCN	pyridine	5.0	NR	starting material recovered
MeCN	DIPEA	3.6	96[a]	98
MeCN	DBU	3.0	89.7[a]	98.5
MeCN	Et_3N	3.0	99[a]	95
THF	Et_3N	3.0	87[a]	98
THF	DBU	3.0	83[b]	incomplete rxn
DME	Et_3N	3.5	87[b]	incomplete rxn
toluene	DBU	3.0	44[b]	isolation issues

[a] Isolated yield. [b] HPLC (area %) yield.

(30) Tamai, S.; Ushirogochi, H.; Sano, S.; Nagao, Y. *Chem. Lett.* **1995**, 295.

(31) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

Scheme 11 [a]



28 **3, 29a-f** **30**

3: R = Tf
29a: R = P(O)(OPh)$_2$
29b: R = Ms
29c: R = Ts
29d: R = SO$_2$Ph-4Cl
29e: R = SO$_2$Ph
29f: R = SO$_2$Ph-4F

[a] *Reagents and conditions:* a) R-Cl, Et$_3$N, MeCN 75−85%; b) **2a**, Na$_2$CO$_3$, PdCl$_2$(PPh$_3$)$_2$, PPh$_3$, 85−95% (for **3**, **29e**, **29f**).

Table 4. **Catalyst, ligands, and bases for preparation of 30 from 3 and 2a**

catalyst	ligand	catalyst load (%)	base	yield (%)	comment
PdCl$_2$(PPh$_3$)$_2$	2 PPh$_3$	0.3	Na$_2$CO$_3$	94.6[a]	best pilot plant yield
Pd(OAc)$_2$	4 PPh$_3$	0.3	K$_2$CO$_3$	89[a]	
PdCl$_2$dppp[33]	none	2.5	Na$_2$CO$_3$	16[b]	triflate hydrolysis
NiI$_2$dppp[34]	2 PPh$_3$	5	Na$_2$CO$_3$	5[b]	
Pd(OAc)$_2$[35]	2 PCy$_3$[c]	3	KF	7[b]	
PdCl$_2$P(oTol$_3$)$_2$[36]	2 P(oTol)$_3$	0.5	K$_2$CO$_3$	27[b]	triflate hydrolysis
Pd$_2$(dba)$_3$	2 PPh$_3$	0.8	Na$_2$CO$_3$	92[a]	
PdCl$_2$	4 PPh$_3$	0.5	K$_2$CO$_3$	60[b]	
Pd/C[37]	none		K$_2$CO$_3$	55[b]	triflate hydrolysis

[a] Isolated yield. [b] HPLC yield. [c] Tricyclohexylphosphine.

Coupling Strategy. With both the northern half boronic acid **2a** and the southern half triflate **3** in hand, we were ready to assemble the two halves using a palladium-catalyzed Suzuki coupling reaction. A solution of boronic acid **2a** was transferred into a vessel containing triflate **3**, Na$_2$CO$_3$, and the catalyst system of PdCl$_2$(PPh$_3$)$_2$/2 PPh$_3$. This catalyst system was efficient and robust, with the reaction going to completion in several hours with a mere 0.3 mol % catalyst load. After an aqueous workup, ester **30** crystallized directly from the complex solvent system in 90−95% isolated yield (Scheme 11).

A number of other catalyst systems were reviewed for this transformation (see Table 4), but none proved as reliable and robust as the PdCl$_2$(PPh$_3$)$_2$/2 PPh$_3$ system. For example, Pd(OAc)$_2$/4 PPh$_3$[32] performed well, but was not as robust (the reaction frequently would stop due to formation of "palladium black"), as the PdCl$_2$(PPh$_3$)$_2$/PPh$_3$ system.

We were concerned that the use of palladium metal so late in the synthesis would present a serious problem with its removal from the final product. Recrystallization alone was not effective nor was treatment with various commercial carbons. However, we found that reaction with several molar equivalents of trithiocyanuric acid[38] was quite effective, reducing levels of palladium to <10 ppm. Thus, we were not concerned with using palladium metal in the next-to-last step of the synthetic sequence.

Triflate **3** proved to be a superb coupling partner in the assembly of CI-1034. However, triflic anhydride is very expensive and has an "atom efficiency"[39] of zero. Thus, we felt it was imperative to find a suitable replacement if the current synthetic strategy was to remain viable as a commercial route. Significant advances have been realized recently in Suzuki-type couplings,[40] suggesting a number of coupling strategies worthy of investigation. However, a number of criteria had to be met: (1) the catalyst load must not substantially increase due to the high cost of metal catalysts, (2) the ligand must be commercially available and non-proprietary, (3) the process with the new catalyst must be robust on scale, and (4) the triflate substitute must be inexpensive and easy to prepare.

A number of suitable southern half coupling entities (**29 a**−**f**) were prepared and evaluated in reactions with boronic acid **2a.** The coupling partners studied included the mesylate,[41] tosylate,[42,43] phosphate,[43] benzenesulfonate,[44] 4-fluorobenzenesulfonate,[43] and 4-chlorobenzenesulfonate esters. Couplings with **2a** were conducted using a variety of catalyst/ligand combinations as guided by literature precedent (Table 5). The mesylate and phosphate groups were poor coupling partners, primarily due to their instability in the basic aqueous reaction mixture. The tosylate had limited success, but the reaction was not fast enough to avoid precipitation of the

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(43) (a) Badone, D.; Cecchi, R.; Guzzi, U. *J. Org. Chem.* **1992**, *57*, 6321. (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075.
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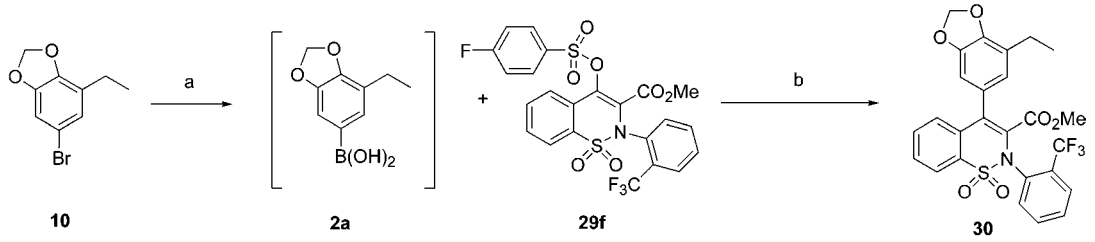
Scheme 12 [a]



[a] *Reagents and conditions:* a) i *n*-BuLi, ii $B(OiPr)_3$, iii HOAc(aq) b) $PdCl_2(PPh_3)_2$, 2 PPh_3, Na_2CO_3, 87%.

Table 5. **Results of leaving group, catalyst, and ligand for coupling of 29a−f with 2a**

entry	compound	X	catalyst	ligand	catalyst load (mol %)	yield (%)
1	**29a**	$P(O)(OPh)_2$	$PdCl_2$(dppf)		3.0	2[a]
2	**29b**	Ms	$PdCl_2(PPh_3)_2$	2 PPh_3	5.0	2[a]
3	**29b**	Ms	$Pd(OAc)_2$	2 PCy_3	3.0	15[a]
4	**29c**	Ts	$PdCl_2(PPh_3)_2$	2 PPh_3	1.0	46[a]
5	**29d**	4-$ClPhSO_2$	$PdCl_2(PPh_3)_2$	2 PPh_3	0.3	46[a]
6	**29d**	4-$ClPhSO_2$	$Pd(OAc)_2$	2 PCy_3	0.3	43[a]
7	**29e**	SO_2Ph	$PdCl_2(PPh_3)_2$	2 PPh_3	0.3	87[b]
8	**29f**	4-$FPhSO_2$	$PdCl_2(PPh_3)_2$	2 PPh_3	0.2	87[b]

[a] HPLC yield. [b] Isolated yield.

Table 6. **Results of leaving group, catalyst, and ligand for coupling of 2a with 29e and 29f to prepare 30**

entry	compound	catalyst	ligand	catalyst load (mol %)	isolated yield (%)
1	**29e**	$PdCl_2(PPh_3)_2$	−	0.3	51[b]
2	**29e**	$PdCl_2(PPh_3)_2$	2 PPh_3	0.3	87[a]
3	**29e**	$Pd_2(dba)_3$	2 PCy_3	1.0	91[a]
4	**29e**	$Pd(OAc)_2$	2 $P(^nBu)_3$	0.5	72[a]
5	**29e**	$Pd(OAc)_2$	2 PCy_3	0.5	73[a]
6	**29e**	$PdCl_2$(dppf)	−	0.5	31[b]
7	**29f**	$PdCl_2(PPh_3)_2$	2 PPh_3	0.23	87[a]
8	**29f**	$PdCl_2$(dppf)	−	0.5	43[b]
9	**29f**	$Pd(OAc)_2$	2 PCy_3	0.3	91[a]
11	**29f**	$Pd_2(dba)_3$	2 PCy_3	1.0	87[a]

[a] Isolated yield. [b] HPLC yield.

catalyst as palladium black. The 4-chlorobenzenesulfonate coupled fairly effectively, but a major side reaction was coupling at the 4-chloro position of the benzenesulfonate!

By far the two most promising entities proved to be benzenesulfonate ester **29e** and 4-fluorobenzenesulfonate ester **29f**. A series of parallel experiments were set up to guide the research towards development of a synthetic process (Table 6). Although benzenesulfonate **29e** was slightly less expensive to prepare, in general it required longer reaction times and a larger catalyst load to drive the reaction to completion. A key concern with this chemistry was the precipitation of the catalyst as "palladium black", which stops the progress of the reaction. This problem occasionally plagued both groups, but overall, 4-fluorobenzenesulfonate **29f** provided more reliable and consistent yields of **30** in coupling with boronic acid **2a**. Several other catalysts, such as $Pd_2(dba)_3$/2 PCy_3 and $Pd(OAc)_2$/2 PCy_3 had better or comparable yields in a single experiment but were unreliable for reasons that were not clear. A multigram scale-up of the Suzuki coupling was performed using $PdCl_2(PPh_3)_2$/2 PPh_3 as the catalyst system, providing ester **30** in 86.9% yield on a 50-g scale. This yield was comparable to the yield obtained using triflate **3**, but the reaction time was significantly longer. Unfortunately, the project was canceled before we had the opportunity to test this route to ester **30** in the pilot plant. Nonetheless, a viable substitute to the triflate group was discovered and was demonstrated successfully on a moderate laboratory scale (Scheme 12).

The final transformation in the synthesis was the saponification of ester **30** and isolation as the potassium salt, CI-1034 (**1**). The original route employed a classic hydrolysis in water/methanol followed by acidification and then titration with stoichiometric KOH to obtain CI-1034. This simple hydrolysis requires surprisingly forceful conditions, several hours at reflux with a large excess of hydroxide. We desired a more streamlined approach. A report in the literature described the use of potassium trimethylsilanolate[45] to convert esters directly to potassium carboxylates. We found that this reagent converted ester **30** directly to the potassium salt in THF over several hours at room temperature. While this was a surprisingly facile transformation, for unknown reasons the CI-1034 produced was unsuitable for filtration on a multikilogram scale. A solvent exchange with IPA was required to obtain a product with acceptable physical properties. Because of the high cost of this reagent and the poor filterability of the ensuing salt, a more direct method was investigated. On the basis of the success in a similar molecule, a stoichiometric quantity of KOH in IPA with 10% water was investigated. This method worked quite well as did 2-butanol with 10% water, providing CI-1034 in 78−83% yield after azeotropically removing most of the water. This procedure allowed the efficient preparation and isolation of CI-1034 with excellent purity and in an acceptable yield (Scheme 13).

Conclusions

An efficient synthesis of CI-1034 was developed and run in the pilot plant on a multikilogram scale. The process involved eight linear steps (15 total synthetic steps) with an overall yield of 50.4% starting from commercially available materials and with no chromatographic separations. A total of 200 kg of CI-1034 was prepared under cGMP conditions in our pilot plant in support of this project. The key step, a remarkably robust Suzuki coupling of an aryl boronic acid and a triflate, was demonstrated on an 80-kg scale with a

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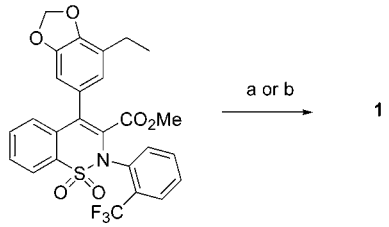
Scheme 13 [a]



30

[a] *Reagents and conditions:* a) KOTMS, THF, then IPA, rt, 60%; b) KOH, 2-butanol, water, 80 °C, 78.3%.

very low catalyst load of 0.3 mol %. Several key improvements were made to decrease the cost and improve processing. An efficient $MgCl_2$-catalyzed Dieckmann condensation was developed to replace $TiCl_4$ and was demonstrated on large laboratory scale. Suitable replacements for the expensive triflate group, 4-fluorobenzenesulfonate ester, were demonstrated on a modest laboratory scale in excellent yield.

Experimental Section

General Methods. Commercially available solvents and reagents were used as received without further purification. All reactions were performed under nitrogen unless otherwise noted. ^{1}H and ^{13}C spectra were determined in DMSO-d_6 using a Varian INOVA 400 spectrometer at 400 and 100 MHz, respectively. HPLC analysis performed using a Waters Symmetry Shield RP8 column, 150 mm × 3.9 mm, 5 μm using a water/acetonitrile gradient method at 2.0 mL/min at 210 nm. Mass spectrometry was performed using a Finnegan 4500 in DCI (isobutane) mode. Melting points were obtained using a Thomas-Hoover capillary apparatus and were uncorrected. Parallel reactions were performed using either a Radley's Carousel Reaction Station or a Bohdan Process Development Workstation.

Bromide 7. A 2000 L vessel was charged with *o*-vanillin (160.0 kg, 1.05 kmol), acetic acid (800 kg), potassium bromide (250 kg, 2.10 kmol), and water (440 L). The reaction mixture was heated to 100 ± 5 °C, and bromine (175.0 kg, 1.09 kmol) was charged over the course of 55 min. After stirring at 100 ± 5 °C for 90 min, the mixture was cooled to about 70 °C and distilled under vacuum until the volume was reduced to about 450 L total volume. Water (1000 L) was charged and the mixture cooled to 0−5 °C. After 2 h at this temperature the product was isolated by centrifugation, washed with water (2 × 100 L), and dried for 21 h in a vacuum oven at 50−55 °C. Yield: 222.7 kg (91.8%), mp: 122−124 °C, literature:[5] 128 °C; HPLC purity: 97.4% (area %).

Bromocatechol 8. A 2000 L reaction vessel was charged with bromide **7** (224.8 kg, 973 mol), acetic acid (1428.7 kg), and water (100 L) and heated to 55 ± 5 °C. Under a vacuum blank, anhydrous hydrogen bromide (210 kg, 2.60 kmol) was charged over a period of 3 h. Upon completion of HBr addition, the reaction mixture was heated at 85 ± 5 °C for 18 h, keeping pressure <10 psi by occasional venting. The reaction mixture was cooled to 55 ± 5 °C, and an additional charge of anhydrous HBr (70 kg, 865 mol) was executed. The mixture was heated at 85 ± 5 °C, for an additional 18 h at <10 psi maximum pressure. Upon reaction completion (<2% starting material present) the mixture was cooled to about 50 °C and the solvent reduced under vacuum by approximately 50%. The mixture was cooled to ambient temperature, diluted with water (700 L), and cooled to 0−5 °C for 2 h. The product was collected by centrifugation, washed with water (2 × 100 L, each load), and recrystallized (water wet) from heptane/ethyl acetate to yield 187.2 kg of **8**. The relatively unstable and solvent-wet **8** (172.9 kg calculated dry weight, 797 mol, 81.9%) was carried on to the next step without drying or further characterization. HPLC: 98.4%; MS *m*/*z* 217/219 $(M + H)^+$.

Aldehyde 4. The solvent-wet catechol **8** (172.9 kg, calculated dry wet), K_2CO_3 (216 kg, 1.56 kmol), DMF (865 kg, 916 L), and CH_2Br_2 (211 kg, 1.21 kmol) were charged to a 2000 L reactor and heated to 85 ± 5 °C for 5 h. The mixture was cooled to about 50 °C and vacuum distilled to remove about half of the solvent. Water (500 L) was added, the mixture was cooled to ambient temperature, and HOAc (75 kg, 1.25 kmol) was slowly added followed by additional water (500 L). The contents were cooled to 0−5 °C and held at that temperature overnight (14 h). The crude product was collected by centrifugation and washed with water; the solvent-wet **4** was recrystallized from heptane/ethyl acetate to yield, after vacuum-drying, 124.8 kg of **4** (68.4%) as a tan-colored solid; mp: 107 °C; HPLC: 99.2% (by area %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7. 39 (d, J = 2.0 Hz,1H), 6.26 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 187,9, 150.9, 149.3, 123.5, 120.1, 116.7, 113.2, 104.5; MS *m*/*z*: 229/231 $(M + H)^+$.

Alcohol 9a. To a 2000 L reactor were charged methylmagnesium chloride solution (189 kg of 3.0 M in THF; 561 mol) and THF (350 L), and the solution cooled to 0 ± 5 °C. In a separate 2000 L vessel were charged aldehyde **4** (100.0 kg, 437 mol) and THF (500 L). The solution of aldehyde **4** was cooled to 0−5 °C and transferred to the reactor containing the Grignard reagent over about 75 min, keeping the temperature below 15 °C during the addition. Upon reaction completion, the reaction was quenched by careful addition of cold, aqueous HCl (2.3 M, 560 L). The phases were separated, and the organic phase was reduced under vacuum and diluted with ethyl acetate (388 L). After stirring with carbon/filtercel (4.0 kg/3.0 kg) and filtering, the solution was reduced by vacuum distillation to a total volume of about 200−250 L. The solution was diluted with heptane (220 L) and cooled to 0 ± 5 °C for 2 h. The product was isolated by centrifugation, washed with heptane (2 × 55 L) and dried under vacuum to yield 97.6 kg, (91.1%) of **9a** as an off-white solid. This material was used in the next step without further purification. A sample for characterization was recrystallized from heptane/ethyl acetate; mp: 74−75 °C; HPLC: 96.1% (area %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07 (d, J = 1.3 Hz, 1H), 7.03 (d, J = 1.3 Hz, 1H), 6.05 (d, J = 13.6 Hz, 1H), 6.05 (d, J = 13.6 Hz, 1H) 5.33 (d, J = 4.6 Hz, 1H), 4.78 (m, 1H), 1.31 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.0, 142.8, 130.2, 121.2, 112.1, 110.0, 62.8, 23.8; MS *m*/*z*: 244/246 (M^+), 227/229 $(M - OH)^+$.

Benzylic Chloride 14. Alcohol **9a** (97.6 kg, 398 mol) was charged to a 2000 L vessel with heptane (585 L) and catalytic DMF (1.5 kg), and the resulting slurry was cooled to 5 ± 5 °C. Thionyl chloride (75.0 kg, 630 mol) was slowly added over about 1 h. The mixture was stirred at 0−10 °C until the reaction was complete (about 2 h) upon which time the reaction was quenched by careful addition of water (500 L). The phases were separated, the aqueous layer was extracted with heptane (365 L), and the combined organic layers were washed with a dilute NaOH solution (2 × 400 L, 1 M). The organic solution was filtered through carbon and reduced in volume under vacuum to provide a solution of chloride **14**, which was carried on as a solution to the next step without isolation or purification. A sample was retained, and the solvent was removed under vacuum for analysis. HPLC: 99.8% (area %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07 (d, J = 1.8 Hz, 1H), 6.88 (d, J = 1.8 Hz, 1H), 6.01 (s, 2H), 5.13 (d, J = 6.8 Hz, 1H), 1.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.5, 143.8 125.3, 122.3, 113.2, 111.9, 102.0, 52.0, 24.8; MS m/z 227/229 $(M - 35)^+$.

Bromide 10. To a 2000 L reactor were charged $NaBH_4$ (22.0 kg, 582 mol), $ZnCl_2$ (38.7 kg, 284 mol), and heptane (220 L); the slurry was stirred at 10 ± 10 °C while THF (450 L) was carefully added (exothermic!). The slurry was heated at 55 ± 5 °C for about an hour, upon which time a solution of chloride **14** (in THF, 75 L, and residual heptane) was transferred over about 30 min. The reaction mixture was heated at 70 ± 5 °C for about 3 h until all starting material was consumed. The reaction mixture was cooled to 40 °C and quenched by addition of water (400 L). The organic solvent was reduced by vacuum distillation and the residue extracted with heptane (2 × 175 kg). The product solution was filtered through carbon and distilled under vacuum, collecting the fractions that distilled at 65−149 °C at 5−8 mmHg. The isolated oil (71.3 kg) was stirred in a mixture of hexane (670 L), MeCN (84 L), and water (8 L) for 30 min. The lower MeCN/water layer was discarded and the organic solvent removed under vacuum to provide bromide **10** as a light-yellow oil. Yield: 63.7 kg, (69.9% from alcohol **9a**); HPLC purity: 98.4% (area %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.95 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 6.02 (s, 2H), 2.49 (q, J = 7.4 Hz, 1H), 1.12 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.9, 144.6, 126.4, 124.1, 112.1, 109.5, 101.5, 21.8, 13.6; MS m/z 228/230 (M^+).

Sulfonamide 20. To a solution of 2-(trifluoromethyl)-aniline (160.0 kg, 993 mol) and pyridine (97.0 kg, 1226.3 mol) in acetonitrile (78 kg) preheated to 35 ± 5 °C was added neat benzenesulfonyl chloride (170 kg, 962.5 mol) over about 2 h, maintaining a temperature of 35−45 °C. The mixture was then heated for 4.5 h at 45−55 °C and cooled to <10 °C. The reaction mixture was quenched by slow addition to a solution of HCl(aq) (66.0 kg 37% HCl, 1810 mol, in 660 L water) containing 10 g of seed crystals, maintaining a temperature <10 °C during transfer. The resulting slurry was stirred overnight (16 h) at <10 °C. The product was collected by centrifugation, washed with water (300 L), and dried under vacuum at 40−45 °C, for 24 h. Yield: 280.6 kg, 96.8%; mp: 75−76 °C; HPLC: 98.7% (area %); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.01 (bs, 1H), 7.82−7.79 (m, 2H), 7.71−7.66 (m, 2H), 7.63−7.55 (m, 3H), 7.46−7.42 (m, 2H), 7.03 (d J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6); δ 141.1; 134.1, 134.0, 133.2, 132.9, 129.3, 128.5, 127.4, 127.0 (q, J = 4.9 Hz), 126.6, 126.2 (q, J = 29 Hz), 123.2 (q, J = 274 Hz); MS m/z 302 $(M + H)^+$, 358 $(M + 57)^+$.

Sulfonamide 6. To a solution of sulfonamide **20** (106.0 kg, 351.8 mol) in THF (562 L) cooled to −5 to −10 °C was charged a solution of *n*-butyllithium in hexanes (15% by wt, 330 kg, 773 mol) over several hours, keeping the temperature below 0 °C throughout the course of addition. After a stir time of 2 h at <−5 °C the reaction mixture containing dianion **21** was transferred to a second vessel containing THF (165 L) into which CO_2 was bubbled below the surface of the THF via a sparging tube. The dianion slurry was transferred over 3.75 h at <−5 °C with constant addition of CO_2(g) (53.9 kg, 1.23 kmol) during the transfer. After stirring at <−5 for 2 h, water (225 L) was carefully added, and the temperature was adjusted to 20−30 °C. The organic solvent was removed by distillation at atmospheric pressure and the reaction mixture diluted with water (865 L). The mixture was extracted with MTBE (2 × 114 kg), and the MTBE extracts were back extracted with water (145 L), discarding the MTBE phase. The combined aqueous layers were acidified with HCl (75 kg, 37% HCl, 760 mol) and extracted with MTBE (230 kg). The MTBE was reduced in volume by approximately 75% by distillation at atmospheric pressure. Acetic anhydride (144 kg, 1410 mol) and methanesulfonic acid (1.1 kg) were added, and the distillation was continued as the mixture was heated to 115−125 °C. After holding at this temperature for 3 h the mixture was cooled to 45 °C, and methanol (170 L) was added slowly (very exothermic!) to the reaction mixture. The slurry was cooled to 5 °C and the product collected by centrifugation, washed sequentially with methanol (40 L) and MTBE (20 kg), and dried under vacuum at 50−55 °C for 24 h). Yield: 103.2 kg (89.6%, for two steps from **20**); mp: 203−204 °C; HPLC: 98.9% (area %); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45−8.43 (m, 1H), 8.23−8.21 (m, 1H), 8.16−8.12 (m, 1H), 8.08−8.03 (m, 2H), 77.98−7.92 (m, 1H), 7.90−7.86 (m, 1H), 7.78 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.5, 137.1, 136.4, 135.6, 134.3, 133.5, 132.0, 129.6 (q, J = 31 Hz), 128.5 (q, J = 4.2 Hz), 125.8, 125.7, 125.3, 122.8 (q, J = 274 Hz), 122.2; MS m/z 328 $(M + H)^+$, 384 $(M + 57)^+$.

Diester 26. To a 2000 L vessel were charged sulfonamide **6** (195.0 kg; 596 mol), methanol (488 L), and sodium methoxide in MeOH (25 wt % in MeOH; 138 kg, 639 mol), and the mixture was heated to reflux for about 2 h. The solution was cooled to about 55 °C, whereby methyl bromoacetate (107.3 kg, 701 mol) was charged slowly, keeping the temperature of the mixture below 60 °C during the addition. The reaction mixture was heated at reflux until analysis indicated that the quantity of monoester **27** in the mixture was <0.5% by HPLC analysis. The mixture was cooled to <5 °C and diluted with MTBE (200 L), and the mixture was recooled to 5 °C. The product was collected by

centrifugation and washed sequentially with MTBE (125 L) and water (130 L). The wet cake was reslurried at ambient temperature in water (500 L) (to remove excess salts not removed by washing the cake on the centrifuge) and collected by centrifugation. The product cake was washed with water (130 L) and dried under vacuum at 50−55 °C for 24 h. Yield: 216.2 kg (84.1%); mp: 132−133 °C; HPLC: 99.7% (area %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81−7.78 (m, 2H), 7.77−7.73 (m, 2H), 7.72−7.65 (m, 3H), 7.61−7.59 (m, 1H), 4.79 (d, J = 18.5 Hz, 1H), 4.24 (d, J = 18.5 Hz, 1H), 3.67 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.6, 167.5, 136.4, 133.2, 133.1, 133.0, 132.5, 130.6, 129.7, 129.2, 128.4 (q, J = 29.9 Hz), 128.0, 127.7 (q, J = 5.5 Hz), 122.9 (q, J = 274 Hz), 52.6, 52.4, 51.7; MS m/z 432 $(M + H)^+$.

Alternate Preparation of Diester 26. To a mixture of **6** (66.0 g, 0.20 mol) and methanol (100 mL) was charged NaOMe, 25 wt % in methanol (50 mL, 0.22 mol, 0.93 equiv). The resulting mixture was heated to reflux and held for 4−6 h. Upon completion of the reaction, the mixture was cooled to room temperature and quenched with 1 M HCl (330 mL). The product cake was isolated in two crops upon filtering and washing with water. The two cakes were combined and dried in a vacuum oven at 50 °C to yield 66.0 g (90.5%) of monoester **27** as a white solid; mp: 123.7−124.9 °C; HPLC: 98% (area %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 7.93−7.90 (m, 1H), 7.79−7.71 (m, 5H), 7.65−7.61 (m, 1H), 7.49−7.45 (m, 1H), 7.20 (d, J = 7.8 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.4, 138.4, 133.7, 133.3, 133.0, 131.5, 131.4, 129.2, 128.9, 128.4, 127.4, 126.8 (q, J = 4.9 Hz), 125.3 (q, J = 29.5 Hz), 123.2 (q, J = 273 Hz), 52.9; MS m/z 360 $(M + H)^+$.

To a clean, dry, 1 L three-neck round-bottom flask were charged monoester **27** (66.3 g, 0.185 mol), Na_2CO_3 (45.0 g, 0.423 mol, 2.3 equiv), NaI (6.0 g, 0.04 mol, 0.2 equiv), acetonitrile (340 mL), and methyl bromoacetate (42.2 g, 0.276 mol, 1.5 equiv). The resulting mixture was stirred and heated to reflux under nitrogen until completion of the reaction. The reaction was quenched with water (350 mL) and the acetonitrile removed under vacuum to provide a slurry of **26**. To the resulting slurry was charged heptane (100 mL), and the slurry was chilled to 0 ± 5 °C and held for ∼1 h. Upon filtration, the cake was washed with water and then heptane and dried in a vacuum oven at 50 °C. Yield: 78.9 g of diester **26**, 99.5% yield (90% for the two steps) >98% purity by HPLC (area %).

Ketoester 28. To a 2000 L reactor were charged diester **26** (67.5 kg; 156.5 mol) and CH_2Cl_2 (736 kg), and the solution was cooled to −30 ± 10 °C. $TiCl_4$ (67.5 kg, 356 mol) was charged and the reaction mixture cooled to −60 ± 10 °C. Triethylamine (47.5 kg, 469 mol) was added over about 30 min, maintaining the temperature range. After stirring for 2−3 h at −60 ± 10 °C, the reaction mixture was warmed to −15 ± 10 °C and quenched by careful addition of 3 M HCl(aq) (415 L). The layers were separated, and the aqueous phase was back extracted with CH_2Cl_2 (180 kg). The combined organic extracts were washed with water (210 L) and brine (175 L) and distilled at atmospheric pressure until approximately 400 L remained. At this point the solution of ketoester **28** can be used directly in the next step without isolation, as described in the preparation of triflate **3**. To isolate ketoester **28**, heptane (210 kg) was charged, and distillation was continued until a batch temperature of 70 °C was reached. The mixture was cooled to 5 ± 5 °C and the product collected by centrifugation, washed with heptane (48 kg), and dried for 16 h in a vacuum oven at 50 ± 5 °C. Yield: 61.5 kg (98.5%) of a yellow solid; mp: 191−192 °C; HPLC: 98.5% (area %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (bs, 1H), 8.23−8.21 (m, 1H), 8.00−7.96 (m, 1H), 7.91−7.87 (m, 1H), 7.83−7.81 (m, 2H), 7.57−7.46 (m, 2H), 6.78 (d, J = 7.8 Hz, 1H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 157.3, 135.4, 135.3, 133.6, 133.5, 133.4, 129.5, 128.5 (q, J = 4.2 Hz), 128.3 (q, J = 30.2 Hz), 127.4, 127.0, 126.6, 123.6 (q, J = 273.8 Hz), 123.3, 109.5, 52.7.

Alternate Preparation of Ketoester 27. To a 250 mL three-neck round-bottom flask were charged diester **26** (20.25 g, 46.9 mmol), $MgCl_2$ (9.8 g, 103 mmol), and acetonitrile (75 mL). With vigorous agitation DBU (21.4 g, 140.6 mmol) was added, keeping the temperature at 40 ± 5 °C. The reaction mixture was heated to 50−55 °C, and upon completion of the reaction the acetonitrile was reduced via vacuum distillation to obtain a thick slurry. The reaction was quenched with 1 M HCl (140 mL) and the resulting slurry stirred at 0 ± 5 °C for 1 h. The product was filtered, washed with cold water, and dried in a vacuum oven at 50 °C to yield 16.8 g (89.7%) of a yellow solid. HPLC (area %): 98.5%.

Triflate 3. A solution of ketoester **28** (in 660 L CH_2Cl_2, 156.5 mol maximum) was dried over $MgSO_4$ (25.0 kg) until water by K−F analysis was under 0.1%. The solution was filtered into a 2000 L vessel and cooled to 0 °C. Pyridine (31 kg, 493 mol) was charged and the mixture cooled to −15 ± 5 °C. Trifluoromethanesulfonic anhydride (54.3 kg, 192.5 mol) was added, neat, keeping temperature <0 °C during the addition. The reaction was quenched after 2 h by transfer to a separate reactor containing HCl (aq) (23 kg 37% HCl in 215 L water). The contents were vacuum distilled to remove most CH_2Cl_2; the slurry was diluted with heptane (55 kg) and stirred and cooled to 5 °C. The crude **3** was collected by centrifugation, washed with water and heptane, and then recrystallized, solvent-wet, from IPA and MeCN. The product was isolated by centrifugation and dried in a vacuum oven at 50 ± 5 °C for 24 h. Yield: 77.5 kg (93.2% for two steps); mp: 182.5−185.0 °C HPLC: 99.8% (area %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13−8.05 (m, 2H), 7.99−7.96 (m, 2H), 7.89−7.87 (m, 1H), 7.71−7.69 (m, 2H), 7.32−7.30 (m, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 159.4, 138.3, 134.0, 133.7, 133.5, 132.7, 132.0, 131.0, 128.4 (q, J = 4.9 Hz), 127.5 (q, J = 30.2 Hz), 127.4, 126.0, 125.4, 122.9 (q, J = 274.0 Hz), 122.8, 117.8 (q, J = 321.5 Hz), 53.5; MS m/z 532 $(M + H)^+$.

Ester 29f. To a 1 L flask were charged ketoester **28** (147.8 g, 0.37 mol) and acetonitrile (475 mL). Agitation was started, and pyridine (87.8 g, 1.1 mol) was added via an addition funnel as the reaction mixture was warmed to 55 ± 5 °C. A

solution of 4-fluorobenzenesulfonyl chloride (79.7 g, 0.41 mol) in acetonitrile (150 mL) was added over 20 min. The reaction mixture was heated at 50−60 °C for 6−18 h, then cooled to ambient temperature, and slowly transferred to a 2 L flask containing 0.6 M HCl (1 L). After cooling to 0−10 °C and stirring for 1−2 h the precipitate was filtered, washed with water (2 × 50 mL), and dried in a vacuum oven. The crude sulfonate ester **29f** was charged to a 2 L flask with isopropyl alcohol (1.2 L) and acetonitrile (300 mL) and heated to reflux to dissolve. The mixture was filtered then heated at reflux as water (100 mL) was slowly added. The reaction mixture was reduced in volume under atmospheric pressure, collecting 400−450 mL of distillate, then slowly cooled to 0−5 °C. The product was collected by filtration, washed with isopropyl alcohol (2 × 40 mL), and dried in a vacuum oven at 35 ± 10 °C for 18 h. Yield: 173.8 g (84.3%); mp: 165−166 °C; HPLC purity: 97.1% (area %); ^{1}H NMR (400 MHz, DMSO-d_6) 7.98−7.94 (m, 2H), 7.85−7.82 (m, 2H), 7.80−7.78 (m, 3H), 7.69−7.67 (m, 2H), 7.50−7.45 (m, 2H), 7.26 (d, J = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 164.7, 159.4, 137.2, 133.5, 133.0, 132.6, 132.3, 132.1, 132.0, 131.4, 130.8, 129.1, 128.7 (d, J = 95 Hz), 128.5 (d, J = 95 Hz), 127.8, 127.5 (q, J = 30.2 Hz), 127.4, 125.8, 122.8 (q, J = 274 Hz), 122.1, 117.3, 117.1, 52.9; MS m/z 558 $(M + H)^+$.

Boronic Acid 2a. A 2000 L reactor was charged with THF (284 L) and cooled to −65 ± 10 °C. A solution of *n*-butyllithium in hexanes (15% by wt, 86.2 kg, 201.8 mol) was charged slowly, keeping the temperature below −55 °C. Bromide **10** (42.0 kg, 183.3 mol) was added neat, keeping the temperature at −65 ± 10 °C during the addition. After 30 min at this temperature triisopropyl borate (41.2 kg, 219.1 mol) was added neat at −65 ± 10 °C. The mixture was warmed to −10 ± 10 °C and quenched by addition of a solution of acetic acid (13.1 kg, 218.2 mol) in water (210 L). The mixture was stirred under nitrogen for 30 min and then held for the reaction with triflate **3** in the preparation of ester **30**. A small sample was removed for characterization. HPLC purity: 95.6% (area %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.44 (s, 1H), 6.00 (s, 2H), 2.69 (q, J = 7.7 Hz, 2H), 1.30 (t, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 146.7, 130.7, 124.9, 111.9, 100.5, 22.4, 13.7; MS m/z: 195 $(M + H)^+$, 251 $(M + 57)^+$.

Ester 30. A 1600 L reactor was charged with triflate **3** (84.0 kg, 158.1 mol), Na_2CO_3 (12.6 kg, 118.9 mol), $PdCl_2(PPh_3)_2$, (277 g, 0.39 mol), PPh_3 (208 g, 0.79 mol); this mixture was pressure-purged with nitrogen (3×). The solution of boronic acid **2a** was then transferred to the reactor, and the contents were heated to 65 ± 5 °C until the reaction was complete (overnight). The mixture was treated with 50% NaOH (6 kg) and trithiocyanuric acid (0.55 kg, 3.1 mol) and stirred for 30 min. The lower aqueous layer was removed, the reaction mixture was diluted with IPA (185 L) and water (250 L), and the temperature was adjusted to 50 ± 5 °C and held for 1 h. The mixture was cooled to 0 ± 5 °C, and ester **30** was collected by centrifugation, washed with IPA, and dried in a vacuum oven at 40 ± 10 °C overnight. Yield: 79.5 kg of yellow solid (94.6%); mp: 173−174 °C; HPLC purity: 99.4% (area %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.89 (m, 1H), 7.73−7.71 (m, 1H), 7.61−7.48 (m, 5H), 7.32−7.26 (m, 1H), 6.71 (s, 1H), 6.67 (s, 1H), 6.01 (s, 2H), 2.61 (q, J = 7.7 Hz), 1.12 (t, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 147.1, 145.5, 133.7, 133.6, 132.5, 132.2, 131.3, 129.8, 129.7, 129.4 (q, J = 32.0 Hz), 128.9, 127.7, 127.6, 127.6, 125.3, 123.9, 122.8 (q, J = 274 Hz), 122.0, 108.3, 101.1, 52.1, 22.5, 14.0; MS m/z 532 $(M + H)^+$, 588 $(M + 57)^+$.

Alternate Preparation of Ester 30. A 500 mL flask was charged with **29f** (56.8 g, 102 mmol), Na_2CO_3 (13.5 g, 131 mmol), $PdCl_2(PPh_3)_2$ (106 mg, 0.24 mmol), and triphenylphosphine (132 mg, 0.50 mmol). The flask was swept with N_2, and a boronic acid solution (approximately 116 mmol, prepared as previously described) was transferred to the flask. The flask was covered with foil to protect from light and pressure-purged with nitrogen (10×) with stirring. The reaction mixture was heated at reflux for about 48 h until all starting material was consumed. The mixture was cooled to 55−60 °C, 50% NaOH (4.0 g) and trithiocyanuric acid (200 mg) were added, and the mixture was heated at 60−65 °C for about 30 min. The mixture was cooled to 55 °C and transferred to a separatory funnel, discarding the lower aqueous phase. The organic phase was returned to the flask and reheated to above 55 °C, whereby isopropyl alcohol (75 mL) and then water (60 mL) were added in sequence, keeping the temperature above 55 °C. The reaction mixture was heated at 55 °C for 1 h and then slowly cooled to 0−5 °C. The mixture was held at this temperature for 1 h, filtered, washed with IPA (15 mL), and dried in a vacuum oven at 40 ± 10 °C overnight. Yield: 47.1 g, 86.9%; HPLC purity: 99.8%.

CI-1034 (1). To a 2000 L reactor were charged ester **30** (79.3 kg, 149.2 mol)**,** KOH (10.1 kg, 91%, 163.8 mol), 2-butanol (640 kg), and water (67 L); the mixture was heated at 75 ± 5 °C for about 4 h. After filtering through carbon and a polish filter, the volume was reduced to approximately 600 L by atmospheric distillation. The contents were cooled to −5 ± 5 °C and held in this range for about 1 h. The product was collected by centrifugation, washed with cold 2-butanol, and dried in a vacuum oven at 40−50 °C for 24 h. Yield: 64.9 kg, 78.3%. HPLC purity: 99.68% (area%); $[K^+]$ = 7.22% (theory = 7.04%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76−7.69 (m, 3H), 7.64−7.60 (m, 2H), 7.57−7.53 (m, 1H), 7.46−7.42 (m, 1H), 7.02 (d, J = 8.0 Hz), 6.79 (s, 1H), 6.63 (s, 1H), 2.50 (m, 2H), 1.16 (t, J = 7.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 146.1, 143.9, 143.7, 136.0, 133.7, 133.6, 133.6, 132.5, 131.7, 130.9, 130.3, 129.5, 128.8 (q, J = 30.2 Hz), 126.7 (q, J = 4.9 Hz), 126.4, 126.1, 124.4, 123.7, 123.0 (q, J = 274.5 Hz), 120.8, 111.6, 109.5, 100.6, 22.2, 13.8; MS (of the free acid) m/z 518 $(M + H)^+$, 574 $(M + 57)^+$.

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