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Scalable Synthesis of a Prostaglandin EP4 Receptor Antagonist

Danny Gauvreau,* Sarah J. Dolman, Greg Hughes, Paul D. O'Shea, and Ian W. Davies

Department of Process Research, Merck Frosst Centre for Therapeutic Research, 16711 Trans Canada Hwy, Kirkland, Québec, Canada H9H 3L1

danny_gauvreau@merck.com

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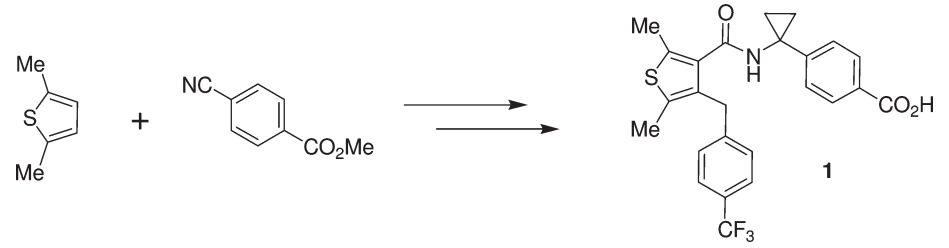

The evolution of scalable, economically viable synthetic approaches to the potent and selective prostaglandin EP4 antagonist **1** is presented. The chromatography-free synthesis of multikilogram quantities of **1** using a seven-step sequence (six in the longest linear sequence) is described. This approach has been further modified in an effort to identify a long-term manufacturing route. Our final synthesis involves no step requiring cryogenic (< -25 °C) conditions; comprises a total of four steps, only three of which are in the longest linear synthesis; and features the use of two consecutive iron-catalyzed Friedel−Crafts substitutions.

Introduction

As part of an ongoing program aimed at developing EP4 inhibitors for the treatment of disorders associated with arachidonic acid metabolism,[1,2] a number of potent and selective inhibitors have been identified, among which the substituted thiophene derivative **1** was found to be particularly promising in preclinical studies.[2] As such, a scalable approach to this compound was required, and the development of a chromatography-free synthesis of its diethyl ammonium salt (**1**·**DEA**) on multikilogram scale is described herein. Further improvements made as the result of an initiative to develop a practical and economically viable long-term manufacturing route to **1** are also disclosed.

The approach used to prepare **1** in support of medicinal chemistry studies is outlined in Scheme 1.[2] Treatment of 2,5-dimethylthiophene **2** with NBS afforded dibromothiophene **3**. Care had to be taken to protect this reaction from light to avoid bromination of the methyl substituents. Furthermore, compound **3** was found to be unstable and has a limited shelf life. Selective monometal−halogen exchange at −78 °C, followed by addition of 4-trifluoromethylbenzaldehyde, afforded benzylic alcohol **4**. Treatment of this material with a mixture of trifluoroacetic acid and triethylsilane afforded the reduced product **5**. A second metal−halogen exchange was conducted in a 2:1 mixture of diethyl ether and THF at −78 °C, followed by the addition of carbon dioxide to afford carboxylic acid **6**. To prepare the amine fragment **8**, 1,4-dicyanobenzene (DCB) was subjected to titanium-mediated Kulinkovich cyclopropanation conditions developed by Szymoniak and Bertus to afford a cyclopropylamino-cyanobenzene.[3] Hydrolysis and esterification of the remaining nitrile afforded **8** in 10−15%

(1) For references on the use of EP4 antagonists for treating inflammation, see: (a) McCoy, J. M.; Wicks, J. R.; Audoly, L. P. *J. Clin. Invest*. **2002**, *110*, 651. For atherosclerosis, see: (b) Cipollone, F.; Fazia, M. L.; Iezzi, A.; Cuccurullo, C.; De Cesare, D.; Ucchino, S.; Spigonardo, F.; Marchetti, A.; Buttitta, F.; Paloscia, L.; Mascellanti, M.; Cuccurullo, F.; Mazzetti, A. *Arterioscler., Throm., Vasc. Biol*. **2005**, *25*, 1925. For cancer, see: (c) Yang, L.; Huang, Y.; Porta, R.; Yanagisawa, K.; Gonzalez, A.; Segi, E.; Johnson, D. H.; Narumiya, S.; Carbone, D. P. *Cancer Res*. **2006**, *66*, 9665. (d) Chell, S. D.; Witherden, I. R.; Dobson, R. R.; Moorghen, M.; Herman, A. A.; Qualthrough, D.; Williams, A. C.; Paraskeva, C. *Cancer Res*. **2006**, *66*, 3106. (e) Ma, X.; Kundu, N.; Rifat, S.; Walser, T.; Fulton, A. M. *Cancer Res*. **2006**, *66*, 2923.

(2) Blouin, M.; Han, Y.; Burch, J.; Farand, J.; Mellon, C.; Gaudreault, M.; Wrona, M.; Lévesque, J.-F.; Denis, D.; Mathieu, M.-C.; Stocco, R.; Vigneault, E.; Therien, A.; Clark, P.; Rowland, S.; Xu, D.; O'Neill, G.; Ducharme, Y.; Friesen, R. *J. Med. Chem*. **2010**, *53* (5), 2227–2238.

(3) Szymoniak, J.; Bertus, P. *Chem. Commun*. **2001**, 1792–1793. For the Kulinkovich cyclopropanation, see: Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A.; Prityts kaya, T. S. *Zh. Org. Khim*. **1989**, *25*, 2244–2245. For a recent review, see: Kulinkovich, O. G.; de Meijere, A. *Chem. Rev*. **2000**, *100*, 2789–2834.

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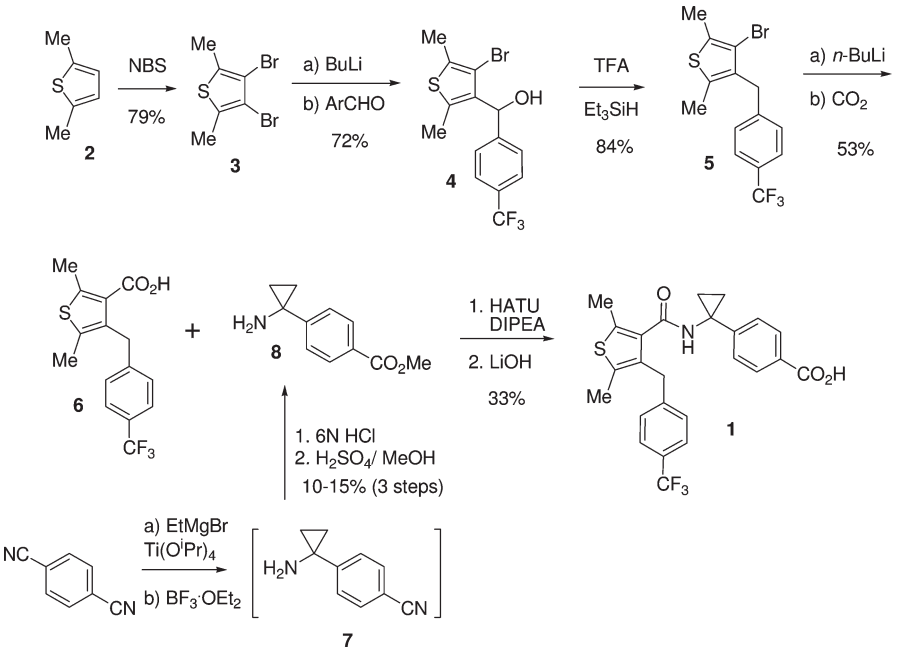
SCHEME 1. Medicinal Chemistry Approach to 1



yield from DCB. The synthesis of **1** was completed by a HATU-mediated coupling of **6** and **8**, followed by hydrolysis of the ester.

To develop a scalable approach to **1**, a number of key issues needed to be addressed: difficulties associated with the bromination of **2** and storage of **3**; the number of cryogenic metal−halogen exchange/electrophilic quench steps, and the use of large amounts of a highly flammable solvent (Et_2O) in the formation of **6**; poor yields in converting DCB to **8**; and the cost associated with the use of HATU as a coupling reagent. An alternative *retrosynthetic* analysis was envisioned that would at least partially address these concerns (Figure 1). As with the medicinal chemistry approach to **1**, the synthesis would be completed by coupling **6** and **8**, although more cost-effective alternatives to HATU were desired. Installation of the 4-trifluoromethyl benzyl substituent by a Friedel−Crafts acylation/reduction sequence would significantly improve efficiency and obviate the preparation and storage of dibromothiophene **3**. Also, literature reports suggested that titanium-mediated cyclopropanations could be chemoselective for nitriles in the presence of ester functional groups.[4] This would allow **8** to be prepared directly from the commercially available nitrile **10** in a single step.

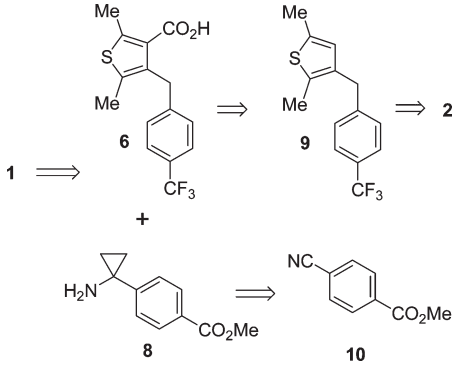
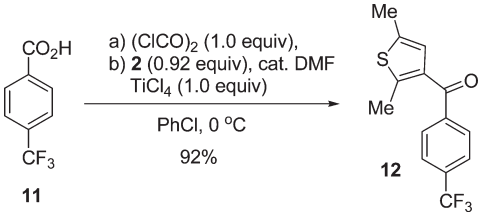


FIGURE 1. First generation *retrosynthetic* approach to **1**.

Results and Discussion

Development efforts were initiated by screening a variety of conditions for effecting the Friedel−Crafts acylation of **2** with an acid chloride derived from **11** (Scheme 2).[5] Mild Lewis acids ($ZnCl_2$, $MgCl_2$, $Zn(OTf)_2$) did not reproducibly afford complete conversion, even after 18 h at 90 °C. In the presence of stronger Lewis acids ($AlCl_3$, $TiCl_4$), acylation of dimethylthiophene proceeded at 0 °C in common solvents such as dichloromethane or 1,2-dichloroethane. However, low yields and intractable byproducts were obtained when the reactions were performed in these solvents, presumably resulting from participation of these haloalkyl solvents in Friedel−Crafts alkylations. Switching to chlorobenzene as a solvent resolved this problem. As such, benzoic acid **11** was treated with oxalyl chloride in chlorobenzene, and then dimethylthiophene and $TiCl_4$ were added directly to the reaction mixture, affording 92% yield of ketone **12** in a one-pot procedure.

SCHEME 2. Acylation of Dimethylthiophene



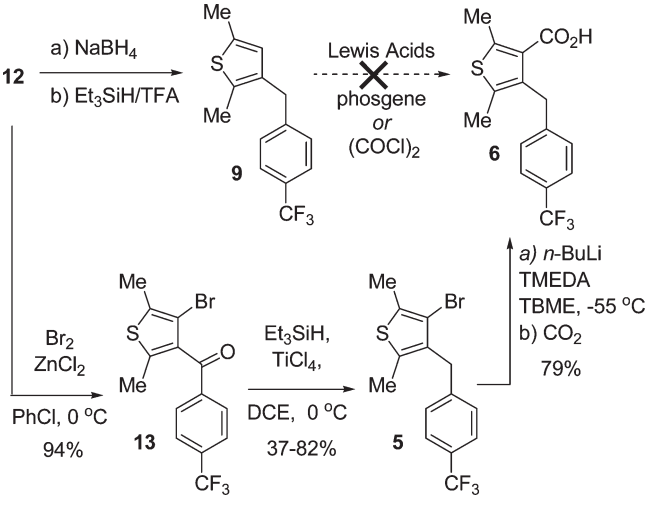
Conveniently, **12** could be reduced to **9** by treatment with $NaBH_4$ followed by Et_3SiH and TFA at 90 °C (Scheme 3). Unfortunately, efforts to introduce a carboxylic acid moiety with oxalyl chloride or phosgene in the presence of a variety of Lewis acids ($AlCl_3$, $TiCl_4$, $ZnCl_2$, ZnI_2) were unsuccessful.

(4) Szymoniak, J.; Bertus, P. *Synlett* **2003**, *2*, 265–267.
(5) Olah, G. A. *Friedel-Crafts and Related Reactions*; Interscience: New York, 1965; Vol. III, part 2, pp 1518 −1593.

In light of this, a more sequential approach to the installation of this functionality was evaluated. Ketone **12** was unreactive toward direct bromination by NBS or elemental bromine. However, in the presence of as little as 1 mol % $ZnCl_2$, clean conversion to **13** occurred upon treatment with bromine within 30 min at 0 °C.[6] Importantly, bromination of the benzylic positions was not observed, even in the presence of excess bromine. This transformation could be carried out on unpurified ketone **12** to afford **13** in 94% yield. Exhaustive ketone reduction could be achieved in a single operation by treating **13** with triethylsilane and $TiCl_4$ in 1,2-dichloroethane. This reaction was found to be particularly sensitive to residual chlorobenzene.[7] However, if care was taken to remove the last traces of Ph−Cl from crude **13** by stripping from toluene prior to solvent switching into 1,2-dichloroethane, yields of >80% could be consistently achieved.

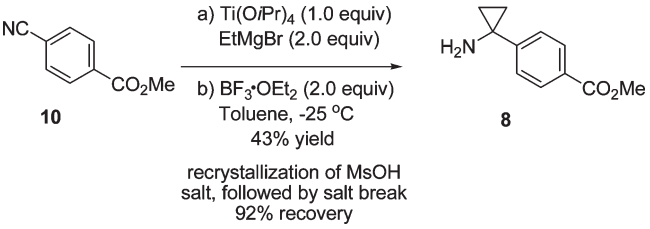
In the medicinal chemistry approach to **1**, the use of a mixed diethyl ether and tetrahydrofuran solvent system was found to be critical for a successful metal−halogen exchange of **5**. The resulting lithium anion was found to be unstable in THF alone unless the reaction was performed at temperature below −80 °C, which is difficult to achieve on multikilogram scale. In other acyclic ethereal solvents such as *tert*-butylmethylether (TBME), very little metal−halogen exchange was seen even at higher temperatures. The addition of 1.1 equiv of TMEDA allowed for smooth metal−halogen exchange at −65 °C. The anion formed under these conditions was found to be stable up to −55 °C, although significant amounts of the quenched anion product **9** were observed upon warming above −55 °C. Alternative metal−halogen exchange strategies (Grignard, Bu_3MgLi) were also found to be ineffective.[8] Quenching the anion by bubbling CO_2 (gas) into the reaction mixture at a rate such that the internal temperature did not exceed −55 °C allowed carboxylic acid **6** to be formed in 79% yield.

SCHEME 3. Preparation of Acid 6 from Thiophene Ketone 12



With the thiophene acid **6** in hand, an improved approach to preparing the cyclopropylamine fragment **8** was thought. Efforts to improve the synthesis of **8** from DCB failed to afford more then a 15% yield of the required amine. As chemoselective titanium-mediated nitrile-cyclopropanations had previously been demonstrated in the presence of an ester,[4] we decided to investigate the preparation of amine **8** from commercially available methyl 4-cyanobenzoate **10**. Using the modified conditions reported by de Meijere ($MeTi(OiPr)_3$, Et_2Zn, LiI or LiO*i*Pr) failed to afford amine **8**.[9] Treating nitrile **10** with $Ti(OiPr)_4$, EtMgBr, and $BF_3 \cdot OEt_2$ at low temperature (−78 to −40 °C) also failed to afford any desired cyclopropylamine. However, at −25 °C, 94% conversion of the starting nitrile after 1 h was observed, with a 43% assayed yield of the desired cyclopropylamine (Scheme 4). Modification of solvent, ratio of reagents, order of addition, and replacement of $BF_3 \cdot OEt_2$ by lithium salts all failed to improve upon the modest yield. However, this procedure did provide a high degree of chemoselectivity with no cyclopropyl alcohol being observed. To purify **8**, the material was extracted into 3 N HCl to remove nonbasic impurities. The HCl salt of **8** could then be extracted into 2-methyltetrahydrofuran to separate the desired material from more polar byproducts. A final purity upgrade was achieved by preparation of the methanesulfonic acid salt of **8**, followed by salt break, to recover 92% of amine **8** in greater than 95% purity as judged by HPLC analysis.

SCHEME 4. Preparation of Cyclopropylamine 8 from Methyl 4-Cyanobenzoate



The synthesis of **1** was completed by a one-pot amidation-hydrolysis procedure (Scheme 5). Thiophene acid **6** was converted in situ to the desired acid chloride with oxalyl chloride and catalytic DMF. The crude acid chloride was coupled with **8** to afford an amide, which was directly saponified to acid **1**. The optimal solvent mixture for the hydrolysis was a 3:1 mixture of THF/MeOH, which allowed for complete hydrolysis of the methyl ester within 2 h at 50 °C.[10] Finally, compound **1** was purified by crystallization of its diethylamine salt from THF/TBME to afford the final compound (> 98% pure by HPLC analysis) in 81% yield from thiophene

(6) (a) Olah, G. A.; Kuhn, S. J.; Flood, S. H.; Hardie, B. A. *J. Am. Chem. Soc.* **1964**, *86* (6), 1039–1044. (b) Olah, G. A.; Kuhn, S. J.; Flood, S. H.; Hardie, B. A. *J. Am. Chem. Soc.* **1964**, *86* (6), 1044–1046. (c) Olah, G. A.; Kuhn, S. J.; Hardie, B. A. *J. Am. Chem. Soc.* **1964**, *86* (6), 1055–1060. (d) Gnanapragasam, N. S.; Joseph, N. *Curr. Sci.* **1971**, *40* (4), 83. (e) Gnanapragasam, N. S.; Ramanujam, R.; Srinivasan, S. P. *Curr. Sci.* **1976**, *45* (24), 862–863. (f) Clark, J. H.; Ross, J. C.; Macquarrie, D. J.; Barlow, S. J.; Bastock, T. W. *Chem. Commun.* **1997**, 1203–1204. (g) Ross, J. C.; Clark, J. H.; Macquarrie, D. J.; Barlow, S. J.; Bastock, T. W. *Org. Proc. Res. Dev.* **1998**, *2* (4), 245–249. (h) Bastock, T. W.; Trenbirth, B.; Clark, J. H.; Ross, J. *Eur. Pat. Appl. EP 866046-A1*, **1998**.

(7) For reasons that are still unclear, with as little as 5 wt % chlorobenzene in the solvent mixture, the yields of the reaction dropped to <40%, via decomposition, presumably polymerization, as observed by HPLC.

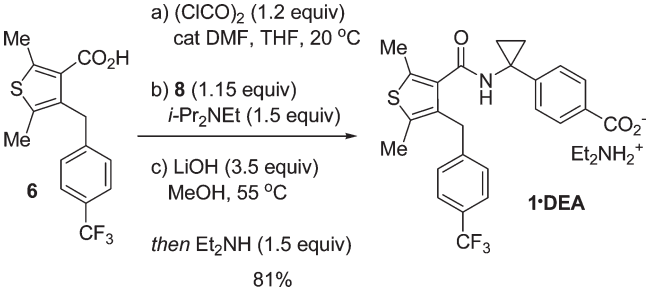
(8) (a) Grignard, V. *Bull. Soc. Chim.* **1910**, *7*, 453. (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302–4320. (c) Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449–7453. (d) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39* (14), 2481–2483. (e) Dolman, S. J.; Gosselin, F.; O'Shea, P. D.; Davies, I. W. *Tetrahedron* **2006**, *62* (21), 5092–5098.

(9) De Meijere, A.; Wiedemann, S.; Frank, D.; Winsel, H. *Org. Lett.* **2003**, *5*, 753–755.

(10) A 5:1 ratio of THF/MeOH required 7 h to achieve complete conversion.

acid **6**. Overall, this first large-scale synthesis of the diethylamine salt of EP4 antagonist **1** was performed in six steps and 21% overall yield from (4-trifluoromethyl)benzoic acid **11**, producing 3.7 kg of the **1·DEA** salt.

SCHEME 5. One-Pot Amidation/Hydrolysis Sequence for the Synthesis of 1



While the chemistry described above was acceptable for the support of preclinical activities, there were opportunities for improvement with regard to the development of a long-term manufacturing route to **1**. For instance, it might be possible to form the amide bond through a palladium-catalyzed 3-component coupling between thiophene bromide **5**, cyclopropylamine **8**, and carbon monoxide. Furthermore, the substitution of the 2,5-dimethylthiophene by direct alkylation with an appropriately activated 4-trifluoromethylbenzyl synthon would remove the need for the exhaustive ketone reduction (Figure 2).

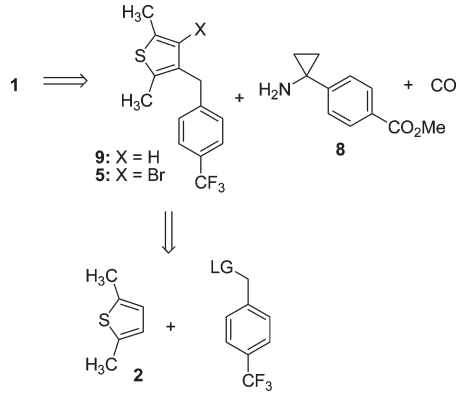
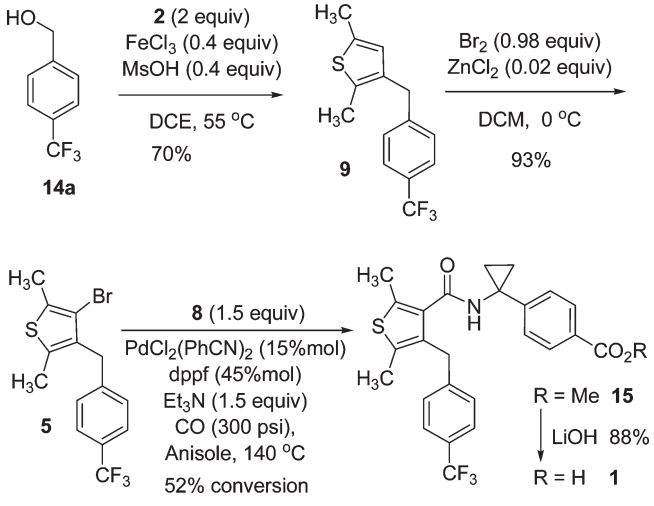


FIGURE 2. Second retrosynthesis: three-component coupling approach to **1**.

Recent work by Beller and Rueping has shown that transition metals catalyze the alkylation of arenes by benzylic alcohols and acetates in good yields with low catalyst loading.[11] However, all reported examples employed electron-rich or -neutral alkylating agents coupled with a large excess (3 to >100 equiv) of arene. To the best of our knowledge, the alkylation of arenes by electron-deficient benzylic alcohols or acetates, such as those bearing a trifluoromethyl substituent, has not been demonstrated. Furthermore, a significant reduction in the excess of arene required for complete conversion would be necessary in order for this transformation to be economically viable on large scale. Using Beller's original conditions ($H_2[PtCl_6]$, dioxane, 120 °C), no arylation product was observed for either 4-(trifluoromethyl)-benzyl alcohol or its related acetate (Table 1, entries 1, 2).[11a] When $IrCl_3$ was used as catalyst,[11a] 81% conversion to desired compound **9** was observed when trifluoromethylbenzylic alcohol was used, but no product was obtained with the acetate analogue (entries 3, 4). Conditions developed by Rueping ($Bi(OTf)_3$, DCE) afforded promising results with both the benzylic alcohol and acetate (entries 5, 6; 74% and 36% conversion, respectively).[11b] However, because of the high cost of both $IrCl_3$ and $Bi(OTf)_3$ and the low yields observed, we investigated less expensive catalysts such as $FeCl_3$ and $ZnCl_2$.[11c] While no product was observed with 40 mol % $ZnCl_2$, we were pleased to observe modest reactivity with 20 mol % $FeCl_3$ with both the benzylic alcohol and acetate (entries 7, 8; 67% and 33% conversion, respectively). By increasing the catalyst loadings from 20 to 45 mol %, complete conversion was obtained within 16 h at 75 °C (entry 9). After screening for additives, three acids (H_3PO_4, DL-tartaric acid, and MsOH) were identified as viable co-catalysts, whereas bases (Na_2CO_3, Et_3N) were found to completely suppress reactivity. Addition of 30 mol % MsOH allowed for 94% conversion with just 20 mol % $FeCl_3$ (entry 10). The impact of MsOH was even more pronounced for $ZnCl_2$ as 61% conversion to **9** was observed in the presence of the acid, while no desired product was observed in its absence (entries 11, 12). Optimal conditions for this transformation were identified as 2 equiv of 2,5-dimethylthiophene, with 40 mol % $FeCl_3$ and 40 mol % MsOH in DCE at 55 °C. After 16 h, complete conversion of the benzylic alcohol was observed with 70% assayed yield of **9**. During the preparation of this manuscript, reports regarding the benzylation of arenes using $FeCl_3$ on benzyl ethers were published.[12] These conditions have not been tested.

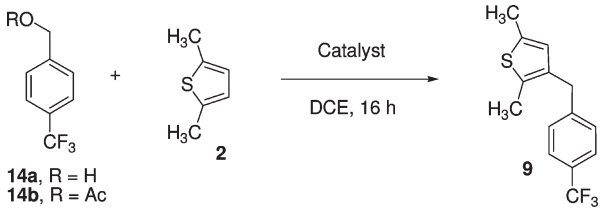
Thiophene **9** was readily brominated under the same conditions as used in the first synthesis (vide supra) to afford bromothiophene **5** in 93% yield (Scheme 6).[13] The three-component coupling was then briefly investigated. Using conditions developed for the carbonylation of haloindoles ($PdCl_2(PhCN)_2$, dppf, CO 300 psi, Et_3N, 140 °C),[14] 52% conversion to the amide **15** was observed in an unoptimized reaction. The methyl ester was hydrolyzed as in the previous

SCHEME 6. Summary of Second Process Research Route to 1



(11) (a) Beller, M.; Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 238–242. (b) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033–1037. (c) Beller, M.; Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913–3917.

TABLE 1. Transition-Metal-Catalyzed Benzylation of 2,5-Dimethylthiophene[a]



entry	catalyst	additive	14a/b	temp (°C)	conversion[b] (%)	assay yield (%)
1	$H_2[PtCl_6]$ (20%)[c]	none	**a**	75	0	0
2	$H_2[PtCl_6]$ (20%)[c]	none	**b**	75	0	0
3	$IrCl_3$ (20%)	none	**a**	75	81	36
4	$IrCl_3$ (20%)	none	**b**	75	0	0
5	$Bi(OTf)_3$ (20%)	none	**a**	75	74	40
6	$Bi(OTf)_3$ (20%)	none	**b**	75	36	22
7	$FeCl_3$ (20%)	none	**a**	75	67	nd
8	$FeCl_3$ (20%)	none	**b**	75	33	nd
9	$FeCl_3$ (45%)[d]	none	**a**	75	99	62
10	$FeCl_3$ (20%)[d]	MsOH (30%)[e]	**a**	50	94	67
11	$ZnCl_2$ (40%)[d]	None	**a**	70	0	0
12	$ZnCl_2$ (40%)[d]	MsOH (20%)	**a**	70	61	nd

[a]All reactions were carried out in DCE for a period of 16 h using 3 equiv of 2,5-dimethylthiophene. [b]Conversions were measured by HPLC at 215 nm. [c]Reaction run in 1,4-dioxane. [d]Reaction performed with only 2 equiv of 2,5-dimethylthiophene. [e]No reaction occurred in the absence of the $FeCl_3$ catalyst.

synthesis to afford **1** in 88% yield. By utilizing the three-component coupling, in addition to direct alkylation of 2,5-dimethylthiophene, we were able to reduce the number of steps in the longest linear sequence from six to four steps in addition to avoiding cryogenic conditions.

While this approach was more efficient, the use of palladium in the penultimate step could represent a problem, as its removal is often tedious. With a straightforward preparation of the thiophene fragment **9**, a direct Friedel−Crafts amidation between this arene and isocyanate **16** would represent an expedient approach to **1** (Figure 3). Amine **8** was readily and cleanly converted to **16** using phosgene and Et_3N. The isocyanate was used without further purification in the Friedel−Crafts amidation, as it was found to decompose rapidly on silica gel.

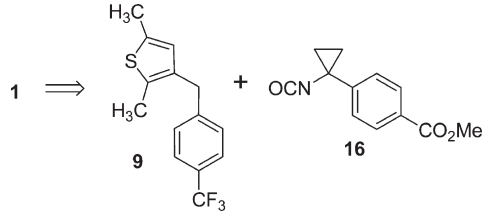


FIGURE 3. Third retrosynthesis: Friedel−Crafts amidation approach to **1**.

The investigation of a variety of Lewis acids for the Friedel−Crafts amidation of **9** with isocyanate **16** revealed that titanium and boron reagents such as $Ti(OiPr)_4$, $TiCl_4$, and $BF_3 \cdot Et_2O$ afforded <30% conversion. Better results were achieved with aluminum and iron chloride salts ($AlCl_3$, $FeCl_3$), which catalyzed the transformation to 93−99% conversion. While 2 equiv of $AlCl_3$ was required to afford only 34% yield of amide **15** contaminated by intractable byproducts, 1.1 equiv of $FeCl_3$ afforded 67% yield within 30 min at 50 °C. It should be noted that the product was unstable to reaction conditions for prolonged periods; aging the reaction mixture for 16 h caused a 17% decrease in yield (50% assayed yield). It was therefore necessary to quench the reaction as soon as sufficient conversion was achieved. Conveniently, this amidation can be performed with crude thiophene **9** and crude isocyanate **16** to afford comparable yields.[15] The synthesis was completed by LiOH-mediated saponification.

This final route to EP4 antagonist **1** affords 41% overall yield, in just three linear steps, from commercially available 4-(trifluoromethyl)benzyl alcohol **14a** (Scheme 7). Importantly, this approach relies only on nontoxic and inexpensive transition metals, and none of the transformations require reaction temperatures below −25 °C.

Conclusion

In summary, three alternatives to the original synthesis of potent and selective EP4 antagonist **1** have been developed. The first approach, which featured a stepwise preparation of carboxylic acid **6**, allowed for the preparation of multikilogram quantities of **1**. The second more efficient synthesis involved an iron-catalyzed benzylation of 2,5-dimethylthiophene followed by a palladium-catalyzed three-component coupling, which reduced the longest linear sequence to four steps. Finally, an iron-catalyzed Friedel−Crafts amidation of thiophene fragment **9** with isocyanate **16** allowed for the preparation of the EP4 antagonist **1** with only three steps in the longest linear sequence. This final approach involves only nontoxic transition metals and no cryogenic steps.

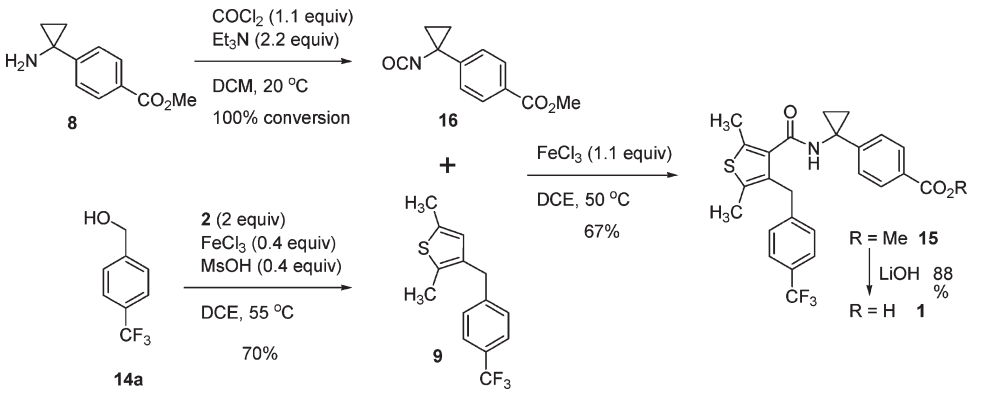
Experimental Section

(2,5-Dimethyl-3-thienyl)[4-(trifluoromethyl)phenyl]methanone (12). A visually clean, 100-L 5-neck round-bottom flask connected

(12) Wang, B.-Q.; Xiang, S.-K.; Sun, Z.-P.; Guan, B.-T.; Hu, P.; Zhao, K.-Q.; Shi, Z.-J. *Tetrahedron Lett.* **2008**, *49*, 4310–4312.
(13) Conditions used to brominate **9**.
(14) Beller, M.; Kumar, K.; Zapf, A.; Michalik, D.; Tillack, A.; Heinrich, T.; Bottcher, H.; Arlt, M. *Org. Lett.* **2004**, *6*, 7–10.

(15) Performing the Friedel−Crafts alkylation of 2,5-dimethylthiophene with isocyanate **16** followed by arylation with benzylic alcohol **14a** to afford **15** failed as a result of low conversion in the second reaction.

SCHEME 7. Final Route to EP4 Antagonist 1



to a scrubber filled with 5 N NaOH (20 L) was charged with chlorobenzene (45 L), benzoic acid **11** (5.96 kg, 31.4 mol), and DMF (10 mL). Oxalyl chloride (2.87 L, 32.9 mol) was added over 45 min. The mixture was heated with a steam bath until the internal temperature reached 50 °C. The reaction maintained an internal temperature of 45−50 °C. After 1 h, the cloudy reaction mixture was assayed by HPLC of an aliquot, which indicated 96% conversion of acid **11** to the corresponding acid chloride. After the internal temperature had dropped to 22 °C, dimethylthiophene (3.25 L, 28.5 mol) was added to the reactor at once, followed by titanium(IV) chloride (3.44 L, 31.4 mol) over 1 h via the addition funnel. The crude reaction mixture was transferred into a visually clean 160-L extractor charged with 1 N HCl (60 L). After vigorous stirring for 5 min, the phases were allowed to separate. The organic layer (bottom) was removed, and the aqueous layer was back-extracted with heptane (40 L). The organic phases were combined and washed with half-brine (20 L), and then the solvent volume was reduced in vacuo to afford a thin brown oil. HPLC analysis determined the material to be 52.77 wt % ketone **12**, or 8.24 kg, a 92.4% assay yield. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.95−7.83 (m, 4 H), 6.83 (s, 1 H), 2.56 (s, 3 H), 2.45−2.32 (m, 3 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 190.5, 147.7, 143.7, 136.4, 136.1, 130.3, 128.3, 126.2, 15.1, 14.6. ^{19}F NMR (375 MHz, acetone-d_6): δ −62.9. IR (NaCl plate): 3061.1 (m), 2923.5 (m), 2862.1 (w), 1651.8 (s), 1556.5 (m), 1480.3 (s), 1327.5 (s). HPLC ret time: 5.98 min. HRMS: calcd for $C_{14}H_{11}F_3OS$ 284.0483, obsd [M + H] 285.0556.

(4-Bromo-2,5-dimethyl-3-thienyl)[4-(trifluoromethyl)phenyl]-methanone (13). A visually clean, 100-L 5-neck round-bottom flask connected to a scrubber filled with 5 N NaOH (20 L) was charged with ketone **12** (13.27 kg, 52.7 wt %, 24.7 mol), chlorobenzene (33 L), and zinc chloride (33.6 g, 0.25 mol) and then cooled until the internal temperature reached 16 °C. Bromine (3.94 kg, 24.7 mol) was added over 1 h, and the mixture was aged for 15 min. The crude reaction mixture was transferred into a visually clean 160-L extractor charged with 1 N HCl (45 L). After vigorous stirring for 5 min, the phases were allowed to separate. The organic (bottom) layer was removed, and the aqueous layer back-extracted with heptane (25 L). The organic phases were combined and washed with half-brine (20 L). The solvent was then evaporated under reduced pressure to afford a thin brown oil. HPLC analysis determined the material to be 80.0 wt % bromoketone **13**, or 8.35 kg, a 93.6% assay yield. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.98 (d, J = 8.13 Hz, 2 H), 7.90 (d, J = 8.27 Hz, 2 H), 2.38 (s, 3 H), 2.35 (s, 3 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 191.9, 141.3, 140.4, 137.2, 134.5 (q, J = 36 Hz) 133.4, 130.9, 128.7 (q, J = 269.4 Hz), 126.6 (q, J = 4.7 Hz), 107.3, 14.4, 14.3. ^{19}F NMR (375 MHz, acetone-d_6): δ −63.1. IR (NaCl plate): 3073.3 (w), 2922.6 (m), 2857.5 (w), 1670.3 (s), 1540.0 (s), 1484.6 (m), 1321.1 (s). HPLC ret time: 6.49 min. HRMS calcd for $C_{14}H_{10}BrF_3OS$: 361.9661, obsd [M+H] 362.9667.

3-Bromo-2,5-dimethyl-4-[4-(trifluoromethyl)benzyl]thiophene (5). A visually clean, 5-L 3-neck round-bottom flask was charged with bromoketone **13** (0.43 kg, 86 wt %, 1.20 mol), triethylsilane (0.48 L, 2.98 mol), and dichloroethane (2.2 L) and then cooled until the internal temperature reached −8 °C. Titanium(IV) chloride (0.13 L, 1.20 mol) was added over 1 h, keeping the internal temperature below 14 °C. The crude reaction mixture was transferred into a visually clean 5-L extractor charged with 1 N HCl (2 L). After vigorous stirring for 5 min, the phases were allowed to separate. The organic (bottom) layer was removed, and the aqueous layer was back-extracted with heptane (1 L). The organic phases were combined and washed with half-brine (1 L). The solvent was removed under vacuum to afford 800 g thick brown oil. HPLC analysis determined the material to be 48 wt % bromoalkane **5**, or 0.384 kg, a 88% assay yield. ^{1}H NMR (400 MHz, dmso-d_6): δ 7.69−7.59 (m, 1 H), 7.31 (d, J = 8.02 Hz, 1 H), 3.98 (s, 1 H), 2.32 (d, J = 20.73 Hz, 3 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 145.1, 134.5, 133.1, 131.1, 128.6 (q, J = 31.9 Hz), 126.0 (q, J = 3.7 Hz), 125.9, 124.4 (q, J = 269.4 Hz), 112.2, 34.1, 14.9, 13.9. ^{19}F NMR (375 MHz, acetone-d_6): δ −62.9. IR (NaCl plates): 3065.3 (w), 2921.6 (m), 2857.5 (w), 1617.2 (s), 1417.4 (m), 1326.5 (s). HPLC ret time: 7.41 min. HRMS calcd for $C_{14}H_{12}BrF_3S$: 347.9795, obsd [M + H] 348.9821.

2,5-Dimethyl-4-[4-(trifluoromethyl)benzyl]thiophene-3-carboxylic Acid (6). A visually clean, 50-L 5-neck round-bottom flask was charged with bromoalkane **5** (4.00 kg, 37.6 wt %, 4.31 mol), tetramethylethylenediamine (711 mL, 4.74 mol), and MTBE (20 L) and then cooled until the internal temperature reached −65 °C. *n*-BuLi (2.24 L, 2.5M, 5.60 mol) was added over 1 h, keeping the internal temperature below −55 °C. The mixture was stirred for 0.5 h, and then CO_2 gas (∼ 300 g) was bubbled into the reaction mixture over 1.5 h, again keeping the internal temperature below −55 °C. After 1.5 h, HPLC analysis indicated ∼85% CO_2 incorporation (vs reduction). HCl (1 N, 13 L) was charged directly to the reactor. The biphasic solution was transferred into a visually clean 100-L extractor, and the phases were allowed to separate. The aqueous layer was removed and the organic layer collected. The aqueous layer was back-extracted with MTBE (6 L). The organic phases were combined and treated with 0.5 N KOH (13.0 L), and the aqueous layer collected. The organic phase was then back-extracted with 0.5 N KOH (6.5 L). The combined aqueous layers were returned to the extractor, which was also charged with MTBE (23 L). The biphasic solution was acidified by addition of 6 N HCl (1.25 L) until pH ∼1. The layers were allowed to separate, and the organic layer was collected and then washed with half-brine (13 L). The crude organic material was concentrated in vacuo, flushing with heptane (10 L) to afford a yellow solid (∼4.5 kg).

The crude solid was charged to a visually clean, 50-L round-bottom flask, suspended with heptane (23 L), and then cooled via an ice/acetone bath until the internal temperature reached 2 °C. The slurry was stirred for 6 h and then filtered over a glass frit, washing with cold heptane (1.25 L). The filter cake was dried via house vacuum under nitrogen overnight and then oven-dried at 50 °C for 24 h. A total of 1.22 kg of dry yellow solid was collected. HPLC analysis indicated the material to be 87 wt % acid **6**, 79% assay yield. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.55 (d, J = 8.02 Hz, 1 H), 7.30 (d, J = 7.97 Hz, 1 H), 4.29 (s, 1 H), 2.71−2.49 (m, 2 H). ^{13}C NMR (100 MHz, acetone-d_6): δ 165.3, 146.7, 145.6, 136.7, 136.6, 132.4, 129.4, 125.7, 125.6, 33.3, 16.0, 12.8. ^{19}F NMR (375 MHz, acetone-d_6): δ −62.2. IR (KBr pellet): 3023.5 (w), 2925.9 (m), 1674.0 (s), 1554.6 (w), 1480.4 (m), 1328.5 (s). HPLC ret time: 5.04 min. HRMS calcd for $C_{15}H_{13}F_3O_2S$: 314.0588, obsd [M + H] 315.0658.

Methyl 4-(1-Aminocyclopropyl)benzoate (8). A visually clean 100-L 5-neck round-bottom flask was charged with methyl 4-cyanobenzoate **10** (2.60 kg, 1.00 equiv) and toluene (40 L, 15 mL/g). The mixture was cooled to −25 °C, and then Ti(OiPr)$_4$ (4.73 L, 1.00 equiv) was added to the solution over 5 min. Ethylmagnesium bromide (10.5 L, 2.0 equiv) was added over a period of 2 h. The mixture was aged at −20 °C for 30 min, and then borontrifluoride diethyl ether (4.09 L, 2 equiv) was added over 40 min. The mixture was aged at −20 °C for 30 min, after which HPLC showed 93% conversion. The reaction was quenched by addition of 3 N HCl (40 L). The biphasic mixture was transferred to a 100-L extractor, and the layers were allowed to separate. The aqueous layer was washed with toluene (13 L, 5 mL/g) and then aqueous extracted with 2-methyltetrahydrofuran (Me-THF) (2 × 26 L) and 2 × 5 mL/g (2 × 13 L). The organic extracts were combined and washed with 3 N NaOH (26 L, 10 mL/g) and then brine (13 L, 5 mL/g). The assay yield of the cyclopropylamine **8** was determined by HPLC and shown to be 43.2% (1.334 kg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.28 Hz, 2 H); 7.33−7.20 (d, J = 8.28 Hz, 2 H); 3.86 (s, 3 H); 2.26 (s, 2 H); 1.17−1.10 (m, 2 H); 1.04−0.99 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9 152.2 129.6 127.6 124.7 51.9 36.4 19.2. IR: 3392.9 (w) 3325.0 (w) 3013.8 (w) 2955.2 (w) 1710 (s) 1609.6 (s) 1281.5 (s) 1107.8 (s). HRMS calcd for $C_{11}H_{13}NO_2$: 191.09463, obsd [M + H] 192.10257. Melting point: 49.6 −50.4 °C.

Methyl 4-(1-Aminocyclopropyl)benzoate·MsOH Salt (8·MsOH). A visually clean 100-L 5-neck round-bottom flask was charged with the cyclopropylamine **8** (2.63 kg, 1.00 equiv) and THF (32 L, 12 mL/g). To the solution was added the MsOH (1.00 L, 1.12 equiv) as a THF (4.0 L, 1.5 mL/g) solution over a period of 2 h. The suspension was stirred at room temperature for 15 h. The suspension was filtered, rinsed twice with cold THF (2 × 8 L, 2 × 3 mL/g), and then dried on the frit for 3 h and then in a vacuum oven first at 50 °C for a period of 60 h. The yield of material obtained was 3.93 kg, which was 94.4 wt % (yield = 92.9%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (s, 3 H); 7.96 (d, J = 8.24 Hz, 2 H); 7.50 (d, J = 8.24 Hz, 2 H); 3.84 (s, 3 H); 2.35 (s, 3 H); 1.46−1.39 (m, 2 H); 1.33−1.22 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 165.8 143.3 129.3 128.8 126.4 52.3 39.7 35.6 13.9. IR: 3017.4 (s) 2959.7 (s) 2721.7 (m) 1710.0 (s) 1612.8 (s) 1546.4 (s) 1435.5 (s) 1290.6 (s). HRMS calcd for $C_{11}H_{13}NO_2$: 191.09463, obsd [M + H] 192.10424. Melting point: 229.2 − 230.7 °C.

4-{1-[({2,5-Dimethyl-4-[4-(trifluoromethyl)benzyl]-3-thienyl}carbonyl)amino]cyclopropyl}benzoic Acid (1). A visually clean 100-L 5-neck round-bottom flask equipped with a NaOH scrubber was charged with thiophene acid **6** (2.95 kg at 91 wt % = 2.68 kg, 1.00 equiv), THF (16 L, 6 mL/g), and DMF (6.64 mL, 1 mol %). Oxalyl chloride (897 mL, 1.20 equiv) was added to the solution over a period of 30 min at room temperature. The mixture was aged at room temperature for 2 h, and then solvent and excess oxalyl chloride were removed under reduced pressure. The residue was treated with THF (27 L, 10 mL/g) and Hunig's base (2.24 L, 1.50 equiv) and then cooled to 3 °C. Cyclopropylamine **9** (1.88 kg, 1.15 equiv) was added to the solution as a THF solution (5 L, 2 mL/g) over a period of 30 min. The mixture was aged 30 min (99.8% conversion). To the solution were added MeOH (4 mL/g, 10.7 L) and 4 N LiOH (7.47 L, 3.5 equiv). The mixture was heated to 55 °C for 1.5 h and then recooled to 22 °C. The reaction was quenched by the addition of 2 N HCl (19 L, 7 mL/g). Organic solvents were removed under reduced pressure, and the residue dissolved in Me-THF (54 L, 20 mL/g). The biphasic mixture was transferred to a 120-L extractor, and the layers were separated. The aqueous layer was back-extracted using Me-THF (13 L, 5 mL/g). The combined organic layers were washed with water (13 L, 5 mL/g); the assay yield of the acid **1** showed to be 88.0% (3.56 kg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.75 (s, 1 H); 8.82 (s, 1 H); 7.71 (d, J = 8.20 Hz, 2 H); 7.57 (d, J = 8.00 Hz, 2 H); 7.24 (d, J = 8.00 Hz, 2 H); 7.06 (d, J = 8.20 Hz, 2 H); 4.00 (s, 2 H); 2.39 (s, 3 H); 2.27 (s, 3 H); 1.23−1.18 (m, 2 H); 1.08−1.04 (m, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 167.1 165.8 148.6 145.2 135.4 134.6 133.7 131.4 129.0 128.8 128.0 126.6 (q, J = 31.5 Hz) 125.0 (q, J = 3.7 Hz) 124.6 124.4 (q, J = 272.0 Hz) 34.3 31.5 18.8 13.9 12.5. ^{19}F NMR (377 MHz, DMSO-d_6): δ −66.9. IR 3291.9 (bw) 2924.6 (w) 1696.3 (m) 1630.2 (m) 1325.8 (s) 1116.7 (m). HRMS calcd for $C_{25}H_{22}NO_3SF_3$: 473.12725, obsd [M + H] 474.13494. Melting point: 254.1 −256.0 °C.

4-{1-[({2,5-Dimethyl-4-[4-(trifluoromethyl)benzyl]-3-thienyl}carbonyl)amino]cyclopropyl}benzoic Acid·DEA (1·DEA). A visually clean 100-L 5-neck round-bottom flask was charged with acid **1** (3.54 kg, 7.48 mol) and THF (21 L, 6 mL/g). Et_2NH (1.18 L, 1.52 equiv) was added to the suspension. Acid **1·DEA** salt seeds (30.0 g) were added, and the salt crystallized out. MTBE (25 L) was added over 2 h. The suspension was aged 13 h at room temperature. The mixture was cooled to 3 °C, and MTBE (27 L, 8 mL/g) was added over 2 h. The suspension was aged for 1.5 h and then filtered. The cake was rinsed with 1 × 7 L MTBE/THF (2:1) and 2 × 7 L MTBE. The cake was dried on the frit for 62 h under nitrogen and then dried in a vacuum oven at 60 °C for 20 h. The yield of **1·DEA** was 3.76 kg (92%) as a beige solid. The purity of the material by HPLC was 97.8 A%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.80 (s, 1 H); 7.68 (d, J = 8.16 Hz, 2 H); 7.56 (d, J = 8.00 Hz, 2 H); 7.24 (d, J = 8.00 Hz, 2 H); 7.02 (d, J = 8.16 Hz, 2 H); 3.98 (s, 2 H); 3.33 (s, 2 H); 2.74 (q, J = 7.18 Hz, 4 H); 2.38 (s, 3 H); 2.26 (s, 3 H); 1.18−1.13 (m, 2 H); 1.09 (t, J = 7.18 Hz, 6 H); 1.03−0.96 (m, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.3 165.7 145.2 145.1 135.8 134.9 134.3 133.8 131.2 128.8 128.7 126.6 (q, J = 31.5 Hz) 125.0 (q, J = 3.3 Hz) 124.4 (q, J = 271.6 Hz) 123.9 41.2 34.2 31.6 18.2 13.8 12.6 11.7. ^{19}F NMR (377 MHz, C_6D_6): δ −66.9. IR: 3219.4 (bw) 2985.6 (w) 2922.9 (s) 1627.0 (m) 1522.4 (m) 1377.4 (s) 1323.9 (s) 1127.9 (m) 1066.4 (m). HRMS calcd for $C_{25}H_{22}NO_3SF_3$: 473.12725, obsd [M + H − Et_2NH] 474.13427. Melting point: 254.1 −256.0 °C (loss of Et_2NH at 170 °C).

2,5-Dimethyl-3-[4-(trifluoromethyl)benzyl]thiophene (9). A visually clean 25-mL round-bottom flask was charged with 4-trifluoromethylbenzyl alcohol **14a** (257 mg, 1.46 mmol) and DCE (1.2 mL). To the solution were added 2,5-dimethylthiophene **2** (0.333 mL, 2.92 mmol), MsOH (38 μL, 0.584 mmol), and $FeCl_3$ (95 mg, 0.584 mmol). The mixture was put under nitrogen atmosphere and heated to 55 °C. The mixture was aged at this temperature for 16 h. The mixture was poured onto a saturated solution of NH_4Cl (20 mL) and diluted with MTBE (20 mL). The aqueous layer was separated and then back-extracted with MTBE (10 mL). Combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Assay yield of **9**: 278 mg (1.028 mmol), 70%. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.61 (d, J = 8.00 Hz,

2 H); 7.40 (d, J = 8.00 Hz, 2 H); 6.45 (s, 1 H); 3.91 (s, 2 H); 2.32 (s, 6 H). ^{13}C NMR (101 MHz, acetone-d_6): δ 146.8 136.1 135.9 132.1 129.9 128.5 (q, J = 31.8 Hz) 128.2 126.1 (q, J = 3.8 Hz) 125.5 (q, J = 271.1 Hz) 34.4 15.0 12.9. ^{19}F NMR (377 MHz, acetone-d_6): δ −66.9. IR: 2922.0 (w) 2861.9 (w) 1617.3 (m) 1324.0 (s) 1161.9 (m) 1123.3 (m) 1065.4 (m). HRMS calcd for $C_{14}H_{13}SF_3$: 270.06901, obsd [M + H] 271.07628.

Methyl 4-(1-Isocyanatocyclopropyl)benzoate (16). A visually clean 25-mL round-bottom flask was charged with phosgene (0.501 mL, 20 wt % toluene solution, 0.947 mmol) and DCM (5 mL) and cooled to 0 °C. To the solution was added the cyclopropylamine **8** (170 mg, 0.888 mmol) and Et_3N (272 μL, 1.953 mmol) as a DCM (2.5 mL) solution over a period of 15 min. The mixture was warmed to 20 °C and aged 30 min. The reaction was quenched by the addition of 1 N HCl and diluted with DCM (20 mL). The layers were separated, and the organic layers was washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used directly in the amidation. The material can be purified by flash chromatography 80:20 hexanes/EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.17 Hz, 2 H); 7.27 (d, J = 8.37 Hz, 2 H); 3.88 (s, 3 H); 1.42−1.40 (m, 2 H); 1.29−1.27 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5 146.2 129.8 128.7 124.3 121.6 52.0 38.4 19.5. IR: 2959.7 (w) 2285.1 (s) 1721.6 (s) 1609.6 (m) 1432.1 (m) 1281.5 (s) 1111.7 (s). HRMS calcd for $C_{12}H_{11}NO_3$: 218.08117, obsd [M + H] 218.08102. Melting point = 42.6 −43.2 °C.

Methyl 4-{1-[({2,5-Dimethyl-4-[4-(trifluoromethyl)benzyl-3-thienyl}carbonyl)amino]cyclopropyl} Benzoate (15). *By Friedel−Craft amidation*: A visually clean 10-mL round-bottom flask was charged with thiophene-alkane **9** (82 mg, 0.304 mmol) and DCE (1.5 mL). To the solution were added the cyclopropyl-isocyanate **16** (60 mg, 0.276 mmol) and the $FeCl_3$ (49 mg, 0.304 mmol). The mixture was put under nitrogen atmosphere and then warmed to 50 °C for 15 min. The reaction mixture was then poured onto a saturated solution of NH_4Cl (20 mL) and diluted with Me-THF (30 mL). The layers were separated, and the aqueous layer was back-extracted with Me-THF (20 mL). Combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated. Assay yield of **15**: 90 mg (0.185 mmol), 67%. *By three-component-coupling amidation*: In a hydrogenation bomb, the thiophene bromide **5** (75 mg, 0.215 mmol) was dissolved in anisole (3 mL). The cyclopropylamine **8** (62 mg, 0.322 mmol) was added to the solution, followed by the addition of dppf (54 mg, 0.097 mmol), bis(benzonitrile)palladium(II) chloride (12 mg, 32 mmol), and Et_3N (45 μL, 0.322 mmol). The mixture was put under a carbon monoxide atmosphere (300 psi) and heated to 140 °C. The mixture was kept at this temperature for 16 h and then checked by HPLC;. 52% conversion to the thiophene-amide **15** was observed. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.83 (s, 1 H); 7.71 (d, J = 8.20 Hz, 2 H); 7.57 (d, J = 7.96 Hz, 2 H); 7.23 (d, J = 7.96 Hz, 2 H); 7.07 (d, J = 8.20 Hz, 2 H); 4.01 (s, 2 H); 3.81 (s, 3 H); 2.39 (s, 3 H); 2.27 (s, 3 H); 1.25−1.21 (m, 2 H); 1.11−1.04 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 166.5 166.3 149.6 145.7 135.8 135.2 134.2 131.9 129.3 129.2 127.3 127.1 (q, J = 31.7 Hz) 125.5 (q, J = 3.7 Hz) 125.2 124.9 (q, J = 271.9 Hz) 52.4 34.8 32.0 19.4 14.4 13.0. ^{19}F NMR (377 MHz, acetone-d_6): δ −66.9. IR 3276.8 (w) 2923.0 (w) 1718.0 (s) 1638.2 (s) 1329.4 (m) 1118.7 (m) 1068.1 (w). HRMS calcd for $C_{26}H_{24}NO_3SF_3$: 487.14290, obsd [M + H] 488.15191. Melting point: 220.9 −221.7 °C.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **1**, **1·DEA**, **5**, **6**, **8**, **8·MsOH**, **9**, **12**, **13**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.