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Development of a Scaleable Synthesis of a 3-Aminopyrazinone Acetamide Thrombin Inhibitor

Michael S. Ashwood,*,† Ramon J. Alabaster,† Ian F. Cottrell,† Cameron J. Cowden,‡ Antony J. Davies,† Ulf H. Dolling,‡ Khateeta M. Emerson,† Andrew D. Gibb,† David Hands,† Debra J. Wallace,‡ and Robert D. Wilson†

Department of Process Research, Merck Sharp and Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK, and Department of Process Research, Merck Research Laboratories, Rahway, New Jersey 07065, U.S.A.

Abstract:

A scaleable route to 2-{3-[(2,2-difluoro-2-(2-pyridyl)ethyl)-amino]-6-chloro-2-oxohydropyrazinyl}-*N*-[(3-fluoro(2-pyridyl))-methyl]acetamide 1 is described in which various scaleup issues were addressed to provide a safe, efficient, and robust route for the preparation of multi-kilo amounts of the compound. The use of expensive and toxic reagents, notably sodium azide, TMS-cyanide, and Deoxo-Fluor, and the need for specialist equipment were overcome in the preparation of the key fluorinated intermediates 2,2-difluoro-2-(2-pyridyl)ethylamine 3 and 2-aminomethyl-3-fluoropyridine 2. With minimal isolations and through processing of intermediates, the thrombin inhibitor 1 was isolated in 36% overall yield.

Introduction

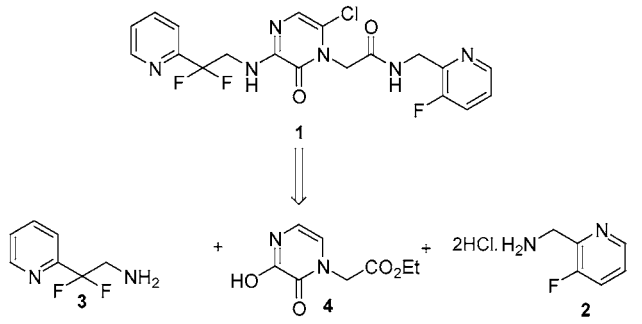
2-{3-[(2,2-Difluoro-2-(2-pyridyl)ethyl)amino]-6-chloro-2-oxohydropyrazinyl}-*N*-[(3-fluoro(2-pyridyl))methyl]acetamide **1** is a potent, orally active, reversible competitive inhibitor of thrombin with potential for the treatment and prevention of deep vein thrombosis and cardiogenic thromboembolism. Its preparation was recently described in the literature.[1−3]

Compound **1** was constructed from the three key intermediates (Scheme 1) 2-aminomethyl-3-fluoropyridine (AMFP·2HCl) **2**, 2,2-difluoro-2-(2-pyridyl)ethylamine (difluoroamine) **3**, and ethyl 2-(2,3-dioxo-1,4-dihydropyrazinyl)acetate (pyrazinone) **4**. The preparation of these three key intermediates and their coupling together posed several synthetic challenges for a large-scale synthesis. This paper describes how these challenges were overcome in designing a safe and efficient large-scale synthesis of **1**.

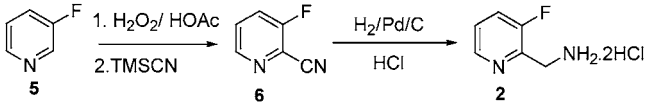
Results and Discussion

Preparation of AMFP·2HCl 2. The initial synthesis of AMFP·2HCl (Scheme 2) involved oxidation of 3-fluoropyridine **5** and reaction of the formed *N*-oxide with TMS-cyanide[4] to give 2-cyano-3-fluoropyridine **6** in 77% yield.[1] Hydrogenation of the nitrile **6** under aqueous acidic conditions gave the amine **2** in 72% yield. At least three recrystallizations of the crude product **2** from acetic acid/HCl were required to reduce the level of the 6-regioisomer from 3% to <1%. For safety and economic reasons, we were keen to eliminate the oxidation procedure, the use of TMS-cyanide, and the multiple recrystallizations.

Scheme 1



Scheme 2



The regioselective lithiation of 3-fluoropyridine **5** at C-2 or C-4 has been reported in the literature.[5] The use of 1,4-diazabicyclo[2.2.2]octane (DABCO) and diethyl ether was found to be critical for selective C-2 deprotonation with *n*-BuLi at low temperatures.[6] We discovered that substituting the less volatile methyl *tert*-butyl ether (MTBE) for diethyl ether and quenching the formed anion into a THF solution of carbon dioxide at −40 °C gave the required lithium 2-carboxylate **7** as a mixture of the 2- and 4-regioisomers in a 94:6 ratio[7] (Scheme 3). Although the isolation of the free acid has been reported,[8] it was not a straightforward procedure as it is very difficult to extract the acid from aqueous mixtures. The lithium salt **7** prepared following the

* To whom correspondence should be addressed. Telephone: +44 1992 452338. Fax: +44 1992 470437. E-mail: ashwood@merck.com.

† Merck Sharp and Dohme Research Laboratories.

‡ Merck Research Laboratories.

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(3) Dolling, U. H.; Alabaster, R. J.; Ashwood, M. S.; Cottrell, I. F.; Cowden, C. J.; Davies, A. J.; Hands, D.; Wallace, D. J.; Wilson, R. D. Patent WO 2002046160.

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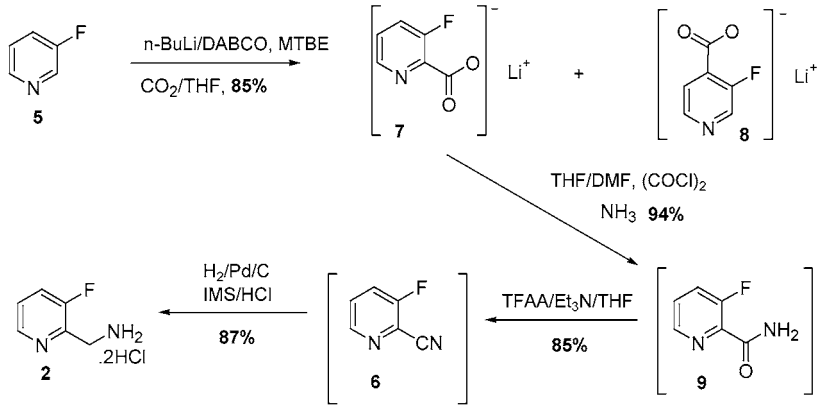
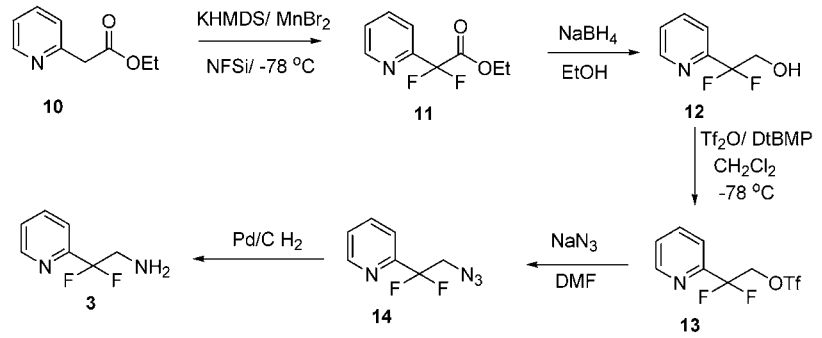
10.1021/op0341420 CCC: $27.50

Scheme 3



Scheme 4



above procedure was insoluble in the reaction mixture. Filtration of this amorphous solid and drying in vacuo gave the required salt **7** 83% pure contaminated with DABCO (5%), lithium valerate (from the reaction of carbon dioxide with *n*-BuLi, 7%), and the 4-regioisomer **8** (5%). Solubility studies indicated that all these impurities were highly soluble in methanol, whereas the required 2-regioisomer **7** was sparingly soluble (20 mg/mL). These observations prompted us to examine the use of methanol as a cosolvent once the lithium salt had formed.

The addition of methanol to the cold reaction mixture caused selective crystallization of the 2-regioisomer **7**, resulting in the isolation of lithium 3-fluoropyridine-2-carboxylate **7** in 83% yield, >99% pure contaminated with less than 0.5% of the 4-regioisomer **8**.

Conversion of the lithium 2-carboxylate **7** in THF to the acid chloride and treatment with gaseous ammonia gave, after filtration of the lithium and ammonium salts, the amide **9** in 94% yield. The THF solution was suitable for use in the next step. Attempts at reducing this amide **9** directly to the amine **2** using a variety of conditions (borane·THF, $LiAlH_4$) had failed. The THF solution of the amide **9** was treated with trifluoroacetic anhydride (TFAA) and triethylamine[9] to give the nitrile **6** in 85% yield, isolated as an IMS (ethanol containing 5% methanol) solution. This solution was hydrogenated over palladium on carbon in the presence of gaseous HCl to give the required AMFP·2HCl **2** in 92% yield. Aqueous HCl had been used in the hydrogenation initially, but this resulted in up to 20% of 2-hydroxymethyl-3-fluoropyridine being formed. Anhydrous conditions in the hydrogenation minimized the hydrolysis of the imine intermediate and its subsequent reduction to the alcohol to <1%.

As the 4-regioisomer **8** had essentially been removed in the carboxylation step, there was no need for the multiple recrystallizations associated with the previous route. A single recrystallization of the crude AMFP·2HCl **2** from acetic acid/HCl gave the product as a crystalline solid in 59% overall yield, >98% pure from 3-fluoropyridine **5**.

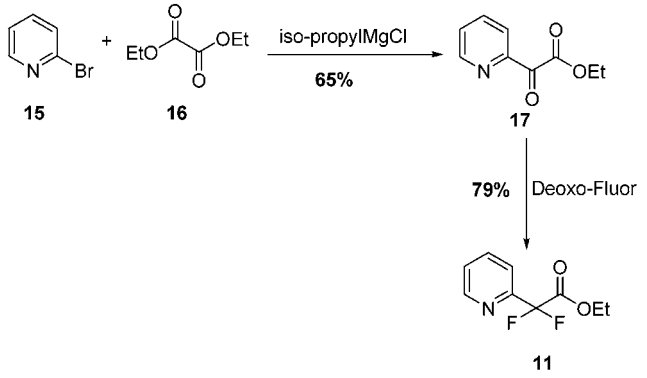
Although the preparation of AMFP·2HCl **2** was now carried out in four steps, significant improvement had been made to the process. The overall yield had been increased from 41% to 59%, but more significantly the use of TMS-cyanide and the potentially hazardous peroxide oxidations had been eliminated, as had the multiple recrystallizations needed to reduce the regioisomer content. This resulted in a convenient, scaleable, and reproducible route to prepare multi-kilo quantities of the AMFP·2HCl **2**.

Preparation of Difluoroamine 3 as Its Benzenesulfonate Salt. The preparation of 2,2-difluoro-2-(2-pyridyl)-ethylamine **3** as shown in Scheme 4[1] presented several challenges for large-scale operations: the cost and availability of **10**, the need for low temperatures and fluorinating agents in the first step, and serious safety issues with the use of sodium azide were far from ideal. The five-step synthesis had an overall yield of only 11% and required column chromatography to purify a number of the intermediates.

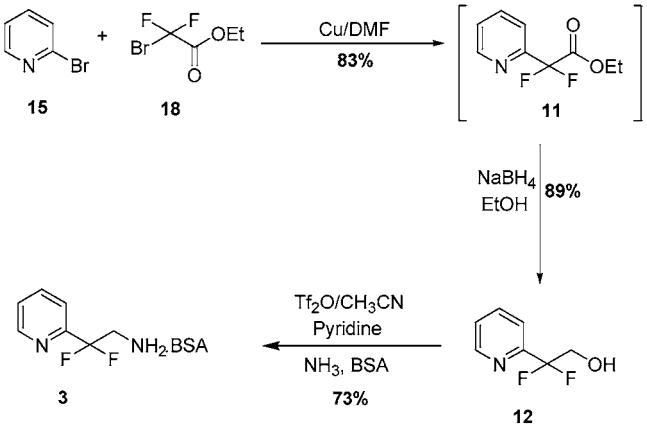
An alternative procedure for the preparation of the ester **11** is shown in Scheme 5. Formation of the anion of 2-bromopyridine **15** with isopropylmagnesium chloride at

(9) Rhee, J.; Lim, J.; Im, W.; Yang, J. *Bull. Korean Chem. Soc.* **1993**, *14* (4), 301−302.

Scheme 5



Scheme 6



34 °C followed by acylation with diethyl oxalate gave the keto ester **17** in up to 65% yield. Fluorination of **17** with Deoxo-Fluor[10] in toluene at 70 °C gave the required ester **11** in 79% yield. The use of highly toxic fluorinating reagents with the need for specialist equipment, the cost and availability of the reagent, and the relatively low yield over the two steps (51%) also ruled out this procedure for multi-kilo scale reactions. A shorter, safer, and higher yielding synthesis of **3** was required.

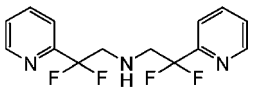
Both 2-bromopyridine **15** and ethyl bromodifluoroacetate **18** (Scheme 6) are available in bulk quantities. Encouraged by literature reports of metal-initiated coupling reactions to prepare the aryldifluoroesters,[11−13] it was shown that stirring **15** and **18** together with copper powder in DMSO at 50 °C gave the required difluoroethyl ester **11**.[13,14] Operational safety testing indicated that carrying out the reaction in DMSO at 50 °C on a large scale could lead to an uncontrollable exotherm resulting in a hazardous operation. Other solvents including DMF, *N*-methyl pyrrolidinone, *N*,*N*-dimethylacetamide (DMA), acetonitrile, ethanol, tetrahydrofuran, and isopropyl acetate were screened as alternatives. Only DMF and *N*-methyl pyrrolidinone gave complete conversion to the difluoroester **11** within 24 h. However, on scaleup DMF gave product **11** in an identical yield (83%) and purity, whereas *N*-methyl pyrrolidinone gave a lower 50% isolated yield. Operational safety testing indicated DMF was safe to use as the solvent on scaleup, and so it became the solvent of choice for this coupling reaction.

After an aqueous workup and the removal of the copper salts, the ester **11** was obtained as a solution in ethanol in 83% assay yield that was suitable for further processing.

As in the original synthesis,[1] the difluoroethylester **11** was reduced to the difluoroethanol **12** using sodium borohydride in an 89% yield, isolating the product as an off-white crystalline solid.

Research quantities of **3** were prepared according to Scheme 4.[1] The difluoro alcohol **12** was converted to the stable triflate **13** with triflic anhydride (Tf_2O) and 2,6-di-*tert*-butyl-4-methylpyridine (DtBMP) in methylene chloride at −78 °C in quantitative yield. This was isolated and treated with sodium azide to give the azide **14** in 75% yield. Hydrogenation of this azide **14** over 10% Pd/C gave the required difluoroamine **3** in only 78% yield.

We envisaged a more direct method of preparing the difluoroamine **3** without using sodium azide. We knew that the difluoro alcohol **12** could be converted to the triflate **13** in quantitative yield and isolated as an oil. Dissolving the crude triflate **13** in ethanolic ammonia[15] (2.0 M) gave a 1:1 mixture of the required difluoroamine **3** and a dimer **19**, identified by NMR and mass spectrometry. The crude triflate **13** was not soluble in concentrated aqueous ammonia and did not react. However the addition of a water-miscible cosolvent, e.g., 2-propanol or acetonitrile, solubilized the triflate **13** and allowed it to react. In a later development, we discovered that the triflate **13** could be prepared in acetonitrile, replacing DtBMP with pyridine. The addition of an excess of concentrated aqueous ammonia to this acetonitrile solution at room temperature gave the required difluoroamine **3** with <6% of the dimer **19** formed. An extractive workup gave the difluoroamine free base **3** as a solution in methylene chloride. Initially the difluoroamine free base **3** was purified by short-path distillation (0.4 mmHg and 75 °C). However large-scale distillations gave lower yields due to decomposition. Another scaleable method of purification was sought.



19

The *p*-toluenesulfonic acid (pTSA), benzenesulfonic acid (BSA), and di-HBr salts could all be prepared as crystalline solids. However, the di-HBr salt proved more difficult to crystallize than the other two. Benzenesulfonic acid was the acid of choice as it was easier to dissolve in isopropyl acetate, pTSA at the time being available only as the monohydrate.

The addition of an isopropyl acetate solution of benzenesulfonic acid gave the difluoroamine **3** as its crystalline

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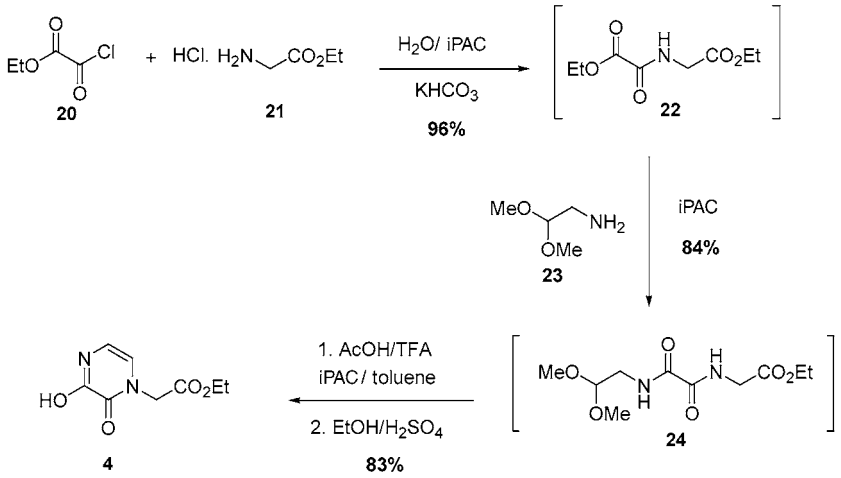
(15) Jpn. Kokai Tokkyo Koho, 06219994 1994.

Scheme 7



BSA salt in 73% yield (>98% pure). The amount of the dimeric impurity **19** present in the isolated salt was reduced to <1%.

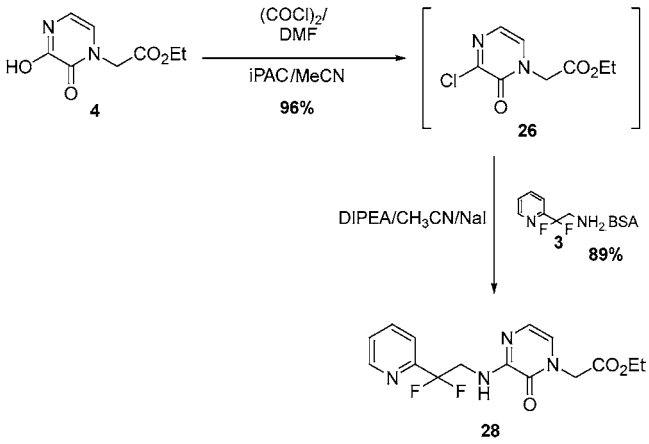
The preparation of this key intermediate had been reduced from five steps to three steps, five isolations to only two both as crystalline solids, and the overall yield increased from 11% to 53%. The use of low-temperature reactions, fluorinating agents, and sodium azide had all been removed from the process.

Preparation of the Pyrazinone 4. The preparation of ethyl 2-(2,3-dioxo-1,4-dihydropyrazinyl)acetate **4** was based on the methods of both Cheeseman[16] and Fleitz.[17]

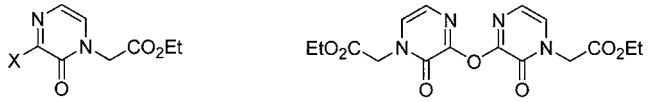
As shown in Scheme 7, the chemistry used in the preparation of this intermediate remained the same as previously published.[1] However, the processing was simplified for large-scale synthesis, the pyrazinone **4** being prepared with just a single isolation of a crystalline solid. Following this procedure, glycine ethyl ester **21** was acylated with ethyl oxalyl chloride **20** (2.0 equiv) at 0 °C under Schotten−Baumann conditions. Ethyl oxamate **22** was obtained as an isopropyl acetate (iPAc) solution in 96% yield. Addition of amino-acetaldehyde dimethyl acetal **23** to this solution at room temperature gave the ethyl oxamide **24** again as a solution in isopropyl acetate in 84% yield. Exchanging acetic acid (AcOH) for isopropyl acetate and heating the crude ethyl oxamide **24** to 78 °C with trifluoroacetic acid (TFA) gave, after crystallization from isopropyl acetate/toluene, the pyrazinone **4** as a crystalline white solid in 72% overall yield from glycine ethyl ester **21**. The solid contained up to 6% of the free acid, produced on a large scale by hydrolysis of the ethyl ester **4** on prolonged heating in acetic acid/isopropyl acetate. Recrystallization of the solid from ethanol containing 5 mol % of sulfuric acid gave the pyrazinone **4** in 67% overall yield from glycine ethyl ester **21**, >99% pure with <0.2% of the free acid present.

First Coupling Reaction. Originally the pyrazinone **4** was coupled with the difluoroamine free base **3** to give the ester **28** via the imidoyl bromide **25**.[1] However, operational safety

Scheme 8



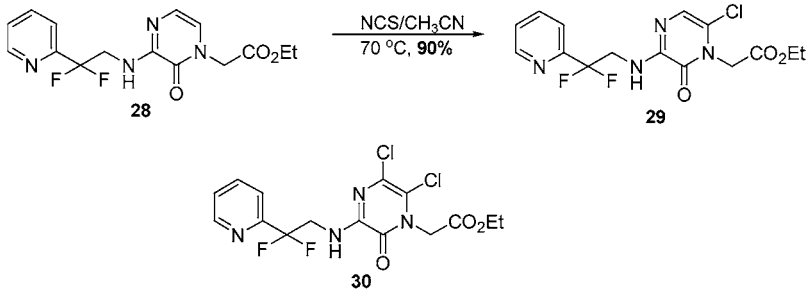
testing indicated that the imidoyl bromide **25** was potentially thermally unstable and shock sensitive. It was therefore unsafe to use in multi-kilo operations. Another coupling procedure was required.



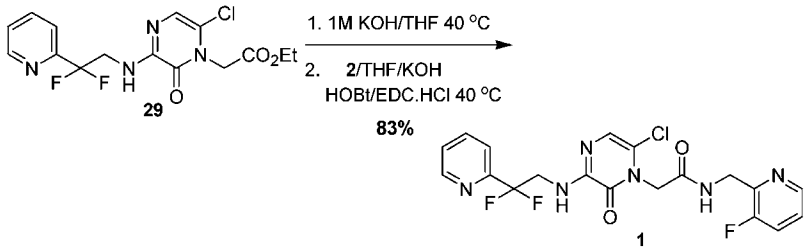
As an alternative to the imidoyl bromide **25**, we investigated the use of the imidoyl chloride **26** (Scheme 8). This was initially prepared by the reaction of the pyrazinone **4** with phosphorus oxychloride in methylene chloride. However, significant amounts of the ether **27** were also formed. This was difficult to remove, the purified imidoyl chloride **26** being isolated after column chromatography. Clean chlorinations could be achieved by using either thionyl chloride or oxalyl chloride in isopropyl acetate or acetonitrile with a catalytic amount of DMF, oxalyl chloride being the reagent of choice due to the formation of easily removable gaseous byproducts. The reaction mixture was initially quenched with the addition of aqueous potassium hydrogencarbonate to remove HCl, but the imidoyl chloride **26** was shown to be unstable to these conditions, decomposing at a rate of up to 6% per hour. Quenching the reaction with

(16) Cheeseman, G. W. H.; Freestone, A. J.; Godwin, R. A.; Hough, T. L. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1888−1891.
(17) Fleitz, F. J.; Lyle, T. A.; Zheng, N.; Armstrong, J. D.; Volante, R. P. *Synth. Commun.* **2000**, *30*, 3171−3180.

Scheme 9



Scheme 10



aqueous sodium chloride reduced this rate of decomposition to <1.5% per hour. In a further development, replacing isopropyl acetate with acetonitrile as solvent allowed for the non-isolation of the imidoyl chloride **26**.

Stirring **26** together with the weakly nucleophilic difluoroamine free base **3** in acetonitrile at 90 °C gave a disappointing 25% conversion to **28** after 16 h. Adding sodium iodide (0.1 equiv) to the reaction mixture increased this to 51%; however, adding 1.0 equiv of sodium iodide dramatically increased this to 97% after 16 h. The ester **28** was isolated in 81% yield by the addition of water followed by filtration of the crystalline solid. Other additives such as tetra-*n*-butylammonium bromide or iodide had little effect on this coupling reaction.

Using difluoroamine·BSA salt **3** in these conditions, a disappointing 23% conversion to the ester **28** was achieved. However, increasing the amount of sodium iodide to 2.0 equiv and adding *N*,*N*-diisopropylethylamine (DIPEA; 1.05 equiv) increased this conversion to 98% after 30 h at reflux temperature (90 °C). The subsequent addition of an aqueous base allowed the ester **28** to be isolated from the reaction mixture.

Thus, the pyrazinone **4** was treated with DMF/oxalyl chloride in isopropyl acetate/acetonitrile at 40 °C, and after an aqueous work up and solvent switch, the imidoyl chloride **26** was obtained in 96% yield as a solution in acetonitrile. Difluoroamine·BSA salt **3**, *N*,*N*-diisopropylethylamine, and sodium iodide were added to this solution, and the mixture was stirred at reflux temperature for 30 h. On controlled addition of aqueous potassium hydrogencarbonate, the coupled ester **28** crystallized as a white solid and was isolated in 85% yield, >99% pure, over the two steps.

Chlorination of the Coupled Ester 28. The coupled ester **28** was chlorinated with *N*-chlorosuccinimide[1] (NCS) (Scheme 9).

To minimize the formation of the dichloro derivative **30**, which proved difficult to remove on recrystallization, careful control over the reaction stoichiometry was required. NCS (1.02 equiv) was added as a solution in acetonitrile to the ester **28** in acetonitrile at 70 °C. When the reaction was complete, the chloro-ester **29** was precipitated with water and isolated as a crystalline solid. This workup avoided a partition between EtOAc/H_2O, with its problematic emulsions, and the need for a silica gel purification. The chloro-ester **29** was obtained in 90% yield, 97.5% pure, with the starting ester **28** (1.2%) and the dichloro derivative **30** (0.7%) as impurities. These low levels of impurities were rejected during the subsequent coupling reaction and recrystallization of **1**, so crude **29** was used without further purification.

Final Coupling Reaction. An aqueous solvent system was chosen for the final coupling reaction (Scheme 10) in order to allow the ester hydrolysis and coupling to be carried out as a through process. The chloro-coupled ester **29** in THF was hydrolyzed with aqueous 1 M KOH and coupled with AMFP·2HCl **2** in the presence of 1-hydroxybenzotriazole (HOBt) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl). HOBt replaced the more expensive 1-hydroxy-7-azabenzotriazole. Again water was added to precipitate the product, which was isolated in 91% yield. Crude **1** was recrystallized from absolute ethanol and isolated as a white crystalline solid in 91% yield (99.6 wt % pure).

Conclusions

This paper describes the preparation of the novel thrombin inhibitor **1** in a safe and efficient manner suitable for multi-kilo amounts. The original medicinal chemistry route[1] was modified suitably so that the use of expensive and hazardous reagents, notably sodium azide, TMS-cyanide, and Deoxo-Fluor was overcome. Productivity and yields were substantially increased by the minimal isolation of crystalline intermediates, several steps being combined as through processes. This together with the optimization of reaction conditions allowed **1** to be prepared in an overall yield of 36% from 2-bromopyridine **15**.

Experimental Section

All reactions were carried out under a positive pressure of nitrogen. ^{1}H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, in the solvent indicated on a Bruker DPX 400 spectrometer. Mass spectrometry results were obtained on an Agilent 1100 MSD HPLC/MS system. Melting points were obtained on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. All purity values were obtained by HPLC analysis at 210 nm.

All compounds were prepared on multi-kilo amounts apart from **2**, **6**, **7**, **9**, and **28**. These compounds were prepared on a multigram scale with processing suitable for multi-kilo amounts.

Lithium 3-Fluoropyridine-2-carboxylate (7).[7] DABCO (0.111 kg; 989 mmol) was dissolved in methyl *tert*-butyl ether (4 L) under a nitrogen atmosphere. The solution was cooled to −45 °C, and *n*-butyllithium in hexane (2.5 M, 0.395 L; 988 mmol) was added slowly while maintaining the temperature below −40 °C. The mixture was aged for 2 h at −40 to −45 °C. A solution of 3-fluoropyridine (**5**, 0.08 kg; 824 mmol) in methyl *tert*-butyl ether (0.4 L) was added over 45 min while maintaining the temperature between −40 and −45 °C. The reaction mixture was aged at −45 °C for 4 h.

A saturated solution of carbon dioxide (ca. 0.18 kg; 4.09 mol) in THF was prepared by bubbling the gas through THF (3.8 L) at −60 °C. The anion reaction mixture was cooled to −60 °C and quenched into the THF/carbon dioxide solution. Carbon dioxide was continuously bubbled into the THF solution during the transfer of the anion. The mixture was aged at −60 °C for 30 min, methanol (1.6 L) was added to the mixture, and the slurry was allowed to warm to 20 °C. The product **7** was collected by filtration under nitrogen, and the wet cake was washed with methanol/THF (1:10, 0.2 L), collected, and dried in vacuo at 45 °C. Lithium 3-fluoropyridine-2-carboxylate (**7**, 0.103 kg) was obtained as a crystalline white solid in 85% yield, >99% pure containing <0.5% 4-regioisomer **8**. ^{1}H NMR (DMSO-d_6, δ) 8.12 (dt, J = 1.3, 4.6 Hz, 1H), 7.45 (dt, J = 1.3, 8.4 Hz, 1H), 7.24 (dt, J = 4.6, 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, δ) 167.3 (d, J = 4 Hz), 157.1 (d, J = 258 Hz), 147.2 (d, J = 15 Hz), 144.3 (d, J = 5 Hz), 125.1 (d, J = 4 Hz), 124.8 (d, J = 20 Hz); MS m/z 142.1 (M + H$^+$).

3-Fluoropyridine-2-carboxamide (9).[6] The lithium carboxylate (**7**, 0.08 kg; 540 mmol) was slurried in THF (4.0 L) at 20 °C, and DMF (2.1 mL) was added. Oxalyl chloride (0.0585 L, 0.085 kg; 680 mmol) was added over 20 min maintaining the temperature below 25 °C. The mixture was stirred at this temperature for 3 h. Ammonia gas (0.055 kg; 3.22 mol) was passed over the solution for 45 min keeping the temperature below 25 °C. The reaction mixture was stirred at room temperature for 1 h and filtered, and the solid was washed with THF (6.0 L). The filtrate was distilled under reduced pressure at below 30 °C to a volume of 0.7 L. The amide **9** crystallized, giving a slurry, used "as is" in the next reaction. 3-Fluoropyridine-2-carboxamide (**9**, 0.072 kg) was obtained in 94% assay yield. Mp 140−2 °C; ^{1}H NMR (CD_2Cl_2, δ) 8.32 (dt, J = 1.6, 4.5 Hz, 1H), 7.51 (ddd, J = 1.43, 8.58, 10.81 Hz, 1H), 7.45 (m, 1H); ^{13}C NMR (CD_2Cl_2, δ) 165.4, 159.4 (d, J = 271 Hz), 144.2 (d, J = 5 Hz), 137.3, 128.6 (d, J = 5 Hz), 126.2 (d, J = 20 Hz); MS m/z 141.2 (M + H$^+$), 163.1 (M + Na$^+$). Anal. Calcd for $C_6H_5FN_2O$: C, 51.43; H, 3.60; F, 13.56; N, 19.99. Found: C, 50.86; H, 3.58; F, 13.11; N, 19.52.

3-Fluoropyridine-2-carbonitrile (6).[1] Trifluoroacetic anhydride (0.145 kg, 0.0976 L; 690 mmol) was added over 40 min to a slurry of the amide (**9**, 0.072 kg) in THF (0.8 L) and triethylamine (0.078 kg, 0.11 L; 770 mmol) maintaining the temperature below 25 °C. The solution was stirred at 25 °C for 10 min. 10 wt % aqueous sodium carbonate (0.5 L), water (0.6 L), and isopropyl acetate (0.7 L) were added, the layers were separated, and the aqueous layer was re-extracted with isopropyl acetate (0.35 L). The organic layers were combined and washed with 1 M aqueous hydrochloric acid (0.7 L). The isopropyl acetate solution was solvent switched under reduced pressure to IMS (ethanol denatured with 5% methanol) to a volume of 0.3 L. The solution was diluted with IMS (final volume = 0.8 L). 3-Fluoropyridine-2-carbonitrile (**6**, 0.053 kg) was obtained as a solution in IMS in 85% assay yield. ^{1}H NMR (CD_3OD, δ) 8.57 (dt, J = 4.6, 1.4 Hz, 1H), 7.89 (td, J = 1.3, 8.7 Hz, 1H), 7.81−7.75 (m, 1H); ^{13}C NMR (CD_3OD, δ) 163.00 (d, J = 265 Hz), 148.66 (d, J = 4 Hz), 131.13 (d, J = 5 Hz), 126.46 (d, J = 18 Hz), 123.47 (d, J = 16 Hz), 114.22 (d, J = 5 Hz); MS m/z 123.2 (M + H$^+$).

2-Aminomethyl-3-fluoropyridine·2 HCl (2).[1] The IMS solution of the nitrile (**6**, 0.053 kg in 0.8 L; 436 mmol) was diluted with 3.65 M HCl in IMS (0.385 L; 1.40 mol) and hydrogenated for 18 h at 50 psi and 20 °C using wet 10% Pd/C (0.013 kg; 58% moisture) as the catalyst. Water (0.175 L) was added, and the catalyst was removed by filtration and washed with 85:15 IMS/water (0.24 L). The combined filtrates were stirred with Darco G60 (activated carbon, 100 mesh) (0.012 kg) for 1 h at 20 °C, the mixture was filtered, and the Darco G60 was washed with 85:15 IMS/water (0.2 L). The combined filtrates were solvent switched to IMS under reduced pressure to give a volume of 0.3 L. The crystallizing mixture was cooled to 20 °C, isopropyl acetate (0.5 L) was added over 1 h, and the mixture was stirred at 20 °C for 30 min. The product was collected by filtration, washed with isopropyl acetate (0.2 L), and dried in vacuo at 40 °C. 2-Aminomethyl-3-fluoropyridine·2HCl (**2**, 0.078 kg) was isolated as a white solid in 92% yield, >98% pure.

Recrystallization. AMFP·2HCl (**2**, 0.065 kg) was slurried in acetic acid (0.65 L) and heated to 95 °C. The solution was allowed to cool slowly, and HCl gas was bubbled through the mixture for 10 min at 50 °C. The mixture was allowed to cool to 20 °C and then stirred for 30 min. The solid was collected by filtration, washed with isopropyl acetate (0.1 L), and dried in vacuo at 40 °C. 2-Aminomethyl-3-fluoropyridine·2 HCl (**2**, 0.0618 kg) was obtained in 95% yield, >99% pure. ^{1}H NMR (DMSO-d_6, δ) 8.78 (bs, 2H), 8.47 (dt, J = 4.8, 1.4 Hz, 1H), 7.87 (bs, 2H), 7.82 (ddd, J = 1.3, 8.4, 9.9 Hz, 1H), 7.56 (m, 1H), 4.20 (m, 2H); ^{13}C NMR (DMSO-d_6, δ) 156.71(d, J = 255 Hz), 145.75 (d, J = 5 Hz),

141.56 (d, $J = 15$ Hz), 125.55 (d, $J = 4$ Hz), 123.94 (d, $J = 18$ Hz), 37.41; MS m/z 127.1 ($M + H^+$). Anal. Calcd for $C_6H_9N_2FCl_2$: C, 36.20; H, 4.56; N, 14.07; Cl, 35.62; F, 9.54. Found: C, 35.91; H, 4.61; N, 14.15; Cl, 35.24; F, 9.29.

Ethyl 2,2-Difluoro-2-(2-pyridyl)acetate (11).[1,14] 2-Bromopyridine (**15**, 4.5 kg; 28.48 mol) and ethyl 2-bromo-2,2-difluoroacetate (**18**, 6.0 kg; 29.56 mol) were added to a stirred suspension of copper bronze[18] (4.5 kg; 70.82 mol) in dimethylformamide (22.5 L). The reaction mixture was stirred under a nitrogen atmosphere at 51 °C for 9 h. Isopropyl acetate (34 L) was added, and the resulting suspension was cooled to 15 °C. Meanwhile a quench solution of potassium dihydrogenphosphate (8.58 kg; 63.04 mol) in water (50 L) was prepared at room temperature and added to the reaction mixture ensuring that the temperature remained <20 °C. The mixture was stirred at room temperature for 30 min before filtering. The solid was washed with isopropyl acetate (2 × 15 L). The upper organic layer in the filtrate was separated and washed twice with water (2 × 22.5 L), and the solvent was switched from isopropyl acetate giving ethyl 2,2-difluoro-2-(2-pyridyl)acetate (**11**, 4.74 kg) as a solution in ethanol (27 L total volume) in 83% assay yield. ^{1}H NMR (CD_2Cl_2, δ) 8.63 (m, 1H), 7.89 (td, $J = 7.7$, 1.7 Hz, 1H), 7.74 (dt, $J = 8.0$, 1.1 Hz, 1H), 7.44 (m, 1H), 4.39 (q, $J = 7.2$ Hz, 2H), 1.29 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CD_2Cl_2, δ) 163.63 (t, $J = 33$ Hz), 151.95 (t, $J = 28$ Hz), 149.85, 137.91, 126.18, 120.73, 112.71 (t, $J = 249$ Hz), 63.62, 14.01; MS m/z 202.2 ($M + H^+$).

2,2-Difluoro-2-(2-pyridyl)ethan-1-ol (12).[1] Ethyl 2,2-difluoro-2-(2-pyridyl)acetate **11** in ethanol (4.74 kg in 27 L; 23.56 mol) was cooled to 15 °C. Sodium borohydride (670 g; 17.71 mol) was added portionwise to the reaction mixture over 1 h maintaining a temperature <30 °C. After the addition, the reaction mixture was stirred at ambient temperature for 1.5 h and then quenched by the dropwise addition of hydrochloric acid (2 M, 12.86 L; 25.72 mol), maintaining a temperature < 30 °C. The solution was concentrated under reduced pressure to a volume of 13 L and basified to pH 14 by the addition of 48% aqueous sodium hydroxide solution (2.0 L; 24.68 mol), again maintaining the internal temperature < 30 °C. The aqueous solution was extracted twice with methyl *tert*-butyl ether (47 L then 24 L), and the organic cuts were combined and evaporated to a volume of 13 L. The solution was cooled to 0 °C, and *n*-heptane (24 L) was added dropwise over 30 min to induce crystallization. The resulting slurry was stirred at 0−3 °C for 1 h and filtered. The filter cake was washed with *n*-heptane (5 L) and dried in vacuo at 30 °C. 2,2-Difluoro-2-(2-pyridyl)ethan-1-ol (**12**, 3.34 kg) was obtained as an off-white crystalline solid in 89% yield, 74% from 2-bromopyridine **15**, >99% pure. Mp 67−69 °C; ^{1}H NMR (CD_2Cl_2, δ) 8.64 (m, 1H), 7.92 (td, $J = 7.8$, 1.8 Hz, 1H), 7.75 (dt, $J = 8.0$, 1.1 Hz, 1H), 7.47 (m, 1H), 4.23 (t, $J = 12.7$ Hz, 2H), 3.61 (bs, 1H); ^{13}C NMR (CD_2Cl_2, δ) 154.00 (t, $J = 29$ Hz), 149.24, 138.10, 125.76, 121.24, 118.55 (t, $J = 241$ Hz), 64.52 (t, $J = 31$ Hz); MS m/z 160.2 ($M + H^+$). Anal. Calcd for $C_7H_7F_2NO$: C, 52.83; H, 4.43; F, 23.88; N, 8.80. Found: C, 52.77; H, 4.44; F, 23.91; N, 8.82.

2,2-Difluoro-2-(2-pyridyl)ethylamine Benzenesulfonic Acid Salt (3). 2,2-Difluoro-2-(2-pyridyl)ethan-1-ol (**12**, 3.5 kg; 21.99 mol) was dissolved in acetonitrile (35 L), and pyridine (2.31 L; 34.96 mol) was added. The solution was cooled to 0 °C, triflic anhydride (6.83 kg; 24.20 mol) was added at below 18 °C over 1 h, and the mixture was stirred at 10 °C for 15 min. Concentrated aqueous ammonia (35 L; 556 mol) was added at room temperature, and the solution was stirred at 20−25 °C for 17 h. The orange solution was concentrated under reduced pressure to a volume of approximately 35 L and basified to pH 14 with 48% aqueous sodium hydroxide (3.5 L; 42 mol). The aqueous solution was extracted with methylene chloride (2 × 35 L), and the combined methylene chloride extracts were evaporated to a volume of 35 L. A solution of benzenesulfonic acid (2.80 kg; 17.70 mol) in isopropyl acetate (28 L) was added at below 10 °C over 20 min causing the salt to crystallize. The mixture was stirred at 5 °C for 1 h. The solid was collected by filtration, washed with isopropyl acetate (2 × 5.0 L), and dried in vacuo at 35 °C. 2,2-Difluoro-2-(2-pyridyl)ethylamine·BSA (**3**, 5.07 kg) was isolated in 73% yield as a light brown, crystalline solid, >98% pure. Mp 178−9 °C; ^{1}H NMR (CD_2Cl_2/CD_3OD, δ) 8.59 (m, 1H), 7.91 (td, $J = 7.8$, 1.8 Hz, 1H), 7.81−7.76 (m, 2H), 7.71 (dt, $J = 8.0$, 1.1 Hz, 1H), 7.50−7.46 (m, 1H), 7.40−7.33 (m, 3H), 4.15 (bs, 1H), 3.81 (t, $J = 14.3$ Hz, 2H); ^{13}C NMR (CD_2Cl_2/CD_3OD, δ) 153.65 (t, $J = 29$ Hz), 151.67, 146.96, 140.57, 132.62, 130.63, 128.70, 128.04, 122.80, 119.36 (t, $J = 241$ Hz), 45.55 (t, $J = 29$ Hz); MS m/z 159.2 ($M + H^+$). Anal. Calcd for $C_{13}H_{14}N_2FO_3S$: C, 49.36; H, 4.46; F, 12.0; N, 8.86; S, 10.15. Found: C, 49.22; H, 4.45; F, 12.02; N, 8.68; S, 10.15.

Ethyl-3-hydroxypyrazin-(1*H*)-2-one-1-acetate (4).[1] Potassium bicarbonate (43.0 kg; 429 mol), water (15 L), and isopropyl acetate (110 L) were stirred at 10−15 °C for 10 min. Ethyl glycine·HCl (**21**, 10.0 kg; 71.64 mol) was added, and the mixture was stirred for 30 min and then cooled to 0 °C. Ethyl oxalyl chloride (**20**, 19.6 kg, 16.07 L; 143.56 mol) was added over 2−2.5 h at 0 °C, stirred for 10 min, and allowed to warm to 10 °C. Water (60 L) was added, the mixture was warmed to 18 °C, and the organic phase was separated. The aqueous phase was re-extracted with isopropyl acetate (100 L), and the combined organic phases were concentrated to a 130 L volume at 35−40 °C. 2,2-Dimethoxyethylamine (**23**, 9.43 kg, 9.77 L; 89.69 mol) was added, and the reaction mixture was aged for 16 h. The solution was filtered, and the solid was washed with isopropyl acetate (5.0 L). The isopropyl acetate solution was washed with aqueous citric acid (2.6 M, 10 L; 26 mol) and aqueous potassium hydrogencarbonate solution (2.8 M, 6.25 L; 17.5 mol). The solution was concentrated to 30 L under partial vacuum at 35 °C. Acetic acid (15 L; 260 mol) was added, and the solution was reconcentrated to 40 L. Acetic acid (15 L; 260 mol) and TFA (5.1 L; 66.2 mol) were added, and the mixture was heated at 78 °C and aged for 3.5 h. The mixture was allowed to cool to 30 °C, diluted with isopropyl acetate (214 L) and toluene (165 L), cooled to 5

(18) Flakes of copper 1 μ thick with a very high surface area purchased from Sigma-Aldrich Chemical Co.

°C, and aged for a further 60 min. The product was collected by filtration, washed with toluene (17 L), and dried in vacuo at 40 °C. Ethyl-3-hydroxypyrazin-(1*H*)-2-one-1-acetate (**4**, 10.66 kg) was obtained as a white crystalline solid in 75% yield, 94% pure, containing 6% of the free acid.

Recrystallization. The crude ethyl pyrazinone acetate (**4**, 10.65 kg; 53.7 mol) was slurried in absolute ethanol (106 L), and concentrated sulfuric acid (146 mL; 2.69 mol) was added. The mixture was heated to reflux temperature, and ethanol (53 L) was removed by distillation at atmospheric pressure. Absolute ethanol (53 L) was added, and distillation continued until a further 74 L of solvent had been distilled. The batch was allowed to cool to 45 °C, and ethyl acetate (64 L) was added over 30 min. The batch was cooled to 5 °C and aged for 1 h. The product was collected by filtration, washed with cold (5 °C) ethanol/ethyl acetate (1:2, 33 L), and dried in vacuo at 45 °C. Ethyl-3-hydroxypyrazin-(1*H*)-2-one-1-acetate (**4**, 9.53 kg) was obtained in 88% recovery, >99% pure, containing <0.2% free acid. Mp 132−4 °C. ^{1}H NMR (CD_3OD, δ) 6.53 (d, J = 5.9 Hz, 1H), 6.40 (d, J = 5.9 Hz, 1H), 4.60 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD, δ) 169.04, 158.97. 158.09, 116.09, 110.53, 63.07, 50.92, 14.55; MS *m*/*z* 197.1 ($M - H^-$). Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.35; H, 5.01; N, 14.10.

Ethyl 2-{3-[(2,2-Difluoro-2-(2-pyridyl)ethyl)amino]-2-oxohydro-pyrazinyl}acetate (28).[1] To a stirred mixture of DMF (7.5 mL) and acetonitrile (0.075 L) in isopropyl acetate (0.105 L) was added ethyl pyrazinone ester (**4**, 0.03 kg; 151 mmol). Oxalyl chloride (0.0215 kg; 166 mmol) was added over 30 min, and the temperature was gradually raised to 35−40 °C. The solution was aged at 40 °C for 2 h, cooled to 20 °C, and diluted with isopropyl acetate (0.165 L). The reaction was quenched with 15% sodium chloride solution (0.15 L), and the phases were separated. The organic layer was washed with 15% sodium chloride solution (0.075 L). The organic layer was concentrated under reduced pressure to ca. 90 mL and flushed with acetonitrile (2 × 0.15 L). The mixture was diluted with acetonitrile to give a final volume of 240 mL. The assay yield of **26** was 31.5 g (96%).

To the above solution were added 2,2-difluoro-2-(2-pyridyl)ethylamine·BSA salt (**3**, 0.051 kg; 153 mmol) and *N*,*N*-diisopropylethylamine (0.020 kg; 153 mmol). Sodium iodide (0.044 kg; 291 mmol) was added, and the mixture was stirred and heated at reflux for 30 h. The reaction mixture was cooled to 20 °C, and water (0.378 L) added over 20 min. Aqueous potassium hydrogencarbonate solution (2 M, 0.073 L; 146 mmol) was added, and the slurry was cooled to 5 °C and stirred for 1 h. The product was collected by filtration, washed with acetonitrile/water (10:90, 0.36 L). and dried in vacuo at 40 °C. Ethyl 2-{3-[(2,2-difluoro-2-(2-pyridyl)ethyl)amino]-2-oxohydro-pyrazinyl}acetate (**28**, 0.044 kg) was obtained as a white crystalline solid in 85.0% yield, >99% pure from **4**. Mp 105−6 °C. ^{1}H NMR (CD_2Cl_2, δ) 8.66 (dq, J = 0.8, 4.9 Hz, 1H), 7.84 (td, J = 1.8, 8.0 Hz, 1H), 7.68 (dt, J = 8.0, 1.11 Hz, 1H), 7.41 (m, 1H), 6.82 (d, J = 4.8 Hz, 1H), 6.51 (bt, J = 5.9 Hz, 1H), 6.45 (d, J = 4.6 Hz, 1H), 4.52 (s, 2H), 4.36 (dt, J = 6.5, 14.3 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CD_2Cl_2, δ) 167.48, 153.71 (t, J = 29 Hz), 152.02, 151.71, 149.90, 137.83, 125.77, 122.15, 120.09, 119.71 (t, J = 243 Hz), 118.15, 62.49, 50.29, 45.79 (t, J = 29 Hz), 14.41; MS *m*/*z* 339.4 ($M + H^+$). Anal. Calcd for $C_{15}H_{16}F_2N_4O_3$: C, 53.25; H, 4.77; F, 11.23; N, 16.56. Found: C, 53.08; H, 4.70; F, 11.27; N, 16.54.

Ethyl 2-{3-[(2,2-Difluoro-2-(2-pyridyl)ethyl)amino]-6-chloro-2-oxohydro-pyrazinyl}acetate (29).[1] Ethyl 2-{3-[(2,2-difluoro-2-(2-pyridyl)ethyl)amino]-2-oxohydro-pyrazinyl}acetate (**28**, 3.22 kg; 9.53 mol) was slurried in acetonitrile (16.15 L) and heated to 70 °C. A solution of *N*-chlorosuccinimide (1.30 kg, 9.75 mol) in acetonitrile (16.15 L) was added over 15 min. The solution was stirred and heated at 70 °C for 1.25 h. The reaction mixture was cooled to 25 °C, and water (73 L) was added to precipitate the product. The batch was cooled to 5 °C and aged for 1 h, and the product was collected by filtration. The product was washed with water (81 L) and dried in vacuo at 45 °C. Ethyl 2-{3-[(2,2-difluoro-2-(2-pyridyl)ethyl)amino]-6-chloro-2-oxohydro-pyrazinyl}acetate (**29**, 3.21 kg) was isolated as a crystalline off-white solid in 90% yield, 97.5% pure. Mp 101−2 °C; ^{1}H NMR (CD_2Cl_2, δ) 8.67 (dq, J = 0.8, 4.8 Hz, 1H), 7.85 (td, J = 1.8, 7.9 Hz, 1H), 7.68 (dt, J = 1.1, 7.8 Hz, 1H), 7.42 (ddd, J = 0.8, 4.9, 7.8 Hz, 1H), 6.93 (s, 1H), 6.48 (br t, J = 6.2 Hz, 1H), 4.86 (s, 2H), 4.34 (dt, J = 6.5, 14.2 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CD_2Cl_2, δ) 167.11, 153.63 (t, J = 28 Hz), 153.06, 152.36, 149.90, 137.89, 125.85, 121.00 (t, J = 4 Hz), 120.82, 119.58 (t, J = 244 Hz), 118.48, 62.65, 46.77, 44.82 (t, J = 29 Hz), 14.41; MS *m*/*z* 373.3 ($M + H^+$). Anal. Calcd for $C_{15}H_{15}ClF_2N_4O$: C, 48.33; H, 4.06; Cl, 9.51; F, 10.19; N, 15.03. Found: C, 48.60; H, 4.09; Cl, 9.32; F, 10.19; N, 14.78.

2-{3-[(2,2-Difluoro-2-(2-pyridyl)ethyl)amino]-6-chloro-2-oxohydropyrazinyl}-*N*-[(3-fluoro(2-pyridyl))methyl]-acetamide (1).[1] Ethyl 2-{3-[(2,2-difluoro-2-(2-pyridyl)ethyl)-amino]-6-chloro-2-oxohydro-pyrazinyl}acetate (**29**, 4.12 kg; 11.06 mol) was dissolved in THF (41.2 L), treated with Darco G60 (206 g), and stirred at ambient temperature for 30 min. The mixture was filtered through Hyflo, and the filtered solution was diluted with THF (61.0 L). 1 M KOH (27.14 L; 27.14 mol) solution was added, and the two-phase mixture was stirred at 40 °C for 2.25 h. HOBt (0.74 kg; 5.48 mol) and 2-amino-3-fluoropyridine·2HCl (**2**, 2.65 kg; 13.3 mol) were added, and a solution of EDC·HCl (2.70 kg; 14.08 mol) in water (9.6 L) was added over 1.5 h. The mixture was stirred at 40 °C for 1.75 h. The batch was filtered (1 μm cartridge, Whatman Polycap 36HD), and the equipment was rinsed with water (9.6 L) and THF (9.6 L). The mixture was cooled to 25 °C, and crystallization was completed by the addition of water (138.0 L). The batch was stirred at 20 °C for 2 h. The product was collected by filtration, washed with (2 × 13.5 L), and dried in vacuo at 40 °C. The thrombin inhibitor (**1**, 4.53 kg) was obtained in 91% yield, >99% pure.

Recrystallization. Compound **1** (4.53 kg) was slurried in absolute ethanol (156 L), and the batch was heated to 80

°C. The solution was cooled to 60 °C over 30 min and seeded (0.6 kg). The crystallizing mixture was cooled to 20 °C over 2 h and stirred at 20 °C for a further 2 h. The product was collected by filtration, washed with ethanol (10.0 L), and dried in vacuo at 40 °C. The product (**1**, 4.134 kg) was obtained as a crystalline white solid in 91% yield, >99% pure. Mp 187−8 °C; ^{1}H NMR (CD_2Cl_2, δ) 8.86 (t, J = 5.65 Hz, 1H), 8.70 (bd, J = 4.8 Hz, 1H), 8.40 (dt, J = 1.4, 4.6 Hz, 1H), 7.99 (td, J = 1.8, 7.8 Hz, 1H), 7.74−7.67 (m, 2H), 7.57 (ddd, J = 0.8, 4.8, 7.6 Hz, 1H), 7.45−7.39 (m, 2H), 6.92 (s, 1H), 4.79 (s, 2H), 4.54 (dd, J = 1.8, 5.4 Hz, 2H), 4.23 (td, J = 6.5, 15.1 Hz, 2H), 4.09 (bs, 1H); ^{13}C NMR (CD_2Cl_2, δ) 165.8 (2 × C═O), 157.4 (d, J = 246.4 Hz), 153.1 (t, J = 27.9 Hz), 151.8, 149.9 (d, J = 5.4 Hz), 145.5 (d, J = 14.3 Hz), 145.4 (t, J = 5.3 Hz), 138.3, 126.1, 124.9 (d, J = 4.0 Hz), 123.7 (d, J = 8.4 Hz), 120.7 (t, J = 3.9 Hz), 119.7 (t, J = 245.1 Hz), 119.7, 118.3, 47.6, 44.3 (t, J = 27.2 Hz), 40.6; MS m/z 453.4 ($M + H^+$). Anal. Calcd for $C_{19}H_{16}ClF_3N_6O_2$: C, 50.40; H, 3.56; Cl, 7.83; F, 12.59; N, 18.56. Found: C, 50.24; H, 3.43; Cl, 7.95; F, 12.61; N, 18.44.

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