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Articles

Process Development of a Novel Non-Xanthine Adenosine A_1 Receptor Antagonist

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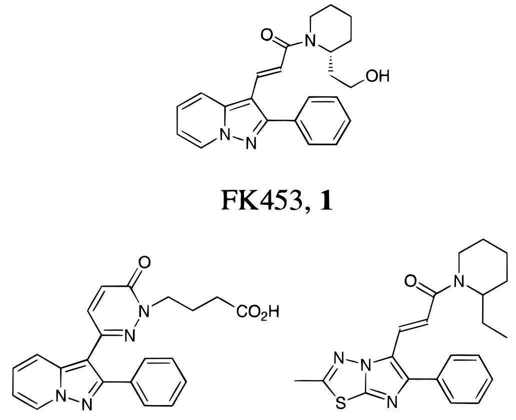
Abstract:

(+)−(*R*)-1-[(*E*)-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)acryloyl]-2-piperidine ethanol (FK453) is a novel, potent adenosine A_1 receptor antagonist for the regulation of renal function. The development of a reliable process suitable for large scale manufacture is described. A Horner−Emmons reaction and a 1,3-dipolar cycloaddition were successfully scaled up to afford ethyl (*E*)-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)acryloylate, with excellent regioselectivity and stereoselectivity. Process improvements and optimization of each step permitted elimination of column chromatography, resulting in a straightforward, practical synthesis of FK453.

Introduction

In recent years adenosine A_1 receptor antagonists have attracted much attention due to their potential therapeutic usefulness for the regulation of renal function.[1] The discovery of Bay n 1468, **3**[2] whose potent effects were attributed to selective adenosine A_1 receptor antagonistic properties, prompted efforts to find novel and selective adenosine receptor antagonists. In our previous papers, we described a pilot scale synthesis of the adenosine A_1 receptor antagonist, FK838 (**2**).[3] This drug has characteristic features related to both diuretic and antihypertensive effects.[4] On the other hand, FK453 (**1**) has been developed mainly focusing on its more potent regulatory effects on renal function.[5] For the purpose of complete pharmacological and toxicological evaluation of FK453 (**1**), we needed to develop a manufacturing process suitable for a large scale synthesis (Figure 1).



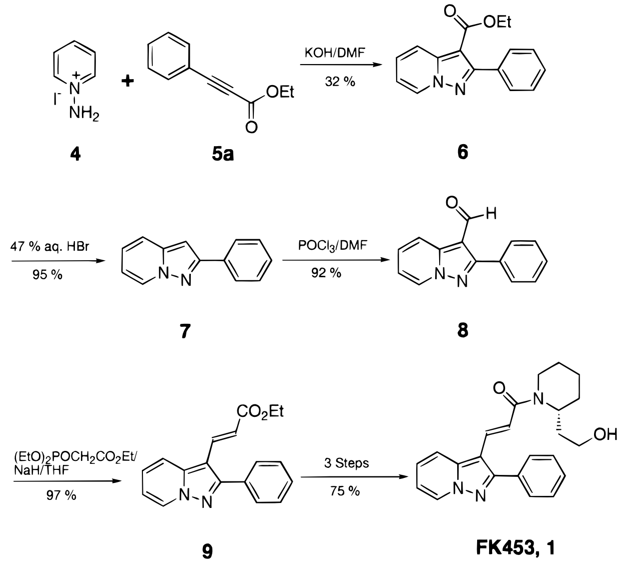
FK453, **1**

FK838, **2**

Bay n 1468, **3**

Figure 1. **Structure of adenosine A_1 receptor antagonists.**

Scheme 1. **Original route to FK453 (1)**



Early synthetic efforts aimed at supplying FK453 (**1**) in gram quantities for the initial pharmacological screening utilized the synthesis outlined in Scheme 1.[6] These methods were useful to generate FK453 (**1**) on a laboratory scale and were scaled up for the first manufacturing trial in a pilot plant with a few modifications. However, these methods

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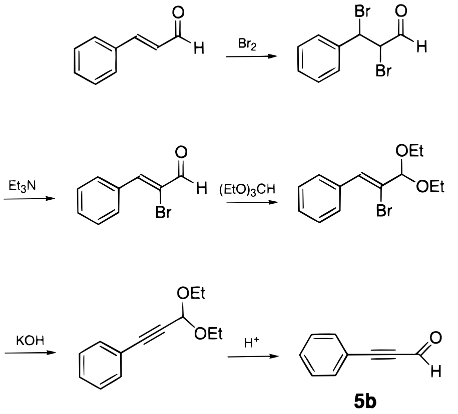
(6) Akahane, A.; Katayama, H.; Mitsunaga, T.; Kita, Y.; Kusunoki, T.; Terai, T.; Yoshida, K.; Shiokawa, Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2059.

10.1021/op990044w CCC: $18.00

Scheme 2. **Route to phenylpropargyl aldehyde (5b) from *trans*-cinnamaldehyde**



involved several shortcomings from the standpoint of large-scale manufacturability. For example, the decarboxylation sequence required severe reaction conditions and column chromatography purification.[3b] In addition, decarboxylation and subsequent re-formylation in a synthetic process leads to a prolonged and inherently inefficient procedure. With a view to develop an alternative and efficient synthesis of FK453 (**1**) on a large scale, we decided to investigate a manufacturing process using phenylpropargyl aldehyde (**5b**). In this paper, we wish to report the results of the process development efforts for FK453 (**1**).

Results and Discussion

Phenylpropargyl aldehyde (**5b)** can be purchased from the Aldrich Chemical Co.; however, this agent is expensive and not available in large quantities. Therefore, we decided to investigate practical and inexpensive preparation methods amenable to a large scale operation. The synthesis of **5b** from *trans*-cinnamaldehyde is known in the literature[7] and was applied to prepare material for the scale-up trial (Scheme 2). One benefit in this method is that *trans*-cinnamaldehyde is inexpensive and readily available in bulk quantities. Each reaction in the process proceeded quantitatively, allowing avoiding isolation of irritant intermediates, and final purification by distillation afforded the aldehyde (**5b**) in satisfactory yield and quality (61% yield, 95% purity, HPLC).

With an efficient preparation of aldehyde (**5b**) in hand, we investigated synthesis of ester (**9**). One of the most practical approaches to pyrazolo[1,5-*a*]pyridines is via 1,3-dipolar cycloaddition of *N*-imine (**4**) with an acetylene. In our early studies, cycloaddition of aldehyde (**5b**) with *N*-imine (**4**) was investigated according to the reported method[8] (Scheme 3, Route A). However, the reaction furnished tarry byproducts along with only small amounts of pyrazolopyridine (**8**) (20% HPLC area). As an alternative approach, we investigated the 1,3-dipolar cycloaddition of alkene (**10**) with *N*-imine (**4**) (Scheme 3, Route B). We investigated a practical method for the preparation of alkene (**10**) on a large scale using Horner−Emmons reaction of aldehyde (**5b**) with triethyl phosphonoacetate, since this reagent is inexpensive and readily available in large quantities. Furthermore, the phosphate byproduct is soluble in water and easily separated from the alkene (**10**) by extraction. Another advantage of this reaction is the excellent (*E*)-stereoselectivity, mainly due to stabilization of the carbanion by the ester moiety.[9] These reactions are usually conducted in ethers such as THF or glyme,[10] but we investigated the reaction in amides or methylene chloride as solvents, aiming for a “one-pot reaction” which would avoid isolation of the pure alkene (**10**), since it is an irritant and difficult to purify, and also because handling of this compound may lead to the *cis*-isomer via photochemical isomerization. The Horner−Emmons reaction of aldehyde (**5b**) with triethyl phosphonoacetate proceeded smoothly in the presence of KOH, affording the *trans*-alkene (**10**) stereoselectively. As shown in Table 1, *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMA) gave superior yields in this step (entry 3, 4). Next, we examined the subsequent cycloaddition. As

Scheme 3. **Synthetic routes to the ester 9**

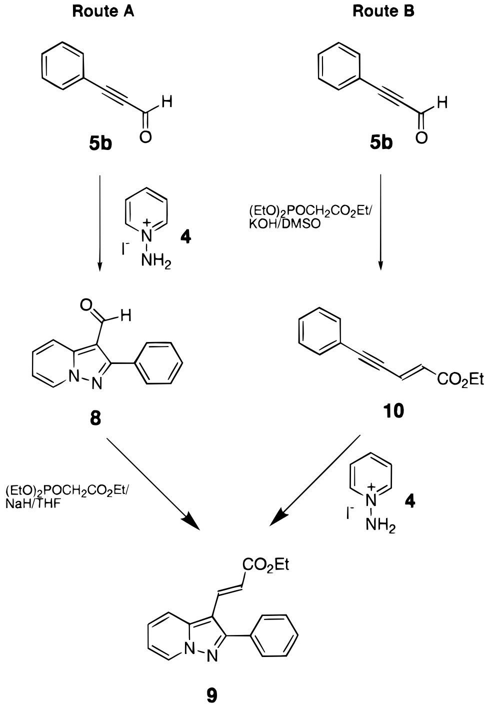


Table 1. **Horner−Emmons reaction of aldehyde (5b) and triethyl phosphonoacetate**[a]

entry	equiv of TEPA[b]	base (equiv)	solvent	yield (%)[c] of **10** from (**5b**)
1	1.2	KOH(1.1)	DMSO	79
2	1.5	KOH(1.1)	DMSO	77
3	1.2	KOH(1.1)	DMF	82
4	1.2	KOH(1.1)	DMA	85
5	1.2	^{t}BuOK (1.2)	CH_2Cl_2	79

[a] Reaction was conducted at 20 °C for 2 h on a 20 g scale. [c] Yield was determined by quantitative HPLC. [b] TEPA: triethyl phosphonoacetate.

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[8] (a) Anderson, P. L.; Hasak, J. P.; Kahle, A. D. *J. Heterocycl. Chem.* **1981**, *18*, 1149. (b) Huisgen. R.; Grashey, R.; Krischke, R. *Tetrahedron Lett.* **1962**, 387.

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[10] Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73−253.

Table 2. **1,3-Dipolar cycloaddition of the alkene 10 with *N*-imine (4)**[a]

entry	equiv of **4**	base (equiv)	solvent	yield (%)[b]
1	1.2	KOH(1.2)	DMSO	46
2	1.6	KOH(1.6)	DMSO	62
3	2.0	KOH(1.0) K_2CO_3(0.5)	DMSO	67
4	2.0	KOH(1.0) K_2CO_3(0.5)	DMF	52
5	2.0	KOH(1.0) K_2CO_3(0.5)	DMA	55
6	2.0	^{t}BuOK (1.0)	CH_2Cl_2	<5

[a] Reaction was conducted at 20 °C on a 20 g scale. [b] Yield from the aldehyde **5b** was determined by quantitative HPLC.

shown in the previous reports, 1,3-dipolar cycloadditions were promising in dipolar aprotic solvents such as DMSO or DMF.[8] However, the yields were generally low (<50%) and generated several unknown byproducts, and removal of byproducts required column chromatography purification. During optimization and further investigation, it was found that the byproducts were cleanly removed into the aqueous layer by extraction with CH_2Cl_2 and washing with water. As shown in Table 2, reaction yield was influenced by the amount of *N*-imine (**4**) employed. It was found that about 2 molar equiv relative to the alkene (**10**) were required to drive the reaction to completion (entry 3, 4). These results indicated that *N*-imine (**4**) played the role of oxidizing agent in a manner similar to our previous report.[3b] A slight improvement in yield was also realized by using a mixture of granulated KOH and granulated K_2CO_3 (entry 2, 3). Using the reagent combination established in this way, several solvents were investigated. Whilst reaction proceeded sluggishly in CH_2Cl_2 (entry 6), cycloaddition in DMF or DMA (entry 4, 5) gave inferior results in terms of yield and dark-colored product, compared with the case in DMSO. Thus, optimized reaction conditions used DMSO as solvent (entry 3). The corresponding regioisomer was not detected at all in these reactions. The regioselectivity of cycloaddition of unsymmetrical dipolarophiles is characteristic, and can be interpreted as addition of *N*-imine (**4**) to the most electron-deficient terminus, followed by cyclization. The reaction of conjugated ester (**10**) gave a single stereoisomer in 67% yield (quantitative HPLC) and is noteworthy. The *cis*-isomer was not detected in the small amounts of byproducts. This result indicated that cycloaddition proceeded stereoselectively without involving *cis*−*trans* isomerization of alkene (**10**). However, the obtained pure *trans*-ester (**9**) is readily isomerized to the *cis*-isomer via photochemical *trans*−*cis* isomerization, therefore reaction and all handling of the product should be conducted in the absence of light.

The subsequent ester hydrolysis step proceeded smoothly in the presence of NaOH in water. The reaction was conducted in a mixture of MeOH, acetone and water and the precipitate was collected after acidification to afford the acid (**11**) in high quality and yield (98.9% chemical purity, 96% yield). The corresponding *cis*-isomer was not detected when the hydrolysis was conducted in the dark.

Scheme 4. **Synthetic routes to 1 from 9**

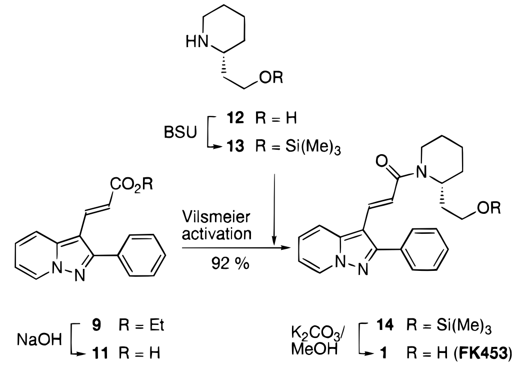

Table 3. **Effect of base on the coupling of 11 with 13**[a]

entry	base (equiv)	temp (°C)/ time (min)	yield (%)[b]
1	*N*-methylmorpholine (2.74)	0/15	34
2	Et_3N (2.74)	0/15	87
3	DIPEA[c] (2.74)	0/15	84
4	Et_3N (2.54), DMAP[d] (0.2)	0/15	93
5	Et_3N (2.54), DMAP[d] (0.2)	20/60	93

[a] Reaction was conducted in CH_2Cl_2 on a 20 g scale. [b] Isolated yield as **1**. [c] DIPEA: diisopropylethylamine. [d] DMAP: dimethylaminopyridine.

Several issues were foreseen in the acylation step, which were addressed before establishing the methods amenable to large scale operation. Chiral 2-hydroxyethylpiperidine (**12)** was obtained by a slight modification of the procedure of Toy.[11] First, *l*-10-camphorsulfonate of **12** (*l*−*l*′ salt) was prepared by optical resolution of racemic compound in ethanol, followed by recrystallization from ethanol. The salt was then treated with Amberlite IRA-910 ion-exchange resin, followed by crystallization from a mixture of *n*-heptane and AcOEt (*n*-heptane:AcOEt = 9:1) to afford optically pure **12** (17% yield). Silylation of the amine (**12**) proceeded smoothly using BSU (*N*,*N*′-bis(trimethylsilyl)urea) in CH_2Cl_2 as solvent and the acid (**11**) was easily activated by the Vilsmeier method ($SOCl_2$, DMF, CH_2Cl_2)[12] (Scheme 4). However, in early studies, acylation in the presence of *N*-methylmorpholine gave **14** in unacceptably low yield (34% yield, Table 3, entry 1), whilst the reaction using Et_3N or DIPEA (diisopropylethylamine) resulted in dark colored product (Table 3, entries 2,3). During further investigations, it was found that a catalytic amount of DMAP (4-dimethylaminopyridine) enhanced the reaction rate and resulted in excellent yield (isolated yield: 93%, loss in the mother liquor: 4%, Table 3, entries 4, 5) and in high quality (Table 3, entry 4; 98.8%, entry 5; 99.1% chemical purity of **1**). Removal of the trimethylsilyl moiety was conducted in the presence of KF on a laboratory scale. However, handling KF in large quantities requires attention to equipment. Investigation of more practical methods revealed that MeONa was effective, but the best results (93% isolated yield) were obtained using granulated K_2CO_3 in MeOH. Final purification of crude **1** by dissolving in ethanol, followed by addition of purified

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(11) Toy, M. S.; Price, C. C. *J. Am. Chem. Soc.* **1960**, *82*, 2613.

(12) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1969; Vol. 1, p 286.

water afforded purified **1** (99.8% purity) suitable for pharmacological and toxicological evaluation.

Conclusions

In this paper we have described process development of a route to novel non-xanthine adenosine A_1 receptor antagonist FK453 (**1**). Horner−Emmons reaction of aldehyde (**5b**) with triethyl phosphonoacetate and 1,3-dipolar cycloaddition in the same solvent (DMSO) avoided isolation of the alkene (**10**). The reaction proceeded regio- and stereoselectively to give a single isomer (**9**) in 67% yield. Process improvement efforts focused on optimized reaction conditions for each step with a view to realizing an efficient and column chromatography free production system.

Experimental Section

General Procedures. Pure grade *N*-aminopyridinum iodide salt was commercially available from Ube Industry Co. Granulated K_2CO_3 (<10 μm) was commercially available and inexpensive from Nippon Soda Co. All other chemicals were obtained from the usual commercial suppliers. IR spectra were recorded on a HORIBA FT-210 spectrometer. NMR spectra were measured on a Bruker AC200P (^{1}H, 200 MHz). Chemical shifts are given in parts per million, and tetramethylsilane was used as the internal standard. Mass spectra were measured on a Hitachi model M-80 mass spectrometer using EI for ionization. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN Elemental Analyzer. HPLC analyses were performed using a YMC GEL ODS 120 Å S-7 column and a MeOH/water mobile phase. The water component was adjusted with citric acid to pH = 4.5. Purity of each obtained product was determined by comparison with purified authentic samples using quantitative HPLC. Optical purity of **1** was determined using a SUMIPAK OA 3100 column and a *n*-hexane/1,2-dichloroethane/ethanol mobile phase. Melting points were measured on a Thomas-Hoover apparatus and are uncorrected. Preparation of **9**, **11**, **14**, and **1** was conducted under conditions where light was passed through a yellow film, since these materials were readily isomerized in solution to the corresponding *cis*-isomers via photochemical *trans*−*cis* isomerization.

Phenylpropargyl Aldehyde (5b). To a solution of *trans*-cinnamaldehyde (100 kgkg, 757 mol) in acetic acid (300 L) was added bromine (121 kg, 757 mol) with stirring at 0−10 °C. After completion of addition, the resulting mixture was further stirred at ambient temperature for 2 h. After addition of $NaHSO_3$ (39.4 kg, 379 mol) to the reaction mixture, Et_3N (76.6 kg, 757 mol) was added dropwise at 0−10 °C. The resulting mixture was then stirred at 60 °C for 1 h and cooled to room temperature. To this solution was added methylene chloride (800 L) and water (400 L). The organic layer was separated and washed with water (400 L) and 3% $NaHCO_3$ in water (500 L), concentrated to ∼250 L under reduced pressure, treated with ethanol (500 L), and again concentrated to 250 L under ambient conditions. To the residue was added ethyl orthoformate (114.7 kg, 774 mol) and ammonium chloride (1.88 kg, 35 mol). The resulting mixture was then refluxed for 2.5 h and cooled to room temperature. To this solution was added methylene chloride (1188 L) and water (594 L). The organic layer was separated and washed with water (594 L) and concentrated to an oil. In another vessel, KOH (65 kg, 1158 mol) was dissolved in EtOH (602 L). To this solution was added the prepared oil, and stirring continued at 70−75 °C for 1 h, followed by cooling to room temperature and concentration to ∼400 L. This solution was added to methylene chloride (803 L), and water (1600 L) was then added. After the pH was adjusted to 7.5 with hydrochloric acid, the layers were separated, and the aqueous layer was re-extracted with methylene chloride (803 L). The organic layers were combined and concentrated to an oil. This oil was then dissolved in EtOH (14.3 L) and added to a solution of H_2SO_4 (89.2 kg, 909 mol) in water (715 L). The reaction mixture was refluxed for 1.5 h, followed by cooling to room temperature. To this solution was added methylene chloride (715 L). The layers were separated, and the aqueous layer was re-extracted with methylene chloride (286 L). The organic layer was combined and concentrated to an oil (103.4 kg) which contained 79.7 kg of **5b** by quantitative HPLC. The crude oil was purified by distillation (91−93 °C/6 mmHg; lit.[7] 114−117 °C/17 mmHg) to afford 60.5 kg of purified aldehyde (**5b**) (95% purity, 61% yield from **10**). Product was identified by comparison with an authentic sample purchased from the Aldrich Chemical Co. by spectroscopic data (NMR, MS).; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35−7.71 (m, 5 H), 9.43 (s, 1H); IR (KBr) 2189, 1660, 1490 cm^{-1}; MS (EI) *m*/*z* 131 $(M + H)^+$.

Ethyl (*E*)-3-(2-Phenylpyrazolo[1,5-*a*]pyridin-3-yl)acryloylate (9). To a mixture of triethyl phosphonoacetate (50.9 kg, 227 mol) and phenylpropargyl aldehyde (**5b**) (24.6 kg, 189 mol) in DMSO (246 L) was added granulated KOH (11.7 kg, 208 mol) maintaining the temperature at <30 °C. Stirring was continued for 1 h at 15−20 °C to afford a solution containing 28.4 kg of alkene (**10**) (75% yield, quantitative HPLC). To this reaction mixture was added 1-aminopyridinium iodide (**4**) (63.1 kg, 284 mol), granulated K_2CO_3 (13.1 kg, 95 mol) and granulated KOH (10.6 kg, 189 mol) at 15 °C. Stirring was continued for 2.5 h at 20−25 °C, followed by cooling to 0−5 °C. To this solution was then added methylene chloride (246 L) and water (492 L) followed by adjusting pH to 5.9−6.1 with 18% hydrochloric acid in water. The organic layer was separated and the aqueous layer was re-extracted by methylene chloride (74 L). The combined organic layers were concentrated to ∼49 L under reduced pressure, treated with ethyl acetate (148 L) and again concentrated to ∼49 L under ambient conditions. After addition of ethyl acetate (25 L), stirring was continued for 1 h at −5−0 °C. The precipitate was filtered off and washed with ethyl acetate (80 L) and dried under reduced pressure to afford **9** (28.6 kg, 52% yield) of 99.8% chemical purity as a yellowish solid: mp 129−130 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (t, 3 H, $J = 7.1$ Hz), 4.25 (q, 2H, $J = 7.1$ Hz), 6.31 (d, 1H, $J = 16.3$ Hz), 6.93 (td, 1H, $J = 6.9$, 1.3 Hz), 7.27−7.72 (m, 6H), 7.84 (d, 1H, $J = 9.0$ Hz), 7.95 (d, 1H, $J = 16.1$ Hz), 8.54 (d, 1H, $J = 9.0$ Hz); IR (KBr) 1690, 1618, 1512, 1482, 1465 cm^{-1}; MS (EI) *m*/*z* 293 $(M + H)^+$,

279. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.62; H, 5.48; N, 9.54.

(*E*)-3-(2-Phenylpyrazolo[1,5-*a*]pyridin-3-yl)acrylic Acid (11). To a solution of the ester **9** (28.6 kg, 97.8 mol) in a mixture of acetone (286 L) and MeOH (57 L) was added dropwise sodium hydroxide (15.6 kg, 390 mol) in water (143 L). The reaction mixture was heated to 48−52 °C over 1 h, followed by adjusting pH to 6.9−7.1 with 18% hydrochloric acid in water. Stirring was continued for 1 h at ambient temperature and additional 18% hydrochloric acid in water was added to this solution to adjust pH to 1.9−2.1. The resulting mixture was further stirred at 0−5 °C for 1 h, and the precipitate was filtered off and washed with water (143 L). Drying under reduced pressure afforded **11** (24.9 kg, 96% yield) of 98.9% purity as a yellowish solid; mp 232−233 °C dec; ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.35 (d, 1H, J = 16.1 Hz), 7.16 (td, 1H, J = 6.9, 1.1 Hz), 7.51−7.70 (m, 6H), 7.77 (d, 1H, J = 16.1 Hz), 8.11 (d, 1H, J = 8.9 H), 8.88 (d, 1H, J = 6.9 H); IR (KBr) 1678, 1664, 1599, 1539, 1511, 1469 cm^{-1} ; MS (EI) *m*/*z* 265 $(M + H)^+$. Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.82; H, 4.54; N, 10.62.

R-(−)-2-Piperidine Ethanol (12). 12 kg of **12** was prepared by optical resolution of racemic compound by a slight modification of the procedure of Toy.[12] Optical purity of **12** was determined to be over 99% ee. by HPLC after coupling with FLEC (1-(9-fluorenyl)ethyl chloroformate).

(+)-(*R*)-1-[(*E*)-3-(2-Phenylpyrazolo[1,5-*a*]pyridin-3-yl)-acryloyl]-2-piperidine Ethanol (FK453, 1). To a mixture of the acid (**11**) (15.0 kg, 57 mol) and thionyl chloride (7.77 kg, 65 mol) in methylene chloride (300 L) was added DMF (4.77 kg, 65 mol) at 5−10 °C, and stirring was continued at ambient temperature for 1.5 h. In another vessel, a mixture of the amine (**12**) (8.08 kg, 62.5 mol) and BSU (18.6 kg, 91 mol) in methylene chloride (120 L) was heated to 35−40 °C for 2 h, followed by cooling to 0−5 °C. After addition of DMAP (1.39 kg, 11 mol) and Et_3N (14.7 kg, 145 mol) to this solution, the acid chloride solution was added. After additional stirring for 1 h, water (120 L) was added. The organic layer was separated, and the aqueous layer was re-extracted with methylene chloride (30 L). To the combined organic layer was added MeOH (150 L) and granulated K_2CO_3 (3.93 kg, 28 mol). Stirring was continued at the same temperature overnight, and to this reaction mixture was added water (90 L). The organic layer was washed with water (90 L × 2). The separated organic layer was concentrated to ∼30 L under reduced pressure. To this residual organic solution was added ethyl acetate (150 L) and then reconcentrated to ∼90 L under reduced pressure. After additional stirring over 1 h at 0−5 °C, the precipitate was filtered off, washed with ethyl acetate (30 L), and dried to afford crude **1** (19.8 kg, 93% yield). A solution of crude **1** (18 kg, 48 mol) in ethanol (90 L) at 50−55 °C was purified by filtration through a 0.45 μ filter, after confirming that no crystals had precipitated, followed by cooling to 5−10 °C. To this solution was added purified water (180 L), and stirring was continued for 1 h at ambient temperature. The precipitate was filtered off, washed with purified water (90 L), and dried under reduced pressure to afford purified **1** (17.7 kg, 98% yield) of 99.8% chemical purity. Optical purity was determined by HPLC to be over 99% ee.; $[\alpha]^{20}_D = + 44.6\,°$ (*c* 2.0, MeOH), mp 147−148 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44−1.65 (m, 7H), 1.98 (t, 1H, J = 14.0 Hz), 2.95 (t, 1H, J = 11.9 Hz), 3.32 (t, 1H, J = 11.5 Hz), 3.61−3.75 (m, 2H), 4.37 (dd, 1H, J = 12.2, 3.5 Hz), 4.90 (br s, 1 H), 6.65 (d, 1H, J = 15.4 Hz), 7.32 (t, 1 H, J = 7.5 Hz), 7.40−7.80 (m, 6H), 7.95 (d, 1H, J = 15.4 Hz), 8.51 (d, 1H, J = 6.9 H); IR (KBr) 1636, 1624, 1573, 1513, 1469, 1444 cm^{-1} ; MS (EI) *m*/*z* 376 $(M + H)^+$, 358, 247. Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.19. Found: C, 73.58; H, 6.70; N, 11.20.

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