JOC Article

Practical Synthesis of a Potent Bradykinin B_1 Antagonist via Enantioselective Hydrogenation of a Pyridyl *N*-Acyl Enamide

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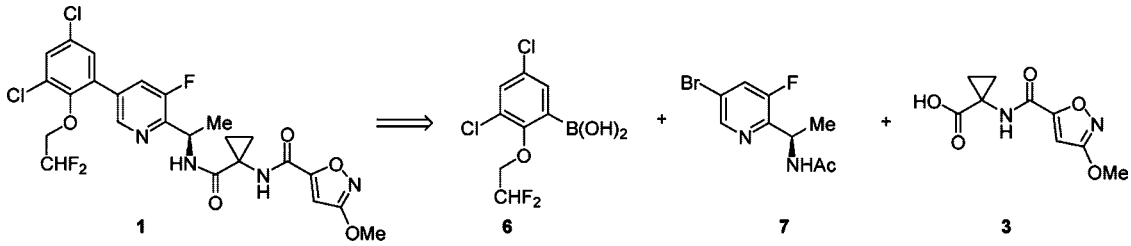

A practical and efficient synthesis of bradykinin B_1 antagonist **1** is described. A convergent strategy was utilized which involved synthesis of three fragments: **3**, **6**, and **7**. Cross coupling of fragments **6** and **7** followed by amidation with **3** enabled efficient synthesis of **1** in 19 steps total, a 35% overall yield from commercially available pyridine **10**. The key to the success of the synthesis was the development of a fluorodenitration step to install the fluorine in pyridine **7** and a catalytic enantioselective hydrogenation of *N*-acyl enamide **9** to set the stereochemistry.

Introduction

Bradykinin is a kinin that mediates the physiological processes accompanying acute and chronic pain and inflammation.[1] Two classes of bradykinin receptors, B_1 and B_2, are known to be activated upon kinin release.[2] The B_2 receptor is present in many cell types and tissues under normal physiological conditions and is believed to be responsible for the immediate acute pain response following tissue injury.[3] In contrast, the B_1 receptor is not normally expressed in most tissues but is induced in response to inflammation, tissue damage, or bacterial infection.[4] This makes the B_1 receptor an attractive drug target that could be potentially useful in the management of pain and inflammation. Compound **1** has been identified as a potent and selective antagonist of bradykinin B_1.[5] We were interested in preparing kilogram quantities of **1** in an effort to further explore its pharmacological properties. Herein, we report our efforts to develop a practical, chromatography-free, enantioselective synthesis suitable for the preparation of **1** on multikilogram scale.

Compound **1** contains a diverse range of functionality, and we were particularly interested in devising a convergent synthesis based on assembling fragments of similar complexity. Our retrosynthetic analysis is shown in Figure 1. We envisioned that **1** could be assembled in a convergent manner via cross coupling of aryl boronic acid **6** and bromopyridine **7** followed by acylation with isoxazole acid **3**. The key chiral center could be installed via asymmetric hydrogenation of pyridine enamide **9**, which in turn could be prepared from commercially available trisubstituted pyridine **10**.

Results and Discussion

Synthesis of Aryl Boronic Acid 6. Our synthesis began with bromination of commercially available 2,4-dichlorophenol. A clean reaction was obtained using NBS in various solvents;

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(2) Regoli, D.; Barabé, J. *Pharmacol. Rev.* **1980**, *32*, 1.
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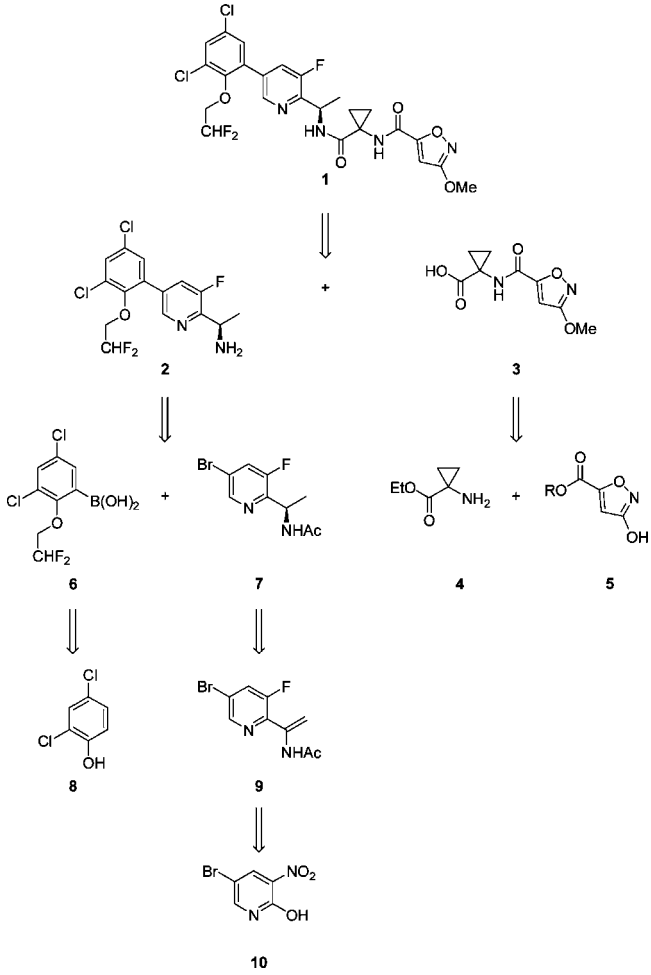


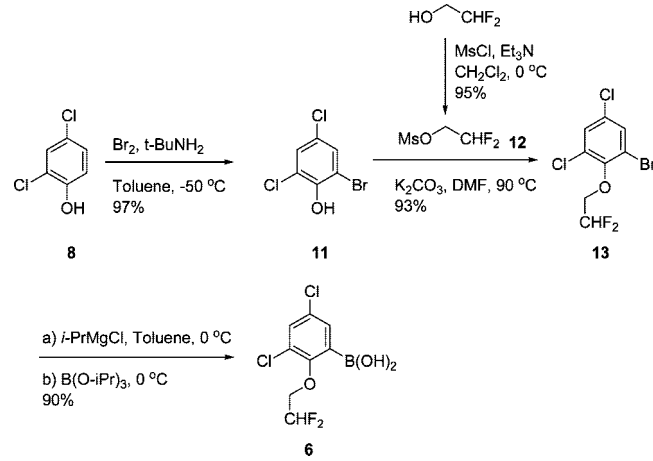
FIGURE 1. Retrosynthetic analysis.

however, separation of the product from succinimide was problematic, and **11** could not be isolated pure. To solve the isolation problems, the bromination was investigated using Br_2 in presence of a base. Thus, addition of *t*-$BuNH_2$[6] to a degassed solution of bromine and phenol **8** in toluene at −50 °C in the absence of light gave a clean reaction to **11**. The reaction was quenched with $NaHSO_3$, and following aqueous workup, bromide **11** was obtained in 97% yield (Scheme 1).

An investigation of possible electrophiles for the alkylation of phenol **11** indicated that mesylate **12** gave excellent results. The mesylate was prepared in a straightforward manner in 95% yield from commercially available 2,2-difluoroethanol (Scheme 1). Phenol **11** was then alkylated in DMF using K_2CO_3 at 90−95 °C for 16 h to yield difluoroethylether **13** in 93% yield. Treatment of bromide **13** with *i*-PrMgCl[7] at 0 °C cleanly generated the corresponding aryl Grignard reagent. Addition of triisopropyl borate followed by acidic workup gave the desired boronic acid **6** in an excellent 90% isolated yield (Scheme 1).

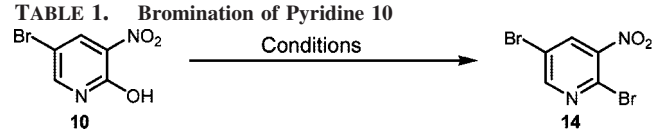
Synthesis of Chiral Pyridine 7. The preparation of trisubstituted pyridine **7** poses an interesting synthetic challenge, and a number of potential routes were investigated. The route chosen is outlined in Scheme 2, starting from commercially available 5-bromo-3-nitropyridin-2-ol **10**.

SCHEME 1. Synthesis of Aryl Boronic Acid 6



A number of 2-substituted pyridines were prepared from **10** to evaluate the reactivity of various groups toward cyanation. The corresponding 2-chloride and 2-triflate were prepared but were found to be unreactive in the subsequent cyanation step under a variety of reaction conditions. Initial experiments with the 2-bromo pyridine **14** indicated that selective cyanation was possible at the 2-position (over the 5-position), and efforts were focused on the development of an efficient procedure for its preparation. Treatment of **10** with NBS/Ph_3P[8] or P_2O_5/Bu_4NBr[9] following reported procedures did not lead to useful yields of **14** (Table 1, entries 1, 2). 2-Bromo pyridines have also been prepared by treatment of pyridones with $POBr_3$ in DMF.[10] However, treatment of **10** using these conditions led to low yields of the desired bromide. Switching to toluene as the solvent at 110 °C led to **14** in 80% yield. Interestingly, the addition of 10 mol % of DMF to toluene increased the yield of the desired product to 92% and enabled a complete reaction at 90 °C within 16 h. It is important to add a solution of $POBr_3$ in toluene slowly to the pyridine at 90 °C to avoid a significant exotherm that was observed at 80 °C when all the reagents were mixed at room temperature and then heated to the reaction temperature.

TABLE 1. Bromination of Pyridine 10



entry	reagent	solvent	*T*	time	yield
1	NBS/Ph_3P	dioxane	100 °C	15 h	15%
2	P_2O_5/Bu_4NBr	toluene	100 °C	3 h	68%
3	$POBr_3$	toluene	110 °C	4 h	80%
4	$POBr_3$	toluene/DMF (10 mol %)	90 °C	16 h	92%

Transition-metal mediated displacement of aryl halides by a cyanide ion is a convenient method for the preparation of aryl nitriles.[11] We investigated a number of reaction conditions and

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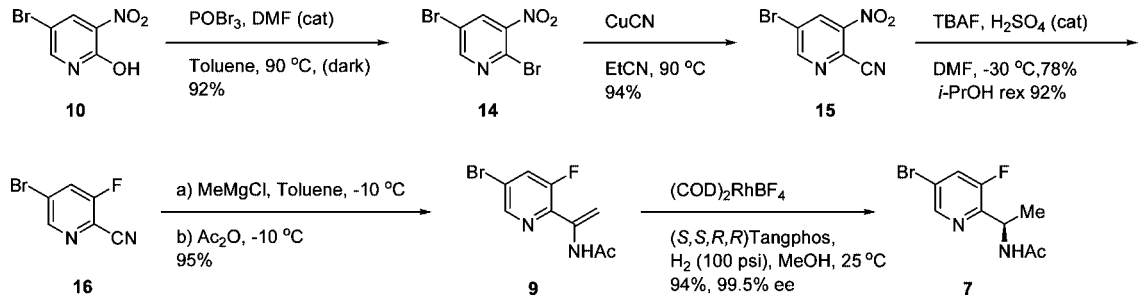
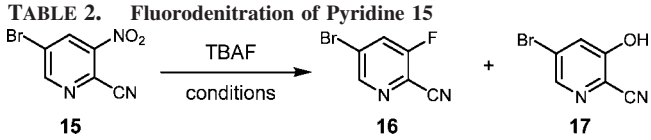
SCHEME 2. Synthesis of Pyridine 7



found that treatment of dibromopyridine **14** with CuCN in propionitrile at 90 °C gave excellent results. Thus, a solution of **14** in propionitrile was treated with CuCN and heated to 90 °C. The reaction was complete after aging for 15 h at 90 °C, and following aqueous workup, pyridine nitrile **15** was obtained in 94% yield. It was deemed essential to remove residual copper to avoid detrimental effects on the downstream chemistry, and this was easily achieved by washing the toluene solution of **15** with saturated aqueous NaCl.

A key step in our strategy involved installation of the fluorine at the 3-position of the pyridine ring. There are a number of available methodologies such as diazotization of amines in the presence of HF[12] or thermal decomposition of diazonium salts[13] to prepare fluoropyridines. However, these methodologies require specialized equipment and pose significant safety concerns, making them unattractive for large scale experiments.

TABLE 2. Fluorodenitration of Pyridine 15



entry	solvent	TBAF	T (°C)	time	conversion **15**	**17**	yield[a]
1	THF	3.0 equiv	−10	120 min	95%	15%	50%
2	CH_3CN	1.5 equiv	20	30 min	99%	11%	78%
3	DMF	1.5 equiv	−15	60 min	95%	10%	75%
4	DMF[b]	1.5 equiv	−15	15 min	88%	2%	85%
5	DMF[b]	3.0 equiv	−30	45 min	90%	1%	89%

[a] Assay yield measured by HPLC. [b] Predried DMF solution of TBAF.

Therefore, we were interested in evaluating fluorodenitration as a potentially milder and scaleable method to prepare **16**. Fluorodenitrations have been reported for electron-poor aryl substrates[14] using a number of fluoride sources and have been recently extended to pyridines using TBAF as the fluoride source.[15] Pyridine **15** underwent fluorodenitration in a number of solvents using TBAF to give the desired fluoride **16**. The main byproduct observed was the corresponding 3-hydroxy pyridine **17** (Table 2, entries 1−3). It was found that treatment of a DMF solution of TBAF with molecular sieves to reduce the water content reduced the level of the hydroxy pyridine **17** (Table 2, entry 4) leading to a higher yield. It was also found that the addition of H_2SO_4 (2 mol %) significantly reduced the low-level impurities and improved the product color. Thus, the optimal conditions were found to be the addition of a DMF solution of **15** to a predried (molecular sieves) solution of TBAF in DMF containing H_2SO_4 (2 mol %) at −35 °C (Table 2, entry 5). The reaction was complete within 30 min at −30 °C, and fluoropyridine **16** was isolated in 78% yield following precipitation by addition of aqueous 1 N HCl to the reaction mixture and filtration. The material was recrystallized from 2-propanol in 92% yield to remove residual quaternary ammonium salts which interfered with the performance of the subsequent enamide formation and hydrogenation steps (Scheme 2).

The synthesis of optically active α-methylpyridyl amines has received much attention in the literature,[16] and a number of approaches including enzymatic resolution[17] and diastereoselective reduction of chiral imines[18] have been reported. An attractive methodology for the preparation of chiral amines is via enantioselective hydrogenation of *N*-acyl enamides. Rhodium-catalyzed enantioselective hydrogenation of aryl *N*-acyl enamides has been achieved with high levels of enantioselectivity using a number of chiral phosphine ligands providing access to a variety of chiral benzyl amines.[19] A survey of the literature revealed scant examples of the synthesis and subsequent enantioselective hydrogenation of the corresponding pyridyl *N*-acyl enamides.[20] Despite their broad utility in asymmetric hydrogenation, general methodologies for the synthesis of *N*-acyl enamides still remain a significant challenge. Methodologies involving organometallic addition to nitriles,[21] a Heck reaction of aryl triflates with *N*-vinyl acetamide,[22] and Pd-catalyzed coupling of enol triflates or tosylates with amides and carbamates[23] have been reported. We were interested in examining organometallic methyl addition to nitrile **16** followed by in situ acylation of the intermediate metallo-imine **18** as a straightforward approach to access *N*-acyl enamide **9** (Table 3). An initial

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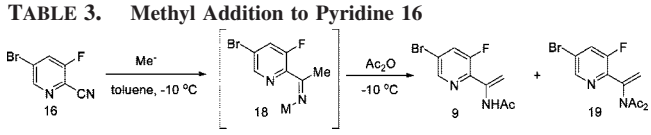
TABLE 3. Methyl Addition to Pyridine 16



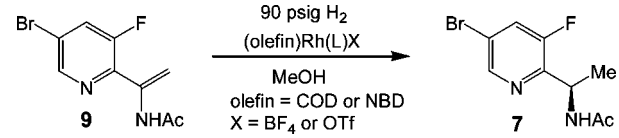
entry	Me^- (1.5 equiv)	Ac_2O (equiv)	**18**[a]	**9**[b]	**19**[c]
1	MeMgBr (3 M THF)	2	ND	29	ND
2	MeMgI (3 M THF)	2	ND	16	ND
3	MeLi (1.6 M Et_2O)	2	ND	3	ND
4	MeLi−LiBr (1.5 M Et_2O)	2	ND	<2	ND
5	MeMgCl (3 M THF)	2	97	55	2.8
6	MeMgCl (3 M THF)	2.5	97	69	2
7	MeMgCl (3 M THF)	5	98	79	0.6
8	MeMgCl (3 M THF)	10	>99	97	0.2

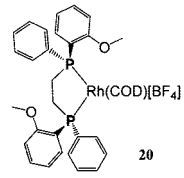
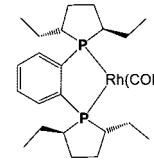
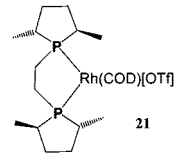
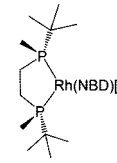
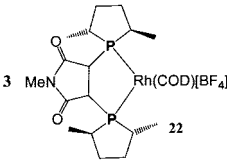
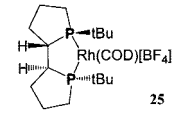
[a] % conversion measured as methyl ketone by HPLC. [b] Assay yield by HPLC. [c] % measured by HPLC.

investigation of solvents indicated that toluene was superior for this reaction relative to methyl-*t*-butyl ether (MTBE), THF, 1,2-dimethoxyethane, and 1,2-dichloroethane. The source of methyl anion proved crucial with methylmagnesium bromide or iodide, methyllithium, or methyllithium−lithium bromide complex, affording poor yields of desired product (Table 3, entries 1−4). Methylmagnesium chloride gave high conversion to the desired metallo-imine (measured as the corresponding methyl ketone by HPLC); however, the yield of the corresponding enamide was only modest following quenching with 2 equiv of Ac_2O (Table 3, entry 5). Increasing the amount of Ac_2O to 10 equiv gave improved results, with reactions reaching 97% HPLC assay yield of enamide **9** (Table 3, entries 6−8). Interestingly, using this large excess of Ac_2O led to lower formation of bis-acetamide impurity **19**, typically observed at <0.5 A% by HPLC analysis. Thus, methylmagnesium chloride (3 M THF) was added to a solution of **16** in toluene at −10 °C. After ∼30 min complete conversion to **18** was observed by HPLC. Ac_2O was added at −10 °C and the mixture aged for 18 h to obtain **9** in 97% yield following workup. We observed variable performance of enamide in the enantioselective hydrogenation step depending on the method used to work up the reaction mixture. A systematic analysis of workup procedures was performed to correlate the effects of acetate, chloride, and magnesium ions with respect to hydrogenation efficiency. We found that samples with high acetate levels (∼1.5 wt %) performed poorly in the hydrogenation step. Thus, working up the reaction by quenching with 0.5 M aqueous $NaHCO_3$ followed by washing with water, 10% aq Na_2SO_4, and water gave material of a consistent quality which underwent efficient asymmetric hydrogenation.

We began our investigation of the enantioselective hydrogenation of enamide **9** by completing a comprehensive screen using a variety of chiral phosphines and rhodium sources at 10 mol % and loading in methanol at 90 psi hydrogen and 25 °C. Clean hydrogenation with high enantiomeric excess was observed for a variety of Rh-phosphine catalysts, and a selection of the best results are summarized in Table 4. Good ee (84%) was observed using DiPAMP[24] ligand **20** (Table 4, entry 1). High ee's of 92%, 94%, and 96% were obtained using MeBPE[25] **21**, Catasium MN[26] derivative **22**, and EtDuphos[27] **23**, respectively, as ligands (Table 4, entries 2, 3, 4). However, ee's of

TABLE 4. Enantioselective Hydrogenation of Enamide 9[a]



Entry	Catalyst	e.e.	Entry	Catalyst	e.e.
1		84%	4		96%
2		92%	5		99%
3		94%	6		99%

[a] All reactions were run either using preformed catalyst or prepared from 10% COD_2RhBF_4 and 10.5% ligand. The hydrogenations were carried out at 90 psi in MeOH (25 mL/g of **1**) at 25 °C and were complete in 18 h.

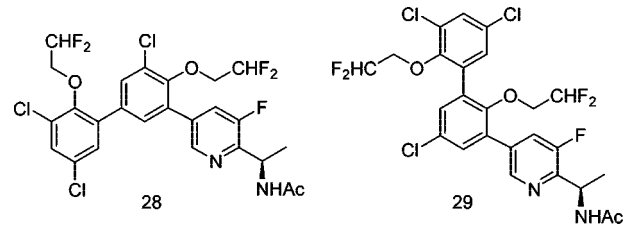


FIGURE 2. Impurities from Suzuki coupling.

99% were observed with the BisP[28] **24** and Tangphos[29] **25** ligands (Table 4, entries 5, 6). On the basis of several factors including cost, availability, and reaction performance we chose to develop the Tangphos/$(COD)_2RhBF_4$ catalyst system for this transformation.

Using (*S*,*S*,*R*,*R*)-Tangphos with $Rh(COD)_2[BF_4]$, full conversion was achieved at catalyst loadings as low as 0.1 mol % while maintaining excellent enantioselectivity (>99%) using a sample of **9** purified by column chromatography. However, the reaction rate and catalyst performance were dependent upon the quality of enamide **9**, and upon scale up (and without chromatography) an increased catalyst charge (ca. 0.3 mol %) was

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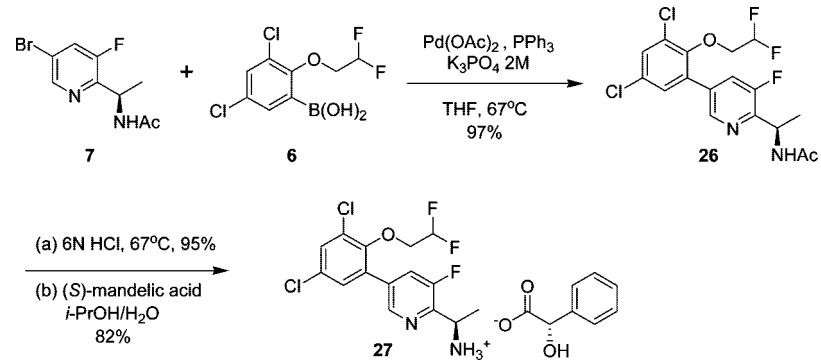
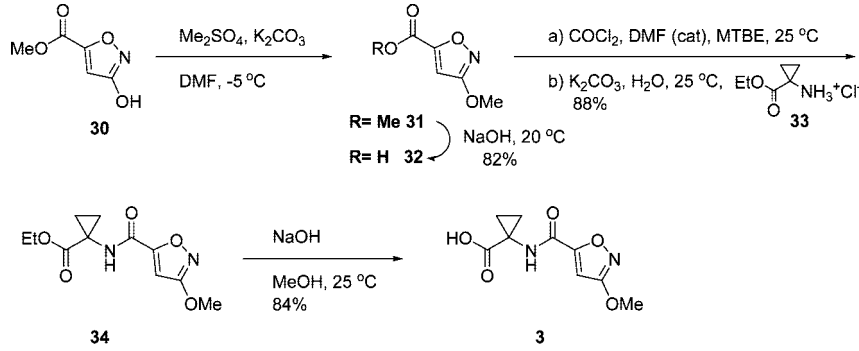
SCHEME 3. Synthesis of Biaryl 27



SCHEME 4. Synthesis of Isoxazole 3



required to achieve full conversion. It is not atypical for the performance of low catalyst loading reactions to be impacted by the quality of the materials used. However, it is expected that following further optimization of the workup conditions for enamide **9** and hydrogenation reaction parameters the catalyst loading would be reduced. Thus, treatment of **9** in MeOH with (*S*,*S*,*R*,*R*)-TangphosRh(COD)[BF_4] and 6.9 bar of H_2 at 25 °C for 4 h gave the desired amide **7** in 94% yield and 99.5% ee.

Synthesis of Biaryl Amine 2. A study of the Suzuki coupling between aryl boronic acid **6** and bromopyridine amide **7** identified the optimal reaction conditions as using $Pd(OAc)_2$ and PPh_3 in a 1:2 ratio with 2 M K_3PO_4 in refluxing THF, using chromatographed **7** (Scheme 3). However, the use of crude **7** (directly from the hydrogenation reaction without workup) gave poor results in the Suzuki coupling requiring >6 mol % of Pd to obtain >95% conversion. A correlation was observed between the level of residual Rh in **7** and the performance in the cross coupling. This necessitated the development of a workup to reduce Rh levels. Attempts to purify **7** and reduce Rh levels by extractive workup or crystallization were unsuccessful. However, Rh levels were significantly reduced by treatment with silica gel and activated carbon. Thus, **7** was purified by filtration of an isopropyl acetate (IPAc) solution through a pad of silica gel followed by treatment of the filtrate with activated carbon (Darco KB-B). Material obtained from this protocol contained <20 ppm Rh and performed reproducibly in the Suzuki coupling, requiring ~3 mol % Pd to obtain complete conversion. While this loading may appear high, further optimization of the reaction conditions would be expected to lower the required catalyst levels significantly.

An investigation of the Pd loading and reaction times indicated that longer reaction times (>2 h) significantly increased the formation of triaryl impurities **28** and **29** (Figure 2). The formation of the triaryls is more significant after the bromo cross coupling is complete, so it is important to stop the reaction as soon as it reaches >99% conversion, and this was achieved by cooling to <45 °C, where formation of the **28** and **29** did not occur. Thus, heating a mixture of **6** and **7** with $Pd(OAc)_2$ (3 mol %) and PPh_3 (6 mol %) in THF with aqueous K_2PO_3 for 1 h afforded complete conversion to biaryl **26**. Following extractive workup, **26** was obtained in 97% HPLC assay yield as a THF solution which was used directly in the amide hydrolysis step.

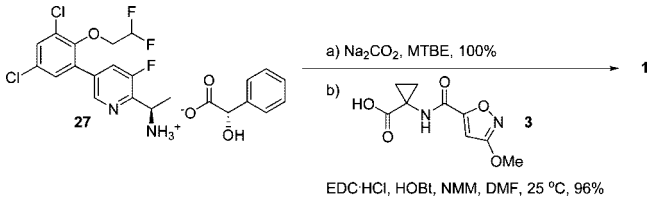
Hydrolysis of the acetamide **26** to the primary amine **2** was completed in a straightforward manner by addition of 5 equiv of aqueous 6 N HCl to the THF solution of **26**. Heating at 65 °C for 15 h gave the desired amine in 95% assay yield by HPLC. Salt formation of the amine **2** was used as a key purification step to remove triaryl impurities as well as residual palladium. Moreover, this step was required to afford a stable form of the amine. Amine **2** as a free base was unstable at 20 °C and degraded at a rate of >1 A% loss per day by HPLC analysis. A screen of acids indicated that the (*S*)-mandelate salt **27** was stable and crystalline. Isolation of **27** following precipitation gave high purity salt and reduced residual Pd levels to ~100 ppm. Thus, a water/2-propanol solution of (*S*)-mandelic acid was added to a 2-propanol solution of **2**. The mixture was heated to 75 °C and cooled over 16 h to 20−25 °C, and the precipitate was isolated by filtration to give **27** in 82% yield.

Synthesis of Isoxazole 3. Alkylation of isoxazole **30** with MeI[30] suffered from poor regioselectivity (~1.5:1) leading to a low yield of the desired O-methyl isomer **31** (Scheme 4). Methylation of isoxazole **30** with 1.1 equiv of dimethyl sulfate in the presence of solid K_2CO_3 in DMF at −5 °C gave much improved selectivity (85:15) and afforded the desired *O*-methyl isoxazole **31** in 84% HPLC assay yield. Addition of aqueous 2 N NaOH directly to the alkylation reaction mixture in DMF led to hydrolysis of the methyl ester in ~30−60 min at rt, and following aqueous workup the desired acid **32** was obtained as a toluene solution in 82% yield (by HPLC) over two steps. The

N-methyl isomer was highly water-soluble and readily separated in the aqueous layer during workup.

Peptide coupling was performed under Schotten−Bauman conditions with the first activation of the isoxazole acid **32** using oxalyl chloride in MTBE, followed by addition over 1 h to a solution of cyclopropane amino ester **33** in aqueous K_2CO_3 at 0−5 °C. Following removal of the volatiles the dipeptide ester **34** was isolated as a solid in 88% yield. Hydrolysis of the ethyl ester was performed with aqueous NaOH in MeOH at rt and gave the desired dipeptide acid **3** in 84% yield and high purity (99.7 wt % by HPLC).

SCHEME 5. End Game



Synthesis End Game. Mandelate salt **27** was treated with K_2CO_3 to give free amine **2** in quantitative yield. Coupling with acid **3** was effected using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC·HCl) and 10 mol % 1-hydroxybenzotriazole (HOBT) with *N*-methyl morpholine (NMM) as base (Scheme 5). Thus, to a DMF solution of **2** and **3** were added HOBT and NMM, followed by portion-wise addition of EDC·HCl. After 1 h at 30 °C the coupling reaction was complete. The product was precipitated directly from the reaction mixture by addition of water to give **1** as a white solid in 96% yield and >99% purity by HPLC.

In summary, a practical and efficient chromatography-free synthesis of bradykinin B_1 inhibitor **1** was developed. A convergent strategy was utilized involving synthesis of three fragments **3**, **6**, and **7**. Cross coupling of **6** and **7** followed by amidation with **3** enabled efficient assembly of **1**. The key to the success of the synthesis was the development of a fluorodenitration step to install the fluorine in pyridine **7** and a catalytic enantioselective hydrogenation of *N*-acyl enamide **9** to set the stereochemistry. The synthesis was completed in 19 steps total and 35% overall yield (in 9 steps) from commercially available pyridine **10**.

Experimental Section

5-Bromo-3-fluoropyridine-2-carbonitrile (16). A 20 L round-bottomed flask (RBF) was charged with TBAF (10.3 kg, 39.5 mol) and DMF (9 L) under an inert atmosphere. The mixture was stirred for 6 h to dissolve the TBAF. KF analysis showed 8.2% water. Molecular sieves (4 Å, 8−12 mesh, 3.44 kg) were added, and the mixture was stirred for 9 h. KF analysis showed 6.5% water. The mixture was decanted off of the sieves by vacuum transfer into a 100 L reaction flask equipped with a mechanical stirrer, a thermocouple, and an addition funnel. The sieves were washed with DMF (2 × 4 L). Sulfuric acid (0.014 L, 0.263 mol) was added, and the mixture was cooled to −38 °C. A solution of nitropyridine **15** in DMF/IPAc (45.4 wt %, 93/7 DMF/IPAc, 6.61 kg, 13.2 mol) was added via addition funnel over 20 min maintaining the internal temperature below −33 °C. HPLC analysis of a sample after 10 min showed an 85:8 ratio of product to starting material. After aging 20 min, 2 N HCl (10.8 L) was added over 30 min. The internal temperature rose to 6 °C. After aging 17 h, the mixture was warmed to 18 °C, and 1 N HCl (52.5 L) was added over 50 min. After aging 16 h, the mixture was cooled to 2.5 °C and filtered, and the cake was washed with DMF/water (10% (v/v), 2 × 6 L) to afford, after drying in a vacuum oven at 35 °C for 40 h, 2.26 kg of **16** (91.6 wt %, 78% yield), which was obtained as a brown solid. A 2.06 kg portion of crude **16** (1.88 kg at 91.6 wt %, 9.46 mol) was suspended in 2-propanol (9.4 L) in a visually clean and dry 50 L RBF. With mechanical stirring, the mixture was warmed to 67 °C over 20 min to give a dark brown solution. The mixture was cooled to 37 °C over 1 h at which point solids began to precipitate. Water (200 mL) was added, and the mixture was aged for 5 min before adding additional water (18.6 L) over 75 min. The mixture was cooled to 18 °C and filtered, and the cake was washed with H_2O/2-propanol (2:1 (v/v), 2 × 5 L) and water (2 × 5 L). The solids were dried at 35 °C under vacuum for 20 h to afford **16** at 1.73 kg and 92% yield. An analytically pure sample was obtained by sublimation and was characterized as follows. Mp 103−105 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.74 (s, 1 H), 8.36 (dd, 1 H, J = 1.8, 8.4 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 161.4 (d, J = 274 Hz), 149.5 (d, J = 4 Hz), 192.2 (d, J = 21 Hz), 126.2 (d, J = 4 Hz), 121.7 (d, J = 16 Hz), 113.6 (d, J = 5 Hz); ^{19}F NMR (377 MHz, acetone-d_6) δ −120.5 (d, J = 9 Hz). Anal. Calcd for $C_6H_2BrFN_2$: C, 35.85; H, 1.00; N, 13.94. Found: C, 35.53; H, 0.83; N, 13.93. HRMS (ESI) calcd for $C_6H_2BrFN_2$ [M − H] 198.9312, found 198.9337; IR (film, cm^{-1}) 3030, 1572, 1435, 1407, 1283, 1155, 1084, 908. HPLC, Zorbax Rx-C8 4.6 mm × 25 cm column; eluents, A, 0.1% aqueous H_3PO_4; B, acetonitrile; 2 mL/min; gradient, A/B 70:30 to 5:905 over 20 min; λ = 220 nm; temperature, 35 °C; t_R, **16** = 6.2 min.

***N*-[1-(5-Bromo-3-fluoropyridin-2-yl)vinyl]acetamide (9).** Author: A 50 L RBF was charged with nitrile **16** (1.30 kg, 1.35 kg @ 96.4 wt %, 6.48 mol) and toluene (13 L). The batch was cooled to −10 °C, and MeMgCl (3.24 L, 9.72 mol, 3 M in THF) was added over 35 min during which time the temperature rose to 0 °C. The batch was allowed to stir at −10 °C for 1 h. HPLC showed >99.8% conversion to the magnesium amide adduct as ascertained by hydrolysis of an aliquot to the corresponding ketone. Acetic anhydride (6.13 L, 64.8 mol) was added over 30 min via an addition funnel. An exotherm was observed during addition of the first portion of Ac_2O (−10 to 0 °C). The exotherm subsided rapidly afterward, and the internal temperature returned to −10 °C. The batch was stirred at −10 °C for 18 h. HPLC analysis showed >99% conversion to enamide **9**. The reaction was quenched with 0.5 M $NaHCO_3$ (6.5 L), the batch was stirred at rt for 30 min, and the layers were cut. The upper organic layer was washed with water (6.5 L), 10% aqueous Na_2SO_4 (2 × 6.5 L), and water (2 × 6.5 L). The batch was concentrated, flushed with toluene (6.5 L), and flushed with MeOH (6.5 L). HPLC assay indicated 1.64 kg of **9**, with 97% yield as an oil. A pure sample (solid) was obtained following chromatography. Mp 46−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (bs, 1H), 8.44 (d, 1H, J = 0.8 Hz), 7.68 (dd, 1H, J = 1.8, 11.0 Hz), 6.77 (d, 1H, J = 4.8 Hz), 5.88 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 157.0 (J = 269 Hz), 144.5 (J = 5 Hz), 138.8 (J = 7.9 Hz), 133.1 (J = 7.7 Hz), 127.6 (J = 23.8 Hz), 118.9 (J = 3.2 Hz), 105.9 (J = 18.0 Hz), 24.9; ^{19}F NMR (377 MHz, $CDCl_3$) δ −113.4; HRMS (ES) calcd for $C_9H_8BrFN_2O$ [M + H]$^+$ 258.9882, found 258.9880; IR (thin film, cm^{-1}) 3351, 3057, 1686, 1506, 897. HPLC, Zorbax Rx-C8 4.6 mm × 25.0 cm column; eluents, A, 0.1% aqueous H_3PO_4; B, acetonitrile; 2 mL/min; gradient, A/B 70:30 to 5:95 over 25 min; λ = 220 nm; temperature, 35 °C; t_R, enamide **9** = 5.22 min, ketone = 5.92 min, bis-acetamide **19** = 7.37 min.

***N*-[(1*R*)-1-(5-Bromo-3-fluoropyridin-2-yl)ethyl]acetamide (7).** In a nitrogen filled glovebox (<10 ppm O_2), (*S*,*S*,*R*,*R*)-Tangphos (12.89 g, 45.0 mmol) was combined with $(COD)_2RhBF_4$ (17.40 g, 42.8 mmol). Methanol (400 mL) was added to dissolve, and the solution was aged for 1 h. A portion of the catalyst solution (177.4 g, 21.7 mmol ((*S*,*S*,*R*,*R*)-Tangphos)Rh(COD)[BF_4]) was transferred

(30) Schlewer, G.; Krogsgaard-Larsen, P. *Acta Chem. Scand., Ser. B* **1984**, *B38*, 815.

to a 500 mL stainless steel vessel. The catalyst solution was further diluted with methanol (100 mL). To a separate 150 mL stainless steel vessel was added an additional charge of methanol (100 mL). These two vessels were connected with a ball valve separating the two vessels. The enamide **9** (3.66 kg, 54 wt % in MeOH, 1.97 assay kg, 7.6 mol) was drawn into a 40 L stirred autoclave via vacuum followed by a methanol (15 L) rinse. The solution was then degassed with nitrogen (3×). The stainless steel vessels containing the catalyst solution were connected to the autoclave via flexible tubing. The autoclave was placed under partial vacuum, and the catalyst solution was drawn into the autoclave followed by the MeOH rinse (100 mL). The solution was degassed with H_2 (6.9 bar, 3×) and the final pressure adjusted to 1.4 bar. The reaction temperature was set to 25 °C and agitation initiated. The reaction pressure was increased to 6.9 bar after 20 min and aged for 4 h. The reaction was sampled and conversion determined to be >99.5% with 99.5% ee by HPLC. The HPLC assay yield of **7** was 1.87 kg, 93.9%. A second reaction was performed which yielded 1.1 kg, 94%, 99.5% ee and combined with the first MeOH solution for workup. The MeOH was removed in vacuo, and the residue was flushed with IPAc (12 L). Additional IPAc (3 L) was added to obtain a 2 mL/g solution. The dark solution was filtered through a pad of silica gel (8 kg) and the pad rinsed with IPAc (80 L). Activated carbon Darco KB-B (1.5 kg) was added, and the mixture was stirred under N_2 at rt for 16 h. The slurry was filtered on a pad of filter aid Solka floc, and the cake was washed with IPAc. The solvent was removed in vacuo to afford **7** as a yellow solid (2.9 kg, 97% yield by HPLC assay). Mp 94−95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.59 (dd, 1H, J = 8.6, 1.8 Hz), 6.75 (br s, 1H), 5.44 (quint, 1H, J = 6.7 Hz), 2.04 (s, 3H), 1.42 (d, 3H, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 155.3 (d, J = 264 Hz), 148.1 (d, J = 15 Hz), 145.7, 126.4 (d, J = 21 Hz), 118.6, 44.0, 23.3, 21.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −123.0; HRMS calcd for $C_9H_{10}BrFN_2O$ [M + ^{7}Li] 267.0121, found 267.0124; IR (KBr, cm^{-1}) 3280, 1635, 1540, 1455, 1400, 1372; $[\alpha]_D^{20}$ − 103.66 (MeOH, *c* 12.2). HPLC, Inertsil ODS-3 4.6 mm × 25.0 cm column; eluents, A, 0.1% aqueous H_3PO_4; B, acetonitrile; 1.5 mL/min; gradient, A/B 20:80 to 10:90 over 20 min; λ = 210 nm; temperature, 25 °C; t_R, acetamide **7** = 7.5 min, enamide **9** = 9.8 min. Chiral HPLC, Chiralpak AD-H 4.6 mm × 25.0 cm column; eluents, A, *n*-heptane; B, EtOH; 2 mL/min; isocratic, A/B 90:10; λ = 224 nm; temperature, 20 °C; t_R, (*R*)-**7** = 9.5 min, enamide **9** = 14.0 min, (*S*)-**7** = 23.0 min.

Supporting Information Available: Experimental procedures for compounds **1**, **2**, **6, 11**, **12**, **13**, **14**, **15**, **26**, **27**, **31**, **32**, and **34**. Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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