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New Synthetic Route to a Dipeptidyl Peptidase-4 Inhibitor

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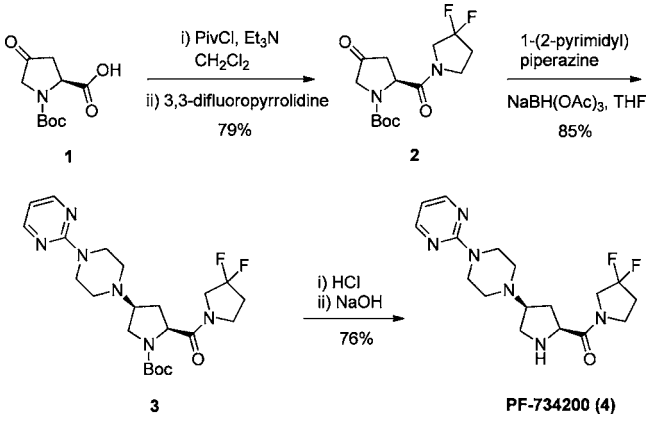
ABSTRACT: A new synthetic route to a dipeptidyl peptidase-4 (DPP4) inhibitor was developed and demonstrated on a multigram scale. This approach takes advantage of the cheap and readily available Boc-*trans*-4-hydroxy-L-proline methyl ester as starting material which was derivatized through an S_N2 reaction. Several leaving groups were studied, and the nosylate group showed superiority over other derivatives. Formation of an amide using the most costly starting material, 3,3-difluoropyrrolidine, was performed late in the synthesis to minimize its economical impact on the overall cost of the API.

INTRODUCTION

PF-734200 is a dipeptidyl peptidase-4 (DPP4) inhibitor for the treatment of diabetic neuropathy.[1,2] The initial synthetic route (Scheme 1), was successfully scaled up to support early development efforts. This approach begins with *N*-*t*-Boc-4-oxo-L-proline (**1**) that undergoes a mixed anhydride activation with pivaloyl chloride at 0 °C, followed by amidation with 3,3-difluoropyrrolidine to yield the intermediate **2**. Reductive amination with 1-(2-pyrimidyl)piperazine using sodium triacetoxyborohydride in THF/AcOH provided the desired stereoisomer **3** in high yield and selectivity, the undesired diastereomer being completely removed by crystallization. Deprotection of **3** with 6 N HCl, followed by neutralization with 50% NaOH and extraction provided PF-734200 (**4**) in good yield.

Scheme 1. Initial route to PF-734200 (4)



One of the problems associated with this route is the absence of a chromophore in the first step, making the in-process analytics for reaction completion difficult to establish, for both the activated ester intermediate and the amide product. The introduction of the expensive 3,3-difluoropyrrolidine in the first step is also not ideal in terms of bond disconnection.[3] Finally, the starting keto-L-proline (**1**) is relatively expensive ($2400/kg), considering that it is being made from the oxidation of the readily available and cheap Boc-*trans*-4-hydroxy-L-proline methyl ester (**5**) ($325/kg). A synthetic route to PF-734200 that would utilize **5** as starting material is desirable from an economical standpoint. Results related to this work are summarized in this manuscript.

DISCUSSION

Scheme 2 presents an outline of the proposed new synthetic route. The nucleophilic displacement of alcohol **5** is well documented for the Mitsunobu-type reaction using DPPA.[4,5] Although the displacement of an activated form (**6**) such as the mesylate with sodium azide is known,[6−8] direct S_N2 substitutions of a sulfonyl-activated hydroxyproline by simple amines are surprisingly absent from the literature. Some of the rare examples include S_N2 substitution with adenine[9] and a protected L-serine[10] as the nucleophiles. If amine **7** could be accessed diastereoselectively, completion of the synthesis through carboxylic acid **8** should be straightforward. In light of the few precedents for the key displacement to form intermediate **7**, we first sought to establish proof of concept for the proposed bond disconnection by submitting the activated hydroxyproline (**6**) to S_N2 conditions with 1-(2-pyrimidyl)-piperazine as the nucleophile. Results are summarized in Table 1.

It became apparent that the selection of the leaving group was extremely important for this nucleophilic substitution to proceed. The difference in reactivity between the mesylate (**6a**), benzenesulfonate (**6b**), and nosylate (**6c**) (Table 1, entries 1−3) was significant and prompted us to concentrate on the more reactive nosylate. The lack of reactivity of **6a** could be one of the reasons why the nucleophilic displacement of an activated 4-hydroxyproline derivative with a primary or secondary amine is unprecedented, as the choice of the nosylate is not as common as that of the mesylate, which performed poorly. The use of a nosylate on pilot-plant scale is precedented in the alkylation of (*R*)-glycidyl nosylate[11] and gave us confidence that this method of activation would be acceptable for commercial use. A rapid solvent screen showed that acetonitrile was superior to THF and DMF for this reaction (entries 3−5). The addition of a crown ether had an unfavorable effect on the reaction (entry 6). The nature of the carbonate base was investigated, and it was found that the rate

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Scheme 2. Proposed synthetic strategy to PF-734200 (4)

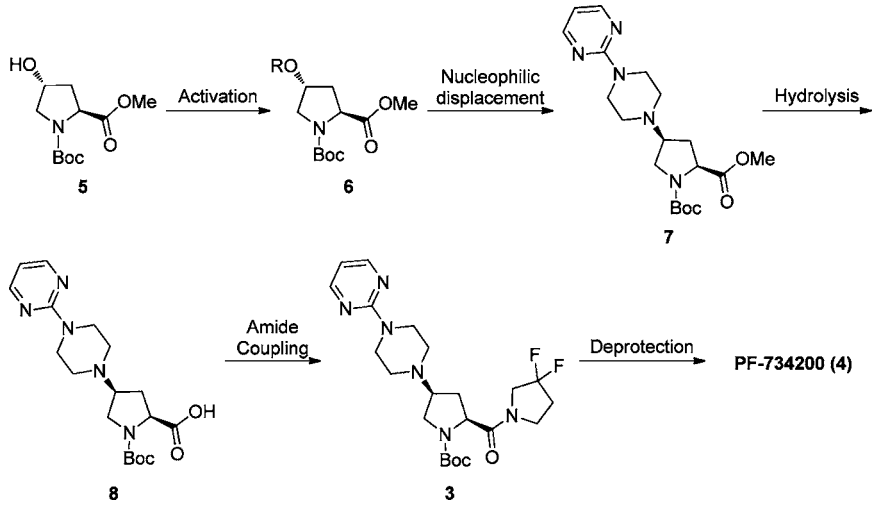
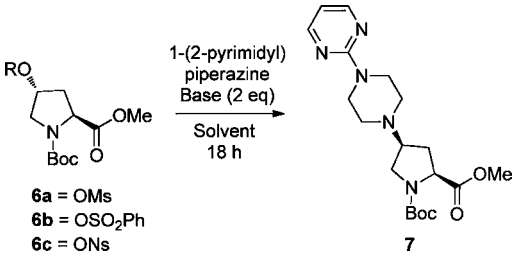


Table 1. Screen of various S_N2 reaction conditions



entry	substrate	base	solvent	*T*	% yield
1	**6a**	K_2CO_3	MeCN	reflux	12
2	**6b**	K_2CO_3	MeCN	reflux	<10
3	**6c**	K_2CO_3	MeCN	reflux	92
4	**6c**	K_2CO_3	THF	reflux	39
5	**6c**	K_2CO_3	DMF	70 °C	62
6	**6c**	K_2CO_3 18-crown-6	DMF	70 °C	31
7	**6c**	Na_2CO_3	MeCN	reflux	>95
8	**6c**	Li_2CO_3	MeCN	reflux	65
9	**6c**	Cs_2CO_3	MeCN	reflux	nd

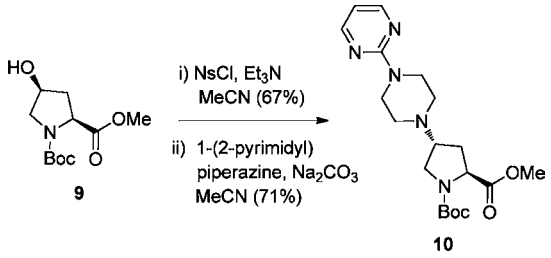
*Crude reaction mixture yield measured by ^{1}H NMR.

of the reaction followed roughly the following order: Na, K ≫ Li, Cs (entries 3, 8−9). Results also suggested that powdered solids were more efficient than granular types. Sodium carbonate powder was eventually selected as the optimal base due to inducing high reaction conversion.

In order to confirm stereochemical integrity of the product, the potential formation of the undesired diastereoisomer **10** through chiral inversion at C4 was ruled out. An authentic sample of **10** was prepared using *N*-Boc-*cis*-4-hydroxy-L-proline methyl ester (**9**) as the starting material (Scheme 3), and no trace of the C4 inversion product **10** was detectable in our experiments.

To further understand the stability of the nosylate ester **6c** towards potential undesired side reaction, a control experiment was carried out in which **6c** was treated with 1 equiv of 4-nitrobenzenesulfonic acid, 1.5 equiv of triethylamine and sodium carbonate under reflux for 18 h (Scheme 4). We were pleased to observe that our starting material was very stable under the reaction conditions employed for the nucleophilic displacement, producing no detectable C-4

Scheme 3. Preparation of 1,4-*trans*-isomer (10)



inversion product **11**, and less than 2% (by ^{1}H NMR) of the elimination product (**12**). The 4,5-dehydro elimination product **13** was not detectable, in line with previous reports where the 3,4-elimination product is formed predominantly.[12−14] Interestingly, when the 1,4-*cis*-nosylate ester **11** is submitted to the same control reaction, up to 20% of dehydro-elimination product **12** was observed. In addition, the rate of the nucleophilic substitution reaction to produce the undesired 1,4-*trans* stereoisomer **10** (Scheme 3) was much greater than

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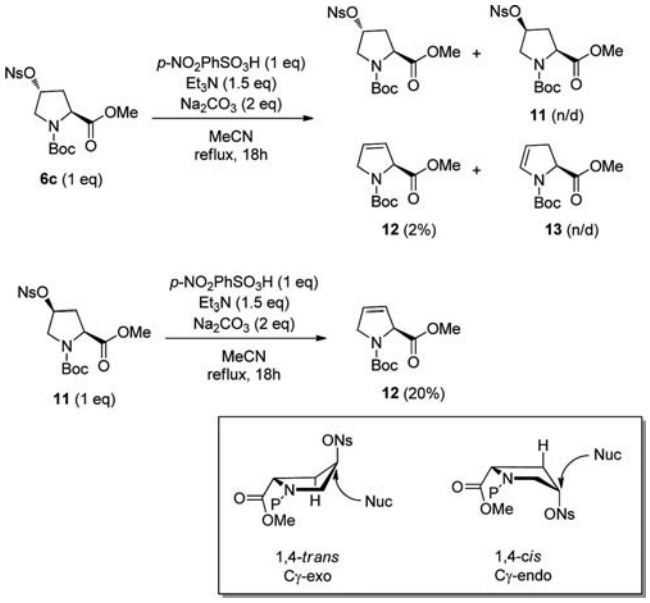
Scheme 4. Differences in the stabilities of nosylate 6c and 11

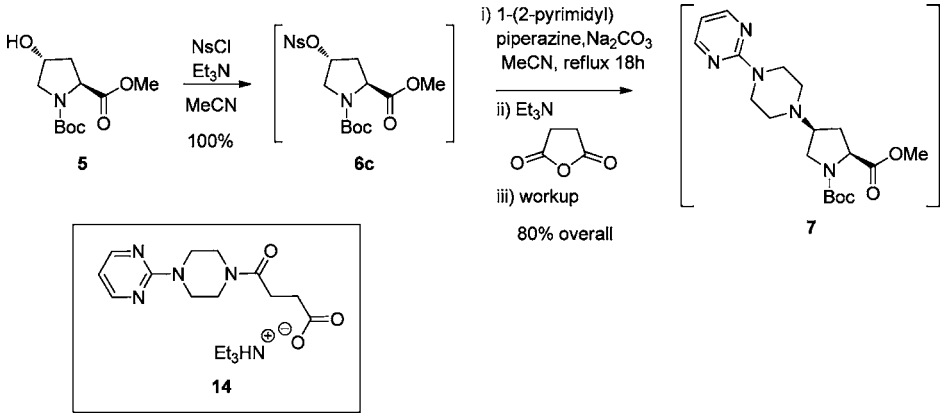


the corresponding reaction starting with **6c**.[15] This is consistent with a ring pucker stereochemistry as depicted in Scheme 4, where 1,4-*trans*-substituted proline favors an exo conformation, while 1,4-*cis*-substitution favors an endo form.[16]

Having demonstrated the key nucleophilic substitution for diastereoselective introduction of the piperidine moiety, we optimized the first step of the synthesis. In an initial screen, reaction of methyl ester **5** proceeded smoothly but no further than 80% with *p*-nitrosulfonyl chloride in THF using Et_3N as the base. The use of DMAP as a catalyst, use of excess base, and selection of acetonitrile as the solvent were all effective in bringing the reaction to completion in less than one hour at room temperature. The final reaction condition selected utilized a slight excess of NsCl and two equivalents of the base in MeCN leading to full conversion of the starting material (Scheme 5). Excess NsCl was completely removed during aqueous workup, making it possible to telescope the crude reaction mixture directly to the next step. The crude nosylate (**6c**) was reacted under the preferred conditions described in Table 1 to afford **7** in high yield. Although this intermediate was found to be crystalline, attempts to develop a crystallization method from the crude reaction mixture failed to produce robust conditions. It was initially believed that the presence of excess 1-(2-pyrimidyl)piperazine could inhibit the product crystallization. In order to facilitate the isolation of the desired product, 1-(2-pyrimidyl)piperazine was acetylated by acetic anhydride to form the acetamide derivative, but this failed to improve crystallization from the crude mixture. Alternatively, reaction with succinic anhydride produced amide **14** bearing a free carboxylate group. Initial attempts to keep the salt in solution with potassium carbonate produced a difficult to stir gel-type suspension. Instead, filtration of residue from the nucleophilic substitution and use of triethylamine as the base for the derivatization, leading to a more soluble ammonium carboxylate, proved to be the solution as **14** could be removed in the aqueous phase as part of the extraction. Furthermore, ester **7** was found to be very soluble in slightly acidic water; thus, the crude product was treated with aqueous HCl. This brought **7** into the aqueous phase, allowing for the removal of all the nonpolar impurities in the organic layer, including unreacted starting material and the 3,4-elimination product (**12**) produced in the reaction. Control of the pH between 4 and 6 in this operation was important to avoid deprotection of the carbamate. Extraction of **7** in EtOAc was achieved by neutralization of the acidic aqueous phase with NaOH. Following the workup procedure described above, isolation of **7** with satisfactory purity (>95%) was achieved in 80% yield, which also made it possible to telescope the crude solution directly to the next step without crystallization following a solvent swap to THF/H_2O.

The initial strategy for the completion of the synthesis was to hydrolyze the ester and isolate the resulting carboxylic acid as the penultimate intermediate. Although the saponification proceeds smoothly using lithium hydroxide, the isolation of either the carboxylic acid or its salt proved very challenging due to the high solubility in water. The strategy was modified to telescope the crude carboxylate to the amidation step and rely on a robust crystallization of either the API or the protected carbamate **3**. The first approach investigated involved neutralization of the crude carboxylate with triethylamine hydrochloride, followed by azeotropic distillation of the residual water in toluene. Generation of the mixed anhydride with pivaloyl chloride followed by addition of 3,3-difluoropyrrolidine generated the amide (**3**) in moderate yield (45%). In order to take advantage of the high water solubility of the carboxylate intermediate, we turned our attention to a water-soluble amide coupling agent, namely 1-ethyl-3-(3′-dimethylaminopropyl)-

Scheme 5. Preparation and purification of ester 7



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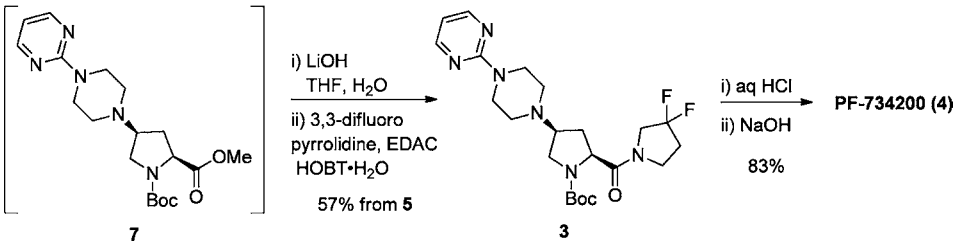
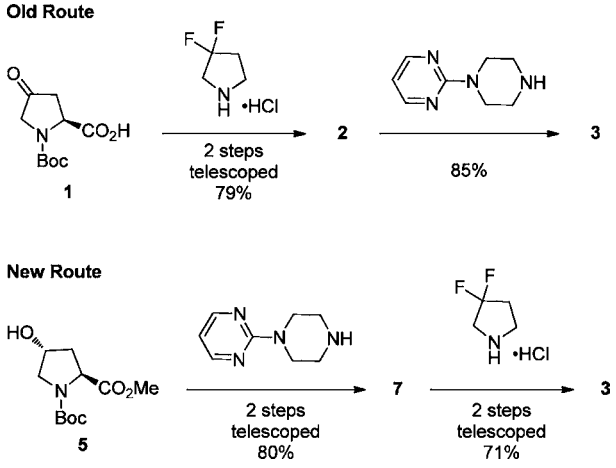
Scheme 6. Final 3 step approach

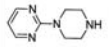
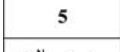


carbodiimide (EDAC or EDC).[17] Following the hydrolysis of the ester **7** with lithium hydroxide, the resulting carboxylate solution was directly subjected to the amidation step (Scheme 6). The reaction mixture was simply cooled down to 10 °C followed by addition of the hydrochloride salt of 3,3-difluoropyrrolidine. The salt was neutralized by the one equivalent excess of base already present in the system to liberate the nucleophilic amine. Addition of HOBt[18,19] and EDAC led to formation of the desired amide (**3**). Attempts to perform the reaction without HOBt or using a substitute (such as DMAP), failed to generate good conversion. Using this simple and straightforward strategy, the desired penultimate intermediate **3** was produced in good yield (70−75%) and isolated by crystallization. The final deprotection of the carbamate was performed using the known methodology from the initial route, to provide the final product PF-734200 (**4**). Analysis of the product generated with the new synthetic route showed no new impurities, and the overall purity profile was similar by HPLC to the one generated using the enabling synthetic route shown in Scheme 1. The products of either route proved to be equivalent through other analytical methods.

While the new procedure requires one additional synthetic step compared to the synthesis described in Scheme 1, it provides a significant economical advantage upon a cost analysis (Table 2). Since it was believed that both processes could be reduced to a similar number of units of operation and used common and inexpensive reagents, it was concluded that the price of the building blocks would be the best predictor of the cost efficiency of each synthesis. In the previous synthesis, the ketone starting material (**1**) cost 7 times the quotes obtained for the new starting material, alcohol **5**, at the same scale. The choice of either **1** or **5** as starting material between the two syntheses represents the largest cost difference between the two routes illustrated. In the previous synthesis, the most expensive building block, the 3,3-difluoropyrrolidine, is used in the second step of a telescoped process while in the new synthesis, it is used in the fourth and last step. Since 3,3-difluoropyrrolidine has a small molecular weight and the telescoped last two steps of the new synthesis suffer from the lowest reported yield, the difference between the two routes in contributions from this fragment is minimal. However, further optimization of the last step of the new route would represent the biggest opportunity for further cost improvements. Finally, contributions from the 1-(2-pyrimidyl)piperazine building block are minimal in either synthesis since this starting material has a low cost and fairly small molecular weight. Obviously, it is used more efficiently in the first synthesis as it is introduced in the last step. This analysis helped us conclude that the new route identified offered economical advantage based on input costs.

Table 2. Cost comparison of two synthetic routes to intermediate 3



SM	Used in Steps	Mw	Relative Cost	Utilization Factor*	Total Cost
Old Route					**19.34X**
1	1/2	229.2	7X	0.73	5.11X
	1/2	143.6	30X	0.46	13.8X
	3	164.2	1X	0.41	0.41X
New Route					**13.45X**
5	1/2	245.3	1X	0.93	.93X
	1/2	164.2	1X	0.62	.62X
	3/4	143.6	30X	0.43	12.9X

*Kilograms of SM for each kilogram of **3** produced.

CONCLUSIONS

A new synthetic route to PF-734200 that takes advantage of the inexpensive and readily available Boc-*trans*-4-hydroxy-L-proline methyl ester (**5**) building block was demonstrated. The synthesis highlights the importance of the selection of the leaving group for a key nucleophilic substitution. In this case, the key *p*-nitrobenzenesulfonyl ester (**6c**) provided unique properties for the introduction of a piperidine fragment while preserving diastereoselectivity. This new route offers multiple advantages, namely the introduction of a chromophore early in the synthesis, providing access to conventional HPLC analysis for in-process control, an economic advantage due to the selection of the starting material, and introduction of the most

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expensive building block (3,3-difluoropyrrolidine) in the last step. Preservation of the penultimate intermediate allowed for the opportunity to prepare API of comparable purity. The new route would benefit from further process development and optimization before introduction into a manufacturing setting.

EXPERIMENTAL SECTION

NMR data were collected on a Bruker Ultrashield 400 plus instrument. HRMS data were collected on a Thermo-Fisher LTQ-Orbitrap spectrometer. IR monitoring was performed using a Thermo Nicolet Nexus-470 FTIR instrument. Optical rotations were measured using a Jasco P-1020 polarimeter.

(2*S*,4*R*)-1-*tert*-Butyl-2-methyl-4-(4-nitrobenzenesulfonyloxy)pyrrolidine-1,2-dicarboxylate (6c). To a solution of Et_3N (1.14 mL, 8.18 mmol) and *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester (**5**) (1.00 g, 3.95 mmol) in MeCN (15 mL) at 0 °C was added *p*-nitrobenzenesulfonyl chloride (1.31 g, 5.93 mmol). The suspension was allowed to warm up to rt and stirred for 18 h. Water (5 mL) was added, and the reaction mixture was stirred at rt for 30 min and concentrated in vacuo. EtOAc (20 mL) was added, and the organic solution was washed sequentially with of saturated aqueous Na_2CO_3 (10 mL), 1 N HCl (10 mL), saturated aqueous Na_2CO_3 (10 mL), and brine (10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo to provide an oil that slowly crystallized upon standing. The crystals were triturated in Et_2O (10 mL) at rt, filtered, and dried in a vacuum oven at 55 °C to afford **6c** as a light-yellow solid (1.14 g, 67% yield). Mp 95 °C. $[\alpha]_D = -30.0$ (T = 24 °C, c = 1, $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.35 (d, J = 8 Hz, 2H), 8.05 (d, J = 8 Hz, 2H), 5.12 (s br, 1H), 4.4–4.25 (m, 1H), 3.66 (s, 3H), 3.65–3.55 (m, 2H), 2.6–2.35 (m, 1H), 2.25–2.05 (m, 1H), 1.36, 1.32 (2s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.54, 172.36, 153.72, 153.10, 150.91, 142.11, 129.10, 124.71, 81.01, 79.96, 57.24, 56.96, 52.35, 51.80, 37.26, 36.07, 28.25, 28.13. IR (neat): 2972br, 1743s, 1693vs, 1531s, 1411s, 1363s, 1347s, 1287m, 1159s(br), 1041m, 910m, 747br, 616s, 578m, 551m. HRMS (ES sodiated, N_2) Calcd for $C_{17}H_{22}N_2O_9SNa$: 453.09382, found: 453.09377. Characterization data match those of previous report.[9]

(2*S*,4*S*)-1-*tert*-Butyl-methyl- 4-(4-nitrobenzenesulfonyloxy)pyrrolidine-1,2-dicarboxylate (11). The same procedure as for the preparation of **6c** was used starting with Boc-*cis*-Hyp-OMe (**9**, 1.00 g). This provided **11** as an off-white solid (1.24 g, 71% yield). Mp 119 °C. $[\alpha]_D = -26.2$ (T = 24 °C, c = 1, $CHCl_3$) ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.41 (d, J = 8 Hz, 2H), 8.11 (d, J = 8 Hz, 2H), 5.22 (s br, 1H), 4.55–4.35 (m, 1H), 3.71 (s, 3H), 3.69–3.60 (m, 2H), 2.60–2.42 (m, 2H), 1.43, 1.40 (2s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.73, 171.46; 153.60, 153.24; 150.80; 142.37; 129.03; 124.56; 80.82; 79.58; 57.21, 56.94; 52.34; 51.68; 37.08, 36.12; 28.29, 28.17. IR (neat): 2980br, 1752s, 1681vs, 1531s, 1410s, 1363br, 1188s(br), 1155s(br), 927m, 910m, 758m, 745m, 660m, 554 m. HRMS (ES sodiated, N_2) Calcd for $C_{17}H_{22}N_2O_9SNa$: 453.09382, found: 453.09407.

(2*S*,4*R*)-1-*tert*-Butyl-2-methyl-4-(4-(pyrimidin-2-yl)-piperazin-1-yl)pyrrolidine-1,2-dicarboxylate (10). In a 20 mL pressure tube was added **11** (0.50 g, 1.16 mmol), 1-(2-pyrimidyl)piperazine) (0.25 g, 1.52 mmol), and Na_2CO_3 (0.25 g, 2.36 mmol) in MeCN (2.5 mL). The tube was sealed, and the reaction mixture was stirred at reflux for 6 h, cooled to rt, and filtered over a frit funnel. The solid residue was washed with MeCN and the filtrate was concentrated in vacuo. The crude product was purified by chromatography using DCM (3% MeOH) as the eluant. The product containing fractions were pooled and concentrated in vacuo to give an oil that crystallized upon trituration with pentane to afford **10** as an off-white solid (0.32 g, 71% yield). Mp 135–136 °C. $[\alpha]_D = -11.7$ (T = 24 °C, c = 1, $CHCl_3$) ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.32 (m, 2H), 6.50 (m, 1H), 4.5–4.3 (m, 1H), 3.95–3.75 (m, 5H), 3.74 (s, 3H), 3.35–3.2 (m, 1H), 3.05–2.9 (m, 1H), 2.6–2.4 (m, 4H), 2.25–2.05 (m, 2H), 1.48, 1.42 (2s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 173.36, 173.12; 161.53; 157.73; 154.24, 153.50; 110.05; 80.20; 62.59, 61.74; 58.55, 58.11; 52.31, 52.13; 51.53, 51.48; 50.25, 49.91; 43.43; 34.31, 33.43; 28.42, 28.25. IR (neat): 2975br, 1745m, 1695vs, 1592m, 1542m, 1398m(br), 1363m, 1186m(br), 1150m(br), 984m, 898m, 796m, 571w. HRMS (ES, N_2) Calcd for $C_{19}H_{29}N_5O_4$: 392.22923, found: 392.22935.

(2*S*,4*S*)-1-*tert*-Butyl-2-methyl-4-(4-(pyrimidin-2-yl)-piperazin-1-yl)pyrrolidine-1,2-dicarboxylate (7). A Boc-*trans*-4-hydroxy-L-proline methyl ester (**5**) (10.0 g, 0.041 mol) and Et_3N (11.4 mL, 0.082 mol) solution in 150 mL of acetonitrile was cooled to 5 °C, and 4-nitrobenzenesulfonyl chloride (12.8 g, 0.057 mol, 1.4 equiv) was added portionwise at 5 °C (±5 °C) throughout the addition. The reaction mixture was stirred at 5 °C for 1 h, warmed to 20 °C over 1 h, and stirred at 20 °C for 1 h. The reaction mixture was quenched with water (10 mL), stirred at rt 1 h, and concentrated to a low stirrable volume. EtOAc (120 mL) and water (60 mL) were added and stirred vigorously at rt for 30 min. The phases were separated, and the organic layer was washed with 10% aq NaCl (60 mL) and water (60 mL). The EtOAc was distilled and replaced with MeCN (40 mL) that was distilled. To the crude product was added MeCN (80 mL), powdered Na_2CO_3 (8.64 g, 0.082 mol), and 1-(2-pyrimidinyl)piperazine 8.7 g, 0.053 mol), and the suspension was stirred at reflux until reaction completion (typically 18 h). The mixture was cooled to rt, filtered through a pad of Celite, and washed with MeCN (40 mL). To the filtrate was added Et_3N (2.84 mL (203 mmol)) and succinic anhydride (2.04 g of 204 mmol), and the mixture was stirred at rt for 1 h, concentrated to a low stirrable volume, and diluted with EtOAc (100 mL). The solution was washed with 0.5 N NaOH (60 mL), and 10% aq NaCl (60 mL). The organic layer was extracted with 0.5 N HCl (120 mL, 1.5 mol equiv) and washed with water (20 mL). The aqueous extracts were combined, cooled to 10 °C, and treated with 2 N NaOH (32 mL, 1.07 equiv vs HCl). EtOAc (100 mL) was added, and the mixture was stirred vigorously for 30 min. The layers were separated, and the organic phase was concentrated to a low stirrable volume. The residue was dissolved in 4:1 THF/H_2O (100 mL) and telescoped directly to the next step. Compound **7** can alternatively be isolated as a crystalline solid as described for compound **10** (reflux 18 h instead of 6 h). Mp 109 °C. $[\alpha]_D = -42.2$ (T = 24 °C, c = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.32 (m, 2H), 6.50 (m, 1H), 4.35–4.2 (m, 1H), 3.95–3.75 (m, 5H), 3.74 (s, 3H), 3.35–3.25 (m, 1H), 2.9–2.75 (m, 1H), 2.75–2.4 (m, 5H), 2.0–1.85 (m, 1H), 1.48, 1.42 (2s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 173.05, 172.82; 161.51; 157.73; 154.16, 153.49; 110.04; 80.30; 63.29, 62.64; 58.38, 57.88; 52.20, 52.03; 51.73, 51.59; 52.24, 49.97; 43.38; 34.92, 33.79; 28.41, 28.25. IR (neat): 2951br, 1734m, 1694vs, 1592s, 1527m, 1399m(br), 1366m, 1203m, 1164s(br), 983m, 792m, 770m, 562w. HRMS (ES, N_2) Calcd for $C_{19}H_{29}N_5O_4$: 392.22923, found: 392.22939.

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(2*S*,4*S*)-*tert*-Butyl-2-(3,3-difluoropyrrolidine-1-carbonyl)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidine-1-carboxylate (3). The THF/H_2O solution of **7** described above was added LiOH (1.96 g, 0.0816 mol). The reaction mixture was stirred at rt for 4 h, cooled to 0 °C and 3,3-difluoropyrrolidine hydrochloride (6.17 g, 0.043 mol) was added followed by portionwise addition of HOBT·H_2O (5.81 g, 0.043) (**CAUTION:** Vacuum-drying of HOBT while heating can generate a violent explosion) and EDAC (8.24 g, 0.043 mol) over 1 h. The reaction mixture was allowed to warm-up to 20 °C, stirred for 18 h, and was concentrated to a low stirrable volume. Water (100 mL) was added, and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic extrects were washed with brine (100 mL) and concentrated, and the residue was triturated with 95:5 heptane/EtOAc (75 mL). The solid was filtered, washed with heptane, and dried in a vacuum oven at 45 °C to afford **3** as an off-white solid (10.9 g, 57% yield over two steps). Mp 194 °C (decomp). $[\alpha]_D = -22.9$ (T = 24 °C, c = 1, $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.32 (dd, J = 8, 4 Hz, 2H), 6.51 (t, J = 8 Hz, 1H), 4.5−4.25 (m, 1H), 4.0−3.5 (m, 9H), 3.4−3.25 (m, 1H), 2.95−2.75 (s br, 1H), 2.7−2.2 (m, 7H), 2.0−1.75 (m, 1H), 1.46, 1.41 (2s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.98, 170.84; 161.51; 157.73; 154.21, 153.36; 127.35 (t, 1 J C−F = 248 Hz), 125.97 (t, 1 J C−F = 246 Hz), 110.05; 80.35, 80.20; 63.38, 62.73; 57.57, 56.75; 52.85 (m, 1C); 51.66, 51.49; 50.07; 43.98, 43.89; 43.35; 34.56 (t, 2 J C−F = 23 Hz), 32.57 (t, 2 J C−F = 25 Hz), 34.21; 28.45, 28.27. ^{19}F NMR (377 MHz, $CDCl_3$) δ −101.4 (m, 2F). IR (neat): 2948w, 2826w, 1698vs, 1646vs, 1587m, 1544m, 1484m, 1448s, 366s, 1267m, 1165m, 1113s, 984w, 805m, 777m, 556 m. HRMS (ES, N_2) Calcd for $C_{22}H_{32}F_2N_6O_3$: 467.25767, found: 467.25832.

(3,3-Difluoropyrrolidin-1-yl)-(2*S*,4*S*)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone (4). A 10 mL water solution of **3** (5.0 g, 0.011 mol) at rt was added conc. HCl (10 mL) over 4 h. The mixture was cooled to 5 °C and 50% NaOH (∼ 6.5 mL) was slowly added, keeping the temperature <15 °C, until the pH reached 10−11. The mixture was allowed to warm-up to rt and was extracted with EtOAc (60 and 30 mL). The combined organic extracts were dried with $MgSO_4$ (2.5 g) and stirred at rt for 30 min. The solids were filtered, washed with EtOAc (5 mL), and concentrated to a volume of 10 mL, at which point the product began to crystallize. The solids were stirred at rt for 30 min, and hexane (10 mL) was added over a period of 1 h. The solids were filtered, washed with hexane/EtOAc (1:1) (10 mL), and dried in vacuum oven at 45 °C for 12 h to afford **4** (3.25 g, 83% yield). Mp 149 °C (decomp). $[\alpha]_D = -31.1$ (T = 24 °C, c = 1, $CHCl_3$). Specific rotation of product **4** prepared using the initial route: $[\alpha]_D = -31.5$ (T = 24 °C, c = 1, $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.30 (d, J = 4 Hz, 2H), 6.48 (t, J = 4 Hz, 1H), 3.95−3.6 (m, 9H), 3.25−2.85 (m, 4H), 2.6−2.25 (m, 7H), 1.75−1.6 (m, 1H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.28; 161.55; 157.70; 127.22 (t, 1J C−F = 248 Hz), 126.22 (t, 1J C−F = 246 Hz), 109.95; 66.54; 58.87; 57.99; 52.71 (t, 2 J C−F = 32 Hz); 52.00; 50.41; 43.03; 34.46, 34.37, 34.25; ^{19}F NMR (377 MHz, $CDCl_3$) δ −102.1 (m, 2F). IR (neat): 2951w, 2864w, 2799w, 2759w, 1630s, 1585vs, 1547m, 1449m, 1172m, 1254m, 1129m, 982w, 923m, 796m, 638w. HRMS (ES, N_2) Calcd for $C_{17}H_{24}F_2N_6O$: 367.20524, found: 367.20592.

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