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Practical Synthesis of a Neuropeptide Y Antagonist via Stereoselective Addition to a Ketene

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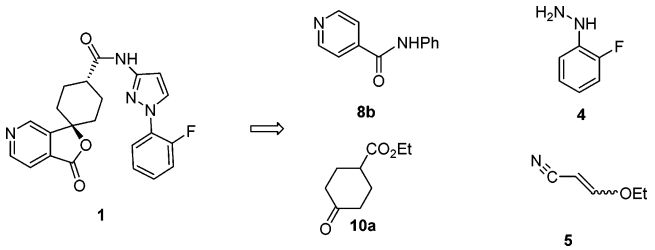

The synthesis of neuropeptide Y antagonist **1**, currently under clinical investigation for the treatment of obesity, is described. The convergent synthesis from *trans*-spirolactone carboxylic acid intermediate **2a** and aminopyrazole **3** is predicated on a stereoselective route to the former. The coupling reaction of ethyl 4-oxocyclohexanecarboxylate (**10a**) with lithiated isonicotinamide **11** was investigated in detail, but even optimized conditions only provided a 45:55 ratio of trans:cis isomers (**12a:12b**). While selective crystallization schemes were developed to isolate the thermodynamically less stable trans isomer **2a**, improved stereocontrol was subsequentially achieved by the application of ketene chemistry. The ketene formation and quench was investigated under a variety of conditions aimed at maximizing the trans:cis ratio. Reacting a mixture of carboxylic acids **2a** and **2b** with $POCl_3$ in THF, followed by concomitant addition of *tert*-butyl alcohol in the presence of TMEDA at 35 °C provided a 4:1 ratio of trans:cis *tert*-butyl esters (**18a:18b**) via in situ ketene formation. Ester hydrolysis, followed by selective crystallization of undesired **2b** as the HCl salt, led to isolation of **2a** in 47% overall yield. Aminopyrazole intermediate **3** was synthesized via the condensation reaction of 2-fluorophenylhydrazine hydrochloride (**4a**) with acrylonitrile derivative **5** in 65−70% yield. Coupling of advanced intermediates **2a** and **3b** via activation with thionyl chloride gave a 92% yield of **1**.

Introduction

The World Health Organization acknowledged that obesity represents a global epidemic that poses "one of the greatest threats to human health and well being". In the United States, 50−60% of the population is classified as obese or overweight with the levels escalating in developed countries throughout the world. This disease is directly linked to increased risk of hypertension, cardiovascular and respiratory disease, and type II diabetes.[1] As a result, the economic burden on the health care system and lost workplace productivity is estimated at $70−100 billion annually. Recent drug development efforts in the field[2] have focused on reducing caloric intake via appetite suppression as a means of combating obesity. Advances in the understanding of biological mechanisms have led to the identification of specific targets, including neuropeptide Y (NPY), a 36 amino acid peptide that has emerged as an important regulator of feeding behavior.[3] Recent biological studies have suggested that NPY receptor antagonists may become thera-

(1) Dove, A. *Nat. Biotech.* **2001**, *19*, 25−28.

(2) For a recent review, see: Wilding, J. *Curr. Drug Targets* **2004**, *5*, 325−332.

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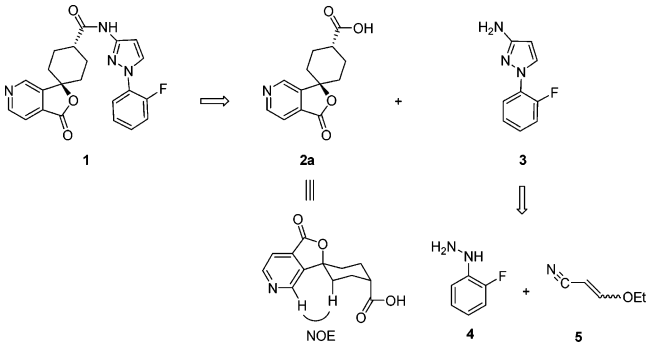
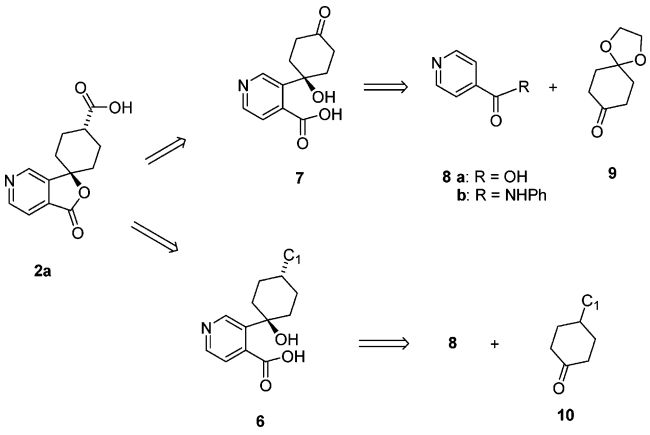
SCHEME 1



SCHEME 2



peutic agents for treating human obesity.[3c] Herein, we describe the synthesis of NPY antagonist **1**,[4] currently under clinical investigation, that features a unique and challenging 1,4-trans-substituted cyclohexane ring within a spirolactone framework.

Synthetic Strategy

Compound **1** is retrosynthetically disconnected at the amide bond to give *trans*-spirolactone carboxylic acid **2a** and 3-aminopyrazole derivative **3** (Scheme 1). Intermediate **3** was envisioned arising from the condensation reaction of arylhydrazine **4** and ethoxyacrylonitrile (**5**), based on literature precedent.

Our strategy for the stereoselective synthesis of intermediate **2a** was predicated on preparing hydroxy acids **6** or **7**, derived from the coupling of a metalated pyridine species with a cyclohexanone derivative with subsequent acidification to provide the spirolactone (Scheme 2). The *trans*-spirolactone **2a** can be derived from either lactonization of (i) hydroxy acid **7**, prepared via coupling of **8** and 1,4-cyclohexadione synthon **9**, which contains a masked carbonyl functionality in the 4-position, or (ii) hydroxy acid **6**, prepared via coupling of metalated isonicotinic acid derivative **8** and ketone **10**, which possesses a C_1 unit in the 4-position. The former approach allows for predictable induction of the desired stereochemistry according to well-established stereochemistry of the reduction of 4-substituted cyclohexanone derivatives.[5] In fact, this approach provided **2a** with high levels of stereoselectivity via a subsequent homologation of the 4-position of the spirolactone derived from **6** by using NaCN as a C_1 source.[4] However, this approach required several synthetic transformations and was not suitable for scale-up due to low productivity and the use of toxic NaCN. The application of other known homologation methods was investigated, but without success. Accordingly, we pursued the latter approach, which would make the synthetic route more concise. Achieving the required trans stereochemistry in **2a** was expected to be quite challenging, due to the propensity of the carboxylate in the 4-position of the cyclohexane to occupy the thermodynamically favored equatorial position.[6] The lactone oxygen atom and the carboxylate in **2a** both were found to occupy axial positions based on NMR/NOE experiments.[7] These difficulties were overcome by developing a *kinetically* controlled synthesis via a ketene intermediate. Herein, we wish to report on the synthesis of NPY antagonist **1** that was achieved via the stereoselective synthesis of **2a**.

Results and Discussion

The ortho-lithiation of isonicotinic acid (**8a**) was first attempted by using LiTMP,[8] but it was not effective. Changing the carboxyl group to a phenylamide moiety (e.g., **8b**) had a dramatic effect on the reaction outcome. The ortho-metalation of **8b**[9] was performed with 2.1 equiv of *n*-BuLi in THF at −60 °C. It was reported that lithiation of **8b** at −78 °C followed by treatment with $PhCONMe_2$ gave only a low yield of the corresponding benzoylanilide, in contrast to lithiation followed by treatment with MeOD, which gave quantitatively ortho-deuterated **8b**.[9b] This report described the existence of a semimetalated species at −78 °C. Accordingly, the reaction temperature was raised to −60 °C to encourage the complete formation of lithiated species **11**, while minimizing decomposition.

The coupling reaction of **11** with ethyl 4-cyclohexanecarboxylate (**10a**; $C_1 = CO_2Et$) at −60 °C gave a hy-

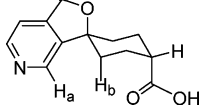
(3) (a) Zimanyi, I. A.; Fathi, Z.; Poindexter, G. S. *Curr. Pharm. Des.* **1998**, *4*, 349−366. (b) Sato, N.; Takahashi, T.; Shibata, T.; Haga, Y.; Sakuraba, A.; Hirose, M.; Sato, M.; Nonoshita, K.; Koike, Y.; Kitazawa, H.; Fujino, N.; Ishii, Y.; Ishihara, A.; Kanatani, A.; Fukami, T. *J. Med. Chem.* **2003**, *46*, 666−669 and references therein. (c) For a review, see: Wieland, H. A.; Hamilton, B. S.; Krist, B.; Doods, H. N. *Exp. Opin. Invest. Drugs* **2000**, *9*, 1327−1346.

(4) Fukami, T.; Kanatani, A.; Ishihara, A.; Ishii, Y.; Takahashi, T.; Haga, Y.; Sakamoto, T.; Itoh, T. US Patent 6326375 B1, 2001; *Chem. Abstr. 134*, 207809.

(5) Hudlicky, M. *Reduction in Organic Chemistry*, American Chemical Society: Washington, DC, 1996; pp 157−164.

(6) Eliel, E. L.; Haubenstock, H.; Acharya, R. V. *J. Am. Chem. Soc.* **1961**, *83*, 2351−2354.

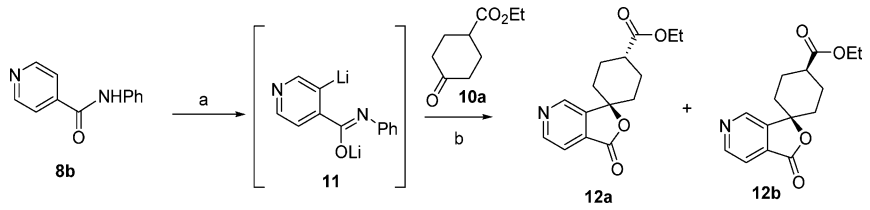
(7) Support for the conformation favoring the carboxyl group and the oxygen atom of spirolactone in axial positions is found in the ^{1}H NMR of **2a** in DMSO-d_6 that showed the diagnostic methine resonance at δ 2.72 to only exist as a distinct triplet of triplets (J = 5.1, 4.9 Hz), indicative of that proton residing in an equatorial position. 2.9% NOE was observed between H_a on the pyridine ring and H_b, as shown below.



(8) Mongin, F.; Trécourt, F.; Quéiguiner, G. *Tetrahedron Lett.* **1999**, *40*, 5483−5486.

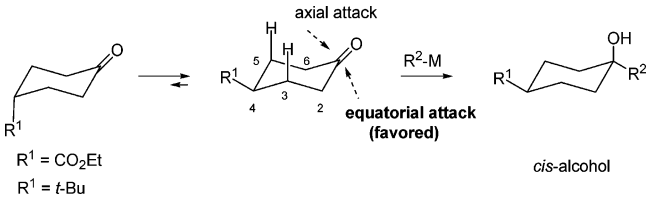
(9) (a) Epsztajn, J.; Jozwiak, A.; Szczesniak, A. *Synth. Commun.* **1994**, *24*, 1789−1798. (b) Epsztajn, J.; Jozwiak, A.; Czech, K.; Szczesniak, A. *Monatsh. Chem.* **1990**, *121*, 909−921.

SCHEME 3[a]



[a] Reagents/conditions: (a) 2.1 equiv n-BuLi/−60 °C/3 h/THF; (b) −60 °C, then AcOH/rt.

SCHEME 4



droxyamide product that upon subsequent quenching with AcOH/EtOH provided the expected spirolactone esters (**12a/12b**) in 69% yield (Scheme 3). The desired trans isomer **12a** (26% yield), however, was the minor product with only 37:63 trans:cis selectivity. It proved difficult to alter this ratio, as evidenced by an attempt to equilibrate pure **12a**[10] with catalytic NaOEt in EtOH at 50 °C for 1 h, only to obtain a 30:70 ratio of trans:cis isomers.[11] This confirmed that desired isomer **12a** was thermodynamically less stable than **12b**. A single-crystal X-ray of **12a** shows the expected arrangement whereby the lactone oxygen atom and the carboxylate in the 4-position both occupy axial positions.

Thus, a kinetically controlled method was required to achieve the desired trans stereochemistry. As shown in Scheme 4, however, this was quite challenging. The selectivity of the coupling reaction depends on the direction of the nucleophilic attack of metalated pyridine **11** to the 4-substituted cyclohexanones (**10**). The direction is governed by avoidance of steric interactions of the incoming group (R−M) with the 3,5-axial hydrogens, thus favoring the equatorial attack to give the undesired cis alcohol.[12] In fact, the reaction of **11** with 4-*tert*-butylcyclohexanone (**10b**: R^1 = t-Bu) showed relatively high cis selectivity (trans:cis ∼ 14:86). It is also plausible that **10a** exists as an equilibrium mixture of **10a-ax** and favored **10a-eq**,[13] though the ratio would be smaller than that of **10b** based on the *A* values of the susbstituents (CO_2Et moiety, 1.1−1.2 kcal/mol; t-Bu, 4.9 kcal/mol).[14] High selectivity to provide *trans*-alcohols are limited to only a few examples, such as those utilizing the MAD reagent (methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)), developed by Maruoka and Yamamoto,[15] which is known to enhance axial attack of organolithium nucleophiles to cyclohexanones by blocking the equatorial face. The addition of MAD (1 equiv) to our system, however, gave only 6% of **12a**:**12b** with an unchanged isomeric ratio (trans:cis = 37:63). It has been also reported that the reaction of a methyl ester (**10c**: $R^1 = CO_2Me$) with MeMgI in benzene gives predominantly *trans*-alcohol.[16] The use of nonpolar solvents for the reaction of **8b** with **10a** as well as transmetalation of Li to Mg and Zn was investigated, but it was unsuccessful due to the low solubility of both **8b** and **11**.

TABLE 1. Effect of LiBr on the Stereochemical Outcome of the Reaction of 10a with 8b

					isomer ratio	
	LiBr	% yield				recovered
entry	(equiv)	overall	**12a**	**12b**	trans:cis	**8b**
1	0	69	26	43	37:63	22
2	1	80	33	47	42:58	*a*
3	3	87	39	48	45:55	7
4	10	87	39	48	45:55	*a*

[a] Not determined.

The low reactivity observed with MAD appeared to be due to the bulkiness of the reagent. Subsequently, the effect of other Lewis acids was examined.[17] While the addition of $CeCl_3$, $Al(O\text{-}i\text{-}Pr)_3$, $B(OMe)_3$, or $Ti(O\text{-}i\text{-}Pr)_4$ did not improve the stereoselectivity (∼ 37:63) or yield (50−69%), we found that the addition of lithium salts did improve the stereoselectivity (Table 1). The addition of 1 equiv of LiBr improved the selectivity to 42:58, while adding 3 equiv of LiBr further raised it to 45:55. The addition of LiCl or LiI gave slightly worse results, while the addition of $LiBF_4$ or $LiClO_4$ showed slightly better selectivity than LiBr, but their use for scale-up was undesirable due to cost and safety concerns, respectively.

(10) The mixture of esters **12a/12b** was chromatographed on silica gel eluting with 2:1 EtOAc:hexanes to provide the pure isomers with **12a** eluting first. Selected data for **12a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 1.0 Hz, 1H), 8.85 (d, J = 5.0 Hz, 1H), 7.75 (dd, J = 5.0, 1.0 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 2.79 (br m, 1H), 2.22−2.10 (overlapping m, 6H), 1.84−1.74 (overlapping m, 2H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.5, 167.9, 150.2, 147.6, 144.2, 133.2, 118.9, 86.6, 60.5, 38.0, 33.0, 23.6, 14.2. A single-crystal X-ray structure for **12a** is located in the Supporting Information.

(11) Similar ratios have been observed for related 1,1-disubstitutedcyclohexane-4-carboxylate systems: (a) Caron, S.; Vazquez, E. *Org. Proc. Res. Dev.* **2001**, *5*, 587−592. (b) Badham, N. F.; Chen, J.-H.; Cummings, P. G.; Dell'Orco, P. C.; Diederich, A. M.; Eldridge, A. M.; Mendelson, W. L.; Mills, R. J.; Novack, V. J.; Olsen, M. A.; Rustum, A. M.; Webb, K. S.; Yang, S. *Org. Proc. Res. Dev.* **2003**, *7*, 101−108.

(12) For a review on the stereochemistry of organometallic addition to ketones, see: Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521−546.

(13) Support for the equilibrium favoring the carboethoxy group in the equatorial position is found in the ^{1}H NMR of **10a** in $CDCl_3$ that showed the diagnostic methine resonance at δ 2.72 to only exist as a distinct triplet of triplets (J = 9.7, 4.0 Hz), indicative of that proton residing in an axial position.

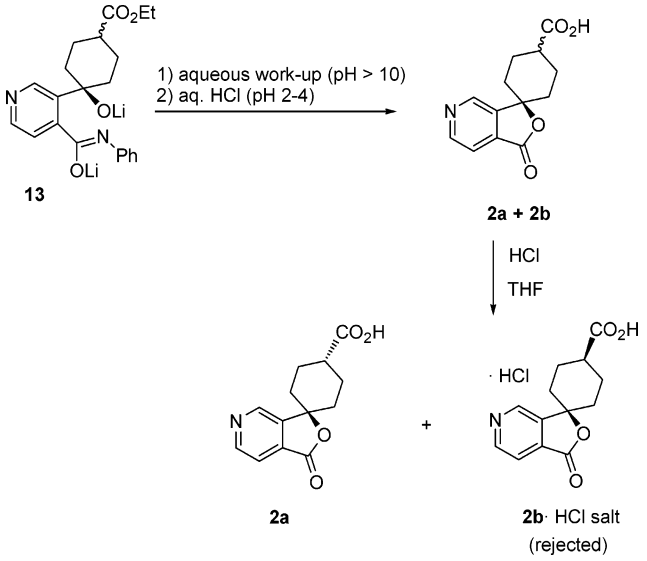
(14) (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; p 686. (b) Smith, M. B. *Organic Synthesis*; McGraw-Hill: New York, 1994; p 52. (c) Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1984**, *25*, 3267−3268.

(15) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588−3597.

(16) (a) Cauletti, C.; Di Maio, G.; Li, W.; Vecchi, E.; Vondrak, T. *Tetrahedron* **1986**, *42*, 3677−3682. (b) Di Maio, G.; Li, W.; Vecchi, E. *Tetrahedron* **1985**, *41*, 4891−4896.

(17) The effect of additives on the stereoselectivity in the reaction of cyclohexanones with organolithium reagents has been discussed: Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371−4377.

SCHEME 5

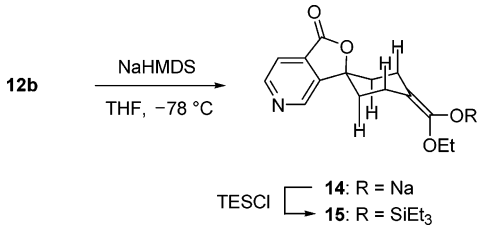


Other benefits of employing LiBr in the reaction are as follows: (1) it improves the yield of the reaction from 69% to 82%, as it minimizes intermolecular proton transfer from **10a** to **11**, as evidenced by the reduced recovery of anilide **8b** (22% to 7%); (2) it results in an improved aggregation state of **11** as the reaction solution is heterogeneous without LiBr versus a homogeneous solution with it; and (3) it is expected to raise the polarity of the solvent, resulting in a more stabilized metalated species.

Due to the inherent shortcomings of the stereoselective coupling approach, we initially investigated selective crystallization as a means of separating the isomers (Scheme 5). The optimized coupling reaction of **8b** with **10a** in the presence of LiBr gave **13**, which was quenched with water, resulting in a basic solution that served to saponify the ethyl ester to give the corresponding hydroxyacid (**6a**). Subsequent acidification (pH 2.5−4) formed the spirolactone as a mixture of **2a** and **2b**. Treating a THF solution of this mixture with HCl (1.05 equiv to assay of **2b**) served to selectively crystallize cis isomer **2b** as the HCl salt, which was removed by filtration. Crystallization of the *filtrate* gave pure **2a** in 85% recovery from initial isomer mixture. Thus, desired acid **2a** was prepared in 33% overall yield (based on the anilide **8b**) in only two steps.[18]

2. Second-Generation Synthesis of 2a via Ketene Chemistry. Prior reports of enantioselective protonation[19] of prochiral enolates[20] led to considering this approach to improve the isomeric ratio (Scheme 6). The reaction of **12b** with NaHMDS at −78 °C provided the

SCHEME 6



corresponding Na enolate **14**, but subsequent reaction with a series of proton sources, both chiral and achiral (normal and inverse addition modes), led to predominantly cis products or a mixture with minimal selectivity, even at −78 °C. The protonation of a ketene silyl acetal **15**, derived from **14** upon reaction with TES−Cl, was similarly unsuccessful.

Alternatively, we investigated utilizing a ketene to facilitate a facially selective protonation.[21] The highly stereoselective addition of chiral alcohols to unsymmetrical ketenes has been reported to give optically active carboxylic acid derivatives.[22] Stereoselective additions to symmetrical ketenes have also been reported on a highly hindered bicyclic ketene with water[23] and a highly hindered caged ketene with methanol.[24]

Ketene formation was initially studied using the individually isolated acid chloride HCl salts (**16a/16b**) derived from **2a/2b**, respectively, upon reaction with $SOCl_2$ in THF (Scheme 7). Subsequently, **16a** was reacted with TEA (5 equiv) in $CHCl_3$ at 0 °C for 1 h, and the ^{13}C NMR spectrum of the resulting solution showed chemical shifts for Cα (δ: 200.8 ppm) and Cβ (δ: 23.8 ppm) consistent with ketene (**17**) formation and concurrent disappearance of the C-4 signal of **16a**.[25] Monitoring the reaction using in-situ IR spectroscopy also revealed a new absorption at 2107 cm^{-1}, also consistent with known values for ketenes.[25a] The quenching of **17** with *tert*-butyl alcohol at 0 °C gave a favorable 93:7 ratio of *trans:cis* esters (**18a**:**18b**), while quenching with H_2O or *i*-PrOH gave a mixture of the corresponding trans:cis products in 84:16 and 89:11 ratios, respectively.

In comparison to **16a**, the reaction of cis isomer **16b** under the identical ketene-forming conditions was sluggish, even at 40 °C. The difference in reactivity is attibuted to the relatively facile *equatorial* deprotonation of the *trans*-acylammonium intermediate **19a**, as compared to deprotonation from the sterically congested axial site in **19b** (Scheme 8).

(18) Alternatively, quenching the metalation reaction into EtOH/AcOH provided a 42% yield of cis ester **12b** and a 39% yield of trans ester **12a**. The ester mixture was dissolved in EtOAc and treated with 1 equiv (relative to **12a**) of (+)-CSA, which served to selectively crystallize the corresponding **12a**−CSA salt in 76% recovery with 98% selectivity. The ester moiety of the salt could be hydrolyzed under either acidic conditions or basic conditions to give **2a** in 97% and 92% yield, respectively. We wish to acknowledge Matt Heileman for this contribution.

(19) For a review of enantioselective protonations, see: Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653−3691.

(20) For a review of enantioselective protanation of enolates, see: Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566−2587.

(21) For seminal papers on this topic, see: (a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9−22. (b) Pracejus, H.; Mätje, H. *J. Prakt. Chem.* **1964**, *24*, 195−205.

(22) (a) Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 7650−7651. (b) Fehr, C.; Guntern, O. *Helv. Chim. Acta* **1992**, *75*, 1023−1028. (c) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc*. **1999**, *121*, 2637−2638. (d) Tandon, V. K. *Tetrahedron Lett*. **2001**, *42*, 5985−5987. (e) Akkari, R.; Calmes, M.; Mai, N.; Rolland, M.; Martinez, J. *J. Org. Chem*. **2001**, *66*, 5859−5865. (f) Kanoh, N.; Tomatsu, A.; Nishikawa, T.; Ide, M.; Tsuchida, T.; Isshiki, K.; Nakata, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1251−1253. (g) for a review, see: Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545−3565. (h) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176−6177.

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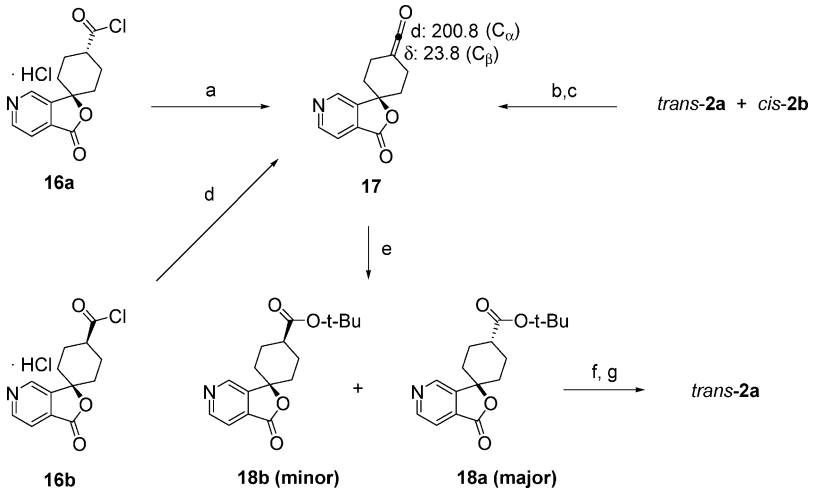
(24) Fessner, W.-D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H. *J. Am. Chem. Soc*. **1987**, *109*, 4626−4642.

(25) (a) Tidwell, T. T. *Ketenes;* John Wiley & Sons: New York, 1995. (b) Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587−2613.

SCHEME 7[a]



[a] Reagents/conditions: (a) Et_3N (5 equiv)/$CHCl_3$/0 °C; (b) $POCl_3$ (1.15 equiv)/DMF (1.1 equiv)/THF/40 °C; (c) TMEDA (3.5 equiv)/LiCl (1 equiv)/35 °C; (d) Me_2NEt or TMEDA (5 equiv)/THF/40 °C; (e) t-BuOH (1.5 equiv); (f) 33% H_2SO_4 (8 equiv)/50 °C/3 h; (g) concd HCl (1.0 equiv).

SCHEME 8

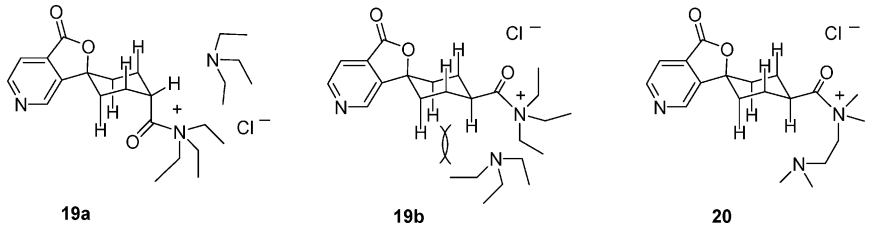


TABLE 2. Effect of Base on Reaction of 16b and *tert*-Butyl Alcohol via Ketene 17

entry	amine base[a]	yield (%) **18a** + **18b**	stereoselectivity **18a**:**18b**	% convn[b] 1-h reaction
1	Et_3N	27	81:19	–
2	Me_2NEt	89	85:15	17 (21)[c]
3	Me_2NEt[d]	89	90:10	–
4	DABCO	55	85:15	–
5	*N*-methylpyrrolidine	65	84:16	–
6	*N*-methylpiperidine	56	86:14	–
7	TMEDA	89	83:17	48
8	$Me_2N(CH_2)_3NMe_2$	87	84:16	51
9	$Me_2N(CH_2)_6NMe_2$	90	84:16	51

[a] In THF at 35−40 °C (14−17 h) with 5 equiv of base. [b] Refers to HPLC % relative to starting material. [c] Used 10 equiv of the base. [d] 1,4-Dioxane was used as a solvent.

Thus it was necessary to find ketene-forming conditions from *cis*-acid chloride **16b**. First, amine bases were screened in THF (Table 2) from which Me_2NEt (5 equiv) showed higher reactivity than Et_3N, but the reaction still needed warming to 40 °C. Since ketene **17** is not stable at 40 °C,[26] quenching of the ketene with *tert*-butyl alcohol gave low yields. This was overcome by concomitant addition of *tert*-butyl alcohol and the base to acid chloride **16b**. This resulted in an improved yield of esters **18** (89%) with good trans selectivity (85:15, entry 2). A control reaction showed that acid chloride **16b** was unreactive to *tert*-butyl alcohol in the absence of base under the reaction conditions, thus lending additional support for the ketene intermediate. The use of Me_3N, a less sterically hindered base, was not successful, due to its volatility at 40 °C. Several *N*-methyl cyclic amines showed slightly less reactivity than Me_2NEt but similar stereoselectivity (entries 4−6). The rate of ketene formation from **16b** was further improved by the use of diamines such as TMEDA with similar stereoselectivity (83:17) (entry 7). The conversion after 1 h using TMEDA (5 equiv) and Me_2NEt (10 equiv) was 48% and 21%, respectively. The expansion of the methylene chain between the two amine moieties showed similar reactivity and stereoselectivity (entries 8, 9). We speculate that the enhanced rate with diamines is due to an *intramolecular* deprotonation of acylammonium intermediate **20**.

These optimized conditions were applied toward developing a practical ketene-mediated procedure using the 55:45 isomeric mixture of acids **2b**:**2a** derived from the metalation/coupling reaction. The mixture of acids was combined in THF at room temperature with 1.1 equiv of DMF and treated with 1.15 equiv of $POCl_3$ at 35 °C for 3 h to provide >98% conversion to the corresponding acid chlorides (**16**). Ultimately, $POCl_3$ was utilized for the activation in place of thionyl chloride due to the generation of SO_2 that was found to be detrimental to ketene stability. Ketene formation and subsequent protonation/esterification via ketene **17** were optimized with respect to proton source, base, and solvent. A screening of hindered alcohols revealed that *tert*-butyl alcohol provided the highest level of trans selectivity (Table 3). A screen

(26) The decomposition rate of ketene **17**, prepared from **16a**, was determined at room temperature in $CHCl_3$ by estimation of the yields of the corresponding Et ester by quenching a reaction aliquot with EtOH: 66% (1 h), 47% (2 h), 36% (4 h), 30% (8 h), and 22% (16 h).

TABLE 3. Effect of Alcohol on Stereochemical Outcome of Ketene Reaction[a]

alcohol	ratio[b]	alcohol	ratio[b]
rac-pantolactone	64:36	1-Me-cyclopentanol	77:23
(−)-pantolactone	55:45	L-borneol	71:29
tert-amyl alcohol	77:23	(*S*)-Me-lactate	70:30
t-BuOH	80:20	1-adamantol	79:21

[a] Ketene was formed from a mixture of **2a** + **2b** as noted in Experimental Section and then treated with 1.5 equiv of the alcohol and 5 equiv TMEDA and aged at 45 °C for 18 h. [b] Refers to HPLC % ratio of trans:cis ester.

TABLE 4. Effect of the Addition of Li Salt on the Ketene Reaction[a]

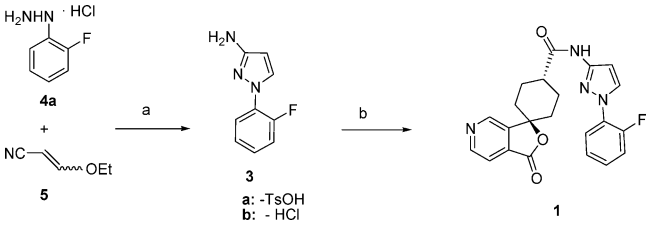
additive	ratio **18a**:**18b**	overall % yield[b]	% yield of **18a**[b]
TMEDA	83:17	60	50
TMEDA (LiBr, 0.7 equiv)	80:20	65	52
TMEDA (LiCl, 0.5 equiv)	80:20	75	60

[a] Reaction performed as noted in Experimental Section; THF, 5 equiv of TMEDA, and 1.5 equiv *tert*-butyl alcohol employed. [b] As measured by HPLC vs reference standard.

of amine bases in conjunction with *tert*-butyl alcohol showed that TMEDA provided the best combination of yield and trans selectivity. Also, the yield was found to be improved by the addition of LiCl (Table 4). A solvent screen revealed that use of many solvents is limited due to the insolubility of acids **2a/2b**. Among several ethereal solvents,[27] THF was optimal in the presence of 5 equiv of TMEDA, 1.5 equiv of *tert*-butyl alcohol, and 1 equiv of LiCl. Applying the optimized conditions led to complete conversion of acid chlorides **16a/16b** to the *tert*-butyl esters after 16 h at 35 °C to provide a 70% assay yield of the desired *trans-tert*-butyl ester **18a**.[28] In situ hydrolysis of the esters with sulfuric acid at 50 °C, followed by application of the previously described procedure for removal of **2b** as the HCl salt, and subsequent crystallization of **2a** from THF−heptane provided a 46% overall isolated yield from anilide **8**. This procedure was amenable to scale-up, as 400 g of **2a** was prepared using this procedure.

3. Synthesis of Aminopyrazole 3 and Amide Formation. Aminopyrazole **3** was synthesized using an existing methodology[29] via the condensation of 2-fluorophenylhydrazine HCl (**4a**) and 3-ethoxyacrylonitrile (**5**) with NaOEt in EtOH at 80 °C. After an aqueous workup with MTBE and a subsequent solvent switch into EtOH, the product (**3**) was crystallized by either the addition of TsOH (70% yield) or HCl/EtOAc (65% yield) as the corresponding salts **3a** or **3b**, respectively (Scheme 9). The coupling of acid **2a** with aminopyrazole **3b** was accomplished by activating the former with 1.05 equiv of $SOCl_2$ in DMAC at −10 °C, followed by addition of a DMAC/pyridine solution of pyrazole **3b** at −10 °C. After warming to room temperature, water was added to the reaction to crystallize **1** in 92% yield.[30]

SCHEME 9[a]



[a] Reagents/conditions: (a) (i) NaOEt (2.8 equiv)/EtOH/82 °C/20 h; (ii) TsOH (70%) or HCl/EtOAc (65%); (b) acid **2a** (0.94 equiv)/$SOCl_2$ (1.0 equiv)/DMAC/−14 to −10 °C (92%).

In conclusion, a convergent and practical synthesis of NPY antagonist **1**, an antiobesity drug candidate, has been achieved featuring the stereoselective synthesis of the key trans spirolactone carboxylic acid **2a**. The thermodynamic bias against the required spirolactone carboxylic acid **2a** was overcome by the trans-selective protonation of ketene **17** by *tert*-butyl alcohol.

Experimental Section

***trans*-1′-Oxospiro[1,3′-cyclohexane(1′*H*)-furo[3,4-*c*]pyridine]-4-carboxylic Acid (2a). (a) Via Separation of 2b·HCl.** Anilide **8b** (100 g, 0.50 mol, Kingchem), THF (500 mL), and 1 M LiBr−THF solution (1.5 L) were combined, and the resulting solution was degassed with nitrogen and cooled to −65 °C. *n*-BuLi (1.56 M in hexane; 666 mL, 1.04 mol) was added while the batch temperature was maintained below −55 °C. The resulting solution was then aged below −55 °C for 3 h. A solution of ethyl 4-oxocyclohexanecarboxylate **10a** (100 mL, 0.63 mol, EMS Dottikon AG) in THF (1 L) was cooled in a separate flask to below −60 °C. To the solution of **10a** was added the metalated anilide mixture, while the batch temperature was maintained below −55 °C. The resulting solution was aged below −55 °C for 1 h and then carefully quenched into water (1 L). The resulting mixture was warmed to 40 °C and aged for 1 h. After cooling to 22 °C, the organic layer was removed and the aqueous layer (1.3 L, pH ∼11) washed with THF (1 L). The pH of the aqueous layer was adjusted to 2−3 by adding water (500 mL) and 47% aq H_2SO_4, while the temperature was maintained below 30 °C. The resulting white suspension was aged at 60 °C for 3 h. After the cooling to room temperature, THF (2.5 L) and 20% aq NaCl (600 mL) were added to extract the product. After separation of layers, the aqueous layer was extracted with THF (1 × 1.0 L). The combined THF extracts (3.5 L) were concentrated to 1.25 L, during which the mixture became a suspension of spirolactone acids **2a/2b**. Then, 3.3 M HCl in AcOEt (67 mL, 221 mmol) was added to the suspension at 22 °C, and the mixture aged at 50 °C for 12 h. The batch was filtered at 22 °C to remove **2b**·HCl and the filter cake washed with THF (2 × 100 mL). The combined filtrate and washings were concentrated to 800 mL under reduced pressure, DMF (80 mL) and water (80 mL) were added, and the mixture was concentrated to 160 mL by

(27) Effect of other solvents on the conversion and the stereochemical outcome of the ketene reaction are as follows (yield, trans:cis ratio): diglyme (88%, 85:15), DME (80%, 77:23), EtOAc (77%, 84:16), dimethyl carbonate (80%, 88:12).

(28) Pure **18a** was obtained by selective formation/crystalization of the (+)-CSA salt from a mixture of **18a/18b** from THF, followed by free basing of the salt. Selected data for **18a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (d, J = 1.0 Hz, 1H), 8.85 (d, J = 5.2 Hz, 1H), 7.75 (dd, J = 5.2, 1.0 Hz, 1H), 2.69 (br m, 1H), 2.19−2.06 (overlapping m, 6H), 1.82−1.75 (overlapping m, 2H), 1.31 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 173.8, 167.9, 150.2, 147.6, 144.1, 133.3, 118.9, 86.7, 80.6, 38.9, 33.1, 28.0, 23.7. HRMS: calcd for $C_{17}H_{21}NO_4$ M^+ 304.15433, found 304.15498. An authentic sample of **18b** was prepared from **2b** (see Supporting Information) for comparison and confirmation purposes.

(29) (a) Ege, G.; Frantz, H. *J. Heterocycl. Chem*. **1982**, *19*, 1265−1266. (b) Ege, G.; Frantz, H. *J. Heterocycl. Chem*. **1982**, *19*, 1267−1268.

(30) The reaction of aminopyrazole **3** with ketene **17**, prepared from *trans*-**16a** in $CHCl_3$ at 0 °C, provided a desired trans-predominant mixture (**1**:cis isomer = 86:14). However, the concomitant addition required for the ketene reaction from *cis*-**16b** was unsuccessful due to the competitive direct amidation under the conditions.

vacuum distillation. Water (800 mL) was added to the suspension, followed by aging at 22 °C for 2 h. The batch was filtered, and the solids washed with water (2 × 80 mL) and dried at 45 °C to afford **2a** (40.8 g, 33% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.35 (br s, 1H), 9.06 (d, J = 1.0 Hz, 1H), 8.87 (d, J = 5.0 Hz, 1H), 7.84 (dd, J = 1.0, 5.0 Hz, 1H), 2.68−2.74 (m, 1H), 1.90−2.11 (m, 6H), 1.76−1.85 (m, 2H). ^{13}C NMR (100.6 MHz, DMSO-d_6): 175.9, 167.9, 150.6, 147.5, 144.9, 133.1, 119.1, 87.2, 38.1, 33.1, 23.9. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.34; H, 5.19; N, 5.65. Mp: 240.5−243.5 °C.[31]

Compound 2b (free base). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (d, J = 0.7 Hz, 1H), 8.86 (d, J = 5.0 Hz, 1H), 7.83 (dd, J = 0.7, 5.0 Hz, 1H), 2.43−2.50 (m, 1H), 2.20 (td, J = 4.0 Hz, 2H), 2.02−1.93 (m, 2H), 1.81−1.64 (m, 4H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 176.1, 167.6, 150.0, 147.6, 144.5, 132.8, 118.7, 86.2, 40.5, 34.2, 24.8. Mp: >260 °C.

(b) Via the Ketene-Mediated Isomerization of 2a and 2b. A mixture of spirolactone acids **2a/2b** (800 g, 3.23 mol; 55% **2b**/45% **2a**) obtained from the previously described metalation reaction (vida supra) was charged to a 50-L vessel containing THF (17.6 L). The slurry was treated with DMF (260 mL, 3.2 mol) and then at 22 °C with $POCl_3$ (350 mL, 3.7 mol) over 10 min to form the acid chloride. The solution was warmed to 40 °C over 45 min, aged for 2 h, and then cooled to 24 °C. In a separate 12-L flask was sequentially added THF (3.3 L), TMEDA (1.7 L, 11.3 mol), *tert*-butyl alcohol (465 mL, 4.9 mol), and LiCl (143 g, 3.3 mol). After aging at 25 °C for 1 h, the resulting solution was added to the acid chloride at 24−30 °C over 25 min and aged for 19 h at 35−39 °C. The reaction mixture was cooled to 0 °C and quenched by adding 33% aq H_2SO_4 (4.2 L) slowly over 20 min, during which time the internal temperature rose to 22 °C. The resulting solution was heated to 50 °C for 3 h and then cooled to 22 °C and the pH adjusted to 2.4 with 6 N NaOH (7.0 kg). The organic layer was separated, washed with aq HCl/NaCl (pH 2.5, 2 × 8 L), and azeotropically dried via a constant volume distillation at atmospheric pressure until the KF was <0.3%. The solution of spirolactones **2a/2b** was cooled to 22 °C, and concentrated HCl (60 mL) was slowly added to the solution. The resulting slurry was aged at 25 °C for 3 h, and the precipitate (**2b·HCl**) removed via filtration and washed with THF (1 × 1 L). The filtrate containing *trans*-spirolactone acid **2a** was concentrated to 6.5 L in vacuo (internal temp = 38−42 °C), and the resulting slurry cooled to 22 °C over 1 h and aged for 1 h. Heptane (6 L) was added over 2 h and the slurry was cooled to 0 °C and aged for 20 h, followed by vacuum filtration. The product cake was rinsed with THF−heptane (2/3, 2 × 600 mL) and dried in vacuo at 45 °C to provide **2a** (445 g, 97.8% purity). NMR values were identical to previously reported values (vida supra).

***trans*-1′-Oxospiro[1,3′-cyclohexane(1′*H*)-furo[3,4-*c*]pyridine]-4-carboxylic Acid Chloride Hydrochloride (16a).** Acid **2a** (2.1 g, 8.50 mmol) was combined with THF (18 mL) and DMAC (3 mL) at 35 °C for 10 min and then the mixture cooled to 2 °C, followed by the dropwise addition of thionyl chloride (0.78 mL, 10.7 mmol). The solution was aged at 2 °C for 1 h, warmed to room temperature, aged for 1 h, and then cooled to 2 °C for 30 min prior to isolation by filtration. The cake was washed with THF (1 × 7 mL) and hexanes (1 × 7 mL) followed by drying in vacuo at room temperature to a constant weight (2.44 g, 77%). Compound **16a** exists as a 1:1 THF solvate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (d, J = 0.8 Hz, 1H), 8.94 (d, J = 5.2 Hz, 1H), 8.03 (dd, J = 0.8, 5.2 Hz, 1H), *3.58* (m, 4H), 2.70 (m, 1H), 2.12−2.10 (m, 4H), 1.97−1.87 (m, 2H), 1.84−1.76 (m, 2 H), *1.74* (m, 4H). ^{13}C NMR (100.6 MHz, DMSO-d_6): 175.6, 167.2, 148.3, 148.2, 142.9, 135.5, 120.6, 87.5, *67.4*, 32.8, *25.5*, 23.7 (italicized NMR peaks are from THF).

***cis*-1′-Oxospiro[1,3′-cyclohexane(1′*H*)-furo[3,4-*c*]pyridine]-4-carboxylic Acid Chloride Hydrochloride (16b).** Acid **2b** (1.0 g, 4.0 mmol) was combined with oxalyl chloride (4 mL), DMF (50 μL), and THF (4 mL) and the mixture heated to 65 °C for 7 h. On cooling to room temperature, the slurry was filtered, and the flask and cake were washed with THF (2 × 5 mL). The wet cake was stirred with THF (10 mL) at room temperature for 10 min and filtered. The solid was dried in vacuo at 30 °C for 2 h to provide 0.96 g of product **16b** as a colorless powder (79%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (s, 1H), 8.96 (d, J = 5.3 Hz, 1H), 8.05 (d, J = 5.3 Hz, 1H), 2.44 (dt, J = 12.5, 3.5 Hz, 1H), 2.23 (td, J = 12.5, 3.5 Hz, 2H), 1.97 (dd, 2H), 1.80 (d, 2H), 1.68 (qd, 2H). ^{13}C (100.6 MHz, DMSO-d_6): δ 176.1, 166.8, 148.5, 147.6, 142.3, 135.4, 120.4, 86.6, 40.5, 34.0, 24.8.

1-(2-Fluorophenyl)-1*H*-pyrazole-3-amine Tosylate (3a). To a suspension of 2-fluorophenylhydrazine hydrochloride (**4a**) (50 g, 307 mmol; JEMCO, Inc.) in EtOH (300 mL) was added 20 wt % NaOEt in EtOH (293 g, 861 mmol; Nihon Soda). Ethoxyacrylonitrile (**5**) (53.8 g, 554 mmol; Degussa) was then added at ambient temperature. The reaction mixture was heated to 82 °C and aged for 20 h. The reaction mixture was cooled to 20 °C, followed by addition of water (250 mL) and 6 N HCl to adjust the pH to 2.9−3.1. The resulting aq EtOH solution was stirred at 20 °C for 2 h. After treatment with 5 N NaOH and adjusting the solution to pH 6.5−8.0, the reaction mixture was concentrated to ca. 600 mL, and IpAc (750 mL) was added. The layers were separated, and the organic layer was washed with 10% aq NaCl (200 mL). Activated carbon (Sirasagi P, 1.8 g) was added to the resulting solution at 22 °C. After 2 h, the activated carbon was removed by filtration through Celite, and the bed was washed with IpAc (1 × 200 mL). The combined organic layers were concentrated to ca. 460 mL.

A solution of TsOH·H_2O (27.1 g 142.2 mmol) in EtOH (67 mL) was added to the pyrazole solution over 3 h, followed by IpAc (53 mL) over 1 h at 22 °C. The mixture was stirred at 22 °C for 14 h, cooled to 0 °C, aged for 2 h, and filtered. The cake was washed with EtOH−IpAc (1:9, 84 mL) and IpAc (84 mL) and then dried in vacuo at 30 °C to give **3a** (66.5 g, 62%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.68 (br s, 3H), 8.24 (dd, J = 2.0, 2.0 Hz, 1H), 7.72 (dd, J = 8.0, 8.0 Hz, 1H), 7.51−7.42 (m, 4H), 7.37 (dd, J = 7.6, 7.6 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 6.44 (d, J = 2.3 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 153.57 (d, J = 248.8 Hz), 145.23, 144.59, 137.93, 134.16 (d, J = 7.2 Hz), 129.12 (d, J = 7.9 Hz), 128.14, 127.3 (d, J = 9.6 Hz), 125.5, 125.47 (d, J = 5.4 Hz), 124.7, 117.1 (d, J = 19.9 Hz), 101.0, 20.8. Anal. Calcd for $C_{22}H_{19}FN_4O_3S$: C, 55.00; H, 4.62; N, 12.03. Found: C, 55.13; H, 4.51; N, 12.00. Mp: 142−145 °C.

1-(2-Fluorophenyl)-1*H*-pyrazole-3-amine Hydrochloride (3b). An ethanolic solution (24 mL) of free base **3** (5.87 assay g, 33 mmol) was treated with 4N HCl/EtOAc (9.1 mL, 36.4 mmol) over 30 min at 22 °C. The resulting slurry was aged at 22 °C for 1 h, followed by the addition of EtOAc (132 mL) over 2 h. The slurry was aged at 22 °C for 13 h and filtered. The cake was washed with EtOAc (1 × 25 mL) and dried in vacuo to give **3b** (6.4 g, 91% recovery). ^{13}C NMR data (100.6 MHz, DMSO-d_6): δ 153.9 (d, J = 249 Hz), 144.2, 134.4, 129.5 (d, J = 7.9 Hz), 127.6 (d, J = 9.7 Hz), 125.1, 117.5 (d, J = 19.9 Hz), 101.7. Anal. Calcd for $C_9H_9ClFN_3$: C, 50.60; H, 4.25; N, 19.67. Found: C, 50.45; H, 4.01; N, 19.57. Mp: 146−149 °C.

***trans*-*N*-[1-(2-Fluorphenyl)-1*H*-pyrazol-3-yl]-1′-oxospiro[cyclohexane-1,3′(1′*H*)-furo[3,4-*c*]pyridine]-4-carboxamide (1).** Dimethylacetamide (DMAC; 5.65 L) was charged to a nitrogen-purged flask, followed by acid **2a** (712 g, 2.85 mol) at 22 °C. The solution was cooled to −14 °C and treated with thionyl chloride (357 g, 3.0 mol) over 30 min. The internal temperature did not exceed −10 °C during the addition. The solution was aged at −10 °C for 10 min and then treated over 1 h at −11 (±3) °C with a previously prepared solution of

(31) XPRD and DSC indicate that **2a** exists as a mixture of two distinct crystals forms, thus explaining the 3 °C melting point range. DSC: form I-endotherm peak at 245.0 °C; form II-endotherm peak at 247.4 °C.

pyrazole salt **3b** (654 g, 3.03 mol) in DMAC (2.1 L) and pyridine (855 mL) held at 20 °C. After 15 min, the batch was warmed to 18 °C and aged for 1 h. The solution was treated with water (470 mL) over 10 min and the resulting slurry aged at 22 °C for 30 min. A second charge of water (10.4 L) was made over 2 h at 22−33 °C. The slurry was cooled to 20 °C and aged for 15 h. The solids were isolated by filtration and the flask and cake were rinsed with water (1 × 3.6 L) and methanol (2 × 3.6 L), followed by drying in vacuo at 40 °C for 18 h to give **1** (1.08 kg, 92% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.82 (s, 1H), 9.13 (s, 1H), 8.89 (d, J = 4.8 Hz, 1 H), 8.10 (t, J = 2.6 Hz, 1H), 7.86 (dd, J = 4.9, 1.1 Hz, 1H), 7.75 (td, J = 7.8, 2.2 Hz, 1H), 7.47−7.40 (m, 1H), 7.40−7.30 (m, 2H), 6.91 (d, J = 2.6 Hz), 2.80 (br, 1H) 2.21−1.96 (m, 6H), 1.96−1.85 (m, 2H). ^{13}C (125.7 MHz, DMSO-d_6): δ 173.1, 167.6, 153.2 (d, J = 248 Hz), 150.3, 149.1, 147.0, 144.4, 133.1, 131.8 (d, J = 8.7 Hz), 127.9 (d, J = 7.8 Hz), 127.7 (d, J = 9.2 Hz), 125.3 (d, J = 3.5 Hz), 124.0, 119.0, 117.1 (d, J = 20.1 Hz), 100.0, 87.0, 40.1, 33.2, 24.6. Anal. Calcd for $C_{22}H_{19}FN_4O_3$: C, 65.02; H, 4.71; N, 13.79. Found: C, 65.08; H, 4.51; N, 13.72. Mp: 240.0−240.6 °C.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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