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Synthesis of an H_3 Antagonist via Sequential One-Pot Additions of a Magnesium Ate Complex and an Amine to a 1,4-Ketoester followed by Carbonyl-Directed Fluoride Addition

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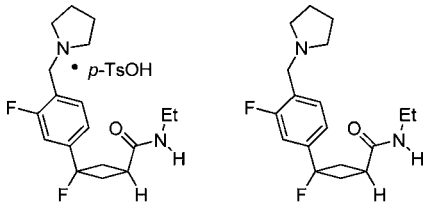
ABSTRACT: We describe the development of an efficient and scalable process for the preparation of fluorocyclobutane-containing H_3 antagonist, **1**. The synthesis was accomplished by the chemoselective addition of a magnesium ate complex and an amine to a 1,4-ketoester in a one-pot sequence, followed by a diastereoselective carbonyl-directed fluorination. The chemoselective addition of the magnesium ate complex to the ketoester benefited from tight stoichiometric control, short addition times, and lower reaction temperatures, and thus was amenable to rapid mixing and excellent heat transfer in a flow reactor.

INTRODUCTION

H_3 receptors, G protein-coupled receptors which decrease the Ca^{2+} influx into cells, function in a wide variety of tissues as feedback inhibitors of histamine and other neurotransmitters.[1] H_3 receptor agonists cause sedation by opposing H_1-induced wakefulness,[2] and H_3 receptor antagonists have the potential to counteract the inhibitory effect of histamine and increase its presynaptic release. Compound **1** was discovered and developed within Pfizer as a potent H_3 antagonist for multiple indications related to neurological disorders including excessive daytime sleepiness and Alzheimer's disease.[3] Herein we report the identification and development of a scalable route to this drug candidate.



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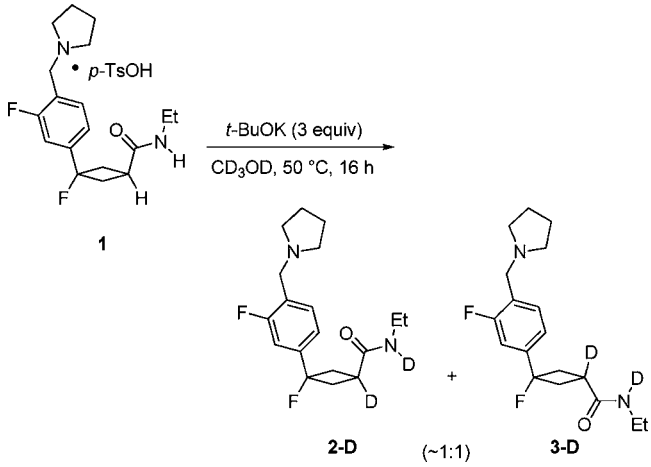
RETROSYNTHETIC ANALYSIS

The synthesis of **1** requires control of the relative stereochemistry on the fluorocyclobutane ring, where the amide and aryl groups are cis to one another. Four general possibilities to prepare the cyclobutane with desired stereochemistry were considered: (1) separate and discard the undesired isomer, (2) separate and epimerize the undesired isomer for recycle, (3) kinetic stereocontrol, and (4) thermodynamic stereocontrol. The cost and wastefulness of a late-stage diastereomer separation and the additional unit operations required for isomer recycle disfavored the first two options. In order to determine whether thermodynamic stereocontrol was possible, the relative energies of free base **2** and the corresponding trans isomer (**3**) were determined. COSMO-RS[4] calculations at BP/TZVP/COSMO level of theory in THF using Turbomole[5] and COSMOtherm[6] software packages revealed that the desired cis isomer was more stable than trans isomer **3**, but by only 0.245 kcal/mol.[7] Furthermore, base-catalyzed equilibration of a sample of **1** led to an approximately 1:1 mixture of the deuterated analogues of **2** and **3** (**2-D** and **3-D**), as observed by ^{19}F NMR spectroscopy (Scheme 1). These results precluded the use of a thermodynamic stereocontrol strategy, and left the kinetic control of stereochemistry as the only viable option.

Several approaches to achieve the desired cis disposition of the carbon substituents on the cyclobutane ring via kinetic control were considered (Scheme 2). In principle, this could be accomplished either during the formation of the cyclobutane ring, or during the installation of the substituents on the cyclobutane ring. Control of stereochemistry during the

Scheme 1. Base-catalyzed equilibration of 1



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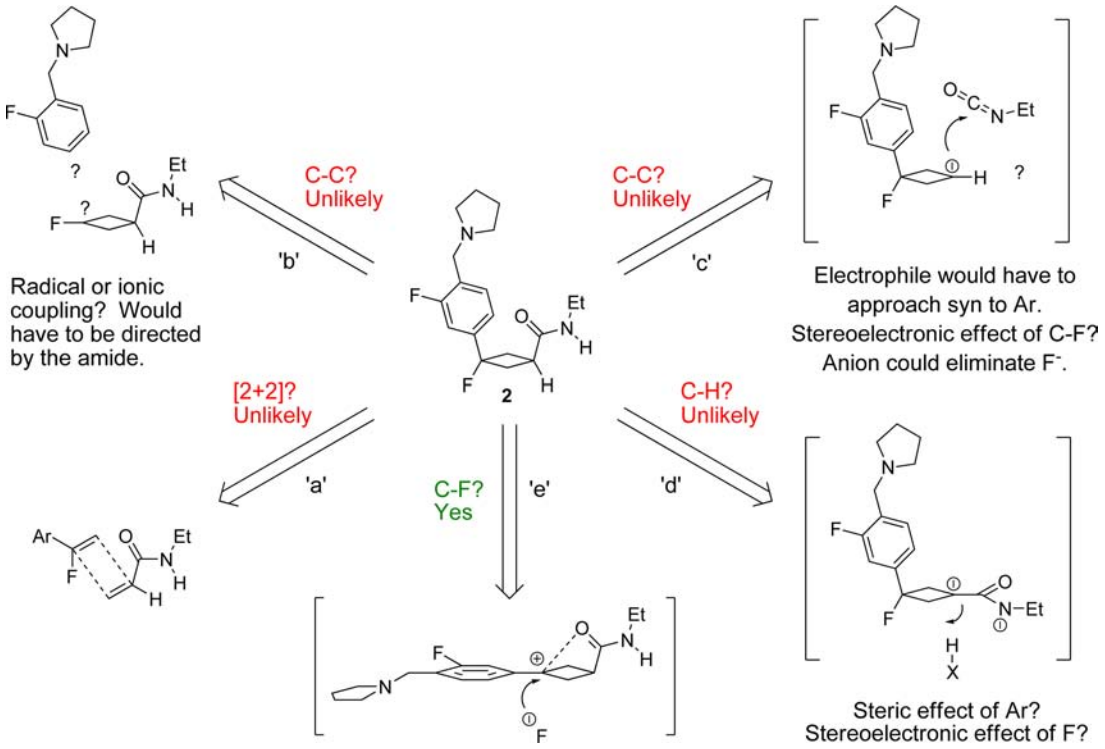
Scheme 2. Analysis of potential methods for kinetic stereocontrol on the cyclobutane ring



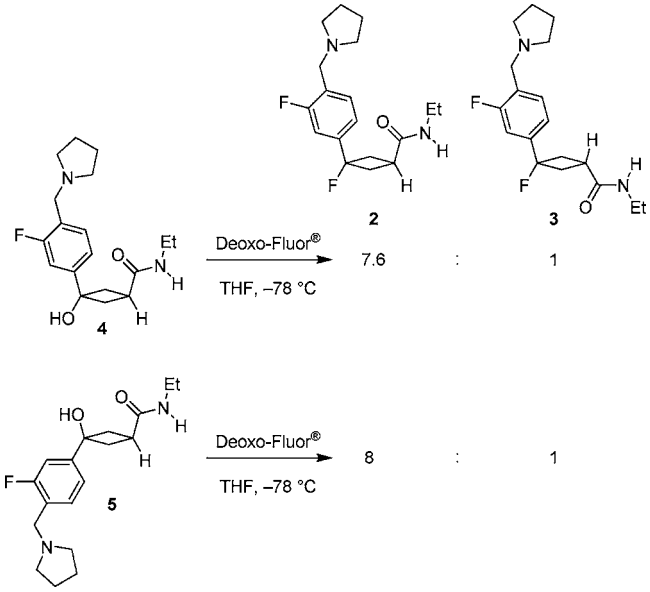
formation of the cyclobutane ring by, for instance, a [2 + 2] addition approach (strategy 'a', Scheme 2) seemed unlikely. Installation of either of the two carbon-bearing substituents on the cyclobutane ring, i.e. formation of the cyclobutane−arene C−C bond, or the cyclobutane−carbonyl C−C bond (strategies 'b' and 'c', respectively) were also deemed unlikely to give the necessary kinetic stereocontrol. Stereoselective kinetic protonation to form the C−H bond (strategy 'd') was considered as a possibility, but calculations predicted that protonation would occur from the undesired face. Stereoselective C−F bond formation (strategy 'e') appeared viable, especially if the carbonyl oxygen could internally ligate to the carbocation generated by solvolysis of the corresponding alcohol or activated alcohol as shown in Scheme 2.

The choice of strategy 'e' was further supported by two observations. First, fluorination of either of the alcohol diastereomers (**4** or **5**) with bis(2-methoxyethyl)amino sulfur trifluoride (Deoxo-Fluor) furnished the desired fluorinated cyclobutane **2** as the predominant diastereomer (Scheme 3). Second, hydrolysis of free base **2** by extended exposure to aqueous media gave the alcohol with retention of stereochemistry, i.e., the water approaches the carbocation from the same face as the fluoride, opposite the amide carbonyl (Scheme 4). This directed us to the bond construction strategy outlined in Scheme 5, wherein **2** is synthesized via aryl anion addition to an appropriately substituted cyclobutanone, followed by fluorination of the resulting alcohol. Further efforts therefore focused on identifying the optimal carbonyl substituent Y, metal M, and fluorinating agent X-F, as depicted in Scheme 5.

CHOICE OF ARYL NUCLEOPHILE

A range of aryl organometallic compounds was considered for the synthesis of **1** (Figure 1). The organo-zinc (**11**), -aluminum (**12**), and -boron (**13**) compounds were not pursued due to their anticipated low reactivity, although the strained cyclo-

Scheme 3. Stereoselective fluorination of alcohol diastereomers 4 and 5 favoring fluoride isomer 2



butanone may react under Lewis acid catalysis.[8] The organolithium species (**8**) was not pursued due to its likely need for cryogenic conditions.[9] Thus, further efforts focused on organomagnesium reagents, both the conventional Grignard reagent (**10**) and other, more reactive, organomagnesium species such as ate complex **9**.[10,11]

The conventional Grignard reagent (**10**) could be readily prepared from arylbromide **14** and magnesium turnings, but it appeared to lose potency at room temperature over time. Aliquots quenched with deuterated methanol showed significantly decreased ArD/ArH ratios over one week at ambient

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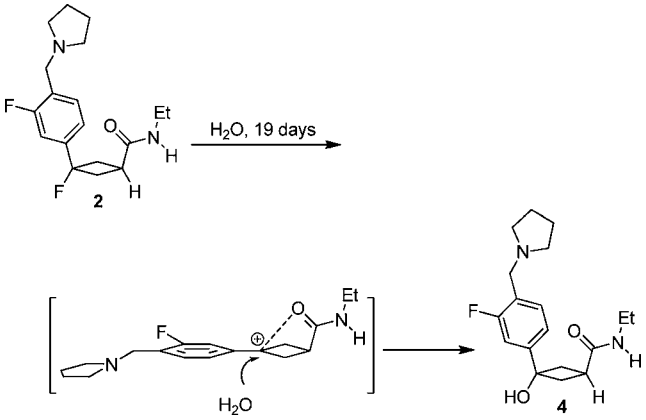
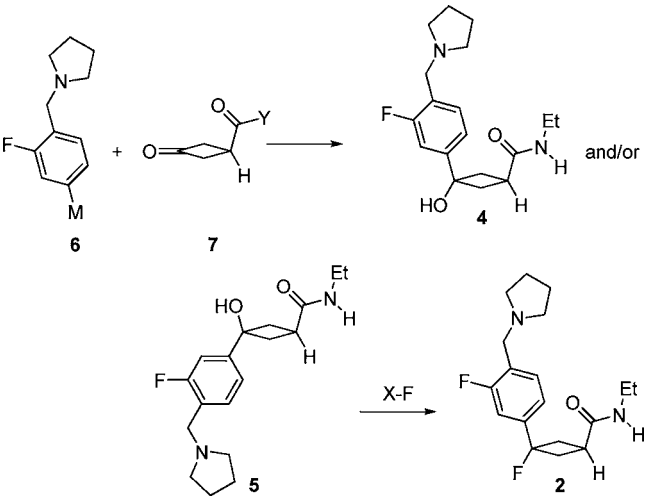
Scheme 4. Solvolysis of fluoride 2 with carbonyl-directed addition of water



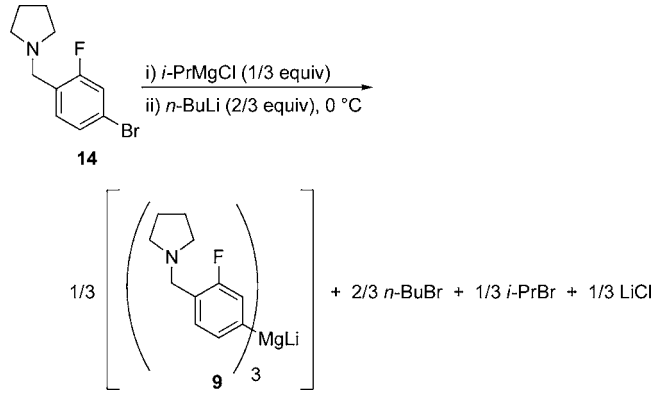
Scheme 5. Preferred general approach to the stereoselective synthesis of 2



temperature under nitrogen in THF, while the stability was much improved when maintained at 0−5 °C. This suggested that the Grignard reagent could not be readily stored or purchased. It would need to be generated in-house, where the use of magnesium turnings is not preferred.[12] Given its apparent instability at ambient temperature, the conventional Grignard reagent was not evaluated further.

The formation of Grignard-type species under *homogeneous* conditions, thus avoiding magnesium turnings, was pursued with the successively more reactive reagents *i*-PrMgCl,[13] *i*-PrMgCl·LiCl,[14] and 1:2 *i*-PrMgCl/*n*-BuLi.[15] Of these, *i*-PrMgCl (2 M in THF) and *i*-PrMgCl·LiCl (1.3 M in THF) only gave partial conversion of aryl bromide **14** to its anion as judged by quenching aliquots of the reaction with benzaldehyde. In contrast, magnesium ate complex **9** could be cleanly generated by the dose-controlled addition of 1/3 equiv of *i*-PrMgCl and 2/3 equiv of *n*-BuLi at 0 °C (Scheme 6). The

Scheme 6



addition of this reagent to various cyclobutanone coupling partners was studied in detail (vide infra). All three of the aryl groups of complex **9** are active nucleophiles, and typically 0.33 equiv of **9** was utilized as described below. Considering that magnesium ate complexes like **9** are relatively recent additions to the long history of organomagnesium reagents, the stability of **9** was examined in order to ensure that it would be a viable, scalable reagent.

In these experiments, stock solutions of **9** in THF, 2-MeTHF, and MTBE were stirred under nitrogen at 0, 10, and 20 °C in an Anachem robotic workstation.[16] These nine reactions were run simultaneously, and the solutions were automatically sampled, quenched with deuterated methanol, and analyzed by HPLC and mass spectrometry. Profiles of this data showed that **9** was stable in THF at 0 °C, losing only about 1% potency in 24 h. The reagent was less stable at higher temperatures or in the other solvents, losing 3−10% potency over 24 h, primarily due to the formation of the butylated impurity **15** (Figure 2) via reaction of **9** with *n*-butylbromide. These studies confirmed the stability of **9** as required for it to be a scalable reagent and favored the use of THF over 2-MeTHF or MTBE.

THE COUPLING STEP

It was envisioned that, in its simplest manifestation, the Y group in the cyclobutanone coupling partner **7** would be an ethylamino moiety (**16**, Scheme 7). However, treatment of magnesium ate complex **9** with the anion of **16** (generated by

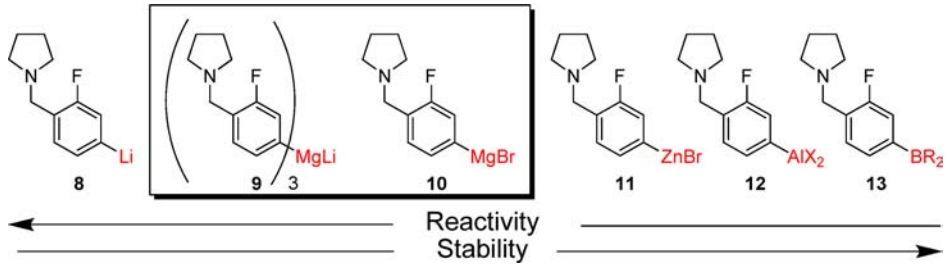


Figure 1. Range of potential aryl organometallic nucleophiles.

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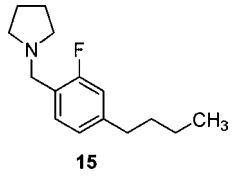

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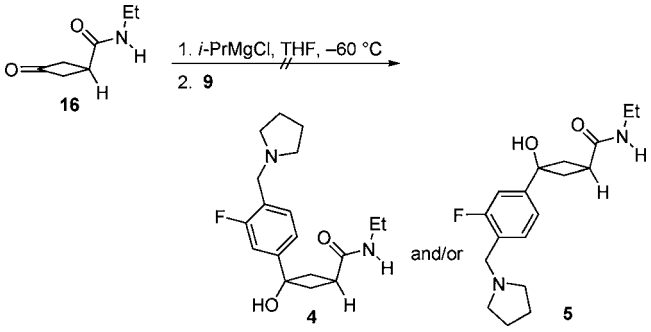
Figure 2. Butylated impurity.

Scheme 7



reaction of **16** with *i*-PrMgCl in THF at −60 °C) did not give any detectable adduct **4** or its epimer **5**, presumably due to the insolubility of the anion of **16**.[17] Therefore, further efforts focused on identifying an appropriate ester or carboxylate coupling partner.

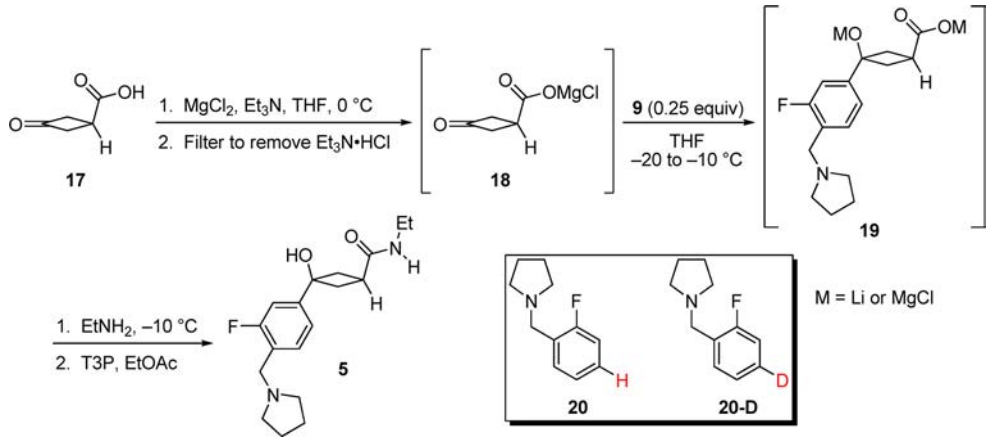
The ideal Y group in cyclobutanone coupling partner **7** would be aprotic so as not to quench an equivalent of aryl organometallic **9**. Moreover, it would have to be resistant to aryl anion addition during addition of the aryl anion to the ketone functionality, and yet be receptive to ethylamine addition during the amidation step, preferably without the need for additional coupling or activating reagents. These seemingly conflicting chemoselectivity requirements for the addition of organometallic and amine reagents were pursued with carboxylate and ester groups for C(O)Y in **7** (Scheme 5), where the ester has the added advantage of not requiring a carboxyl-activating step during the amidation.

Davies showed that Grignard reagents can be added to the ketones of ketoacids if the acids are first converted to their magnesium salts by treatment with Et_3N and $MgCl_2$ in THF, followed by filtration of $Et_3N{\cdot}HCl$.[18] Accordingly, treatment of acid **17** with $MgCl_2$ and Et_3N furnished carboxylate **18**, which was treated with **9**. The reaction proceeded at ambient temperature, remained homogeneous, and provided adduct **19** in situ. The addition of ethylamine and amide coupling agent T3P to the reaction mixture furnished **5** in 45% overall yield from **17** (Scheme 8). The main byproduct of the arylation reaction was des-bromoarene **20**, which was formed at ∼25−30 area % according to HPLC. Interestingly, when aliquots of the arylation reaction were quenched with CH_3OD at different stages of the reaction, the amount of deuterium incorporation in the des-bromoarene (i.e., the ratio of **20-D**:**20**) decreased from 0.85:1 at the beginning of the reaction to 0.19:1 at the end of the reaction. This suggested that some of the des-bromoarene forms early in the reaction from enolization (giving **20**) of the ketone with a significant amount of **9** remaining (which gives **20-D** upon quenching with CH_3OD). Stability tests of the THF solution of magnesium carboxylate **18** showed that homogeneity is maintained for 24 h at 0 °C, yet precipitation occurred after 15−20 h at 20 °C. This precipitation at higher rather than lower temperatures suggested that the precipitation is due to side reactions of the magnesium carboxylate rather than supersaturation. The moderate yields, significant des-bromoarene formation, stability concerns with the magnesium carboxylate solution, and the need for coupling reagents in the subsequent amidation step led us to abandon the magnesium carboxylate route in favor of the keto ester route (Y = OR in **7**).

Reaction of **9** with methyl ester **21** proved capricious, leading to multiple byproducts in addition to the desired adduct, **22**. However, initial small-scale experiments with isopropyl ester **23** at −20 °C suggested that the addition of **9** was cleaner than with **21**, giving an adduct/ArH (**24**:**20**) ratio of 5:1 with very little of the multiple addition products, **25** and **26** (Schemes 9 and 10). Since these initial results with the isopropyl ester were promising, this reaction was explored in further detail in an effort to identify the best conditions to effect the transformation. Specifically, the reaction temperature, and the rate and order of addition were investigated with the goal of maximizing the product/ArH ratio, minimizing the formation of multiple addition products (**25** and **26**), and avoiding the use of conditions that would require cryogenic tanks for scale-up.

On a small scale, isopropyl ester **23** could be added in just a few minutes while maintaining the desired reaction temperature of −20 °C. When scaling up to a 500 mL RC-1 reactor, **23** was added to a −10 °C solution of **9** over 1 h in order to simulate

Scheme 8



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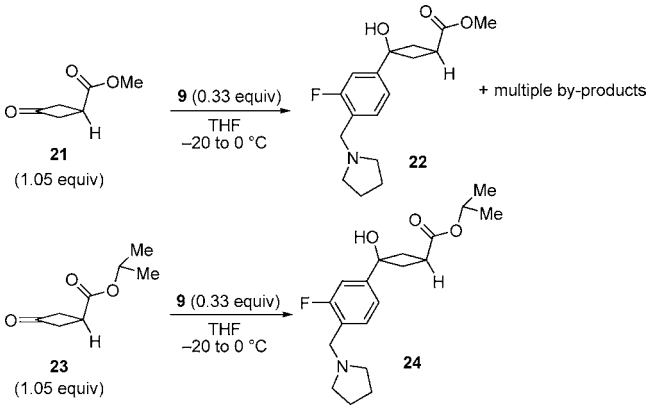
Scheme 9

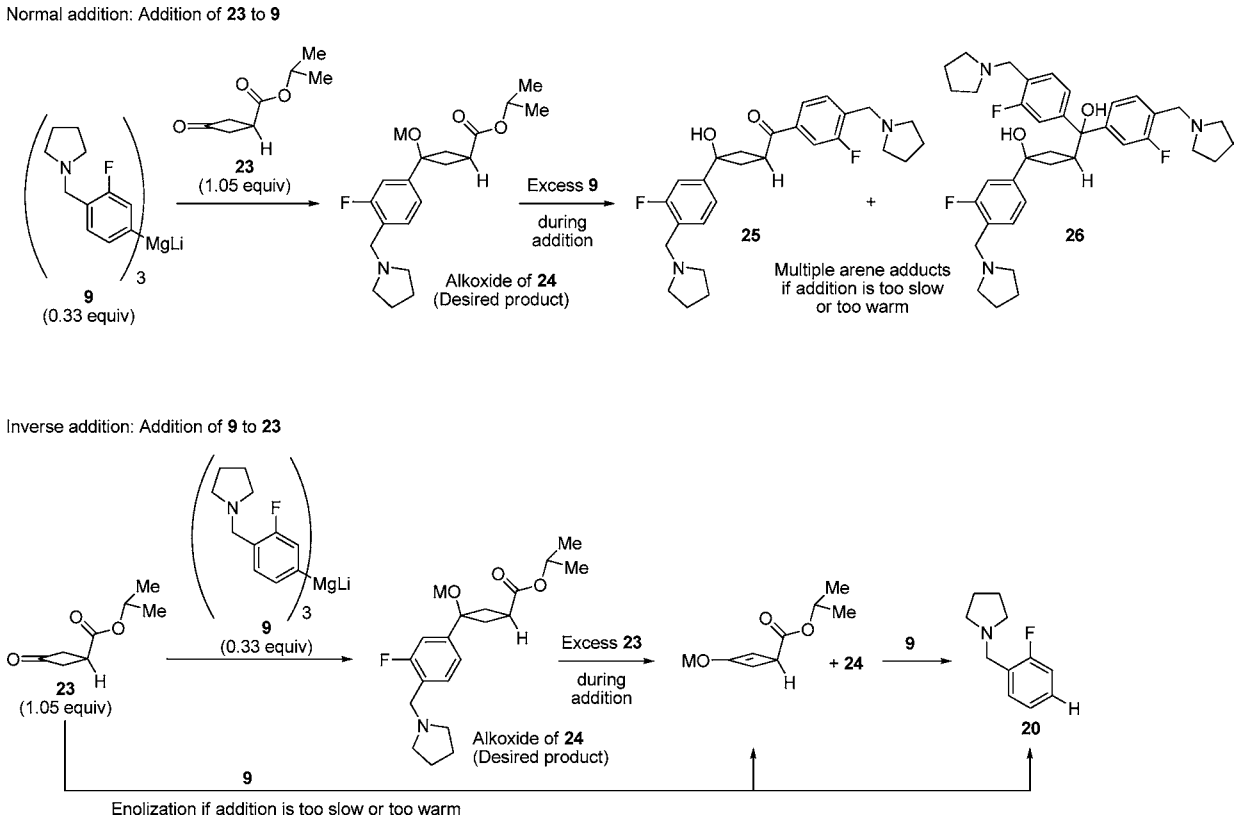


heat transfer in a typical noncryogenic 1600 L reactor with a −25 °C cooling jacket.[19] These conditions provided a 2:1 ratio of **24** to **20**, but the predominant product of the reaction was triple addition product **26** (~30 area %). IR data acquired during this experiment indicated that ketoester **23** began to accumulate after one-third of **23** had been added, implying that all of the organometallic reagent had been consumed by that point, which is consistent with the formation of the triple addition product, **26**. Reversing the addition order (i.e., adding a solution of **9** to a solution of **23**) at −10 °C decreased the amount of triple adduct **26** to ~1−2 area %, but increased the amount of protonated arene **20** to ~50 area %.

Some of the possible side reaction pathways leading to **20**, **25**, and **26** are shown in Scheme 10. The strong temperature dependence of the selectivity under normal addition conditions (addition of **23** to **9**) implies that the activation energies for the formation of **25** and **26** are larger than that of the desired reaction, i.e., lower reaction temperatures result in a significant reduction in the relative rates of undesired to desired reactions. Also, the order of addition of the reagents affects the relative concentration of each species during the addition, which then affects possible side reactions. In the normal addition mode (addition of **23** to **9** where intermediates are exposed to excess **9** during the addition), the ester moiety of the alkoxide of **24** can react with **9** giving multiple arene adducts (**25** and **26**) if the addition is too slow or too warm. Similarly, in the inverse addition mode (addition of **9** to **23** where intermediates are exposed to excess **23** during the addition), the alkoxide of **24** can act as a base and enolize **23**, leading to arene **20** if the addition is too slow or too warm. A third option, simultaneous addition of **23** and **9**, could serve to minimize side reactions by maintaining a stoichiometric balance between the reacting species **23** and **9** and was also investigated (vide infra).

The long (1 h) addition time required to absorb the heat of reaction in a noncryogenic tank seemed problematic with both addition orders. In a noncryogenic tank, speeding up the addition would require an even warmer reaction temperature (to increase ΔT between the reactor and the jacket, and therefore, the rate of heat transfer), while a lower reaction temperature would require a longer addition time (to absorb the heat of reaction with a lower ΔT relative to the jacket). This quandary required one of two solutions: a cryogenic tank to lower the reaction temperature so that the desired reaction is favored, or a reactor configuration that provides stoichiometric balance of **9** and **23** during the entire reaction along with efficient heat removal, such as that of a plug flow reactor.

Scheme 10



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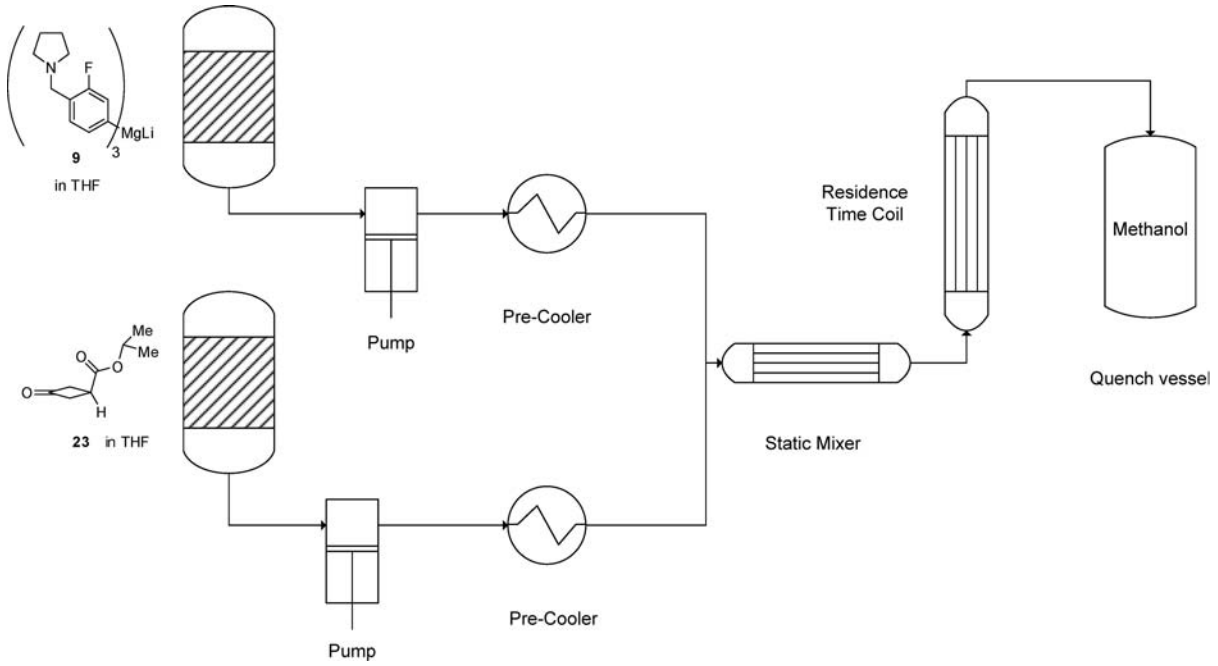

Figure 3. Kilo Lab flow chemistry rig.

The cryogenic option proved successful: a 40-min normal addition (addition of **23** to **9**) was well tolerated at −37 °C, providing a 4:1 ratio of **24**:**20**, and no **26** was detected under these conditions. These conditions could be accommodated in a cryogenic tank, and provided us with a reasonable option for future scale-up. Nevertheless, we wanted to avoid the use of cryogenic conditions so that this reaction could be carried out in any of our scale-up facilities.

As a convenient, first-pass approximation to the stoichiometric balance provided by plug flow, solutions of **9** and **23** were added simultaneously into a batch reactor with appropriate flow rates to maintain the desired stoichiometry (a 0.33:1.05 molar ratio of **9** to **23**). At a −10 °C reaction temperature and a 1-h addition time, excellent results were obtained, with a **24**:**20** ratio of 4.5:1 and <2% total multiple addition products. No improvement in selectivity was seen for simultaneous addition at −30 °C.

The success of the simultaneous addition protocol led us to examine the reaction further in a continuous plug flow reactor. Initial screening was done in a Conjure segmented flow reactor to demonstrate proof of concept, and the reaction selectivity was seen to be comparable to the simultaneous addition conditions (vide supra). This was then successfully scaled up to a 12-g scale at −5 °C in a Vapourtec reactor system to provide a 65% in situ yield of **24** (with a ∼4:1 ratio of **24**:**20**).

On the basis of this positive outcome, we scaled up this reaction in our Kilo Lab flow chemistry rig (Figure 3). In this configuration, solutions of **9** (0.17 M in THF) and **23** (1.05 M in THF) were precooled independently before being combined in a 9-mL static mixer and then flowed through a residence time coil. The relative flow rates of the two solution streams were adjusted to attain the desired stoichiometry (0.33 equiv:1.05 equiv of **9**:**23**). The total flow volume for the system, about 260 mL, was estimated by charging a slug of colored solution to the organometallic (**9**) feed tanks and timing its observed exit from the system. The volume of the system from the reactor inlet to outlet (static mixer + residence time coil) was about 190 mL, so that for a total flow rate of 30 mL/min, the residence time would be 6−7 min. The reaction was quenched by flowing into an agitated tank of methanol.

All experiments were run with 20 mL/min of a solution of **9** in THF (0.17 M) and 10 mL/min of a 1.05 M solution of **23** in THF, while the reaction temperature was varied from −25 to 0 °C. These experiments indicated that for temperatures as low as −16 °C, the reaction was complete (as evidenced by the absence of **20-D** when quenched with deuterated methanol) with the standard flow rates, which correspond to a 6−7 min residence time. Excellent selectivity was obtained for all conditions, with the ratio of **24**:**20** ranging from 3.5−4.5:1 while the level of multiple adducts was 2−3%. At −25 °C, a small amount of unreacted **9** (∼5%) was seen in the reactor outlet sample that was quenched with deuterated methanol, indicating that the reaction was not complete. Overall, these results indicate that this reaction can be run in flow as warm as 0 °C with acceptable selectivity.

■ AMIDATION AND WORKUP

While the reaction conditions were being optimized, concurrent work focused on streamlining the conversion of the ester (**24**) to the ethyl amide (**5**), and its ultimate isolation and purification. Preliminary experiments involved addition of a solution of ethylamine in methanol to the reaction mixture at the end of the Grignard reaction, and heating to 80 °C to provide the two diastereomers, **5** and **4**, in a 7.4:1 ratio. It was subsequently demonstrated that a simple methanol quench of the Grignard reaction mixture readily provided the methyl ester, **22**. Treatment of this quenched solution with ethylamine in methanol furnished a 24:1 ratio of diastereomers (**5**:**4**). The direct amidation of the isopropyl ester in methanol proceeds via transesterification to methyl ester **22**, and may be facilitated by assistance from the neighboring alkoxide, or via the intermediacy of a strained lactone (Scheme 11).[20]

During early development, the procedure to crystallize and isolate **5** involved a long series of operations with multiple distillations and extractions. Once the reaction conditions were

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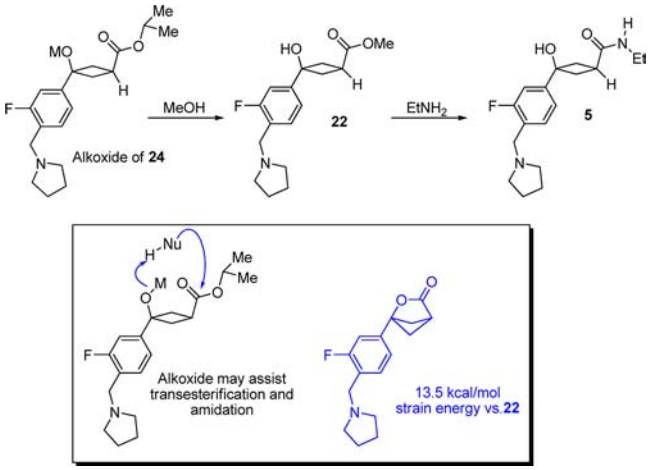
Scheme 11



established for the use of isopropyl ester **24**, a concerted effort was made to streamline the isolation of **5**. A comparison of the early and optimized procedures is shown in Figure 4.

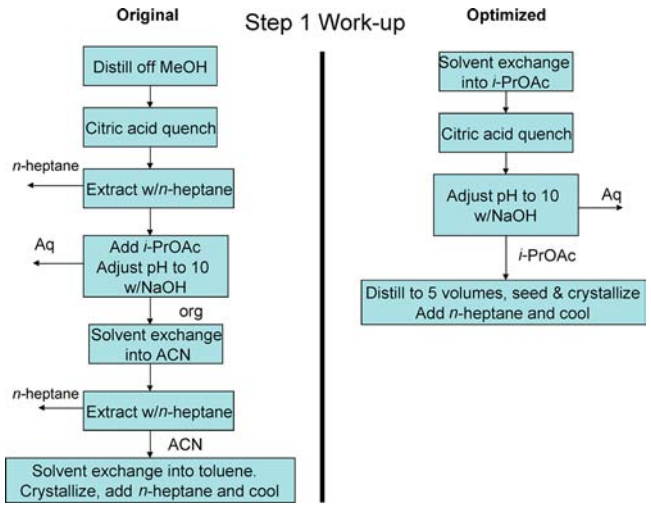


Figure 4. Comparison of old and improved workup procedures to isolate **5**.

In the original procedure, methanol was removed from the product solution via distillation, and then the mixture was quenched with a citric acid quench to dissolve the magnesium and lithium salts. The mixture was extracted with *n*-heptane to remove nonpolar impurities, and the product was extracted into *i*-PrOAc at high pH. Next, *i*-PrOAc was replaced with acetonitrile, and the mixture was extracted with *n*-heptane in order to remove the primary impurity, **20**. Finally, solvent exchange of the product-containing acetonitrile solution to toluene, followed by the addition of *n*-heptane, led to crystallization of **5**.

The acetonitrile/*n*-heptane extraction was especially warranted if selectivity was poor during formation of **24**, resulting in levels of **20** that were too high to purge effectively in the final crystallization. Further investigation of this extraction revealed that either methanol or acetonitrile product solutions could be extracted with *n*-heptane to selectively remove **20**. In addition, a more selective extraction could be obtained if a third component, water, is added. Best results were obtained with a volumetric solvent ratio of 1:1:0.2 methanol/*n*-heptane/water. Unfortunately, the addition of water resulted in slow extractions, and thus we reverted to the simpler methanol/*n*-heptane system while suffering only a slight decrease in selectivity.

In the optimized isolation procedure, the ethyl amide **5** product solution was distilled to replace methanol with *i*-PrOAc, and then a citric acid solution was added to dissolve salts associated with the Grignard reaction. Since the improved reaction conditions gave higher selectivity (increased **24**:**20**), extraction of the methanol solution with *n*-heptane was not required prior to distillation. The pH was adjusted to >10 with aqueous NaOH, and then the phases were separated. The organic (*i*-PrOAc) phase was then concentrated and seeded. Addition of *n*-heptane followed by cooling to 0 °C led to crystallization of the product. These streamlined workup and isolation procedures resulted in a >50% reduction in cycle times and processing costs for the production of **5**.

The crystallization conditions for **5** were optimized to provide efficient purification while integrating smoothly into the preceding workup steps. As a result, the early procedure using the toluene/*n*-heptane mixture was abandoned in favor of the *i*-PrOAc/*n*-heptane system. When the coupling of **9** with **23** proceeds normally (with a **24**:**20** ratio of 3−5), ethyl amide **5** is typically isolated in 98 area % purity with <1% **20**, and no improvement in quality is seen when *n*-heptane extractions are performed on the methanol product solution prior to subsequent workup. For cases when the selectivity in the Grignard coupling is significantly lower, *n*-heptane extractions of the methanol product solution (as described above) may be needed to decrease the level of **20** prior to crystallization and isolation.

THE FLUORINATION STEP

The original scale-up conditions for the fluorination reaction involved treatment of **5** with 1.5−1.8 equiv of Deoxo-Fluor (**27**) at −78 °C in methylene chloride or THF to furnish **2**.[39] While the ratio of diastereomers (**2**:**3**) was ∼8:1, the need to use, and subsequently quench, an excess of Deoxo-Fluor, coupled with the need for cryogenic equipment prompted us to explore alternative conditions. Several deoxofluorination conditions were evaluated for the conversion of tertiary alcohol **5** to the free-base form of API, **2**. These included not only other fluorinating reagents but also involved attempts to render the Deoxo-Fluor amenable to scale-up in noncryogenic vessels. In the initial stages of the screening exercise, it became apparent that the main byproducts of the fluorination were diastereomer **3** and olefin **28**. These two impurities were tracked throughout the screen, and process development efforts focused on minimizing, if not eliminating, the formation of these byproducts (Scheme 12). The three most promising leads from the initial screen (apart from Deoxo-Fluor) were 2,2-difluoro-1,3-dimethylimidazolidine (DFI, **29**), XtalFluor-E (**30**), and *N*,*N*,*N*′,*N*′-tetramethylfluoroformamidinium hexafluorophosphate (TFFH, **31**). A comparison of the best ratios of the desired product **2** and impurities **3** and **28** formed under optimized conditions using each of these reagents is presented in Figure 5.

The reaction of **5** with DFI,[21] a fuming liquid, furnished **2** in ∼60% yield at −20 °C. However, the reaction mixture quickly degraded at temperatures near 0 °C. The other issue was that the urea byproduct could only be partially purged with an aqueous workup and isolation. These factors, coupled with the

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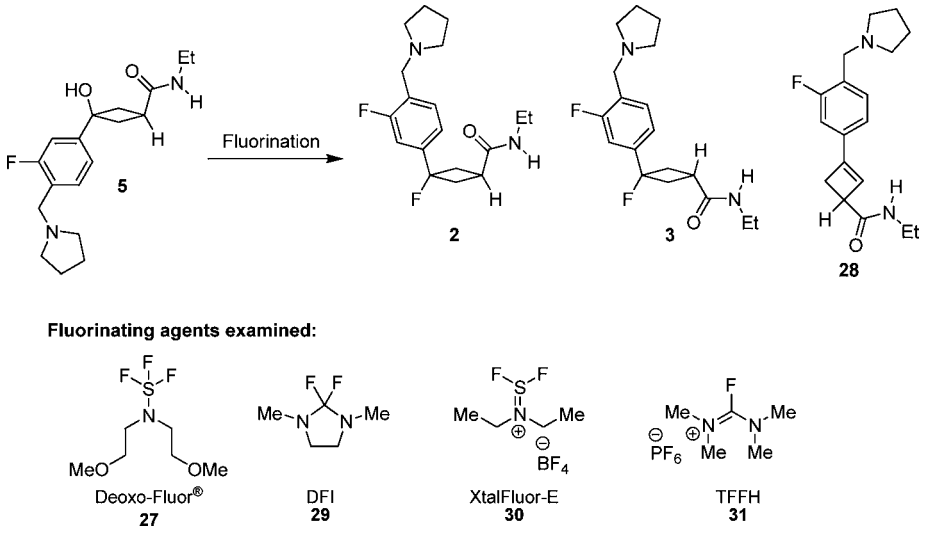
Scheme 12



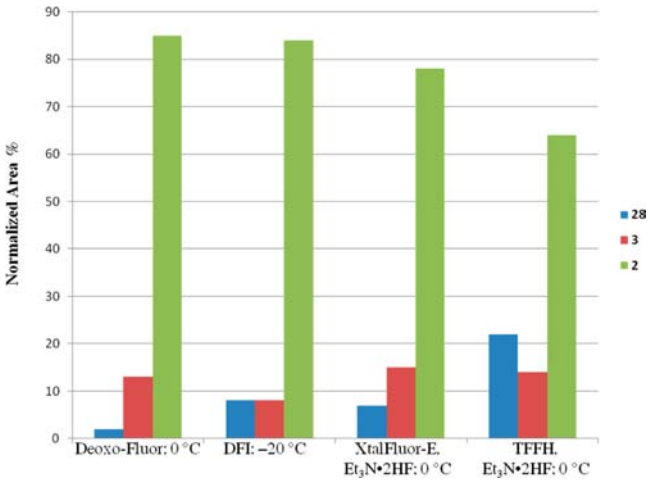


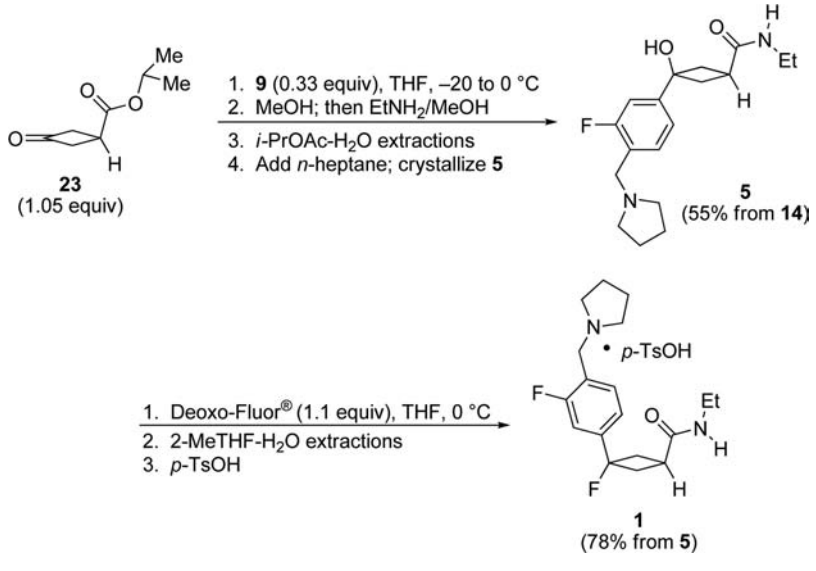
Figure 5. A comparison of different deoxofluorinating agents for the conversion of **5** to **2**.

lack of a long-term supplier of DFI prompted us to halt further development using this reagent.

XtalFluor-E and its analogues are a series of novel reagents for the deoxofluorination of alcohols and carboxyl groups.[22] In contrast to the Deoxo-Fluor and DFI, these compounds are crystalline solids. These mild reagents require buffered HF additives to enable clean reactions with alcohols. In our investigations, $Et_3N{\cdot}2HF$[23] proved to be the best additive for our specific alcohol, **5**.[24] The reaction proceeded smoothly in THF at 0 °C, providing a mixture of **2** and its diastereomer, **3**, in a 5:1 ratio in ~60% yield. Attempts to improve this isomeric ratio by performing the transformation at lower temperatures failed due to the solidification of the reaction mixture at −15 °C.

TFFH (**31**) is a nonhygroscopic, crystalline solid used for peptide synthesis via acylfluoride formation.[25] We recently reported the use of TFFH in deoxofluorination reactions.[26] Following the basic reactivity pattern exhibited by the XtalFluor reagents, our initial focus was to evaluate the impact of HF additives on the reaction of TFFH with **5**. This screen further

Scheme 13. Optimized process for the synthesis of 1



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reinforced the unique ability of $Et_3N{\cdot}2HF$ to promote the desired deoxofluorination. Moreover, THF was found to be the optimal solvent for this transformation and yields up to 60% were obtained on small scale, with a dr of 5:1 (Figure 5). Analogous to the DFI reaction, the presence of large quantities of the urea byproduct proved problematic in this case and led us to halt our efforts.

Concurrent examination of the Deoxo-Fluor-mediated deoxofluorination reaction revealed that a lower stoichiometry of Deoxo-Fluor (<1.5 equiv) could be used when the incoming **5** was of high purity. Moreover, identical impurity profiles and isomeric ratios (8:1 ratio of **2**:**3**) could be obtained when performing the reaction at or below −40 °C. Importantly, it was discovered that addition of a THF solution of **5** to Deoxo-Fluor allowed us to carry out the reaction at 0 °C, while still providing similar yields and isomeric ratios. Reaction kinetics revealed that the reaction of **5** with Deoxo-Fluor was dose limited and the substrate could be added over 10 min to 3 h with no loss in conversion or selectivity at a reaction temperature of 0 °C. When reaction was deemed complete, it could be held for up to 48 h at 0 °C with no loss in selectivity or purity. Ultimately, this procedure was streamlined to a point where the transformation could be carried out with just 1.1 equiv of Deoxo-Fluor at 0 °C.

Upon reaction completion, the reaction mixture was quenched via subsurface addition into a mixture of aqueous 30% w/w potassium carbonate (9 equiv) and 2-methyltetrahydrofuran, at −10−0 °C. Adequate mixing during the quench was important to prevent localized accumulation of hydrofluoric acid, which could degrade the product. Experimental evidence suggested that a final aqueous pH 10−11 was ideal to ensure that all of the hydrofluoric acid had been quenched and converted to potassium fluoride and to ensure that the desired product resided in the organic layer. The reaction mixture after the extractive workup was treated with *p*-toluenesulfonic acid to form the tosylate salt **1**. The overall process for the synthesis of **1** is depicted in Scheme 13.

CONCLUSION

In summary, a concise process for the manufacture of H_3 antagonist **1** was developed in our laboratories. This process relies on the chemoselective addition of an organometallic reagent to a cyclobutanone carbonyl in the presence of an ester group, the addition of an amine to the preserved ester group, and a diastereoselective deoxofluorination to provide the target compound. A retrosynthetic analysis which included the calculation and measurement of the relative stabilities of the cis and trans isomers of the target molecule and observations of the stereochemistry of the solvolysis of the fluorocyclobutane focused our efforts on this strategy. Among the many types of organomagnesium reagents, a relatively new type of reagent, a triaryl magnesium ate complex (**9**), was employed since it can be prepared in a homogeneous dose-controlled reaction under noncryogenic conditions and has good reactivity. The stability of this reagent was rapidly screened vs temperature and solvent with the aid of an automated workstation, deuterium quenching, and LC/MS. The addition order, reaction temperature, and addition rate for the addition of organometallic **9** to ketone **23** was optimized by considering heat removal on scale and the competing reactions of the starting materials and intermediates during the addition. The continuous simultaneous combination of ketone **23** and organometallic **9** was preferred and implemented via a simultaneous semibatch reaction and in a flow reaction. The isopropyl ester was chosen to be large enough to protect the ester during the organometallic addition, yet small enough to allow transesterification with methanol and ultimate amination with ethylamine. The work up of this step was streamlined to minimize the number of unit operations and solvent volumes by carefully considering material and solvent properties and monitoring mass balance throughout the process. Of the various deoxofluorinating reagents screened and studied for the second step, Deoxo-Fluor was found to give high yield, diastereoselectivity and chemoselectivity in the formation of **1**, provided that alcohol **5** was pure, that the solution of **5** was added to the solution of Deoxo-Fluor, and the reaction was quenched by subsurface inverse addition with good mixing and pH control. The close collaboration between synthetic chemists, automation specialists, chemical engineers, and analytical chemists greatly facilitated this process research and development.

EXPERIMENTAL SECTION

Preparation of Propan-2-yl 3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-3-hydroxycyclobutanecarboxylate 24. *Batch Process.* To THF (150 mL) was added 1-(4-bromo-2-fluorobenzyl)pyrrolidine **14** (39 g, 150 mmol, 1 equiv), and the mixture was cooled to −10 °C. Isopropylmagnesium chloride (2.0 M in THF, 32 mL, 63 mmol, 0.42 equiv) was added over 20 min at ≤5 °C. *n*-Butyllithium (2.5 M in hexane, 50 mL, 126 mmol, 0.84 equiv) was added over 30 min at ≤5 °C. After an additional 30 min stir at 0 °C, the reaction was deemed complete via HPLC (<1% **14** remaining). The reaction mixture containing the magnesium ate complex **9** was cooled to −35 °C, and propan-2-yl 3-oxocyclobutanecarboxylate (**23**, 25 g, 158 mmol, 1.05 equiv) was charged over 40 min at ≤−30 °C. The reaction mixture was stirred for 1 h at −30 °C, warmed to 20 °C, and then quenched by addition of methanol (40 mL). The potency of the solution was measured by HPLC, indicating a yield of 65% of propan-2-yl 3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-3-hydroxycyclobutanecarboxylate, **24**.

Simultaneous Addition Process. The magnesium ate complex **9** mixture in THF was prepared as above and diluted with THF to form a 0.5 M solution (Solution A) and held at 0 °C. In a separate vessel, propan-2-yl 3-oxocyclobutanecarboxylate **23** (25 g, 158 mmol, 1.05 equiv wrt **14**) was diluted with THF to form a 1.05 M solution (Solution B). THF (60 mL) was charged to a separate vessel and cooled to −10 °C. Solution A and Solution B were added to the vessel containing THF simultaneously over a period of 1 h using pumps with flow rates of 5.0 mL/min (Solution A) and 2.5 mL/min (Solution B). The reaction mixture was stirred at −10 °C for 1 h after the additions were complete, warmed to 20 °C, and then quenched by the addition of methanol (40 mL). The potency of the solution was measured by HPLC, indicating a yield of 65% of propan-2-yl 3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)-phenyl]-3-hydroxycyclobutanecarboxylate, **24**.

Continuous Plug Flow Process. The magnesium ate complex **9** mixture in THF was prepared as above but on a 75 mmol scale of **14** and diluted with THF as needed to form a 0.5 M solution wrt **14** (Solution A) and held at 0 °C. In a separate vessel, propan-2-yl 3-oxocyclobutanecarboxylate **23** (12.3 g, 79 mmol, 1.05 equiv wrt **14**) was diluted with THF to form a 1.05 M solution (Solution B). The flow reactor was cooled to −5 °C, and the pumps were started simultaneously to begin flow of Solution A (1.3 mL/min) and Solution B (0.65 mL/min). On the basis of the reactor volume (10 mL), these

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conditions correspond to a 5-min residence time. The product solution was flowed into an agitated vessel containing MeOH (20 mL). The potency of the solution was measured by HPLC, indicating a yield of 65% of propan-2-yl 3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-3-hydroxycyclobutanecarboxylate, **24**. This procedure was scaled successfully to 750 mmol of the starting material **14**.

Preparation of N-Ethyl-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-3-hydroxycyclobutanecarboxamide ***5***. With a solution of propan-2-yl 3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-3-hydroxycyclobutanecarboxylate, **24** produced at 150 mmol scale by one of the methods above, a solvent exchange into MeOH (2 × 265 mL) was performed. To this solution, ethylamine (2.0 M in MeOH, 300 mL, 600 mmol, 4 equiv) was added and the reaction mixture was stirred at 45 °C for 4 h at which time it was deemed complete by HPLC (<2% starting material **24**). After solvent exchange into *i*-PrOAc (3 × 265 mL), a solution of citric acid (72 g, 375 mmol, 2.5 equiv) dissolved in H_2O (190 mL) was added. The pH was adjusted to >10 via slow addition of 50 wt % aqueous NaOH (60 mL, 1130 mmol, 7.5 equiv) and the phases were separated. The organic phase was distilled under vacuum to a volume of about 100 mL, cooled to 20 °C, and seeded. After stirring for 1 h, *n*-heptane (42 mL) was added over 30 min, and the resultant suspension was cooled to 0 °C and stirred for 2 h. The suspension was filtered, and the cake was washed with a 50:50 volume mixture of *i*-PrOAc/*n*-heptane (2 × 30 mL). The cake was dried under vacuum at 50 °C for 12 h to give *N*-ethyl-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-3-hydroxycyclobutanecarboxamide, **5** as an off-white solid (26.4 g, 55% from **14**; 85% from **24**).[27]

Preparation of N-Ethyl-3-fluoro-3-[3-fluoro-4-pyrrolidin-1-ylmethyl)phenyl]cyclobutanecarboxamide ***1***. Bis(2-methoxyethyl)amino)sulfur trifluoride (Deoxo-Fluor) (22 mL, 120 mmol, 1.1 equiv) was added to THF (350 mL) that was precooled to 0 °C. A solution of *N*-ethyl-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-3-hydroxycyclobutanecarboxamide **5** (35 g, 109 mmol, 1.0 equiv) in THF (140 mL) was added to the Deoxo-Fluor solution over 45 min while maintaining the temperature at ≤0 °C. The reaction was deemed complete by HPLC (<1% starting material) after stirring for 1.5 h at 0 °C, and the reaction mixture was transferred to an addition funnel. Into a separate vessel were charged K_2CO_3, 30% w/v (350 mL, 980 mmol, 8 equiv) and 2-MeTHF (525 mL); the mixture was cooled to −5 °C. With an addition funnel, the reaction mixture containing the product was transferred below the liquid surface into the K_2CO_3 mixture over a period of about 2 h at ≤0 °C. The phases were separated, and the organic phase was washed with 20% aqueous NaCl (175 mL). The organic layer was distilled under vacuum to remove water and was finally reduced to a volume of about 200 mL. The solution was filtered to remove salts, and the solids were washed with 2-MeTHF (40 mL). To the filtrate (product solution), a solution of *p*-toluenesulfonic acid monohydrate (24.3 g, 125 mmol, 1.15 equiv) in 2-MeTHF (105 mL) was added over 30 min during which time the product crystallized. The slurry was stirred at 15−20 °C for 2 h. The product was filtered and washed with 2-MeTHF (70 mL) and dried under vacuum at 50 °C to provide **1** (42.4 g, 78% yield) in 94.3 area % purity by HPLC.[27]

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Notes

The authors declare no competing financial interest.

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