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Synthesis of the γ-Secretase Modulator MK-8428

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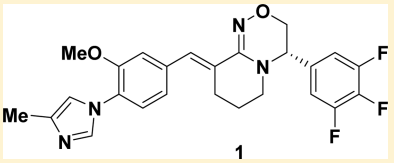
Supporting Information

ABSTRACT: The synthesis of the γ-secretase modulator MK-8428 (**1**) is described. The synthesis is highlighted by an enzyme-catalyzed reaction to access 3,4,5-trifluoro-(*S*)-phenylglycine, a 1-pot activation/displacement/deprotection sequence to introduce the aminooxy functionality and a dehydrative intramolecular cyclization under mild conditions to form the oxadiazine heterocycle of **1**. In situ reaction monitoring was employed to understand the deleterious role of water during the formation of a methanesulfonate ester in the 1-pot activation/displacement/deprotection sequence.



INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder that results in gradual loss of memory and impairment of vocal and motor control before ultimately resulting in death. By 2025, it is estimated that greater than 7 million Americans will be suffering from AD, a number that represents a 40% increase from the number of Americans living with the disease in 2015.[1] The current standard of care involves treatment with a cholinesterase inhibitor to improve cognition, but there are currently no disease-modifying therapies available to treat AD. Patients suffering from AD possess two distinctive biomarkers: extracellular amyloid plaques and intracellular neurofibrillary tangles, both of which are believed to result in the loss of neurons in the cerebral cortex. The amyloid plaques are formed when amyloid precursor protein (APP) is cleaved sequentially by proteases BACE1 and γ-secretase, leading to the formation of $A\beta_{42}$. Novel inhibitors or modulators of the γ-secretase protease can therefore be assessed as possible treatments for AD.[2]

During the course of their clinical evaluation, γ-secretase inhibitors were found to lead to higher incidence of adverse events, likely due to the promiscuity of the γ-secretase enzyme, which possesses a range of endogenous substrates and is involved in a variety of key cellular processes.[3] To mitigate these concerns, a new class of molecules was developed that changes the enzyme's interaction with APP without further cellular impact. These new molecules, γ-secretase modulators, alter the APP specificity and result in the elevated formation of the shorter, less toxic $A\beta_{37}$ and $A\beta_{38}$ fragments, resulting in lower levels of $A\beta_{42}$.[4] MK-8428 (**1**) was identified as a novel γ-secretase modulator possessing favorable in vitro activity and an excellent pharmacokinetic profile and was subsequently targeted for further development. To support preclinical and early clinical development of this compound, a robust and efficient synthesis of **1** was required.

RESULTS AND DISCUSSION

The retrosynthesis of **1** is presented in Figure 1. The key oxadiazine pharmacophore[5] was generated via intramolecular dehydrative cyclization of an intermediate aminooxy nucleophile derived from carbinol **2**. This carbinol was accessible after coupling of α,β-unsaturated acid **3** with amino-alcohol **4**. Acid **3** was formed via Horner–Wadsworth–Emmons olefination of aldehyde **5**, and the amino-alcohol **4** was prepared via an enzyme-mediated conversion of an α-keto carboxylic acid **6** to an optically pure α-amino acid followed by reduction of the carboxylic acid.

The route employed to produce α,β-unsaturated acid **3** is shown in Scheme 1. 3-Hydroxy-4-nitro benzoic acid (**7**) underwent bis-alkylation with dimethylsulfate to generate **8**. The nitro group was reduced in the presence of Raney-Ni to provide aniline **9**. This aniline was formylated and subsequently alkylated with chloroacetone to yield **11**, which upon treatment with ammonium acetate in acetic acid underwent dehydrative cyclization to afford 4-methyl-imidazole **12**. The methyl ester was subsequently converted to aldehyde **5**[6] using a two-step reduction/oxidation sequence. Aldehyde **5** was coupled to phosphonate **13**[5a] under Horner–Wadsworth–Emmons[7] conditions, yielding a mixture of olefin isomers (*E*:*Z* 4.7:1). Finally, exposure to trifluoroacetic acid resulted in the cleavage of the *tert*-butyl ester to afford the trifluoroaceate salt of **3**.

The synthesis of the amino-alcohol coupling partner **4** is shown in Scheme 2. Readily available 5-bromo-1,2,3-trifluorobenzene (**15**) was acylated with diethyl oxalate, and the resulting ester was hydrolyzed to yield α-keto carboxylic acid **6**. In a key transformation, exposure of **6** to an amino acid dehydrogenase (L-AADH-108)[8] produced 3,4,5-trifluoro-(*S*)-phenylglycine **16** in high yield and with excellent enantioselectivity (>99% ee). Glucose and glucose dehydrogenase were used to regenerate the NADH cofactor from NAD^+, producing D-glucono-1,5-lactone (Figure 2) in the process. The carboxylic

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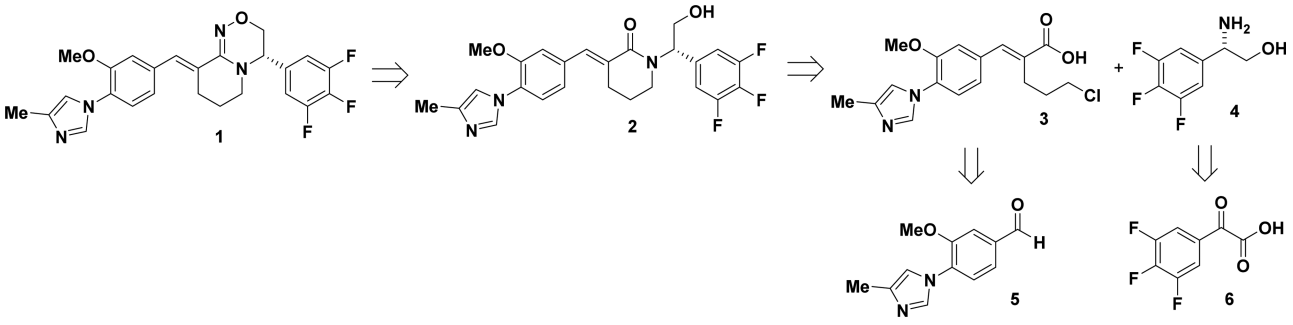
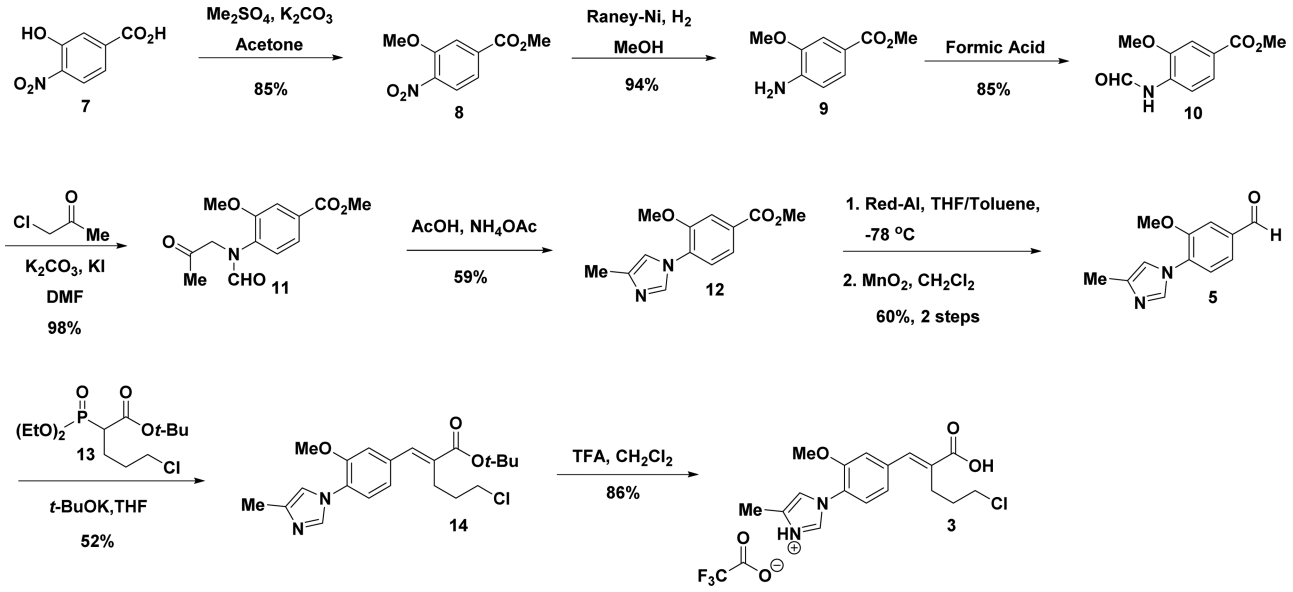
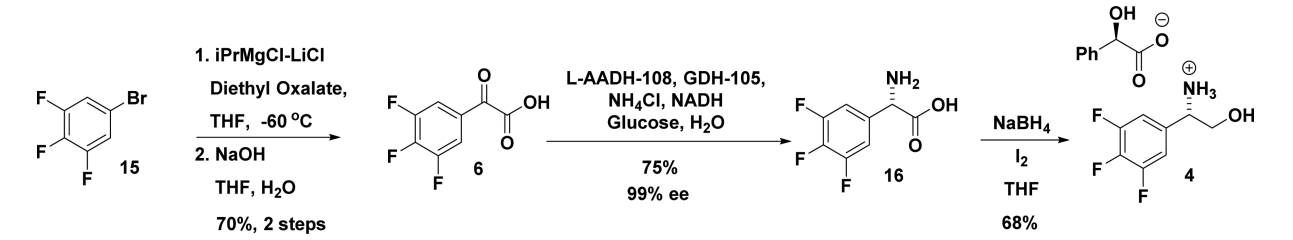


Figure 1. Retrosynthesis of 1.

Scheme 1. Preparation of α,β-Unsaturated Acid 3



Scheme 2. Preparation of Amino Alcohol 4



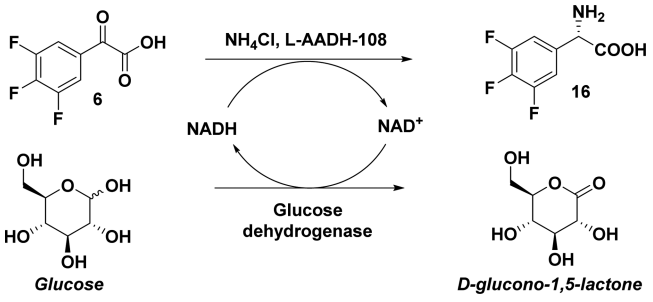


Figure 2. Enzymatic mediated conversion of keto-acid **6** to amino acid **16**.

acid of **16** was then reduced to provide **4**, which was isolated as the mandelate salt.[9] The targeted amino alcohol was prepared in 3 steps with an overall yield of 42% and provided advantages to previously disclosed routes to **4** with respect to overall yield and stereocontrol.[5e]

Amino-alcohol **4** was coupled to unsaturated acid **3** under HOBT/EDC conditions, resulting in the formation of amide **17** (Scheme 3). Treatment of amide **17** with NaOMe promoted the intramolecular alkylation, yielding the δ-lactam **2**. Assembly of the aminooxy moiety was carried out in a 2-step sequence beginning with the addition of *N*-hydroxyphthalimide after activation of **2** as the methanesulfonate ester[10] to yield **18**. It was determined that isolation of **18** was not required, as direct addition of aqueous hydroxylamine resulted in the cleavage of the phthalimide to provide **19**. Hydroxylamine was chosen as the nucleophile for this transformation, as the byproduct of the reaction (*N*-hydroxyphthalimide) was easily separated from **19** by washing with aqueous base during the reaction workup. The overall yield from **2** to **19** was 86% and

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Scheme 3. Installation of the Aminooxy Moiety

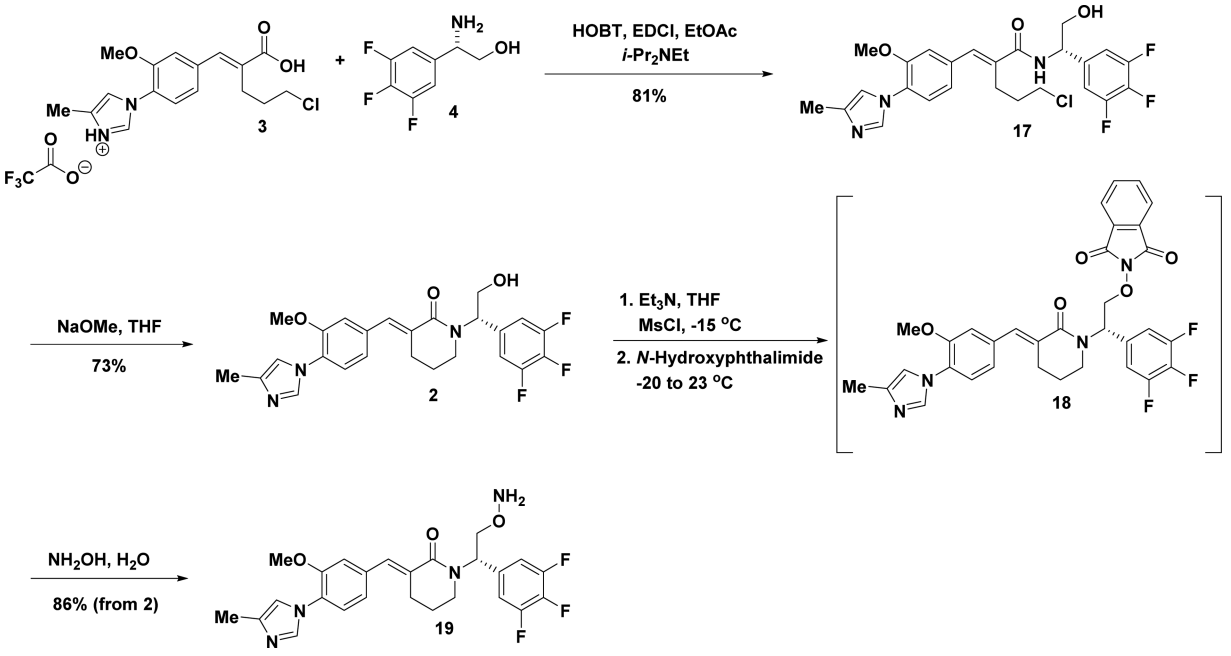
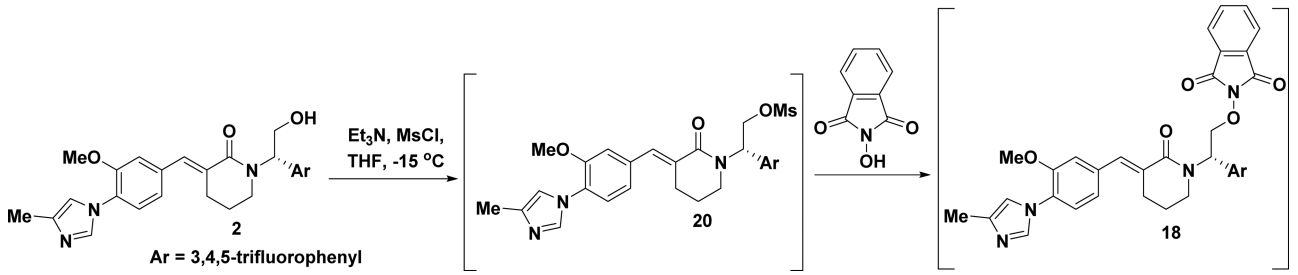


Table 1. Impact of Water on the Activation/Displacement Approach to 18



entry	H_2O content (mol %)	age time (h)[a]	2 (%)[b]	18 (%)[b]
1	60[c]	0.5	3.7	91.9
2	6[d]	0.5	0.3	97.2
3	60	3	11.0	81.2
4	5	3	0.3	96.7

[a]Time between the end of the MsCl addition and the *N*-hydroxyphtalimide charge. [b]Content was recorded after reaction was deemed complete by HPLC. Numbers shown are HPLC area percents. [c]KF values were recorded for individual components (**2** and THF, respectively) for this analysis. [d]KF value was the solution of **2** in THF.

yielded the precursor for the pivotal oxadiazine formation (vide infra).

During the course of our optimization work on installing the *N*-hydroxyphthalimide group of **18**, it was observed that small amounts of **2** persisted at the end of the reaction (Table 1, entry 1). Given the stoichiometry of the methanesulfonyl chloride employed (1.5 equiv), we considered it unlikely that the carbinol was not fully converted to the methanesulfonate ester. A more plausible scenario was that adventitious water reacted with the newly formed methanesulfonate ester **20** to return carbinol **2**. To evaluate this hypothesis, water introduced from **2** and THF was azeotropically removed prior to addition of the methanesulfonyl chloride and triethylamine. This operation reduced the measured water content to 6 mol % (Table 1, entry 2). Following formation of the methanesulfonate ester and addition of the *N*-hydroxyphthalimide, the amount of **2** observed was lowered to 0.3% by HPLC with a concomitant increase in the purity of **18** by HPLC.

The impact of water on the conversion of **2** to **18** was further explored using in situ IR spectroscopy.[11] In situ IR provided a tool to monitor the formation of the methanesulfonate ester **20**, as this reactive intermediate was unstable under reverse phase HPLC conditions.[12] An experiment was carried out where water removal by azeotropic distillation was omitted (Table 1, entry 3). Following the addition of methanesulfonyl chloride, the batch was aged for 3 h. The IR spectroscopy data showed initial formation of the of the methanesulfonate ester (Figure 3, orange band), which was followed by clear decomposition of this reactive intermediate during the course of the 3 h holding period (Figure 3, red band). *N*-Hydroxyphthalimide was then added to the reaction, and the final content of **2** was observed to be 11% by HPLC.

A subsequent experiment was conducted in which water was removed by azeotropic distillation (Table 1, entry 4). Following completion of the methanesulfonyl chloride addition, the reaction was again aged for 3 h (Figure 4, pink band). In stark

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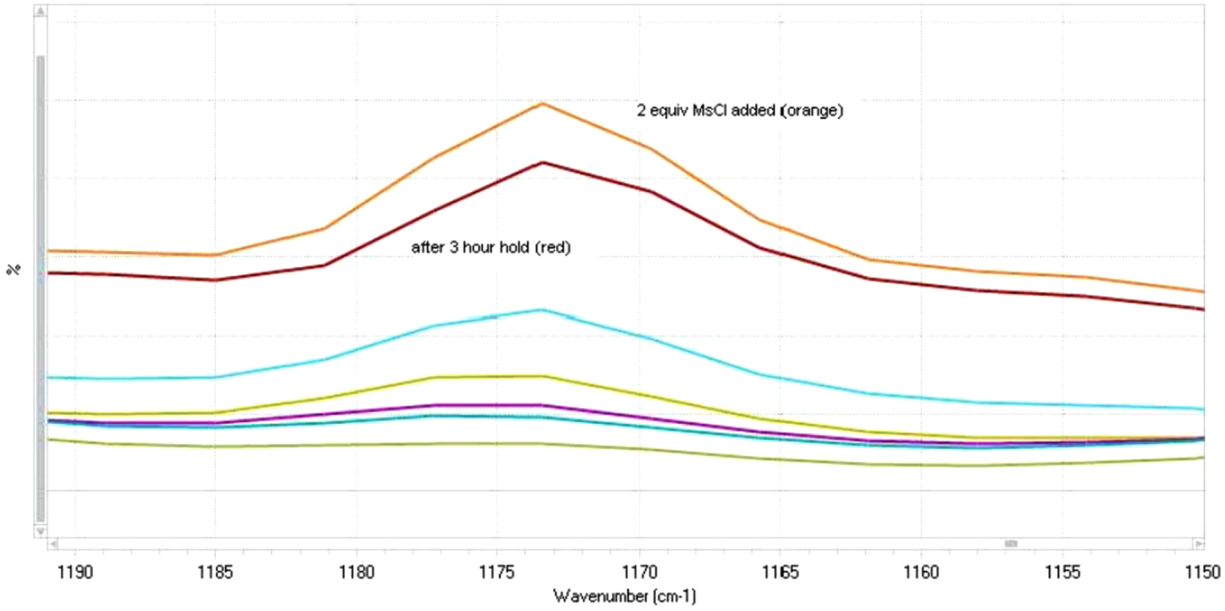

Figure 3. IR spectrum from mesylation of **2** without distillation prior to reaction (3 h hold). Formation of the intermediate methanesulfonate ester **20** was established by monitoring the appearance of the S−O stretch in the IR spectrum. Unlabeled stretches represent time points prior to the completion of the MsCl addition.

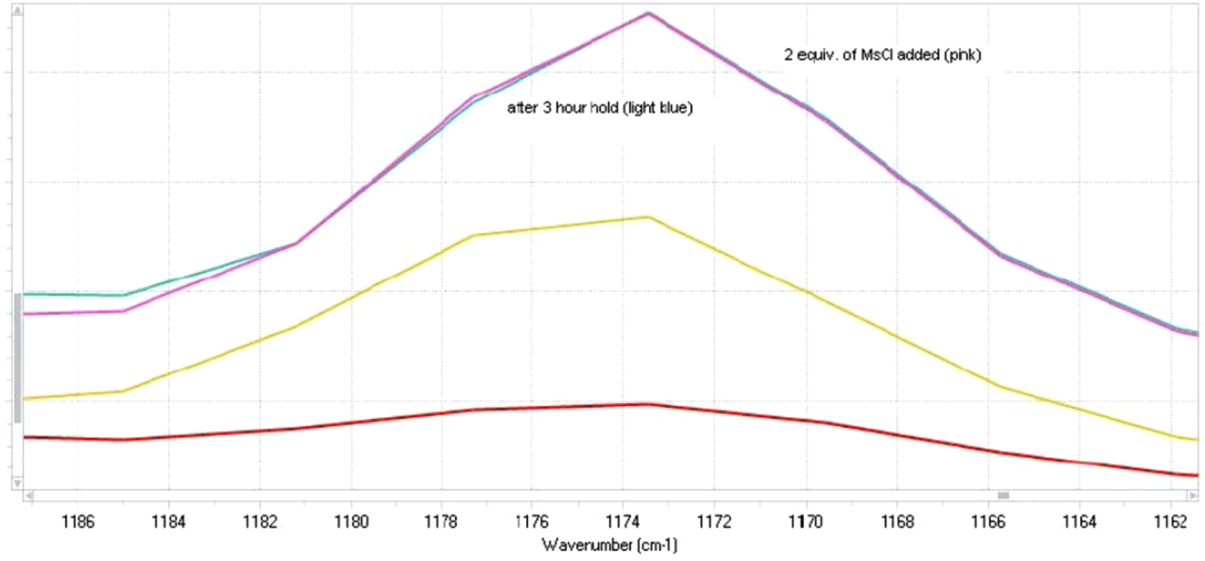

Figure 4. IR spectrum from mesylation of **2** with distillation prior to reaction (3 h hold). Formation of the intermediate methanesulfonate ester **20** was established by monitoring the appearance of the S−O stretch in the IR spectrum. Unlabeled stretches represent time points prior to the completion of the MsCl addition.

contrast to the experimental data shown in Figure 3, no discernible mesylate decomposition was observed by IR when the water was removed prior to the addition of methanesulfonyl chloride and triethylamine (Figure 4, light blue band). Following completion of the reaction, the final content of **2** was determined to be 0.3% by HPLC. Taken together, the water titration and in situ IR data provided strong support that water dramatically impacts the conversion of **2** to **18** presumably by reacting with the intermediate mesylate to regenerate carbinol **2**.

With an understanding of the conversion of **2** to **19** in place, we were poised to introduce the oxadiazine heterocycle using an intramolecular dehydrative cyclization. Previously reported conditions using P_2O_5 in EtOH[5a] led to the formation of polyphosphate byproducts[13] which complicated the isolation of **1**. Acids were screened to determine their effectiveness in promoting the conversion of **19** to **1** (Table 2). While the conversion in the presence of most acids was high, the assay yields of the desired oxadiazine product were low due to the competing side reactions. Gratifyingly, we discovered that when treating a solution of **19** with hexamethyldisilazane (HMDS) and catalytic amounts of trimethylsilyl trifluormethanesulfonate (TMSOTf), the desired intramolecular cyclization took place in high yield.[14] This silyl-mediated dehydration provided a milder alternative to Brønsted acids and a new approach to access this interesting heterocycle (**1**). Finally, isolation as the hemi-fumarate salt provided access to our targeted γ-secretase modulator **1** (Scheme 4).

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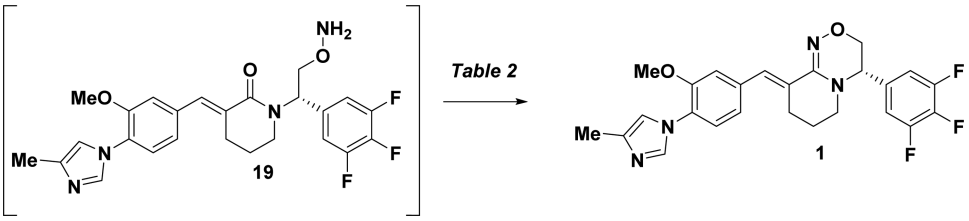
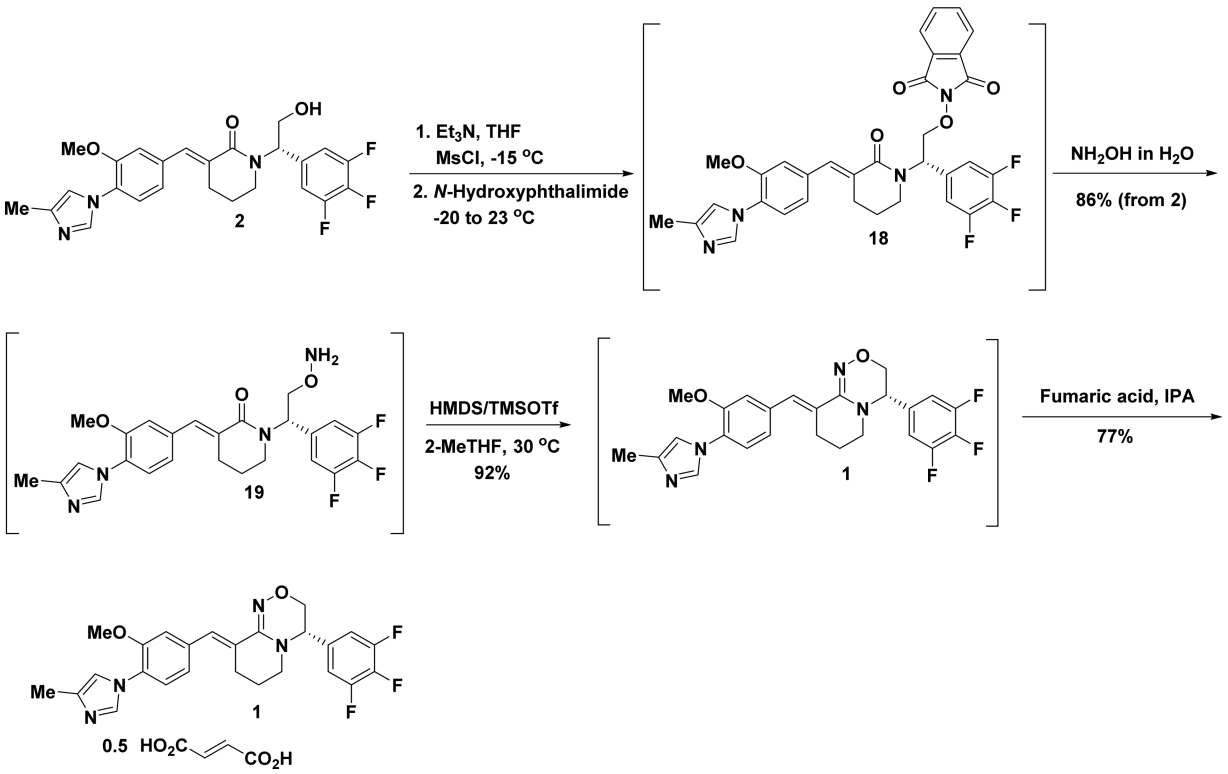
Table 2. Acid Screen for Intramolecular Dehydration



entry[a]	acid	conversion (%)[b]	assay yield of **1** (%)
1	none	0	0
1	HCl	60	42
2	MsOH	98	65
3	AcOH	98	54
4	TFA	99	52
5	HBF_4	99.5	70
6	H_3PO_4	99.5	68
7	Tf_2NH	99.8	75
8[c]	HMDS/TMSOTf	99.9	92

[a]Entries 1−7 were run using EtOH as a solvent under reflux conditions for 14 h. [b]Based on HPLC area percent of **19**. [c]Reaction solvent was 2-Me-THF, and reaction temperature was 30 °C.

Scheme 4. End Game Approach to 1



CONCLUSION

A convergent synthesis of γ-secretase modulator **1** was described. Highlights of this synthesis included an enzyme-mediated conversion of an α-keto carboxylic acid to access an enantiopure 3,4,5-trifluoro-(*S*)-phenylglycine (**16**). In situ reaction monitoring was employed to understand the deleterious role of water on the 1-pot mesylation/displacement sequence that was employed to introduce the aminooxy functionality. Finally, mild dehydration conditions were identified to form the key oxadiazine heterocycle in high yield. The route described enabled production of **1** to support preclinical development of this potentially important disease-modifying therapy for AD.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under a nitrogen atmosphere in dried glassware with either magnetic stirring or overhead agitation. ^{1}H NMR spectra were recorded on either a 500 or 400 MHz spectrometer and are reported in ppm using deuterated solvent as an internal standard. Data are reported as ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a 125 or 100 MHz spectrometer and are

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reported in ppm using deuterated solvent as an internal standard. Electrospray mass spectra (ESI-MS) were obtained using a triple quadrupole mass spectrometer. L-AADH-108 and GDH-105 were purchased from Codexis.

*(E)-1-(4-(2-Carboxy-5-chloropent-1-en-1-yl)-2-methoxyphenyl)-4-methyl-1H-imidazol-3-ium 2,2,2-trifluoroacetate (**3**).* To a round-bottom flask at 5 °C were added potassium *tert*-butoxide (3.5 g, 31.1 mmol) and THF (100 mL). A solution of *tert*-butyl diethylphosphonoacetate (7.5 g, 29.7 mmol) in THF (19 mL) was added to the potassium *tert*-butoxide solution at a rate to maintain the internal temperature <10 °C. After the addition was complete, the solution was warmed to 25 °C and aged for 45 min. 1-Bromo-3-chloropropane (9.4 g, 59.4 mmol) was added to the anion solution of *tert*-butyl diethylphosphonoacetate at 25 °C. The reaction was warmed to 60 °C and aged for 3 h. The reaction was cooled to 25 °C, and aldehyde **5** (5.78 g, 21.6 mmol) was charged in a single portion. The reaction was further cooled to −5 °C, and a solution of potassium *tert*-butoxide (3.02 g, 26.9 mmol) was added to the reaction at a rate to maintain the internal temperature <0 °C. The reaction was aged for 60 min at 0 °C. Ethyl acetate (100 mL) was added to the reaction; the temperature was raised to 25 °C, and the reaction mixture was transferred to a separatory funnel. The organic layer was washed with water (90 mL), and the resulting aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (90 mL) and treated with activated charcoal (500 mg) for 30 min at 25 °C. The activated charcoal was removed by filtration over Celite, and the ethyl acetate solution was dried over Na_2SO_4. The Na_2SO_4 was removed by filtration, and the resulting solution was concentrated to dryness. The unpurified *tert*-butyl ester **14** was dissolved in dichloromethane (50 mL), cooled to 0 °C, and treated with trifluoroacetic acid (12 mL, 156 mmol). The reaction was warmed to 25 °C and aged for 3 h. The dichloromethane was removed by evaporation; ethyl acetate (30 mL) was added, and the residue was stirred for 1 h. The solids were filtered and dried over nitrogen, yielding TFA salt **3** (4.33g, 45%), mp 163−166 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.38 (s, 1H), 7.76 (s, 1H), 7.71 (s, 1H), 7.67 (m, 1H), 7.37 (s, 1H), 7.25 (m, 1H), 3.94 (s, 3H), 3.71 (t, J = 6.3 Hz, 2H), 2.65 (t, J = 7.9 Hz, 2H), 2.39 (s, 3H), 2.01 (quintuplet, J = 6.3 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 169.1, 159.1 (q, J = 35.8 Hz), 152.6, 138.8, 137.7, 136.1, 134.7, 130.0, 126.6, 123.8, 121.9, 120.1, 116.4 (q, J = 292.4 Hz), 114.2, 56.8, 45.8, 31.9, 25.4, 9.9. HRMS calcd. for $C_{17}H_{20}ClN_2O_3$ ($[M + H]^+$) 335.1157, found 335.1162.

*2-Oxo-2-(3,4,5-trifluorophenyl)acetic Acid (**6**).* To a solution of isopropylmagnesium chloride−lithium chloride in THF (50.8 mL, 66.2 mmol) at −10 °C was added 5-bromo-1,2,3-trifluorobenzene (13.9 g, 66 mmol). After being stirred for 4 h at −10 °C, the solution was cooled to −70 °C, and diethyl oxalate (19.4 g, 132 mmol) was added dropwise. The reaction was warmed to room temperature over 4 h and then quenched into saturated ammonium sulfate. The ester was extracted with MTBE (200 mL), washed with water (100 mL) and 1 M HCl (100 mL), and concentrated in vacuo to afford a crude oil. The crude oil was then charged to a flask and then dissolved in 40 mL of THF with stirring. The mixture was cooled to 0 °C, and NaOH (40 mL, 198 mmol) was added dropwise. After being warmed to room temperature and stirred overnight, 1 M HCl was added to the solution until the pH was 2−3. The product was then extracted with dichloromethane (200 mL), and the solvent was removed. The crude oil was then crystallized from dichloromethane (20 mL) and heptane (20 mL) to afford **6** as a white solid (9.44 g, 70%). This crude solid was used in the downstream processing without further purification. For analytical purposes, the material was chromatographed on a SiO_2 ISCO cartridge using 100% hexane to 30% EtOAc over 12 column volumes, mp 164−165 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88 (t; J = 7.47 HZ; 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 115.2 (dd, J = 5.62, 17.1 Hz), 128.9 (td; J = 3.9, 6.4 Hz), 143.6 (dt; J = 15.3, 259.6 Hz), 150.8 (dd; J = 3.2, 10.3, 250.7 Hz), 164.3, 184.9. HRMS calcd. for $C_8H_2F_3O_3$ ($[M - H]^-$) 202.9962, found 202.9959.

*(S)-2-Amino-2-(3,4,5-trifluorophenyl)acetic Acid (**16**).* L-AADH-108 (450 mg) and GDH-105 (150 mg) were dissolved in pH 7 kPi buffer (75 mL). In a separate flask, keto acid **6** (6 g, 29 mmol) and NH_4Cl (3.18 g, 59.7 mmol) were dissolved in pH 7 kPi buffer (75 mL), and the pH was adjusted to pH 8 using NH_4OH. Glucose (8.1 g, 45 mmol) and NAD (195 mg, 0.3 mmol) were then added to this solution. The solution containing L-AADH-108 and GDH-105 was added to the keto acid solution, resulting in a pH drop to 7.4. The pH was adjusted back to pH 8 using 2 M NaOH, and the reaction was aged for 10 h at 25 °C. MeOH (24 mL) was added to the mixture, and the reaction was heated to 70 °C for 1 h. The reaction was cooled to 25 °C over 1 h and further stirred for 1 h. 1-Butanol was added (50 mL), and the mixture was distilled at 70 °C under vacuum to 20 mL total volume. The solids were collected by filtration and dried over nitrogen, yielding amino acid **16** (4.5 g, 75%), mp 201−202 °C. ^{1}H NMR (D_2O, 500 MHz) δ 7.18 (m, 2H), 5.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 151.2 (ddd, J = 249.8, 10.0, 4.0 Hz), 140.6 (dt, J = 252.4, 14.9 Hz), 127.5 (td, J = 8.0, 5.0 Hz), 113.2 (dd, J = 17.6, 6.0 Hz), 55.3. HRMS calcd. for $C_8H_5F_3NO_2$ ($[M - H]^-$) 204.0278, found 204.0276. Chiral analysis performed using Zwix (−) column (150 × 3 mm, 3 μm); mobile phase: isocratic elution (49% MeOH, 49% MeCN, 2% water, 50 mM formic acid, 25 mM diethylamine), 0−6 min, 0.75 mL/min, 45 °C, 99% ee.

*(S)-2-Hydroxy-1-(3,4,5-trifluorophenyl)ethan-1-aminium-(R)-2-hydroxy-2-phenylacetate (**4**).* $NaBH_4$ (1.33 g, 35.2 mmol) and THF (60 mL) were added to a round-bottom flask, and the solution was cooled to 0 °C. A solution of iodine (3.72 g, 14.6 mmol) in THF (14 mL) was slowly added to this solution at a rate to maintain the internal temperature, <5 °C. 3,4,5-Trifluoro-(*S*)-phenylglycine (3 g, 14.6 mmol) was added in 1 portion, and the mixture was warmed to 55 °C for 16 h. The mixture was cooled to 23 °C, and MeOH was added until the batch became clear. The mixture was concentrated, and EtOAc (12 mL) was added. In a separate flask, (*R*)-mandelic acid (2.4 g, 15.8 mmol) was dissolved in EtOAc (24 mL) and MeOH (0.8 mL) and heated to reflux. The EtOAc solution containing amino alcohol was added to the mandelic acid solution and heated to reflux for 1 h before being cooled to 10 °C over 3 h. The solids were collected by vacuum filtration and dried over nitrogen, yielding mandelate salt **4** as a white solid (3.4 g, 68%), mp 163−165 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.40 (m, 4H), 7.27 (s, 2H), 7.20 (m, 1H), 6.68 (bs, 4H), 4.72 (s, 1H), 7.08 (m, 1H), 6.64 (s, 1H), 4.57 (s, 1H), 4.16 (dd, J = 5.7, 4.4 Hz, 1H), 3.61 (dd, J = 11.2, 5.0 Hz, 1H), 3.54 (dd, J = 10.7, 6.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 175.5, 150.4 (ddd, J = 246.8, 9.7, 3.7 Hz), 142.9, 138.5 (dt, J = 248.8, 15.8 Hz), 137.2, 128.1, 127.1, 126.9, 112.7 (dd, J = 17.2, 4.6 Hz), 73.6, 64.6, 55.6. HRMS calcd. for $C_8H_9F_3NO$ ($[M + H]^+$) 192.0631, found 192.0632. Chiral analysis performed on the free base of **4** using Chiralcel AD-RH column (4.6 × 150 mm, 3 um); isocratic elution (17% MeCN, 83% 5 mM $Na_2B_4O_7$, pH 9.2), 0−8 min, 1.00 mL/min, 25 °C, 99% ee.

*(S,E)-5-Chloro-N-(2-hydroxy-1-(3,4,5-trifluorophenyl)ethyl)-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)pentanamide (**17**).* Mandelate salt **4** (3.3 g, 9.62 mmol) was slurried in EtOAc (25 mL) and treated with 1 M NaOH (10 mL, 10 mmol) for 30 min. The stirring was stopped, and the aqueous layer was removed. To the resulting EtOAc layer containing the free base of **4** was added **3** (4.33 g, 9.64 mmol) at 25 °C. HOBT hydrate (738 mg, 4.82 mmol), *N*,*N*′-diisopropylethylamine (9.21 mL, 53 mmol), and EDCI-HCl (6.2 g, 67.5 mmol) were added at 25 °C. The reaction was stirred at 25 °C for 90 min. The reaction mixture was transferred to a separatory funnel and washed with saturated $NaHCO_3$ (3 × 30 mL), water (2 × 20 mL), and brine (1 × 20 mL) and dried over Na_2SO_4. The drying agent was removed by filtration, and the organic layer was concentrated to afford a pale yellow solid. The solid was treated with MTBE (20 mL) and stirred at 20−24 °C for 30 min. The solid material was collected by filtration and dried over nitrogen, yielding **17** as a white solid (4.06 g, 83%), mp 151−152 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (s, 1H), 7.37 (m, 1H), 7.07 (m, 4H), 6.91 (m, 3H), 5.03 (dd, J = 5.3 Hz, 1H), 4.03 (dd, J = 11.5, 3.6 Hz, 1H), 3.91 (dd, J = 11.6, 5.0 Hz, 1H), 3.83 (s, 3H), 3.56 (t, J = 6.1 Hz, 2H), 2.70 (t, J = 4.7 Hz, 2H); 2.26 (s, 3H), 1.98 (quintuplet, J = 6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 151.9, 151.2 (ddd, J = 250.1, 10.0, 3.7 Hz), 138.9 (dt, J = 251.0, 15.3 Hz), 138.1, 137.5, 136.9 (td, J = 4.4 Hz), 136.7, 135.9, 132.3, 125.8, 124.6, 121.6, 116.7, 112.8, 111.0 (dd, J = 16.7, 5.1 Hz), 64.5,

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J. Org. Chem. XXXX, XXX, XXX−XXX

56.0, 55.0, 44.9, 31.5, 25.8, 13.3. HRMS calcd. for $C_{25}H_{26}ClF_3N_3O_3$ ($[M + H]^+$) 508.1609, found 508.1604.

*(S,E)-1-(2-Hydroxy-1-(3,4,5-trifluorophenyl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one (**2**).* To a solution of **17** (3.5 g, 6.9 mmol) in THF (35 mL) was added NaOMe (559 mg, 10.4 mmol) at 25 °C. The reaction was stirred for 2 h at 25 °C. Saturated aqueous $NaHCO_3$ (40 mL) was added at 25 °C, and the reaction mixture was aged for 30 min (pH 8−9). The aqueous layer was extracted with ethyl acetate (3 × 25 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was removed by filtration, and the filtrate was concentrated to 10 mL, at which time the product crystallized from solution. The slurry was cooled to 10 °C and stirred for 12 h. The solids were collected by filtration and dried over nitrogen, yielding lactam **2** as a pale yellow solid (3.2 g, 97%), mp 158−160 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (s, 1H), 7.73 (s, 1H), 7.26 (s, 1H), 7.02 (m, 4H), 6.94 (s, 1H), 5.76 (dd, J = 6.5, 6.3 Hz, 1H), 4.19 (dd, J = 11.6, 5.2 Hz, 1H), 4.12 (dd, J = 11.5, 8.0 Hz, 1H), 3.86 (s, 3H), 3.42 (m, 1H), 3.18 (m, 1H), 2.82 (m, 1H), 2.30 (s, 3H), 1.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9, 151.9, 151.2 (ddd, J = 250.6, 9.9, 3.8 Hz), 139.0 (dt, J = 252.1, 15.1 Hz), 137.8, 136.7, 136.1, 135.4, 133.7 (td, J = 6.8, 4.7 Hz), 130.3, 126.2, 124.6, 122.1, 116.2, 113.7, 111.9 (dd, J = 16.6, 5.2 Hz), 61.4, 58.8, 55.7, 44.3, 26.3, 22.9, 13.4. HRMS calcd. for $C_{25}H_{24}F_3N_3O_3$ ($[M + H]^+$) 472.1842, found 472.1843.

*(S,E)-1-(2-(Aminooxy)-1-(3,4,5-trifluorophenyl)ethyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzylidene)piperidin-2-one (**19**).* Lactam **2** (3.0 g, 6.4 mmol) in THF (60 mL) was atmospherically distilled to 30 mL (internal temperature 64−67 °C) to reduce water content to 6 mol %. Triethylamine (5.4 mL, 38.4 mmol) was added, and the batch was cooled to −25 °C. Methanesulfonyl chloride (0.74 mL, 9.6 mmol) was added as a solution in THF (1 mL) at a rate such that the internal temperature did not exceed −15 °C. After addition was complete, the reaction mixture was stirred for 30 min between −25 and −15 °C. *N*-Hydroxyphthalimide (1.57 g, 9.6 mmol) was added as a solid in a single portion at −10 °C. The batch was warmed to 25 °C and aged for 18 h. Hydroxylamine (50% wt. solution in water, 0.75 mL) was added at 25 °C and aged for 2 h. 2-Methyltetrahydrofuran (2-Me-THF) was added (40 mL) at 25 °C, and the contents of the reaction were transferred to a separatory funnel. The mixture was washed with 5% aqueous $NaHCO_3$ (15 mL) at 25 °C followed by 5% aqueous NaCl (15 mL). The organic layer was treated with 15 g of 4 Å molecular sieves (8−12 mesh) for 18 h (KF < 0.1%). The molecular sieves were removed by filtration, and the 2-Me-THF was removed by vacuum distillation to a volume of 24 mL (internal temperature <30 °C) and maintained as a solution in 2-Me-THF for the next step. Yield in solution: 2.67 g, 86%.

*(S,E)-1-(2-Methoxy-4-((4-(3,4,5-trifluorophenyl)-3,4,7,8-tetrahydropyrido[2,1-c][1,2,4]oxadiazin-9(6H)-ylidene)methyl)-phenyl)-4-methyl-1H-imidazol-3-ium-hemi-(E)-3-carboxyacrylate (**1**).* To a solution of hexamethyldisilazane (2.2 mL, 10.8 mmol) in 2-Me-THF(5 mL) was added trimethylsilyl trifluoromethanesulfonate (1.95 mL, 10.8 mmol) at a rate to maintain an internal reaction temperature <20 °C. The solution of **19** (2.67 g, 5.4 mmol) in 2-Me-THF (24 mL) was added to the HMDS/TMSOTf solution at a rate to maintain the internal reaction temperature <20 °C. The reaction was warmed to 30 °C and aged for 12 h. HCl (3 N, 8 mL) was slowly added while maintaining the batch temperature below 30 °C. The resulting aqueous layer was extracted with MTBE 3 times (150 mL total), and the these combined aqueous layers were discarded. Isopropyl acetate (50 mL) was added to the aqueous layer followed by the addition of K_3PO_4 (30 g). The organic layer was removed, and the aqueous layer was extracted with IPAc (50 mL). The combined IPAc layers were washed with water and concentrated under vacuum. Isopropyl alcohol (10 mL) was added followed by a solution of fumaric acid (313 mg, 2.7 mmol) in isopropyl alcohol (4 mL). The mixture was heated to 60 °C and aged for 30 min. The solution was cooled to 40 °C and aged for 30 min, at which time the product crystallized from solution. The slurry was further cooled to 0 °C over 3 h, aged for 1 h at 0 °C, and then filtered. Hemifumarate **1** was dried under vacuum at 45 °C for 12 h, yielding **1** as a white solid (2.5 g, 4.7 mmol), mp 164−168 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 13.16 (s, 1H), 7.80 (s, 1H), 7.38 (m, 2H), 7.25 (m, 3H), 7.15 (s, 1H), 7.08 (m, 1H), 6.64 (s, 1H), 4.57 (s, 1H), 3.93 (dd, J = 91.4, 11.1 Hz, 2H), 3.86 (s, 3H), 3.09 (m, 2H), 2.78 (m, 2H), 2.16 (s, 3H), 1.78 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 166.5, 152.1, 151.5, 150.7 (ddd, J = 247.9, 9.8, 3.6 Hz), 138.5 (dt, J = 248.5, 15.7 Hz), 138.4 (td, J = 3.9 Hz), 137.2, 137.0, 134.5, 130.4, 126.7, 125.5, 125.3, 122.4, 117.1, 114.5, 112.0 (dd, J = 16.8, 4.5 Hz), 68.6, 59.2, 56.5, 48.0, 25.7, 23.1, 13.9. HRMS calcd. for $C_{25}H_{24}F_3N_4O_2^+$ ($[M + H]^+$) 469.1846, found 469.1861.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02979.

Spectroscopic data for compounds **6**, **16**, **4**, **3**, **17**, **2** and **1** (PDF)

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The authors declare no competing financial interest.

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J. Org. Chem. XXXX, XXX, XXX−XXX