Communication

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Synthesis, optimization and large-scale preparation of low-dose CNS-penetrant BACE inhibitor LY3202626 via a [3 + 2] nitrone cycloaddition

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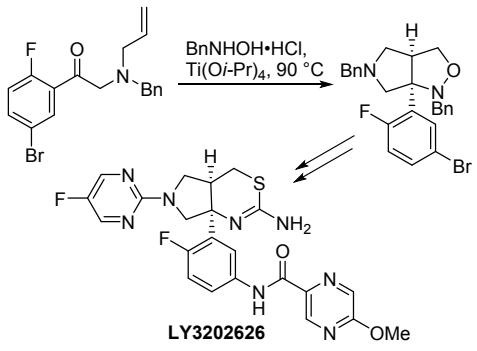


ABSTRACT: Herein we report a summary of the synthetic development for LY3202626 from the initial discovery route to a final route which was scaled to make 150 kg. Key developments include the use of a [3 + 2] cyclization to set the *cis*-ring junction of the formed isoxazoline, a one-pot thiazine formation and three different ways of installing the aniline: 1. Cu-azide coupling and reduction; 2. nitration and reduction and 3. Buchwald-coupling with acetamide.

KEYWORDS: BACE inhibitor, thermal nitrone cyclization, classical resolution, thiazine formation

We previously described the fragment-based discovery of thiazine **1**,[1] the first BACE1 inhibitor reported to demonstrate robust reduction of human CSF Aβ in a Phase 1 clinical trial, and subsequently bicyclic furano-thiazine LY2886721 (**2**), the first BACE1 inhibitor to reach Phase 2 clinical trials. We subsequently discovered a highly potent, low dose BACE1 inhibitor, LY3202626 (**3**, the focus of this paper),[2] which advanced to Phase 2 clinical trials as a potential treatment for Alzheimer's disease.

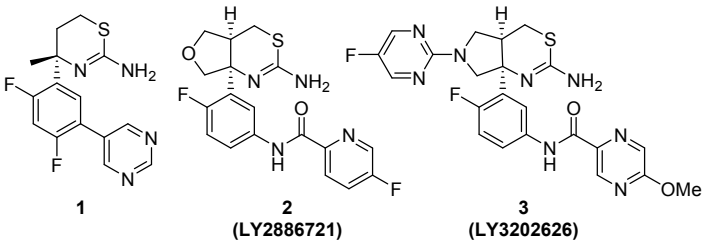
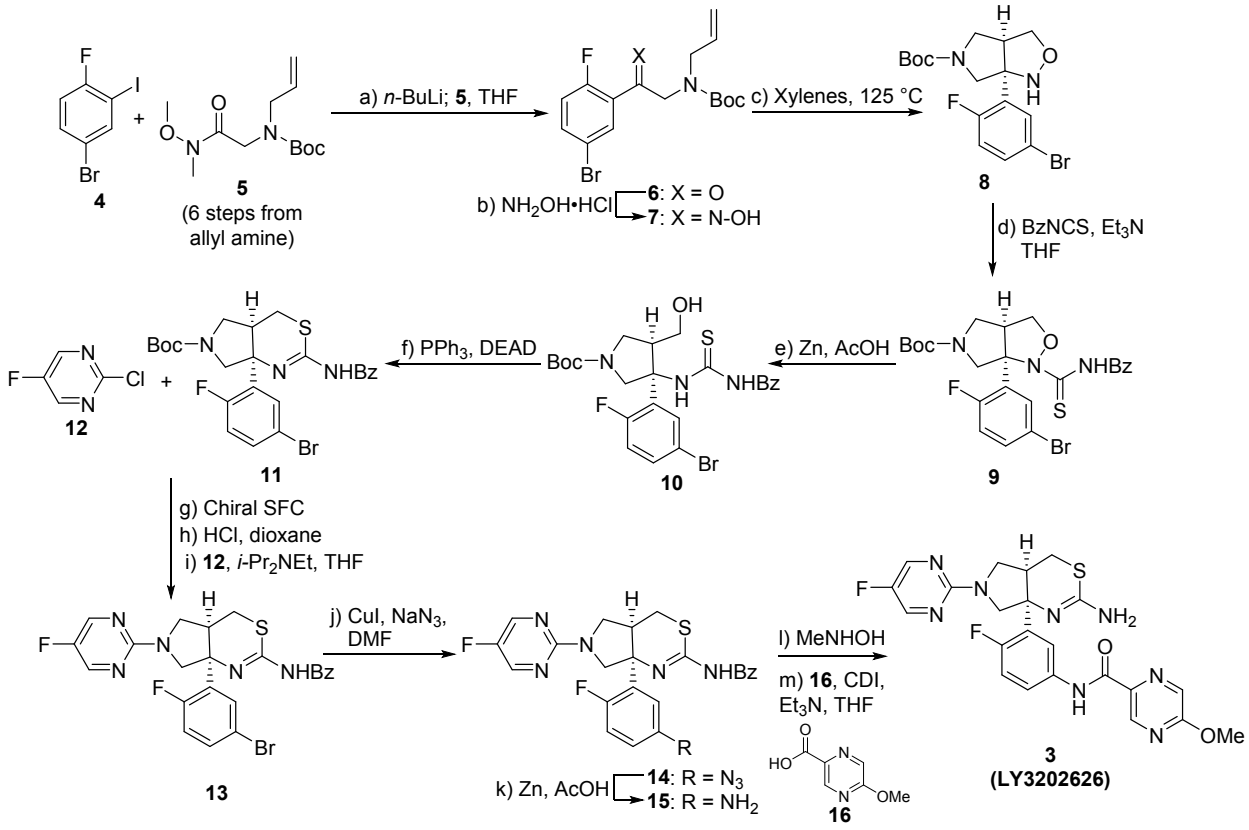


Figure 1. BACE1 clinical candidates **1**, **2** (LY2886721) and **3** (LY3202626).

The discovery route to LY3202626 (**3**, Scheme 1) leveraged knowledge that was gained from synthetic efforts towards **1** and **2**.[1,3] The route to prepare **3** began with the lithium-iodide exchange (*n*-BuLi) in 4-bromo-1-fluoro-2-iodo-benzene **4** followed by the condensation with Weinreb amide[4] **5** (available in six steps from allyl amine)[5] at –78 °C to afford ketone **6** in 45% yield after silica gel purification. The reaction suffered from debromination through the use of *n*-BuLi resulting in the low yield. The resulting ketone (**6**) was transformed into oxime **7** (NH_2OH•HCl, 75% yield), a compound that underwent [3 + 2] cycloaddition by heating to 125 °C to construct bicyclic isoxazoline **8** in 40% yield after silica gel chromatography. Although **8** was racemic, the cycloaddition was completely selective, setting the desired *cis*-stereochemistry at the ring junction.

Reaction of isoxazoline **8** with benzoyl isothiocyanate (BzNCS) afforded thiourea **9** in 70% yield after silica gel chromatography, which was exposed to zinc in acetic acid to cleave the N–O bond to arrive at primary alcohol **10** in 55% yield. Cyclization under Mitsunobu conditions (DEAD, PPh_3)[6] resulted in the formation of thiazine **11**. At this stage a chiral SFC purification was performed to remove the undesired enantiomer providing the desired isomer in 20% yield. Hydrolysis of the Boc carbamate protecting group followed by alkylation with pyrimidine **12** afforded aryl amine **13** in 55% yield over the two steps. Copper-mediated C-N coupling with copper (I) iodide and sodium azide[7] afforded aryl azide **14**. Reduction of the azide functionality with zinc in acetic acid provided aniline **15** in a disappointing 30% yield over the two steps.[8] Final benzoyl deprotection in the presence of methylhydroxyl amine, followed by CDI-mediated amide coupling with carboxylic acid **16** and terminal purification through reverse phase chromatography afforded the desired compound **3** (LY3202626) in 55% yield.



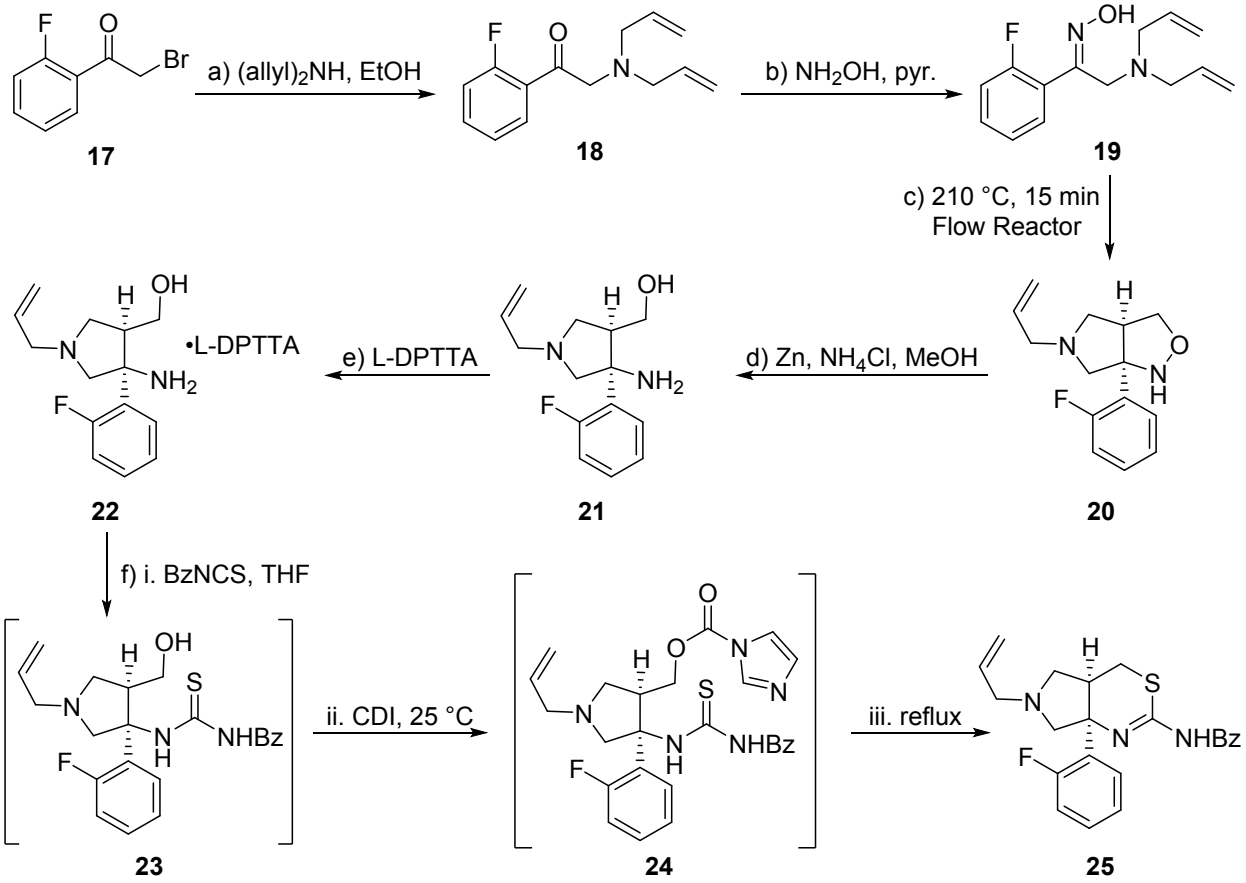
Scheme 1. Discovery approach towards compound **3**. Reagents and Conditions: a) *n*-BuLi, THF, –78 °C; 5; Silica Gel Chromatography, 45% yield; b) NH_2OH•HCl, KOAc, EtOH, 75% yield; c) Xylenes, 125 °C, 15 h; Silica Gel Chromatography, 40% yield; d) BzNCS, Et_3N, THF; Silica Gel Chromatography, 70% yield; e) Zn, AcOH; Silica Gel Chromatography, 50% yield; f) DEAD, PPh_3, THF; Silica Gel Chromatography; g) Chiral SFC, 20% yield over two steps; h) HCl, dioxane; i) **12**, *i*-Pr_2NEt, THF; Silica Gel Chromatography, 55% yield over two steps; j) NaN_3, CuI, DMF; k) Zn, AcOH; Silica Gel

Chromatography, 30% yield over two steps; l) MeNHOH•HCl, Et_3N EtOH; m) **16**, CDI, Et_3N, THF; Reverse Phase Chromatography, 55% yield over two steps.

While the initial discovery synthesis took advantage of some key transformations that were implemented during the development of **2** and allowed the delivery of milligram quantities of **3**, the route suffered from several shortcomings that needed to be addressed before providing kilogram quantities of **3**. The main points of focus were: 1) decrease safety critical operations, specifically potentially hazardous copper azide chemistry,[9] Mitsunobu conditions and cryogenic *n*-BuLi; 2) reduce the number of steps requiring chromatography, especially chiral SFC, focusing more on crystallizations for purification (original route used 9 chromatographic purifications); and 3) increase yields at several steps using more stable intermediates.

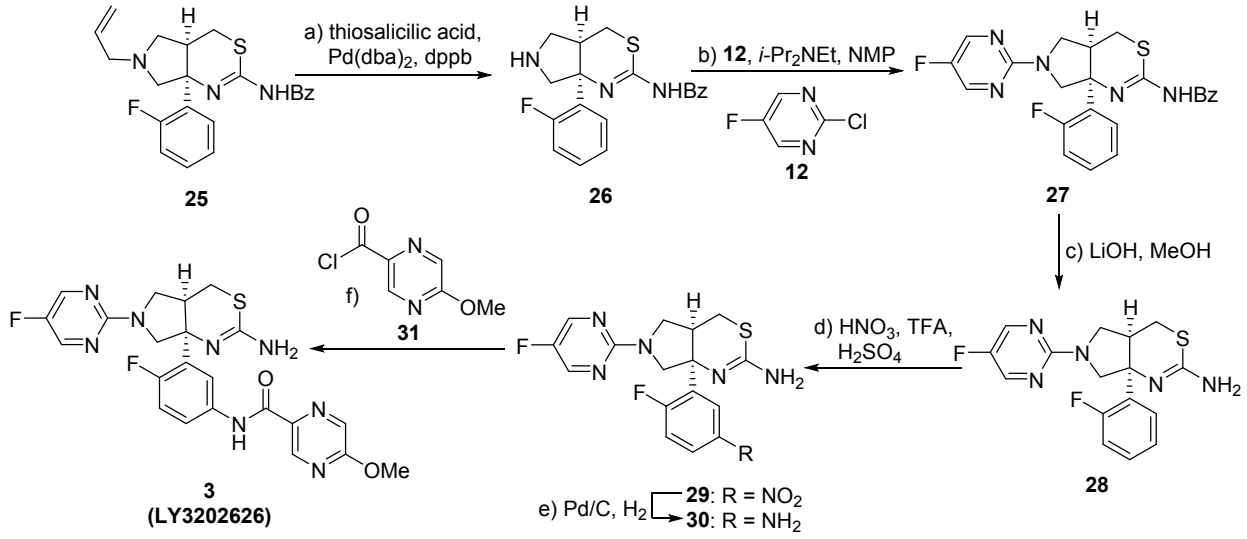
The new route started with fluorinated-aryl ketone **17**, as a fluorine-directed nitration and reduction was planned for aniline installation instead of the copper catalyzed azide coupling (Scheme 2). S_N2-displacement of the alkyl bromide with diallylamine yielded tertiary amine **18**, followed by treatment with NH_2OH•HCl to form

oxime **19**. Cyclization under thermal conditions at 210 °C using a plug flow reactor (PFR)[10] afforded bicyclic isoxazoline **20** in 55% total yield from alpha-bromoketone **17**. Higher temperatures and shorter reaction times were found to be beneficial to avoid significant decomposition as seen in Scheme 1. Development of this reaction has been previously described[11] and allowed for the preparation of material at a rate of 120 g/h, making multiple kilograms in total without safety issues or intermediate degradation. In order to remove chiral chromatography from the process a classical resolution[12] was targeted. A screen of chiral acids identified (–)-Di-*p*-toluoyl-L-Tartaric acid (L-DPTTA)[13] as a suitable resolving agent, producing the desired enantiomer **22** in 38% yield and 98% ee. Treatment of amino alcohol **22** with benzoyl isothiocyanate (BzNCS) provided the intermediate thiourea **23**. To avoid Mitsunobu conditions, carbonyl diimidazole (CDI) was used to activate the alcohol as the carbamate **24** which was heated to reflux to cyclize and form thiazine **25** in 98% yield over the telescoped process.



Scheme 2. Second generation route to intermediate **25**. Reagents and Conditions: a) $(allyl)_2NH$, EtOH; b) NH_2OH, pyr.; c) toluene, 210 °C, 15 min, plug flow reactor, 55% yield over 3 steps; d) Zn, NH_4Cl, MeOH, 18 h, reflux, 65% yield; e) L-DPTTA, MeO-2-propanol, 35% yield, 98% ee; f) i. BzNCS, THF, 0 °C; ii. CDI, 25 °C; iii. reflux, 18 h, 98% yield.

Initial studies on the functionalization of thiazine **25** found that it was prone to hydrolysis and ring opening (believed to be the corresponding thiol-urea) and appropriate conditions for the remaining steps were needed. Fortunately, allyl removal catalyzed by $Pd(dba)_2$ with dppb and thiosalicylic acid[14] as the reducing agent worked well to produce amine **26** (97% yield) which was reacted with pyrimidine **12** under basic conditions (*i*-Pr_2NEt) to form **27** in 95% yield. Nitration of **28** proceeded smoothly, provided the desired regioisomer (due to the fluoride directing effect[15]) with minimal hydrolysis under the reaction conditions (HNO_3, TFA, H_2SO_4). Hydrogenative reduction of the nitro to aniline **30** (85% yield over two steps) set the stage for the final step. Reaction of acid chloride **31** with diamine **30** afforded the desired product **3** (LY3202626) in 60% yield after a terminal silica gel chromatography.[3c]



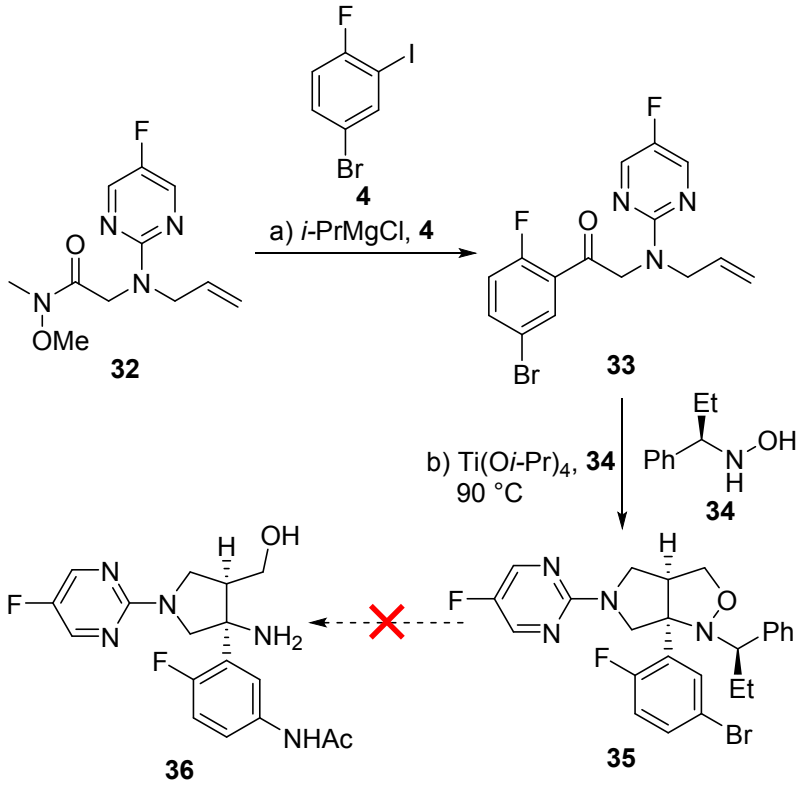
Scheme 3. Second generation route to **3**. Reagents and Conditions: a) thiosalicilic acid, $Pd(dba)_2$, dppb, 2-MeTHF, 40 °C, 16 h, 97% yield; b) **12**, *i*-Pr_2NEt, NMP, 100 °C, 18 h, 95% yield; c) LiOH, MeOH, 95% yield; d) HNO_3, H_2SO_4, TFA, 0 °C to 25 °C; e) Pd/C, H_2, EtOH, H_2O, 85% yield over 2 steps; f) **31**, EtOH, H_2O, CH_3CN; Silica Gel Chromatography, 60% yield.

The new route was successfully applied to make several hundred grams of **3**, addressing many of the previous concerns including: 1) removal of safety critical operations such as azide chemistry, Mitsunobu conditions, and cryogenic reactions; 2) reducing the synthetic length (26 steps improving to 12 steps); and 3) removing almost all of the chromatographic purifications including the chiral separation of diastereomers

by developing crystallizations. However, scaling up to multi-kilogram scale drove us to explore other improvements such as a later installation of the thiazine ring and Buchwald coupling to install the aniline to avoid the previously observed hydrolysis risk. Some effort was also spent on developing an enantioselective route to avoid the resolution and chiral SFC purifications previously used.

Although many enantioselective routes were explored, none of them proved more efficient than a classical resolution. The most promising route was the use of a chiral hydroxylamine as depicted in Scheme 4. A Grignard reaction between aryl iodide **4** and Weinreb amide **32** formed ketone **33** in 78% yield. Reacting ketone **33** with chiral hydroxylamine **34** in the presence of titanium isopropoxide resulted in the [3 + 2] cycloaddition to form **35** in an unoptimized 60% yield. As observed previously, the cis-ring junction was formed selectively, unfortunately the diastereomeric ratio (dr) was only 3:1. Further complicating the route, the planned N–O cleavage/debenzylation did not provide the desired product under numerous conditions. Smaller chiral auxiliaries could be cleaved (eg. Me vs Et at the benzylic position of the chiral hydroxylamine) but dr was

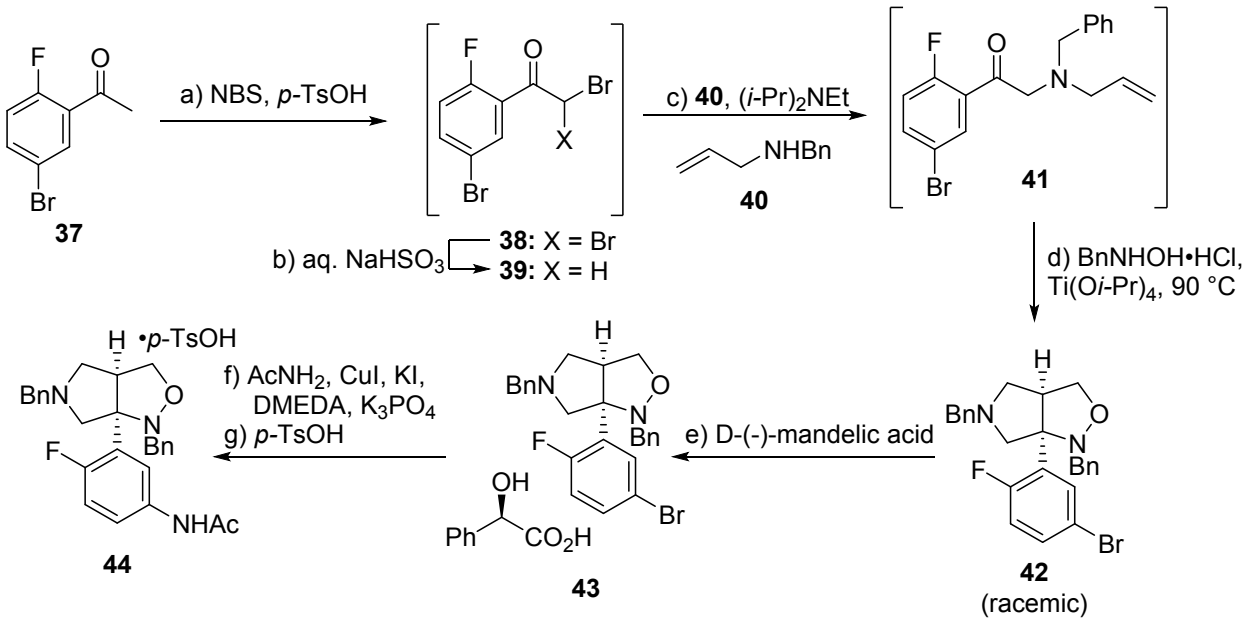
typically near 1:1 making the route no more attractive than the previous route using a resolution. As a result, a classical resolution remained in the route as the means to obtain a single enantiomer. One learning from the route development that was impactful was that using alkyl hydroxylamines decreased the temperature required for cyclization and resulted in higher stability and higher yields.



Scheme 4. Failed attempt at an enantioselective route. Reagents and Conditions: a) **4**, *i*-PrMgCl, THF, –30 °C, 78% yield; b) Ti(O*i*-Pr)$_4$, toluene, 90 °C, 60% yield, 3:1 dr.

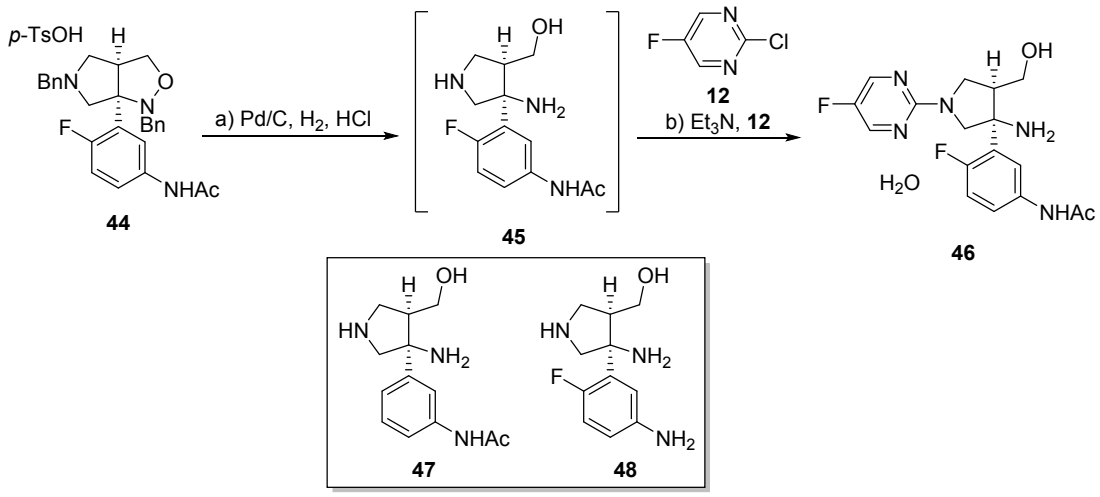
The new route started with α-bromination of 5-bromo-2-fluoro-acetophenone **37** to afford the desired mono-brominated compound **39** with roughly 10% of the dibrominated species (**38**, Scheme 5). Aqueous work-up with $NaHSO_3$ was sufficient to convert all of the dibromo-species **38** to monobrominated product **39**, with a total yield of 91%. Allylation with benzylallylamine (**40**)[16] afforded intermediate tertiary amine **41**, and addition of hydroxylbenzylamine and $Ti(O\mathit{i}Pr)_4$ at 90 °C resulted in the [3 + 2] nitrone cycloaddition product **42** in 75% yield over the two steps. The nitrone cycloaddition was more facile than the previously used oxime cycloaddition allowing lower temperatures (90 °C vs. 210 °C) without the decomposition observed in Scheme 1 providing a higher yield (75% vs 40%). Only a single isomer is observed during the cyclization, however the material is racemic and a resolution with D-mandelic acid was necessary to provide enantiopure intermediate **43** in a 40% yield with enantiomeric excess greater than 99.5%. Differing from the previous routes, the aniline would be installed prior to thiazine formation to minimize the risk of hydrolysis. Amidation was accomplished through modified Buchwald-type conditions (CuI, KI, DMEDA, K_3PO_4) with acetamide to forge the desired

C–N bond,[17] and the product **44** was crystallized as a *para*-toluenesulfonic acid salt in 77% yield over the two operations.



Scheme 5. Synthesis of intermediate **44** for the final route. Reagents and Conditions: a) NBS, *p*-TsOH, CH_3CN; b) aq. $NaHSO_3$, 91% over 2 steps; c) **40**, (*i*-Pr)$_2$NEt, toluene; d) BnNHOH•HCl, Ti(O*i*-Pr)$_4$, toluene, 90 °C, 75% yield over 2 steps; e) D-(–)-mandelic acid, CH_3CN, 40% yield; f) $AcNH_2$, CuI, KI, DMEDA, K_3PO_4, DMF; g) *p*-TsOH, IPA, 77% yield.

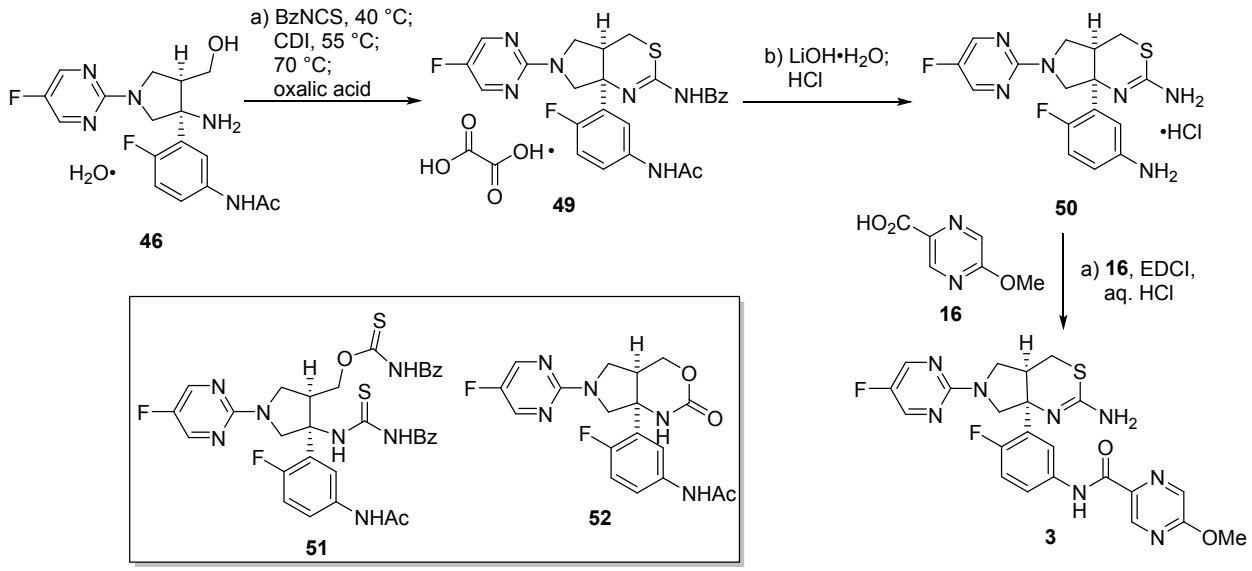
With the aniline functionality in place, the next steps were to convert the isoxazoline ring to the desired thiazine. Opening of the isoxazoline with concomitant bis-debenzylation worked well under hydrogenative conditions (Pd/C, H_2) to give intermediate amino alcohol **45**, however two major by-products needed to be controlled, des-fluoro **47** and des-acetyl **48** (Scheme 6). Of the two, des-fluoro **47** was more problematic as it would not purge in the subsequent steps and isolations. Key to limiting the de-fluorination was the presence of HCl during the reduction as it was only observed under basic conditions. The des-acetyl could not be avoided, but fortunately could be rejected in the crystallization of product **46**. If levels of the des-acetyl by-product were too high, a reslurry with ethyl acetate and heptane could further reduce to non-detect levels. With the by-products understood and controllable, the reduction product **45** could be telescoped in to the subsequent S_NAr with chloropyrimidine **12** with triethylamine to afford arylamine **46** in 67% yield.[18]



Scheme 6. Synthesis of intermediate **46** for the final route. Reagents and Conditions: a) Pd/C, H_2, MeOH, HCl, 87% yield; b) **12**, Et_3N, MeOH, 67% yield.

The formation of the thiazine proceeded well with the acetamide in place (Scheme 7). Similar to Scheme 2, the thiazine ring could be formed through a step-wise charge of benzoyl isothiocyanate to form the intermediate thioamide (not pictured), followed by activation of the alcohol via the carbamate with CDI and then heating to 70 °C to effect thiazine cyclization providing **49** which was isolated as the oxalic acid salt in 87% yield. Controlling stoichiometry is important for this reaction as over-charging of the BzNCS affords the double addition product **51** whereas undercharging results in carbamate **52**.

Both impurities have poor rejection in the final steps and must be controlled through precise charging of BzNCS. One-pot removal of the benzoate protecting group ($LiOH•H_2O$ in MeOH) followed by acetate removal through a pH adjustment with HCl afforded diamine **50** as the HCl salt in 87% yield over the two steps. The final bond-forming step was an acylation with carboxylic acid **16** mediated by EDCI. This reaction proved quite selective, but highly pH dependent. If the acylation was attempted with the freebase of **50** a mixture of amidation on the thiazine ring and the aniline were produced along with the bis-amide. However, the presence of 1.0 equiv. of HCl served to “protect” the thiazine amine and the sole product would be the desired product **3** in 95% yield as the freebase.



Scheme 7. Synthesis of **3** through the final route. Reagents and Conditions: a) BzNCS, THF, 40 °C; CDI, 55 °C; 70 °C; oxalic acid, 84% yield; b) LiOH•H_2O, MeOH, H_2O; aq. HCl, 87% yield; c) **16**, EDCI, aq. HCl, MeOH, 95% yield.

In conclusion, the synthetic route optimization for BACE1 Inhibitor LY3202626 (**3**) has been described. Key developments include the optimization of the [3 + 2] cycloaddition, first through the implementation of flow chemistry (allowing higher temperatures with shorter reaction times) and later through the use of benzylhydroxylamine with titanium isopropoxide to increase the yield further allowing a lower temperature for cyclization. Additionally, conditions for an optimized thiazine

cyclization were developed and optimized in total. The result is a dramatically improved route which decreased the number of steps from 26 to 9, increased safety and overall yield.

EXPERIMENTAL SECTION

42: To a 8000 L glass-lined reactor was charged acetonitrile (1450 kg), **37** (265.1 kg, 1.0 equiv., 1221 mol) and *p*-TsOH (347 kg, 1.5 equiv., 1824 mol) under nitrogen at 15–30 °C. To the stirred solution was charged *N*-bromosuccinimide (262 kg, 1.2 equiv., 1469 mol) in portions, maintaining a temperature ≤30 °C. The resulting mixture was stirred at 20–30 °C for 8 hours and to the completed reaction (**37** ≤1.0% by HPLC) was charged aqueous $NaHSO_3$ (20% aq. solution, 1521 kg). The resulting biphasic mixture was stirred at 20–30 °C for 2 hours and then extracted with toluene (1614 kg). The aqueous layer was separated and further extracted with toluene (692 kg). The organic layers were then combined and washed with aqueous $NaHCO_3$ (20% aq. solution, 1350 kg) and then water (1060 kg). The organic phase was concentrated under reduced pressure (internal temperature ≤60 °C) until 700–1000 L remained and the light-yellow solution of **39** (326.7 kg potency corrected, 91% yield, 1110 mol) without further purification.

To a 8000 L glass-lined reactor was charged a toluene solution of **40** (195.8 kg potency corrected, 1.2 equiv., 1330 mol), toluene (1561 kg), diisopropylethylamine (215 kg, 1.5 equiv., 1663 mol) under a nitrogen atmosphere at 15–30 °C. The mixture was purged with nitrogen at 15–30 °C for 30 minutes and then heated to 60–65 °C. To the heated solution was charged a toluene solution of **39** (from above, 327 kg potency corrected, 1.0 equiv., 1110 mol) over the course of one hour. The solution was stirred at 60–65 °C for 3 hours and the completed reaction solution (**39** ≤3.0% by HPLC) was cooled to 0–5 °C to obtain **41** as a solution in toluene which was telescoped into the next step without isolation.

To the cooled solution of **41** obtained above was charged BnNHOH•HCl (212.2 kg, 1.2 equiv., 1330 mol), diisopropylethylamine (214.8 kg, 1.5 equiv., 1660 mol) and $Ti(O\textit{i}\text{-}Pr)_4$ (535.6 kg, 1.7 equiv., 1885 mol). The resulting mixture was heated to 60–70 °C for 3 hours and the completed reaction (**41** ≤0.5% by HPLC) was cooled to 15–20 °C. The solution was quenched by the addition

of aqueous citric acid (50% aq. solution, 822 kg) and the resulting biphasic mixture was stirred for 6 hours. The mixture was neutralized to a pH 7–8 by the addition of 20% aqueous Na_2CO_3 and stirred for 1 h. The aqueous phase was removed and extracted with toluene (1136 kg). The combined organic phases were washed with 20% aq. $NaHCO_3$ (292 kg) and water (1650 kg). The organic layer was concentrated under reduced pressure (internal temperature ≤60 °C) to 1500–2000 L. The concentrated solution was filtered through celite (50 kg) and rinsed with toluene (555 kg) twice. The filtered solution was concentrated under reduced pressure (internal temperature ≤60 °C) to 500–800 L and then diluted with MeOH (1300 kg). The concentration and dilutions were repeated until toluene ≤2.0% by GC. The mixture was stirred for 4–8 hours at 20–30 °C, then cooled to 0–10 °C and stirred for an additional 2 hours. The cooled slurry was filtered and the collected solid was washed with MeOH (186 kg) three times and the solid was dried under vacuum at 30–40 °C to afford **42** (387.9 kg, 75% yield, 833 mol) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.66 (dd, *J* = 6.8, 2.0 Hz, 1 H), 7.56–7.52 (m, 1 H), 7.39–7.33 (m, 4 H), 7.30–7.17 (m, 7 H), 4.13 (t, *J* = 8.0 Hz, 1 H), 3.86 (d, *J* = 14.4 Hz, 1 H), 3.68–3.61 (m, 4 H), 3.38 (br s, 1 H), 3.15 (d, *J* = 10.0 Hz, 1 H), 2.79–2.67 (m, 3 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.5, 159.0, 155.4, 139.3, 139.2, 132.7, 132.6, 132.5, 132.4, 128.8, 128.4, 127.4, 127.2, 119.2, 119.0, 116.5, 77.7, 71.9, 59.0, 58.5, 54.9 ppm.

43: To a 8000 L glass-lined reactor was charged **42** (395.8 kg, 1.0 equiv., 850 mol) and acetonitrile (2185 kg) under a nitrogen atmosphere at 15–30 °C. The mixture was stirred to ensure complete dissolution of **42** and then heated to 65–70 °C. A solution of D-(–)-mandelic acid (128.8 kg, 1.0 equiv., 850 mol) in acetonitrile (936 kg) was added dropwise at 65–70 °C. The resulting mixture was stirred for 1 hour at 65–70 °C and then slowly cooled to 45 °C over 4–8 hours. To the heated solution was added seed of **43** (0.4 kg, 0.001 equiv., 0.6 mmol) and the thin slurry was cooled to 20–25 °C and stirred for an additional 20 hours. The resulting slurry was filtered and the collected solid was washed with cold acetonitrile (625 kg) and dried under reduced pressure at 25–35 °C to give **43** (210.1 kg, 40% yield, 340 mol) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.67–7.65 (m, 1 H), 7.57–7.52 (m, 1 H), 7.43–7.33 (m, 8 H), 7.30–7.18 (m, 8 H), 5.02 (s, 1 H), 4.13 (t, *J* = 8.0 Hz, 1 H), 3.86 (d, *J* = 14.4 Hz, 1 H), 3.70–3.60 (m, 4 H), 3.39 (br s, 1 H), 3.16 (d, *J* = 10.4 Hz, 1 H), 2.81–2.69 (m, 3 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.6, 161.5, 159.0, 140.7, 139.1, 132.7, 132.6, 132.5, 132.4, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.5, 127.2, 127.1, 119.2, 119.0, 116.5, 77.7, 72.8, 71.9, 59.0, 58.5, 54.9 ppm.

44: To a 5000 L glass reactor was charged **43** (240.3 kg, 1.0 equiv., 388 mol), aqueous NaOH (5% aq. solution, 960 kg) and toluene (1674 kg) at 15–30 °C. The biphasic mixture was stirred at 15–30 °C for 2 hours. The aqueous phase was removed and extracted with toluene (836 kg). The combined organic phases were washed with water (960 kg) twice and concentrated under reduced pressure (internal temperature ≤70 °C) to 275–460 L. The solution was cooled to 15–30 °C and to

it was charged DMF (344.2 kg). The solution was concentrated and diluted with DMF until residual toluene is no more than 20% by GC.

To the freebased DMF solution of **43** was charged additional DMF (570 kg), acetamide (98.4 kg, 4.3 equiv., 1666 mol), KI (45.6 kg, 0.7 equiv., 274.7 mol), K_3PO_4 (180.6 kg, 2.2 equiv., 850.8 mol) and *N*,*N'*-dimethylethylenediamine (26.4 kg, 0.8 equiv., 300 mol). Nitrogen was bubbled through the solution for 30 minutes at 25 °C to purge out oxygen. To the degassed solution was charged CuI (21.1 kg, 0.3 equiv., 110.8 mol) and the reaction was heated to 95–105 °C for 14 hours. The resulting suspension was cooled to 20–30 °C and added to a solution of aqueous ammonium chloride (10% aq. solution, 2340 kg) in a separate 8000 L glass-lined reactor. The reactor was rinsed with EtOAc (816 kg) and the resulting biphasic mixture was separated. The aqueous phase was extracted with EtOAc (490 kg) and the combined organic layers were combined and washed with aqueous LiCl (20% aq. solution, 1440 kg) and water (960 kg). The organic phase was concentrated under reduced pressure (internal temperature ≤50 °C) until 275–459 L remained. IPA (801 kg) was added and the mixture was concentrated under reduced pressure (internal temperature ≤50 °C) until 275–459 L remained. The dilution and concentrations continued until residual EtOAc and toluene were both ≤5% by GC. The resulting light-yellow solution was used directly in the next step without isolation.

The IPA solution above was transferred to a separate 5000 L glass-lined reactor along with an additional IPA rinse (560 kg). To the solution at 20–30 °C under a N_2 atmosphere was charged a solution of *p*-TsOH (36.8 kg, 0.5 equiv., 193 mol) in IPA (236 kg). To the solution is then charged **44** seed (0.8 kg, 0.005 equiv., 194 mmol) and the mixture was stirred until precipitation was observed. To the slurry was charged an additional solution of *p*-TsOH (47.8 kg, 0.65 equiv., 252 mol) in IPA (306 kg). The slurry was stirred for 4 hours and the solid was collected by filtration, washed with IPA (356 kg) and dried at 35–45 °C under vacuum to afford **44** (184.5 kg, 77% yield, 299 mol) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.1 (s, 1 H), 7.58–7.47 (m, 9 H), 7.27–7.21 (m, 7 H), 7.12–7.10 (m, 2 H), 4.48 (dq, *J* = 12.8, 4.0 Hz, 2 H), 4.30 (t, *J* = 7.6 Hz, 1 H), 4.01–3.97 (m, 1 H), 3.79–3.71 (m, 3 H), 3.66 (d, *J* = 14.8 Hz, 1 H), 3.61–3.53 (m, 2 H), 2.98 (d, *J* = 14.8 Hz, 1 H), 2.29 (s, 3 H), 2.06 (s, 3 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.9, 146.2, 138.0, 137.5, 136.2, 131.6, 130.8, 130.1, 129.4, 129.2, 128.5, 128.4, 127.5, 126.0, 121.6, 116.7, 76.1, 76.0, 71.8, 58.9, 58.8, 57.4, 57.3, 55.2, 52.4, 26.0, 24.4, 21.2 ppm.

46: To a 5000 L glass-lined flask under a nitrogen atmosphere at 15–20 °C was charged **44** (182.8 kg, 1.0 equiv., 296 mol), MeOH (1592 kg), concentrated HCl (35.8% HCl in water, 33.5 kg, 1.1 equiv.) and 10% Pd/C (50% water wet, 83.2 kg, 45% kg/kg). The stirred mixture was purged with nitrogen five times and then exchanged with hydrogen five times. The reaction mixture was stirred with a hydrogen pressure of 0.01 MPa at 15–20 °C for 14 hours. The completed reaction (≤1.0% **44** by HPLC) was purged with nitrogen and then passed through an in-line filter into an 8000 L glass lined reactor. To the filtered solution was charged Et_3N (90.5 kg, 3.0 equiv., 894.4 mol) and water (83.5 kg). The combined filtrate was transferred to a 3000 L glass-lined reactor and concentrated under reduced pressure (internal temperature <45 °C) to 500–600 L and the resulting solution of **45** was carried into the subsequent step without isolation.

To the solution of **45** obtained above at 15–20 °C was charged Et_3N (89.5 kg, 3.0 equiv., 844.5 mol) and **12** (43.5 kg, 1.1 equiv., 328.3 mol). The reaction solution was heated to 55–65 °C and stirred for 12 hours. The completed reaction (residual **45** ≤1.0% by HPLC) was cooled to 15–20 °C and to it was slowly charged an aqueous solution of NaOH (30% aq. solution, 34.1 kg) to obtain a pH of 9–9.5. The reaction mixture was concentrated under reduced pressure (temperature ≤45 °C) to 300–350 L. To the concentrated mixture at 15–30 °C was charged a solution of aqueous NaCl (15% aq. solution, 455 kg). The resulting mixture was stirred for 1 hour at 15–25 °C and an additional 12 hours at 0–10 °C to allow product to crystallize. The precipitated product was filtered and washed with water (~120kg) twice. The filter cake was dried under reduced pressure at 50–60 °C until KF ≤10%. The dried solid and EtOAc (285 kg) were added to a 1000 L glass-lined reactor and then heated to 45–55 °C for 2 hours. To the heated solution was added n-heptane (108 kg) and the mixture was stirred for 2 hours. The slurry was cooled to 15–20 °C and stirred for an additional 5 hours and then filtered. The wetcake was rinsed with EtOAc:n-heptane (1:1, 125 kg) and then dried under reduced pressure (temperature 30–40 °C) to give **46** (65.7 kg, 58% yield, 172.5 mol) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.99 (s, 1 H), 8.43 (s, 2 H), 7.75–7.72 (m, 1 H), 7.65–7.62 (m, 1 H), 7.10 (dd, *J* = 12.0, 8.8 Hz, 1 H), 4.55 (br s, 1 H), 3.86–3.81 (m, 2 H), 3.68 (dd, *J* = 11.2, 2.8 Hz, 1 H), 3.55–3.51 (m, 3 H), 2.87–2.81 (m, 1 H), 2.03 (s, 3 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.6, 157.9, 157.5, 155.1, 153.1, 150.7, 145.8, 135.8, 120.0, 116.5, 61.6, 61.2, 59.9, 50.3, 48.5, 24.3 ppm.

49: To a 3000 L glass-lined reactor was charged **46** (72.3 kg, 1.0 equiv., 189.7 mol) and THF (969.6 kg) under a nitrogen atmosphere at 20–30 °C. The stirred solution was heated to 40–50 °C for 1 hour and to the solution was added a solution of BzNCS (32.3 kg, 1.03 equiv., 194.8 mol) in THF (130.3 kg) dropwise and the solution was stirred at 40–50 °C for 1 hour. The solution is analyzed by HPLC and additional BzNCS is added if **46** ≥1.0%, otherwise the stirred solution is heated to 55–70 °C. To the heated solution is charged CDI (33.0 kg, 1.0 equiv., 190 mol) in 3–5 portions and the solution was stirred for 1 hour. The solution is analyzed by HPLC and additional CDI is added if the intermediate is ≥1.0%, otherwise the solution is concentrated under reduced pressure (temperature ≤40 °C) to 150–250 L. To the concentrated solution was charged EtOAc (330 kg). The concentration and EtOAc additions are repeated until THF ≤5.0% by GC. The solution was washed with aqueous citric acid (10% aq. solution, 365 kg) twice followed by aqueous NaCl (20% aq. solution, 730 kg) twice. The resulting organic solution was concentrated under reduced pressure (temperature ≤40 °C) to ~150–250 L and diluted with acetonitrile (290 kg). The concentrations and acetonitrile additions are repeated until residual EtOAc ≤1.0% by GC. The solution was heated to 25–35 °C and to the stirred solution was charged a solution of oxalic acid (24.1 kg, 1.0 equiv., 190 mol) in acetonitrile (289 kg) at a rate of 100–200 kg/hr. The resulting mixture was cooled to –5–5 °C and stirred for 20 hours. The slurry was filtered and the wetcake was washed with acetonitrile (100 kg) and then dried under reduced pressure (temperature ≤35 °C to obtain **49** (95.3 kg, 84% yield, 159.3 mol) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.10 (s, 1 H), 8.49 (s, 2 H), 8.04 (d, *J* = 7.6 Hz, 2 H), 7.80–7.76 (m, 1 H), 7.55–7.49 (m, 2 H), 7.44 (t, *J* = 7.2 Hz, 2 H), 7.23 (dd, *J* = 12.0, 8.8 Hz, 1 H), 4.18 (d, *J* = 12.0 Hz, 1 H), 4.08 (d, *J* = 11.2 Hz, 1 H), 3.84 (dd, *J* = 10.8, 8.0 Hz, 1 H), 3.68 (dd, *J* = 10.8,

8.0 Hz, 1 H), 3.35–3.33 (m, 1 H), 3.12 (dd, *J* = 13.6, 5.2 Hz, 1 H), 2.97 (dd, *J* = 13.6, 3.6 Hz, 1 H), 2.00 (s, 3 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.8, 161.4, 157.7, 156.6, 154.2, 153.5, 151.1, 146.3, 146.0, 136.4, 132.2, 129.2, 128.5, 121.1, 119.9, 117.6, 117.4, 64.4, 64.3, 57.6, 48.8, 24.4, 24.3 ppm.

50: To a 3000 L glass-lined reactor was charged MeOH (360 kg) and water (360 kg) under a nitrogen atmosphere at 20–25 °C. To the stirred solution was charged LiOH•H_2O (19.0 kg, 3.2 equiv., 452.8 mol) and then **49** (85.5 kg, 1.0 equiv., 142.8 mol), and the mixture was heated to reflux (approximately 60–70 °C) for 6 hours. The completed reaction mixture (**49** ≤ 0.5% by HPLC) was cooled to 30–40 °C and to it was slowly charged concentrated HCl (30% aq., 219.6 kg, 15.2 equiv., 2168 mol). The resulting solution was heated to 60–70 °C for 7 hours. The completed reaction (intermediate ≤0.5% by HPLC) was cooled to 30–40 °C and concentrated under reduced pressure (temperature ≤45 °C) to 600–650 L. The residual solution was cooled to 15–30 °C and diluted with water (721 kg) and then extracted with toluene (393 kg) twice to remove the organic impurities. The aqueous layer (containing **50**) was pH adjusted to 6–8 at 15–30 °C with 30% aqueous NaOH and then diluted with 2-MeTHF (388 kg). The pH of the biphasic mixture was adjusted to 11–13 with 30% aqueous NaOH and the organic phase was removed. The aqueous phase was extracted with 2-MeTHF (384 kg) twice and the combined organic layers were washed with water (450 kg) twice. The solution was concentrated under reduced pressure (temperature ≤45 °C) to 150–250 L. The concentrated solution was diluted with 2-MeTHF (360 kg) and the concentrations and 2-MeTHF additions are continued until KF ≤1.0%. The solution was heated to 40–50 °C and to it was charged a solution of HCl in 2-MeTHF (5.4% anhydrous HCl in 2-MeTHF, 95 kg, 1.0 equiv., 142.8 mol) dropwise at 40–50 °C. The resulting mixture was cooled to 15–25 °C and stirred for 4 hours. The slurry was filtered and the solid was washed with cooled 2-MeTHF (350 kg) and then dried under reduced pressure at 40–50 °C to obtain **50** (49.2 kg, 87% yield, 123.5 mol) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.83 (br s, 1 H), 8.52 (s, 2 H), 6.98 (dd, *J* = 12.4, 8.4 Hz, 1 H), 6.60–6.57 (m, 1 H), 6.47 (dd, *J* = 7.2, 2.4 Hz, 1 H), 5.23 (br s, 2 H), 4.19 (d, *J* = 12.0 Hz, 1 H), 4.03 (d, *J* = 12.0 Hz, 1 H), 3.77 (dd, *J* = 11.2, 7.2 Hz, 1 H), 3.59 (dd, *J* = 11.2, 7.2 Hz, 1 H), 3.40 (dd, *J* = 13.2, 6.4 Hz, 1 H), 3.33–3.27 (m, 1 H), 3.16 (dd, *J* = 13.2, 3.2 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.1, 157.4, 153.6, 151.2, 150.4, 146.4, 146.1, 146.0, 117.9, 117.7, 115.3, 112.7, 63.8, 56.3, 48.6, 24.8 ppm.

3: To a 3000 L Reactor at 20–30 °C was charged water (437 kg), MeOH (367 kg) and **50** (50 kg, 1.0 equiv., 125.6 mol). The pH of the solution was adjusted to 3.7–3.9 (this pH represents ~1.2 equiv. HCl and serves to "protect" the second amine) by the addition of either 30% aq. NaOH or 33% aq. HCl. To the solution was charged **16** (20.3 kg, 1.05 equiv., 132 mol) and EDCI (28.8 kg, 1.5 equiv., 185.6 mol). The reaction mixture was stirred at 20–30 °C for 2 hours. To the completed reaction (residual **50** ≤1.0%, if not complete more EDCI could be added) is charged water (25 kg) and MeOH (20 kg). The mixture was heated to 45–55 °C and over ~8 hours was charged 5% aq. NaOH (approximately 200 kg) to reach a pH between 8–10. The resulting slurry is stirred at 45–

55 °C for an additional 2 hours and then filtered. The wetcake is washed with water (200 kg) four times and the wetcake is dried under reduced pressure (jacket temperature 30–45 °C) to obtain **3** (59.4 kg, 95% yield, 119.3 mol) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.58 (s, 1 H), 8.88 (s, 1 H), 8.44 (s, 2 H), 8.40 (s, 1 H), 7.87–7.82 (m, 2 H), 7.19 (dd, *J* = 12.0, 8.8 Hz, 1 H), 6.06 (br s, 2 H), 4.07 (d, *J* = 10.8 Hz, 1 H), 4.02 (s, 3 H), 3.81–3.77 (m, 1 H), 3.72 (dd, *J* = 10.4, 7.6 Hz, 1 H), 3.63 (dd, *J* = 10.8, 8.8 Hz, 1 H), 3.12–3.03 (m, 3 H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.1, 162.0, 157.9, 157.8, 155.3, 153.2, 150.8, 146.1, 145.9, 142.0, 138.4, 134.9, 134.0, 130.7, 122.8, 121.7, 117.0, 116.7, 64.4, 54.8, 48.8, 24.1 ppm.

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