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Development of a Pilot-Plant Process for a Nevirapine Analogue HIV NNRT Inhibitor

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Abstract:

The pilot-plant synthesis of nevirapine analogue 1 is described. The compound was prepared in eight steps from substituted pyridine raw materials and 4-hydroxyquinoline. The key transformation involves a novel one-pot conversion of an arylhalide to arylacetic acid under palladium catalysis, followed by regioselective reduction via *in situ* generated BH_3/THF to the arylethanol intermediate 2. All stages were carried out on 10−150-kg scale.

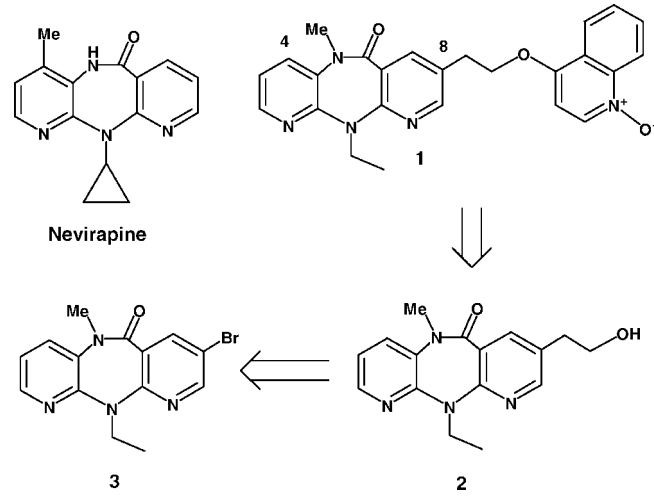
Introduction

Nevirapine is a non-nucleoside reverse transcriptase inhibitor marketed for the treatment of HIV infection. Compound **1** is an analogue of nevirapine which was selected for further evaluation.[1a] The structures of nevirapine and analogue **1** are shown in Scheme 1. The tricyclic cores of each are nearly identical, the only differences being migration of the methyl substituent from the 4- to the 5-position, and replacement of the *N*-cyclopropyl substituent by *N*-ethyl in **1**. The principal change is the installation at the 8-position of the two carbon ether linkage with a 4-quinoline-*N*-oxide terminus. Tricyclic halides similar to **3** were recognized early on[1] as valuable platforms for functionalization of the 8-position in these systems, and thus bromide **3** was considered to be a potential advanced intermediate for the synthesis of **1**.

Results and Discussion

Condensation of the acid chloride of 5-bromo-2-hydroxynicotinic acid[1d] **4** with 2-chloro-3-aminopyridine furnished bromodichloroamide **5** in nearly quantitative yield. Nucleophilic aromatic substitution with ethylamine then led regiospecifically to amide **6**. Cyclization and N-methylation were achieved in a one-pot transformation with NaHMDS as base, furnishing bromide **3** in 80% yield for the step. Removal of excess MeI from the waste stream was achieved by distilling the volatiles into a solution of 4-picoline, which was readily quaternized. Haloaminopyridine derivatives are often highly colored by low levels of impurities, and charcoal treatment of **3** was required to provide the advanced intermediate as a yellow solid. The route described in Scheme 2 was used to prepare 350 kg of bromide **3**.

Scheme 1. **Retrosynthesis of 1**



Attempts at halogen metal exchange using bromide **3** were completely unsuccessful, including the use of alkyl lithiums, magnesium metal, and organomagnesium reagents which have specifically been used for the generation of pyridyl Grignards.[2a,b] The shortcomings of this approach are well illustrated by the reaction of **3** with *i*-PrMgBr with electrophile quenching shown in Scheme 3.

Rather than effecting the desired bromine−magnesium exchange, directed metalation at the 7-position occurs, and the tricycle **4a** *with the bromine intact*[2c] was isolated. Use of stronger bases/higher temperatures or diorganomagnesium reagents invariably led to complex mixtures where ring opening of the lactam was a common reaction motif. Palladium-catalyzed cross coupling of bromide **3**, however, was found to be extremely general, with standard Heck, Stille, Suzuki, and

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§ Boehringer-Ingelheim Canada.

⊥ Boehringer-Ingelheim Chemicals Inc.

(1) (a) Simoneau, B. U.S. Patent 6,420,359, 2002. (b) Klunder, J. M.; Hoermann, M.; Cywin, C. L.; David, E.; Brickwood, J. R.; Schwartz, R.; Barringer, K. J.; Pauletti, D.; Shih, C.-K.; Erickson, D. A.; Sorge, C. L.; Joseph, D. P.; Hattox, S. E.; Adams, J.; Grob, P. M. *J. Med. Chem.* **1998**, *41*, 2960. (c) Grozinger, K. G.; Byrne, D. P.; Nummy, L. J.; Ridges, M. D.; Salvagno, A. *J. Heterocycl. Chem.* **2000**, *37*, 229. (d) Beaulieu, P. L.; Duceppe, J.-S.; Haché, B. *Synthesis* **2002**, *4*, 528.

(2) (a) Knochel, P.; Bonnet, V.; Mongin, F.; Trécourt, F.; Breton, G.; Marsais, F.; Quéguiner, G. *Synlett* **2002**, *6*, 1008. (b) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56* (10), 1349. For a very similar finding see: (c) Pierrat, P.; Gros, P.; Fort, Y. *Synlett* **2004**, *13*, 2319.

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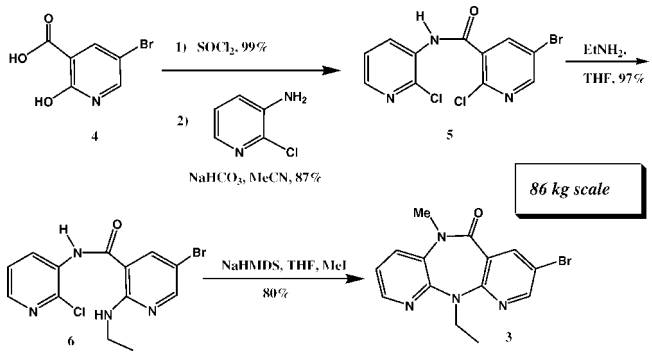
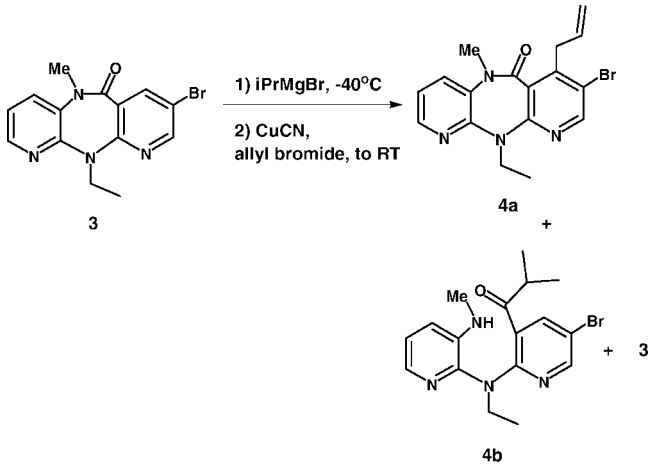
Scheme 2. **Synthesis of bromide 3**



Scheme 3. **Metalation of bromide 3**

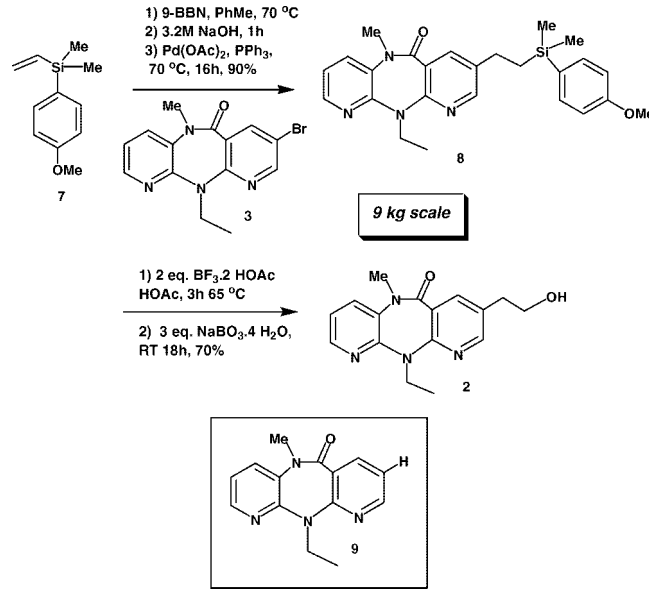


Sonogashira reactions successful in nearly all cases.[1] We therefore looked to develop an efficient route from **3** to two-carbon alcohol **2** using palladium C−C bond formation.

Hydroboration/Suzuki/Tamao (HST) Route. There is no cross-coupling methodology to directly couple an ethanol fragment to an arylhalide. We therefore sought a two-pot method to effect this transformation. Silicon is a well-established surrogate for oxygen, accessible through the Tamao/Fleming oxidation of activated silanes.[3] Our first pilot-plant route to alcohol **2** therefore commenced with hydroboration/Suzuki coupling utilizing vinylsilane **7** as raw material as shown in Scheme 4. The vinylsilane chosen possessed the *p*-methoxyphenyl group to both facilitate protodesilation and to generate anisole rather than the carcinogen benzene after its reaction.

Hydroboration with 9-BBN in toluene was regiospecific, and following *in situ* formation of the borate with aqueous sodium hydroxide, Suzuki coupling with bromide **3** using $Pd(OAc)_2$/PPh_3 proceeded smoothly in a one-pot operation to furnish silane **8** in 90% yield. Optimization of this step consisted primarily of minimizing the formation of reduced impurity **9**. This was achieved by performing the reaction in a nonpolar solvent (toluene), and especially by having a very high ligand-to-palladium ratio. A plot of log (**8**/**9**) as a function of this parameter is shown in Figure 1. Only at high (∼20:1) ratios could reduction be held to 4−5%.

Scheme 4. **HST route**



Since we could perform the cross coupling with a very inexpensive monodentate ligand, more expensive ligands, such as bidentate bisphosphines, were not examined. Silane **8** was used crude in the following step in a one-pot conversion to alcohol **2**. The material was first converted to the intermediate fluorosilane (not isolated) by treatment with 2 equiv of $BF_3 \cdot 2HOAc$[4] at 65 °C for 2−4 h, followed by cooling to ambient temperature and charging 3 equiv of sodium perborate. It was found that 18 h stirring at ambient temperature completed the Tamao−Fleming oxidation to alcohol **2**. We first evaluated peracetic acid for this oxidation and found the reaction to be very exothermic and hazardous. Calorimetry showed that a significant portion of the energy involved was caused by decomposition of peracetic acid by residual palladium (∼2000 ppm) contaminating silane **8**. The reaction could be performed by slow (∼8 h) addition of peracetic acid and triethylamine, yet we sought a safer alternative. While sodium perborate has been used for the oxidation of organoboranes to alcohols,[5] we are not aware of any published use of this inorganic oxidant for the Tamao oxidation. Although the adiabatic temperature rise was similar for the two oxidants, the decomposition onset temperature for the sodium perborate reaction was ∼55 °C, significantly higher than peracetic acid containing residual Pd. Sodium perborate proved to be a very safe reagent as direct charging of the entire quantity led to no significant exotherm using acetic acid as solvent. The reaction may well be controlled

(3) (a) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317. (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599. (c) Hosomi, A.; Iijima, S.; Sukarai, H. *Chem. Lett.* **1981**, 243. (d) Tamao, K. *Advances in Silicon Chemistry*; JAI Press: Greenwich, CT, 1996; Vol. 3, pp 1−62.

(4) (a) Knölker, H.-J.; Wanzl, G. *Synlett* **1995**, 378. (b) Fleming, I.; Henning, R.; Plaut, H. *J. Chem Soc., Chem. Commun.* **1984**, 29 See also ref 5a.

(5) (a) Kabalka, G. W.; Maddox, J. T.; Shoup, T. *Org. Synth.* **1996**, *73*, 116. (b) Kabalka, G. W.; Shoup, T. M.; Goudagon, N. M. *J. Org. Chem.* **1989**, *54*, 5930. (c) McKillop, A.; Sanderson, W. R. *Tetrahedron* **1995**, *51*, 6145.

(6) (a) Buchwald, S. L.; Moradi, W. A. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (b) Buchwald, S. L.; Fox, J. M.; Huang, X.; Chieffi, A. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (c) Buchwald, S. L.; Old, D. W.; Wolfe, J. P.; Palucki, M.; Kamikawa, K. U.S. Patent 6,307,087, CAN 135: 318588, 2001. (d) Hartwig, J. F.; Hamann, B. C. U.S. Patent 6,057,456, CAN 132:293568, 2000. (e) Hartwig, J. F.; Kawatsura, M. U.S. Patent 6,072,073, CAN 133:30376, 2000. (f) Busacca, C. A.; Eriksson, M. C.; Kim, J.-Y. U.S. Patent 6,759,533, CAN 140:59670, 2004. (g) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.

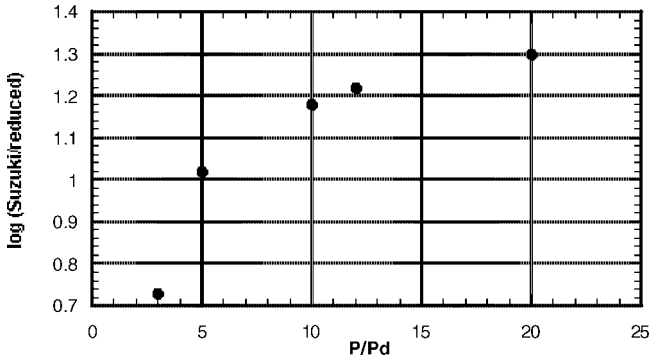


Figure 1. **Suzuki chemoselectivity as a function of phosphine-to-palladium ratio.**

by the slow reaction of sodium perborate with acetic acid,[5c] generating the active oxidant. We were able to reproducibly prepare alcohol **2** in ~65% yield using this procedure, and the two-pot conversion of **3** to **2** described was used to produce 70 kg of the desired alcohol.

The hydroboration/Suzuki/Tamao route did present some disadvantages, however. The reaction mass efficiency (RME) was low, due to the high molecular weight of both BBN and the silane substituents. In addition, the workup of the Tamao oxidation required a large number of manipulations in the pilot plant. Finally, the first crop yield was only ~50%, and a silica gel filtration was required for second crop isolation to give 65% overall yield for the step. Therefore, we examined other efficient routes to introduce the ethanol fragment of **2** from bromide **3**.

Malonate Route. A three-step sequence from bromide **3** to alcohol **2** utilizing malonate arylation was developed, as shown in Scheme 5. Diethylmalonate was arylated under palladium catalysis, although only the Buchwald biphenyl ligands[6a] and *t*-Bu_3P[6g] (**12**−**14**) were found to be successful after an extensive ligand screen.

Krapcho monodecarboxylation[7] of malonate **10** gave ester **11**, which could be reduced with 6 equiv of sodium borohydride in ethanol at 50 °C to the desired alcohol **2** in 63% overall yield. Although this approach eliminated 9-BBN and the Tamao workup problems, it presented many issues of its own. The ligand *t*-Bu_3P is expensive and extremely pyrophoric and was not considered suitable for plant use. Although the malonate chemistry was successful, it requires the use of costly, specialized ligands and procedures which are also covered by patents.[6c–e] We also examined cross coupling of a Reformatsky reagent to give an ester precursor to alcohol **2**. The major product observed, however, was the symmetric dimer of the tricycle. In addition, the desired Reformatsky reagent was not available in bulk, so this route would have required additional steps, reactors, and time. For these reasons, the malonate and Reformatsky routes were thus rejected, leading to the creation of our current pilot-plant synthesis.[6f]

Malonate Surrogate Route. It has been known for some time that carbon acids very similar to malonates can be arylated under palladium catalysis using triphenylphosphine as ligand.[8] We thus first examined an assortment of these materials as shown in Chart 1, and all coupled in high yield to bromide **3** using $Pd(OAc)_2/PPh_3$ and NaH as base, using essentially the Beletskaya protocol.[9] The malonate surrogate carbon acids were thus more "forgiving" than the malonates themselves with respect to ligand tolerance. We settled on cyanoisopropylacetate as the carbon acid of choice for our synthesis of alcohol **2**. As shown in Scheme 6, slow addition (2 h) of the carbon acid at 60 °C to a mixture of all other components in toluene allowed control over both the formation of the anion and its accompanying evolution of hydrogen and heat. The mixture was then heated at 100 °C for 1.5 h to complete the C−C bond-forming event furnishing **15**.

THF and dioxane could also be used as solvent, and tertiary alkoxide bases could be substituted for NaH as well. We ultimately chose NaH/oil beause of its lower unit cost, its successful use in the manufacture of Nevirapine, and our experience in the safe handling of NaH at our production facility.

We then needed to carry out a complete hydrolysis/decarboxylation to carboxylic acid **16**. At low pH, the conversion was poor and the reaction sluggish, yet under basic conditions, **16** could be prepared in high yield. We found that the hydrolysis reaction worked best under biphasic conditions, and thus when the arylation was complete we simply quenched residual NaH with *i*-PrOH, then added 1 M NaOH and heated at 80 °C for 8 h. This furnished the desired acid **16**, yet in several laboratory runs with two different ester starting materials, 10−35% of a byproduct was observed. This material was isolated and characterized, and then shown by independent synthesis (palladium-catalyzed carbonylation of bromide **3** with H_2O) to be the one-carbon carboxylic acid **17**. This byproduct appears to be formed by air oxidation of the enolate of **15** when reactor inertion was incomplete.[10] We were able to control this impurity to <1% by careful inertion of the reactor prior to the hydrolysis/decarboxylation. The one-pot conversion of bromide **3** to acid **16** was then accomplished in 90−92% yield. Several observations were made during the optimization of this step. First, alcohol quenches of residual NaH were absolutely essential. Quenching under aqueous conditions at any pH led to insoluble organic "balls" that were broken up only with great difficulty, while *i*-PrOH and MeOH quenches led to readily stirrable slurries.

The concentration and quantity of base were also carefully studied. At least 3.5 equiv of hydroxide was required to effect complete conversion to acid **16**, and concentrations in excess of 1 M led to decomposition

(7) Krapcho, A. P. *Synthesis* **1982**, 805.

(8) (a) Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1985**, 506. (b) Yamanaka, H.; Sakamoto, T.; Katoh, E.; Kondo, Y. *Chem. Pharm. Bull.* **1988**, *36*, 1664. (c) Yamanaka, H.; Sakamoto, T.; Katoh, E.; Kondo, Y. *Heterocycles* **1988**, *27*, 1353. (d) Yamanaka, H.; Sakamoto, T.; Katoh, E.; Kondo, Y. *Chem. Pharm. Bull.* **1990**, *38*, 1513. (e) Yamanaka, H.; Sakamoto, T.; Kondo, Y.; Suginome, T.; Ohba, S. *Synthesis* **1991**, 552. (f) Sakamoto, T.; Kondo, Y.; Masumoto, K. *Heterocycles* **1993**, *36*, 2509 For a review see: (g) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041.

(9) Beletskaya, I. P.; Kashin, A. N.; Mitin, A. V.; Wife, R. *Tetrahedron Lett.* **2002**, *43*, 2539.

(10) Treatment of the enolate of **15** in a pressure vessel under 100 psi O_2 led to acid **17** in high yield.

Scheme 5. **Malonate route**

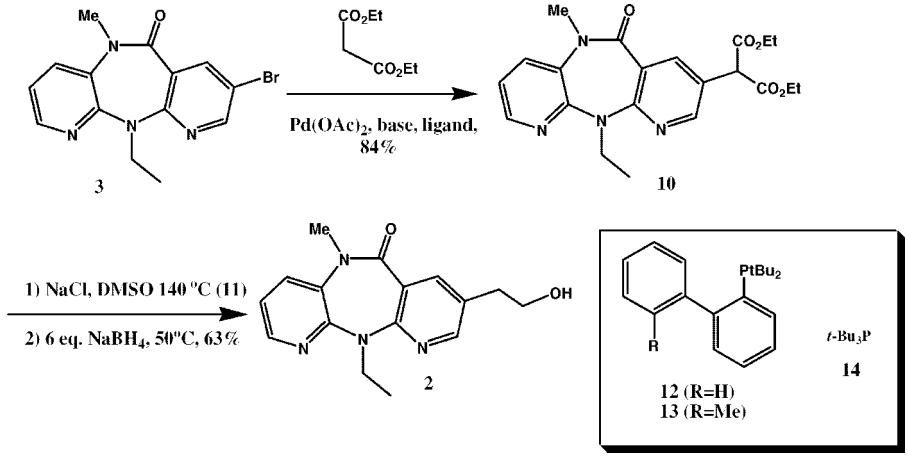
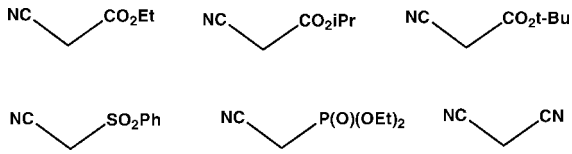


Chart 1. **Carbon acids arylated with bromide 3**



products arising from hydrolysis of the lactam linkage. The most surprising result was the low rate of hydrolysis when performed under homogeneous conditions using, for example, THF as solvent for both arylation and hydrolysis. Despite the success of "classical" ester saponification conditions[11] using THF/aqueous base, this was a very poor choice for the generation of carboxylic acid **16**. Both **15** and **16** are soluble in 1 M NaOH, and the two-phase conditions may simply sequester all organic impurities and byproducts away from these components in the toluene phase. Alternatively, the ternary azeotrope of *i*-PrOH/toluene/H_2O might be involved, essentially removing some *i*-PrOH and thereby facilitating the hydrolysis. We were curious what the mechanism of the hydrolysis might be, specifically whether the ester or nitrile was hydrolyzed first, or whether they were hydrolyzed at similar rates. We therefore prepared the ^{13}C-labeled isopropylcyanoacetate[12a,b] and processed the material through to acid **^{13}C-16**. As shown in Scheme 7, ^{13}C NMR and HRMS showed greater than 95% ^{13}C retention in the product. The isopropylester is thus clearly hydrolyzed first, and apparently then undergoes decarboxylation, followed by nitrile hydrolysis in a stepwise manner.[12c]

When the one-pot arylation/hydrolysis was completed, we simply separated the aqueous phase, washed once with EtOAc, and then adjusted the pH to 3.3 to cause crystallization of acid **16** from water. Simple centrifugation and drying under vacuum then furnished **16** in high yield with HPLC purity >98%.

Reduction of acid **16** to alcohol **2** could be readily achieved under a variety of conditions. Using 1.4 equiv of BH_3/THF furnished the product in 85% yield without any over-reduction of the lactam to the tertiary amine. Alternatively, acid **16** could be treated first with 1 equiv of catecholborane, followed by addition of 1 equiv of sodium borohydride in the same pot to generate the alcohol in similar yield. Borane and catecholborane are far more expensive than sodium borohydride, though, and require special material handling. Borane can be generated in situ under a variety of conditions, typically involving the interaction between a Lewis or protic acid and sodium borohydride.[13] Addition of a variety of Lewis acids (BF_3, BCl_3, $ZnCl_2$) to acid **16** led to thick mixtures that were very difficult to stir under any conditions, so we focused on protic acids. When commercial solutions of concentrated HCl and H_2SO_4 were used, the reaction mixtures were also extremely thick. We found that simply treating a THF mixture of **16** with 1.5 equiv of anhydrous HCl/THF, followed by slow addition (2 h) of 1.5 equiv of $NaBH_4$/diglyme, led after a 3-h hold to complete conversion to alcohol **2**. NMR experiments in HCl/d_8-THF established that no acid-promoted decomposition of THF would occur for more than 48 h at ambient temperature. Slow addition of $NaBH_4$ was required to prevent lactam reduction. The mixture was quenched with MeOH, volatiles were removed in vacuo, and the product then precipitated from the two-phase mixture of 0.5 M NaOH/heptane and centrifuged to furnish the product in 80−85% yield. This two-pot conversion of bromide **3** to alcohol **2** was successfully carried out on a 40kg scale.

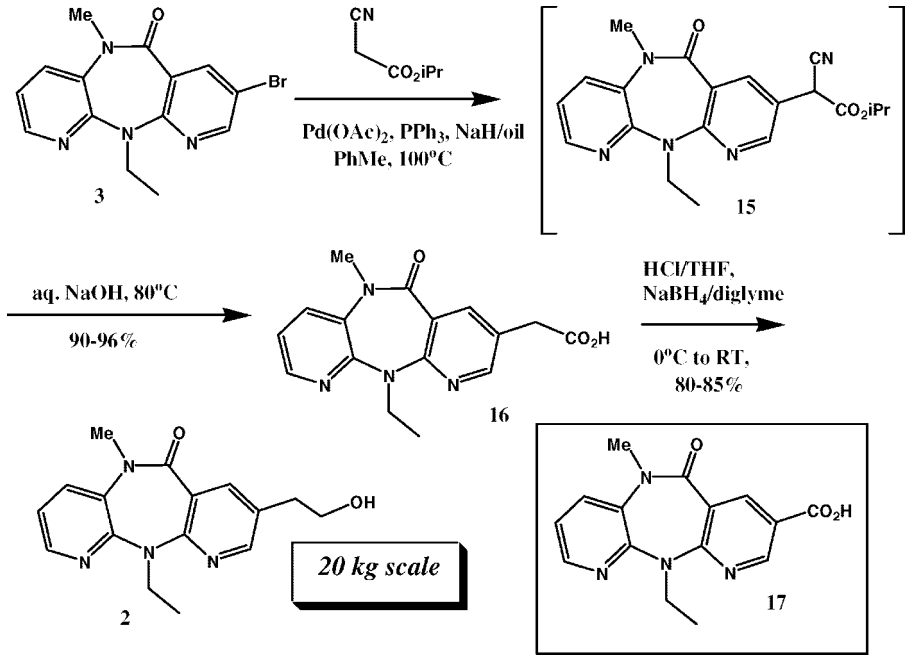
A number of different strategies were initially examined to convert alcohol **2** to target **1**. A representative group of results is shown in Table 1, where S_NAr reactions using both 4-nitro- and 4-chloro-quinoline-*N*-oxide were studied. With NO_2 as leaving group (entries 1, 2), **1** was formed in low yield, accompanied by elimination product **18**. A range of bases and solvents were screened with the chloro electrophile. In general, organic bases were completely ineffective (entries 4−7), and most inorganic bases gave low conversion. The best result found was with CsOH·H_2O in DME (entry 12), where 61% conver-

(11) For recent examples, see: (a) Mannekens, E.; Tourwe, D.; Lubell, W. D. *Synthesis* **2000**, *9*, 1214. (b) Springer, D. M.; Luh, B.-Y.; Bronson, J. J.; McElhone, K. E.; Mansuri, M. M.; Gregor, K. R.; Nettleton, D. O.; Stanley, P. L.; Tramposch, K. M. *Bioorg. Med. Chem.* **2000**, *8*, 1087.

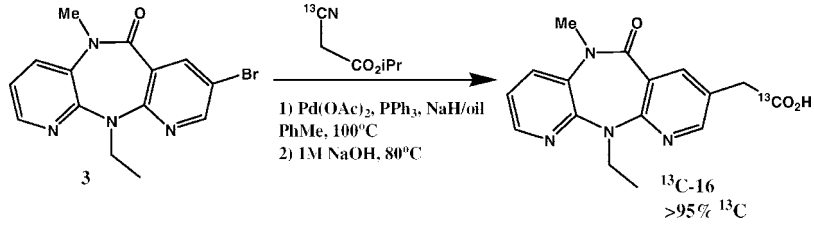
(12) (a) Holmes, D. L.; Lightner, D. A. *Tetrahedron* **1996**, *52*, 5319. (b) Silverman, R. B.; Lu, X.; Blomquist, G. D.; Ding, C. Z.; Yang, S. *Bioorg. Med. Chem.* **1997**, *5*, 297. (c) In situ React-IR might be suitable for monitoring this hydrolysis as well.

(13) (a) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517. (b) Periasamy, M.; Prasad, A. S. B.; Kanth, J. V. B. *Tetrahedron* **1992**, *48*, 4623. (c) Meyers, A. I.; Dickman, D. A.; Smith, G. A.; Gawley, R. E. Organic Syntheses; Wiley & Sons: New York, 1990; *Collect. Vol. VII*, p 530.

Scheme 6. **Malonate surrogate route**



Scheme 7. **^{13}C-Labeling experiment**



sion was obtained. We were unable to obtain full conversion, however, and the use of reaction temperatures even slightly above ambient led to significantly more formation of the elimination product **18**. 4-Chloroquinoline was also investigated as an electrophilic partner. Conversions were far lower than with the analogous *N*-oxide, however, and elimination was a serious side reaction. Alcohol **2** was also converted to a variety of leaving groups (mesylate, tosylate, brosylate, acetimidate, etc.) to try and use this fragment as the electrophilic partner with 4-hydroxyquinoline as nucleophile. The best isolated yield of ether **19** under any conditions was ~40%, however, with significant elimination again plaguing the transformation. In *all* S_NAr attempts, conditions more vigorous than those in Table 1 led to elimination product **18** as the predominant species. We decided therefore to optimize the Mitsunobu etherification[1a,6f] of alcohol **2** as shown in Scheme 8.

Initial optimization showed the principal byproduct in the reaction to be the regioisomeric Mitsunobu adduct **20**. 4-Hydroxyquinoline is of course an ambident nucleophile,[14] and the task rapidly reduced to one of establishing high regiocontrol for ether **19**. THF, DME, CH_2Cl_2, and DMF were evaluated for the etherification at ambient temperature, and DME gave far higher ratios of **19**:**20** (ca. 15:1) than any of the other solvents. The amount of **20** was still unacceptably high, though, so we lowered the initial reaction temperature to −25 °C and ramped to ambient temperature over 12 h. In this way the total amount of **20** produced was minimized to ~4%. The product was conveniently purified by simple precipitation of the crystalline HCl salt, and **19** was isolated in 80% yield as a nonhygroscopic, free-flowing solid. The Mitsunobu was successfully executed on a 110 kg scale.

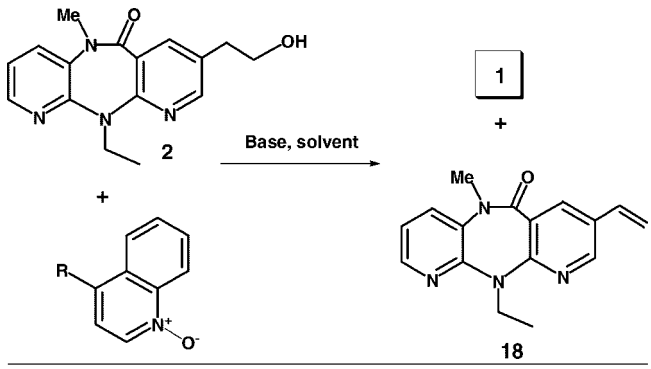
Target **1** was then produced from **19** with *m*-CPBA using a two phase aqueous Na_2CO_3/CH_2Cl_2 solvent system. It was found to be critical to maintain high pH (~10) throughout the oxidation to ensure complete conversion.[15] Since *m*-chlorobenzoic acid is produced as the reaction proceeds, the pH steadily drops over time, necessitating a large initial base charge. The quinoline nitrogen (estimated pK_a 6) was selectively oxidized with no competing oxidation of the less basic nitrogens (pK_a 2.5, determined on the API after oxidation), and the reaction was complete in 90 min at ambient temperature. The reaction was then quenched (Na_2SO_3), and organic solvents removed in vacuo, leaving an aqueous slurry of **1**. Analysis of the impurities in the crude drug substance revealed two in particular, lactam **21** and anilinoester **22**. Typical levels of these two impurities in the API were 0.20 A% and 0.15 A% by HPLC, respectively. The lactam was formed via the known photorearrangement[16] of aromatic N-oxides, and photolysis of a solution of **1** was shown to generate this material cleanly. The exact

(14) Black, T. H. *Org. Prep. Proced. Int.* **1989**, *21*, 179.

(15) For a possible explanation, see: (a) Houk, K. N.; Washington, I. *Org. Lett.* **2002**, *4*, 2661.

(16) (a) Hata, N. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2723. (b) Hata, N.; Norisuke, Y.; Yagi, A. *Chem. Lett.* **1983**, 309. (c) Kaneko, C.; Okuda, W.; Karasawa, Y.; Somei, M. *Chem. Lett.* **1980**, 547.

Table 1. **S_NAr approaches to 1**



entry	R	base	solvent	% conv.[a]	% **18**
1	NO_2	NaH	DME	8.5	0
2	NO_2	Cs_2CO_3	MeCN	20	5
3	Cl	$NaHCO_3$	DMSO	NR	NA
4	Cl	DBU	DMSO	NR	NA
5	Cl	DIPEA	DMSO	NR	NA
6	Cl	TEA	DMSO	NR	NA
7	Cl	2,6-lutidine	DMSO	NR	NA
8	Cl	NaOH/PTC	CH_2Cl_2	NR	NA
9	Cl	Cs_2CO_3	DMSO	35	ND
10	Cl	NaOH	DME	43	0
11	Cl	KOH	DME	46	0
12	Cl	$CsOH \cdot H_2O$	DME	61	0

[a] HPLC % conversion to **1**.

mechanism of formation of **22** is not known, yet it might arise from oxidative degradation of **21**. The structure of **22** was unequivocally established by independent synthesis.[17] The drug substance was isolated by centrifugation in 86% yield.

In summary, we have developed a four-step process for the drug substance production of drug candidate **1** from advanced intermediate bromide **3**, which is itself produced in four steps from bulk pyridine building blocks. The chemistry employs as a key transformation the one pot conversion of aryl bromide **3** to arylacetic acid **16** under palladium catalysis using inexpensive raw materials and nonproprietary ligands.

Experimental Section

General. HPLC analyses were performed under standard gradient conditions on an Agilent 1100 using a Zorbax SB-CN column, 150 mm × 4.6 mm, 5 μm particle size; flow rate 1.5 mL/min, temp 50 °C, detection @ 220 nm, 10 μL injection volume, run time 57 min. Mobile phase A: 80/20 (v/v) H_2O/MeOH with 0.05% TFA; Mobile phase B: 35/65 (v/v) H_2O/MeOH with 0.05% TFA. Gradient: 100% A to 100% B in 43 min., 10 min. hold at 100%B. Retention times (RT, min) and relative retention times (RRT) for the key compounds are as follows: (RT, RRT): 4-OH-quinoline (3.8, 0.16); *m*-Cl-benzoic acid (9.1, 0.39); alcohol **2** (9.9, 0.43); ether **19** (15.6, 0.67); $Ph_3P{=}O$ (18.9, 0.81); API **1** (23.2, 1.00); impurity **22** (26.7, 1.15); impurity **21** (27.2, 1.17).

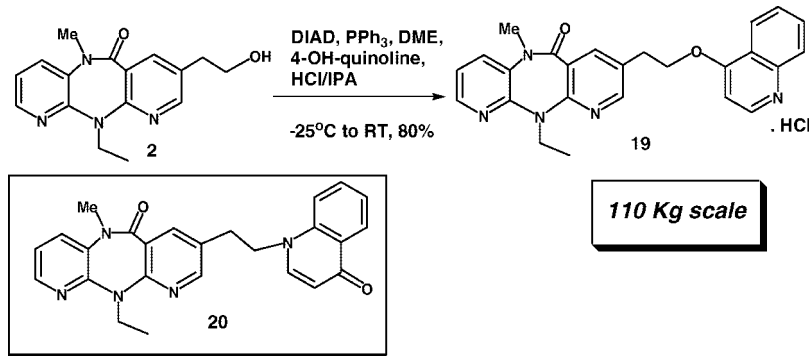
5-Bromo-2-hydroxynicotinic Acid (4). An aqueous solution of sodium hypobromite was generated using the following procedure: Water (88 kg) and sodium bromide (44.53 kg, 432.8 mol, 1.505 equiv) were charged to a 120 L glass-lined reactor and stirred under an inert atmosphere. Sodium hypochlorite (269.2 kg of a freshly titrated 10.8 wt % solution, 345.1 mol, 1.2 equiv) was added to a 800 L glass-lined reactor and cooled to 5 °C. The aqueous NaBr solution was then slowly transferred to this reactor with cooling so that the internal temperature did not rise above 20 °C. A second 800 L glass-lined reactor was charged with 56.6 kg (707.4 mol, 2.46 equiv) of 50% aqueous NaOH, followed by 40 kg (287.5 mol, 1.0 equiv) of 2-hydroxynicotinic acid and the solution cooled to 5 °C. The aqueous solution of sodium hypobromite was added to the solution of 2-hydroxynicotininic acid at such a rate that the internal temperature did not rise above 20 °C. After the addition was complete, the reaction mixture was stirred for 90 min. After this time the reaction mixture was quenched by the sequential addition of 120.3 kg of water, 116.3 kg (1002 mol, 3.5 equiv) of 31.5% HCl, and 15.62 kg of isopropanol. The desired product precipitated as a white solid which was collected by filtration. The filter cake was then slurried with an additional 400 kg of water and stirred for 30 min, then filtered a second time. The filter cake and methanol (160 L) were then added to a 800 L reactor and heated to reflux for 1 h, and allowed to cool to between 0 and 5 °C over a 3 h period and maintained at that temperature for an additional 4 h. The resultant slurry was then filtered and dried at 70 °C at 20 torr to constant weight. This afforded 39.1 kg (74%) of 5-bromo-2-hydroxynicotinic acid **4**. (For characterization, see ref 1d).

5-Bromo-2-chloronicotinoyl Chloride, Solution in Acetonitrile. An 800 L glass-lined reactor was charged with 416 L of toluene, 1.37 kg of DMF (18.8 mol, 0.05 equiv), and 83.3 kg (382.0 mol, 1.0 equiv) of 5-bromo-2-hydroxynicotinic acid **4**, and the resulting slurry heated to 60 °C. Thionyl chloride (136.4 kg, 1146 mol, 1.5 equiv) was then added over a 4 h period at a rate which kept the internal temperature below 70 °C. After the addition was complete, the mixture was heated to 100−105 °C for 3 h. The mixture was then heated to 125 °C, and the volatile materials were removed by distillation. When the distillation process slowed, the reaction was allowed to cool to ~20 °C, then the internal pressure was lowered to 50 torr and the mixture heated to 100 °C, and further volatile materials were removed. Thirty kilograms of acetonitrile was then added while distilling solvents from the reactor while maintaining the temperature between 95−100 °C until no more distillate was received at 100 °C. While maintaining the temperature of the reactor at >40 °C, 37.04 kg of acetonitrile was then added. The resultant solution was shown to contain 97.4 kg (>99% yield, >380 mol) of 5-bromo-2-chloronicotinoyl chloride. The solution was used in the subsequent step without further purification.

5-Bromo-2-chloronicotinoyl-*N*-(2-chloropyridin-3-yl)nicotinamide (5). An 800 L glass- lined reactor was charged with 460 L of acetonitrile, 88.0 kg (1047 mol, 3.21 equiv) of $NaHCO_3$, and 41.68 kg (324.4 mol, 1.0 equiv) of 3-amino-2-chloropyridine and the solution mixture stirred for 30 min at 25 °C. The solution of 5-bromo-2-chloronicotinoyl chloride in acetonitrile, 140.95 kg of a 73% solution (85.6 kg, 334.1 mol, 1.03 equiv), was added over a 4 h period at a rate which

(17) See Experimental Section.
(18) Busacca, C. A.; Cerreta, M.; Varsolona, R.; Smoliga, J.; Lorenz, J. Vitous, J. U.S. Patent 7,309,700, CAN 143:353310, 2007.

Scheme 8. **Mitsunobu etherification**



maintained the internal reaction temperature between 25 and 34 °C. The mixture became thinner as the reaction progressed. After the addition was complete, the mixture was allowed to stir for 18 h at ambient temperature. After this time an aliquot was removed and analyzed by HPLC. This showed 5.4 area % residual 3-amino-2-chloropyridine remained. To consume the remaining 3-amino-2-chloropyridine, 10.6 kg of the 5-bromo-2-chloronicotinoyl chloride solution was added over a 1.5 h period. Analysis of this mixture showed that the level of 3-amino-2-chloropyridine was <1%. Water (1200 kg) and isopropanol (64.38 kg) were added to a separate, clean 2000 L reactor, and this mixture was cooled to ∼5 °C. The acetonitrile solution was added to this mixture over a 1 h period while maintaining the temperature <10 °C, and the resultant slurry was stirred for 1 h. The mixture was then filtered through a paper filter, and the filter cake was then slurried with 320 kg of water, stirred for 30 min, and then filtered again. The filter cake was dried for 24 h at 50 °C under 25 torr. This afforded 97.9 kg (282 mol, 87% yield) of **5** as a tan solid. KF 0.27% H_2O. Mp 180−182 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.64 (s, 1H), 8.72 (d, J = 2.3 Hz, 1H), 8.43 (d, J = 2.2 Hz, 1H), 8.28 (m, 1H), 7.52 (dd, J = 4.7, 7.9 Hz, 1H), 3.36 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.97 (s), 151.28 (d), 146.60 (d), 145.53 (s), 144.18 (s), 140.56 (d), 135.12 (d), 133.55 (s), 131.34 (s), 123.55 (d), 118.87 (s). Anal. Calcd for $C_{11}H_6BrCl_2N_3O$·[0.27% H_2O]: C, 37.88; H, 1.79; N, 12.05. Found: C, 37.63; H, 1.51; N, 11.78.

5-Bromo-*N*-(2-chloropyridin-3-yl)-2-ethylaminonicotinamide (6). To an inerted 6000 L reactor were charged 150 kg of dichloroamide **5** (432 mol, 1 equiv) and 792 kg of THF, and the mixture was cooled to 5 °C. Fifty-nine kilograms of $EtNH_{2(g)}$ (1309 mol, 3 equiv) was then introduced subsurface over 4 h, maintaining the contents temperature below 10 °C. The mixture was agitated at this temperature for 15 min, then ramped to 90 °C over 2 h, and held at this temperature for 8 h. The mixture was then cooled to 25 °C, and an HPLC sample showed the S_NAr reaction was complete. A 2050 kg amount of H_2O was then charged, and the pH was adjusted by the addition of 25 kg of HOAc to a final pH of 5.77. The mixture was stirred 1 h, then centrifuged, using three ∼1000 L washes of 1% aq HOAc to wash the cake. The crude solid was then dried at 50 °C under full vacuum for 10 h to give 149.3 kg of aminoamide **6** (97%). Mp 149−151 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.33 (s, 1H), 8.30 (m, 2H), 8.11 (t, J = 5.0 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.47 (dd, J = 1.2, 7.8 Hz, 1H), 3.38 (q, J = 6.9 Hz, 2H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.88 (s), 156.10 (s), 152.28 (d), 146.99 (d), 146.74 (s), 139.05 (d), 137.37 (d), 131.65 (s), 123.40 (d), 110.05 (s), 103.36 (s), 35.26 (t), 14.53 (q). Anal. Calcd for $C_{13}H_{12}BrClN_4O$: C, 43.91; H, 3.40; N, 15.75. Found: C, 43.99; H, 3.29; N, 15.72.

2-Bromo-5-ethyl-10-methyl-5,10-dihydro-4,5,6,10-tetraazadibenzo[*a*,*d*]cyclohepten-11-one (3). A 4000 L inerted reactor (reactor 1) was charged with 114 kg of crude aminoamide **6** (321 mol, 1 equiv); 323 kg of THF were then added, and the temperature of the contents was adjusted to 50 °C. To this mixture was then added 650 kg of 1 M NaHMDS/THF (719 mol, 2.2 equiv) over 2 h, maintaining the temperature of the contents below 55 °C. The reactor was maintained at ∼50 °C for 1 h. HPLC showed incomplete consumption of aminoamide **6**, so an additional 59.2 kg of 1 M NaHMDS (66 mol, 0.2 equiv) was charged. After 1 h at 50 °C, cyclization was complete. The contents were then cooled to 25 °C, and 119 kg of MeI (836 mol, 2.6 equiv) were then charged over 2 h while maintaining the contents temperature below 30 °C. The contents were then agitated at 25 °C for 10 h, at which time HPLC analysis showed complete conversion to bromide **3**. To a second, 6000 L reactor (reactor 2) was then charged 600 g of 2,6-di-*tert*-butyl-4-methylphenol, followed by 168 kg of 4-picoline (1803 mol, 5.6 equiv) and 88 kg of MeOH. The volatiles from reactor 1 were then distilled at 5 kPa into reactor 2 until distillation ceased. Additional MeOH was then charged (240 kg each time) to reactor 1, and two additional distillations were performed as described above. The combined distillates were then heated at 50 °C for 5 h to complete destruction of MeI, in accordance with earlier runs in 200 L equipment.

To the contents of reactor 1 at 25 °C were then charged 930 kg of EtOAc and 369 kg of H_2O, and the contents agitated well for 15 min at 40 °C. The lower aqueous phase was then dropped to drums, and an additional 369 kg charge (performed 2×) of H_2O was added to the reactor, agitating and dropping the lower phase to drums as described above. The organic solvents were then distilled to minimal stirrable volume. To the reactor were then charged 3.3 kg of Darco G60 and 3.3 kg of Hyflo Supercel. The reactor was then inerted, and 399 kg of EtOAc and 383 kg of isooctane were charged, and the contents were heated at 45 °C for 2 h. The mixture was then filtered warm through a Seitz filter/inline filter combination. The reactor was then charged with 295 kg of EtOAc, the contents were heated to reflux, and this hot solution was then filtered as described above. The combined filtrates were then distilled at 50 °C and ∼10 kPa until the amount of distillate collected was

~1025 L. The contents were then cooled to 5 °C over 1 h and then held at 5 °C for 2 h. The resulting slurry was then centrifuged, and the solid obtained was packed out and dried at 45 °C under full vacuum for 4 h to give 86 kg of bromide **3** (80%) as a yellow solid. Mp 144−145 °C. ^{1}H NMR (500 MHZ, DMSO-d_6) δ: 8.51 (d, J = 2.5 Hz, 1H, H9), 8.21 (dd, J = 4.6, 1.6 Hz, 1H, H2), 8.11 (d, J = 2.5 H, 1H, H7), 7.84 (dd, J = 8.0, 1.6 Hz, 1H, H4), 7.27 (dd, J = 4.6, 8.0 Hz, 1H, H3), 4.04 (q, J = 7.0 Hz, 2H), 3.42 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 164.93 (s), 157.74 (s), 153.10 (s), 151.00 (d), 144.24 (d), 142.49 (d), 131.94 (d), 130.94 (s), 121.96 (s), 120.61 (d), 113.04 (s), 40.63 (t), 36.70 (q), 13.23 (q). Anal. Calcd for $C_{14}H_{13}BrN_4O$: C, 50.47; H, 3.93; N, 16.82; Br, 23.98. Found C, 50.37; H, 3.59; N, 16.70; Br, 23.69.

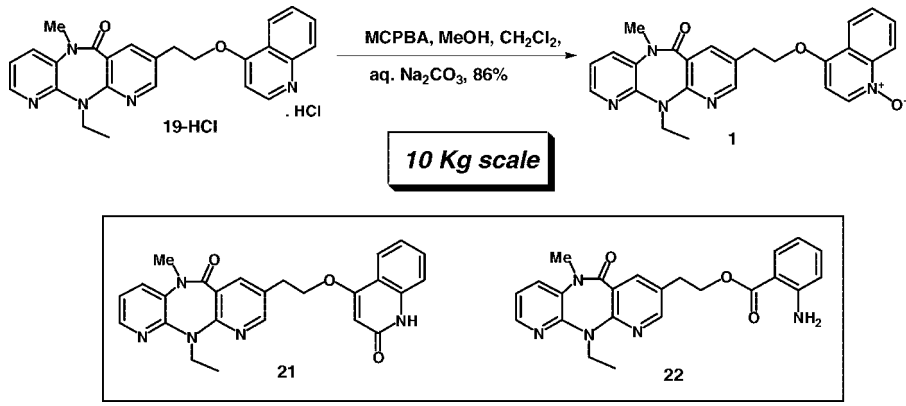
5-Ethyl-2-(2-hydroxyethyl)-10-methyl-5,10-dihydro-4,5,6,10-tetraazadibenzo[*a*,*d*]cyclohepten-11-one (2) via HST Protocol. An inerted 400 L reactor was charged with 9.1 kg of (9-BBN)$_2$ (74 mol monomer, 1.4 equiv) and then carefully reinerted before 66 kg of PhMe and 11.9 kg of vinyldimethyl-*p*-methoxyphenylsilane (62 mol, 1.16 equiv) were added. The resulting mixture was then heated to 70 °C and maintained at that temperature for 2 h, at which time HPLC showed hydroboration was complete. The solution was then cooled to 22 °C, and 46.9 kg of 3.2 M NaOH (134 mol, 2.5 equiv) was added. The mixture was well agitated for 45 min at 22 °C, and then 17.8 kg of bromide **3** (53 mol, 1 equiv), 4.22 kg of PPh_3 (16 mol, 0.30 equiv), and 178 g of $Pd(OAc)_2$ (1 mol, 0.015 equiv) were then charged through the manway in the order given. The resulting mixture was then agitated at 140 rpm at 40 °C for 30 min, then linearly heated to 70 °C over 3 h, and maintained at 70 °C for 10 h. HPLC showed the Suzuki coupling was complete. The mixture was then cooled to 22 °C, and 9.1 kg of ethanolamine (149 mol, 2.8 equiv) was added over 20 min, maintaining the internal temperature below 50 °C. The mixture was then agitated at 22 °C for 1 h, and then the precipitate of 9-BBN-ethanolamine complex was filtered off, washing the cake with 31 kg of PhMe. The phases were then separated, and the lower aqueous layer was extracted with 20 kg of PhMe. The lower aqueous layer was then discarded to waste, and the combined organic phases were washed once with 50 kg of H_2O. The organic layer was then distilled to minimal stirrable volume, collecting 127 L of distillate. The reactor was then cooled to 22 °C to give crude silane **8** as a thick, light-yellow oil which crystallized on standing. To the crude silane was then charged 56 kg of HOAc followed by 20.0 kg of BF_3·2HOAc (106 mol, 2 equiv). The resulting mixture was then heated to 65 °C and maintained at that temperature for 4 h and then cooled to 22 °C. To the mixture was then added 24.6 kg of $NaBO_3$·4H_2O (160 mol, 3 equiv) through the manway. The mixture was then well agitated at this temperature for 12 h, and HPLC showed the Tamao oxidation was complete. To the reactor was then charged 39.8 kg of 1 M K_3PO_4 solution (34.3 mol, 0.65 equiv), then 104 kg of 2 M $Na_2S_2O_3$ (160 mol, 3 equiv) was added slowly over 45 min while maintaining the internal temperature below 30 °C. The mixture was agitated well for 45 min, and then the volatiles were removed by distillation at 40 °C/10 mm to give 94 L of distillate. Then to the reactor was charged 107 kg of H_2O, and the mixture was cooled to 10 °C. The pH was then cautiously adjusted with 5 M NaOH to a final pH of 8.0, requiring 79 kg of the caustic solution. The mixture was warmed to 22 °C, 182 kg of CH_2Cl_2 was charged, and the mixture was agitated well for 20 min. The two-phase mixture was then filtered through a Celite pad which was previously wetted with CH_2Cl_2. The filter pad was then washed with 71 kg of H_2O. From the combined filtrates, the bottom organic layer was then transferred to a second reactor, while the upper aqueous phase was re-extracted with 150 kg of CH_2Cl_2. The combined CH_2Cl_2 layers were then back-extracted with 100 kg of H_2O, and the organic solvents were removed by distillation at atmospheric pressure, collecting 201 L of distillate. The reactor was then cooled to 22 °C, and 13.4 kg of MTBE was charged, followed by 5 g of crystalline alcohol **2**. The resulting mixture was agitated at 22 °C for 8 h, and the resulting slurry was filtered, washing the cake with 40 kg of MTBE. The solid was then packed out and dried at 35 °C to a constant weight of 9.15 kg of alcohol **2** (57.4% first crop overall yield from bromide **3**) as a light-yellow solid. Silica gel filtration (EtOAc) of the mother liquors could then provide a further 5−10% product after concentration and seeding as described above. (For characterization of alcohol **2** see below.)

5-Ethyl-2-{2-[(4-methoxyphenyl)dimethylsilanyl]ethyl}-10-methyl-5,10-dihydro-4,5,6,10-tetraazadibenzo[*a*,*d*]cyclohepten-11-one (8): mp 103.1−104.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (m, 2H), 7.09 (d, J = 2.5 Hz, 1H), 7.46 (dd, J = 1.6, 7.9 Hz, 1H), 7.41 (m, 2H), 7.06 (dd, J = 4.7, 7.9 Hz, 1H), 6.89 (m, 2H), 4.16 (br s, 2H), 3.80 (s, 3H), 3.50 (s, 3H), 2.54 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.03 (m, 2H), 0.26 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.76 (s), 160.34 (s), 157.52 (s), 155.09 (s), 150.05 (d), 144.22 (d), 140.03 (d), 135.09 (s), 134.89 (d), 131.59 (s), 130.54 (d), 129.10 (s), 120.67 (s), 119.42 (d), 113.57 (d), 54.94 (q), 41.05 (t), 37.32 (q), 26.15 (t), 17.58 (t), 13.54 (q), −3.05 (q). Anal. Calcd for $C_{25}H_{30}N_4O_2Si$: C, 67.23; H, 6.77; N, 12.54; Found: C, 67.16; H, 6.83; N, 12.66.

5-Ethyl-10-methyl-5,10-dihydro-4,5,6,10-tetraazadibenzo[*a*,*d*]cyclohepten-11-one (9): white solid, mp 99.0−100.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (dd, J = 2.0, 4.7 Hz, 1H), 8.19 (dd, J = 1.6, 4.7 Hz, 1H), 8.08 (dd, J = 2.0, 7.6 Hz, 1H), 7.47 (dd, J = 1.6, 8.0 Hz, 1H), 7.07 (dd, J = 4.7, 8.3 Hz, 1H), 6.98 (dd, J = 4.8, 7.6 Hz, 1H), 4.18 (br s, 2H), 3.49 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.60 (s), 159.57 (s), 154.81 (s), 150.75 (d), 144.30 (d), 140.97 (d), 131.67 (s), 130.62 (d), 121.08 (s), 119.64 (d), 118.49 (d), 41.12 (t), 37.25 (q), 13.55 (q). Anal. Calcd for $C_{14}H_{14}N_4O$·[0.1 H_2O]: C, 65.66; H, 5.59; N, 21.88. Found: C, 65.66; H, 5.32; N, 21.76.

2-(5-Ethyl-10-methyl-11-oxo-10,11-dihydro-5*H*-4,5,6,10-tetraaza-dibenzo[*a*,*d*]cyclohepten-2-yl)-malonic Acid Diethyl Ester (10; see ref 6f). A 500 mL two-neck round-bottom flask fitted with mechanical stirrer, reflux condenser, and thermocouple was purged with argon for 20 min, and then 404 mg $Pd(OAc)_2$ (1.80 mmol, 0.03 equiv), 1.08 g of ligand **12** (3.60 mmol, 0.06 equiv), and 20.0 g of bromide **3** (60.0 mmol, 1 equiv) were charged. To this mixture in an inerted flask were added 25.5 g of K_3PO_4 (120 mmol, 2 equiv), 100 mL of PhMe, and 13.8 mL of diethylmalonate (90.0 mmol, 1.5 equiv). The

Scheme 9. **Synthesis of 1**



stirred suspension was placed in an oil bath and heated at reflux under nitrogen for 24 h until the bromide was consumed by HPLC. The reaction mixture was cooled to room temperature and diluted with water (150 mL), and toluene (50 mL) was added. The mixture was stirred for 1 h at room temperature until all solids had dissolved. The two-phase solution was then transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with toluene (50 mL). The combined organic layers were filtered through a pad of Celite and concentrated under vacuum to give a viscous oil, which was evaporated to dryness to furnish an orange solid. HPLC analysis of this material indicated 83% **10**, 8.8% monoester, and 8.8% reduced impurity **9**. Silica gel chromatography (1:1 EtOAc/Hex) provided 20.5 g of pure **10** (83%) as a white solid; mp 122−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, J = 2.5 Hz, 1H), 8.19 (dd, J = 1.5, 4.6 Hz, 1H), 8.16 (d, J = 2.4 Hz, 1H), 7.47 (dd, J = 1.5, 8.0 Hz, 1H), 7.09 (dd, J = 4.7, 8.0 Hz, 1H), 4.56 (s, 1H), 4.20 (m, 6H), 3.49 (s, 3H), 1.25 (t, J = 7.1 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.30 (s), 167.23 (s), 159.31 (s), 154.50 (s), 151.18 (d), 144.34 (d), 141.93 (d), 131.63 (s), 130.74 (d), 123.52 (s), 120.57 (s), 119.78 (d), 62.17 (t), 54.80 (d), 41.24 (t), 37.30 (q), 13.96 (q), 13.58 (q). Anal. Calcd for $C_{21}H_{24}N_4O_5$: C, 61.15; H, 5.87; N, 13.58. Found: C, 61.14; H, 5.66; N, 13.51.

(5-Ethyl-10-methyl-11-oxo-10,11-dihydro-5*H*-4,5,6,10-tetraazadibenzo[*a*,*d*]cyclohepten-2-yl)acetic Acid (16. See ref 6f). An inerted 800 L glass-lined reactor fitted with an H_2 vent was charged with 12.0 kg of 60% NaH/oil (300 mol, 2.5 equiv), 0.27 kg of $Pd(OAc)_2$ (1.2 mol, 0.01 equiv), 1.26 kg of PPh_3 (4.8 mol, 0.04 equiv), and 40 kg of bromide **3** (120 mol, 1 equiv). The reactor was again inerted, 70 kg of PhMe was charged, and the mixture was heated to 60 °C. To this mixture was then added a solution of 17.4 L of cyanoisopropylacetate (138 mol, 1.15 equiv) in 20 L of PhMe via metering pump at a fixed rate over 2 h (CAUTION: H_2 gas evolution). The reactor contents were then heated to 100 °C and maintained for 1.5 h. HPLC of an aliquot showed the arylation was complete. The mixture was then cooled to 35 °C and quenched by the addition of 19 kg of *i*-PrOH (308 mol, 2.6 equiv) over 20 min (CAUTION: H_2 gas evolution). The batch was then transferred to a stainless steel reactor, and 438 kg of 1 M NaOH solution (417 mol, 3.5 equiv) was then added. The mixture was heated to 80 °C and maintained there for 8 h. HPLC of an aliquot showed the hydrolysis was complete to acid **16**. The mixture was cooled to 25 °C, and the phases were separated. The upper phase was discarded to waste, while the lower aqueous phase was returned to the reactor; 218 kg of EtOAc was then charged, and the mixture agitated for 15 min; then the phases were allowed to separate. The lower aqueous phase was returned to the reactor and cooled to 10 °C. To this mixture was then slowly added 6 N H_2SO_4 with continuous monitoring of pH until a final pH of 3.3 was achieved: this required 133 kg of H_2SO_4 solution. The resulting slurry was then warmed to 25 °C and maintained there for 1 h. The batch was then centrifuged and washed twice with 40 kg of H_2O. The solid was then dried at full vacuum at 40 °C until LOD <1% to give 36.0 kg of carboxylic acid **16** (96%) as an off white solid; mp 226−228 °C. ^{1}H NMR (500 MHZ, DMSO-d_6) δ: 12.47 (s, 1H), 8.32 (d, J = 2.0 Hz, 1H), 8.20 (dd, J = 4.6, 1.5 Hz, 1H), 7.96 (d, J = 2.3 Hz, 1H), 7.81 (dd, J = 8.0, 1.6 Hz, 1H), 7.24 (dd, J = 4.6, 8.0 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 3.63 (s, 3H), 3.43 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 172.22 (s), 166.26 (s), 157.47 (s), 153.96 (s), 151.32 (d), 144.06 (d), 141.59 (d), 131.72 (d), 131.14 (s), 126.01 (s), 120.28 (d), 120.12 (s), 40.45 (t), 36.74 (q), 36.34 (t), 13.42 (q). Anal. Calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.28; H, 4.94; N, 17.56.

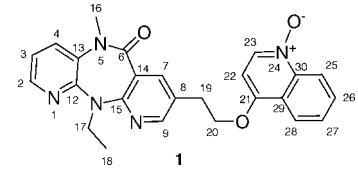
5-Ethyl-10-methyl-11-oxo-10,11-dihydro-5*H*-4,5,6,10-tetraazadibenzo[*a*,*d*]cycloheptene-2-carboxylic acid (17): mp 251−253 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.84 (d, J = 2.3 Hz, 1H), 8.40 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 4.6, 1.6 Hz, 1H), 7.82 (dd, J = 8.0,1.6 Hz, 1H), 7.27 (dd, J = 8.0, 4.6 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.39 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.18 (s), 165.80 (s), 161.84 (s), 152.89 (s), 152.19 (d), 144.81 (d), 142.49 (d), 132.54 (d), 131.60 (s), 121.87 (s), 121.43 (d), 119.94 (s), 41.51 (t), 37.16 (q), 13.84 (q). Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found C, 60.27; H, 4.64; N, 18.50.

5-Ethyl-2-(2-hydroxyethyl)-10-methyl-5,10-dihydro-4,5,6,10-tetraazadibenzo[*a*,*d*]cyclohepten-11-one (2) via Malonate Surrogate Protocol. An 800 L reactor (reactor 1) was inerted, then charged with 4.70 kg of $NaBH_4$ (124 mol, 1.5 equiv) and reinerted, and 90 kg of diglyme was added. The mixture was agitated at 25 °C for 3 h. In a separate inerted 800 L reactor (reactor 2) was charged 27 kg of THF, and the mixture was cooled to 0 °C. Then 4.60 kg of $HCl_{(g)}$ was introduced subsurface over 1 h. Titration of an aliquot showed 15.3% HCl by weight. In

a third inerted 800 L reactor (reactor 3) equipped with a hydrogen sensor were charged 26.0 kg of acid **16** (83.2 mol, 1 equiv) and 90 kg of THF, and the resultant slurry was then cooled to 0 °C. To this slurry was then added the contents of reactor 2 (HCl/THF) under N_2 pressure over 30 min, causing the formation of a thicker slurry. This mixture was stirred for 30 min, then the contents of reactor 1 ($NaBH_4$/diglyme) were added to it at a fixed rate over 2 h (CAUTION: H_2 gas evolution). The contents temperature of this reactor was then ramped to 25 °C over 1 h and held at that temperature for 2.5 h. HPLC of an aliquot showed the reduction was complete. The reactor contents were then cooled to 0 °C, and 206 kg of MeOH was added at a fixed rate over 30 min and then agitated vigorously for 30 min. The temperature of the contents was slowly raised to 50 °C, and THF and MeOH were removed via distillation under vacuum (60 mm). The distillate was dropped from the receiver and discarded, and then vacuum was reintroduced (14 mm); the contents were then heated to a maximum of 69 °C as diglyme was distilled off. The contents were then cooled to 25 °C, and 437 kg of H_2O was charged. Azeotropic distillation of this mixture at full vacuum and ~50 °C was then carried out until minimum stirrable volume was achieved. The contents were again cooled to 25 °C; then 39 kg of 0.5 M NaOH and 57 kg of heptane were charged to the reactor. The resultant two-phase slurry was agitated for 10 h and then centrifuged, washing the solids with 40 kg of H_2O. The material was packed out to a dryer and dried at 35 °C and 10−50 mBar vacuum for 6 h to give 20.5 kg of alcohol **2** (80%) as an off-white solid. KF water analysis showed 0.55%, and HPLC purity 99.1%; mp 139.0−140.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, J = 2.4 Hz, 1H), 8.15 (dd, J = 4.6, 1.6 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.43 (dd, J = 8.0, 1.6 Hz, 1H), 7.05 (dd, J = 8.0, 4.6 Hz, 1H), 4.12 (b, 2H), 3.75 (b, 2H), 3.46 (s, 3H), 2.76 (t, J = 6.5 Hz, 2H), 2.63 (br s, 1H), 1.21 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.97 (s), 158.40 (s), 155.17 (s), 151.48 (d), 144.52 (d), 141.25 (d), 131.78 (s), 130.87 (d), 129.47 (s), 120.78 (s), 119.76 (d), 62.90 (t), 41.23 (t), 37.55 (q), 35.32 (t), 13.73 (q). Anal. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found C, 64.26; H, 6.15; N, 18.58.

4-[2-(5-Ethyl-10-methyl-11-oxo-10,11-dihydro-5*H*-4,5,6,10-tetraazadibenzo[*a*,*d*]cyclohepten-2-yl)ethoxy]quinolinium Chloride (19). An inerted 2000 L reactor (reactor 1) was charged with 90 kg of alcohol **2** (302 mol, 1 equiv). A separate, inerted, 3000 L reactor (reactor 2) was charged with 118.7 kg of PPh_3 (452.6 mol, 1.5 equiv), and 47.7 kg of 4-hydroxyquinoline (329 mol, 1.09 equiv). Reactor 1 was reinerted; 1202 kg of DME was charged, and agitation was started with heating to 50 °C. After 2 h at 50 °C, the mixture was cooled to 25 °C and held there. Reactor 2 was then reinerted, and 475.3 kg of DME was charged, and the contents agitated at 25 °C for 20 min. To this mixture was then added 85.4 kg of DIAD (422.3 mol, 1.4 equiv) via metering pump over 90 min. The resulting mixture was held at 30 °C for 40 min and then cooled to −22 °C. The contents of reactor 1 (containing alcohol **2**) were then added to reactor 2 over 2 h, through the hard pipe riser, maintaining the reactor 2 contents temperature below −15 °C. Reactor 1 was then rinsed with 154 kg of DME, and this wash was transferred to reactor 2. The batch contents were then warmed linearly at 0.07 °C/min to 22 °C, requiring 8 h. Reactor 1 was then cooled to −5 °C, and distillation of DME from reactor 2 to reactor 1 was carried out at 1−25 °C/1−7 kPa, collecting 1880 L of DME, requiring 14 h. To reactor 2 was then charged 1564 kg of *i*-PrOH; then azeotropic distillation of *i*-PrOH was carried out at 15−23 °C/2−13 kPa, collecting 2000 L distillate, requiring 9 h. Then charged to reactor 2 was 737 kg of *i*-PrOH, and to reactor 1 (empty) was charged 463 kg of *i*-PrOH. Reactor 1 contents were then cooled to −10 °C, and $HCl_{(g)}$ was charged subsurface to reactor 1, using 10.7 kg of HCl (293.5 mol, 0.97 equiv), requiring 1 h. The batch in reactor 2 was then warmed to 74 °C, and the HCl/*i*-PrOH solution in reactor 1 was then transferred to reactor 2 through the bottom valve over 30 min. The batch contents (reactor 2) were then cooled linearly to 60 °C at 0.2 °C/min, and held at 60 °C for 2 h. The batch was then cooled linearly to 20 °C at 0.1 °C/min. requiring 7 h. The resultant slurry was then aged 12 h at 20 °C and then centrifuged at 740 rpm, performing three 82 kg of *i*-PrOH washes of the cake. The cake was then cut out, placed in a dryer, and dried at 38 °C under full vacuum with a nitrogen purge to constant weight: 111.69 kg of **19**, 80.2% yield, as a white solid; mp 206.2−207.9 °C. ^{1}H NMR (400 MHz, MeOH-d_4) δ: 8.95 (d, J = 6.7 Hz, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.15 (m, 2H), 8.07 (d, J = 3.5 Hz, 2H), 7.84 (m, 1H), 7.75 (dd, J = 1.5, 8.0 Hz, 1H), 7.47 (d, J = 6.7 Hz, 1H), 7.19 (dd, J = 4.7, 8.0 Hz, 1H), 4.76 (t, J = 5.6 Hz, 2H), 4.10 (m, 2H), 3.49 (s, 3H), 3.34 (t, J = 6.1 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, MeOH-d_4) δ: 170.23 (s), 169.21 (s), 160.16 (s), 156.04 (s), 152.79 (d), 147.58 (d), 145.86 (d), 142.84 (d), 140.46 (s), 136.13 (d), 133.26 (s), 133.14 (d), 130.27 (d), 130.00 (s), 124.67 (d), 122.28 (s), 122.19 (s), 121.72 (d), 121.35 (d), 103.80 (d), 72.91 (t), 42.18 (t), 37.77 (q), 32.18 (t), 14.00 (q). Anal. Calcd for $C_{25}H_{24}ClN_5O_2$: C, 65.00; H, 5.24; N, 15.16. Found: C, 64.86; H, 5.09; N, 14.87.

5-Ethyl-10-methyl-2-[2-(1-oxyquinolin-4-yloxy)ethyl]-5,10-dihydro-4,5,6,10-tetraazadibenzo[*a*,*d*]cyclohepten-11-one (1).

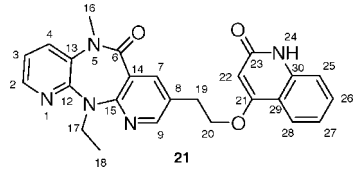


1

All operations were performed in the dark. An inerted 400 L reactor was charged with 9.24 kg of **19** (19.8 mol, 1 equiv) and then reinerted by two vacuum/N_2 cycles. MeOH (3.4 kg) and CH_2Cl_2 (42.3 kg) were then charged, and the internal temperature of the agitated slurry was adjusted to 25 °C. Over 45 min was charged 133 kg of 2.7 M Na_2CO_3, giving a batch pH of 10.0. To this mixture was then added an aqueous slurry of 26.5 kg of 60% *m*-CPBA (92 mol, 4.6 equiv) + 22.3 kg of H_2O over 45 min, maintaining the batch temperature not more than 30 °C, and using 3 kg of H_2O to rinse the charging lines. H_2O (13.1 kg) and CH_2Cl_2 (7.7 kg) were then charged, and

the mixture was agitated at 120 rpm for 90 min, when HPLC indicated the reaction was complete. Over 30 min, was charged 64.4 kg of 2 M Na_2SO_3, maintaining the batch temperature not more than 30 °C. The mixture was then aged 50 min with agitation, and volatiles were removed by distillation (38 °C/98 kPa), collecting 42 L. H_2O (153 kg) was then charged to the reactor, and the batch was agitated for 8 h at 40 °C and cooled to 30 °C; the solids were isolated by centrifugation, at high speed, until mother liquors ceased to flow (~3 h). The cake was then washed in the centrifuge twice with 30 kg of H_2O and dried to constant weight: 9.85 kg of **1** as an off-white solid, 10.7% H_2O by KF (weakly crystalline trihydrate by XRPD. CH_2Cl_2 < 400 ppm. For a discussion of the crystalline forms of compound **1**, see ref 18). HPLC purity 98.1A%, 86% yield. CAUTION: This solid is a dust explosion hazard! DSC showed an endotherm at ~94 °C, followed by a melt at ~136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (d, J = 7.0 Hz, 1H,), 8.62 (d, J = 8.7 Hz, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.18 (dd, J = 4.7, 1.6 Hz, 1H), 7.8 (dd, J = 5.4, 5.4 Hz, 1H), 7.70 (dd, J = 7.2, 7.2 Hz, 1H), 7.47 (dd, J = 8.0, 1.6 Hz, 1H), 7.07 (dd, J = 7.9, 4.7 Hz, 1H), 6.78 (d, J = 7.0 Hz, 1H), 4.42 (dd, J = 6.2, 6.2 Hz, 2H), 4.18 (q, J = 6.9 Hz, 2H), 3.50 (s, 3H), 3.22 (dd, J = 6.2, 6.2 Hz, 2H), 1.24 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 166.25 (C6), 157.68 (C15), 153.95 (C12), 151.31 (C21), 151.13 (C9), 144.02 (C2), 141.21 (C7), 140.47 (C30), 135.36 (C23), 131.70 (C4), 131.11 (C13), 130.58 (C26), 128.86 (C8), 128.02 (C27), 122.28 (C28), 122.07 (C29), 120.24 (C3 + C14), 119.24 (C25), 101.92 (C22), 68.87 (C20), 40.36 (C17), 36.71 (C16), 30.59 (C19), 13.40 (C18). Anal. Calcd for $C_{25}H_{23}N_5O_3$·[10.7% H_2O]: C, 60.60; H, 5.90; N, 14.13. Found C, 60.46; H, 5.45; N, 14.22.

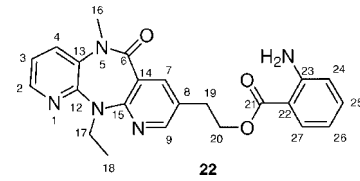
5-Ethyl-10-methyl-2-[2-(2-oxo-1,2-dihydroquinolin-4-yloxy)-ethyl]-5,10-dihydro-4,5,6,10-tetraazadibenzo[*a*,*d*]cyclohepten-11-one (21).



21

A solution of 0.48 g (1.00 mmol, 1 equiv) of **1** in 0.7 L of MeOH was photolyzed with a 200 W floodlamp for 7 days in a glass flask. The solvent was then evaporated and the residual solid dissolved in CH_2Cl_2/MeOH and adsorbed onto a plug of silica gel. This material was then chromatographed on silica gel using 5% MeOH/CH_2Cl_2 to give 240 mg (50%) lactam **21** as a white solid; mp 281 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.45 (d, J = 1.8 Hz, 1H, H9), 8.18 (d, J = 4.0 Hz, H2), 8.08 (d, J = 1.8 Hz, H7), 7.82 (d, J = 7.8 Hz, H4), 7.71 (d, J = 7.8 Hz, H28), 7.47 (t, J = 7.8 Hz, H26), 7.25 (m, H3 + H25), 7.11 (t, J = 7.8 Hz, H27), 5.85 (s, H22), 4.30 (br s, H20), 4.08 (br s, H17), 3.27 (s, H16), 3.16 (t, J = 6.6 Hz, H19), 1.21 (t, J = 7.0 Hz, H18). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.25 (C15), 163.07 (C23), 162.95 (C21), 157.64 (C15), 153.94 (C12), 151.09 (C9), 144.00 (C2), 141.16 (C7), 138.56 (C30), 131.67 (C4), 131.11 (C13), 130.83 (C26), 128.94 (C8), 122.12 (C28), 121.21 (C27), 120.25 (C14), 120.22 (C3), 115.08 (C25), 114.39 (C29), 97.24 (C22), 68.25 (C20), 40.37 (C17), 36.71 (C16), 30.49 (C19), 13.39 (C18). Anal. Calcd for $C_{25}H_{23}N_5O_3$·[0.5 H_2O]: C, 66.65; H, 5.37; N, 15.55. Found C, 66.47; H, 5.02; N, 15.33.

2-Aminobenzoic acid 2-(5-ethyl-10-methyl-11-oxo-10,11-dihydro-5*H*-4,5,6,10-tetraazadibenzo[*a*,*d*]cyclohepten-2-yl)-ethyl ester (22).



22

A flask was charged with 596 mg of alcohol **2** (2.10 mmol, 1 equiv), 1.22 g of DMAP (10.0 mmol, 5 equiv), 1.63 g of isatoic anhydride (10.0 mmol, 5 equiv) and 15 mL DMF. The mixture was heated to 60 °C under N_2 and maintained there for 2 h. The cooled mixture was then diluted with 50 mL of EtOAc and 50 mL of H_2O, and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic phases were washed with saturated NaCl (2 × 100 mL) and dried (Na_2SO_4), and the solvents were removed in vacuo to give a solid. The solid was dissolved in EtOAc and filtered through a pad of silica gel to remove polar material, and then the filtrate was chromatographed on silica gel eluting with 1:1 Hex/EtOAc to give 600 mg of anilinoester **22** (72%) as a white solid; mp 107 °C. HRMS Calcd for $C_{23}H_{23}N_5O_3$: 418.1879; Found: 418.1878 (error 0.2 ppm); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.38 (d, J = 2.2 Hz, H9), 8.19 (dd, J = 1.6, 4.6 Hz, H2), 8.01 (d, J = 2.3 Hz, H7), 7.61 (dd, J = 1.6, 8.1 Hz, H27), 7.25 (m, H3 + H25), 6.74 (dd, J = 0.8, 8.3 Hz, H24), 6.58 (br s, NH_2), 6.47 (t, J = 7.1 Hz, H26), 4.36 (t, J = 6.6 Hz, H20), 4.06 (m, H17), 3.42 (s, H16), 3.01 (t, J = 6.6 Hz, H19), 1.16 (t, J = 7.1 Hz, H18). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 167.11 (C21), 166.23 (C6), 157.64 (C15), 153.92 (C12), 151.35 (C23), 150.94 (C9), 144.01 (C2), 140.99 (C7), 133.98 (C25), 131.69 (C4), 131.12 (C13), 130.41 (C27), 128.98 (C8), 120.28 (C14), 120.23 (C3), 116.46 (C24), 114.67 (C26), 108.54 (C22), 63.82 (C20), 40.38 (C17), 36.73 (C16), 30.41 (C19), 13.40 (C18). Anal. Calcd for $C_{23}H_{23}N_5O_3$·[0.27 H_2O]: C, 65.41; H, 5.62; N, 16.58. Found: C, 65.79; H, 5.52; N, 16.18.

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