Organic Process Research & Development **2007**, *11*, 441–449

# The Preparation of Two, Preclinical Amino-quinazolinediones as Antibacterial Agents

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**Abstract:**

**This paper describes the synthesis of two amino-quinazolinediones which are potent gyrase/topoisomerase inhibitors and useful as antibacterial agents. The early scale-up work to prepare a chiral side chain on multigram scale and two different amino-quinazolinedione cores is detailed. The enabling synthesis for the side chain employed a previously reported Michael addition of $MeNO_2$ to an enantiomerically enriched $\delta$-amino-enoate and a two-step de-oxygenation of a lactam. Key synthetic steps for core preparation and completion of the amino-quinazolinediones include dianion-promoted cyclization via intramolecular, nucleophilic aromatic substitution, electrophilic amination, nucleophilic aromatic substitution of the side chain to the core, deprotection and isolation of the hydrochloride salt in acceptable yield.**

## Introduction

This report describes the preparation of two early development compounds, 3-amino-quinazoline-2,4-diones (AQDs), **1** and **2** (Figure 1). These two amino-quinazoline-2,4-diones are potent gyrase/topoisomerase inhibitors and are useful as antibacterial agents.[1a] Key to the development of an enabling synthesis for these two 3-amino-quinazoline-2,4-diones required improving the resolution of the side-chain **5**, modifying previously reported conditions for the desulfurization of lactam **9** (Scheme 1), improving the intramolecular cyclization of **16** and **29**, subsequent side-chain coupling, and conversion to the final products which were delivered as HCl salts. The preparation of these two AQDs required large amounts of the side-chain **5** and both AQD cores **3** and **4**. Initially, our focus was on 8-methoxy AQD **1**; however, after the preparation of small batches, **1** was determined to be amorphous, and our focus was shifted to 8-methyl AQD analogue **2**.

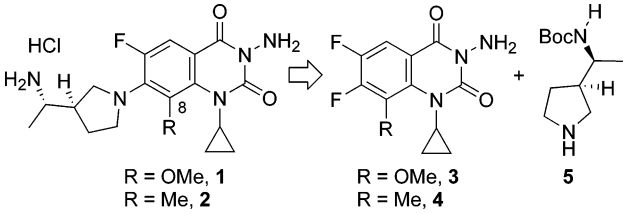
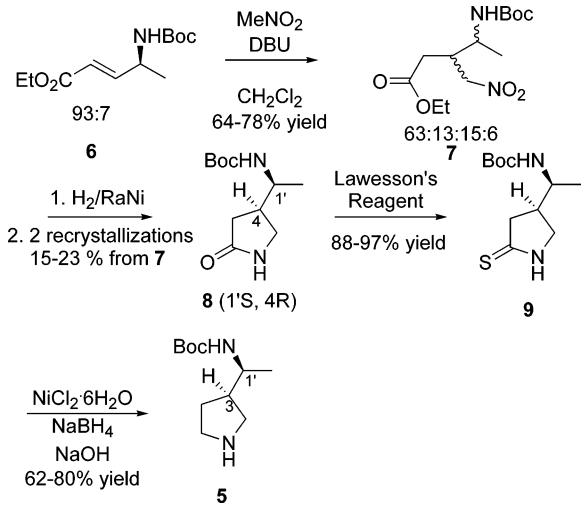



***Figure 1.*** **8-Methoxy and 8-methyl AQDs with cores and side chain.**

***Scheme 1.*** **Preparation of side-chain 5**




## Results and Discussion

The synthesis of the required side-chain **5** followed the strategy reported by Plummer and co-workers (Scheme 1).[1b] Olefin **6**[1c–e] was treated with $MeNO_2$ and DBU in $CH_2Cl_2$ to give crude **7**, which was carried on to **8** without purification. Based on the recovered mass and HPLC purity, 64−78% of **8** was obtained from **6**. HPLC analysis using a chiral column showed that crude **8** was a mixture of four stereoisomers in a 63:13:15:6 ratio[2] with the desired 1′*S*,4*R* isomer being the major component. The measured ratio of 63:13 at C4 is similar to the reported ratio of 80:20. Lactam **8** was more easily crystallized than amine **5** and did not have the stench associated with thiolactam **9**; thus, efforts for stereochemical purification were focused on lactam **8**. Crude **8** was recrystallized twice from $(CH_2Cl)_2$ to give **8** (1′*S*,4*R*) in

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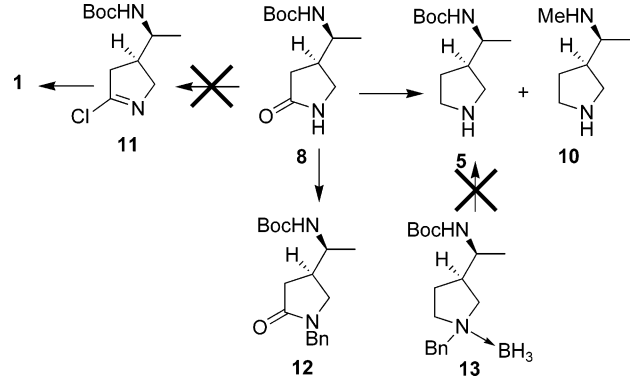
(1) (a) Bird, P.; Ellsworth, E. L.; Nguyen, D. Q.; Sanchez, J. P.; Showalter, H. D. H.; Singh, R.; Stier, M. A.; Tran, T. P.; Watson, B. M.; Yip, J. 3-Aminoquinazoline-2,4-diones Antibacterial Agents. WO 2001053273, July 26, 2001. (b) Plummer, J. S.; Emory, L. A.; Stier, M.; Suto, M. *Tetrahedron Lett.* **1993**, *34*, 7529. (c) Olefin **6** was prepared as a 93:7 ratio of enantiomers from *N*-Boc-alanine in 3 steps by: (1) Weinreb amide formation, (2) LAH reduction to the aldehyde, and (3) Horner−Emmons olefination of the corresponding aldehyde as previously reported: Reetz, M. T.; Röhrig, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1706. (d) While we were able to reproduce the reported enantiomeric retention (>99:1) on small scale, on scale-up, both we and an outside CRO reproducibly obtained **6** as a 93:7 ratio of enantiomers. (e) Kimura, Y.; Atarashi, S.; Takahasi, M.; Hayakawa, I. *Chem Pharm. Bull*. **1994**, *42*, 1442.

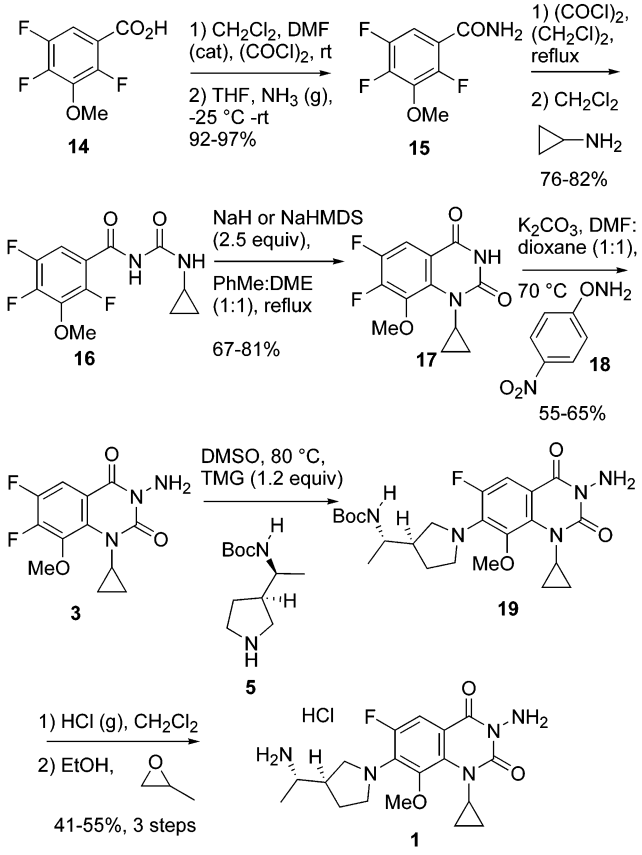
(2) The ratio of compounds has been assigned to the respective isomers as follows: 63:13:15:6; 1′*S*,4*R*:1′*S*,4*S*:1′*R*,4*S*:1′*R*,4*R*. Studies used to assign the absolute stereochemistry of the side chain have been reported: Schroeder, M. C.; Kiely, J. S.; Laborde, E.; Johnson, D. R.; Szotek, D. L.; Domagala, J. M.; Stickney, T. M.; Michel, A.; Kampf, J. W. *J. Heterocycl. Chem.* **1992**, *29*, 1481.

10.1021/op7000639 CCC: $37.00 
Published on Web 05/04/2007

***Scheme 2.*** **Alternative routes to 5 from 8**



***Scheme 3.*** **Preparation of 8-methoxy AQD 1**



>97% de and 15−23% recovery. Other solvents screened for recovery and resolution and found to be inferior were EtOH, IPA, toluene, EtOAc, and EtOH/$H_2O$.

Thiolactam **9** was prepared by treatment of **8** with Lawesson's reagent in THF at room temperature. Yields for **9** ranged from 88% to 97%, and purities ranged from 94% to 98%. The reduction of **9** to amine **5** was accomplished with $NaBH_4/NiCl_2{\cdot}6H_2O$ in water/THF (in situ formation of Ni/boride). The reduction was extremely exothermic and difficult to control. For scale-up purposes, $NaBH_4$ was stabilized by dissolving it in caustic MeOH, which allowed for controlled addition. Thiolactam **9** was treated with the caustic $NaBH_4/NiCl_2{\cdot}6H_2O$ solution at −50 to −20 °C to give **5** in a 62−80% yield. HPLC with Marfey's reagent derivatization showed that **5** was >98% de.

All attempts to directly convert **8** to **5** failed. Reagents such as LAH, Red-Al, and $LiBH_4$ gave mixtures of the product contaminated with **10** and starting material (Scheme 2). Reagent combinations of $NaBH_4/I_2$ and $NaBH_4/TiCl_4$ gave mixtures of product and starting material. Boron reagents such as $BH_3/Me_2S$, $BH_3$/THF, and 9-BBN failed to produce product in isolable quantities. Conversion of **8** to **5** via iminoylchloride **11** using $POCl_3$ or $PCl_5$ also failed. Couturier et al.[3] have shown that benzylated imides are reduced with $BH_3$/THF and can subsequently undergo a tandem debenzylation/decomplexation when treated with 10% Pd/C in MeOH. Our attempt to apply Couturier's methodology to this system was unsuccessful. While reduction of **12** was successful, tandem debenzylation/decomplexation did not occur under the reaction conditions tried, and this approach was deemed no better than the chemistry in hand for our rapid needs.

Concurrent with the synthesis of side-chain **5** was the preparation of the two AQD cores, **3** and **4**. 8-Methoxy AQD core **3** was synthesized in six steps from 3-methoxy-2,4,5-trifluorobenzoic acid (**14**) (Scheme 3).[1a,4,5]

Formation of amide **15** by generation of the acid chloride from acid **14** with oxalyl chloride and subsequent amidation with ammonia gave amide **15** in 92−97% yield. Schötten−Bauman conditions were also used to form amide **15** from the acid chloride, but the workup proved difficult, and long drying times were required. Reaction of amide **15** with oxalyl chloride in refluxing $(CH_2Cl)_2$ gave the aroylisocyanate.[6] It was important to remove any excess $(COCl)_2$ as the bis-*N*-cyclopropyloxalylamide proved difficult to remove from the desired product.[7] Reaction of the aroylisocyanate intermediate with cyclopropylamine provided **16** in 76−82% yield. It was difficult to determine the end point of the formation of the aroylisocyanate using classical methods (GC, NMR, HPLC). We found that monitoring the reaction by ReactIR worked well, and the reaction required 8−10 h at reflux to completely consume the starting amide **15**.[8] Alternatively, phosgene and CDI were tried but led to inferior results (lower yield). A base screen for the cyclization of urea **16** to form quinazoline-2,4-dione core, **17**, was undertaken. Strong bases (NaH, NaHMDS, KHMDS) were required to promote dianion formation and cyclization to provide the desired product. Potassium *tert*-butoxide ($K^{+-}O$*t*-Bu) resulted in the desired cyclization but also led to the formation of up to 15% of **20**

(3) Couturier, M.; Tucker, J. L.; Andresen, B. M.; Dube, P.; Negri, J. T. *Org. Lett*. **2001**, *3*, 465.

(4) Tran, T. P.; Ellsworth, E. L.; Watson, B. M.; Sanchez, J. P.; Showalter, H. D. H.; Rubin, J. R.; Stier, M. A.; Yip, J.; Nguyen, D. Q.; Bird, P.; Singh, R. *J. Heterocycl. Chem*. **2005**, *42*, 669.

(5) Some alternative approaches to the quinazoline-2,4-dione system are: (a) Aziane, D.; Soukri, M.; El Hakmaoui, A.; Lazar, S.; Essassi, E. M.; Guillaumet, G.; Akssira, M. *J. Heterocycl. Chem*. **2002**, *39*, 271. (b) Mizuno, T.; Iwai, T.; Ishino, Y. *Tetrahedron Lett.* **2004**, *45*, 7073. (c) Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. *Tetrahedron Lett.* **1998**, *39*, 7235. (d) Makino, S.; Suzuki, N.; Nakanishi, E.; Tsuji, T. *Synlett* **2001**, 333. (e) Smith, A. L.; Thomson, C. G.; Leeson, P. D. *Biorg. Med. Chem. Lett*. **1996**, *6*, 1483.

(6) Speziale, A. J.; Smith, L. R. *J. Org. Chem*. **1962**, *27*, 3742.

(7) Residual oxalyl chloride was not monitored, but solvent removal by evaporation (rotary evaporator) proved adequate to remove excess oxalyl chloride and mitigate the formation of the bis-oxalylamide.

(8) React IR stretches followed were: 1686 $cm^{-1}$ (amide) converting to 1737 $cm^{-1}$ (oxalylamide) converting to 2250 $cm^{-1}$ (aroylisocyanate).

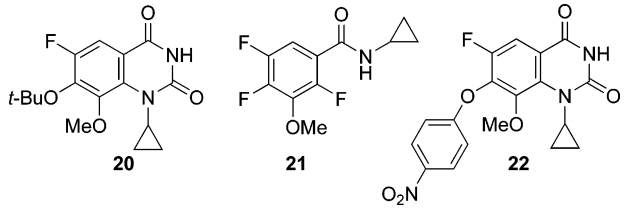
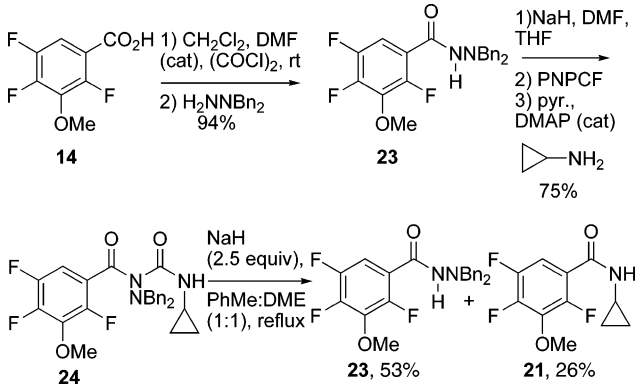



***Figure 2.*** **Byproducts observed in the synthesis of 8-methoxy core 3.**

***Scheme 4.*** **Alternative approach to 8-methoxy core 3**




(Figure 2). Treatment of **16** with weak inorganic bases ($Cs_2CO_3$ or $K_3PO_4$) produced amide **21** in 15−19% with recovered starting material (Figure 2). Whether **21** is formed via intra- or intermolecular cyclization or by fragmentation and recombination was not determined, but this impurity was not formed to an appreciable extent (<3%, HPLC) under conditions in which strong bases were used to provide the desired cyclized product **17**.

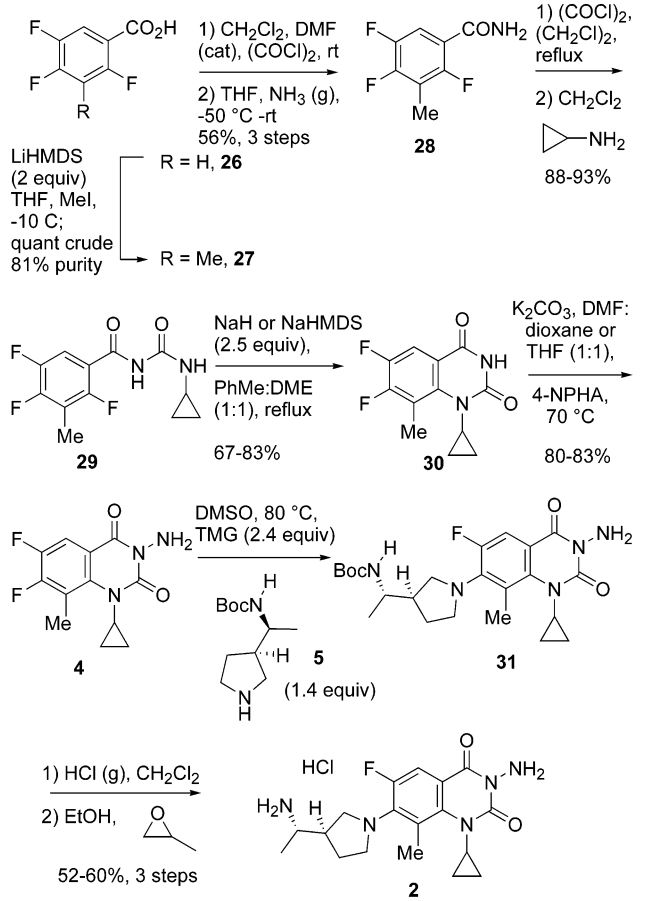
Electrophilic amination of imide **17** using 4-nitrophenylhydroxylamine (**18**, 4-NPHA) produced 3-amino-quinazoline-2,4-dione core **3** in 60−70% yield. Amination product **3** was contaminated with 3−6% of **22** (Figure 2, HPLC/MS). A study regarding the potential thermal hazard of substituted phenylhydroxylamines as electrophilic aminating reagents was previously reported.[9] Coupling of side-chain **5** with core **3** using a slight excess of **5** and tetramethyl guanidine (TMG) as the base in DMSO at 80 °C provided the crude product. Boc deprotection using HCl(g), followed by propylene oxide[10] treatment and recrystallization led to the formation of the final product **1**, in 41−55% overall yield from **3**.

In the desire to circumvent the use of an electrophilic aminating reagent, one alternative approach to prepare core **3** was attempted (Scheme 4). Acid chloride formation from acid **14** with $(COCl)_2$ and treatment with *N*,*N*-dibenzyl hydrazine provided hydrazide **23** in good yield. Formation of the anion with NaH and reaction with *p*-nitrophenylchloroformate (PNPCF) and quenching with cyclopropyl amine gave urea **24**. Attempted cyclization of *N*,*N*-dibenzyl-*N*-cyclopropyl urea **24** with NaH served to fragment the starting material and produced a mixture of **23** and **21** in 53% and 26% isolated yields, respectively.

(9) Boyles, D. C.; Curran, T. T.; Davis, M.; Mauro, F.; Parlett, R. V., IV. *Org. Process Res. Dev.* **2002**, *6*, 230.

(10) It was critical in the isolation of the final HCl salts to remove all of the excess HCl; thus, propylene oxide was used. Without removing excess HCl, the final product was extremely hygroscopic and would deliquesce on standing.

***Scheme 5.*** **Preparation of 8-methyl AQD 2**




The preparation of 8-methyl AQD **2** (Scheme 5) commenced with the methylation of 2,4,5-trifluorobenzoic acid (**26**). Formation of the dianion from **26** with LiHMDS and reaction with iodomethane afforded crude **27** in quantitative mass recovery with 81% purity. This material was contaminated with **32** and starting acid **26** (Figure 3).

Acid **27** could be further purified, but at the cost of losing a lot of material. The crude mixture was typically carried forward into the next step and purified more easily after amide **28** was formed. Acid chloride formation of the crude mixture **27** with $(COCl)_2$ and subsequent amide formation with ammonia and recrystallization gave amide **28** in 56% overall yield from **26**. Treatment of the amide with $(COCl)_2$

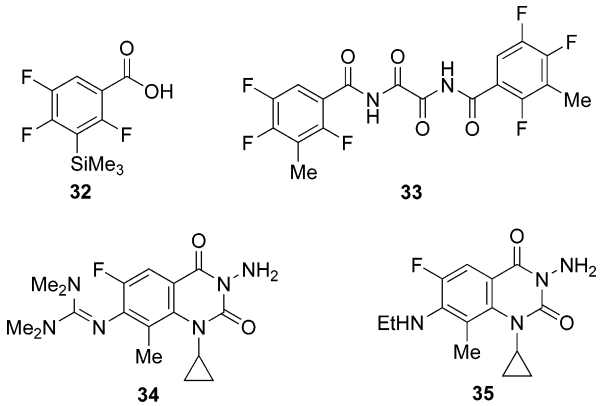
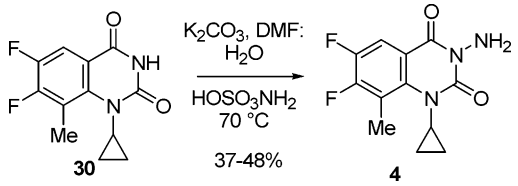



***Figure 3.*** **Byproducts observed in the synthesis of 8-methyl AQD 2.**

***Scheme 6.*** **Alternative amination strategy**

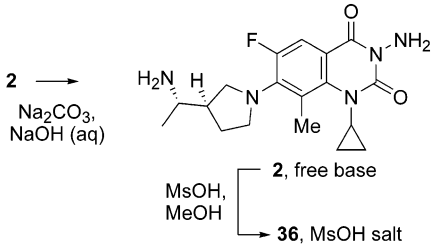



in refluxing $(CH_2Cl)_2$ to form the aroylisocyanate and subsequent reaction with cyclopropylamine provided *N*-cyclopropyl urea **29** in 88−93% yield. *It is important to note that amide attack on the intermediate acid chloride is quite facile*. Slow addition of $(COCl)_2$ to amide **28** with warming resulted in significant amounts of dimer **33** (Figure 3). Dianion formation with NaH or NaHMDS in a mixture of PhMe and DME produced cyclic urea **30** in 67−83% yield.

Amination of cyclic urea **30** with 4-NPHA afforded AQD core **4** in 80−83% yield. A commercially available and relatively inexpensive electrophilic amination was tried using $H_2NOSO_3H$ (Scheme 6). This procedure provided very high-quality material in low yields (due to base-promoted opening of the AQD core **4**). These conditions were not further studied.

Coupling of side-chain **5** with core **4** proved to be much more difficult than the previously described coupling with core **3**.[11,12] A number of organic bases were screened, the stoichiometry of the base and side chain were increased, in comparison to that of the methoxy core **3** (which coupling was complete in 15 h with half as much side chain), in order to improve this transformation. Of the organic bases screened, TMG (2.8 equiv) again proved to be the best base, and it was important to use side-chain **5** in excess (1.4 equiv). These conditions minimized a TMG adduct impurity **34** (Figure 3) and converted (<3 area % core **4** by HPLC) the core into desired product after stirring for 53 h. It was important to remove the TMG adduct as early as possible because downstream processing converted the TMG adduct **34** into **35**, which was difficult to remove through recrystallization of the final product. In contrast, TMG adduct **34** was readily removed by washing the coupled product **31** with 0.5 M HCl. This provided crude coupled product **31** in >90% crude yield and >90% purity (HPLC area %). Other organic bases that were screened and found to be inferior to TMG were DBN, DABCO, EtN*i*-$Pr_2$, and pyridine. Addition of a Lewis acid ($ZnBr_2$, $BF_3$, or $MgBr_2$) in attempts to activate the electrophile also failed to improve the side-chain coupling reaction.

***Scheme 7.*** **Preparation of methanesulfonate salt 36**




Removal of the Boc group by bubbling HCl(g) into a cooled solution of crude **31** in $CH_2Cl_2$ resulted in the crude HCl salt after solvent evaporation. Propylene oxide treatment in EtOH and recrystallization from IPA/$H_2O$ provided final product **2** as the mono-HCl salt in 52−60% yield. This material was crystalline; yet, to determine the absolute configuration by single-crystal X-ray, additional salts were prepared. The free base was formed by treatment with aqueous base followed by extraction (Scheme 7).

The mesylate salt **36** was subsequently formed by treating free base **2** with methanesulfonic acid in MeOH. Crystals suitable for single X-ray crystal structure determination were grown using slow vapor diffusion technique. The single X-ray crystal structure was obtained of the mesylate salt **36** (Figure 4).

## Conclusion

In summary, we have demonstrated the preparation of stereochemically enriched **1** and **2** on multigram scale. In accomplishing this, we have shown an enabling route to produce multigram quantities of side-chain **5**, and two AQD cores **3** and **4**. Side-chain **5** was prepared from enriched enoate **6** in four steps and 9% overall yield. Compound **3** was prepared in six steps and 19% overall yield, whereas compound **4** was prepared in seven steps and 18% overall yield. Subsequent coupling of cores with side-chain **5**, deprotection, and isolation led to compounds **1** and **2** in 41−55% and 52−60% yield, respectively.

## Experimental Section

**General.** $^1H$ and $^{19}F$ NMR spectra were recorded on Varian Unity instruments at 400 and 376 MHz, using internal

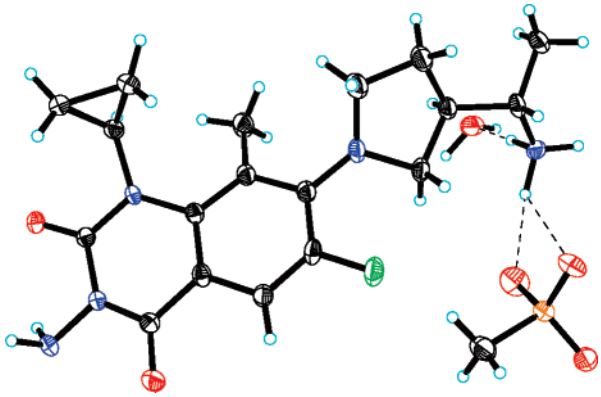


***Figure 4.*** **X-ray crystal structure of 8-methyl AQD MsOH salt 36.**

(11) While a single reference was not found on the direct comparison of rate differences between the $S_NAr$ reaction on 8-methyl and 8-methoxy quinolones, the references here do show a difference in reactivity. (a) Sanchez, J. P.; Gogliotti, R. D.; Domagala, J. M.; Gracheck, S. J.; Huband, M. D.; Sesnie, J. A.; Cohen, M. A.; Shapiro, M. A. *J. Med. Chem.* **1995**, *38*, 4478. (b) Cecchetti, V.; Fravolini, A.; Palumbo, M.; Sissi, C.; Tabarrini, O.; Terni, P.; Xin, T. *J. Med. Chem.* **1996**, *39*, 4952. While ref (a) describes the substitution of 6,7-diflouro-8-methoxy-3-quinolone carboxylic acid ethyl ester with a pyrrolidine in MeCN at 50 °C (89%, **10e** in the paper), ref (b) describes the substitution of the 7-fluoro-8-methyl-3-quinolone carboxylic acid difluoroborinate (34 × 88%, **6j** in the paper) using DMSO at 80 °C. The activation of the borate and the more stringent reaction conditions in the 8-methyl-quinolone carboxylic acid case as well as our experience with the difference in reactivity of the 8-Me and 8-OMe derivatives in the AQD cores shows a significant reactivity difference which is proposed to be stereoelectronic.

(12) A meta-alkoxy or -halo accelerating effect has been reported for the $S_NAr$ addition of Grignard reagents to multisubstituted aromatic compounds. See: (a) Hattori, T.; Takeda, A.; Suzuki, K.; Koike, N.; Koshiishi, E.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3661. (b) Hattori, T.; Koike, N.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2273.

and external references, respectively. Chemical shifts are reported in ppm, and the same solvents used to acquire data for $^{1}H$ NMR were used for $^{19}F$ NMR. IR was recorded neat on a Biorad FTS45 FTIR. GCs were recorded on an HP 6890 using an HP-1 (30 m × 0.32 mm × 0.35 μm; 100 °C for 5 m, 15 °C/min to 250 °C for 10 min). HPLCs were recorded on a Perkin-Elmer series 200 system using one of the various methods at 210 nm (for side-chain **5** synthesis) or 225 nm (work toward cores **3** and **4** or when core attached) with a flow of 1 mL/min unless otherwise noted. HPLC1: Waters Symmetry C18 column (150 mm × 4.6 mm × 3 μm), using an isocratic mobile phase of 55% Solvent A (100 mL MeCN, 2.5 mL $H_3PO_4$, 3 mL of triethylamine, diluted to 1 L with $H_2O$), 15% Solvent B (MeOH), and 30% Solvent C (MeCN). HPLC2: Chiralpak AS column (Daicel Chemical Industries LTD) using an isocratic mobile phase of 80% Solvent A (hexane) and 20% Solvent B (EtOH). HPLC3: samples were derivatized using Marfey's reagent, Zorbax Extend C18 column (150 mm × 4.6 mm × 3.6 μm), using a gradient of Solvent A (0.1% $NH_4OH$ in $H_2O$) and Solvent B (MeOH), starting at 50:50 ratio and going to 10:90 ratio over 30 min. HPLC4: YMC ODS-AM (150 mm × 4.6 mm, 3 μm), using a gradient of solvent A ($MeCN/H_2O/Et_3N/H_3PO_4$, 100:900:3.5:2) and solvent B (MeCN), starting at a 90:10 ratio and going to 10:90 (A:B). HPLC5: Zorbax Bonus RP (15 × 4.6 cm, 3.5 μm), using solvent A (0.05% TFA in water) and solvent B (MeCN) starting at 85:15 to 10:90 (A:B). HPLC6: YMC ODS-AM (150 mm × 4.6 mm, 3 μm), using a gradient of solvent A (0.2% $HClO_4/H_2O$) and solvent B (MeCN), starting at 90:10 ratio and going to 10:90 (A:B). HPLC7: crownpak Cr+ (150 × 4.6 cm, 5 um), 0.8 mL/min, MeOH/$H_2O$, 85:15. HPLC8: YMC Pack Pro C-18 (50 × 4.6, 3.5 μm) using gradient 90:10 to 10:90, solvent A (0.1% TFA/water) and solvent B (MeCN). HPLC9: Zorbax C18 Extend (15 × 3.5 cm, 3.5 μm) using A (0.1% TFA in water) and B (MeCN) gradient elution 70:30 to 10:90.

**Ethyl-3-nitromethyl-4-[*tert*-(butoxycarbonyl)amino]-pentanoate (7).** In a 10-L jacketed flask, 1200 g (5.13 mol) of **6** was stirred with 626 g (10.25 mol, 2 equiv) of $MeNO_2$ in $CH_2Cl_2$ (3 L). The circulating bath temperature was set at 20 °C and DBU, 781 g (5.13 mol, 1 equiv), was slowly dripped into the flask keeping the temperature below 30 °C. Upon completion of the addition, the reaction was stirred at 25 °C overnight. 2 N citric acid (2.8 L) was added in one portion to the reaction. The layers were separated, and the lower organic layer was washed with $H_2O$ (2 L). The aqueous layers were combined and extracted with $CH_2Cl_2$ (1 × 2 L). The organic layers were combined and dried over $MgSO_4$. The solution was filtered, and the filtrate was concentrated to give 1423 g (94% of theory) of a reddish-brown oil. For **7**: (HPLC1) = 9.1 min, 73.6 area %.

**4(*R*)-[1(*S*)-*tert*-(Butoxycarbonyl)amino]ethyl]-2-pyrrolidinone (*8*)**. The intermediate **7** (1238 g, 73.6% pure, 2.99 mol) was dissolved in MeOH (15 L) and placed in a 30-L hydrogenation apparatus.[13] Raney nickel (300 g wet) was added to the vessel rinsing with MeOH. The vessel was then sealed and purged with nitrogen. The reactor was pressurized to 50 psi $H_2$ (the reaction was performed at 50 psi $H_2$ constant pressure) and stirred with a magnetically coupled air driven motor. The reaction was run at room temperature with no external cooling (although a cooling coil is present in the reactor for use in the event of an exotherm). The reaction was monitored by measuring hydrogen uptake. After 4 h the reaction reached a maximum temperature of ~30 °C. The hydrogen uptake was complete after 8 h. The reaction was sampled and deemed complete by HPLC1. The Raney nickel was then filtered from the reaction mixture, and the crude solution was concentrated to dryness. NMR was taken of the crude material to determine MeOH content. If MeOH was present, crude material was slurried in $(CH_2Cl)_2$ (4 L) and then concentrated to dryness at 60 °C and 35 mmHg to yield 1281 g of a brown tar-like product. For **8**: (HPLC1) = 2.09 min, 72.7 area %; (HPLC2) = 19.00 min, 53.96 by area % 1*S*,4*R* isomer.

A slurry of crude **8** (1191 g) in $(CH_2Cl)_2$ (2.7 L) in a 5-L reaction vessel equipped with a heating mantle and reflux condenser was heated to reflux until the solution was homogeneous. Power to the heating mantle was turned off, and the solution was allowed to cool to room temperature; the reaction vessel was then transferred to a 4 °C refrigerator and held overnight. Solid was collected by filtration, washed with $(CH_2Cl)_2$ (0.5 L, 0 °C), and dried (60 °C, 35 mmHg) to give 354 g of **8**, (HPLC2) = 90 area %. This solid was recrystallized a second time in an analogous fashion to give 259 g (29% of theory) of **8** as a white solid. For **8**: (HPLC2) = 18.87 min, 99.11 area %.

**4(*R*)-[1′(*S*)-[*tert*-(Butoxycarbonyl)amino]ethyl]pyrrolidinone-2-thione (9).** A slurry of **8** (254 g, 1.114 mol) in THF (2.285 L) in a 5-L reaction flask under nitrogen was treated with Lawesson's Reagent (225 g, 0.557 mol, 0.5 equiv) in three portions over a 15-min period. The reaction was stirred at room temperature for 4 h. The solid was collected by filtration and washed with toluene (200 mL). The collected solid was dried (45 °C, 35 mmHg) to give 173 g of **9**, (HPLC1) = 3.03 min, 96.71 by area %. The filtrates were combined and held at −10 °C for 2 days, solid was collected by filtration, washed with toluene (50 mL), and dried as before to give 70 g of **9**, 89.6% total yield, (HPLC1) = 2.96 min, 92.35 area %.

**3(*R*)-[1′(*S*)-[*tert*-(Butoxycarbonyl)amino]ethyl]pyrrolidine (5).** A 22-L reaction vessel equipped with a dry ice/acetone bath, thermocouple, gas inlet, and addition funnel was charged with **9** (173 g, 0.709 mol), $NiCl_2 \cdot 6H_2O$ (502.5 g, 2.12 mol), THF (1.91 L), and MeOH (5.73 L) under nitrogen. The solution was chilled to −50 °C. A solution of $NaBH_4$ (256 g, 6.76 mol) and NaOH (80 mL, 50 wt %) in MeOH (2.43 L) was slowly added to the $NiCl_2$/**9** solution, keeping the reaction temperature <−20 °C. The dry ice/acetone bath was removed, and the reaction was allowed to warm to 10 °C over 3 h. The reaction mixture was diluted with solvent system B (73:22:5 $CH_2Cl_2$/MeOH/$NH_4OH$, 5 L). The reaction solution was filtered through a 1 in. Celite

(13) Raney nickel (Batch 71225, Product A-7000) was supplied by Activated Metals and Chemicals, Inc (Sevierville, TN 423−453-7177). The nickel was supplied under water. Prior to use, the nickel was weighed wet and then washed five times with distilled water.

pad in a 3-L fritted funnel to give Filtrate A. The collected solids were washed three times with $CH_2Cl_2$ (1.5 L) to give Filtrate B. Filtrate A was concentrated to give a light-green residue. The residue was stirred with $MgSO_4$ (100 g) in $CH_2Cl_2$ (3 L) and filtered to give Extract A. The residue was triturated with $CH_2Cl_2$ (3 × 2 L) to give Extracts B, C, and D. Filtrate B was combined with Extracts A−D and concentrated to give 153 g of crude **5**. Crude **5** was chromatographed with silica (1.3 kg, 230−400 mesh) in a 3-L fritted funnel. The column was eluted with solvent system A (9:1 $CH_2Cl_2$/MeOH, 5 L) followed by stepwise elution with 20% solvent system B in A, followed by 40%, then 60%, then 80% (1 L each) and finally eluting with 100% solvent system B. Fractions were analyzed by TLC eluting with solvent system B and staining in an iodine chamber. Product fractions were combined and concentrated to dryness. The resultant solid was dried (45 °C, 35 mmHg) to give 121 g of **5**. For **5**: (HPLC3) = 13.87 min, 98.63 area %; $^1$H NMR ($CDCl_3$) $\delta$ 4.61 (bd, 1H, $J$ = 7.57), 3.54 (m, 1H), 3.32 (bs, 1H), 3.00 (m, 2H), 2.82 (m, 1H), 2.02 (m, 1H), 1.86 (m, 1H), 1.40 (s, 9H), 1.11 (d, 3H, $J$ = 6.59). This product was identical to an authentic sample by $^1$H NMR and HPLC analysis.

**Preparation of 2,4,5-Trifluoro-3-methoxybenzamide (15).** A 12-L reaction vessel equipped with a caustic scrubber containing a slurry of acid **14** (943 g, 4.57 mol) in $CH_2Cl_2$ (7.2 L) was treated with DMF (2 mL) and then oxalyl chloride portionwise (443 mL, 5.10 mol, 1.1 equiv). The reaction was stirred for 20 h at rt, and consumption of starting material was monitored by GC. The reaction mixture was then concentrated in vacuo to give the crude acid chloride as an oil. The crude acid chloride was dissolved in THF (2 L) and added dropwise to a cooled THF (5.2 L) solution which had previously had $NH_3$ bubbled through it for 40 min at −50 °C. Addition was done at such a rate to keep the temperature below −40 °C. After acid chloride addition was complete, $NH_3$ was again bubbled into the reaction mixture for 30 min to ensure that the reaction was complete. The cold bath was removed and the reaction warmed to rt while stirring overnight. The reaction mixture was filtered (to remove solid $NH_4Cl$), and the solid was washed with THF (2 × 1.2 L) and TBME (2 × 1.2 L). The combined washings and filtrate were then concentrated in vacuo. The resulting solid was treated with water (4.2 L) and stirred vigorously for 2 h. The solid was collected by filtration, and the collected solid was dried (40 °C, 15 mmHg. Note: This material sublimes at higher temperature.) to provide a white solid (**15**, 909.5 g, 97%). For amide **15**: mp = 130−133 °C; $t_R$ (GC) = 4.6 min (acid chloride), 8.1 min (amide); $^1$H NMR ($CDCl_3$) $\delta$ 7.60 (m, 1H), 6.53 (bs, 1H), 6.20 (bs, 1H), 4.00 (s, 3H); $^{19}$F NMR $\delta$ −133 (s), −139 (m), −144 (m); IR (KBr) $\nu_{max}$ 3488, 3182, 1700 and 1390 cm$^{-1}$. Anal. Calcd for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83. Found: C, 46.95; H, 3.25; N, 6.74.

**Preparation of 1-Cyclopropyl-3-(2,4,5-trifluoro-3-methoxybenzoyl)urea (16).** A slurry of amide **15** (909 g, 4.42 mol) in $(CH_2Cl)_2$ (6.3 L) in a 12-L reaction vessel equipped with a caustic scrubber was treated dropwise (2 h) with $(COCl)_2$ (520 mL, 5.96 mol, 1.35 equiv) at rt. The reaction was then warmed to 55 °C for 1 h and was then further warmed to reflux for 21 h. The reaction mixture was concentrated in vacuo to afford the crude aroylisocyanate as a yellow oil. A solution of crude aroylisocyanate in $CH_2Cl_2$ (2 L) was added dropwise over 90 min to a cooled solution of cyclopropylamine (363 mL, 5.23 mol, 1.13 equiv) in $CH_2Cl_2$ (6 L) at −6 °C. The addition was done at such a rate to keep the internal temperature below +10 °C. The ice bath expired, and the reaction mixture warmed to rt overnight. The crude reaction mixture was concentrated in vacuo to provide a crude, yellow solid which was recrystallized from toluene (1.7 L) and heptane (3.7 L) and then again from IPA (4 L) and heptane (4 L). The resulting white precipitant was filtered and dried (15 mmHg, 50 °C) to give 1 kg, 78% of urea **16**. For urea **16**: mp = 115−117 °C; $t_R$ (HPLC4) = 15.8 min, 99.8 area %; $^1$H NMR ($CDCl_3$) $\delta$ 9.06 (bd, 1H, $J$ = 9.2 Hz), 8.45 (bs, 1H), 7.48 (m, 1H), 4.06 (s, 3H), 2.74 (m, 1H), 0.80 (m, 2H), 0.61 (m, 2H); $^{19}$F NMR $\delta$ −132 (m), −138 (m), −143 (m); IR (KBr) $\nu_{max}$ 3294, 3098, 3051, 2955, 1704, 1677, 1550, 1495, 1472, 1356 cm$^{-1}$. Anal. Calcd for $C_{12}H_{11}F_3N_2O_3$: C, 50.01; H, 3.85; N, 9.72. Found: C, 50.09; H, 3.81; N, 9.71.

**Preparation of 1-Cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (17).** A slurry of urea **16** (520 g, 1.81 mol) in toluene (3.4 L) and DME (3.4 L) was cooled to −4 °C and treated portionwise (7 portions; 90 min) with NaH (60% in oil, 221 g, 5.53 mol, 3.1 equiv). After effervescence subsided, the cold bath was removed, and the reaction was stirred at rt until visible off-gassing ceased and then further warmed to reflux for 23 h and monitored by TLC (EtOAc/hexanes, 1:1, $R_{fSM}$ = 0.75, $R_{fprod}$ = 0.55). Heating was stopped and the reaction mixture cooled to rt while stirring overnight. The reaction was poured into aqueous HCl (3 M, 2.1 L) and ice (2.1 L). The resulting mixture was stirred vigorously and the solid was filtered (solid 1). The phases separated, and the aqueous phase was extracted with THF/EtOAc (1:1, 2 × 4.8 L). The combined organic phases were concentrated in vacuo to obtain a brown solid (Solid 2). Solids 1 and 2 were combined and recrystallized from dioxane (1.7 L) and heptane (3.4 L) to afford a light-brown solid which, after drying, weighed 484 g, 81% yield. For cyclic urea **17**: mp = 233−234 °C; $t_R$ (HPLC4) = 15.8 min, 99.8 area %; $^1$H NMR (DMSO-$d_6$) $\delta$ 11.6 (s, 1H), 7.6 (m, 1H), 3.90 (s, 3H), 3.2 (m, 1H), 0.97 (m, 2H), 0.62 (m, 2H); $^{19}$F NMR $\delta$ −142 (m), −144 (m); IR (KBr) $\nu_{max}$ 3167, 3039, 2845, 1686, 1405 cm$^{-1}$. Anal. Calcd for $C_{12}H_{10}F_2N_2O_3$: C, 53.74; H, 3.76; N, 10.44. Found: C, 53.59; H, 3.79; N, 10.26.

**Preparation of 3-Amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione, AQD Core (3).** A slurry of cyclic imide **17** (302 g, 0.56 mol) in dioxane (2.7 L), DMF (2.7 L), and $K_2CO_3$ (332 g, 2.4 mol, 2.1 equiv) was stirred for 1 h. After gas evolution subsided, the reaction mixture was warmed to 70 °C, and *O*-4-(nitrophenyl)-hydroxylamine (**18**; 194 g, 0.63 mol, 1.1 equiv) was added in one portion which resulted in a 2 °C endotherm. After 4 h at 72 °C, additional aminating agent (**18**, 17.6 g, 0.11 mol,

0.2 equiv) was introduced. After stirring for 15 h, the reaction was judged complete (TLC; 1:1 EtOAc/hexanes). The reaction mixture was allowed to cool to rt and filtered, and the filtrate was concentrated in vacuo to remove dioxane and some DMF and then poured into water (1.9 L) and crushed ice (1.9 L) with vigorous stirring. The formed solid was collected and washed with TBME (2 L). The resulting solid was recrystallized from IPA (2.2 L) and heptane (2.4 L). The crystals were collected and air-dried to provide **3** (183 g, 57% yield). For **3**: mp 148−150 °C; $t_R$ (HPLC5) = 8.8 min, 92 area % of **3** and 13.4 min 4 area % of **22**; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.7 (m, 1H), 5.5 (bs, 2H), 3.93 (s, 3H), 3.3 (m, 1H), 0.99 (m, 2H), 0.64 (m, 2H); $^{19}$F NMR $\delta$ −141 (m), −145 (m); IR (KBr) $\nu_{max}$ 3359, 3251, 1729, 1658, 1482, 1407 cm$^{-1}$. Anal. Calcd for $C_{12}H_{11}F_2N_3O_3$: C, 50.89; H, 3.91; N, 14.84. Found: C, 51.40; H, 4.13; N, 14.61.

**Preparation of {1(*S*)-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-7-yl)pyrrolidin-3-(*R*)-yl]ethyl}carbamic Acid *tert*-Butyl Ester (19).** A mixture of hydrazide **3** (35.5 g, 0.125 mol) and side-chain **5** (30.3 g, 0.14 mol, 1.1 equiv) in DMSO (126 mL) was treated with TMG (19 mL, 0.15 mol, 1.2 equiv) and warmed to 73 °C for 15 h. The reaction mixture was cooled to rt and poured into half-saturated aqueous $NH_4$-Cl (360 mL). The resulting yellow solid was filtered, and the solid was redissolved in TBME (800 mL). The organic phase was washed with half-saturated brine (1 × 500 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo to give 61.8 g of a crude foam. This foam was carried into the next step. For crude **19**: $t_R$ (HPLC5) = 13.5 min, 93 area %; $^1$H NMR ($CDCl_3$) $\delta$ 7.47 (d, 1H, $J$ = 13.4 Hz), 4.5 (bd, 1H, $J$ = 8 Hz), 3.7 (m, 2H), 3.6 (m, 4H), 3.5 (3, 3H), 3.3 (m, 1H), 2.2 (m, 1H), 2.1 (m, 1H), 1.7 (m, 1H), 1.43 (s, 9H), 1.22 (d, 3H, $J$ = 6.6 Hz), 1.0 (m, 1H), 0.75 (m, 1H), 0.65 (m, 1H); $^{19}$F NMR $\delta$ −127 (m).

**Preparation of 3-Amino-7-[3(*R*)-(1(*S*)-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methoxy-1H-quinazoline-2,4-dione Hydrochloride (1).** Crude foam **19** (isolated from two batches as described above; 86.2 g, ca. 0.22 mol) was dissolved in $CH_2Cl_2$ (900 mL) and cooled to −3 °C. HCl(g) was bubbled into this solution for 6 h, keeping the temperature below 15 °C. The reaction was judged complete by LC/MS analysis. The reaction mixture was allowed to warm to rt while stirring overnight. The reaction mixture was concentrated to dryness. PhMe (200 mL) was added and concentrated to dryness. The resulting solid was dissolved in absolute EtOH (425 mL,), cooled to 5 °C, and treated with propylene oxide (80 mL). The mixture stirred for 1.5 h, and then TBME was added (100 mL), and the resulting precipitate was filtered off. The solid was then dried in vacuo (vacuum pump, rt) to provide 69 g of a crude solid which was recrystallized from hot MeOH (750 mL) and toluene (650 mL). The resulting precipitate was filtered off and dried (15 mmHg, 75 °C), providing 37.4 g (41% from **3**) of **1** as a greenish yellow powder. For **1**: mp 175−179 °C; $t_R$ (HPLC6) = 13.1 min, 99.2 area %; $t_R$ (HPLC7, chiral) = 30.1 min, 100 area %; $[\alpha]^{20}_D$ = −58.9° ($c$ = 1, $H_2O$); $^1$H NMR (DMSO-$d_6$) $\delta$ 8.1 (bs, 3H), 7.33 (d, 1H, $J$ = 13.4 Hz), 5.4 (bs, 2H), 3.7 (m, 2H), 3.5 (m, 2H), 3.48 (s, 3H), 3.2 (m, 2H), 2.3 (m, 1H), 2.0 (m, 1H), 1.7 (m, 1H), 1.26 (d, 3H, $J$ = 6.6 Hz), 1.0 (m, 1H), 0.90 (m, 1H), 0.60 (m, 1H), 0.52 (m, 1H); $^{19}$F NMR $\delta$ −128 (m); IR (KBr) $\nu_{max}$ 3440, 1698, 1646, 1610, 1469, 1439, 1414, 1391 cm$^{-1}$. Anal. Calcd for $C_{18}H_{24}FN_5O_3HCl$ containing 3.16% $H_2O$: C, 50.58; H, 6.25; N, 16.39; Cl, 8.30. Found: C, 50.84; H, 6.35; N, 16.32; Cl, 8.49 with 3.09% $H_2O$ by KF analysis.

**Preparation of 2,4,5-Trifluoro-3-methylbenzoic Acid (27).** A solution of LiHMDS (1 M in THF, 6.5 L, 6.5 mol, 2.3 equiv) in THF (5.5 L) was cooled to −10 °C. A solution of 2, 4, 5-trifluorobenzoic acid (**26**; 501 g, 2.8 mol) in THF (1.5 L) was added dropwise over 1 h. During the addition, the pot temperature was maintained between −13 and −10 °C. The resulting solution stirred for 1.5 h at −10 °C. MeI (192 mL, 3.1 mol, 1.1 equiv) was added dropwise over 1 h while keeping the temperature below −10 °C. The resulting mixture was then stirred for 1 h at −10 to −5 °C. Analysis by GC showed no SM ($t_R$ of **26** = 4.3 min; $t_R$ of **27** = 6.3 min). Cold HCl (3 M, 2 L) was added to the mixture, followed by the addition of cold HCl (6 M, 2.5L). The mixture was then stirred overnight while warming to rt. TBME (1 L) was added, and the phases were separated. The organic phase was washed sequentially with $Na_2S_2O_3$ (1 M, 2 × 650 mL) and brine (2 × 500 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to give 545 g of crude acid **27**. This material was carried onward into the next step without purification. For crude **27**: $t_R$ (HPLC6) = 21.0 min, 81 area %, $t_R$ = 17 min, 8 area %, **26**; $t_R$ = 28.5 min, 9 area %, **32**; $^1$H NMR ($CDCl_3$) $\delta$ 7.7 (m, 1H), 2.30 (s, 3H); $^{19}$F NMR $\delta$ −112 (s), −127 (m), −142 (m).

**Preparation of 2,4,5-Trifluoro-3-methylbenzamide (28).** A solution of acid **27** (535 g, 2.8 mol) in $CH_2Cl_2$ (6 L) was treated sequentially with DMF (2 mL), followed by dropwise addition (3 h) of $(COCl)_2$ (301 mL, 3.4 mol, 1.2 equiv). The reaction mixture stirred at rt for 16 h and was monitored by GC ($t_R$ of **27** = 6.3 min; $t_R$ of acid chloride = 3.2 min). The reaction mixture was concentrated in vacuo to provide an oil, which was used in the subsequent step without purification.

Excess $NH_3$(g) was condensed into THF (3.3 L) at −50 °C for 30 min. A solution of crude acid chloride in THF (2.1 L) was added dropwise, keeping the temperature below −40 °C. After complete addition of the acid chloride/THF mixture, $NH_3$(g) was condensed into the reaction vessel for 10 min. The mixture was allowed to warm to rt while stirring overnight. The resulting reaction mixture was filtered, and the solid was washed with THF (1 L). The filtrate was concentrated in vacuo to give a yellow solid that was dissolved in EtOAc (4 L) and was washed sequentially with water (2 × 750 mL) and brine (1 × 500 mL) and then dried ($MgSO_4$). The drying agent was filtered off, and the filtrate was concentrated in vacuo to give a yellow solid that was approximately 80% pure. Recrystallization from TBME (1.5 L) afforded two crops of crystals which were combined and recrystallized again from TBME (1.2 L) to produce 300 g or 56% yield from trifluorobenzoic acid **26**. For **28**: mp =

106−109 °C; $t_R$ (HPLC8) = 5.8 min, 99 area %; $^1$H NMR ($CDCl_3$) $\delta$ 7.8 (m, 1H), 6.6 (bs, 1H), 6.0 (bs, 1H), 2.26 (t, 3H, $J$ = 2 Hz); $^{19}$F NMR $\delta$ −118 (s), −130 (m), −141 (m); IR (KBr) $\nu_{max}$ 3523, 3510, 3171, 1704, 1603, 1434, 1383 cm$^{-1}$. Anal. Calcd for $C_8H_6F_3NO$: C, 50.80; H, 3.20; N, 7.41. Found: C, 50.65; H, 2.95; N, 7.32.

**Preparation of 1-Cyclopropyl-3-(2,4,5-trifluoro-3-methylbenzoyl)urea (29).** A solution of amide **28** (121 g, 0.64 mol) in $(CH_2Cl)_2$ (1.08 L) was treated at rt with $(COCl)_2$ (72 mL, 0.82 mol, 1.3 equiv) dropwise over 30 min. The resulting reaction mixture was then heated to and held at 55 °C for 45 min and then warmed to reflux for 17 h. The resulting reaction mixture was allowed to cool to rt and concentrated in vacuo to give the crude aroylisocyanate that was used in the subsequent step without purification. The crude aroylisocyanate was dissolved in $CH_2Cl_2$ (1 L), cooled to 0 °C, and treated dropwise (1.25 h, −6 to 0 °C) with a solution of cyclopropylamine (58 mL, 0.83 mol, 1.3 equiv) in $CH_2Cl_2$ (660 mL). The solution was allowed to warm to rt with stirring overnight (monitoring of the reaction using TLC and LC/MS). The solvent was removed in vacuo, and the crude resulting solid was recrystallized from hot toluene (500 mL) and heptane (200 mL). The resulting white crystals were collected and dried (15 mmHg, rt) to give 156 g, 90% yield of **29**. For **29**: mp = 146−149 °C; $t_R$ (HPLC9) = 9.2 min, 99 area %; $^1$H NMR ($CDCl_3$) $\delta$ 8.5 (bd, 1H, $J$ = 6.1 Hz), 8.4 (bs, 1H), 2.8 (m, 1H), 2.29 (t, 3H, $J$ = 2 Hz), 0.83 (m, 2H), 0.64 (m, 2H); $^{19}$F NMR $\delta$ −117 (s), −128 (m), −140 (m); IR (KBr) $\nu_{max}$ 3309, 3075, 1705, 1676, 1491, 1228 cm$^{-1}$. Anal. Calcd for $C_{12}H_{11}F_3N_2O_2$: C, 52.95; H, 4.07; N, 10.29. Found: C, 52.90; H, 3.94; N, 10.20.

**Preparation of 1-Cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (30).** A slurry of NaH (60% in oil, 112 g, 2.79 mol, 3 equiv) in toluene (2 L) was cooled to 0 °C and treated with DME (1 L). The solid cyclic urea **29** (254 g, 0.931 mol) was then added in 20-g portions over 20 min, while keeping the temperature between −9 and 0 °C. Once the urea addition was complete, the remaining DME was added (1 L), and the reaction was allowed to warm to rt. The reaction vessel was then further warmed to reflux for 46 h (monitored by TLC and LC/MS). The reaction mixture was cooled to rt and was poured into a mixture of HCl (2 M, 600 mL) and ice (600 mL) and this mixture was stirred overnight, forming a precipitate. The resulting solid was filtered (*filtrate* set aside) and recrystallized from THF (550 mL), toluene (550 mL), and heptane (700 mL). Much of what was recrystallized was not soluble and was filtered off (119 g). This material (119 g) along with the 54 g of crystals that crystallized proved to be pure. The *filtrate* mentioned above was placed in a separatory funnel, and the phases were separated; the aqueous phase was extracted with THF/EtOAc (1:1, 1 × 1.5 L). The organic phases were combined and concentrated. This material was recrystallized (THF 120 mL, PhMe 300 mL, and heptane 200 mL; hot) and filtered to give an additional 13 g of **30**. A total of 186 g of **30** was obtained in 79% yield. For **30**: mp = 231−235 °C; $t_R$ (HPLC9) = 10.8 min, 99 area %; $^1$H NMR ($CDCl_3$) $\delta$ 8.5 (bs, 1H), 7.8 (m, 1H), 3.3 (m, 1H), 2.6 (d, 3H, $J$ = 3 Hz), 1.2 (m, 2H), 0.71 (m, 2H); $^{19}$F NMR $\delta$ −126 (m), −141 (m); IR (KBr) $\nu_{max}$ 3170, 3043,1684, 1472, 1403, 1315 cm$^{-1}$. Anal. Calcd for $C_{12}H_{10}F_2N_2O_2$: C, 57.15; H, 4.00; N, 11.11. Found: C, 57.13; H, 3.85; N, 11.02.

**Preparation of 3-Amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione, AQD Core (4).** A slurry of cyclic imide **30** (190 g, 0.754 mol) and $K_2CO_3$ (156 g, 1.13 mol, 1.5 equiv) in dioxane (2.1 L) and DMF (2.1 L) was warmed to 72 °C for 30 min, and then *O*-(4-nitrophenyl)-hydroxylamine (122 g, 0.793 mol, 1.05 equiv) was added to the reaction mixture (an endotherm of 2 °C resulted). After 2 h at 72 °C an additional portion of aminating agent (12.3 g, 0.08 mol, 0.1 equiv) was added, and heating continued for 20 h. The reaction mixture was allowed to cool, and the solids that formed were filtered and washed with THF (3 × 250 mL). The filtrate was concentrated to approximately 1/10 volume (600 mL) in vacuo. The concentrated solution was poured into ice (1 L) and water (1.4 L) with stirring. Precipitation of the thick syrup was initiated by adding 1 L of TBME to the mixture with vigorous stirring for about 15 min providing a powdery beige solid. The solid was collected and washed with water (2 × 300 mL). The crude solid was recrystallized from hot IPA (1.5 L) and heptane (1.5 L). The resulting solid was filtered off and dried (15 mmHg, rt) to provide pure **4** as a light brown solid, 166 g, 83%. For **4**: mp = 163−164 °C; $t_R$ (HPLC8) = 14.2 min, 99 area %; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.73 (t, 1H, $J$ = 9.3 Hz), 5.4 (s, 2H), 3.4 (m, 1H), 2.6 (t, 3H, $J$ = 3 Hz), 1.0 (m, 2H), 0.62 (m, 2H); $^{19}$F NMR $\delta$ −129 (m), −143 (m); IR (KBr) $\nu_{max}$ 3333, 3244, 1716, 1637, 1474, 1410, 1308 cm$^{-1}$. Anal. Calcd for $C_{12}H_{11}F_2N_3O_2$: C, 53.93; H, 4.15; N, 15.72. Found: C, 53.72; H, 4.10; N, 15.57.

**Preparation of {1(*S*)-[1-(3-Amino-1-cyclopropyl-6-fluoro-8-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-7-yl)pyrrolidin-3(*R*)-yl]ethyl}carbamic Acid *tert*-Butyl Ester (31).** A mixture of AQD core **4** (158 g, 0.59 mol) and side-chain **5** (178 g, 0.83 mol, 1.4 equiv) in DMSO (600 mL) was treated with TMG (195 mL, 1.55 mol, 2.6 equiv) and warmed to 83 °C and held for 53 h. The reaction mixture was allowed to cool to rt, poured into half saturated $NH_4Cl$ (3 L), and stirred for 1 h. The resulting precipitate was filtered, and the collected solid was washed with water (1 L). The solid was dissolved in TBME/EtOAc (1:1, 3 L) and washed sequentially with half saturated $NH_4Cl$ (1 × 1 L) and 0.5 M HCl (2 × 1.5 L). The organic phase was dried ($MgSO_4$) and filtered and the filtrate was concentrated in vacuo to obtain a reddish brown foam, 255 g crude, 93%. For crude **31**: $t_R$ (HPLC6) = 26.2 min, 90 area %; $^1$H NMR ($CDCl_3$) $\delta$ 7.73 (d, 1H, $J$ = 12.9 Hz), 4.5 (bd, 1H, $J$ = 8.3 Hz), 3.7 (m, 1H), 3.6 (m, 1H), 3.4 (m, 4H), 2.4 (s, 3H), 2.3 (m, 1H), 2.1 (m, 1H), 1.7 (m, 1H), 1.4 (s, 9H), 1.2 (m, 3 H), 1.2 (d, 3H, $J$ = 6.5 Hz), 1.1 (m, 1H), 0.60 (m, 2H); $^{19}$F NMR $\delta$ −127 (m).

**Preparation of 3-Amino-7-[3(*R*)-(1(*S*)-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione Hydrochloride (2).** A solution of crude coupled product **31** (294 g, ca. 0.89 mol) in a solution of $CH_2Cl_2$ (2.4 L) was cooled to 5 °C, and HCl(g) was bubbled into this solution for 3.5 h (5−15 °C). The reaction was monitored

by LC/MS until complete consumption of **31** was observed. The reaction mixture was concentrated in vacuo, azeotroped with toluene (600 mL), and concentrated to dryness. The resulting solid was dissolved in EtOH (2.6 L), cooled to 15 °C, and treated with propylene oxide (portionwise, 30 m, 165 mL, 2.4 mol, 3.4 equiv; up to rt). This mixture was stirred for 4 h at rt, TBME (1.3 L) was added, with continued stirring for 1 h, and then the resulting solid was filtered. The solid was washed with TBME (1 × 700 mL) and allowed to air dry at rt. The resulting mustard-colored powder (211 g) was dissolved in hot water (2.5 L) and filtered, and the filtrate was treated with hot IPA (6.5 L). The resulting solid (Crop 1) was filtered off, and the mother liquor was concentrated to 1.5 L. IPA (1 L) was added to the concentrated filtrate, and the resulting precipitate was filtered off (Crop 2). Crops 1 and 2 were mixed together, slurried with IPA (1 L) for 30 min, and filtered. The solid was dried (75 °C, 15 mmHg, 3.5 d) to give 164 g of **2**, 60% from hydrazide **4**. For **2**: mp > 250 °C; $t_R$ (HPLC6) = 12.7 min, 97.2 area %; $t_R$ (HPLC7, chiral) = 33.5 min, 99.9 area %; $[\alpha]^{20}_D = -54.4°$ ($c$ = 0.5, $H_2O$); $^1$H NMR (DMSO-$d_6$) $\delta$ 8.0 (bs, 3H), 7.40 (d, 1H, $J$ = 12.9 Hz), 5.4 (bs, 2H), 3.6 (m, 1H), 3.4 (m, 4H), 3.2 (m, 2H), 2.48 (s, 3H), 2.0 (m, 1H), 1.7 (m, 1H), 1.25 (d, 3H, $J$ = 6.6 Hz), 1.1 (m, 2H), 0.50 (m, 2H); $^{19}$F NMR $\delta$ −128 (d); IR (KBr) $\nu_{max}$ 3219, 3123, 2874, 1711, 1633, 1608, 1443 cm$^{-1}$. Anal. Calcd for $C_{18}H_{24}FN_5O_2HCl$: C, 54.34; H, 6.33; N, 17.60; Cl, 8.91. Found: C, 54.37; H, 6.26; N, 17.45; Cl, 8.61 with 0.32% $H_2O$ by KF analysis.

**Preparation of 3-Amino-7-[3(*R*)-(1(*S*)-aminoethyl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-8-methyl-1H-quinazoline-2,4-dione Methanesulfonate (36).** Free base **2** was recovered from HCl salt **2** by treating HCl salt **2** with 1 M sodium carbonate aqueous solution, with a small amount of sodium hydroxide added, and extracting with ethyl acetate. The organic solvent was then evaporated and the resulting solid slurried in water overnight to eliminate inorganic impurities. The solid was filtered and dried.

The free base **2** was used to synthesize mesylate salt **36** by mixing a stock solution of methanesulfonic acid (aqueous) and free base **2** in methanol in equimolar proportions and evaporating the stock solutions. To grow single crystals, the salt was dissolved in 5:1 MeCN/$H_2O$ and was crystallized by slow vapor diffusion using a 1:1 mixture of MeCN/*i*-$Pr_2O$.


## Acknowledgment

We thank Edmund Ellsworth, Mike Stier, Tuan Tran, Brian Watson, Joe Sanchez, and Hollis Showalter (Discovery Chemistry) for helpful discussions during the conduct of this work. In addition, we thank James Davidson for encouragement, helpful discussions, and starting materials for this work and James Wemple for a description of the alternate amination conditions using $H_2NOSO_3H$. We also thank Bogda Leja, Mike Lovdahl, Derek Greene, Doug Durham, Qun Gu (Analytical Development), and Jeff McMahon (Analytical Chemistry) for the numerous analytical results and Mike Waldo for assistance with the ReactIR.

Received for review March 12, 2007.

OP7000639