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An Efficient Multikilogram Synthesis of ABT-963: A Selective COX-2 Inhibitor

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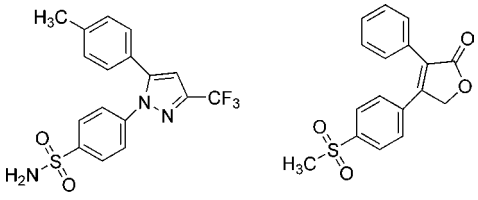
Abstract:

An efficient chemical process for the multikilogram synthesis of ABT-963 (3) is described. The potent and selective COX-2 inhibitor was prepared in four steps in 36% overall isolated yield from commercially available 3,4-difluoroaniline (4). The chemistry, which required no chromatography, involved a facile one-pot synthesis of the pyridazinone core, a selective alkoxylation, a high yielding Suzuki coupling, and a very efficient oxidation.

Introduction

There is considerable scientific interest in the development of cyclooxygenase-2 (COX-2) inhibitors.[1] Clinical experience with representative compounds such as Celecoxib (**1**)[2] and Rofecoxib (**2**)[3] have confirmed the usefulness of these agents in the treatment of inflammatory pain with an improved gastrointestinal safety profile as compared to nonsteroidal anti-inflammatory drugs (NSAIDs). ABT-963 (**3**)[4] has recently been shown to be a potent and highly selective COX-2 inhibitor that may have utility for the treatment of rheumatoid arthritis and osteoarthritis. The compound is efficacious in preclinical inflammation models and causes less gastric irritation than NSAIDs in animal models. In this paper, we wish to report an efficient chemical process for its production on a multikilogram scale that involves four steps in 36% overall isolated yield from commercially available 3,4-difluoroaniline (**4**).



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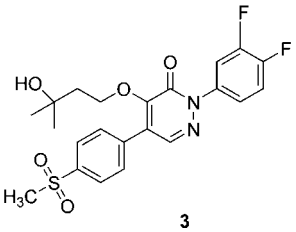

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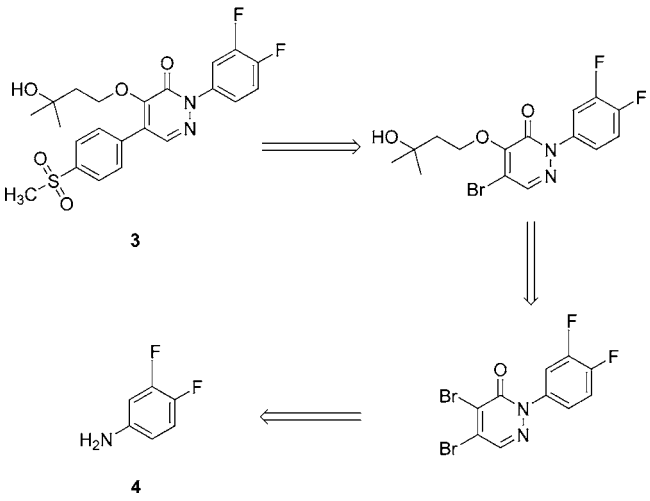
Our synthetic strategy for the preparation of the pyridazinone **3** from commercially available 3,4-difluoroaniline (**4**) focused on several synthetic objectives: (1) one-pot synthesis of the pyridazinone core, (2) selective alkoxylation of the dibromide, (3) high yielding Suzuki coupling of the aryl bromide with the boronic acid, and (4) very efficient oxidation of the sulfide to the sulfone.

Synthetic Strategy



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Results and Discussion

ABT-963 (**3**) was synthesized as shown in Scheme 1. The one-pot preparation of the pyridazinone[5] core (Scheme 2) was accomplished by first dissolving 3,4-difluoroaniline (**4**) into 12% HBr and treating with 1.05 equiv of $NaNO_2$ while maintaining an internal temperature < 0 °C.

Higher reaction temperatures resulted in significant decomposition of the resulting diazonium intermediate **8**. Diazonium salt **8** was further reduced in 30 min with 2 equiv of $SnCl_2$ to form the hydrazine **9**. After another 30 min, 1 equiv of mucobromic acid[6] was added and the reaction mixture was refluxed for 2 h and allowed to cool to room temperature overnight. The pure product crystallized out of solution and was collected by filtration, affording dibromide **5** in 68% overall yield from the difluoroaniline **4**. The product

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(1) Goldstein, *J. Inflammopharmacology* **2001**, *9*, 91.

(2) Miyashiro, J. M.; Bertenshaw, S. R.; Carter, J. S. et al. Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, August 26−30, 2001. ORGN-423

(3) Chan, C.C.; Boyce, S; Brideau, C. et al. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 551.

(4) (a) Harris, R. R.; Black, L.; Surapaneni, S. et al. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 904. (b) Black, L. A.: Basha, A.; Kolasa, T. et al. U.S. Patent 6,307,047 B1.

(5) Santagati, N. A.; Duro, F.; Caruso, A.; Trombadore, S.; Amico-Roxas, M. *Farmaco, Edizione Scifientifica* **1985**, *40*, 921.

(6) (a) Allen, C. F. H.; Spangler, F. W. *Org. Synth.* **1947**, *27*, 60. (b) Aldrich Catalogue No. M8, 962-5.

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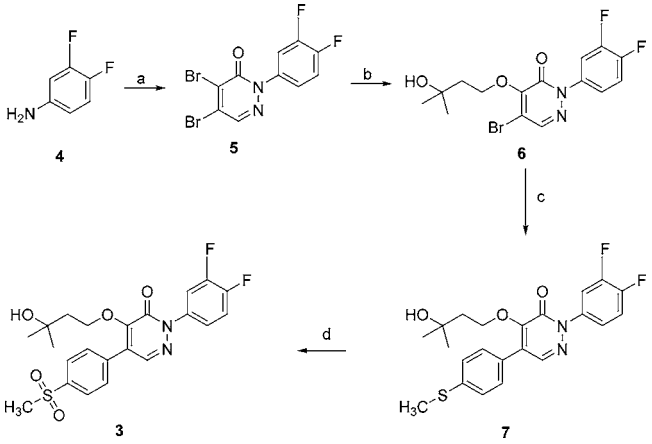
Scheme 1[a]



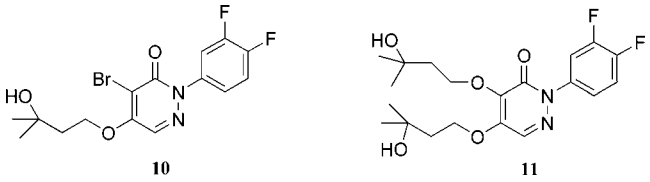
[a] (a) $NaNO_2$/HBr, $SnCl_2$, mucobromic acid, 68%; (b) 3-methyl-1,3-butanediol, NaHMDS, 78%; (c) 4-(methylthio)phenylboronic acid, $Pd(OAc)_2$, PPh_3, 88%; (d) Oxone, 85%.

was typically contaminated with 1−4 wt % Sn. The Sn salts were removed in subsequent steps (vide infra). The typical potency of the isolated material was 94−97% (HPLC assay). This procedure has been utilized to produce more than 22 kg of dibromide **5**.

Selective monoalkoxylation of dibromide **5** was achieved by treatment with the monoalkoxide of the butanediol. The dibromide **5** was dissolved in THF and cooled to −15 °C and treated with 1.1 equiv of the monoalkoxide of 3-methyl-1,3-butanediol, prepared by the addition of 1.05 equiv of NaHMDS to a THF solution of the butanediol.

The butanediol was contaminated with as much as 40 mol % water. This amount of water was inconsequential to the overall success of the reaction. In fact, comparing "azeodried diol" with "wet diol" afforded no observable differences in terms of yield or quality of crude product. Careful monitoring of the endpoint was the key to prevent excessive overalkoxylated byproduct **11**. A typical reaction outcome (absence of dibromide **5**) was an 85:7:8 ratio of compounds **6**/**10**/**11**. Once starting material was consumed, as judged by HPLC, the reaction was quenched into aq. HCl and the pH was adjusted to 3. This rendered the Sn salts soluble in the aqueous waste streams. The product was extracted out with EtOAc, converted to an IPA solution (typically 12 wt %), and used without any further purification. The solution assayed for a 78% yield of aryl bromide **6**.

Both regioisomer **10** and bis-ether **11** were easily removed in the subsequent Suzuki cross-coupling step. Additionally, as part of a stress test, the alkoxylation reaction was prematurely stopped with 10% starting dibromide **5** remaining. This mixture was carried on to determine the fate of unreacted **5** in subsequent reactions. It was shown that **5** was converted to two new impurities, presumably cross-coupled regioisomers and were rejected in the step two crystallization.



In our investigation to identify the base that would provide the highest yield of aryl bromide **6**, we attained a reversal of selectivity when LiHMDS was used (Table 1). Similar lithium ion-dependent regioselective results have been reported for alkylation/cyclization reactions in the literature.[7] The observed counterion effect (lithium versus potassium or sodium) in the monoalkoxylation study is an interesting example of how modifying reaction conditions can provide either regioisomer as the major product. It was also found that the higher the dilution of solvent, the more selective the reaction with respect to the compound **6**/**10** ratio.

Suzuki coupling[8] of aryl bromide **6** with 4-(methylthio)-phenylboronic acid[9] provided the pyridazinone **7**. The aryl bromide **6** in 4:1 IPA/H_2O containing 1.1 equiv of the boronic acid, 1 mol % of $Pd(OAc)_2$, 2 mol % PPh_3, 1 equiv of K_3PO_4, and 2 equiv of K_2HPO_4 was heated at 70−75 °C for 2−4 h. After workup, which involved passing the crude product through a silica cartridge filter, pure sulfide **7** was obtained by recrystallization from 4:1 heptane/EtOAc. Assayed HPLC yields were 95−98%, while isolated yields were 84−88%.

To proceed in high yields, degassing (sparging with nitrogen) of the reaction mixture to remove oxygen just prior to heating was essential. Interestingly, the amount of impurities increased (hydrolysis to compounds **12** and **13**) as the stirring rate increased. The use of less than 1.1 equiv of the boronic acid resulted in incomplete consumption of starting material. However, if the reaction does not go to completion, the addition of extra boronic acid will consume the remaining bromide **6**. IPA was the organic solvent of choice, although the reaction can also be done in toluene or THF. Employing EtOH or tBuOH resulted in inferior yields. The selection of base was crucial, as a buffered system decreased the amounts of hydrolytic byproducts **12** and **13**.

A mixture of K_2HPO_4 and K_3PO_4 gave a cleaner and slightly slower reaction than using exclusively K_3PO_4. The employment of K_2HPO_4 resulted in slow conversion and did not go to completion. The reaction proceeded in high yield (87%) with as low as 0.1 mol % $Pd(OAc)_2$ provided P(*o*-tolyl)$_3$ is used in place of PPh_3 (Table 2). The low catalyst loads required longer reaction times with slightly higher

Scheme 2

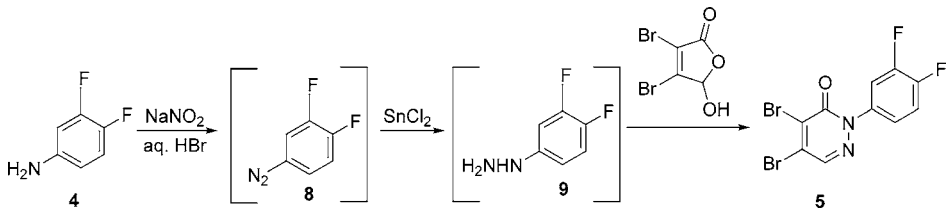
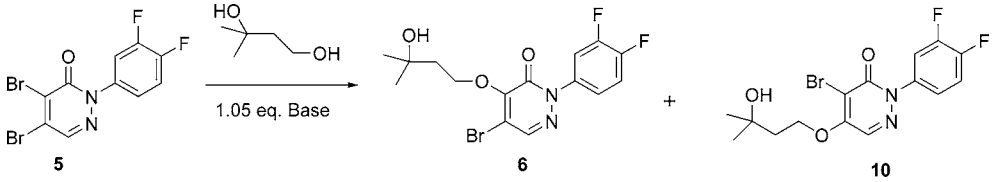


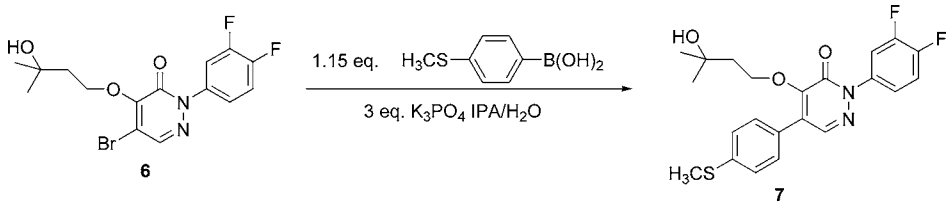
Table 1. **Alkoxylation Study**



base	solvent	temp (°C)	time (h)	yield[a] **6** (%) + **10** (%)
NaHMDS	THF	−20	3	74 4
NaHMDS	THF	−10	3	78 5
NaHMDS	THF	−40	3	63 8
LiHMDS	THF	−40	3	15 60
KHMDS	THF	−40	3	52 14
DBU	THF	−15 to 50	12	no reaction
NaH	THF	0	12	44 6
NaHMDS	toluene	−25	12	62 5

[a] Yield determined by HPLC analysis.

Table 2. **Suzuki Coupling Investigation**



reagent	ligand	temp (°C)	time (h)	yield[a] (%)
0.1 mol% $Pd(OAc)_2$	0.2 mol% P(o-tolyl)$_3$	75	17	87
0.25 mol% $Pd(OAc)_2$	0.5 mol% PPh_3	75	32	93
0.5 mol% $Pd(OAc)_2$	1 mol% PPh_3	75	16	94
1 mol% $Pd(OAc)_2$	2 mol% PPh_3	75	2	98
1 mol% $Pd(PPh_3)_2Cl_2$		75	2	95
2 mol% Pd/C		75	3	87

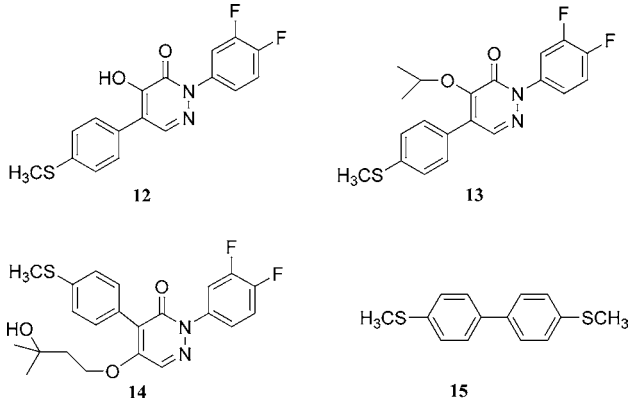
[a] Yield determined by HPLC analysis.

reaction temperatures to consume bromide **6** (17 h at 80 °C required). Other sources of palladium investigated for utilization in this reaction were $Pd(PPh_3)_2Cl_2$[10] and Pd/C.[11] $Pd(PPh_3)_2Cl_2$ afforded similar yields as $Pd(OAc)_2$, while Pd/C (from PMC, activity index > 800) afforded slightly lower yields.

The method of purification of the Suzuki product was very important. The reaction generated four major impurities: the hydroxy derivative **12** (2.1%), the isopropoxy analogue **13** (0.7%), the regioisomer **14** (5.8%), and the bis-sulfide **15** (3.1%). Recrystallization employing 4:1 heptane/EtOAc reduced the amount of the hydroxyl **12** to 0.8%, the propoxy **13** to <0.1%, the regioisomer **14** to 0.16%, and the bis-sulfide **15** to 0.32%.

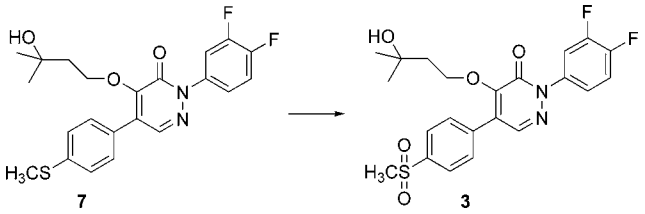
The filtration with silica was necessary not only for substantially reducing the amount of Pd in the product but also for eliminating black amorphous impurities which cannot be removed by crystallization, simple filtration, or filtration through Celite.

ABT-963 (**3**) was formed by oxidizing the sulfide to the sulfone using Oxone[12] in acetone/H_2O (10:1) at 5−10 °C. The propensity of Oxone to oxidize acetone to dimethydioxirane[13] at neutral to basic pH led us to investigate the use of alternate solvents for this conversion. Due to the low solubility of the sulfide **7** or the intermediary sulfoxide **16**, THF was found to be of limited use. The use of THF gave



(7) (a) Mannien, P. R.: Little, H. A.: Brickner, S. J. Abstracts of Papers, 212th ACS National Meeting, Orlando, FL, August 25−29, 1996. ORGN-389. (b) Mannien, P. R.; Brickner, S. J. *Organic Syntheses* **2005**, *81*, 112..
(8) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(9) (a) Brikh, A.; Morin, C. *J. Organomet. Chem*. **1999**, *581*, 82. (b) Commercially available from a number of sources.
(10) Jacks, T. E.; Belmont, D. T.; Briggs, C. A. et al. *Org. Process Res. Dev.* **2004**, *8*, 201.
(11) Marck, G.: Villager, A.; Buchecker, R. *Tetrahedron Lett*. **1994**, *35*, 3277.

Table 3. **Oxidation Methods**



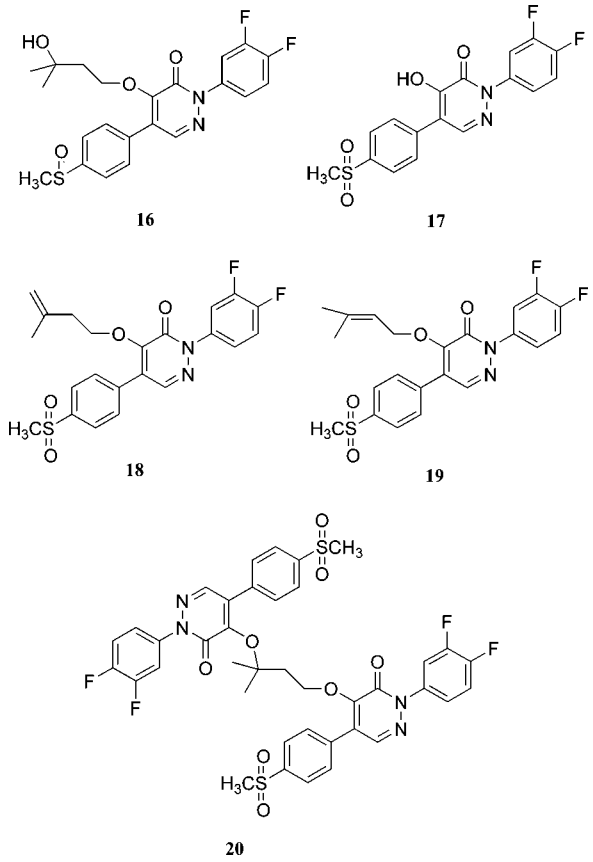
reagent	solvent and/or catalyst	temp (°C)	time (h)	yield[a] (%)
Oxone (3 equiv)	acetone and H_2O	5	4	95
30% H_2O_2 (3.5 equiv)	EtOAc/0.1 equiv of Na_2WO_4 0.25 equiv of H_2SO_4	20	5	88
CH_3CO_3H (6 equiv)	acetone	−10	5	85
urea−H_2O_2 (8 equiv)	acetone/6 equiv of $(CF_3CO)_2O$	20	1	92
$NaBO_3$ (5 equiv)	AcOH	55	1.5	73

[a] Yield determined by HPLC analysis.

slightly lowered yields with concomitant increased levels of impurities coupled with colored crystallized product. Furthermore, investigation into alternate oxidants revealed the H_2O_2/cat. Na_2WO_4 system[14] as a potential replacement, although this system gave slightly lower yields and required longer reaction times (Table 3).

To alleviate the high levels of Pd contaminating the penultimate, sulfide **7** was treated with Deloxan resin[15] in acetone. This reduced Pd levels typically from 200 ppm to 20−40 ppm.

After the Deloxan resin was filtered off, the sulfide **7** was added to 3 equiv of Oxone in acetone at 5 °C followed by the addition of water. Water served to initiate the reaction by dissolving Oxone in this heterogeneous reaction. The oxidation of sulfide **7** to sulfone **3** was a two-step reaction via its sulfoxide **16**. It was observed that the formation of intermediate sulfoxide **16** was quite fast and exothermic. Complete conversion of sulfide **7** to sulfoxide **16** was typically accomplished in less than 1 h, and further oxidation to sulfone **3** usually required an additional 4 h of stirring at 5 °C. During the workup, the filtrate was treated with 10% $NaHSO_3$ to destroy any residual Oxone remaining. This step was necessary as residual Oxone will react with acetone to produce dimethyldioxirane, which is both toxic and potentially explosive during the subsequent neutralization and slight basification (pH 8) with 10% K_2CO_3 solution. The crystallization was effected by slow addition of water at ambient temperature. Experiments showed that slow addition favorably formed the desired more stable crystal form and effectively rejected the impurity **17**, the side-chain cleavage byproduct, which was formed during the reaction. This crystallization gave ABT-963 (**3**) in 85% yield with 98.8% HPLC purity. The Pd residual level was 2.6 ppm, while no traces of Sn or phosphine oxide (from the Suzuki coupling step) were detected. The product was further recrystallized from EtOAc/heptane (3:1, v/v) to enhance its purity and potency. The recovery yield after recrystallization was typically 90%. The recrystallized ABT-963 (**3**) was a white solid that had an HPLC purity and potency of >99%. The identified impurities were as follows: byproduct **17** (0.09%), 1′-olefin-side byproduct **18**/2′-olefin byproduct **19** (0.12%), and pseudo-dimer **20** (0.05%). Over 6.7 kg of ABT-963 (**3**) were prepared via this synthetic route.



Conclusion

In summary, a practical and scaleable process for the multikilogram preparation of ABT-963 (**3**) has been developed. It proceeded in four steps and 36% overall isolated yield from the commercially available 3,4-difluoroaniline (**4**). The synthesis described utilized a facile one-pot synthesis of the pyridazinone core, a selective alkoxylation of the dibromide intermediate, a high yielding Suzuki coupling, and an efficient oxidation. In addition, this flexible chromatography-free process is amenable to the synthesis of a wide variety of analogues and derivatives.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were obtained on a General Electric QE-300 NMR instrument at 300 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. ^{1}H NMR data are tabulated in the following order: chemical shift, mutiplicity (s, singlet; d, doublet; t, triplet; q, quartet;

(12) (a) Webb, K. S. *Tetrahedron Lett*. **1994**, *35*, 3457. (b) Oxone (potassium peroxymonosulfate) is a DuPont product commercially available from Aldrich.
(13) Murray, R. W.; Jeyaraman, R. *J. Org. Chem*. **1985**, *50*, 2847.
(14) Vittai, T. V. S. K; Hari, K. M. Patent No. WO 2005016906 A1.
(15) Zhang, T. Y.; Allen, M. J. *Tetrahedron Lett.* **1999**, *40*, 5813.

m, multiplet), number of protons, coupling constant(s) in hertz. Mass spectra were recorded with a Finnagan LCQ mass spectrometer. All new compounds were characterized by full spectroscopic and analytical data, and yields refer to spectroscopically homogeneous materials. Microanalyses were performed by the Abbott Analytical Department.

4,5-Dibromo-2-(3,4-difluorophenyl)-2*H*-pyridazin-3-one (5). To a 3 L flask equipped with a mechanical stirrer, thermometer, an additional funnel, and a reflux condenser under nitrogen was added 3,4-difluroanilline (**4**) (32.0 g), followed by 480 mL of 12% HBr at −5 °C with a cooling bath. A $NaNO_2$ solution (18.0 g in 180 mL H_2O) was added slowly over 30 min keeping the reaction temperature < 0 °C. After the addition was complete, the light brown solution was stirred for 30 min at −10 °C to −5 °C. A solution of $SnCl_2$ (112.0 g of $SnCl_2$ dissolved in 480 mL of 24% HBr) was slowly added at −10 °C to −5 °C over 1 h. The reaction mixture was stirred at −10 °C to −5 °C. After 1 h, HPLC analysis indicated the reaction was complete. Mucobromic acid[6] (64.0 g) was added all at once as a solid. The resulting mixture was heated to reflux until less than 1 area % of hydrazine remained. The mixture was allowed to cool slowly to room temperature overnight, whereupon the product precipitated out of solution. The product was isolated by filtration and washed with water. The solid was dried to constant weight at 50 °C with a N_2 bleed. The yield of product **5** was 62.6 g (68.9% yield). Mp: 187−190 °C. Spectral data: ^{1}H NMR ($CDCl_3$/300 MHz): δ 7.94 (s, 1H), 7.52 (ddd, J = 3.7, 2.3, 0.9 Hz, 1H), 7.42−7.39 (m, 1H), 7.32−7.22 (m, 1H). MS *m*/*e* 367 $(M + H)^+$. Anal. Calcd for $C_{10}H_4Br_2F_2N_2O$: C,32.82; H, 1.10; N, 7.65. Found: C, 32.71; H, 1.10; N, 7.74.

5-Bromo-2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-2*H*-pyridazin-3-one (6). Into a reactor was charged 3-methyl-1,3-butanediol (3.43 kg, 32.98 mol) and THF (45 kg). The resulting solution was cooled to −20 °C and was charged with a 1 M solution of NaHMDS in THF (29.9 kg, 33.1 mol). Into a different reactor was charged with 4,5-dibromo-pyridazine-6-one (**5**) (10.5 kg @ 95% potency or 9.98 kg, 27.26 mol) and THF (245 kg). The resulting mixture was cooled to −20 °C, and the previously prepared alkoxide/THF solution was charged at such a rate as to maintain an internal temperature < −8 °C. The mixture was stirred at −20 °C until less than 1 area% dibromide remains. The reaction mixture was quenched by transferring the reaction mixture into a reactor containing precooled 13% NH_4Cl (316 kg), while maintaining an internal temperature of <25 °C. The pH of the quenched reaction mixture was adjusted to 3 with 3 M HCl (typically 22 kg). The biphasic reaction was allowed to settle for typically 30 min. The bottom layer was discarded. The organic layer was filtered into another reactor to remove any emulsionary solids. The filter was washed with EtOAc (245 kg). The filtrates were combined and washed twice with 200 kg of water. The organic extract was concentrated to minimum volume, and the solvent was switched to IPA by chasing twice with IPA (65 kg). The reaction mixture was concentrated to a final volume such that the product concentration was approximately 12%. The solution assayed for 8.3 kg (78% of theory) of compound **6**. The product is typically 88−91 HPLC area% and is contaminated with 4−9% regioisomer and 2−6% bis-ether. Spectral data: ^{1}H NMR ($CDCl_3$/300 MHz): δ 7.94 (s, 1H), 7.51 (ddd, J = 3.7, 2.3, 0.9 Hz, 1H), 7.37 (m, 1H), 7.28 (m, 1H), 4.75 (t, J = 6.6 Hz, 2H), 2.50 (bs, 1H), 2.03 (t, J = 6.6 Hz, 2H), 1.32 (s, 6H). MS *m*/*e* 390 $(M + H)^+$. Anal. Calcd for $C_{15}H_{15}BrF_2N_2O_3$: C,46.29; H, 3.88; N, 7.20. Found C, 46.35; H, 3.89; N, 7.11.

2-(3,4-Difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-(methylsulfanylphenyl)-2*H*-pyridazin-3-one (7). A nitrogen purged reaction vessel was charged with 4-(methylthio)-phenylboronic[9] acid (4.2 kg), palladium(II) acetate (46 g), triphenylphosphine (108 g), potassium tribasic phosphate (4.4 kg), and potassium dibasic phosphate (7.2 kg). The mixture was evacuated and purged (nitrogen/vacuum) 3 times. The alkoxylated bromide **6** in IPA solution (40.1 kg) was added. The mixture was agitated and purged (nitrogen/vacuum) 4 times. The mixture was heated to 70−75 °C for 3.5 h until <0.6 A% starting material remained as monitored by HPLC analysis. After the reaction mixture was cooled to 25 ± 5 °C, distilled water (40 kg) and EtOAc (80.1 kg) were added. The solution was stirred for 30 min, and the aqueous layer was removed. The organic layer was washed with 10% aqueous potassium phosphate (2 × 80.2 kg), 5% aqueous $NaHCO_3$ (80.2 kg), and saturated aqueous NaCl (80 kg). The solvent was distilled at 50 °C to a volume of 40 L, and EtOAc (80.5 kg) was added after the reaction mixture cooled to 30 °C and a GC sample was taken. The reaction mixture was distilled again at 50 °C under vacuum to 40 L. This procedure was repeated until the GC analysis of the amount of IPA in the EtOAc solvent was less than 3%. Heptane (42.5 kg) was added, and a sample was taken for GC analysis. Additional heptane or EtOAc was then added to adjust the heptane/EtOAc ratio determined by GC to approximately 2:1. Silica gel (3 kg) was added, and the mixture was heated to 70 °C for 30 min. While hot, the mixture was filtered through a cartridge filter. The filtrate was distilled under vacuum at 35 °C to a volume of approximately 70 L. A GC sample was taken, and the ratio of solvents was determined. Based on this analysis, EtOAc and heptane were added to give a ratio of approximately 1:4 and an overall volume of 120 L of solvent. The solution was heated to 70 °C for 30 min, and then the solution was allowed to cool at a rate of 5 °C per hour to 5 °C. The solid was not filtered until the supernatant level was less than 10 mg/mL. After 10 h at 5 °C, the supernatant level was 7.1 mg/mL. The solid was filtered and washed with cold 6:1 heptane/EtOAc (25 kg) and heptane (40 kg). The wetcake was dried at 45−50 °C in a vacuum oven with a nitrogen purge to yield 6.75 kg (76%) of product having a potency of 98.4%. An additional 0.832 kg (9.4%) of product was recovered from the walls of the reactor having a potency of 98%. The overall weight adjusted yield of recovered, isolated product **7** was 84%. The palladium content of the crystallized product was 50 mcg/g. Analysis of the mother liquors showed another 0.977 kg (11%) of product giving a HPLC yield of 95% for this reaction. Spectral data: ^{1}H ($CDCl_3$) δ 7.96 (s, 1H), 7.61 (m,

1H), 7.55 (d, $J = 9.0$ Hz, 2H), 7.49 (m, 1H), 7.36 (d, $J = 9$ Hz, 2H), 7.28 (dd, $J = 18.4$ Hz, $J = 8.8$ Hz, 1H), 4.39 (t, $J = 6.6$ Hz, 2H), 2.94 (bs, 1H), 2.53 (s, 3H), 1.88 (t, $J = 6.3$ Hz, 2H), 1.26 (s, 6H). MS *m*/*e* 433 $(M+H)^+$. Anal. Calcd for $C_{22}H_{22}F_2N_2O_3S$: C,61.10; H, 5.13; N, 6.48. Found C, 61.28; H, 5.15; N, 6.38.

ABT-963 (3). A reactor was charged with 3.0 kg of Deloxan resin and 75 kg of acetone. The mixture was stirred under N_2 for 1 h 50 min and then filtered. The resin was washed with 125 kg of acetone and blown dry with N_2 to obtain 1.8 kg of dry resin. The dry resin, sulfide **7** (3.0 kg, 6.94 mol) and acetone (19 kg), was charged to a reactor and mixed under N_2 for 16 h. The resulting slurry was filtered and washed with acetone (5 kg). The filtrate was assayed by HPLC to determine the recovery of sulfide **7** after Deloxan treatment. 2.80 kg (93.3%) of sulfide **7** were present. A reactor was charged with Oxone monopersulfate compound (12.8 kg, 20.8 mol) and purged with N_2. To this reactor were added the acetone/sulfide **7** solution and acetone (4 kg). The reaction mixture was cooled to 5 °C, and then water (3.6 kg) was added at such a rate that the temperature of the reaction mixture did not exceed 12 °C. The mixture was stirred at 10 ± 5 °C until less than 0.5% of the sulfoxide **16** intermediate remains by HPLC analysis. The reaction mixture was filtered through a filterpot, and the solids (excess Oxone and inorganic byproduct) were washed with acetone (10 kg). The wash and filtrate were combined and treated with 10% aqueous $NaHSO_3$ solution (7.8 kg) maintaining a temperature at 18 °C. The mixture was stirred until a test sample showed that a less than 1 ppm peroxide is present with J.T. Baker "Testrips for Peroxide". The mixture was filtered through a filterpot to remove salts. Salts were washed with acetone (4 kg). The wash and filtrate were combined and adjusted with 10% aqueous K_2CO_3 solution (14.6 kg) to a pH of about 8.0 as measured by a pH meter. Water (14.2 kg) was added slowly over 45 min. At this point the crystallization occurred and the slurry was stirred for 30 min. An additional amount of water (68.8 kg) was added over 2.25 h. The slurry was stirred at room temperature until the concentration of the product in the supernatant solution was less than 1 mg/mL. The slurry was filtered and washed with a 2:1 (v/v) mixture of acetone/water (11.2 kg) and then with water (50 kg). The wet product was dried under vacuum at 45 °C. The dry weight of product **3** was 2.66 kg, and the potency adjusted yield was 85% (sulfide **7** is 97% potent). The material was an off-white solid with 98.8% purity and 98.6 wt % potency by HPLC analysis. The solid had a palladium content of 2.6 ppm. This batch of ABT-963 (**3**) and other batches were combined to perform a single recrystallization from EtOAc/heptane (3:1, v/v). To a reactor were charged ABT-963 (**3**) (7.76 kg) and EtOAc (43 kg). The slurry was heated to 70 ± 5 °C and stirred until the mixture became clear. This solution was hot filtered through a six-pack cartridge filter set up with 0.5 μ cartridges to remove any inorganic salts carried over from the previous step. The filtrate was heated again to 73 °C, and heptane was slowly added over 35 min. The mixture was stirred at 70−75 °C for 15 min and then slowly cooled to 5 ± 5 °C. The slurry was stirred until the concentration of the product in the supernatant solution was less than 10 mg/mL. The slurry was filtered and washed with a mixture of EtOAc/heptane (1:1, v/v, prepared from 11 kg of EtOAc and 8.3 kg of heptane). The product was dried under vacuum at 60 °C. The dry weight of the product was 6.75 kg, and the potency-adjusted yield was 88% (sulfone before recrystallization was 98.6% potent). The final material **3** was a white solid with 99.2% purity and 99.8 wt % potency by HPLC analysis. The identified impurities were byproduct **17** (0.09%), 1′-olefin byproduct **18**/2′-olefin byproduct **19** (combined 0.12%), and pseudo-dimer **20** (0.05%). Spectral data: ^1H ($CDCl_3$) δ 8.00 (d, $J = 9$ Hz, 2H), 7.86 (s, 1H), 7.72 (d, $J = 9.0$ Hz, 2H), 7.51 (ddd, $J = 11.0$ Hz, $J = 7.0$ Hz, $J = 2.6$ Hz, 1H), 7.39 (m, 1H), 7.20 (dd, $J = 18.4$ Hz, $J = 8.8$ Hz, 1H), 4.47 (t, $J = 6.6$ Hz, 2H), 3.05 (s, 3H), 2.55 (bs, 1H), 1.81 (t, $J = 6.3$ Hz, 2H), 1.15 (s, 6H). MS *m*/*e* 465 $(M + H)^+$. Anal. Calcd for $C_{22}H_{22}F_2N_2O_5S$: C, 56.89; H, 4.77; N, 6.03. Found C, 56.91; H, 4.77; N, 6.00.

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