Organic Process Research & Development **2006**, *10,* 556–560

Communication to the Editor

Synthesis of Imidazole Based p38 MAP (Mitogen-Activated Protein) Kinase Inhibitors under Buffered Conditions

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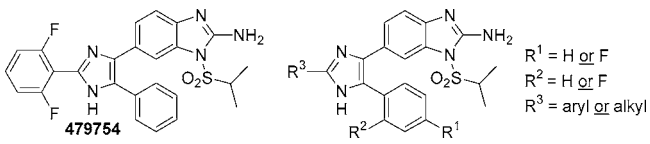
Abstract:

This article describes chemistry that was developed to give access to multigram quantities of imidazole 479754 and several related analogues for Eli Lilly's p38 MAPK program targeting therapies to address inflammation. The molecules of interest have an isopropyl sulfonyl group present on the 2-aminobenzimidazole heterocycle that was found to be labile when heated in polar solvents and/or exposed to high or low pH. Due to this instability issue, the syntheses of the target molecules required optimizing Sonogashira reaction conditions, employing a buffered oxidative method to produce α-diones, developing buffered reaction conditions to generate imidazoles, and developing final recrystallization conditions.

Introduction

The inhibition of p38 MAP kinase has been targeted for its potential therapeutic benefits with respect to inflammation.[1] A series of compounds based upon a substituted 2-aminobenzimidazole showed promise as inhibitors of p38 MAP kinase thereby requiring the preparation of larger quantities of both intermediates and final compounds.[2] Imidazole **479754** was the lead molecule from the 2-aminobenzimidazole series of compounds and was therefore our initial focus. The technology we developed for the synthesis of **479754** was also applied towards the synthesis of a series of analogues needed on a multigram scale.



Results and Discussion

The imidazole **479754** had been prepared previously using the chemistry illustrated in Scheme 1.[2] The molecules **4**, **6**, and **479754** in Scheme 1 contain isopropyl sulfonyl groups that are labile if exposed to acid, base, and/or heat in polar solvents such as DMSO or AcOH.

The Scheme 1 synthesis of imidazole **479754** presented a few issues: (1) the expense of preparing the silyl-protected Weinreb amide **3**; (2) the Grignard chemistry gave about a 60% yield of the desired ketone **6** with **4** and des-iodo **4** as the major impurities; (3) the oxidative imidazole formation was plagued with competitive loss of the isopropyl sulfonyl group to give **8**, oxazole formation to give **9**, and a challenging purification by chromatography due to persistent copper salts and poor separations. These issues motivated us to develop alternative chemistry for the synthesis of imidazole **479754**.

The hydroarylation/Sonogashira type chemistry described by Mitchell et al. (Scheme 2) demonstrated that aryl iodide **4** is proficient in Sonogashira couplings.[3]

This led us to propose the retrosynthetic plan illustrated in Scheme 3 for the synthesis of imidazole **479754**. Phenylacetylene **12** would serve as an inexpensive surrogate for the Weinreb amide **3** (in the Scheme 1 synthesis), and oxidation of the alkyne **13** to the α-dione **14** would give the correct oxidation state for the imidazole preparation and perhaps avoid the purification issues that the previously mentioned copper salt chemistry had presented.

The Sonogashira reaction described by Mitchell (Scheme 2) involved dissolving aryl iodide **4** in DMSO at 23 °C, adding catalytic $Pd(PPh_3)_2(OAc)_2$ (bis(triphenylphosphine) palladium(II) acetate), catalytic copper(I) iodide, and excess triethylamine, followed by the addition of an excess of alkyne **10**. After the reaction was deemed complete, solids were precipitated from the reaction mixture by adding water. The resulting crude solids were purified by slurrying in toluene, followed by recrystallization from EtOAc.

We made only minor modifications to the aforementioned Sonogashira reaction conditions when applying them to the coupling of aryl iodide **4** and alkyne **12** (Scheme 4). (Note: the isopropylsulfonyl group of aryl iodide **4** is thermally

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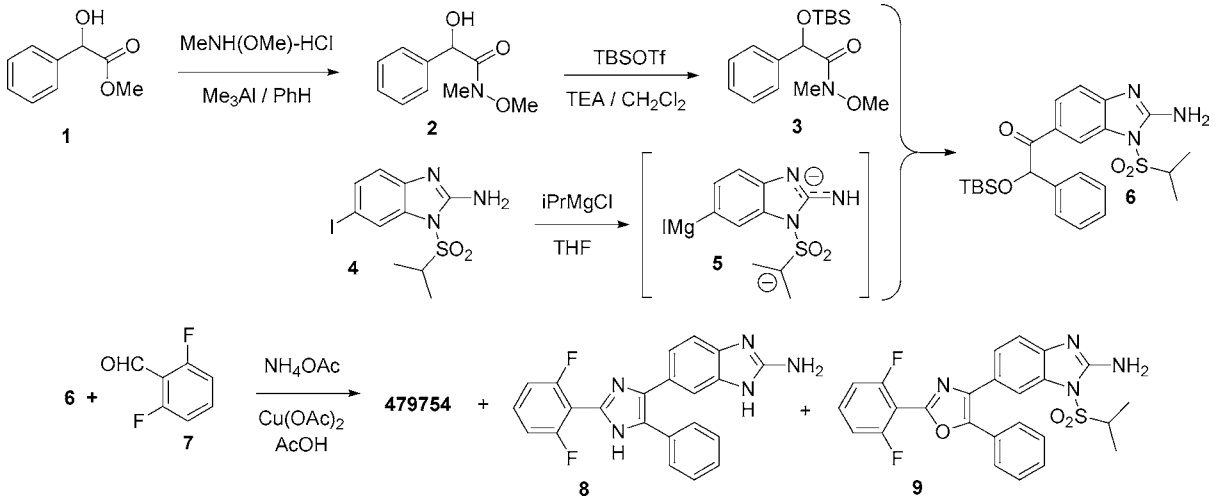
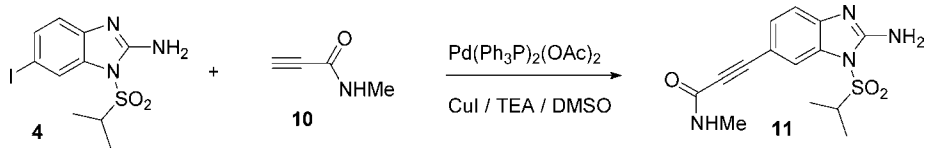
Published on Web 04/15/2006

10.1021/op060042t CCC: $33.50

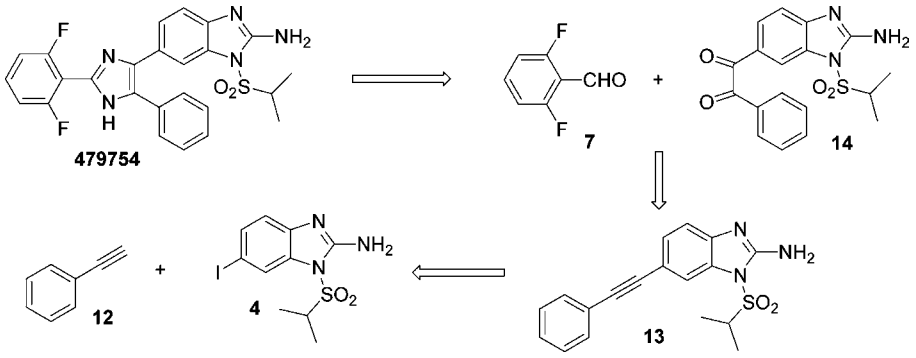
Scheme 1



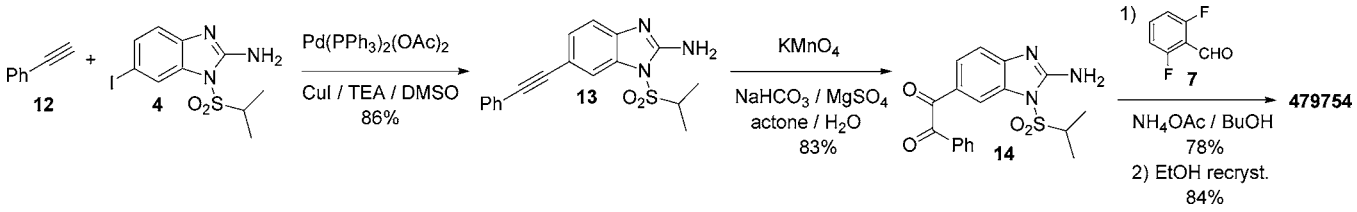
Scheme 2



Scheme 3



Scheme 4



labile in DMSO, so the reagents were combined at 23 °C and allowed to exotherm to 35 °C, but not physically heated as this induced desulfonylation.) We examined reducing the palladium catalyst load, as well as the equivalents of phenylacetylene **12**. The $Pd(PPh_3)_2(OAc)_2$ charge was examined at the 1.0 mol % level (based on aryl iodide **4**) and was found to be too unreactive, with roughly a quarter of the starting aryl iodide **4** remaining after an "overnight" reaction. Eventually, 4.0 mol % of $Pd(PPh_3)_2(OAc)_2$ was found to give a complete reaction within 15 h. We also reduced the charge of phenylacetylene **12** from the prescribed 3.5 equiv to 1.5 equiv. A fortunate observation was made in the water addition after reaction completion. It was observed that an initial portion of water caused a very fine dark precipitate to form, which was filtered off and found to be primarily catalyst. The resulting clarified filtrate was subsequently treated with a further portion of water to induce the alkyne **13** to precipitate in 86% yield. One impurity typically remained with the alkyne **13**, which was the dimer of phenylacetylene **12**. However, the dimer did not adversely affect the subsequent chemistry. If a higher quality of alkyne **13** was required, it could be purified further by slurrying the solids in hot toluene.

The alkyne **13** was oxidized to the α-dione **14** by treatment with $KMnO_4$ in buffered media.[4] Other protocols for this transformation, I_2/DMSO/heat[5] and $PdCl_2$/DMSO/

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heat,[6] required heating in polar solvent which resulted in significant to complete loss of the isopropylsulfonyl group. We settled on reaction conditions described by Lee et al., which involved aqueous acetone with $NaHCO_3$ and $MgSO_4$ as a buffer mixture (initially pH 7.0 to 7.5) and $KMnO_4$ as the oxidant.[7] The buffer mixture serves to neutralize hydroxide ions produced during the reduction of permanganate. If the $NaHCO_3$ was excessive with pH $\geq$ 7.8 this would result in oxidation of the solvent as well as lower yields of the α-dione **14**. The changes we made to the Lee procedure were to reduce the volume (i.e., increase the throughput) and modify the workup. The $NaHCO_3$ and $MgSO_4$ were dissolved in water, and acetone was added causing the mixture to become cloudy. The alkyne **13** was added to the reaction mixture to give a slurry (~30 °C), and $KMnO_4$ was added giving an exotherm to 40 °C. The reaction was typically complete, if run at 40 °C, within 2 h. The reaction was clean, but the workup was messy! The workup involved adding EtOAc to the reaction mixture, followed by Na_2SO_3 and aqueous sulfuric acid to reduce the unreacted $KMnO_4$ and give a phase separation. The organic phase was concentrated, and after solvent removal, the α-dione **14** was obtained as a yellow solid in 83% yield.

The conversion of α-diones into imidazoles is classically conducted in aqueous or alcoholic ammonia with an aldehyde present.[8] There are also numerous examples of this reaction type employing ammonium acetate in acetic acid.[9] These reaction types were investigated for the preparation of imidazole **479754** and were found to induce considerable to complete loss of the isopropylsulfonyl group. The use of ammonium acetate in alcohols to affect the condensation of ammonia, aldehyde **7**, and α-dione **14** to give imidazole **479754** is a variation of the previously mentioned reaction conditions that gave a form of buffering which retarded the loss of the ispropylsulfonyl group. Indeed, it was found that α-dione **14** could be converted into imidazole **479754** productively by reaction with 2,6-difluorobenzaldehyde **7** and ammonium acetate, in MeOH, EtOH, IPA, or *n*-BuOH at or below 55 °C (higher temperatures gave more desulfonylation). The eventual reaction that was developed to prepare multigram quantities of imidazole **479754** employed *n*-BuOH as the reaction solvent, due to improved workup characteristics (i.e., *n*-BuOH facilitates phase separation from water). The α-dione **14** was combined with ammonium acetate, *n*-BuOH, and 2,6-difluorobenzaldehyde **7**, and the resulting slurry was heated to 55 °C and held at that temperature for 24 h to give an almost homogeneous mixture (some ammonium acetate remained out of solution). The workup consisted of removing salts from the reaction mixture with water washes and concentrating the resulting organic phase to an oil. The oil was taken up in MeOH and diluted with MTBE to induce crystallization of the product, imidazole **479754**. The crystals were filtered, washed with MTBE, and dried to give imidazole **479754** that was contaminated with <2 area% of the desulfonylated product **8** and <1 area% of α-dione **14** by HPLC and percent levels of MTBE and MeOH by ^1H NMR. The crude imidazole **479754** was dissolved in EtOAc, slurried with silica gel, and filtered through a pad of silica gel to remove the desulfonylated product **8** (Scheme 1), and afforded imidazole **479754** in 78% yield with >99 area% purity with α-dione **14** and EtOAc as the only minor contaminants after solvent removal.

A large effort was put into selecting an appropriate salt form of imidazole **479754** (see Experimental Section for the preparation of the **479754** bis-mesylate salt). However, salts of **479754** were found to be unstable during stability testing, with considerable loss of the isopropylsulfonyl group. The imidazole **479754** salt instability issues directed us towards a free base form of the drug candidate. Eventually, the EtOH solvated form of imidazole **479754** was discovered and developed. The imidazole **479754** EtOH solvate has excellent purity and stability and is a very tightly held solvate that does not release the EtOH until it is melted. The solid imidazole **479754** containing EtOAc that was produced from the silica gel treatment was dissolved in EtOH, and the solvent distilled off to remove the residual EtOAc. This was done because EtOAc at low concentrations in EtOH would preferentially solvate with imidazole **479754** over EtOH. This protocol gave crystalline EtOH solvated imidazole **479754**, which was suspended in EtOH, and the resulting slurry was brought to 55 °C momentarily and allowed to cool slowly to 23 °C. This procedure gave imidazole **479754** EtOH solvate in 84% yield (the mother liquor contained high quality imidazole **479754** that was recovered).

The p38 MAPK program also required several other analogues of **479754** be prepared on a multigram scale (Table 1). Aryl iodide **4** gave access to these analogues via the chemistry utilized for the preparation of **479754** (Scheme 5). We found that the Songashira coupling of aryl iodide **4** with 2,4-difluorophenylacetylene could be run in neat triethylamine without added CuI and with a catalyst loading as low as 1.5 mol % of $Pd(PPh_3)_2(OAc)_2$. The procedures for the preparation of these analogues can be found in the Supporting Information.

Conclusion

In conclusion, we developed chemistry that gave access to multigram quantities of imidazole **479754** and several related analogues for Eli Lilly's p38 MAPK program. This was accomplished by optimizing Sonogashira reaction conditions, employing a buffered oxidative method to produce the requisite α-diones, developing buffered reaction conditions to generate imidazoles **479754** and related analogues, and final recrystallization conditions.

Experimental Section

Useful HPLC Method To Analyze Reactions for Preparing 479754. Column: Zorbax SB-C8, 4.6 mm × 250 mm, 5 micron. UV = 218 nm. Buffer: 1 L water + 1 mL

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(8) Radziszewski, B. *Ber*. **1882**, *15*, 1493.
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Table 1

compound	R^1	R^2	R^3	salt	yield[a] (%)
18	H	H	4-Cl-phenyl	MsOH	58
19	H	H	2-CF_3-phenyl	none	61
20	H	H	2-Cl-6-F-phenyl	MsOH	24
21	H	H	2-F-6-CF_3-phenyl	MsOH	58
22	F	F	2-Cl-6-F-phenyl	MsOH	68
23	H	H	*i*-propyl	MsOH	46
24	H	H	*c*-hexyl	none	50
25	F	F	*t*-butyl	MsOH	76
26	H	H	*t*-butyl	2MsOH	63

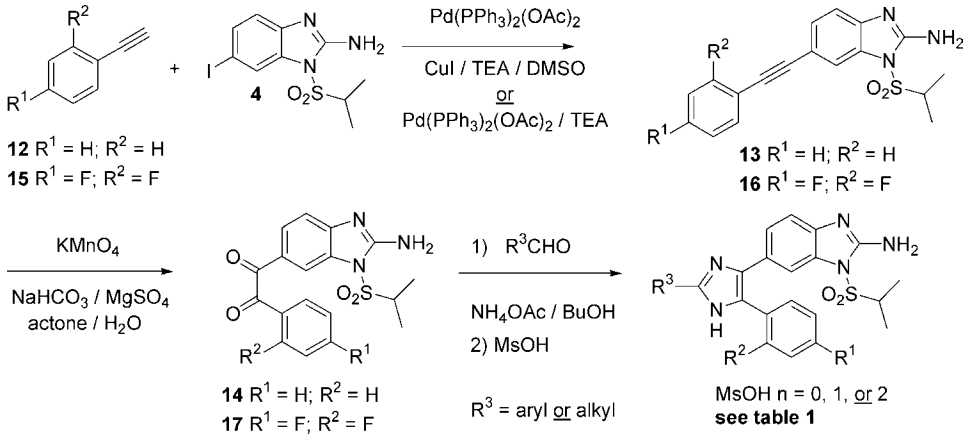
[a] yield is calculated from the corresponding starting α-dione.

of 85% H_3PO_4 (pH ~2.3). Gradient: $T = 0$ min. 5% CH_3CN 95% buffer, $T = 10$ min. 80% CH_3CN 50% buffer, $T = 15$ min. 95% CH_3CN 5% buffer, $T = 20$ min. 95% CH_3CN 5% buffer, post-time = 3 min. 5% CH_3CN 95% buffer. Flow rate 1.5 mL/min. Oven temp 40 °C. Retention times: aryl iodide **4** ~8.4 min, alkyne **13** ~10.7 min, α-dione **14** ~9.9 min, **479754** ~7.1 min, imidazole **8** ~5.1 min.

6-Phenylethynyl-1-(propane-2-sulfonyl)-1*H*-benzoimidazol-2-ylamine (13). Under a nitrogen atmosphere, aryl iodide **4** (400 g, 1.095 mol), bis(triphenylphosphine) palladium(II) acetate (32.8 g, 0.044 mol), and CuI (41.7 g, 0.219 mol) were combined, followed by DMSO (8.4 L) and triethylamine (317 g, 3.133 mol). The resulting mixture was stirred at 20 to 25 °C for 15 min, and phenylacetylene **12** (168 g, 1.645 mol) was added over 30 min giving a temperature rise to 35 °C. The reaction cooled slowly to 20 to 25 °C, and after 15 h, an aliquot of the reaction was quenched into water and diluted with CH_3CN for HPLC analysis. The HPLC chromatogram indicated complete consumption of the aryl iodide **4** with the production of two new less polar products (desired alkyne **13** and phenylacetylene dimer). Water (4 L) was added to the reaction over 1 h giving a temperature rise to 40 °C and a dark precipitate (mainly catalyst). The reaction was filtered through a thin layer of Celite (24 cm diameter) with no washing of the catalyst waste cake. The filtrate was returned to the reactor, and an additional 4 L of water were added over 1 h giving an ending temperature of 45 °C and a yellow slurry. The mixture was left to cool overnight to 20 to 25 °C with stirring. The solids were collected by vacuum filtration and washed with 4 L of water. The solids were dried at 60 °C under a vacuum to constant weight. The yield of alkyne **13** was 319 g (86%) of a light yellow granular solid. Mp (recrystallized from toluene) 226.8 to 229.2 °C. IR (ATR) 3439, 3081, 1654, 1553 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 1.26 (6H, d, $J = 6.9$ Hz), 3.92 (1H, sep, $J = 6.9$ Hz), 7.14 (2H, bs), 7.22 (1H, d, $J = 7.9$ Hz), 7.32−7.41 (4H, m), 7.49−7.57 (2H, m), 7.58 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ 16.3, 56.2, 88.6, 91.0, 114.3, 115.3, 116.8, 123.4, 129.0, 129.1, 129.4, 131.9, 133.1, 143.7, 154.6. MS (ES+) calcd for $(M + H)^+$, 339.4; found, 340.2, 234.3. MS (ES−) calcd for $(M - H)^-$, 339.4; found, 338.3, 232.4.

1-[2-Amino-3-(propane-2-sulfonyl)-3*H*-benzoimidazol-5-yl]-2-phenyl-ethane-1,2-dione (14). Water (4 L), $NaHCO_3$ (30 g, 0.357 mol), and $MgSO_4$ (145 g, 1.205 mol) were combined at 20 to 25 °C and stirred until homogeneous (exotherm to 30.5 °C). Acetone (4 L) was added to the reaction giving a cloudy mixture, followed by alkyne **13** (200 g, 0.590 mol). The resulting slurry was treated with $KMnO_4$ (360 g, 2.278 mol) giving a gradual exotherm to 40 °C over 1 h. After an additional 1 h (35 °C), an aliquot of reaction mixture was diluted with CH_3CN for HPLC analysis. The HPLC chromatogram indicated complete consumption of the alkyne **13** with clean production of a slightly more polar product. Na_2SO_3 (400 g) was added to the reaction mixture, followed by EtOAc (3 L). 20% H_2SO_4 in water (300 mL) was added to the reaction mixture over 25 min (temperature range 30 to 40 °C, large amount of solid MnO_2 produced). The phases were allowed to separate, and an aliquot of the top organic phase was collected for HPLC analysis (HPLC chromatogram indicated clean product). The organic phase was separated and clarified by filtration through Celite. The aqueous phase (black and thick) was back extracted with EtOAc (2 L), and the resulting organic phase was clarified by filtration through Celite. EtOAc (1 L) was used to rinse the Celite. The organic phases were combined and concentrated (7 L removed) at 40 °C under vacuum causing two phases to form. EtOAc (2 L) was added to the mixture, followed by water (0.5 L) and NaCl (30 g). The layers were separated, and the aqueous phase was back extracted with EtOAc (0.5 L). The organic phases were combined and dried with $MgSO_4$, and EtOAc (2 L) was used to wash the $MgSO_4$. The solvent was removed under a vacuum at 40 °C to give

Scheme 5



189 g of yellow solids. The solids were dried under a vacuum at 60 °C to constant weight to give a final weight of 182 g (83% yield, **14** could be further purified by slurrying in hot IPA or concentrating the final EtOAc phase and letting the α-dione **14** crystallize with excellent purity but poor recovery). Mp (recrystallized from IPA) 172.8 °C. IR (ATR) 3469, 3440, 3065, 1678, 1668, 1646, 1598, 1539 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.27 (6H, d, $J = 6.8$ Hz), 3.94 (1H, sep, $J = 6.8$ Hz), 7.33 (1H, d, $J = 8.8$ Hz), 7.59−7.65 (5H, m), 7.77 (1H, dd, $J = 1.5$, 7.3 Hz), 7.97 (2H, dd, $J = 1.5$, 8.3 Hz), 8.04 (1H, d, $J = 1.5$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.4, 55.8, 111.9, 115.6, 124.2, 128.0, 129.2, 129.3, 131.8, 132.4, 135.1, 149.1, 155.8, 193.2, 195.0. MS (ES+) calcd for $(M + H)^+$, 371.4; found, 372.2. MS (ES−) calcd for $(M - H)^-$, 371.4; found, 370.3.

6-[2-(2,6-Difluoro-phenyl)-5-phenyl-1*H*-imidazol-4-yl]-1-(propane-2-sulfonyl)-1*H*-benzoimidazol-2-ylamine (479754). Under a nitrogen atmosphere, α-dione **14** (225 g, 0.606 mol), NH_4OAc (700.4 g, 9.08 mol), *n*-BuOH (4.5 L), and 2,6-diflurorobenzaldehyde **7** (172.2 g, 1.212 mol) were combined. The resulting mixture was heated to 55 °C to give a yellow slurry. After 24 h, the reaction was almost homogeneous, and an aliquot of the reaction was removed for HPLC analysis (2.6 area% α-dione **14**, 88.4 area% **479754**, 8.8 area% desulfonylated **479754**). The reaction mixture was cooled to 15 °C, and water (2.5 L) was added. After mixing for 15 min, the layers were separated, and the organic phase was back extracted with water (2.5 L). The organic phase was separated and concentrated under a vacuum at 55 °C to give 513 g of a black oil. The oil was dissolved in MeOH (505 mL) at 50 °C, and MTBE (2.25 L) was added to the mixture over 1.5 h (crystals had begun forming after the first liter of MTBE was added). The resulting slurry was cooled slowly to 22 °C and stirred overnight. The light brown solids were filtered and washed with MTBE (750 mL). House vacuum was pulled on the solids for 1.5 h to give 239 g of solid (DSC onset 106.65 °C, maximum 116.79 °C, 18.67 J/g). The solids were dissolved in EtOAc (3.85 L) at 50 °C, and silica gel (250 g) was added to the mixture. After 0.5 h, the mixture was allowed to cool to 35 °C, vacuum filtered over silica gel (250 g wet with EtOAc), and rinsed through with EtOAc (6 L). The resulting mixture was concentrated under a vacuum at 50 °C to give a light brown solid (233.6 g, 78%; HPLC >99 area% **479754**; ^1H NMR indicates EtOAc included in the solid). Note: the silica gel treatment removed desulfonylated **479754** and was a precaution to remove metals from earlier in the synthesis.

Preparation of **479754**−EtOH solvate: **479754** (395 g) was dissolved in EtOH (2 L) at 53 °C and vacuum distilled to dryness (this procedure was repeated to remove residual EtOAc from the **479754**; confirmed by ^1HNMR). The resulting solids were slurried in EtOH (1.185 L) at 50 °C for a few minutes and slowly cooled to 22 °C overnight. The resulting slurry was cooled to −3 to 0 °C and held for 1 h. The crystals produced were filtered, washed with EtOH (395 mL, 0 °C), and dried under a vacuum at 50 °C to constant weight. **479754** EtOH solvate (324 g, 84%) was isolated as a light pinkish solid. HPLC indicated the product to be 99.5 area% pure, and ^1H NMR confirmed a 1 to 1 ratio of **479754** to EtOH. Mp (DSC) (5 °C/min; peak melt ambiguous, large shoulder) onset 128.18 °C, maximum 147.55 °C. IR (ATR) 3452, 2970, 1665, 1554 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6; EtOH omitted) δ 1.16 (3H, d, $J = 5.27$ Hz), 1.18 (3H, d, $J = 5.27$ Hz), 3.50−3.75 (1H, m), 6.89 (1H, s), 7.01 (1H, s), 7.12−7.56 (11H, m), 12.74 (1H, s). ^{13}C NMR (75 MHz, methanol-d_4) δ 16.1, 56.9, 110.0 (t, $J = 18.5$ Hz), 113.0 (dd, $J = 18.1$, 7.3 Hz), 113.4, 117.0, 126.2, 127.1, 128.6, 129.5, 129.7, 132.3, 132.7 (t, $J = 10.4$ Hz), 133.8, 136.7, 142.3, 155.3, 162.2 (dd, $J = 251.3$, 8.0 Hz). MS (ES+) calcd for 493.5 $(M + H)^+$, found 494.2. MS (ES−) calcd for 493.5 $(M - H)^-$, found 492.3. Metals analysis: Mn nondetect and Pd < 10 ppm.

Preparation of 479754 Bismesylate salt. 479754 (428 mg, 0.87 mmol) was dissolved in EtOH/EtOAc (1:2, 8.56 mL) at 23 °C giving a yellow homogeneous solution. Methanesulfonic acid (113 uL, 1.73 mmol) was added to the reaction mixture, which removed the yellow color and gave a temperature rise to 27 °C. After a few minutes, nucleation was apparent. After 3 h at 23 °C, the crystals were filtered and washed with EtOAc (10 mL). The white crystals (540 mg, 90%, HPLC 100 area%) were dried under a vacuum at 65 °C. ^1H NMR indicated EtOAc inclusion that could not be removed by drying. Mp (DSC) (5 °C/min) onset 165.68 °C, maximum 172.01 °C.

Supporting Information Available

Synthetic procedures and characterization for compounds **16**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review February 23, 2006.
OP060042T