Organic Process Research & Development

Article

pubs.acs.org/OPRD

The Use of Glycidyl Ethers Involving Aziridinium Intermediates and Other Methodology for the Preparation of Enantiomerically Pure Drug Candidates

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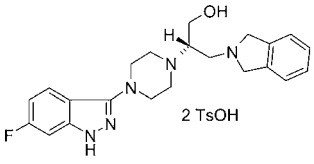
Supporting Information

ABSTRACT: An enantiospecific 1,2-amine migration process through an aziridinium intermediate involving ring-opening with potassium phthalimide derivatives to produce precursors to drug candidates was developed. The precursor amine derivatives were readily available by epoxide opening of simple glycidyl ether derivatives. The regioselectivity of the process was shown to provide approximately 85% of the desired rearranged product with subsequent conversion to the desired drug candidate occurring with excellent purity. An alternative approach using the same glycidyl ether derivatives as starting materials that overcame this regiochemical limitation was subsequently demonstrated.

INTRODUCTION

Drugs for the treatment of psychiatric disorders such as obsessive compulsive disorder and attention deficit disorder are continuing targets of the pharmaceutical industry. Indazole **1** and benzisoxazole **2** bearing an isoindoline appendage[1] were advanced as potential drug candidates, and kilogram supplies of active pharmaceutical ingredient (API) were required to support their development. Recently, we described process improvements in the syntheses of isoindolines **1** and **2** leading



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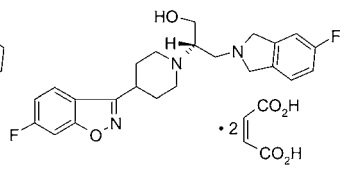


2

to the preparation of kilogram (kilo) quantities of each of these compounds.[2]

With the increasing availability of glycidol derivatives **3**[3] owing to the Jacobsen kinetic resolution process,[4] we anticipated that these materials could be readily elaborated to a precursor **4** that would provide a suitable aziridinium intermediate **5** under the proper conditions. Aziridinium **5** might then undergo selective ring-opening[5−7] upon addition of a nucleophile to provide product **6** for a new route for the preparation of **1** and **2** (Scheme 1). We now report our studies showing that these aziridinium intermediates are viable and do indeed rearrange in an enantiospecific manner.

DISCUSSION OF RESULTS

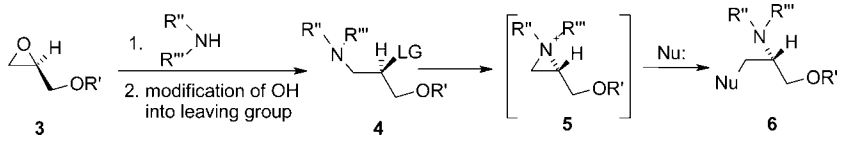
The previously reported key step to install the stereocenter in high optical purity for the kilo synthesis of **1** and **2** involved the S_N2 displacement of triflate **7** with the appropriate amine nucleophile **8** or **9** to give **10** and **11**, respectively (Schemes 2 and 3).[2,8] The major drawback to this process is that the triflate was prepared in three steps from the corresponding D-benzylserine derivative via diazotization chemistry and subsequent elaboration. Thus, removal of the serine nitrogen followed by the incorporation of a new nitrogen moiety makes this process inefficient and costly owing to the use of the D-isomer of serine. Finally, reduction of the ester to alcohols **12** and **13** followed by reaction with a phthalimide nucleophile provided access to key intermediates **14** and **15**. It was anticipated that opening of aziridinium intermediate **5** with the appropriate phthalimide nucleophile (phth = phthalimido) would provide a more direct route for the preparation of compounds **14** and **15**. We focused our attention on the benzyl glycidol derivative **3** (R′ = Bn), because it would provide access to intermediates that were well characterized from the kilo synthesis.

Initial studies were conducted with indazole **16** in order to avoid complications with an unprotected indazole in both the epoxide reaction and in the subsequent formation and ring-opening of the aziridinium intermediate. Indazole **16** was prepared in suitable quantities for the aziridinium studies by reaction of the Boc-piperazine with chloroimidate **17**,[2] cyclization and removal of the Boc-group (Scheme 4). Ring-opening of glycidyl ethers **3** with indazoles **8** or **16** occurred smoothly to provide the desired amino alcohols (Scheme 5). For example, reaction of *N*-Ts piperazine **16** with either benzyl or trityl glycidyl ether in refluxing ethanol provided the corresponding secondary alcohols **18a** and **18b**, respectively. The use of glycidyl butyrate ester was problematic as cleavage of the ester group was a major side reaction especially when EtOH was the solvent. However, the use of THF as the solvent and $Yb(OTf)_3$ in catalytic amounts provided the best conversion to the desired product **18c**. It was subsequently shown that the unprotected indazole **8** reacts smoothly with benzyl glycidyl ether to provide alcohol **18d**. Isoxazoles **19** were prepared in a similar fashion (Scheme 6) from piperidine **9**.

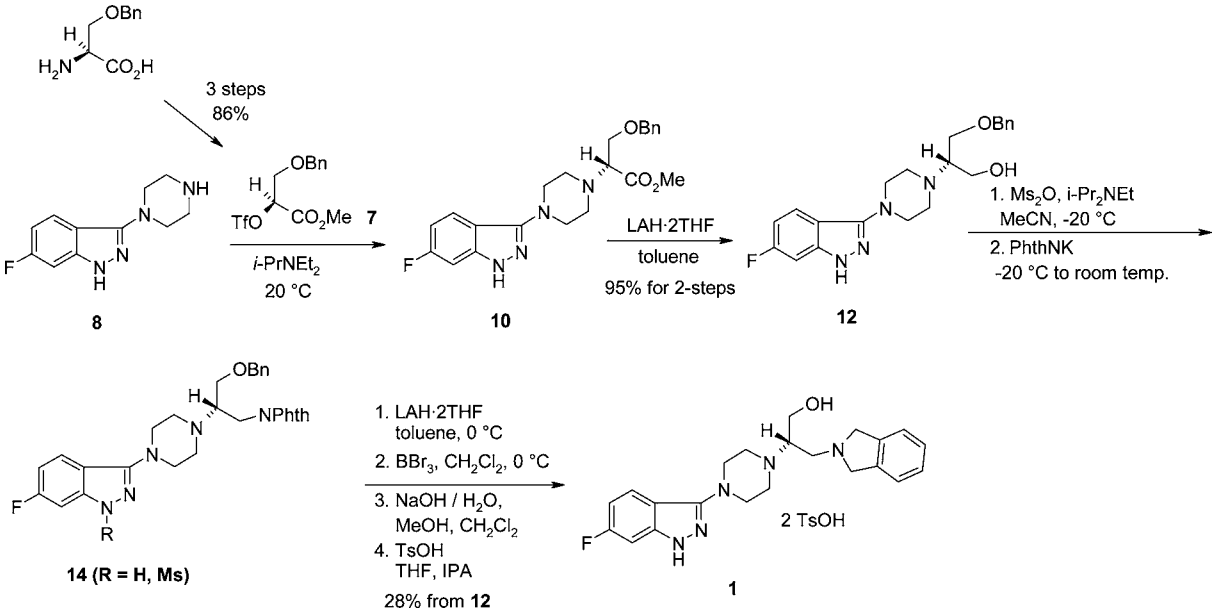
Received: October 31, 2011
Published: December 14, 2011

   dx.doi.org/10.1021/op200310y | *Org. ProcessRes. Dev.* 2012, 16, 141−147

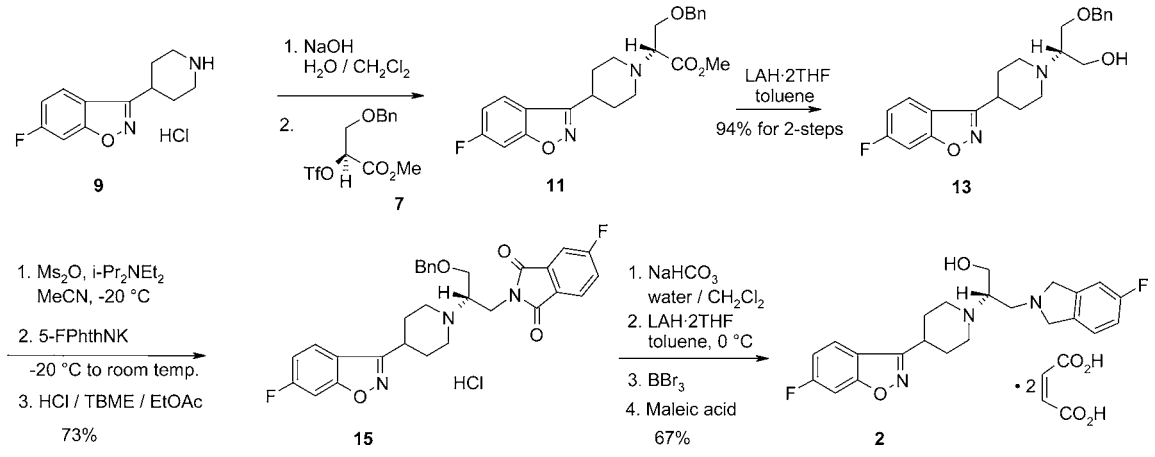
Scheme 1



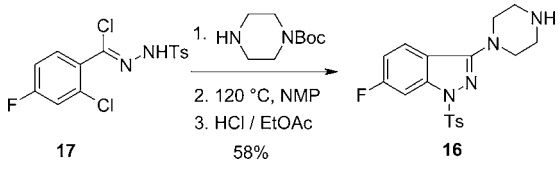
Scheme 2



Scheme 3



Scheme 4



Finally, the enantiomeric compounds were prepared for establishment of the enantiomeric purity.[9]

The aziridinium approach was usually conducted by first preparing and isolating the mesylate intermediate for simplification of the workup of the phthalimide displacement step (Scheme 5). The secondary mesylate **20** is more stable than the primary mesylate used in the kilo synthesis (Scheme 3), as the primary mesylate decomposed above 0 °C and was prepared in situ.[1] However, if mesylate **20** is stored at room temperature, slow decomposition is observed after several hours. Thus, **20** was prepared and used immediately. The reaction of mesylate **20** with PhthNK (Phth = phthalimido) was usually performed at 60 °C in MeCN as solvent and was complete after 4 h; whereas room temperature experiments required at least 18 h. When other solvents such as THF, CH_2Cl_2 or toluene were used, little or very slow reaction was observed, presumably arising from the poor solubility of PhthNK in these solvents. Unfortunately, the aziridinium intermediate **21** was not regioselectively opened because an 87:13 mixture of **14a** and **22a** was obtained, as is often the case

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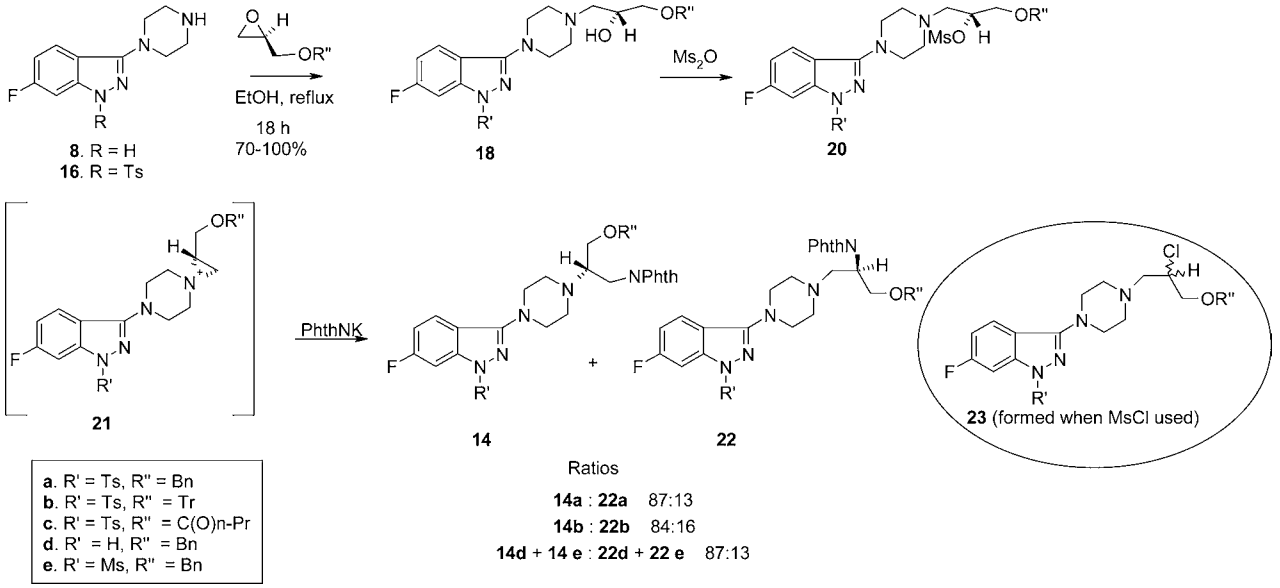
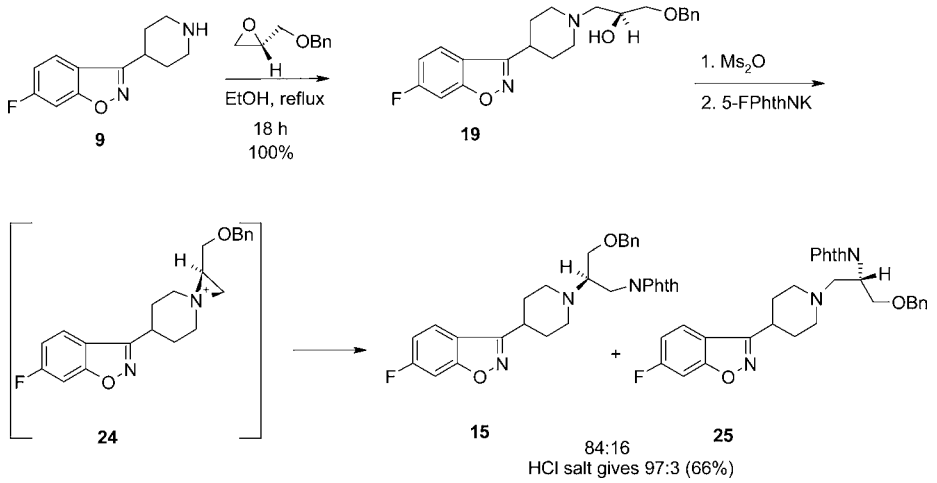
Scheme 5



Scheme 6



for these reactions.[4−6] The ratio of these two products was confirmed by the ^{1}H NMR spectra[10] and HPLC analysis. It was also found that the use of MsCl was detrimental by producing chloride **23** as an impurity. Mesyl anhydride (Ms_2O) was used in subsequent preparations of the mesylate to avoid this complication. However, in the MsCl case, all three compounds were isolated and their structures were confirmed by extensive NMR analyses. Determination of the enantioselectivity of the migration process was accomplished by the synthesis of both enantiomers and HPLC analysis using a chiral column (Chiralpak AD). The ee of phthalimide **14a** was shown to be >99%, which demonstrates that the migration proceeds in an enantiospecific fashion. Reaction of trityl ether **20b** with PhthNK also proceeded in an enantiospecific manner, however the regioselectivity of the pthalimide displacement is slightly lower as an 84:16 mixture of **14b** and **22b** was obtained. Counterion effects were explored briefly and had no observable impact, as the use of the cesium salt of phthalimide did not alter the 84:16 selectivity.

It was also established during the development of the aziridinium approach that the kilo process (Scheme 1) using primary alcohol **12** provided *only* slightly better regioselectivity as a 91:9 mixture of isomers **14d** and **22d** is obtained.[2] Of course, in this reaction a mixture of *N*-H indazole and *N*-Ms indazole is obtained as well (this was not problematic as the methanesulfonamide is cleaved in the subsequent LAH reduction). For direct comparison, the free indazole derivative **18d** was also treated with Ms_2O followed by PhthNK and once again an 87:13 mixture of regioisomers **14d**, **14e** and **22d**, **22e** was obtained. All products were isolated to clearly establish the intermediacy of an aziridinium species for the primary mesylate derivative. These results demonstrate that both reactions are proceeding mostly through the aziridinium intermediate, and perhaps, 31% of a direct S_N2 displacement process occurs in the primary mesylate reaction.[11]

With this understanding of the aziridinium process in hand, we now only needed to demonstrate that the 87:13 mixture of regioisomers in the aziridinium route could be purified at the end by formation of the ditosylate salt. It was decided to use the *N*-Ts indazole for the route verification, although the *N*-H indazole should also be suitable. Thus, 15 g of piperazine **16** was converted into 10 g of **1** using the aziridinium process to

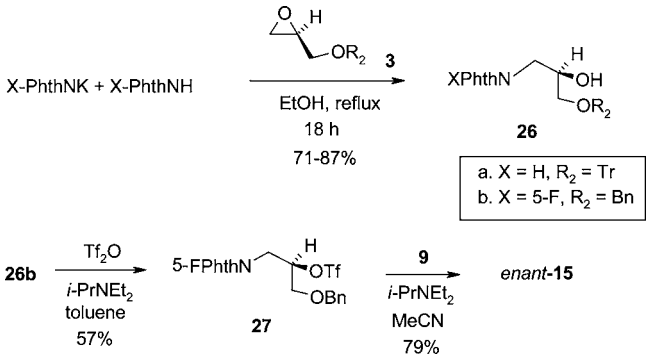
dx.doi.org/10.1021/op200310y | *Org. ProcessRes. Dev.* 2012, 16, 141−147

key intermediate **14a** (>99% ee, but as an 87:13 mixture with **22a**) as shown in Scheme 2. HPLC analysis of the final product showed >96% chemical purity and >99.5% enantiomeric purity. Futhermore, the overall yield (34%) compares well with the kilogram-scale route (28%). More significantly, this process avoids the use of serine and the necessary transformations of the serine to the hydroxy ester and is much more convergent and more cost effective as the required glycidol derivative is now commercially available in production quantities.

Following the demonstration of the aziridinium approach with initial drug candidate **1**, backup compound **2** was selected for further development. The aziridinium approach was also investigated and shown to be an attractive alternative. In this case, the opposite enantiomer of the desired drug substance was prepared to demonstrate this process and to provide analytical data with a reference standard for their use. Now conversion of alcohol **19** to the corresponding mesylate and reaction with 5-FPhthNK occurred via aziridinium intermediate **24** to provide an 84:16 mixture of **15** and **25** (Scheme 6) which is similar to the indazole case. However, formation of the HCl salt removes some of the undesired regioisomer and provided a 97:3 mixture of **15** and **25**. Conversion to the enantiomer of the drug substance **2** was accomplished by reduction of the phthalimide **15** with LAH, removal of the benzyl group with BBr_3, and formation of the dimesylate salt to give 58 g of the enantiomer of **2**. The overall yield of this process from piperidine **9** was 34% and is a significant improvement compared to that of the kilo synthesis.

Finally, we were not satisfied with the regioselectivity of the aziridinium process and were prompted to pursue other applications of glycidol ethers **3** in an alternative process. It was anticipated that, if a nonmigratory amino group could be prepared from glycidyl ethers **3** followed by subsequent conversion of the hydroxy functionality to a leaving group, then direct S_N2 dispacement with the piperidine **9** could be achieved. Thus, we reacted glycidyl ethers **3** with PhthNK in order to produce alcohol **26** (Scheme 7). In the initial

Scheme 7



experiments, we attempted to open the epoxide with only PhthNK in refluxing ethanol and found that the resulting potassium ethoxide reacted with the phthalimido group to give the opened ester/amide derivative. In order to avoid this complication, we found that reaction of 10−50 mol % of PhthNK and 1 equiv of PhthNH (to scavenge the alkoxide and complete the conversion) with the glycidyl ethers smoothly provided the desired alcohols **26** (Scheme 7).

With the kilo-scale synthesis having been completed for both **1** and **2**, and with only **2** still being pursued as a drug candidate, we focused on this alternative route using the fluoro-substituted phthalimide. Thus, generation of triflate **27** under standard conditions and subsequent reaction with piperidine **9** occurred cleanly to provide the desired adduct with >99% ee and 100% regiochemistry as expected in 32% overall yield (unoptimized from glycidol). Once again, subsequent conversion to the desired drug candidate **2** was done as previously described. However, one can quickly envision the use of other nucleophiles and facile cleavage of the simple unsubstituted phthalimide group to provide ready access to a plethora of optically pure 1-amino-3-hydroxy-derivatives from the now readily available glycidyl compounds.

In conclusion, we have demonstrated ready application of glycidyl ethers **3** as key precursors to aziridinium intermediates that can be converted to potential drug candidates. The migration and ring-opening occur in an enantiospecific fashion to provide the desired product with >99% ee. In addition, the aziridinium routes (Schemes 5 and 6) avoided the necessary three-step synthesis of triflate **7** and subsequent LAH reduction (Schemes 1 and 2), thereby shortening the synthesis of both **1** and **2**. A limitation often observed with these aziridinium processes, the nonideal regioselectivity, was not problematic in our case as the unwanted regioisomer is removed in the downstream processing. We subsequently overcame the regioselectivity limitation by avoiding the aziridinium intermediate; however, we still used glycidyl ethers as the key enantiomeric pure precursors for synthesis of the desired enantiomer. This alternative route (Scheme 7) involving phthalimide opening of the glycidyl ether was also shorter, but maintained a potentially unfavorable cost with the use of triflic anhydride. Even though both of the alternative routes were only demonstrated on lab scales, we did not anticipate any road blocks to further scale-up of either route.[12]

EXPERIMENTAL SECTION

General. HPLC conditions used were as follows. Reverse phase separations were conducted on a Waters Symmetry C18, 3.9 mm × 150 mm; wavelength = 214 nm; flow rate = 1 mL/min; solvent A: 25% ACN/75% buffer; solvent B: 45% ACN/55% buffer; buffer = 0.05 M NaH_2PO_4, pH = 3.0; gradient 100% A to 100% B over 30 min. Chiral separations were conducted on a Daicel Chiralpak AD, 250 mm × 4.6 mm, 10 μm packing; IPA and heptane mixture as stated with 0.1% Et_2NH. Additional experimental and spectral data are in the Supporting Information.

6-Fluoro-3-(1-piperazinyl)-1-(4-methylphenyl)-sulfonyl-1*H*-indazole (16). To a solution of Boc-piperazine (105 g, 0.56 mmol) in THF (1.5 L) at room temperature under a nitrogen atmosphere was added chloroimidate **17** (100 g, 0.28 mol) portionwise over 2 h. After 2 h, the mixture was concentrated. NMP (1 L) and powdered K_2CO_3 (100 g, 0.72 mol) were added, and this mixture was heated to 125 °C. After 2 h, the mixture was cooled to room temperature overnight. EtOH (1 L) and water (4 L) were added along with a few seed crystals. After 1 h, the solid was collected and air-dried to give 111 g (85%) of **Boc-16**: ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 1), 7.74 (m, 2), 7.53 (m, 1), 7.19 (m, 2), 6.99 (m, 1), 3.56 (m, 4), 3.40 (m, 4), 2.37 (s, 3), 1.23 (s, 9); ^{19}F NMR ($CDCl_3$) δ −111.4; IR (KBr) 1697, 1437, 1417, 1174 cm^{-1}; MS (APCI) m/z (relative intensity) 419 (M + H) (100), 264 (36). Anal. Calcd for $C_{23}H_{27}FN_4O_4S$: C, 58.21; H, 5.74; N, 11.81. Found: C, 58.22; H, 5.73; N, 11.56.

dx.doi.org/10.1021/op200310y | Org. ProcessRes. Dev. 2012, 16, 141−147

To a solution of **Boc-16** (111 g, 234 mmol) in EtOAc (1 L) and THF (0.2 L) cooled to 0−5 °C was bubbled HCl gas for 0.5 h until saturated. Sat. $NaHCO_3$ (1 L) and 15% NaOH (~1.5 L) were carefully added until pH = 8. The organic phase was washed with brine (0.5 L), dried with $MgSO_4$ (10 g), and concentrated. Plug chromatography on 3.5 L of gravity silica gel in a 4-L fritted funnel using a $MeOH/CH_2Cl_2$ gradient gave 60 g (68%) of **16**: ^1H NMR ($CDCl_3$) δ 7.85 (m, 1), 7.74 (m, 2), 7.56 (m, 1), 7.20 (m, 2), 6.90 (m, 1), 3.43 (m, 4), 3.03 (m, 4), 2.36 (s, 3); ^{19}F NMR ($CDCl_3$) δ −115.4; IR (KBr) 1614, 1594, 1529, 1372, 1190 cm^{-1}; MS (APCI) m/z (relative intensity) 375 (M + H) (100), 220 (33). Anal. Calcd. for $C_{18}H_{19}FN_4O_2S$: C, 57.74; H, 5.11; N, 14.96. Found: C, 57.50; H, 5.04; N, 14.73.

(2*R*)-3-Benzyloxy-1-{4-[6-fluoro-1-(4-methylphenyl)-sulfonyl-1*H*-indazol-3-yl]piperazin-1-yl}propan-2-ol (18a). A solution of piperazine **16** (15 g, 40 mmol) and (*R*)-benzylglycidyl ether (6.7 g, 40.9 mmol) in EtOH (150 mL) was heated to reflux for 18 h. The solution was cooled to room temperature and concentrated. Toluene (100 mL) was added, and the solution was concentrated to give 22 g (100%) of **18a**: ^1H NMR ($CDCl_3$) δ 7.82 (m, 1), 7.78 (m, 2), 7.40−7.28 (m, 6), 7.20 (m, 2), 6.99 (m, 1), 4.60 (s, 2), 3.97 (m, 1), 3.51 (m, 5), 2.82−2.21 (m, 6), 2.38 (s, 3); IR (neat) 3493, 1614, 1594, 1536, 1175 cm^{-1}; MS (APCI) m/z (relative intensity) 539 (M + H) (100), 384 (16).

A sample of the *S*-enantiomer (*enant*-**18a**) was prepared using the (*S*)-benzylglycidyl ether. HPLC separation of the enantiomers was achieved using a Chiralpak AD column as follows: mobile phase (heptane:IPA, 75:25 + 0.1% Et_2NH), flow rate (1 mL/min) and UV detection at 254 nm.

(2*R*)-3-Triphenylmethoxy-1-{4-[6-fluoro-1-(4-methylphenyl)sulfonyl-1H-indazol-3-yl]piperazin-1-yl}-propan-2-ol (18b). A solution of piperazine **16** (10 g, 26.7 mmol) and (*R*)-triphenylmethylglycidyl ether (8.7 g, 27.5 mmol) in EtOH (100 mL) was heated to reflux for 16 h. The solution was cooled to room temperature and a solid was observed. The mixture was concentrated to ~50% of the volume. Heptane (50 mL) was added, and the solid was collected, washed with heptane, and oven-dried (70 °C, 20 Torr) to give 13.8 g (75%) of **18b**: ^1H NMR ($CDCl_3$) δ 7.86 (m, 1), 7.75 (m, 2), 7.52 (m, 1), 7.49−7.41 (m, 5), 7.24−7.16 (m, 12), 6.95 (m, 1), 3.96 (m, 1), 3.44 (m, 4), 3.22 (m, 1), 3.12 (m, 1), 2.76 (m, 2), 2.62−2.44 (m, 4), 2.36 (s, 3); ^{19}F NMR ($CDCl_3$) δ −111.6 (m); MS (APCI) m/z (relative intensity) 691 (M + H) (100), 243 (75).

A sample of the *S*-enantiomer (*enant*-**18b**) was prepared using the (*S*)-triphenylmethylglycidyl ether. HPLC separation of the enantiomers was achieved using a Chiralpak AD column as follows: mobile phase (heptane:IPA, 75:25 + 0.1% Et_2NH), flow rate (1 mL/min) and UV detection at 254 nm.

(2*R*)-3-Benzyloxy-1-[4-(6-fluoro-1*H*-indazol-3-yl)-piperazin-1-yl]propan-2-ol (18d). A mixture of 6-fluoro-3-(1-piperazinyl)-1*H*-indazole (**8**) (5.0 g, 23 mmol) and (*R*)-benzylglycidyl ether (3.8 g, 23 mmol) in EtOH (50 mL) was heated at reflux for 18 h. Upon cooling to room temperature, complete crystallization had occurred. Heptane (25 mL) was added, and the solid was collected. After oven-drying (60 °C, 100 Torr) for 10 h, 6.2 g (70%) of **18d** was obtained: ^1H NMR ($CDCl_3$) δ 9,43 (br s, 1), 7.58 (m, 1), 7.40−7.26 (m, 5), 6.94 (m, 1), 6.82 (m, 1), 4.58 (s, 2), 4.14 (m, 1), 3.58 (m, 7), 3.04−60 (m, 6); ^{19}F NMR ($CDCl_3$) δ −115.8; IR (KBr) 3266, 1629, 1520, 1443, 1148, 1124 cm^{-1}; MS (APCI) m/z (relative intensity) 385 (M + H) (100). $[\alpha]_D$ (MeOH) = +2.32. Anal. Calcd. for $C_{21}H_{25}FN_4O_2$: C, 65.61; H, 6.55; N, 14.57. Found: C, 65.56; H, 6.59; N, 14.27.

2-(3-Benzyloxy-2*S*-{4-[6-fluoro-1-(4-methylphenyl)-sulfonyl-1*H*-indazol-3-yl]piperazin-1-yl)propyl-isoindole-1,3-dione (14a). To a solution of **18a** (22 g, 40 mmol) and *i*-$PrNEt_2$ (8.0 g, 62 mmol) in THF (200 mL) cooled below −10 °C was added Ms_2O (10.5 g, 60 mmol) portionwise over 15 min. After 1.5 h, sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL) were added. The organic phase was washed with brine (20 mL), dried with $MgSO_4$ (2 g), and concentrated (30 °C, 30 Torr). MeCN (100 mL) was added, and the solution was concentrated (30 °C, 30 Torr). The crude oil was dissolved in MeCN (200 mL), and PhthNK (9.3 g, 50 mmol) was added. The mixture was heated to 60 °C for 4 h. The solids were removed by filtration. The filtrate was concentrated. Toluene (200 mL) was added, and this mixture was filtered and concentrated. HPLC analysis showed an 87:13 mixture of **14a** (>99% ee) and **22a**. [Note: Reaction of the *R*-enantiomer (*enant*-**14a**) under the same conditions gave an 87:13 mixture of *enant*-**18a** and *enant*-**22a** to demonstrate the optical purity of **14a** to be (>99% ee.) The absolute configuration of **22a** was not determined but was shown to be (>99% ee)]. Further conversion of this solution to the drug candidate **1** was performed as before (Scheme 2) and is described in the Supporting Information.

In a separate experiment using mesyl chloride, HPLC analysis showed a 79:11:10 mixture of **14a**, **22a**, and **23** was obtained. These compounds were separated by flash chromatography. Compound **14a** showed: ^1H NMR ($CDCl_3$) δ 7.82 (m, 3), 7.74 (m, 4), 7.44 (m, 1), 7.36−7.21 (m, 5), 7.18 (m, 2), 6.94 (m, 1), 4.50 (s, 2), 3.97 (m, 1), 3.70−3.57 (m, 3), 3.28−3.20 (m, 5), 3.01 (m, 2), 2.61 (m, 2), 2.35 (s, 3); ^{19}F NMR ($CDCl_3$) δ −109.8 (m); IR (KBr) 1771, 1712 cm^{-1}; MS (CI, CH_4) m/z (relative intensity) 668 (M + H) (26), 546 (95), 507 (100); $[\alpha]_D$ (MeOH) = −54.51. Undesired regioisomer **22a** showed: ^1H NMR ($CDCl_3$) δ 7.82 (m, 3), 7.74 (m, 4), 7.51 (m, 1), 7.33−7.20 (m, 5), 7.18 (m, 2), 6.95 (m, 1), 4.73 (m, 1), 4.50 (m, 2), 4.00 (m, 1), 3.79 (m, 1), 3.30 (m, 4), 3.06 (m, 1), 2.69 (m, 2), 2.64 (m, 1), 2.48 (m, 2), 2.33 (s, 3); ^{19}F NMR ($CDCl_3$) δ −109.7 (m); IR (KBr) 1773, 1709 cm^{-1}; MS (CI, CH_4) m/z (relative intensity) 668 (M + H) (26), 512 (84), 387 (100). Chloride **23** showed: ^1H NMR ($CDCl_3$) δ 7.82 (m, 3), 7.76 (m, 4), 7.55 (m, 1), 7.40−7.22 (m, 5), 7.19 (m, 2), 6.97 (m, 1), 4.60 (m, 2), 4.17 (m, 1), 3.80−3.64 (m, 2), 3.42 (m, 4), 2.83−2.60 (m, 6), 2.38 (s, 3); ^{19}F NMR ($CDCl_3$) δ −109.6 (m); IR (KBr) 1739 cm^{-1}; MS (CI, CH_4) m/z (relative intensity) 557 (M + H) (10), 541 (14), 401 (100), 387 (92), 219 (79).

Reaction of Mesylate 20b and Phthalimide Nucleophiles. A mixture of **20b** mesylate (384 mg, 0.5 mmol) and PhthNK (120 mg, 0.65 mmol) in MeCN (3 mL) was heated to 60 °C for 4 h. The mixture was filtered through Celite and concentrated. ^1H NMR and HPLC showed an 84:16 mixture of **14b** and **22b**.

In a separate experiment **20b** (100 mg, 0.13 mmol), PhthNH (30 mg, 0.16 mmol) and $Cs(CO_3)_2$ (75 mg, 0.23 mmol) in MeCN (2 mL) were heated to 60 °C. ^1H NMR and HPLC showed an 84:16 mixture of **14b** and **22b**. No reaction is observed if only PhthNH is used.

Reaction of 18d with Mesyl Anhydride and Potassium Phthalimide. To a solution of **18d** (2.0 g, 5.2 mmol) and *i*-Pr_2NEt (1.4 g, 10.8 mmol) in MeCN (20 mL) and THF (15 mL) (note: solubility problems with only MeCN) cooled to

dx.doi.org/10.1021/op200310y | *Org. ProcessRes. Dev.* 2012, 16, 141−147

−10 °C was added Ms_2O (1.45 g, 8.3 mmol) in portions over 20 min. After 2 h, TLC showed complete conversion to mesylate. Potassium phthalimide (2.9 g, 15.5 mmol) was added, and the mixture was heated to 60 °C. After 4 h, the mixture was cooled to room temperature and concentrated. HPLC analysis showed a 73.2:10.9:13.9:1.9 mixture of **14d**, **14e**, **22d**, and **22e**. Flash chromatography on silica gel using 20% EtOAc/heptane as eluant gave samples of pure compounds. Compound **14d** showed: ^{1}H NMR ($CDCl_3$) δ 9.64 (s, 1), 7.82 (m, 2), 7.74 (m, 2), 7.58 (m, 1), 7.43−7.22 (m, 5), 6.94 (m, 1), 6.78 (m, 1), 4.52 (m, 2), 4.00 (m, 1), 3.73−58 (m, 3), 3.40−3.20 (m, 4), 3.10 (m, 2), 2.71 (m, 2), 2.64 (m, 1); ^{19}F NMR ($CDCl_3$) δ −116.1 (m); MS (CI, CH_4) m/z (relative intensity) 514 (M + H) (100). Compound **14e** showed: ^{1}H NMR ($CDCl_3$) δ 7.88−7.63 (m, 7), 7.36−7.24 (m, 4), 7.08 (m, 1), 4.52 (m, 2), 3.97 (m, 1), 3.73−3.58 (m, 3), 3.38 (m, 5), 3.09 (m, 2), 3.03 (s, 3), 2.65 (m, 2); ^{19}F NMR ($CDCl_3$) δ −111.3 (m); MS (CI, CH_4) m/z (relative intensity) 592 (M + H) (100). Compound **22d** showed: ^{1}H NMR ($CDCl_3$) δ 7.83−7.57 (m, 5), 7.36−7.22 (m, 5), 7.01−6.80 (m, 2), 4.75 (m, 1), 4.51 (m, 2), 4.00 (m, 1), 3.81−2.56 (m, 12); ^{19}F NMR ($CDCl_3$) δ −115.9 (m); MS (CI, CH_4) m/z (relative intensity) 514 (M + H) (100). Compound **22e** showed: ^{1}H NMR ($CDCl_3$) δ 8.01−7.61(m, 9), 7.36−7.22 (m, 2), 7.01 (m, 1), 4.73 (m, 1), 4.50 (m, 2), 4.00 (m, 1), 3.81 (m, 1), 3.74−3.59 (m, 2), 3.38 (m, 4), 3.15−3.01 (m, 4), 2.81−51 (m, 3); ^{19}F NMR ($CDCl_3$) δ −111.2 (m); MS (CI, CH_4) m/z (relative intensity) 592 (M + H) (100).

Comparison of these samples with a retained sample of the crude reaction mixture from the kilo synthesis (Scheme 2: conversion of **12** to **14**) confirmed that an aziridinium intermediate is involved in this reaction as a 52.9:38.3:5.0:3.6 mixture of **14d**, **14e**, **22d**, and **22e** was generated.

3-Benzyloxy-2-(*S*)-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-piperidin-1-yl]-1-propanol (19). A solution of piperdine **9** (63 g, 0.29 mol) and (*S*)-benzyl glycidyl ether (48 g, 0.29 mol) in EtOH (0.5 L) was heated to reflux for 18 h. The solution was concentrated to a thick oil. MeCN (100 mL) was added, and the solution was concentrated to give 112 g (>100%) of **19**. A sample of the (*R*)-enantiomer (*enant*-**19**) was prepared in an analogous fashion.

2-{3-Benzyloxy-2-(*S*)-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl]propyl}-5-fluoro-isoindole-1,3-dione Hydrochloride (15). To a solution of **19** (109 g, 0.29 mol) and *i*-PrNEt$_2$ (61 g, 0.47 mol) in MeCN (1.1 L) cooled to 0 °C was added Ms_2O (75 g, 0.43 mol) portionwise over 0.5 h. After 3 h, potassium 4-fluorophthalimide (67 g, 0.33 mol) was added in one portion. The mixture was heated to 60 °C for 4 h. After cooling to room temperature, the mixture was filtered through Celite. HPLC analysis showed an 86:14 mixture of regioisomers **15** and **25**. The filtrate was concentrated. The crude product was dissolved in EtOAc (200 mL), and HCl gas was bubbled through this solution for 15 min until saturated. TBME (100 mL) was added. The solid was collected and air-dried to give 102 g (66%) of **15** (>99% ee) as the hydrochloride salt. HPLC analysis showed a 97:3 mixture of regioisomers **15** and **25**. (Note: A sample of the (*R*)-enantiomer (*enant*-**15**) was prepared in an analogous fashion for optical purity determination.) Compound **15** showed: ^{1}H NMR (d_6-DMSO) δ 10.80 (br s, 1), 8.21 (m, 1), 7.98 (m, 1) 7.81 (m, 1), 7.76−7.60 (m, 2), 7.40−7.22 (m, 6), 4.58 (s, 2), 4.22−3.69 (m, 9), 2.60−2.2 (m, 5); ^{19}F NMR (d_6-DMSO) δ −103.8 (m, 1), −109.8 (m, 1); IR (KBr) 1779, 1719, 1617, 1397 cm^{-1}; MS (APCI) m/z (relative intensity) 532 (M + H) (100). $[\alpha]_D$ (MeOH) = +6.7.

Further conversion of this solution to the enantiomer of drug candidate **2** was performed as before (Scheme 3) and is described in the Supporting Information

2-[3-Triphenylmethoxy-2-(*S*)-2-hydroxyl]-isoindole-1,3-dione (26a). A mixture of (*R*)-triphenylmethylglycidyl ether (1.0 g, 3.2 mmol), PhthNH (0.50 g, 3.4 mmol) and PhthNK (0.60 g, 3.2 mmol) in EtOH (50 mL) was heated to reflux for 20 h. The mixture was cooled to room temperature and concentrated. Flash chromatography on silica gel using 20% EtOAc/heptane gave 1.27 g (87%) of **26a**. ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 2), 7.64 (m, 2) 7.42 (m, 6), 7.24−7.16 (m, 9), 4.16 (br s, 1), 3.96−3.73 (m, 2), 3.12 (m, 2), 3.06 (m, 1); LCMS (ESI) m/z (relative intensity) 486 (M + Na$^+$) (18), 243 (100).

In a separate experiment using only PhthNK, formation of the desired product and cleavage of the phthalimide to generate the mixed amide/ester was observed.

2-[3-Benzyloxy-2-(*S*)-2-hydroxyl]-5-fluoro-isoindole-1,3-dione (26b). A mixture of (*R*)-benzylglycidyl ether (4.00 g, 24.4 mmol), 5-FPhthNH (4.30 g, 26.1 mmol), and 5-PhthNK (4.30 g, 16.6 mmol) in EtOH (110 mL) was heated to reflux for 18 h. The mixture was cooled to room temperature, filtered to remove solids and concentrated. Flash chromatography on silica gel using 20% EtOAc/heptane gave 5.65 g (71%) of **26b**.

Conversion of 26b to Enantiomer of Intermediate 15. A solution of **26b** (6.0 g, 18.2 mmol) and *i*-Pr$_2$NEt (2.42 g, 3.27 mmol) in toluene (60 mL) cooled to 0 °C was added a solution of Tf_2O (5.16 g, 18.3 mmol) in toluene (60 mL) while keeping the reaction temperature below 5 °C. After 1.5 h, the solution was allowed to warm to room temperature. After 1 h, the mixture was filtered, washing the solids with toluene (3 × 20 mL). The combined filtrates were concentrated. Flash chromatography using 25% EtOAc/heptane as eluant gave 4.79 g (57%) of triflate **27** as a white powder.

A solution of **9** (2.0 g, 9.1 mmol) and *i*-Pr$_2$NEt (1.51 g, 14.9 mmol) in MeCN (100 mL) was added dropwise to a solution of **27** (4.78 g, 10.4 mmol) in MeCN (90 mL). After 36 h, HPLC showed 85.3% *enant*-**15** and 14.7% **27** with none of the regioisomer **25** being observed. Work-up and flash chromatography gave 3.85 g (79%) of *enant*-**15**.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra of most compounds are provided. Additional experimental details for the final conversion of the key intermediates to **1** and *enant*-**2** are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

We thank Rick Nevill, Denis Prat, Christian Richard, and Philippe Mackiewicz for their intellectual contributions and passionate discussions. We also acknowledge the extensive NMR experiments performed by Dirk Friedrich for structure elucidation.

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(9) The ee's were obtained using a Chiralpak AD HPLC column.

(10) The methinyl proton adjacent to the phthalimido group in **22** is clearly separated at δ 4.73 ppm as a useful characteristic signal.

(11) In order to obtain 9% of **22**, only 69% needs to go through the aziridinium intermediate, although the reaction was performed at −20 °C instead of 60 °C and the ratio could be influenced by the reaction temperature.

(12) Appropriate process saftey review of the chemistry including the epoxide-opening reaction would be fully addressed before scaling-up.