Organic Process Research & Development **2009**, *13*, 880–887

# Large-Scale Synthesis of a Selective Inhibitor of the Norepinephrine Transporter: Mechanistic Aspects of Conversion of Indolinone Diol to Indolinone Aminoalcohol and Process Implications

Asaf Alimardanov,* Alexander Gontcharov, Antonia Nikitenko, Anita W. Chan, Zhixian Ding, Mousumi Ghosh, Mahmut Levent, Panolil Raveendranath,† Jianxin Ren, Maotang Zhou, Paige E. Mahaney,‡ Casey C. McComas,‡ Joseph Ashcroft, and John R. Potoski

*Wyeth Research, 401 North Middletown Road, Pearl River, New York 10965, U.S.A., and Wyeth Research, 500 Arcola Road, Collegeville, Pennsylvania 19426, U.S.A.*

**Abstract:**

**Development of a scalable synthesis of WAY-315193 is described. Use of LiHMDS as a base and Ti(O-*i*-Pr)$_4$ as a Lewis acid was optimal for efficient and reproducible addition of indolinone anion to epoxyalcohol. Conversion of indolinone diol to indolinone aminoalcohol was achieved via monotosylation−methylamination. The possibility of selective formation of the amidine side product, as well as its utilization for alternative selective preparation of the target aminoalcohol, was demonstrated.**



## Introduction

Drugs that possess norepinephrine reuptake inhibition, either selectively or in combination with serotonin reuptake inhibition, have been used for multiple indications including major depressive disorder, attention deficit hyperactivity disorder, stress urinary incontinence, vasomotor symptoms, and pain disorders such as diabetic neuropathy and fibromyalgia.[1] In the search for new candidates with improvements in both potency and selectivity, one of the lead compounds in the 1-(3-amino-2-hydroxy-1-phenylpropyl)indolin-2-one series, WAY-315193 (**1**), was identified.[2] Development of a scalable process and delivery of kilogram quantities of **1** for further biological evaluation was required.

The synthetic route used initially for preparation of **1** is shown in Scheme 1. The key step of the synthesis was the Sharpless epoxidation of fluorocinnamic alcohol **3** which selectively introduced both relative and absolute configurations at the C-2 and C-3 positions. At the early stages of the project, allylic alcohol **3** was prepared in two steps from commercially available fluorocinnamic acid **2** by treatment with MeI in the presence of $Cs_2CO_3$ in acetone, followed by DIBAL reduction at −78 °C. The epoxide **4** was opened with the sodium salt of dimethylfluoroindolinone in DMF to afford the diol. The diol **6** was further elaborated into the final aminoalcohol hydrochloride **1** in 30−34% yield via tosylation with *p*-toluenesulfonyl chloride (TsCl) in pyridine, isolation of the intermediate monotosylate, treatment with $MeNH_2$, and conversion to HCl salt. Dimethylfluoroindolinone was prepared by reduction and bis-methylation of 7-fluoroisatin by a process developed earlier as described in a prior publication.[3]

In our view, this synthesis appeared simple and straightforward enough to be considered as a basis for preparation of larger quantities of the drug substance for preclinical and early clinical supply. However, several issues had to be addressed: the abundance of chromatographic purifications of the intermediates (**3**, **4**, **6**, and the free base of **1** were oils), the inefficient opening of epoxide **4** with the sodium salt of indolinone **5** requiring two equivalents of the epoxide, the low total yield of the conversion of diol **6** to aminoalcohol **1**, and the variability in the yield of that conversion on larger scale. The development of a scalable process based on this synthetic route, the elucidation of mechanistic aspects of the conversion of **6** to **1**, subsequent studies of properties of uncovered intermediates and side products and their possible utilization are described in this contribution.

## Addition to the Epoxide

The preparation of allylic alcohol **3** was modified to avoid the use of expensive $Cs_2CO_3$, volatile and toxic iodomethane, and cryogenic temperatures. The alcohol **3** was prepared in 95% yield from 3-fluorocinnamic acid **2** via pTSA-catalyzed esterification in methanol followed by DIBAL reduction in toluene at −15 to −8 °C. A Sharpless epoxidation has been successfully scaled up in an industrial environment, but the literature accounts of such work are scarce. We relied on one of the original Sharpless publications describing an example done on a 100-g scale.[4] Treatment of a mixture of allylic alcohol **3**, Ti(O*i*-Pr)$_4$, and D-(−)-diisopropyl tartrate (DIPT) with a solution of *tert*-butylperoxide (TBHP) in methylene chloride afforded

* Corresponding author. E-mail: alimara@wyeth.com.
† Deceased.
‡ Wyeth Research, Collegeville, PA.

(1) (a) For a review on norepinephrine reuptake inhibitors, see: Babu, R. P. K.; Maiti, S. N. *Heterocycles* **2006**, *69*, 539. (b) Krell, H. V.; Leuchter, A. F.; Cook, I. A.; Abrams, M. *Psychosomatics* **2005**, *46*, 379. (c) Hajos, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. W. *CNS Drug Rev.* **2004**, *10*, 23. (d) McCormack, P. L.; Keating, G. M. *Drugs* **2004**, *64*, 2567.

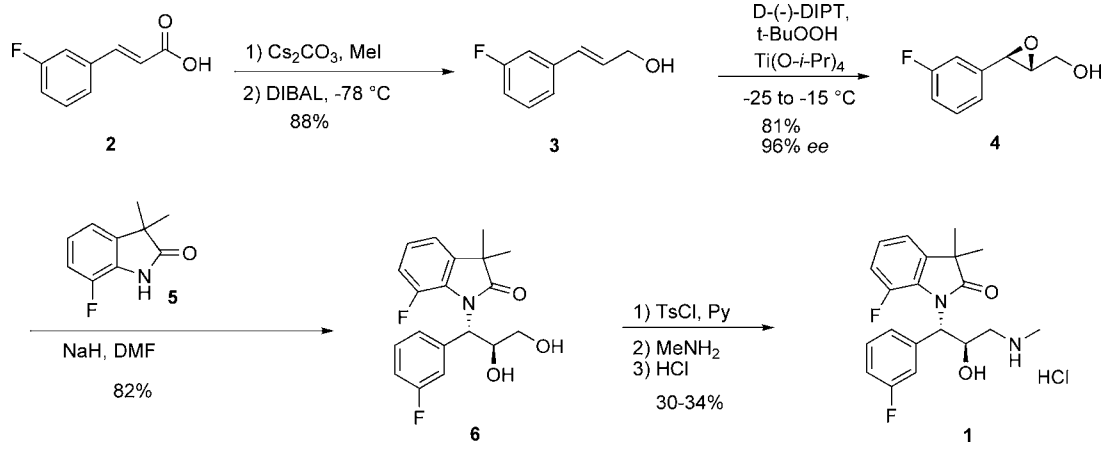
(2) Kim, C. Y.; Mahaney, P. E.; Trybulski, E. J.; Zhang, P.; Terefenko, E. A.; McComas, C. C.; Marella, M. A.; Coghlan, R. D.; Heffernan, G. D.; Cohn, S. T.; Vu, A. T.; Sabatucci, J. P.; Ye, F. Phenylaminopropanol Derivatives and Methods of Their Use. U.S. Patent 7,517,899, 2009.

(3) Wu, Y.; Wilk, B. K.; Ding, Z.; Shi, X.; Wu, C. C.; Raveendranath, P.; Durutlic, H. Process for the Synthesis of Progesterone Receptor Modulators. U.S. Patent Publ. Appl. US 2007/027327, 2007.

(4) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) For a recent example of large-scale asymmetric epoxidation, see: Henegar, K. E.; Cebula, M. *Org. Process Res. Dev.* **2007**, *11*, 354.


10.1021/op900141r CCC: $40.75 
Published on Web 08/17/2009

***Scheme 1.*** **Initial synthesis of aminoalcohol 1**




the epoxide **4** as a clear viscous oil, typically in 90−94% yield and 89−91% ee after workup. The epoxide was of sufficient purity to be used directly in the next step. An alternative protocol was also developed, allowing the epoxidation to be performed in toluene at a higher concentration (10 v) compared to the dichloromethane conditions (30 v) and using TBHP solution in decane to afford epoxyalcohol **4** in 89−93% ee. However, this higher throughput came at the expense of the yield (68−82%), in part due to formation of 5−7% (HPLC) of an epoxyalcohol self-condensation byproduct.

The epoxide opening with indolinone was addressed next. Fluorodimethylindolinone **5**, being an amide, is a poor nucleophile which needs to be deprotonated in order to make it sufficiently reactive towards the epoxide.[5] It is also a weak acid which would require a strong base to effect deprotonation: the p$K_a$ of the parent 3,3-dimethylindolinone is reported to be 18.5 in DMSO.[6] On the other hand, epoxide opening with a nucleophile is known to be greatly facilitated in the presence of a Lewis or Brønsted acid.[7] The reaction in the absence of an acid was found to be sluggish. Thus, presence of both a strong base and an (Lewis) acid is required in the reaction mixture at the same time for the reaction to occur. Figure 1 shows a putative schematic of epoxide opening with Ti(IV) as a Lewis acid. Enhanced acidity of the free OH coordinated to the Lewis acid may complicate the picture further, affecting the balance between the acids and the bases.

Early small-scale batches were prepared using sodium hydride and titanium isopropoxide in DMF. NaH was mixed with indolinone **5** to form the anion while Ti(O-*i*-Pr)$_4$ was aged with the epoxide **4** to form the complex, then the solutions were combined. Extensive decomposition of the epoxide under these conditions led to the need to use 2 equiv of **4**. As the yields varied substantially from run to run and significant amounts of byproducts were present, chromatography was required to isolate diol **6**. The reaction was also hard to control as the mixing of Ti(O-*i*-Pr)$_4$ complex and NaH was exothermic and accompanied by vigorous gas evolution.

A screening of a series of base−Lewis acid combinations was therefore undertaken (NaH, *t*-BuOK, $K_2CO_3$, KOH, *i*-PrMgCl, LiHMDS, $Et_2Zn$, tetramethylguanidine, and BuLi were explored as bases, and Ti(O-*i*-Pr)$_4$, $ZnCl_2$, $BF_3 \cdot Et_2O$, $MgCl_2$, $Et_2AlCl$, $BCl_3$, and $TiCl_4$ as Lewis acids). Incomplete conversion, possibly due to acid−base quench, and epoxide decomposition, possibly due to Payne rearrangement and/or opening with a nucleophilic base, were the major issues observed in these experiments. Gratifyingly, it was found that the use of excess LiHMDS as a base and 1.3 equiv of titanium isopropoxide as a Lewis acid with 1:1.3 molar ratio of the indolinone to the epoxide resulted in virtually complete conversion, giving the desired diol **6** reproducibly. The product was isolated as a solid after crystallization from toluene in 72% yield and >97% purity, sufficient to take it into the next step without further purification.

## Conversion to Aminoalcohol

The conversion of diol **6** to aminoalcohol **1** was performed via tosylation and subsequent amination (Scheme 1). Selective monotosylation of the terminal hydroxy group was carried out with TsCl and triethylamine in dichloromethane in the presence of 1−2 mol % of dibutyltin oxide which has been shown to

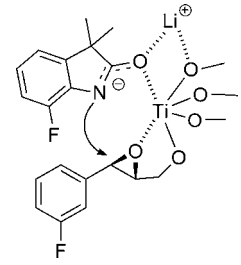


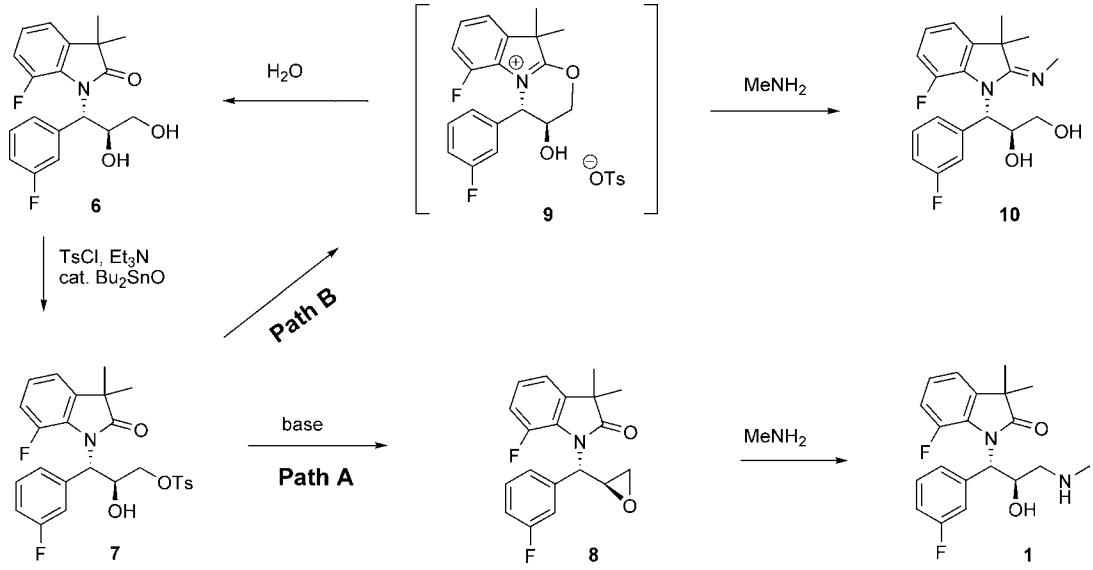

***Figure 1.*** **Assumed intermediate to Ti(IV)- and base-promoted addition to epoxyalcohol.**

(5) (a) For indolinone deprotonation for epoxide opening, see: Proudfoot, J. R.; Regan, J. R.; Thomson, D. S.; Kuzmich, D.; Lee, T. W.; Hammach, A.; Ralph, M. S.; Zindell, R.; Bekkali, Y. Preparation of Propanol and Propylamine Derivatives and Their Use as Glucocorticoid Ligands. WO 2004/063163, 2004. (b) Gillman, K.; Bocchino, D. M. Preparation of Monosaccharides Prodrugs of Fluorooxindoles Useful in Treatment of Disorders Which are Responsive to the Opening of Potassium Channels. U.S. Patent Publ. Appl. US 2004/0152646, 2004. (c) For amide deprotonation for epoxide opening, see: Albanese, D.; Landini, D.; Penso, M. *Tetrahedron* **1997**, *53*, 4787. (d) Chan, W. N.; Evans, J. M.; Hadley, M. S.; Herdon, H. J.; Jerman, J. C.; Morgan, H. K. A.; Stean, T. O.; Thompson, M.; Upton, N.; Vong, A. K. *J. Med. Chem.* **1996**, *39*, 4537.

(6) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218.

(7) (a) Smith, J. G. *Synthesis* **1984**, 629. (b) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737.

***Scheme 2.*** **Transformations of hydroxytosylate 7**




increase the selectivity of tosylation of the terminal hydroxyl.[8] When we attempted to follow the kinetics of tosylation by reverse phase HPLC, a rather unexpected trend was observed: the amount of monotosylate **7** in the reaction mixture increased initially and arrived at a maximum (about 75 area % conversion, bis-tosylate and the starting diol at that point were present at ca. 6−8 area % each), but after approximately 5 h the monotosylate apparently started to convert back to the diol. The latter conversion was puzzling since there was only trace water in the reaction mixture, not sufficient to cause the tosylate hydrolysis, and the monotosylate has been shown to be stable under reverse phase HPLC conditions to eliminate the possibility of its hydrolysis during the analysis. When the reaction mixture containing the "hydrolyzed monotosylate" was treated with an excess of methylamine in ethanol, we observed that instead of the anticipated diol **6** (which would not react with methylamine), the reaction mixture contained a new product with the same molecular ion mass as aminoalcohol **1** ($MH^+$ 361). These observations pointed to a possible participation of the amide carbonyl of the adjacent indolinone fragment in the displacement of the terminal tosylate leading to the formation of a putative cationic intermediate **9** (Scheme 2).[9] This intermediate would accumulate when the tosylation reaction mixture was aged at room temperature for a period of several hours. Nucleophiles would react with **9** at the imidate carbon, displacing the imidate oxygen and opening the six-membered ring.[10] Thus, reaction with water would lead back to the starting amido-diol **6**, while methylamine would give the corresponding amidino-diol **10**.

We could not detect the putative intermediate **9** by a direct analytical technique, but we were able to isolate and characterize the product of its reaction with methylamine. The product proved too unstable to withstand chromatographic isolation on silica gel, affording indolinone diol **6** instead, but it could be crystallized from acetonitrile. NMR analysis of the isolated material confirmed its structure as **10**, thus supporting our assumption as to the nature of the putative intermediate **9**. A full account of the structural assignment of **10** is given in the Supporting Information.

The relatively high rate of decomposition of monotosylate **7** showed that it was critical to ensure that both formation of the monotosylate and its subsequent conversion occur quickly lest we incur higher losses of it to the degradant **9** and, further, to impurity **10** in the final product which was problematic to remove. To accelerate monotosylation of the diol, a catalytic amount of DMAP (10 mol %) was added to the reaction mixture without noticeable effect on the selectivity of the terminal tosylation: the reaction went to completion in less than 1 h, and the amounts of the unreacted diol and the bis-tosylate stayed at 6−8% level.[11] Further screening of tosylation conditions revealed that similar results can be achieved by switching the reaction solvent from methylene chloride to acetonitrile even without DMAP. Complete conversion was achieved in under one hour at 0 °C, and the selectivity of monotosylation was higher than under the previous conditions (only 3% of the bis-tosylate formed).

The reaction of the monotosylate with methylamine (aqueous or ethanolic solution) turned out to be relatively slow, resulting in the formation of significant amounts of amidine **10** even when

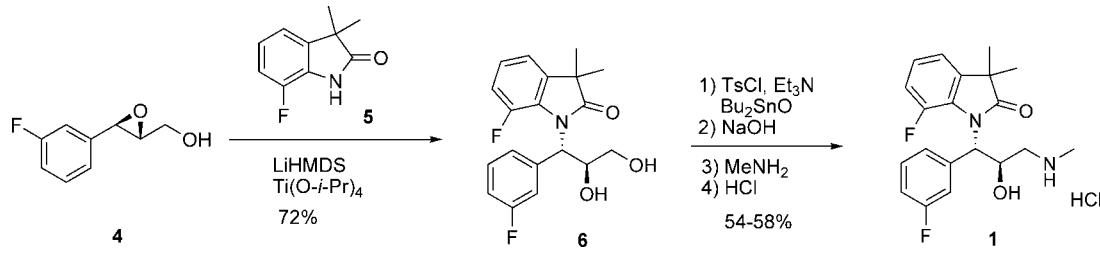
(8) (a) Martinelli, M. J.; Vaidyanathan, R.; Khau, V. V. *Tetrahedron Lett.* **2000**, *41*, 3773. (b) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447. (c) Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V.; Kosmrli, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578.

(9) (a) An example of a related imidate salt formation from tertiary amide at elevated temperature has been reported: Osornio, Y. M.; Miranda, L. D.; Cruz-Almanza, R.; Muchowski, J. M. *Tetrahedron Lett.* **2004**, *45*, 2855. (b) Examples of imidate salt formation from *N*-($\gamma$-haloalkyl)-phthalimide or -amide derivatives on treatment with Ag salts have been reported: Huenig, S.; Geldern, L. J. *Prakt. Chem.* **1964**, *24*, 246. (c) Deslongchamps, P.; Chriyan, U. O.; Taillefer, R. J. *Can. J. Chem.* **1979**, *57*, 3262. (d) For cyclic imide formation via O-alkylation of secondary amides under basic conditions, see for example: Wang, X.; Gross, P. H. *J. Org. Chem.* **1995**, *60*, 1201.

(10) For hydrolysis of imidate salts, see ref 9c and Deslongchamps, P.; Dube, S.; Lebreux, C.; Patterson, D. R.; Taillefer, R. *Can. J. Chem.* **1975**, *53*, 2791, and references cited therein.

(11) Both bis-tosylate and the unreacted diol go through the remaining steps of the synthesis unchanged and can be removed when the HCl salt of the product **1** is prepared.

***Scheme 3.*** **Optimized conditions for the conversion of 4 to 1**




monotosylate formation was fast. We also observed the presence of the intermediate terminal epoxide **8** in the reaction mixture before the reaction reached completion which suggested that tosylate displacement may go through formation of that epoxide, at least as a possible competing process. That prompted us to attempt conversion of the monotosylate to the terminal epoxide **8** with a hope that (1) we may be able to achieve that conversion faster than monotosylate reacts with methylamine and (2) the terminal epoxide may be more stable toward intramolecular attack by the amide oxygen. The latter argument could be made if one envisioned the trajectories of the nucleophilic attack by the amide oxygen on the terminal tosylate and the epoxide: attack on the terminal carbon of the epoxide would lead to a more strained cyclic transition state. That happened to be the case: when treated with concentrated aqueous solution of NaOH in the presence of a phase transfer catalyst, the monotosylate quickly collapsed into epoxide **8** which indeed exhibited enhanced stability toward degradation versus the monotosylate. In fact, the epoxide could be isolated and stored at 0 °C without noticeable decomposition.[12] Weaker bases, e.g., organic tertiary amines, also gave the terminal epoxide, but the reaction rate was much lower which led to competitive degradation of the tosylate. As an added benefit of the treatment with aqueous NaOH, any amount of intermediate **9** that had accumulated in the reaction mixture to that point was converted to diol **6** which was easier to remove from the final aminoalcohol **1** than impurity **10**.

Thus, crucial for the successful transformation of diol **6** to aminoalcohol **1** is the acceleration of monotosylate formation coupled with immediate and rapid in situ conversion to epoxide **8** to ensure conversion via Path A (Scheme 2) and to suppress decomposition via Path B. The optimized protocol involved monotosylation of **6** with TsCl in acetonitrile in the presence of triethylamine and catalytic dibutyltin oxide at 0 °C for 1 h, followed by treatment with aqueous NaOH at 0 °C for 1 h. After a solvent switch to toluene, the resulting terminal epoxide **8** was treated with a solution of methylamine in EtOH that led to slow epoxide opening at the terminal carbon and formation of the desired aminoalcohol **1** devoid of the side product **10**. Aminoalcohol **1** was crystallized from an MTBE−EtOH mixture as a hydrochloride salt to afford the target compound in 54−58% yield, >99% purity and 99.1% ee (Scheme 3).

(12) Alternative approaches involving conversion of diol **6** to the terminal epoxide **8** via Mitsunobu protocol or sequential treatment with trimethyl orthoacetate, acetyl bromide, and base were explored and found to be less efficient.

## Reactions of Amidine 10 and Alternative Routes to Aminoalcohol 1

In the previous section, we reported that the development of conditions for rapid formation of monotosylate **7** and its fast consumption in the subsequent step allowed us to avoid the formation of significant amounts of amidine **10** as a side product resulting from the side reaction of the monotosylate. Here, we will show that this side reaction (Path B, Scheme 2) can be used by leading to an alternative method of conversion of diol **6** to aminoalcohol **1**. This alternative route to **1** was discovered too late for an equal consideration with the first route aforementioned and may be considered for large-scale preparations in the future.

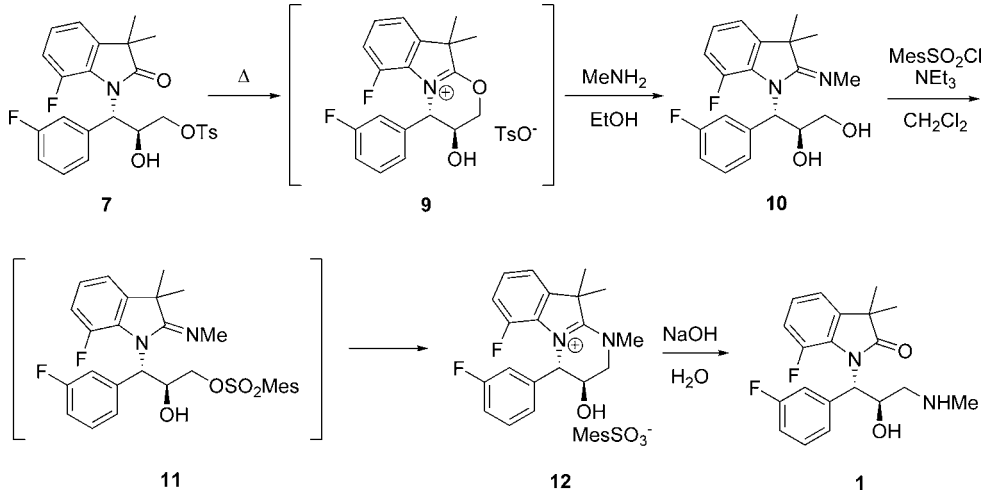
We have shown that conversion of monotosylate to intermediate **9** can be forced to completion by heating the reaction mixture to 40 °C. Subsequent treatment with methylamine afforded amidine **10** which was prepared in this way in multigram quantities.

Amidine-diol **10** was selectively converted to a monomesitylsulfonate **11** (Scheme 4), which spontaneously cyclized to form the cyclic amidinium salt, intermediate **12**. This process is analogous to the degradation route of monotosylate **7** discussed earlier, except that it proceeded instantaneously, presumably due to higher nucleophilicity of the amidine nitrogen compared to that of the amide oxygen. The cyclic amidinium salt **12** proved to be much more stable than the corresponding oxygen analog **9** and could be crystallized from the reaction mixture and isolated by filtration. Cationic intermediate **12** was stable under mildly acidic HPLC conditions and could be characterized by LC/MS. Its facile hydrolysis with aqueous base led to the formation of amino alcohol **1**.

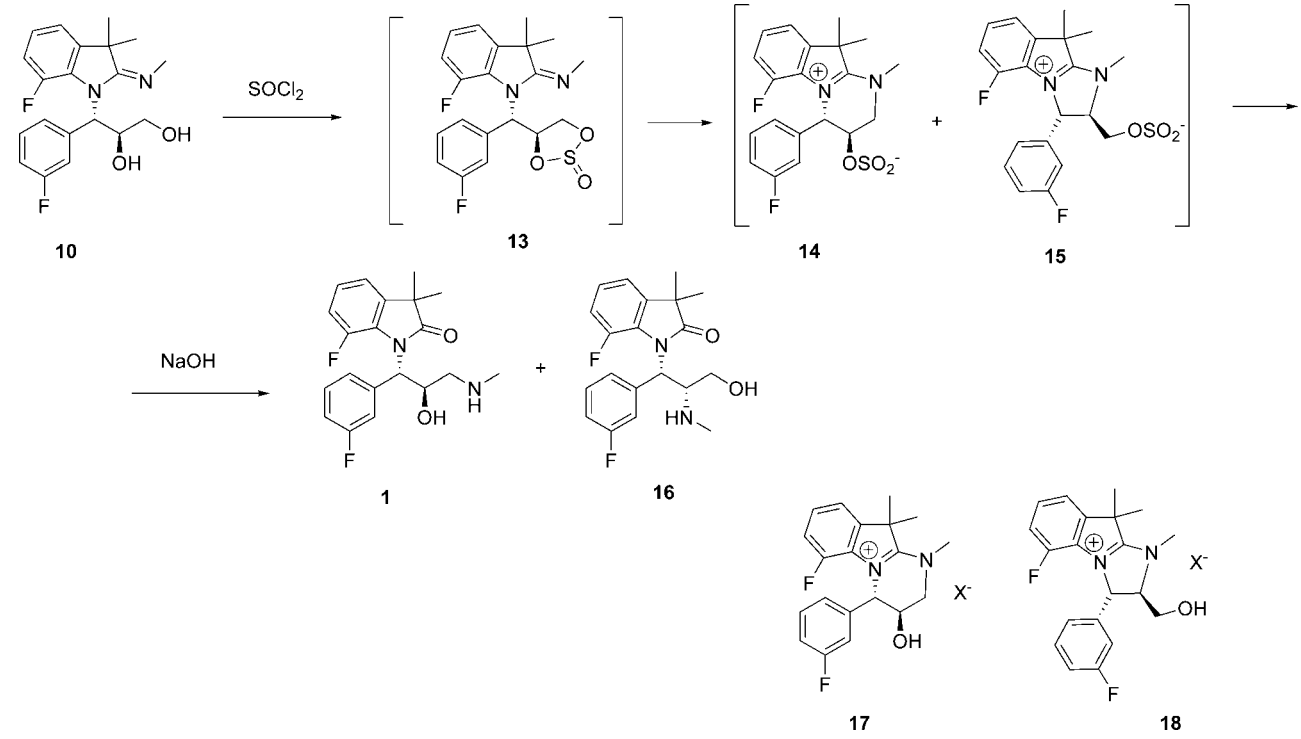
These results prompted us to investigate the behavior of a cyclic sulfate that was derived from amidine diol **10**. Cyclic sulfates can be made from 1,2-diols via initial conversion to cyclic sulfites and subsequent oxidation, and they can be used for reactions with nucleophiles.[13] Typically, the intermediate cyclic sulfites are not useful for ring-opening with nucleophiles and carbon-nucleophile ring formation. But much to our surprise, treatment of **10** with $SOCl_2$ resulted in cyclic sulfite formation and immediate ring-opening with amidine nitrogen to form a 1:1 mixture of cyclic zwitterionic intermediates **14** and **15** (Scheme 5), which were detected by LC/MS as the corresponding hydroxy derivatives **17** and **18** resulting from hydrolysis under HPLC acidic aqueous conditions. Subsequent treatment with NaOH afforded a 1:1 mixture of aminoalcohol **1** and its isomer **16** in quantitative combined yield.

(13) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.

***Scheme 4.*** **Conversion of monotosylate 7 to amino alcohol 1 via amidine intermediate 10**




***Scheme 5.*** **Cyclic sulfite preparation from amidine 10 and formation of isomer 16**






The selectivity of the cyclic sulfite **13** opening was greatly improved when the reaction was conducted at −70 °C, affording a mixture of **16** and **1** in a 6:1 ratio as judged by $^1$H NMR (8:1 ratio of isolated compounds). The isomers were separated by flash chromatography on silica gel, affording the isomeric aminoalcohol **16** in 70% yield.[14]

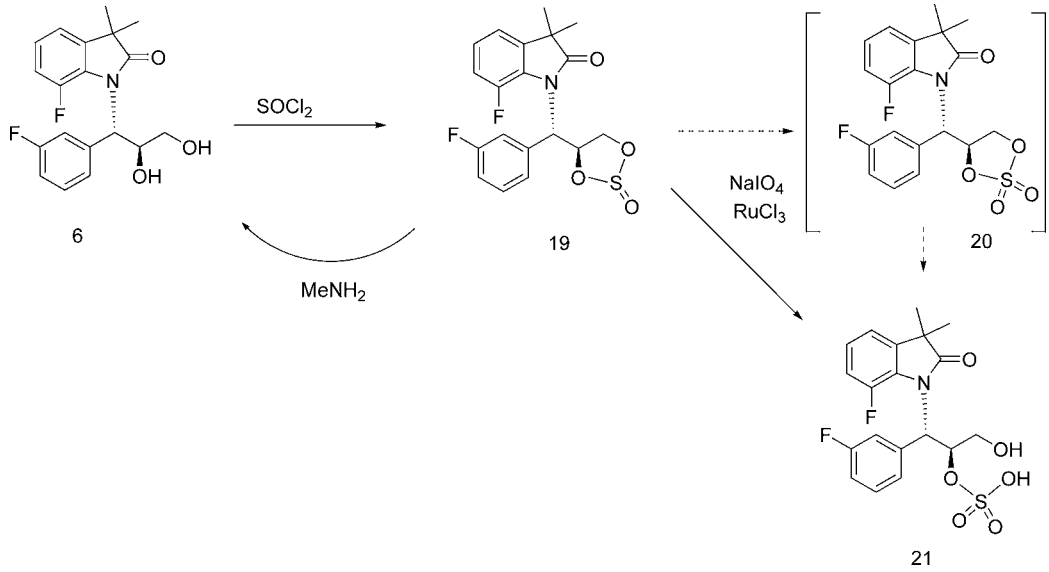
This behavior of amidine diol **10** is in contrast with amide diol **6** (Scheme 6). Cyclic sulfite **19** formed from amide diol **6** exhibited the expected reactivity and did not undergo intramolecular ring-opening - ring closing even at 80 °C. Subsequent aqueous $NaIO_4$ oxidation did not afford the corresponding cyclic sulfate **20**, and only the product of its hydrolysis, hydroxysulfonic acid **21** or its regioisomer, was formed as judged by LC/MS, possibly forming with the anchimeric assistance of the amide carbonyl. It should be noted that direct treatment of cyclic sulfite **16** with methylamine resulted in its hydrolysis to diol **6**.

These results demonstrate that one can use the "unwanted" side-process (Path B, Scheme 2) of cyclization−ring-opening to selectively generate amidine **10**. By applying a second set of cyclization−ring-opening transformations one can effectively achieve a formal nitrogen−oxygen switch to convert an amidine containing an alkyl alcohol to an amide containing an alkyl amine. Moreover, in the case of amidine diol **10**, a selective conversion to either regioisomer of amide aminoalcohol **1** or **16** is possible.

## Conclusions

A scalable process for the synthesis of **1** has been developed. Isolation of an amidine side product led to conclusions about the processes involved in the conversion of diol **6** to aminoalcohol **1**. That allowed the development of a controllable process

***Scheme 6.*** **Approach through cyclic sulfate of indolinone diol**






for the transformation, and the demonstration of an alternative selective approach either to the target aminoalcohol **1** or its isomer.

## Experimental Section

**General.** HPLC analysis of the intermediates and reaction monitoring was carried out on an Agilent 1100 liquid chromatograph equipped with a Phenomenex Prodigy ODS3 4.6 × 50 mm column. Standard method: 90:10 to 10:90 over 8 min gradient of water-acetonitrile containing 0.02% TFA, flow rate 1 mL/min. LC/MS data were obtained on an Agilent 1100 LC system with an Agilent 1100 LC/MS detector equipped with a 4.6 mm × 50 mm Chromolith SpeedROD column. Standard method: 90:10 to 10:90 over 4 min gradient of water−acetonitrile containing 0.02% TFA, flow rate 4 mL/min.

**(*E*)-3-(3-Fluorophenyl)prop-2-en-1-ol (3).** To a slurry of 3-fluorocinnamic acid **2** (6.6 kg, 39.1 mol) in MeOH (39 kg), was added *p*-toluenesulfonic acid (0.8 kg, 3.7 mol, 10 mol %) at 20−25 °C. The suspension was stirred at reflux (65−68 °C) for 4 h. Methanol was replaced with toluene by distillation at atmospheric pressure to the volume of 26 L, addition of toluene (51.5 kg), and distillation at atmospheric pressure to the final volume of 50 L. The resulting solution was washed successively with 5% aq. $NaHCO_3$ (2.5 kg in 49.5 kg of water) and water (49.5 kg) and then concentrated via atmospheric distillation to a volume of ca. 30 L. Karl Fisher titration indicated the presence of <0.05% water.

The solution of 3-(3-fluorophenyl)acrylic acid methyl ester in toluene prepared as described above (30 L, 39.1 mol) was added to a 25% solution of diisobutylaluminum hydride in toluene (51.7 kg, 61.1 L, 89.9 mol, 2.3 equiv) maintaining internal temperature between −15 and −8 °C. The reaction mixture was stirred at −15 to −8 °C for 1 h, then quenched into a 37% aqueous solution of HCl (16 kg, 160 mol, 4 equiv), maintaining the internal temperature below 45 °C. Phases were separated. The aqueous layer was extracted with toluene (11.2 kg). The combined organic phase was washed with 5% aqueous $NaHCO_3$ (1.2 kg) and 10% brine (2.3 kg) and concentrated via atmospheric distillation to afford 15.35 kg of a solution that contained 5.85 kg of the title compound by HPLC strength assay (95% yield) of >97 area% purity. Spectroscopic data are in agreement with reported values.[15]

**(2*R*,3*R*)-3-(3-Fluorophenyl)-2-(hydroxymethyl)oxirane (4).** *Method A.* A reactor was charged with toluene (9.9 kg), powdered 4 Å molecular sieves (3.2 kg) and D-(−)-diisopropyl tartrate (1.00 kg, 4.27 mol). The resulting mixture was cooled to −35 °C, and titanium isopropoxide (0.862 kg, 3.03 mol) was added. The mixture was stirred at −30 to −40 °C for 50 min, then a solution of allylic alcohol **3** (4.61 kg, 30.3 mol) in toluene (7.80 kg) was added over 30 min, keeping the temperature below −30 °C. The mixture was stirred at −30 to −40 °C for 50 min. A 5.3 M solution of TBHP in decane (9.46 kg, 62 mol) was added over 3 h maintaining the temperature in the −30 to −40 °C range. The mixture was stirred at that temperature range, and the reaction progress was monitored by HPLC. After stirring for 16 h (83.4% conversion) the temperature was raised to −20 °C, and the stirring was continued for 6 h until the level of the starting allylic alcohol **3** reduced to below 3%. The mixture was warmed up to 20 °C and filtered through a pad of Celite. The pad was rinsed with toluene (18 kg), and the rinse was combined with the filtrate. A solution of NaCl (0.24 kg) and NaOH (2.8 kg) in water (2.8 kg) was added to the batch at 0 to 10 °C, and the resulting biphasic mixture was stirred at 20 °C for 2 h. A solution of sodium metabisulfite (3.2 kg) and citric acid (2.3 kg) in water (30 kg) was added at 0 to 10 °C (exotherm!), and the resulting mixture was stirred at 20 °C for 1 h until the level of the residual peroxide was

(14) The corresponding cyclic carbonate could also be formed from amidine diol **10** by treatment with triphosgene. However, its intramolecular ring opening−ring closing proceeded much slower and was incomplete even after 1.5 h at 40 °C, with a 4:1 ratio of **16** and **1** observed after basic hydrolysis. The reaction could be accelerated and driven to completion by the addition of $Et_3N$, albeit at the expense of selectivity (1.7:1 ratio of **16** and **1** after NaOH treatment).

(15) Boulet, S. L.; Filla, S. A.; Gallagher, P. T.; Hudziak, K. J.; Johansson, A. M.; Karanjawala, R. E.; Masters, J. J.; Matassa, V.; Mathes, B. M.; Rathmell, R. E.; Whatton, M. A.; Wolfe, C. N. 3-Aryloxy/thio-2,3-substituted Propanamines and their Use in Inhibiting Serotonin and Norepinephrine Reuptake. WO 2004/043903, 2004.

below 0.5 mg/L (determined using peroxide test strips). The aqueous layer was separated and discarded. The organic layer was washed with $NaHCO_3$ solution (1.5 kg of $NaHCO_3$ in 30 kg of water) and brine (3.0 kg of NaCl in 30 kg of water), and concentrated in vacuum to a volume of ca. 15 L, keeping the batch temperature below 50 °C. The resulting solution of the epoxide **4** (13.66 kg, 25.5% assayed concentration) was used in the next step. Assayed yield: 3.48 kg (68% based on the amount of allylic alcohol **3**). Spectroscopic data are in agreement with reported values.[15] Chiral purity: 93% ee. Chiral HPLC conditions: column: Chiralpak ADH, 0.46 cm × 25 cm; mobile phase: isocratic 15% heptane, 85% EtOH; detection wavelength: 215 nm; 1 mL/min, 25 °C.

*Method B.* A reactor was charged with D-(−)-DIPT (13.0 g 46 mmol), 4-Å molecular sieves (90 g), and dichloromethane (4.00 L) and purged with nitrogen. This was cooled to −15 °C. Titanium isopropoxide (12.19 g, 43 mmol) was added rapidly to the reaction mixture via the addition funnel, and the reaction mixture was further cooled to −20 °C. A solution of allylic alcohol **3** (127 g, 0.854 mol) in $CH_2Cl_2$ (380 mL) was added to the reaction mixture via the addition funnel at a rate to keep the temperature below −20 °C. The resulting mixture was allowed to stir at −20 °C for 10 min. A solution of TBHP in $CH_2Cl_2$ (4.5 M, 380 mL, 1.71 mol)[16] was added to the reaction mixture via the addition funnel at a rate to maintain the temperature below −20 °C and above −25 °C (addition rate: 7 mL/min). The reaction mixture was stirred at −20 °C for 4 h, then transferred from the reactor into a solution of $FeSO_4 \times 7H_2O$ (356 g, 1.28 mol), citric acid monohydrate (93 g, 0.39 mol), and deionized water (to the total volume of 1.0 L) chilled to 0 °C. The rate of transfer was adjusted to maintain the temperature of the mixture below 10 °C. The resultant mixture was stirred for 25 min. The organic layer was separated and filtered through a pad of Celite. The aqueous phase was extracted with MTBE (2 × 300 mL). Combined organic solutions were cooled to 0 °C. A 30% solution of NaOH in brine (100 mL, prepared by dissolving 5 g of NaCl in a solution of 30.0 g of NaOH in 90 mL of water) was cooled to 0 °C and added to the combined organic phases. The resulting mixture was stirred for 2 h at 0 °C. Water (400 mL) was added, and the layers were separated. The aqueous layer was extracted with MTBE (2 × 250 mL). The combined organic layers were dried over $Na_2SO_4$ (300 g) and concentrated in vacuum. The residue was mixed with 700 mL of toluene, and the solvent was removed in vacuum to afford 125.9 g of the title product as an oil (88% yield). Chiral purity: 89% ee.

**7-Fluoro-1-[(1*S*,2*S*)-1-(3-fluorophenyl)-2,3-dihydroxypropyl]-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one (6).** Toluene (12.2 kg), DMF (2.63 kg) and 7-fluoro-3,3-dimethyloxindole **5** (2.56 kg, 14.3 mol) were charged to reactor **A**. The temperature of the mixture was adjusted to 5 °C, and a 1 M solution of LiHMDS in toluene (36.7 kg, 42.7 mol) was added over 50 min, maintaining the temperature in the 5−20 °C range. The mixture was warmed up to 20−25 °C, held at that temperature range for 25 min, and cooled to 4 °C.

To a separate reactor (**B**), was charged a solution of epoxide **4** in a toluene−decane mixture (12.7 kg, 25.5% assayed concentration, 19.3 mol). Toluene (12.3 kg) was added, and the resulting solution was cooled to 3 °C. Titanium(IV) isopropoxide (5.1 kg, 17.9 mol) was added over 20 min, keeping the temperature below 20 °C. The resulting solution was added to the contents of reactor **A**, keeping the temperature below 20 °C. This was chased with 8.5 kg of toluene. The mixture was stirred at 35−45 °C for 4.5 h. HPLC assay at that point showed 0.4 area % of unreacted indolinone **5**. The mixture was cooled to 10 °C and added to 18% HCl solution (69 kg), maintaining the temperature below 30 °C. The resulting biphasic mixture was filtered through a pad of Celite. A 32-kg toluene filter rinse was combined with the filtrate. The phases were separated. The aqueous phase was extracted with toluene (48 kg). The combined organic phases were washed with a 2.3% aqueous NaOH (26.2 kg, 15.0 mol) and a 5.3% aqueous NaCl (26.4 kg). The resulting organic solution was dried by azeotropic water removal via atmospheric distillation to a volume of 145 L (ca. 55 L of distillate was removed). The concentrated solution was cooled to 20 °C and filtered through a pad of silica gel (10.8 kg). The silica gel pad was rinsed with ethyl acetate (75 kg), and the rinse was combined with the main filtrate. The solution was concentrated by atmospheric distillation to a volume of ca. 32 L. The product crystallized out of the filtrate on cooling to −5 °C over 5 h. The precipitated solid was filtered at −5 °C, washed with heptane (30 kg), and dried on the filter at 20−25 °C in the stream of nitrogen over 16 h to afford 3.56 kg of the title product (72% yield) as a beige solid. Mp 123 °C. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 7.34−7.15 (m, 3H), 7.05−6.85 (m, 4 H), 5.53 (s, 1 H), 4.73 (dd, $J$ = 5, 5 Hz, 1 H), 3.67 (d, $J$ = 5 Hz, 2 H), 1.45 (s, 3 H), 1.39 (s, 3 H). HRMS (for $MH^+$) calc.: 348.1406; found: 348.1407.

**7-Fluoro-1-[(1*S*,2*R*)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3-dimethylindolin-2-one Hydrochloride (1).**[17] To a solution of diol **6** (53 g, 94% strength, 0.144 mol) in MeCN (400 mL) was added $Bu_2SnO$ (0.36 g, 1.44 mmol, 0.01 equiv) and *p*-toluenesulphonyl chloride (28.8 g, 0.151 mol, 1.05 equiv). Triethylamine (29 g, 0.288 mol, 2 equiv) was added dropwise at 0−5 °C. The mixture was stirred for 1 h at 0−5 °C (HPLC analysis indicated completion of tosylation). A solution of NaOH (58 g, 0.72 mol, 5 equiv) in water (400 mL) was added over 20 min at 0−5 °C. The mixture was stirred at 5 °C for 1 h. Toluene (800 mL) and NaCl (25 g) in water (150 mL) were added to form a biphasic mixture. The layers were separated. The organic layer was washed with 2N HCl (300 mL) followed by brine (300 mL). The organic layer was diluted with toluene (700 mL) and concentrated to a volume of ca. 900 mL. The resultant solution was filtered through silica gel (200 g) plug. The silica gel plug was eluted with toluene (1.5 L). The combined filtrate was concentrated under vacuum to ca. 300 mL. Methylamine solution in EtOH (33 wt %, 287 mL, 2.3 mol, 16 equiv) was added to the toluene solution, followed by 400 mL of EtOH. The reaction mixture was stirred at 40−45 °C for 10 h, concentrated via vacuum distillation to ca. 200 mL, diluted with MTBE (500 mL) and washed with water (500 mL). To the organic layer was added 3 N HCl (500 mL). The

(16) Hansen, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(17) Optimization of preparation of **1** was finalized after the first kilo-lab campaign, in preparation for the second one. The project was deprioritized before the second campaign. Optimized lab-scale demo-run procedure is described.

mixture was stirred for 5 min. The phases were separated. The aqueous layer was washed with MTBE (500 mL). To the acidic aqueous layer was charged MTBE (500 mL), the mixture was cooled to 0−5 °C and basified with NaOH (50% w/w, 150 g, 100 mL) at 0−20 °C. The mixture was stirred for 20 min. The phases were separated. The aqueous phase was extracted with MTBE (500 mL). The combined MTBE solution was washed with 15% NaCl (170 mL) and concentrated to ca. 250 mL via atmospheric distillation. To the MTBE concentrate was added EtOH (2B) (150 mL) followed by HCl (37% aqueous solution, 25.5 g). The mixture was stirred at 20−25 °C for 20 min, cooled to 0−5 °C over 1 h, and stirred at that temperature for 22 h. The precipitate was filtered, washed with MTBE (100 mL), and dried in vacuum at 40 °C for 18 h to afford 33 g of the title product as a white solid (58% yield). Mp 209−212 °C. $[\alpha]_D^{25^\circ} = +10.7°$. $^1$H NMR ($D_2O$, 400 MHz) $\delta$: 7.40−7.25 (m, 3H), 7.16−6.97 (m, 4H), 5.47−5.25 (2H, broad m), 3.27−3.20 (2H, broad m), 2.76 (s, 3H), 1.37 (s, 3H), 1.24 (broad s, 3H). $ES^+$ MS, *m*/*z* 361 ($MH^+$). Anal. Calc'd for $C_{20}H_{23}ClF_2N_2O_2$: C, 60.53; H, 5.84; N, 7.06. Found: C, 60.43; H, 5.69; N, 6.84. Sn content: <1 ppm. Enantiomeric purity: 99.1% ee. Chiral SFC analysis conditions: column: Chiralcel OF 250 mm × 4.6 mm; mobile phase: 30% ethanol, 0.4% diethylamine in $CO_2$; detection wavelength: 254 nm; 2 mL/min, 40 °C.

**(2*S*,3*S*)-3-((*E*)-7-Fluoro-3,3-dimethyl-2-(methylimino)indolin-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (10).** To a solution of diol **6** (11.4 g, 32.9 mmol) in dichloromethane (70 mL), were added $Bu_2SnO$ (0.164 g, 0.66 mmol, 2 mol %) and triethylamine (13.7 mL, 98.7 mmol, 3 equiv). A solution of *p*-toluenesulphonyl chloride (6.27 g, 32.9 mmol) in dichloromethane (30 mL) was added over 15 min at 20 °C. The reaction mixture was stirred at ambient temperature for 3 h, at which point HPLC analysis indicated 80:20 areas ratio of monotosylate: diol. Diisopropylethylamine (5 mL, 28.7 mmol) was added, the reaction mixture was kept at room temperature for 18 h, diluted with acetonitrile (150 mL), and stirred at 40 °C for 7.5 h. Methylamine (41 mL of 8 M EtOH solution, 328 mmol) was added at 10 °C. The reaction mixture was allowed to warm up to room temperature, stirred for 24 h, and then concentrated in vacuum. MTBE (100 mL) was added, followed by 2 N HCl (100 mL). The phases were separated. The aqueous phase was washed with 50 mL of MTBE. The acidic aqueous phase was cooled to 10 °C. MTBE (100 mL) was added, followed by 5 N NaOH (40 mL). The precipitated solids were filtered to afford 4.11 g of crude product. The solids were slurried in 12 mL of acetonitrile at 81 °C, cooled to room temperature, and filtered to afford 2.89 g of the title product. The remaining biphasic aqueous NaOH/MTBE system was further processed to afford a second crop of product. The MTBE phase was separated, the aqueous phase was extracted with 50 mL of MTBE. The combined MTBE phase was dried over $Na_2SO_4$ and concentrated to yield 2.81 g of crude product, which was slurried in 5 mL of acetonitrile at 81 °C, cooled to room temperature, and filtered to afford 1.608 g of the title product (38% combined yield). $^1$H NMR (400 MHz, $CD_3CN$, 55 °C) $\delta$: 7.30−7.19 (m, 3 H), 6.98−6.90 (m, 2 H), 6.86−6.76 (m, 2 H), 5.67 (br, 1 H), 4.40 (br, 1 H), 3.58 (dd, $J$ = 11, 5 Hz, 1 H), 3.46−3.38 (m, 1 H), 3.43 (s, 3 H), 1.66 (s, 3 H), 1.59 (s, 3 H). For detailed 2D NMR studies see Supporting Information. MS (positive ESI, for M + H): *m*/*z* 361.

**Preparation of 7-Fluoro-1-[(1*S*,2*R*)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3-dimethylindolin-2-one (1) from Amidine 10.** To a mixture of **10** (180 mg, 0.5 mmol), triethylamine (0.21 mL, 1.5 mmol), DMAP (1.2 mg, 0.01 mmol), $Bu_2SnO$ (2.5 mg, 0.01 mmol), and THF (4 mL), was added a solution of mesitylenesulphonyl chloride (110 mg, 0.5 mmol) in THF (1 mL) at 0 °C over 5 min. The mixture was allowed to warm up to room temperature and stirred for 4 d. The precipitated solids were filtered to afford 183 mg of the intermediate iminium salt. THF (2 mL) was added to the isolated solid, followed by 2 mL of 1 N NaOH at 0 °C. The resultant mixture was allowed to warm up to room temperature, stirred for 1 h, partially concentrated in vacuum to remove THF, and extracted with 3 × 5 mL of MTBE. Combined MTBE extracts were dried over $Na_2SO_4$ and concentrated to afford 68 mg of the title product (38% yield).

**7-Fluoro-1-((1*S*,2*R*)-1-(3-fluorophenyl)-3-hydroxy-2-(methylamino)propyl)-3,3-dimethylindolin-2-one (16).** To a solution of **10** (1 g, 2.78 mmol) in dichloromethane (15 mL), was added a solution of $SOCl_2$ (0.63 mL, 8.3 mmol) in dichloromethane (5 mL) at −70 °C over 10 min. The mixture was stirred at −70 °C for 1 h, then allowed to warm up to room temperature overnight. The solution was added to 30 mL of 1 N aqueous NaOH at 5 °C over 10 min. The biphasic system was stirred at room temperature for 1 h. Phases were separated. The aqueous phase was extracted with 2 × 10 mL of dichloromethane. The combined organic phase was dried over $Na_2SO_4$ and concentrated to afford 0.856 g of crude products mixture. Flash chromatography separation (silica gel, dichloromethane−MeOH, 97.5:2.5, saturated with conc. $NH_4OH$) afforded 0.7 g of the title product (70% yield), along with 0.09 g of **1** (9%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.47−7.2 (m, 3 H), 7.04−6.89 (m, 4 H), 5.36 (br, 1 H), 4.25 (br, 1 H), 3.55 (br d, $J$ = 10 Hz, 1 H), 3.19 (br, 1 H), 2.4 (s, 3 H), 1.41 (s, 3 H), 1.31 (s, 3 H). For detailed 2D NMR studies see Supporting Information. MS (positive ESI, for M + H): *m*/*z* 361.

## Acknowledgment

We thank M. Young and E. Muczynska for help with chiral HPLC analysis.

## Supporting Information Available

Details of 2D NMR analyses of compounds **10** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review June 5, 2009.

OP900141R