Organic Process Research & Development **2005**, *9*, 174–178

Chemistry Development of a Convergent Route to Trecetilide Hemi-Fumarate

Sonja S. Mackey,[‡] Haifeng Wu,*[,†] Michael E. Matison,[†] and Michael Goble[§]

Chemical Research & Development, Pfizer Corporation, 7000 Portage Road, Kalamazoo, Michigan 49001, U.S.A.

Abstract:

A novel, efficient, stereoselective synthetic route for *N*-(4-{4-[ethyl(6-fluoro-6-methylheptyl)amino]-1-(*S*)-hydroxybutyl}-phenyl)methanesulfonamide hemi-fumaric acid salt (trecetilide hemi-fumarate, Figure 1) has been developed. The process features a convergent approach, which assembles two key intermediates in the last step to form the final molecule, which is then isolated by pH-controlled extraction. The new route offers significant yield and purity advantages over the previous route. However, the solvent volume and cycle time were not fully optimized due to the termination of the project.

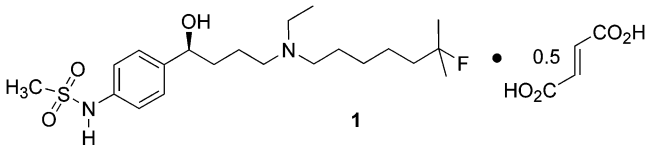
Introduction

Trecetilide hemi-fumarate (**1**) was a compound developed for the chronic treatment of atrial arrythmia. Previous synthetic efforts followed a linear approach (Scheme 1). Each involved early introduction of the unstable tertiary fluorine group that led to quality issues with the final product due to impurities arising from elimination and hydrolysis. Another major issue was the introduction of the chiral aryl alcohol. Early methods involved a nonselective reduction followed by an enzymatic resolution. The enzymatic resolution was highly selective, but chromatographic separation was necessary to purge achiral impurities. Several intermediates also had handling problems due to poor crystallinity. Additionally, the final product prepared by the original method did not meet the developmental purity goals (>96% ee and >95 wt % achiral purity) making it necessary to develop this new process.

Thus, improving both the chiral and chemical purities without column chromatography became the main focus of our efforts to develop a commercializable new route. The success of the new route relied heavily on an asymmetric reduction approach to install the aryl alcohol functionality and efficient late stage installation of the labile tertiary fluoroalkyl group. The convergent route developed for large-scale preparation is outlined in Scheme 2.

Results and Discussion

The new route also starts with 4-{4-[(methylsulfonyl)-amino]phenyl}-4-oxobutanoic acid (**2**), which is commercially available. The Fisher esterification was straightforward to convert **2** to its methyl ester **6** in the presence of 5 mol % of H_2SO_4 at elevated temperature. The product was crystallized directly from MeOH at 0 °C. Residual acid was neutralized by adding Et_3N to the cake wash.



1

Figure 1. **Trecetilide hemi-fumarate.**

Installation and retention of the benzylic chiral center in **7** were major challenges in previous syntheses, and this route was no different. Borane-mediated reduction with oxazaborolidine catalysts [1−3] did not yield a clean reaction. The asymmetric hydrogenation with (1*S*,2*S*)-*N*(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine as described by Noyori and co-workers[4] did not generate any product after 4 days at 80 °C. Blocking the sulfonamide with an *N*-acyl group did not appear to help. Borohydride reduction with 1,2,5,6-di-*O*-isopropylidene-a-D-glucofuranose as the chiral ancillary[5] required a large excess of reagents to achieve higher than 99% conversion. The best reagent we found for ketone reduction was (−)-*B*-chlorodiisopinocampheylborane [(−)-DIP−Cl]. Brown and co-workers reported the use of (−)-DIP−Cl to reduce prochiral ketones to their corresponding secondary alcohols with high enantioselectivity.[6] Using Brown's conditions, reduction of **6** in THF at 0−5 °C was very slow, requiring 3 days for complete consumption of starting material. The low reactivity is likely a consequence of the poor solubility of **6** in THF. A solubility study revealed that the ester had poor solubility in most solvents that were compatible with the reduction conditions; therefore THF was chosen based on the quality of product obtained. Although increasing the reaction temperature helped to reduce the reaction time, lower selectivity was observed (Table 1).

The reduction was quenched with acetone, and the HCl byproduct was neutralized with $NaHCO_3$. After a solvent exchange to methanol, the α-pinene could be completely

* To whom correspondence should be addressed. Telephone: 269-833-3546. E-mail: haifeng.wu@pfizer.com.

† Chemical Research & Development, Pfizer Corporation, Kalamazoo, MI.

‡ Present address: 3M Pharmaceuticals-Chemistry, St. Paul, MN.

§ Present address: Pfizer Global Research & Development, Pfizer Corporation, La Jolla, CA.

(1) (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315−317. (b) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039−2044.

(2) Didier, E.; Loubinoux, B.; Ramos Tombo, G. M.; Rihs, G. *Tetrahedron* **1991**, *47*, 4941−4958.

(3) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (b) Review: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

(4) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562−7563.

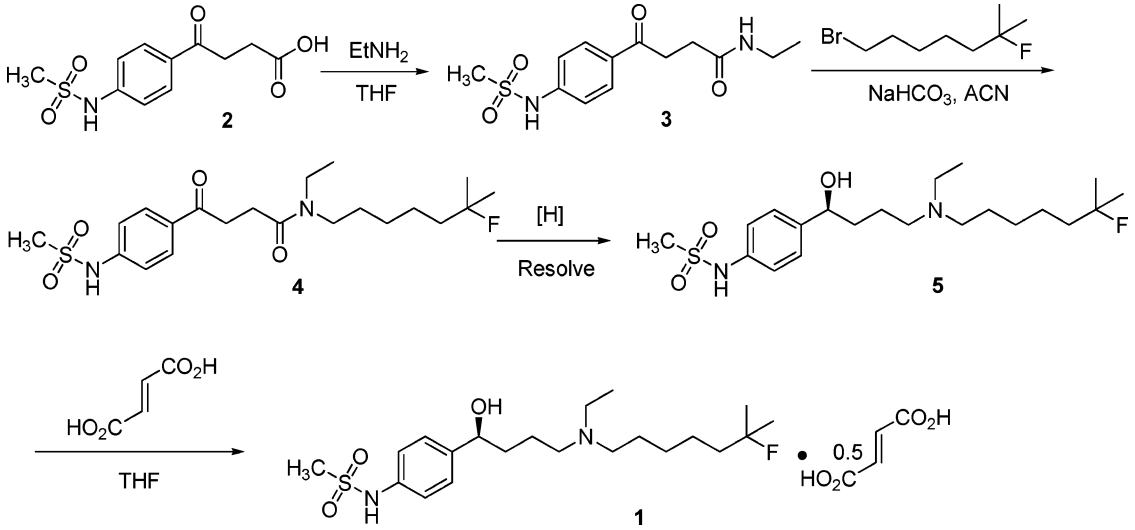
(5) Hirao, A.; Nakahama, S.; Mochizuki, D.; Itsuno, S.; Ohowa, M.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1979**, 807−808.

(6) (a) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446−5448. (b) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16−24.

Published on Web 03/01/2005

10.1021/op049799f CCC: $30.25

Scheme 1. **Initial synthetic route**



Scheme 2. **Convergent route to trecetilide hemi-fumarate**

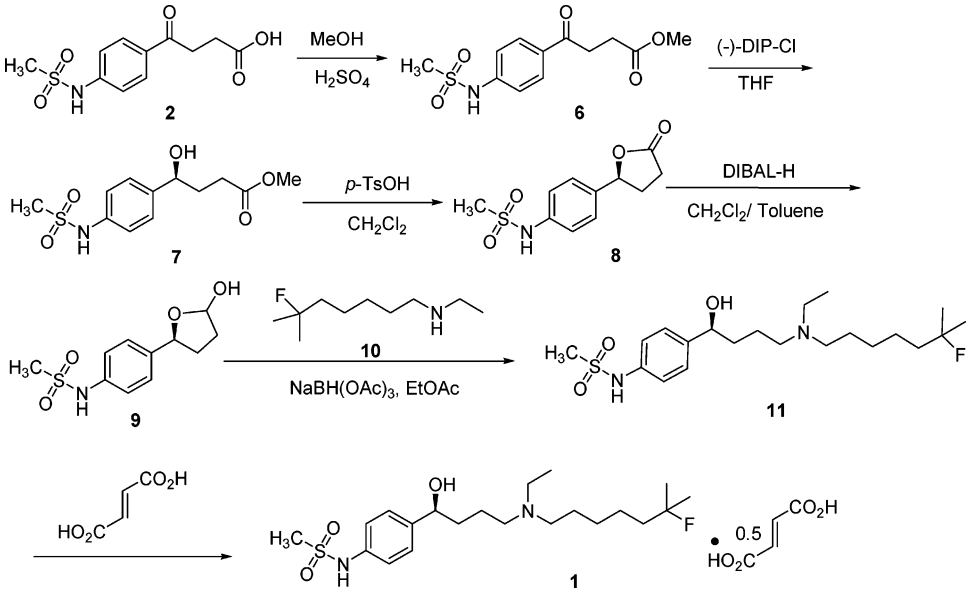


Table 1. **Temperature effect on the (−)-DIP−Cl reduction**

temp (°C)	time (day)	area % purity of crude	% ee of crude
23	1	93.3	93
4	3	94.0	95
−15	5	93.3	97

removed through multiple heptane washes. Another solvent exchange to methylene chloride allowed the isolation of **7** as a crystalline solid in 75−85% yield with greater than 98% ee.

Conversion of the hydroxy methyl ester (**7**) to lactone **8** under acidic conditions resulted in some erosion of chiral purity. An interesting observation was that, under identical conditions, the *N*-acylated hydroxy ester lactonized without racemization. This suggested participation of the sulfonamide functionality in the racemization pathway. A possible mechanism is described in Scheme 3. Thus, after lactonization, protonation of the lactone would set up an equilibrium between **13** and the ring opened *p*-benzoquinone monoimine methide (**12**). Subsequent ring closure of that compound to the lactone would be expected to be an achiral process. We found that the racemization could be minimized by running the reaction at 0 °C. The amount of *p*-TsOH also had significant impact on the chiral purity of the product (Table 2). A catalytic amount of *p*-TsOH, 1.5 mol %, was selected as it provided the highest %ee. Other acids such as trichloroacetic acid (TCA) and trifluoroacetic acid (TFA) also promoted the ring closure at 0 °C, but both required higher loading, 1 equiv and 0.5 equiv, respectively, to achieve complete conversion (Table 3).

Lactone **8** in CH_2Cl_2 was subjected to DIBAL-H reduction in toluene to yield lactol **9** in 64% yield and greater than 93% chemical purity. The crude product was then recrystallized from EtOAc to achieve greater than 99% ee. Reductive amination of the lactol **9** with amine **10** gave the free base (**11**). Due to the equipment limitations that ensue from the use of hydrogenation, we preferred the use of hydride for

Scheme 3. **Proposed mechanism for lactone racemization**

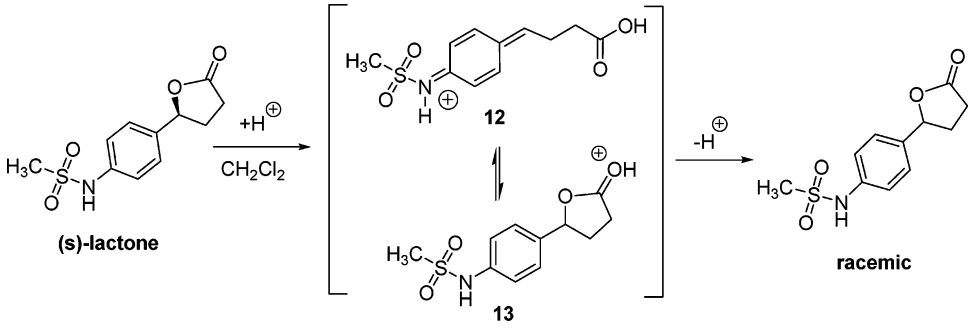


Table 2. **Influence of *p*-TsOH quantity on chiral purity**

equiv of *p*-TsOH	time (h)	% conv	% ee
0.25	1	99	85
0.1	1	98	96
0.015	4	99	98

Table 3. **Results for lactonization at 0 °C using TCA and TFA**

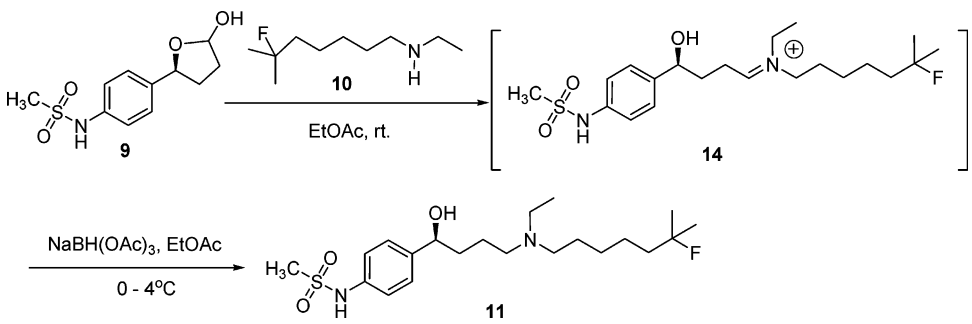
equiv of acid	time (h)	% conv.	%ee
1 equiv of TCA	3	97	98
0.5 equiv of TFA	3.5	99	97

this application. Sodium cyanoborohydride is commonly used in laboratory scale reductive amination reactions, but the toxicity of the reagent and its byproducts make it unattractive for use on large scale. An alternative, sodium triacetoxyborohydride, has been reported as a general reducing agent for reductive aminations[7] and was successful in this case. We chose to run the reductive amination as a two-step process as shown in Scheme 4. The selection of EtOAc as the solvent simplified the workup. The reaction of lactol **9** and fluoroamine **10** at 20 °C afforded the iminium salt **14** as a solution, which was subsequently transferred to a $NaBH(OAc)_3$ slurry at 0−4 °C to afford the desired product. The crude product was purified via a pH-controlled extractive workup. The free base was completely soluble in the aqueous phase below pH 6.5, while most of the impurities were eliminated in the organic phase. After separation, the pH of the aqueous layer was raised to 8−8.5, followed by EtOAc extraction of **11**. This method provided the free base (**11**) with greater than 90% chemical purity and greater than 90% yield. The chemical purity of the product was further upgraded to greater than 98% during the hemi-fumarate salt formation. The chiral purity remained unchanged in the last two steps.

Conclusions

A convergent synthesis for trecetilide hemi-fumarate has been developed. The new process was demonstrated on a 20 g scale in the lab to obtain the final product in 50.9% overall yield in six steps with 99% ee and only 1−1.5 wt % achiral impurities, thus meeting the developmental goals. The intermediates were all easily filterable solids. Clean installation of the benzylic chiral center was accomplished by reduction with (−)-DIP−Cl. The hydroxy methyl ester (**7**) and the lactol (**9**) were capable of chiral upgrading through crystallization. The final coupling of lactol **9** and fluoroamine **10** was achieved through a reductive amination using sodium triacetoxyborohydride. Installation of the labile tertiary fluoroalkyl functionality late in the sequence provided quality advantages over the previous route. A unique use of ethyl acetate as the solvent for the triacetoxyborohydride reductive amination simplified the workup. Use of a pH-controlled extractive procedure allowed the removal of many of the achiral impurities from the free base (**11**) without chromatography. Both the chemical and chiral purity profiles of the hemi-fumarate salt (**1**) prepared by this new route are superior to those from the previous route. However, the efforts to further improve this process, such as increasing the solvent and cycle-time efficiency, were curtailed due to termination of the project.

Scheme 4. **Stepwise reductive amination**



Experimental Section

General. All reagents were purchased from commercial suppliers and used as received unless otherwise noted. NMR spectra were measured on a Bruker AM-400 operated at 400 and 100 MHz, for ^{1}H and ^{13}C, respectively. Elemental analysis was obtained from Pharmacia and Upjohn Physical and Analytical Chemistry. HPLC analyses were carried out on a Dionex DX 500 Chromatography System. Analysis of the chemical purity was conducted by HPLC using the following conditions: column, 4.6 × 150 mm^2 Luna 3m C18; mobile phase, 45:55 acetonitrile/water; flow rate, 1.0 mL/min; detector, 254 nm. Analysis of the chiral purity of **8** was conducted by HPLC using the following conditions: column, 4.6 × 250 mm^2 Chiralpak AS; mobile phase, EtOH (0.05% TFA); flow rate, 0.4 mL/min; detector, 230 nm. Analysis of the chiral purity of **9** was conducted by HPLC using the following conditions: column, 4.6 × 250 mm^2 Chiralcel OF; mobile phase, 50:50 IPA/heptanes (0.05% TFA); flow rate, 0.5 mL/min; detector, 230 nm.

Methyl 4-{4-[(Methylsulfonyl)amino]phenyl}-4-oxobutanoate (6). A 1000 mL round-bottom flask equipped with a reflux condenser, heating mantle, overhead stirrer, and nitrogen inlet was charged with 4-{4-[(methylsulfonyl)amino]-phenyl}-4-oxobutanoic acid (**2**) (50 g, 0.18 mol), methanol (500 mL), and concentrated sulfuric acid (0.92 g, 0.0094 mol). The slurry became a solution after being heated at 60 °C for 4 h. The reaction was monitored by HPLC. After the reaction was complete, the solution was cooled to 0 °C and stirred for 4 h to allow the product to crystallize. The solid product was isolated by filtration and washed with a mixture of cold methanol and triethylamine, followed by cold methanol. Drying afforded ethyl {[(methylsulfonyl)amino]-phenyl}-4-oxobutanoate (**6)** (51.2 g, 97.3% yield) of 99 area % purity. Mp 181−183 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1 H), 7.95 (d, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.8 Hz, 2 H), 3.58 (s, 3 H), 3.32 (s, 1 H), 3.24 (t, J = 6.4 Hz, 2 H), 3.1 (s, 3 H), 2.63 (t, J = 6.4 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ *C* 196.8, 172.8, 143.0, 131.0; *C*H 129.6, 117.5; *C*H$_2$ 32.7, 27.6; *C*H$_3$ 51.3, 39.8; MS *m*/*z* calcd for $C_{12}H_{14}NO_5S$ 284.31 $(M - H)^+$, found 284.00 $(M - H)^+$.

Methyl (4*S*)-4-Hydroxy-4-{4-[(methylsulfonyl)amino]-phenyl}butanoate (7). A 1000 mL round-bottom flask equipped with an overhead stirrer and nitrogen inlet was charged with methyl ester **6** (20.0 g, 0.070 mol) and tetrahydrofuran (300 mL) at 0 °C. A solution of (−)-DIP−Cl (48.3 g, 0.15 mol) in 100 mL of tetrahydrofuran was added dropwise to the above slurry while maintaining the pot temperature below 0 °C. The reaction mixture was stirred for 72−96 h at 0 °C to give a colorless solution. When the reaction was determined to be complete by HPLC, cold acetone (75 mL) was added slowly to quench the reaction while maintaining the pot temperature between 0 and 5 °C. The reaction mixture was stirred at 0 °C for 1 h followed by the addition of EtOAc (100 mL) and warming to 23 °C. The mixture was washed with a 9% aqueous solution of $NaHCO_3$ (2 × 250 mL). The organic layer was concentrated under reduced pressure and swapped to MeOH (200 mL). This MeOH solution was washed with heptanes (4 × 200 mL), followed by distillation to a minimum volume under reduced pressure. CH_2Cl_2 (3 × 100 mL) was added followed by distillation to a volume of 20 mL. After adding CH_2Cl_2 (200 mL), the mixture was cooled to −15 °C and held for 4 h, the product was collected by filtration in 84.9% yield (17.1 g, 92.1% chem, 98.4% ee). Melting point: 70−72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.4 Hz, 2 H), 6.96 (dd, J = 4.9, 8.4 Hz, 2 H), 4.51 (dd, J = 6.3, 6.4 Hz, 1 H), 3.45 (s, 3 H), 2.77 (s, 3 H), 2.21 (t, J = 7.2 Hz, 2 H), 1.81 (dt, J = 6.8, 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *C* 174.4, 141.2, 136.1; *C*H 127.1, 120.9, 72.8; *C*H$_2$ 33.7, 30.3; *C*H$_3$ 51.8, 39.2; MS *m*/*z* calcd for $C_{13}H_{19}NO_5S$ 286.075 $(M - H)^+$, found 285.94 $(M - H)^+$.

***N*-{4-[(2*S*)-5-Oxotetrahydrofuran-2-yl]phenyl}-methanesulfonamide (8).** A 1000 mL round-bottom flask equipped with an overhead stirrer and nitrogen inlet was charged with hydroxy ester **7** (17.9 g, 62.3 mmol) and CH_2Cl_2 (350 mL). The resulting slurry was stirred at −5 to 0 °C followed by the addition of *p*-TsOH (0.12 g, 0.94 mmol). After the reaction was determined to be complete by HPLC, the mixture was washed with cold H_2O (2 × 250 mL) and brine (250 mL) while maintaining the temperature at 0 °C. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting solids were recrystallized from EtOAc (25 mL) to provide 12.1 g (76% yield) of white solids (95 area %, 97% ee). Mp 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dt, J = 8.0, 8.6 Hz, 4 H), 5.43 (m, 1 H), 2.97 (s, 3 H), 2.63 (m, 3 H), 2.14 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *C* 177.0, 137.2, 136.0; *C*H 126.8, 120.7, 80.9; *C*H$_2$ 30.7, 29.0; *C*H$_3$ 39.4; MS *m*/*z* calcd for $C_{11}H_{13}NO_4S$ 255.056 (M^+), found 254.95 (M^+).

***N*-{4-[(2*S*)-5-Hydroxytetrahydrofuran-2-yl]phenyl}-methanesulfonamide (9).** A 500 mL round-bottom flask equipped with an overhead stirrer and nitrogen inlet was charged with lactone **8** (9.8 g, 38.5 mmol), CH_2Cl_2 (125 mL), and toluene (75 mL). After cooling the mixture to −30 °C, DIBAL-H (59 mL, 1.5 M in toluene) was added at a rate of 1 mL/min, keeping the temperature below −25 °C. After the addition was complete, the solution was stirred at −30 °C until HPLC analysis indicated the reaction was complete. Excess DIBAL-H was prequenched with EtOAc (15 mL) at −30 °C, and the reaction was treated with 1 M aqueous disodium citrate (200 mL). The mixture was allowed to warm to 23 °C. Ethyl acetate (200 mL) was added, and the phases were separated. The aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organic layers were washed with brine (2 × 150 mL). After the organic volume was reduced to 60 mL under reduced pressure, the solution was cooled to 0 °C and held at this temperature for 3 h. The product was collected on a filter as a white, powdery solid (6.4 g, 64.9% yield, 93 area %, >99% ee). Mp 129−130 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (d, J = 8.2 Hz, 1 H), 7.29 (d, J = 8 Hz, 1 H), 7.21 (d, J = 8.1 Hz, 2 H), 5.65 (m, 0.5 H), 5.53 (m, 0.5 H), 5.14 (t, J = 6.9 Hz, 0.5 H), 4.93 (t, J = 7.6 Hz, 0.5 H), 2.92 (s, 3 H), 2.49 (m, 1 H),

(7) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862

2.25 (m, 1 H), 1.98 (m, 1 H), 1.92 (m, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ *C* 142.9, 141.2, 140.6, 138.6, 138.5; *C*H 128.4, 127.9, 121.7, 121.6, 99.9, 99.5, 83.2, 80.3, 74.4, 74.3; *C*H_2 35.5, 35.1, 34.4, 34.2, 33.9; *C*H_3 39.1, 39.0. MS (EI) *m*/*z* calcd for $C_{11}H_{15}NO_4S$ 257.07 (M^+); found 256.93 (M^+).

***N*-{4-[(2*S*)-5-Hydroxytetrahydrofuran-2-yl]phenyl}-methanesulfonamide (11).** A mixture of lactol **9** (4.02 g, 15.62 mmol) and fluoroamine **10** (2.77 g, 15.62 mmol) was stirred in EtOAc (30 mL) in a 100 mL flask at 23 °C until a clear solution was obtained. The solution was cooled to 0 °C before being added to a cooled (0 °C) vigorously stirred slurry of sodium triacetoxyborohydride (4.63 g, 21.87 mmol) in EtOAc (10 mL). After HPLC indicated the reaction was complete, cold water (40 mL) was added to quench the excess reagent at 0 to 4 °C. While cooling was maintained, the pH was raised to 6−6.5 using a 10% aqueous sodium hydroxide solution. The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 40 mL). The pH of the aqueous layer was further adjusted to 8−8.5 using a 10% aqueous sodium hydroxide solution, followed by extraction with EtOAc (3 × 30 mL). The combined organic phase was concentrated under reduced pressure to provide **11** as a colorless oil (5.62 g) in 91.1% yield and 96.5% purity.

***N*-(4-{4-[Ethyl(6-fluoro-6-methylheptyl)amino]-1-hydroxybutyl}phenyl)methanesulfonamide Hemi-fumarate Salt (1).** The free base (**11**) (7.78 g, 18.7 mmol) was stirred in 10 mL of THF in a 100 mL flask equipped with an overhead stirrer and a nitrogen inlet. A 125 mL flask was charged with fumaric acid (1.08 g, 9.34 mmol) and THF (80 mL) and heated at 40−45 °C to obtain solution. The THF solution of **11** was then added to the fumaric acid solution, and the mixture was stirred at 45 °C for 30 min. After reducing the total volume to 45 mL under vacuum, 14 mL of branched octane was added while maintaining the pot temperature at 45 to 50 °C. The solids were isolated by filtration, and the cake was washed in two parts using a mixture of 20 mL of THF and 5 mL of branched octane. After a branched octane cake wash (2 × 25 mL) the product was dried in vacuo at 40−45 °C to give 8.1 g of white solid (LC assay 98.9 wt % purity, 92% yield).

Acknowledgment

We are grateful to Timothy W. Evans, Paul M. Herrinton, Dilip K. Joshi, Vikram D. Kalthod, Moses W. McMillan, Mark T. Maloney, and Thomas A Runge for their collaboration on this project. We would especially like to thank Larry D. Kissinger, Simpson D. Putnam, Michael T. Radvan, Fred J. Antosz, and Jerome A. Morris for analytical support.

Received for review November 4, 2004.

OP049799F