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Synthesis of Potent and Orally Efficacious 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitor HSD-016

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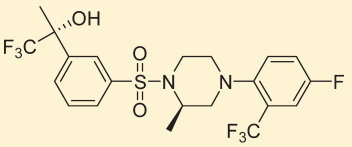
Supporting Information

ABSTRACT: Cortisol and the glucocorticoid receptor (GR) signaling pathway has been linked to the development of diabetes and metabolic syndrome. In vivo, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyzes the conversion of inactive cortisone to its active form, cortisol. Existing clinical data have supported 11β-HSD1 as a valid therapeutic target for type 2 diabetes. In our research program, (*R*)-1,1,1-trifluoro-2-(3-((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-ylsulfonyl)phenyl)propan-2-ol (HSD-016) was discovered to be a potent, selective, and efficacious 11β-HSD1 inhibitor and advanced as a clinical candidate. Herein, a reliable and scalable synthesis of HSD-016 is described. Key transformations include an asymmetric synthesis of a chiral tertiary alcohol via Sharpless dihydroxylation, epoxide formation, and subsequent mild reduction. This route ensured multikilogram quantities of HSD-016 necessary for clinical studies.



HSD-016

human HSD1 IC_{50}: 11 nM
mouse HSD1 IC_{50}: 1 nM
rat HSD1 IC_{50}: 8 nM

INTRODUCTION

A number of therapeutic targets for the treatment of type 2 diabetes have emerged.[1] Glucocorticoids, cortisol in man and corticosterone in mice and rats, stimulate hepatic glucose production and suppress insulin-mediated glucose uptake in peripheral tissues (ie. adipose and muscle).[2,3] Transgenic mice overexpressing 11β-HSD1 in adipose tissue show several features of metabolic syndrome including abdominal obesity, glucose intolerance, dyslipidemia, and hypertension.[4] In humans, 11β-HSD1 activity in adipose tissue correlates positively with body mass index, fat percentage, and fasting glucose and insulin levels. 11β-HSD1 Knockout mice demonstrate reduction in body weight, decreased low-density lipoprotein (LDL) and triglyceride levels, increased high-density lipoprotein (HDL) levels, and increased insulin sensitivity while on a high fat diet.[5] A number of potent and selective 11β-HSD1 inhibitors have been reported in the literature.[6] A few have demonstrated *in vivo* animal,[7] including our own,[6b,7g] and human[8] efficacy related to diabetes.

In our HSD1 program, we discovered a potent, selective, and efficacious HSD1 inhibitor, (*R*)-1,1,1-trifluoro-2-(3-((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-ylsulfonyl)phenyl)propan-2-ol (HSD-016) (Figure 1). This compound had desirable drug properties and demonstrated low nanomolar inhibition of both human and mouse HSD1 enzymes. It also showed promising *in vivo* efficacy in preclinical studies. Advancement into further clinical studies would require significant quantities of HSD-016, and thus a practical and high yielding synthesis had to be developed.

Structurally, compound HSD-016 contains two nonadjacent chiral centers. One within the piperazine ring is readily accessible from a commercially available chiral building block. The tertiary alcohol, however, presents a significant synthetic challenge. Although high enantio- or diastereoselectivity in the synthesis of tertiary alcohols through asymmetric nucleophilic addition to carbonyl compounds has been reported,[9] examples of synthesis of chiral tertiary trifluoromethyl alchohols are scarce. Iseki-Kobayashi[10] and Caron[11] had recently reported a route involving cinchona alkaloid induced asymmetric trifluoromethylation of ketones when we started our synthetic studies on HSD-016. However, only low to moderate selectivity was reported in both studies.[12]

Multiple syntheses of our clinical candidate HSD-016 were explored during the course of our program. Herein, we disclose our efforts toward the development of a reliable and scalable asymmetric synthesis of HSD-016 (Scheme 5).

RESULTS AND DISCUSSION

Initial synthesis relied on the formation of the parent compound mixture **8** (Scheme 1). The synthesis began with an efficient and selective Buchwald amination of 1-bromo-4-fluoro-2-(trifluoromethyl)benzene (**2**) with (*R*)-2-methylpiperazine (**1**) in the presence of BINAP and sodium *tert*-butoxide in toluene to give the desired product **3** in near quantitative yield with no undesired regioisomer observed.[6b] Piperazine **3** could be converted to either 3-acetyl phenyl sulfonamide **5** or 3-bromo phenyl sulfonamide **7** when treated with corresponding sulfonyl chloride **4** (route 1) and **6** (route 2), respectively. Addition of (trifluoromethyl)-trimethylsilane (CF_3TMS) to ketone **5** (route 1) in the presence of TBAF, according to Prakash procedures,[13] led to a clean

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formation of diastereomeric mixture **8**. Alternatively, quenching the lithium anion of 3-bromo phenyl sulfonamide **7** with trifluoromethyl acetone also gave diastereomeric mixture **8** (route 2). Attempted cinchona alkaloid induced CF_3TMS addition to ketone **5** was met with only limited success.[14] Mixture **8** could not be separated using conventional silica gel column chromatography to give pure stereoisomers HSD-016,[15] suggesting that perhaps the substantial distance between both chiral centers resulted in little to no difference in the relative physical properties of each single diastereomer.

Two major drawbacks were associated with the original synthetic routes. First, the high cost of sulfonyl chloride **4** (route 1) as well as safety concerns associated with large scale butyllithium chemistry involving bromide **7** (route 2) were impractical. Second, the chiral separation, required by both routes, not only resulted in the sacrifice of 50% of the material but also was quite tedious. Clearly, an alternative route to a large scale production of the active pharmaceutical ingredient (API) HSD-016 had to be developed.

We envisioned two strategies that would allow us to accomplish a practical synthesis of HSD-016. The first would rely on the formation of a sulfonyl chloride bearing the chiral tertiary alcohol moiety in **10** (Scheme 2, route 3). The second would allow a stepwise building of the desired tertiary alcohol from diol **11**, which could be derived from Sharpless asymmetric dihydroxylation of the olefin precursor (Scheme 2, route 4).

Encouraged by Iseki and Kobayashi's[10] and Caron's[11] early work on the asymmetric trifluoromethylation with Ruppert–Prakash reagent (CF_3TMS), we envisioned that the chiral tertiary alcohol moiety in **10** could be derived from ketone **12**. In fact, asymmetric trifluoromethylation of 3-bromoacetophenone **12** with (trifluoromethyl)trimethylsilane in the presence of cinchona alkaloid ligands **I** and **II** was soon realized to be possible as reported by Mukaiyama[12a] and Nakamura[12b] (Scheme 3, entries 1 and 2).

To validate the transformation of **12** to **15**, we decided to first to investigate synthesis of the recemate before embarking on a larger task of screening other cinchona ligands. A racemic mixture of 2-(3-bromophenyl)-1,1,1-trifluoropropan-2-ol **13** was efficiently prepared in 97% yield using CF_3TMS in the absence of a chiral ligand (Scheme 3). Palladium-catalyzed thiolation followed by oxidation of thiol **14** led to desired sulfonyl chloride **15** in good overall yield. However, chiral separation of **15** to obtain single enantiomer **10** was ultimately deemed impractical. Exploration of this approach using cinchona alkaloids was unsuccessful. Interestingly, it was also noted that an (*S*)-configuration was assigned to tertiary alcohol **13** regardless of the opposite chirality of the secondary alcohol in the ligand **I**[12a] and **II**.[12b] It was thus anticipated that access to necessary chiral ligands for the formation of desired (*R*)-configuration in **15** would be challenging, and an alternative asymmetric synthetic route to chiral sulfonyl chloride **10** would have to be developed (Scheme 4, route 3).

In the third route, Suzuki coupling of boronic acid **16** with vinyl bromide **17** gave the desired olefin **18** in 85% yield. Sharpless asymmetric dihydroxylation with AD mix-α gave corresponding diol **19**

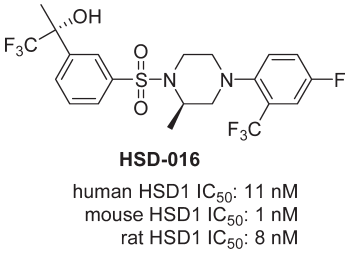
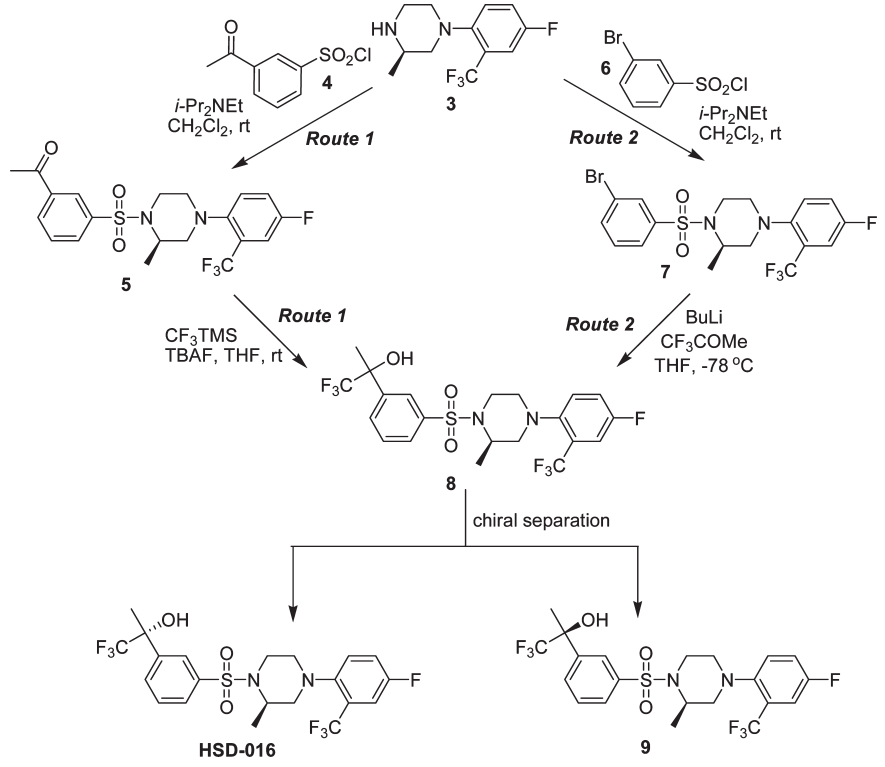


Figure 1. Potent, selective, and efficacious 11β-HSD1 inhibitor HSD-016.

Scheme 1. Routes 1 and 2: Original Synthesis of HSD-016 through Chiral Separation



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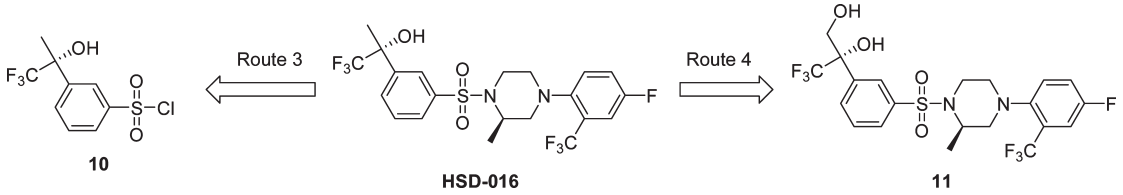
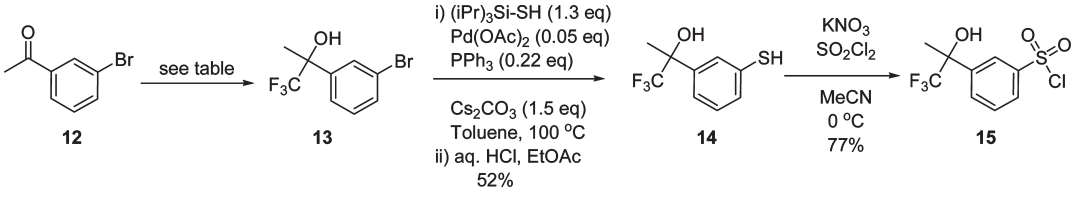
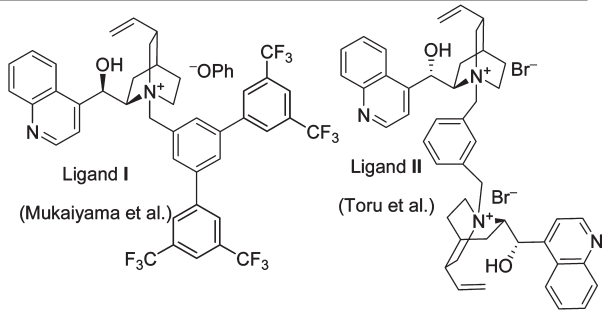
Scheme 2. Approaches to the Synthesis of HSD-016



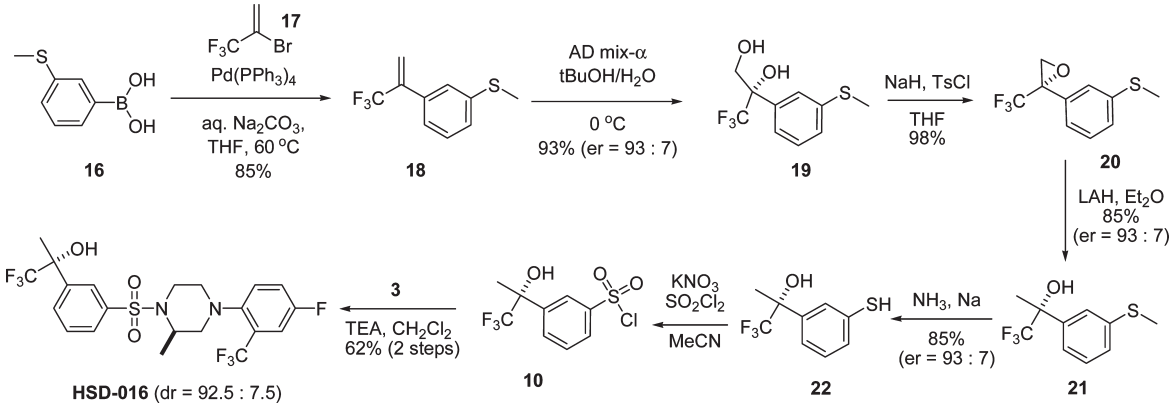
Scheme 3. Formation of Sulfonyl Chloride 15



entry	conditions	yield, ee, config.	ref.
1	i) CF_3TMS (1.4 eq), **I** (0.1 eq) toluene/CH_2Cl_2 (7 /3), -78 °C ii) TBAF, THF	97%, 61%, (*S*)	12a
2	i) CF_3TMS (2.0 eq), **II** (0.1 eq) toluene/CH_2Cl_2 (2 /1), -60 °C ii) TBAF, THF/H_2O	97%, 61%, (*S*)	12b
3	CF_3TMS (2.0 eq), TBAF 1.0 eq) THF, 0 °C - rt	97%	this work



Scheme 4. Route 3: Synthesis of HSD-016 through Chiral Sulfonyl Chloride 10



in 93% combined yield with an enantiomeric ratio of 93:7, favoring the desired enantiomer. Selective tosylation of primary alcohol **19** followed by *in situ* cyclization led to the formation of chiral epoxide **20** in 98% yield. Reduction of expoxide **20** with lithium aluminum hydride in THF furnished tertiary alcohol **21** in 85% yield with a conserved enantiomeric ratio of 93:7. Demethylation under Birch conditions followed by oxidation of thiol **22** gave chiral sulfonyl chloride **10**. Sulfonamide formation of piperazine **3** with **10** provided HSD-016 in 62% overall yield (2 steps from **22**).

While we were encouraged by the successful synthesis of chiral sulfonyl chloride **10**, we were concerned with the potentially troublesome reaction conditions created by the Birch reagents and strong oxidant potassium nitrate (KNO_3) when applied on a large scale synthesis. This study, however, provided us with an encouraging precedent for accessing a chiral tertiary alcohol as existed in HSD-016 through the corresponding diol intermediate **11** as proposed in Scheme 3.

With readily available phenyl bromide **7**, Suzuki coupling with bis(pinacolato)diboron led to formation of boronate **23** in near

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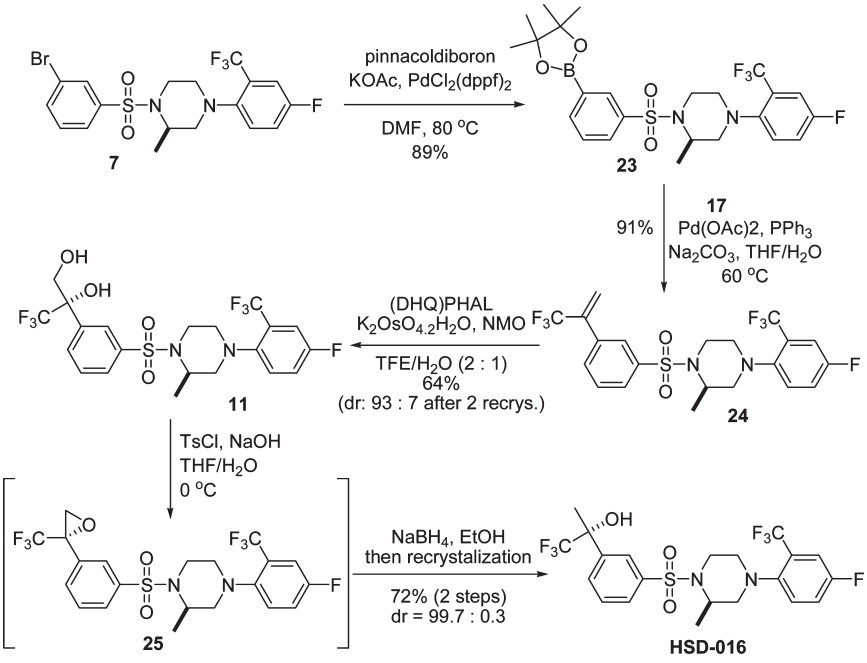
Scheme 5. Route 4: A Practical and Scalable Synthesis of HSD-016 through Diol 11



quantitative yield (Scheme 5, route 4). Large scale synthesis of this intermediate was achieved in 89% yield (>95% purity) after a trituration of the crude product with ethanol. A second Suzuki coupling of boronate **23** to vinyl bromide **17** at 60 °C for 24 h successfully produced the desired olefin **24**. Although this reaction was quite robust, low reaction temperature and long reaction time were required as a result of the volatility of vinyl bromide **17**. Upon completion of the reaction, the organic extracts were concentrated and filtered through a pad of Celite. Analytically pure product (HPLC purity >99.4%) was obtained in 91% yield after trituration/recrystallization from 50% aqueous *i*-PrOH.

The key transformation in this route was the Sharpless asymmetric dihydroxyaltion of olefin **24** to give the desired diol **11**. When olefin **24** was treated with AD mix-α under Sharpless conditions[16] at ambient temperature, diol **11** was observed although at a very slow reaction rate (after 48 h, < 20%) likely due to the strongly electron-deficient nature of the olefin and heterogenicity of the reaction mixture. We were eventually able to drive the reaction to completion by the addition of 1 equiv of $MeSO_2NH_2$ along with additional 0.05 equiv of chiral ligand $(DHQ)_2PHAL$ after 48 h. Compound **11** was obtained with a diastereomeric ratio of 4:1. We eventually discovered that a combination of K_2OsO_4, chiral ligand $(DHQ)_2PHAL$, and 4-methylmorpholine *N*-oxide (NMO)[17] was in fact superior to the use of AD mix-α. Detailed findings of our optimization process are shown in Table 1.

In our screening paradigm, solvent effect was first studied. First, among all solvents tested, *n*-propanol (*n*-PrOH), isopropyl alcohol (*i*-PrOH), and *n*-butanol (*n*-BuOH) gave significant lower conversion (Table 1, entries 1−3) under conventional Sharpless dihydroxylation conditions. Higher conversions were observed with 3-pentanol (75%, entry 4) and acetone (entry 5), however, the lower diastereoselectivity in 3-pentanol (64: 36) and heterogeneous nature of the reaction in acetone made these conditions less attractive for large scale synthesis. Reactions conducted in *tert*-butanol (*t*-BuOH, entry 6) and trifluoroethanol (TFE, entry 11) showed acceptable reaction rates with improved selectivity ratios of 67:33 and 71:29, respectively. Therefore, *t*-BuOH (entries 6−10) and TFE (entries 11−17) were used in

Table 1. Solvent and Ligand Effect on Conversion and Selectivity[a]

entry	solvent	ligand	conversion (%)	dr
1	*n*-BuOH	$(DHQ)_2PHAL$	17	61:39
2	*i*-PrOH	$(DHQ)_2PHAL$	42	63:37
3	*n*-PrOH	$(DHQ)_2PHAL$	26	64:36
4	3-pentanol	$(DHQ)_2PHAL$	74	58:42
5	acetone	$(DHQ)_2PHAL$	93	67:33
6	*t*-BuOH	$(DHQ)_2PHAL$	100	67:33
7		$(DHQ)_2Pyr$	100	47:53
8		$(DHQ)_2AQN$	100	53:47
9		$(DHQ)_2PHAL$	99	78:22[b]
10		$(DHQ)_2PHAL$	38	75:25[b,c]
11	TFE	$(DHQ)_2PHAL$	80	76:24
12		$(DHQ)_2Pyr$	58[d]	46:54
13		$(DHQ)_2AQN$	100	46:54
14		$(DHQ)_2PHAL$	96	82:18[b]
15		$(DHQ)_2PHAL$	83	88:12[b,c]
16		$(DHQ)_2PHAL$	16	70:30[b,e]
17		$(DHQ)_2PHAL$	94	85:15[b,f]
18		$(DHQ)_2PHAL$	>95	93:7[b,g]

[a] [**11**] = 0.067 M, $K_2OsO_4\cdot 2H_2O$ (3 mmol %), ligand (3 mmol %), NMO (2.0 equiv), solvent/water (v/v 2/1), rt, 48 h (dr was determined by ^1H NMR of crude reaction product). [b] Slow addition, rt, 84 h. [c] Reaction run at 0 °C. [d] Monitored at 24 h. [e] Catalyst loading = 1.0 mmol %. [f] [**11**] = 0.134 M, rt, $K_2OsO_4\cdot 2H_2O$ (3 mmol %), ligand (3 mmol %), NMO (2.0 equiv), solvent/water (v/v 2/1), 72 h. [g] [**11**] = 0.19 M (300 g), $K_2OsO_4\cdot 2H_2O$ (3 mmol %), ligand (3 mmol %), NMO (2.0 equiv), solvent/water (v/v 2/1), rt, 16 h; analytic data (yield 64%; HPLC purity 99.5%; dr 93:7) collected after recrystallization in CH_2Cl_2/cyclohexanes.

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subsequent optimization studies focusing on both increasing reaction rate as well as increasing diastereo selectivity.

After examining a number of reaction conditions, the following observations were made: Build-up of substrate early on in the reaction mixture was correlated with lower selectivity. Thus, slow addition was required. Indeed, better selectivities were observed for the reactions in both *t*-BuOH (entry 9 vs entry 6) and TFE (entry 14 vs entry 11). $(DHQ)_2PHAL$ was found to be superior to both $(DHQ)_2Pyr$ (entries 7 and 12) and $(DHQ)_2AQN$ (entries 8 and 13) with regards to desirable diastereo selectivity. Lowering the temperature did not increase selectivity and negatively impacted the reaction rates (entries 10 and 15). Reactions in TFE consistently gave higher selectivity than those in *t*-BuOH (entries 6 vs 11 and 9 vs 14). A decrease in catalyst loading to 1.0 mol % led to diminished reaction rate and selectivity (entry 16). Lastly, while increasing reaction concentration had no effect on selectivity, it did increase reaction rate (entries 17 vs 14). Thus, large scale dihydroxylation of **24** (300 g) under optimized conditions [entry 18: $K_2OsO_4 \cdot 2H_2O$ (3 mmol %), ligand (3 mmol %), NMO (2.0 equiv), TFE/water (v/v 2/1), rt, 16 h] gave the desired diol **11** in 64% yield with a diastereoselectivity of 93:7 after recrystallization in CH_2Cl_2 and cyclohexanes.

With diol **11** in hand, epoxide (**25**) was synthesized by treatment of diol **11** with 50% aqueous NaOH followed by addition of TsCl in TBME. Once the reaction was complete, the organic layer was separated and treated with a suspension of $NaBH_4$ in EtOH, affording the desired API HSD-016. After two successive recrystallizations from isopropyl acetate and heptanes (1:20), HSD-016 was isolated in 72% overall yield (two steps) with a high diastereomeric ratio of 99.7:0.3.

Ultimately, this synthetic route was found to be the most robust and practical. In chemical development laboratories, all reactions were carried out in scales of hundreds of grams to provide more than 5 kg of desired API HSD-016 from bromide **7** in 37% overall yield over 5 steps.

CONCLUSION

A practical synthesis of the 11β-hydroxysteroid dehydrogenase type 1 inhibitor HSD-016 was developed. The reaction sequence began with a selective Buchwald amination of 1-bromo-4-fluoro-2-(trifluoromethyl)benzene with (*R*)-2-methylpiperazine. The key transformations include two consecutive Suzuki couplings and an asymmetric Sharpless dihydroxylation to install the requisite chiral tertiary alcohol moiety in compound **11**, which was then transformed into the desired API HSD-016 via an additional two-step sequence involving a mild epoxide formation followed by $NaBH_4$ reduction. All reactions were carried out on large scale, and products were isolated by trituration and recrystallization. Using these methods, more than 5 kg of HSD-016 could be synthesized to support the clininical advancement.

EXPERIMENTAL SECTION

Materials and Methods. All reagents and solvents were purchased from commercial sources and used without further purification. Unless noted otherwise, reactions were performed under air; reaction progress was monitored by HPLC-MS. Flash chromatography was performed on silica (40−63 μm particle size) column. All reported ^1H and ^{13}C NMR spectra were acquired at a 500.13 MHz spectrometer using a triple resonance $^1H/^{13}C/^{19}F$ probe with dedicated hardware allowing for simultaneous excitation at all three frequencies. Proton data was acquired as 64 K data points over 20 ppm with a total recycle time of 5.3 s using a 45° excitation pulse. Data was processed using exponential multiplication with 0.3 Hz line broadening. Carbon data was acquired as 32 K data points over 250 ppm with a total recycle time of 0.8 s using a 45° excitation pulse (under these conditions all carbon lines are present). Data was processed using exponential multiplication with 1.0 Hz line broadening. Proton decoupling was done using WALTZ16 decoupling with a 70−80 microsecond pulse, and ^{19}F decoupling, when employed, used a 1.5 ms adiabatic pulse which gives reasonable excitation over approximately 80 kHz. These fluorine decoupling parameters provide a reasonable compromise between complete decoupling and sample heating. Line lists and couplings were measured using an NMR Processor. Chemical shifts are reported in parts per million (ppm) on the δ scale and are referenced to residual protonated solvent peaks. Spectra obtained in DMSO-d_6 were referenced to $(CHD_2)(CD_3)SO$ at δH 2.50 and $(CD_3)_2SO$ at δC 39.5; spectra obtained in chloroform-*d* were referenced to $CHCl_3$ at δ_H 7.26 and $CDCl_3$ at δ_C 77.2.[18]

(2*R*)-1-[(3-Bromophenyl)sulfonyl]-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazine (7). To a solution of **3** (5 g, 19 mmol) in DCM (50 mL) at 0 °C were added DIPEA (6.62 mL, 38 mmol) and 3-bromophneylsulfonyl chloride (3.29 mL, 22.8 mmol). The resultant mixture was stirred at rt overnight and then washed with aq $NaHCO_3$. The aqueous layer was extracted with DCM (2 × 50 mL). The combined organic layer was dried over Na_2SO_4. The crude product was purified on SiO_2 gel column eluted with 5−15% EtOAc in hexanes to give **7** as an off-white solid (7.9 g, 86%). Workup procedures for large scale synthesis: Upon completion of the reaction, the crude mixture was subsequently washed with 15% aqueous solution, 5% aqueous H_2SO_4 solution, 5% $NaHCO_3$ aqueous solution, and finally water. The organic layer was treated with small amount of silica gel, and the suspension was stirred at ambient temperature for 1 h and then filtered through a layer of Celite. The crude product was recrystallized with toluene and heptanes to give **7** as a colorless crystals. Mp: 165−168 °C. ^1H NMR (500 MHz, chloroform-*d*) δ ppm 1.23 (d, *J* = 6.71 Hz, 3 H) 2.68−2.82 (m, 2 H) 2.93 (d, *J* = 11.29 Hz, 1 H) 3.03 (dd, *J* = 10.99, 3.36 Hz, 1 H) 3.38 (td, *J* = 12.21, 3.05 Hz, 1 H) 3.74 (d, *J* = 12.82 Hz, 1 H) 4.16−4.31 (m, 1 H) 7.20−7.26 (m, 1 H) 7.27−7.36 (m, 2 H) 7.43 (t, *J* = 7.93 Hz, 1 H) 7.73 (dd, *J* = 7.93, 0.61 Hz, 1 H) 7.79 (d, *J* = 7.93 Hz, 2 H) 8.01 (t, *J* = 1.68 Hz, 1 H). ^{13}C NMR (126 MHz, $^1H/^{19}F$ decoupling, chloroform-*d*) δ ppm 14.6 (s, 1 C) 40.8 (s, 1 C) 50.1 (s, 1 C) 54.2 (s, 1 C) 58.1 (s, 1 C) 114.5 (s, 1 C) 119.7 (s, 1 C) 122.9 (s, 1 C) 123.1 (s, 1 C) 125.6 (s, 1 C) 126.4 (s, 1 C) 129.4 (s, 1 C) 130.0 (s, 1 C) 130.7 (s, 1 C) 135.5 (s, 1 C) 142.8 (s, 1 C) 147.8 (s, 1 C) 159.6 (s, 1 C). HRMS: calcd for $C_{18}H_{17}BrF_4N_2O_2S + H^+$, 481.0203; found (ESI-FTMS, $[M + H]^+$), 481.0208.

Methyl(3-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)sulfane (18). Boronic acid **16** (4.2 g, 26.3 mmol), Na_2CO_3 (5.58 g, 52.6 mmol), and $Pd(PPh_3)_4$ (1.51 g, 1.32 mmol) were mixed and degassed. To this were added THF/H_2O (100 mL, v/v 1/1, predegassed) and vinyl bromide (9.2 g, 52.6 mmol), respectively. The reaction tube was sealed, and the reaction mixture was stirred at rt for 1 h and then 60 °C overnight (~15 h). The organic layer was separated, and the aqueous layer was back extracted with DCM (2 × 50 mL). The combined organic layer was dried over $MgSO_4$ and passed through a column with EtOAc/hexanes (0−10%) to give the desired product **18** as a colorless nonviscous liquid (4.9 g, 85%. Note: the product might be volatile under high vacuum). ^1H NMR (400 MHz, chloroform-*d*) δ ppm 2.50 (s, 3 H) 5.77 (q, *J* = 1.52 Hz, 1 H) 5.97 (q, *J* = 1.26 Hz, 1 H) 7.18−7.23 (m, 1 H) 7.25−7.34 (m, 3 H).

(*S*)-3,3,3-Trifluoro-2-(3-(methylthio)phenyl)propane-1,2-diol (19). To a suspension of AD mix-α (6 g) in water (10 mL) was added a solution of **18** in tBuOH (10 mL total) at 0 °C. The sluggish reaction mixture was stirred at 0 °C for 2 days. It was then quenched with saturated aq $Na_2S_2O_3$ (10 mL) solution, and the mixture was stirred at rt for 1 h before extraction with DCM (3 × 50 mL). The organic layer was

dried over Na_2SO_4. The crude mixture (LC shows a single product) was purified by SiO_2 column EtOAc/hexanes (0−40%) to give the desired product **19** as a colorless liquid (930 mg, 93%). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 1.86 (br s, 1 H) 2.50 (s, 3 H) 3.70 (br s, 1 H) 3.80−3.93 (m, 1 H) 4.29 (dd, J = 11.87, 6.06 Hz, 1 H) 7.19−7.39 (m, 3 H) 7.49 (s, 1 H).

(*S*)-2-(3-(Methylthio)phenyl)-2-(trifluoromethyl)oxirane (20). To a solution of **19** (252 mg, 1 mmol) in THF (5 mL) was added NaH (60% in mineral oil, 100 mg, 2.5 mmol) at 0 °C. The resultant mixture was stirred for 5 min. TsCl was added in one portion (be careful of gas formation!). After 3 h, 1 N NaOH (5 mL) was added, and the mixture was stirred for 5 min and then extracted with DCM (3 × 10 mL). The organic layer was dried over Na_2SO_4. The crude product (one product by LC) was purified by SiO_2 column eluted with EtOAc/hexanes (0−10%) to give the desired product **4** as a colorless liquid (229 mg, 98%). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 2.50 (s, 3 H) 2.92 (dq, J = 5.34, 1.59 Hz, 1 H) 3.40 (d, J = 5.31 Hz, 1 H) 7.24−7.36 (m, 3 H) 7.39 (s, 1 H). HRMS: calcd for $C_{10}H_9F_3OS + NH_4^+$, 252.0664; found (ESI-FTMS, $[M + NH_4]^+$), 252.0664.

(*R*)-1,1,1-Trifluoro-2-(3-(methylthio)phenyl)propan-2-ol (21). To a solution of **20** (69 mg, 0.3 mmol) in ether (2 mL) was added LAH (1.0 M in Et_2O, 0.3 mL, 0.3 mmol) at 0 °C. The resultant mixture was stirred for 30 min and then diluted with Et_2O (10 mL), and aq Na, K tartrate solution (10 mL) was added. After stirring for 2 h at rt, the organic layer was separated, and the aq layer was back extracted with Et_2O (2 × 10 mL). The combined organic layer was dried over $MgSO_4$. The crude product (one product by LC) was purified by SiO_2 gel column eluted with EtOAc/hexanes (0−35%) to give the desired product **5** as a colorless liquid (59 mg, 85%). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 2.45 (s, 1 H) 2.50 (s, 3 H) 7.22−7.27 (m, 1 H) 7.30−7.35 (m, 2 H) 7.50 (d, J = 0.51 Hz, 1 H).

(*R*)-1,1,1-Trifluoro-2-(3-mercaptophenyl)propan-2-ol (22). To a solution of **5** in liquid NH_3 at −78 °C was added a small piece of sodium metal. The dark blue solution was stirred for ∼3 min. Solid NH_4Cl was added, followed by addition of MeOH (2 mL), then Et_2O (10 mL), and then aq NH_4Cl (∼5 mL). Once the temperature of the crude mixture was brought to rt, the organic layer was separated, and the aq layer was back extracted with DCM (2 × 10 mL). The organic layer was dried with $MgSO_4$. The crude product (one product by LC) was purified by SiO_2 gel column eluted with EtOAc/hexanes (0−50%) to give the desired product **22** as a colorless oil/liquid (43 mg, 83%). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 1.76 (d, J = 1.01 Hz, 3 H) 2.39 (s, 1 H) 3.52 (s, 1 H) 7.25−7.32 (m, 2 H) 7.32−7.40 (m, 1 H) 7.52 (s, 1 H).

(*R*)-4-(4-Fluoro-2-(trifluoromethyl)phenyl)-2-methyl-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylsulfonyl)-piperazine (23). Method 1: A flask containing **7** (3.0 g, 6.25 mmol), pinnacoldiboron (1.63 g, 6.88 mmol), KOAc (1.84 g, 18.72 mmol), and $PdCl_2(dppf)_2$ (256 mg, 0.31 mmol) was sealed and purged with nitrogen. Anhydrous DMSO (15 mL) was then added, and the reaction was heated to 100 °C under thermal conditions for 16 h, after which it was judged complete by LC−MS. The reaction was cooled to rt, diluted with EtOAc (300 mL), and washed with saturated aq $NaHCO_3$ (3 × 300 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude oil was purified via normal phase SiO_2 chromatography (2−30% EtOAc/hexanes gradient), affording the desired boronic ester **23** (3.3 g, quantitative yield) in >95% purity (white fluffy solid). **Method 2**: A suspension of bis(pinacolato)diboron(150 g, 0.57 mol), KOAc (160 g, 1.6 mol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (4.4 g, 0.0052 mol) in DMF (0.70 L) was heated to 80 °C and treated dropwise over 2 h with a solution of **7** (250 g, 0.52 mol) in DMF0 (50 L). The reaction was stirred at 80 °C for 18 h, cooled to 20 °C, and treated with Darco KB (75 g), EtOAc (1.4 L), and water (1.3 L). The biphasic mixture was stirred at 20 °C for 2 h and filtered through Celite, and the cake was rinsed with EtOAc (1.0 L). The lower aqueous layer was discarded, and the upper organic layer was washed with 5% NaCl solution (2 × 1.3 L), and concentrated by atmospheric distillation to a volume of 0.75 L. To the concentrate was added EtOH (1.3 L), the solution was concentrated by atmospheric distillation to a volume of 1.3 L, to the concentrate was added EtOH (1.3 L), and the solution was concentrated once again by atmospheric distillation to a volume of 1.3 L. The concentrated solution was cooled to 20 °C, and the resulting suspension was stirred at 20 °C for 1 h, cooled to 0 °C, stirred at 0 °C for 1 h, and filtered. The filter cake was rinsed cold EtOH (2 × 0.25 L) and dried in a vacuum oven at 40 °C for 12 h to afford boronate **23** (243 g, 89%, HPLC purity 95.3%) as a white solid. Mp: 158−160 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ ppm 1.23 (d, J = 6.71 Hz, 3 H) 1.38 (s, 12 H) 2.69−2.82 (m, 2 H) 2.86−2.93 (m, 1 H) 2.99−3.07 (m, 1 H) 3.33−3.42 (m, 1 H) 3.72−3.82 (m, 1 H) 4.21−4.31 (m, 1 H) 7.18−7.26 (m, 2 H) 7.29 (s, 1 H) 7.31−7.35 (m, 2 H) 7.54 (t, J = 7.63 Hz, 1 H) 7.90−7.96 (m, 1 H) 8.02 (d, J = 7.32 Hz, 3 H) 8.30 (s, 3 H); ^{13}C NMR (126 MHz, chloroform-*d*) δ ppm 14.6 (s, 1 C) 24.9 (d, 4 C) 40.7 (s, 1 C) 49.8 (s, 1 C) 54.1 (s, 1 C) 58.1 (s, 1 C) 84.4 (s, 1 C) 114.5 (s, 1 C) 119.6 (s, 1 C) 122.9 (s, 1 C) 126.4 (s, 1 C) 128.5 (s, 1 C) 129.4 (s, 1 C) 129.6 (s, 1 C) 130.6 (br s, 1 C) 133.2 (s, 1 C) 138.7 (s, 1 C) 140.3 (s, 1 C) 148.0 (s, 1 C) 159.5 (s, 1 C). HRMS: calcd for $C_{24}H_{29}BF_4N_2O_4S + H^+$, 529.1957; found (ESI-FTMS, $[M + H]^+$), 529.1965.

(*R*)-4-(4-Fluoro-2-(trifluoromethyl)phenyl)-2-methyl-1-(3-(3,3,3-trifluoroprop-1-en-2-yl)phenylsulfonyl)piperazine (24). Method 1: A flask containing **5** (3.3 g, 6.25 mmol), Na_2CO_3, (2.0 g, 18.8 mmol), and $Pd(PPh_3)_4$ (256 mg, 0.31 mmol) was sealed and purged with nitrogen. Aqueous THF (40 mL, 3:1 vol) was then added, followed by the careful addition of the vinyl bromide, (3.3 g, 18.8 mmol) which was cooled to 0 °C before dispensation, as it is an extremely volatile liquid, and the reaction was heated to 60 °C under thermal conditions for 16 h, after which it was judged complete by LC−MS. The reaction was cooled to rt, diluted with EtOAc (300 mL), and washed with saturated aq $NaHCO_3$ (3 × 300 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude oil was purified via normal phase SiO_2 chromatography (2−20% EtOAc/hexanes gradient), affording the desired olefin **24** (2.3 g, 75%, HPLC purity >95% purity) as a colorless syrup. **Method 2**: A suspension of **23** (350 g, 0.66 mol), vinyl bromide **17** (170 g, 0.99 mol), $Pd(OAc)_2$ (1.5 g, 0.0066 mol), PPh_3 (7.0 g, 0.027 mol), and Na_2CO_3 (84 g, 0.79 mol) in THF/water (v/v 1/1, 2.8 L) was heated in a sealed pressure reactor to 60 °C for 24 h. The pressure reached 16 psi. The reaction was cooled to 20 °C, and filtered through a 0.2 μm filter cartridge, and the reactor and cartridge were rinsed with THF/water (v/v 1/1, 0.60 L)). The filtrate was washed with 20% NaCl solution (3 × 0.75 L) and concentrated by vacuum distillation to a volume of 0.50 L. To the concentrate was added *i*-PrOH (3.0 L), and the solution was concentrated by vacuum distillation to a volume of 1.4 L. The concentrate was warmed to 35 °C, stirred for 30 min, and filtered through Celite, and the filter cake was rinsed with *i*-PrOH (0.30 L). The filtrate was cooled to 5 °C, stirred for 1 h, and treated dropwise over 1 h with water (1.7 L). The resulting suspension was stirred at 5 °C for 1 h and filtered, and the filter cake was rinsed with cold *i*-PrOH/water (v/v 1/1, 2 × 0.60 L) and dried in a vacuum oven at 40 °C for 12 h to afford of **24** (299 g, 91%; HPLC purity 99.4%) as a colorless syrup. ^{1}H NMR (500 MHz, chloroform-*d*) δ ppm 1.23 (d, J = 7.02 Hz, 3 H) 2.68−2.80 (m, 2 H) 2.89 (d, J = 11.29 Hz, 1 H) 2.99 (dd, J = 11.14, 3.20 Hz, 1 H) 3.38 (td, J = 12.21, 3.05 Hz, 1 H) 3.76 (d, J = 12.82 Hz, 1 H) 4.14−4.34 (m, 1 H) 5.89 (d, J = 1.53 Hz, 1 H) 6.09 (s, 1 H) 7.16−7.23 (m, 1 H) 7.23−7.32 (m, 2 H) 7.53−7.64 (m, 1 H) 7.68 (d, J = 7.93 Hz, 1 H) 7.89 (d, J = 7.63 Hz, 1 H) 7.96 (s, 1 H). ^{13}C NMR (126 MHz, ^{1}H/^{19}F decoupling, chloroform-*d*) δ ppm 14.6 (s, 1 C) 40.8 (s, 1 C) 50.0 (s, 1 C) 54.0 (s, 1 C) 57.9 (s, 1 C) 114.4 (s, 1 C) 119.7 (s, 1 C) 122.3 (s, 1 C) 122.9 (s, 1 C) 123.0 (s, 1 C) 125.9 (s, 1 C) 126.4 (s, 1 C) 127.4 (s, 1 C) 129.3 (s, 1 C) 129.6 (s, 1 C) 131.4 (s, 1 C) 134.8 (s, 1 C) 137.6 (s, 1 C) 141.6 (s, 1 C) 147.8 (s, 1 C) 159.5 (s, 1 C). HRMS: calcd for $C_{21}H_{19}F_7N_2O_2S + H^+$, 497.1135; found (ESI-FTMS, $[M + H]^+$), 497.1143.

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(2*S*)-3,3,3-Trifluoro-2-[3-({(2*R*)-4-[4-fluoro-2-(trifluoromethyl)-phenyl]-2-methylpiperazin-1-yl}sulfonyl)phenyl]propane-1,2-diol (11). **Method 1**: The olefin 24 (1.35 g, 2.72 mmol) was dissolved in aqueous *t*-BuOH (v/v 1/1, 15 mL total) with slight heating via heat gun, under continuous stirring until ~75% of the solid was in solution. The solution was allowed to cool slightly (T = 40−50 °C max) and then slowly added to a flask containing (DHQ)Phal ligand (106 mg, 0.14 mmol) and $MeSO_2NH_2$ (258 mg, 2.72 mmol) at 0 °C. Immediately following, AD mix-α (4.1 g) was added to the solution, and it was allowed to stir at 0 °C for 48 h, after which reaction could be judged complete by TLC. Excess saturated aqueous $Na_2S_2O_3$ was added, and the reaction was allowed to stir for 20−30 min, warming to rt, after which it was extracted into DCM (3 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude oil was purified via normal phase SiO_2 chromatography (20−90% EtOAc/hexanes gradient), affording 1.1 g of the desired diol 11 (, 1.1 g, 77%; HPLC purity >95% purity) as a white solid. **Method 2**: A suspension of $K_2OsO_4 \cdot 2H_2O$ (6.7 g, 0.018 mol) and $(DHQ)_2PHAL$ (14 g, 0.018 mol) in TFE/water (v/v 3/2, 1.9 L) was treated dropwise over 10 min with NMO (50 wt % in water, 0.25 L, 1.2 mol). The suspension was stirred at 20 °C for 1 h and then treated dropwise over 6 h with a solution of **24** (300 g, 0.60 mol) in TFE (0.90 L). The reaction was stirred at 20 °C for 16 h, quenched with a solution of sodium sulfite (190 g, 1.5 mol) in water (1.3 L), filtered through Celite, and concentrated by vacuum distillation to a volume of 3.0 L. The concentrate was cooled to 20 °C and extracted with CH_2Cl_2 (1.5 L), and the organic layer was treated with of 3% NaCl solution (1.5 L). The pH was adjusted to 4−5 using H_2SO_4 (100 g), and after the layers were mixed for 15 min, the upper layer (aqueous) was discarded. The organic layer was washed twice with 3% NaCl solution (1.5 L) and treated with silica gel (30 g). The suspension was stirred at 20 °C for 1 h and filtered through Celite, and the filter cake was rinsed CH_2Cl_2 (3 × 0.30 L). The filtrate was concentrated by atmospheric distallation to a volume of 1.1 L, and the concentrated solution was adjusted to 20 °C, treated dropwise with cyclohexane (1.8 L), seeded, cooled to 5 °C over 1 h, and stirred for 1 h. The suspension was filtered, and the filter cake was rinsed with heptanes (2 × 0.15 L) and dried in a vacuum oven at 35 °C for 4 h. The isolated solid was recrystallized twice [by dissolving in CH_2Cl_2 (2.5 L/kg of isolated solid), warming to 35 °C, treating dropwise with cyclohexane (5.0 L/kg of isolated solid), cooling to 20 °C over 1 h, stirring at 20 °C for 6 h, filtering, rinsing the filter cake with heptanes (2.0 L/kg of isolated solid), and drying in a vacuum oven at 40 °C for 1 h], to afford diol **11** (206 g, 64%; HPLC purity 99.6%; diastereomeric ratio 93:7) as a white solid. Mp: 99−102 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ ppm 1.23 (d, J = 6.71 Hz, 3 H) 2.65−2.78 (m, 2 H) 2.85−3.00 (m, 2 H) 3.39 (td, J = 12.36, 3.05 Hz, 1 H) 3.74−3.82 (m, 1 H) 3.93 (dd, J = 11.90, 0.92 Hz, 1 H) 4.18−4.29 (m, 1 H) 4.37 (d, J = 11.90 Hz, 1 H) 7.17−7.26 (m, 2 H) 7.31−7.37 (m, 1 H) 7.61 (t, J = 7.93 Hz, 1 H) 7.82 (d, J = 7.93 Hz, 1 H) 7.85−7.92 (m, 1 H) 8.11 (s, 1 H). ^{13}C NMR (126 MHz, ^{1}H/^{19}F decoupling, chloroform-*d*) δ ppm 14.7 (s, 1 C) 40.8 (s, 1 C) 50.0 (s, 1 C) 53.9 (s, 1 C) 57.7 (s, 1 C) 64.4 (s, 2 C) 76.0 (s, 1 C) 114.5 (s, 1 C) 119.7 (s, 1 C) 122.9 (s, 1 C) 124.8 (s, 1 C) 125.0 (s, 1 C) 126.3 (s, 1 C) 127.5 (s, 1 C) 129.4 (s, 1 C) 129.6−129.8 (m, 1 C) 130.3 (s, 1 C) 137.3 (s, 1 C) 141.4 (s, 1 C) 147.8 (s, 1 C) 159.6 (s, 1 C). HRMS: calcd for $C_{21}H_{21}F_7N_2O_4S + H^+$, 531.1183; found (ESI-FTMS, $[M + H]^+$), 531.1192.

(2*R*)-1,1,1-Trifluoro-2-[3-({(2*R*)-4-[4-fluoro-2-(trifluoromethyl)-phenyl]-2-methylpiperazin-1-yl}sulfonyl)phenyl]propan-2-ol (HSD-016). A solution of diol **11** (200 g, 0.38 mol) in THF (0.6 L) was treated with a solution of NaOH (96 g, 1.2 mol) in water (0.4 L). The mixture was cooled to 5 °C, treated dropwise over 30 min with a solution of TsCl (100 g, 0.52 mol) in TBME (0.4 L), stirred at 5−10 °C for 1 h, warmed to 20 °C, and stirred for 1 h. The reaction mixture was extracted with TBME (0.4 L), and the organic layer was washed with 10% NaCl solution (1.0 L), 10% NH_4Cl solution (1.0 L), and 10% NaCl solution (1.0 L). A suspension of $NaBH_4$ (8.6 g, 0.228 mol) in EtOH (1.0 L) was treated dropwise over 60 min to the organic layer (H_2 evolution), stirred at 20 °C for 5 h, and quenched dropwise with 10% NH_4Cl solution (0.5 L; H_2 evolution was observed) and water (0.50 L). The mixture was stirred at 20 °C for 1 h and extracted with TBME (0.5 L), and the organic layer was washed with 10% aq NH_4Cl solution (2 × 1.0 L) and 10% aq NaCl solution (1.0 L) and concentrated by atmospheric distillation to a volume of 0.40 L. To the concentrate was added heptanes (0.1 L), the solution was filtered through Celite, and the filter cake was rinsed with TBME (0.1 L), diluted with heptanes (1.9 L), and concentrated by atmospheric distillation to a volume of 1.8 L. To the concentrate, cooled to 60 °C, was added *i*-PrOAc (0.2 L), and the solution was cooled to 50 °C, seeded, and stirred at 50 °C for 30 min. The resulting suspension was treated dropwise over 45 min with heptanes (2.2 L), cooled to 0 °C over 1.5 h, stirred at 0 °C for 1 h, and filtered, and the filter cake was rinsed with 0.40 L of *i*-PrOAc/heptanes (1:20) and dried in a vacuum oven at 40 °C for 4 h. The isolated solid was recrystallized by dissolving in *i*-PrOAc (1.0 L/kg of isolated solid), warming to 50 °C, treating dropwise with heptanes (9.0 L/kg of isolated solid), stirring at 50 °C for 1 h (solution precipitated), treating dropwise with heptanes (10 L/kg of isolated solid), cooling to 0 °C over 1.5 h, stirring at 0 °C for 1 h, filtering, rinsing the filter cake with heptanes (2.0 L/kg of isolated solid), and drying in a vacuum oven at 40 °C for 12 h, to afford HDS-016 as a white solid (140 g, 72%; HPLC purity 99.7%; diastereomeric ratio 99.7:0.3). Mp: 102−104 °C. ^{1}H NMR (500 MHz, chloroform-*d*) δ ppm 1.22 (d, J = 6.71 Hz, 3 H) 2.63−2.80 (m, 2 H) 2.81−3.02 (m, 2 H) 3.29−3.47 (m, 1 H) 3.77 (d, J = 12.82 Hz, 1 H) 4.15−4.33 (m, 1 H) 7.15−7.27 (m, 2 H) 7.34 (dd, J = 8.70, 1.98 Hz, 1 H) 7.59 (t, J = 7.78 Hz, 1 H) 7.76−7.96 (m, 2 H) 8.15 (s, 1 H); ^{13}C NMR (126 MHz, ^{1}H/^{19}F decoupling, chloroform-*d*) δ ppm 14.6 (s, 1 C) 23.9 (s, 1 C) 40.8 (s, 1 C) 50.0 (s, 1 C) 54.0 (s, 1 C) 57.8 (s, 1 C) 74.6 (s, 1 C) 114.5 (s, 1 C) 119.7 (s, 1 C) 122.9 (s, 1 C) 125.0 (s, 1 C) 125.3 (s, 1 C) 126.3 (s, 1 C) 127.2 (s, 1 C) 129.2 (s, 1 C) 129.4 (s, 1 C) 130.3 (s, 1 C) 140.1 (s, 1 C) 141.2 (s, 1 C) 147.8 (s, 1 C) 159.6 (s, 1 C). HRMS: calcd for $C_{21}H_{21}F_7N_2O_3S + H^+$, 515.1234; found (ESI-FTMS, $[M + H]^+$), 515.1248.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and ^{1}H and ^{13}C NMR spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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