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Synthesis of a novel farnesyl transferase inhibitor, ABT-100; selective preparation of a stereogenic tertiary carbinol

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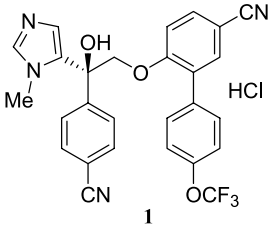
Abstract—A stereoselective synthesis of ABT-100 **1**, a novel farnesyl transferase inhibitor, is described. The key step involves a stereoselective addition of the heterocyclic zinc reagent **10** to chiral α-keto ester **9** in >10:1 diastereoselectivity using menthol as the chiral auxiliary. Crystallization of the product as the dimeric zinc complex facilitates isolation of product in >99:1 dr. The biaryl linkage is formed by the use of a Suzuki coupling employing only 0.06 mol% of the catalyst. Coupling of the two fragments is accomplished using a S_NAr reaction between diol **5** and arylfluoride **4**. The overall yield for the five step sequence is 37% on kilogram scale.

1. Introduction

Mutation of the *ras*-oncogene regulating cell growth and proliferation is implicated in up to 25% of human cancers.[1] After transcription of the protein and further activation by normal *ras*-protein activation processes (cysteine-farnesylation, cleavage of a tripeptide and C-terminal methylation), the mutated *ras*-protein drives uncontrolled cell growth and proliferation.[2] One strategy for disruption of this process is by inhibition of the farnesylation step which is mediated by farnesyl transferase (FT). ABT-100 **1**[3] has been identified as an FT inhibitor possessing excellent potency, bioavailability and pharmacokinetics. Herein, we disclose our development of a kilogram-scale process to prepare ABT-100 to support further biological evaluation. Key to our success was the development of a method for the generation of the chiral quaternary alcohol bearing a heterocyclic substituent.



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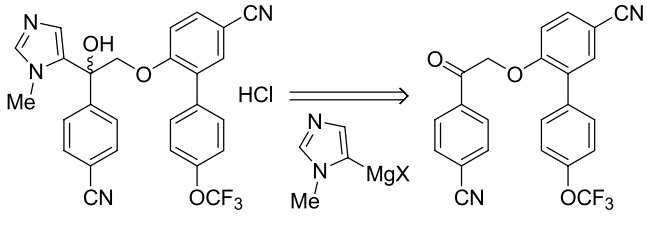
2. Results and discussion

Racemic ABT-100[3] is readily generated by the non-selective addition of imidazolyl Grignard reagent **2** to ketone **3** (Eq. 1). While the enantiomers are readily separated by chromatography on small scale (up to ca. 5 g),[4] the limited solubility of *rac*-ABT-100 in typical mobile phases severely limits the scalability of this method. In addition, experiments conducted to effect a classical resolution of the enantiomers by the formation of chiral salts found no promising leads. Therefore, we desired to develop an efficient and robust means to generate the single enantiomer of ABT-100.



***rac*-1** **2** **3**

(1)

After a brief examination of enantioselective additions of **2** to ketone **3** without success, we shifted to the disconnection

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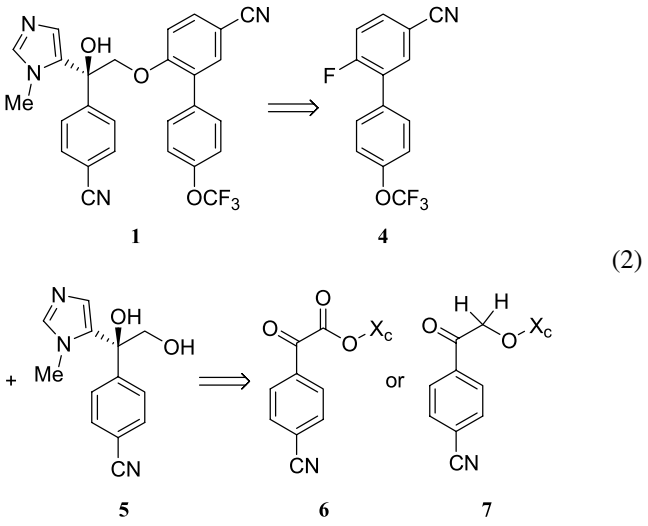
strategy shown in Eq. 2. We reasoned biaryl **4** could be assembled from commercially available starting materials using a Suzuki protocol. Diol **5** could come from the diastereoselective addition of an imidazolyl organometallic to a ketone of the type **6** or **7** with an appropriate chiral auxiliary,[5,6] and the two coupled together using an S_NAr reaction (Eq. 2).[7]

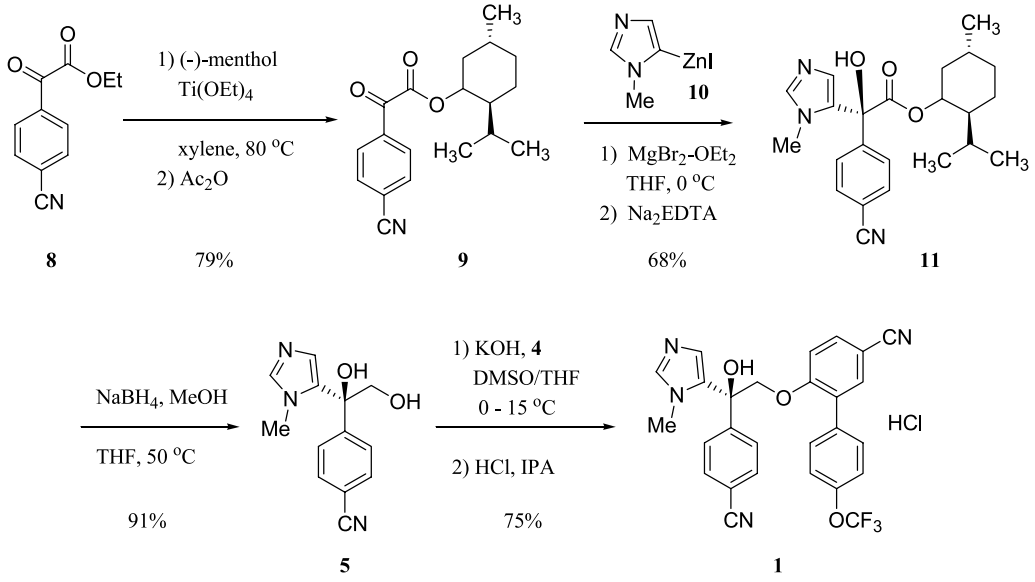


The diastereoselective addition of organometallics to α-keto esters[5] and to a lesser extent α-keto ethers[6] bearing a chiral auxiliary constitutes an efficient method for the stereoselective synthesis of tertiary alcohols. Auxiliaries such as menthol,[5a,b] 8-phenyl-menthol,[5c] *trans*-2-substituted cyclohexanols,[5d,e] carbohydrate[5f] and amino-indanol[5g] based derivatives have found many useful applications. Use of menthol as the chiral auxiliary provides many advantages: low cost, availability, good selectivity (vide infra) and a tendency for intermediates to be crystalline.

Starting from commercially available ethyl (4-cyanophenyl)-oxo-acetate **8** (Scheme 1), the (−)-menthyl ester was prepared using a modification[8] of the titanium (IV) alkoxide-catalyzed transesterification conditions developed by Seebach.[9] Thus, treatment of **8** with (−)-menthol (1.5 equiv) in the presence of a catalytic amount of titanium (IV) ethoxide (15 mol%) in xylene at 80 °C provided (−)-menthyl ester **9** in 79% yield. The reaction was pushed to completion by distillation of the ethanol generated by passing a stream of nitrogen through the reaction vessel. Using fewer than 1.5 equiv of menthol led to incomplete conversion, presumably because the ethoxide ligands on the catalyst were exchanged for menthol during the reaction. While menthyl ester **9** is crystalline, it was difficult to separate the product from the excess (−)-menthol without resorting to a chromatographic purification. To render the (−)-menthol inert in the next step, the hydroxy function was protected in situ as an acetate. This conversion was best accomplished by the addition of acetic anhydride directly to the reaction mixture after cooling and then reheating to 80 °C. After an aqueous work-up, the mixture of menthyl ester **9** and menthyl acetate is carried into the next reaction as a concentrated solution in toluene.

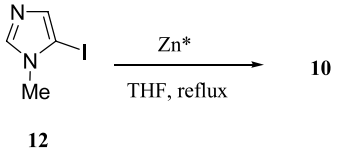
Initial studies into the diastereoselective addition to (−)-menthyl α-keto ester **9** employed Grignard reagent **2**, prepared by magnesium-iodide exchange using ethylmagnesium chloride,[10] and resulted in **11** in a 2.3:1 diastereomeric ratio (dr). Pretreatment of **9** with magnesium bromide etherate at low temperature (−40 °C) afforded slightly better selectivity (dr 4:1). In general, literature examples of the addition of Grignard reagents to (−)-menthyl α-keto esters give the best results when the Grignard reagent is used in the presence of zinc chloride.[5a,b] In our hands, the addition of zinc chloride resulted in precipitation of the Grignard reagent and low conversions, although the stereoselectivity improved to >10:1. Reasoning that in most of these systems the Grignard reagent is first transmetallated to the corresponding zinc reagent, direct preparation of the imidazolyl-zinc reagent was pursued.

Using the zinc activation procedure of Knochel,[11] imidazolyl-zinc reagent **10** was conveniently prepared through the direct insertion of zinc metal on laboratory scale (Eq. 3).



Scheme 1.

On larger scales, it was important to maintain adequate stirring and to control the addition rate of imidazolyl iodide **12** to the activated zinc. If the concentration of **12** becomes too high during the insertion reaction, a precipitate coats the surface of the zinc metal and conversion to the imidazolzinc reagent ceases. It was shown in laboratory experiments that in THF the addition of **12** to **10** forms a stringy insoluble substance, the exact nature of which was not determined, but which is assumed to be a coordination complex between the iodoimidazole nitrogen and imidazolylzinc reagent.[12] Not surprisingly, it was also found that the stirring rate is important for this heterogeneous reaction. Slow stir rates increase the probability of the reaction stalling. Therefore, controlling the addition rate of **12** and ensuring adequate stirring of the heterogeneous reaction mixture led to an efficient and reproducible reaction.



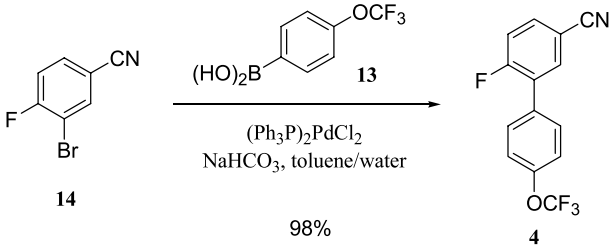
12 (3)

In the absence of a Lewis acid, the imidazolylzinc reagent **10** does not react with the α-keto ester **9**. Of the handful of Lewis acids screened ($ZnCl_2$, $Zn(OTf)_2$, $BF_3{\cdot}OEt_2$, $Ti(OEt)_4$, $MgBr_2{\cdot}OEt_2$), only $MgBr_2{\cdot}OEt_2$ effected the addition of the imidazolyl moiety to the ketone. Thus, in the presence of $MgBr_2{\cdot}OEt_2$ in THF at 0 °C, the tertiary alcohol **11** was generated with a diastereomeric ratio of 10–11:1 and in 75–85% yield. The selectivity of the addition under these conditions is not greatly affected by temperature. Even at elevated temperatures (50 °C), the selectivity decreases only slightly to 7.5:1. At lower temperatures (−40 °C), the reaction becomes gelatinous and difficult to stir and any increase in selectivity is negated by lower conversions.

Due to the propensity of the imidazolyl moiety to bind to zinc,[12] the product is isolated as a 2:1 complex with zinc chloride after washing the reaction mixture with saturated aqueous NH_4Cl and crystallizing from toluene. Using this procedure, the diastereomeric ratio of the isolated ester was increased to greater than 99:1. The structure of the zinc complex has been established by single crystal X-ray analysis of a sample crystallized from acetonitrile (Fig. 1). In order to proceed to the reduction of the ester, the product was liberated from the zinc complex. This was most effectively accomplished by treatment of the complex with the disodium salt of EDTA. Tertiary alcohol **11** is routinely obtained in 65–75% yield and with a diastereomeric ratio of >99.8:0.2.

Ester **11** was selectively reduced to diol **5** by reaction with $NaBH_4$ in methanolic THF at 50 °C (Scheme 1). Under these conditions, concomitant reduction of the nitrile was not observed. The only detected impurity was a trace amount (<0.5%) of the nitrile methanolysis product.[13] Nitrile reduction to the amine becomes more competitive when stronger reducing agents are employed ($NaBH_4$/HOAc or $LiBH_4$). Using the $NaBH_4$ procedure, yields of 90–95% of pure **5** were routinely obtained.

The biphenyl subunit of ABT-100 was assembled from boronic ester **13** and bromofluorobenzonitrile **14** (Eq. 4) using a Suzuki protocol.[14] While as little as 0.025 mol% $(Ph_3P)_2PdCl_2$ effects complete conversion in 15 h, to obtain reasonable reaction times (<6 h), a larger amount of catalyst (0.06 mol%) was typically used. Sodium bicarbonate was used as the base in toluene/water mixtures under an inert atmosphere. Biphenyl **4**[15] was consistently produced in 98% yield and excellent purity.



14 98% **4** (4)

With the two coupling partners in hand, the aryl ether formation was examined. The S_NAr reaction could be accomplished using a variety of bases (LiHMDS, NaHMDS, KHMDS, KOtBu, KOH) in polar aprotic solvents (DMF, DMSO). The reaction is conveniently run with milled KOH in THF/DMSO at low temperature (<15 °C) (Scheme 1). The choice of base and stoichiometry influence not only the reaction rate but also the impurity profile. As shown in Eq. 5, the alkylated diol **1** can react with the excess base to form epoxide **15** and phenol **16**.[16] This degradation is more prevalent with the potassium bases. However, using lithium bases results in slow reactions and incomplete conversions. A balance of a reasonable conversion with acceptable levels of decomposition can be achieved by running the reaction at temperatures below 15 °C. With KOH, trace amounts of

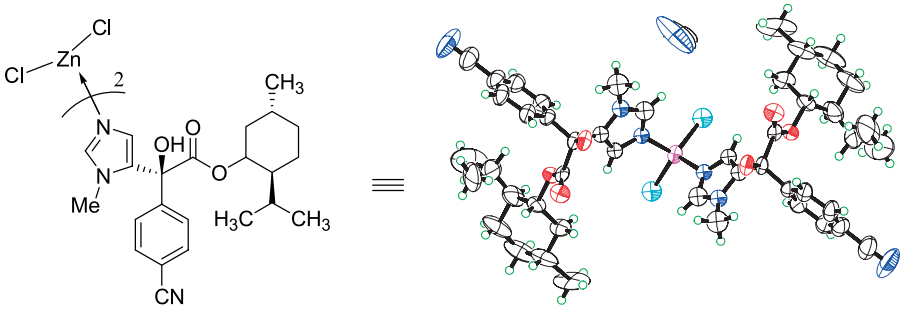
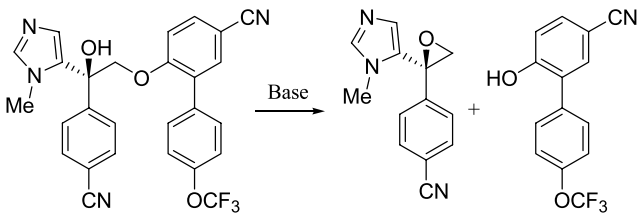


Figure 1.

nitrile hydrolysis products as well as a dialkylated product are also seen.[13] These impurities are rejected in the precipitation of the freebase by the addition of methanol and by final salt formation.



1 15 16 (5)

The final isolation consists of dissolving the unpurified freebase in hot isopropanol, filtering and converting to the HCl salt by the addition of aqueous HCl. The final product can be recrystallized from EtOH to produce larger particles with better handling properties.

In summary, we have developed a stereoselective and scaleable synthesis of ABT-100 that produced material of >99% ee and in an overall yield of 37% in five steps on kilogram scale. The process is highlighted by a diastereoselective addition of an imidazolylzinc reagent to an α-ketoester to produce the stereogenic tertiary alcohol and the formation of the biaryl ether through an S_NAr reaction. In addition, an efficient Suzuki reaction to produce the biaryl moiety and a selective ester reduction to produce the requisite diol were also developed.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were taken in $CDCl_3$ unless otherwise indicated with $CHCl_3$ (7.26 ppm) used as an internal standard. All reactions were performed in appropriate glassware equipped with an overhead stirrer, thermocouple, nitrogen inlet/outlet, and if necessary a reflux condenser or distillation apparatus. All reactions were conducted under positive nitrogen pressure. Commercial grade anhydrous solvents and reagents were used without any further purification. Analytical HPLC conditions were Zorbax Eclipse XDB-C8 column with 5 mM K_2HPO_4/5 mM KH_2PO_4 buffer (pH 7) and acetonitrile mobile phase and detection at 205 nm unless otherwise noted. Analytical GC was done on Alltech DB-1 column and helium make-up gas. Infrared analyses were performed on neat samples on microscope stage (MIC).

3.1.1. (4-Cyanophenyl)-2-oxo-acetic acid (1*R*,2*S*,5*R*)-menthyl ester (9). A suitably equipped reaction vessel was charged with ethyl 4-cyanobenzoylformate **8** (2.94 kg, 14.5 mol), xylene (2.94 kg), (1*R*,2*S*,5*R*)-(−)-menthol (3.39 kg, 21.7 mol, 1.5 equiv), and $Ti(OEt)_4$ (494.9 g, 2.17 mol, 0.15 equiv). Stirring was initiated under a nitrogen atmosphere and the mixture was then heated 80 °C. The ethanol produced was distilled off with the aid of a constant N_2 flow through the reaction mixture. The mixture was stirred for not less than 8 h. The reaction progress was monitored by GC and was considered complete when <1% ethyl ester remains. Upon completion, the reaction mixture was cooled to ambient temperature. Acetic anhydride (2.22 kg, 21.7 mol, 1.5 equiv) was added, the reaction mixture was heated to 80 °C and stirred for not less than 12 h. Upon completion, the reaction mixture was cooled to ambient temperature and diluted with ethyl acetate (44.2 kg). The ethyl acetate solution was washed twice with a 10% HCl solution (2×19.6 L). The organic layer was washed with a solution of $NaHCO_3$ (0.98 kg) in distilled water (19.6 L). *Caution*. CO_2 evolution was observed during neutralization. The organic layer was washed with a solution of NaCl (3.92 kg) in distilled water (19.6 L). The organic layer was filtered through a silica gel pad (1.96 kg) and concentrated to an oil under vacuum. Toluene (8.65 kg) was added and the resulting solution was concentrated under vacuum to an oil. A second portion of toluene (8.65 kg) was added and the resulting solution was concentrated under vacuum to an oil to be used as is in the next reaction. A portion of the oil was analyzed by HPLC and found to be ca. 50% **9** by weight (79% yield) Karl Fischer analysis of the oil indicated the presence of 0.01% water. A sample of the crude toluene solution was purified for characterization by silica gel chromatography (95/5 to 90/10, hexanes/EtOAc). The fractions that contained product were concentrated to an oil that solidified. Mp 41.5–42.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (ddd, J=8.4, 1.7, 1.5 Hz, 2H), 7.80 (ddd, J=8.4, 1.7, 1.5 Hz, 2H), 5.00 (td, J=10.9, 4.5 Hz, 1H), 2.15 (m, 1H), 1.91 (m, 1H), 1.74 (m, 2H), 1.15 (m, 1H), 1.56 (m, 4H), 0.97 (d, J=6.6 Hz, 3H), 0.91 (d, J=7.0 Hz, 3H), 0.83 (d, J=7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.2, 161.9, 135.3, 132.3, 129.9, 117.6, 117.3, 77.7, 46.9, 40.7, 34.2, 31.8, 26.5, 23.6, 22.2, 20.9, 16.5. IR (MIC) 2232, 1714, 1699 cm^{-1}. $[\alpha]_D$=−84.4 (c=0.963, MeOH). Anal. Calcd for $C_{19}H_{23}NO_3$, C 72.82, H 7.40, N 4.47; found C 72.66, H 7.53, N 4.29.

3.1.2. Imidazolylzinc iodide reagent (10). A suitable reaction vessel was charged with zinc dust (1.51 kg, 23.1 mol, 4.5 equiv), THF (3.2 L) and 1,2-dibromoethane (40 mL, 0.46 mol, 0.1 equiv). The resulting slurry was heated to reflux and stirred for not less than 30 min with effervescence observed due to the evolution of ethylene. The reaction mixture was then cooled to <50 °C, the chlorotrimethylsilane (56 mL, 0.44 mol) was added and stirring was continued for not less than 5 min with a slight exotherm of 0.5 °C observed. After heating the reaction mixture back to reflux, a solution of 5-iodo-1-methyl-1*H*-imidazole **12** (1.6 kg, 7.7 mol, 1.5 equiv) in THF (9.6 L) was then added dropwise over 6 h using a metering pump. The reaction mixture was sampled periodically to ensure that reaction is proceeding, monitoring by HPLC the conversion of 5-iodo-1-methyl-1*H*-imidazole **12** to methyl-1*H*-imidazole (hydrolyzed zinc reagent **10**)). After an additional 15 min, the reaction was cooled to ambient temperature, and the stirring was stopped to allow the excess zinc dust to settle. The solution of **10** was decanted from the excess zinc for use in the next step.

3.1.3. *S*-(4-Cyanophenyl)-hydroxy-(3-methyl-3*H*-imidazol-4-yl)-acetic acid (1*R*,2*S*,5*R*)-menthyl ester (11). *Addition of zinc reagent* **10** *to ketone* **9**. A suitable reaction

vessel was charged with THF (12 L) and magnesium bromide diethyl etherate (1.32 kg, 5.1 mol, 1.0 equiv). *Note*. The dissolution of magnesium bromide etherate is exothermic and best performed by adding the solid to the solvent. An external cooling bath is used to keep the temperature below 35 °C. After cooling the resulting slurry to below 25 °C, the (4-cyanophenyl)-oxo-acetic acid menthyl ester **9** (3.12 kg, 51% potent; 1.59 kg, 5.08 mol) was added. After stirring the resulting suspension for 30 min at less than 25 °C, the solution of zinc reagent **10** was added using a metering pump at such a rate to keep the reaction temperature below 30 °C. The reaction mixture was stirred at 25 °C and was considered complete when the ratio of product to starting material remained unchanged by HPLC. The reaction was quenched with a solution of NH_4Cl (3.6 kg) in water (12 L) and filtered through celite (350 g, washing the pad with THF, 4 L). The layers were separated and the organic layer washed with a solution of NH_4Cl (3.6 kg) and water (12 L). The THF layer was distilled down to approximately 16 L then toluene (32 L) was added. The volume was concentrated down to approximately 16 L by distillation. The resulting suspension was heated to 90 °C for not less than 8 h, and allowed to cool slowly over 16 h to ambient temperature. The zinc complex of **11** was then collected by filtration and washed twice with toluene (8 and 4 L). The complex was dried by a N_2 flow. A sample suitable for X-ray analysis was obtained by slow evaporation from acetonitrile.

Decomplexation of zinc complex. The zinc complex of **11** was taken up in ethyl acetate (32 L) and THF (16 L). The organic layer was washed three times with one-third of a Na_2EDTA solution prepared from Na_2EDTA (5 kg) and distilled water (95 L). The layers were allowed to stir for 20 min and then separated. The organic layer was then filtered through celite (300 g), washing with ethyl acetate (8 L), and then distilled down to 4 L. The resulting slurry was heated to reflux to dissolve most of the solids. Heptane (20 L) was added over 30 min maintaining a gentle reflux. The resulting slurry was cooled to ambient temperature and stirred for 10 h. Heptane (8 L) was added and stirred for 1 h. The product was collected by filtration, washed with heptane (4 L), and dried under N_2 flow for 1 h. Product was dried in vacuo at 50 °C for not less than 12 h to afford a white solid **11** (1.38 kg, 68%). The diasteromeric ratio of the product was determined to be 99.8:0.2 by HPLC analysis. Mp 166.5–167.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (dt, J=8.6, 1.8 Hz, 2H), 7.64 (s, 1H), 7.49 (dt, J=8.6, 1.8 Hz, 2H), 6.69 (d, J=1.1 Hz, 1H), 7.07 (s, 1H), 4.61 (td, J=10.9, 4.3 Hz, 1H), 3.29 (s, 3H), 1.96 (m, 1H), 1.60 (m, 1H), 1.53 (m, 1H), 1.45 (m, 1H), 1.18 (m, 1H), 0.90 (m, 4H), 0.89 (d, J=6.6 Hz, 3H), 0.60 (d, J=6.9 Hz, 3H), 0.44 (d, J=6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 144.7, 140.1, 131.6, 129.1, 127.4, 118.1, 112.1, 78.9, 75.4, 47.1, 40.6, 34.1, 33.3, 31.7, 25.7, 23.0, 22.2, 20.7, 15.7 ppm. IR (KBr) 2960, 2240, 1740, 1460, 1200, 1090 cm^{-1}. MS (ESI) (M+1) 396. $[\alpha]_D$=−113.4 (c=0.991, MeOH). Anal. Calcd for $C_{23}H_{29}N_3O_3$, C 69.85, H 7.39, N 10.62; found C 69.65, H 7.51, N 10.53. ICP Zn=12 ppm.

3.1.4. *S*-4-[1,2-Dihydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-benzonitrile (5). A suitable reaction vessel was charged with **11** (1.34 kg, 3.39 mol) and $NaBH_4$ (256 g, 6.77 mol, 2.0 equiv) followed by THF (13.3 L, 10 vol). To the resulting slurry was added MeOH (2.69 L, 2 mL/g) over not less than 30 min in 3 portions. *Caution*. A large amount of headspace should be allowed due to the large amount of gas evolution in the quench step. A slow addition of MeOH is used to minimize a small exotherm (6–7 °C) that is otherwise experienced. The reaction mixture was then warmed to 50±10 °C over 20–30 min. After less than 0.1% of ester remains by HPLC (Zorbax Extend-C18 column, mobile phase 10 mM NH_4OH/MeOH), the mixture was cooled to less than 30 °C and slowly quenched with aqueous citric acid (40% w/w, 13.3 L) maintaining the temperature below 40 °C. *Caution*. Care should be exercised in the rate of addition of the quenching solution because the large amount of heat and gas evolution can cause frothing and foaming. After stirring overnight (12–18 h), the reaction mixture was extracted with heptane (2×13.3 L), mixing the contents for not less than 10 min. After the addition of THF (13.3 L), a 50% w/w aqueous KOH solution was used to adjust the pH to between 8 and 9. A water bath was used to maintain temperature below 40 °C. The layers were separated after the temperature is below 30 °C. To the organic layer was added a solution of 40% w/w aqueous citric acid (6.7 L) and the THF was removed by distillation. The distillation was complete when the amount of THF remaining was less than 1.6% (v/v) by GC analysis. Crystallization of **5** was accomplished by adjusting the pH to 8.5±0.5 using an aqueous KOH solution (50% w/w, 4.3 L). *Note*. A cooling bath was used to keep the internal temperature below 35 °C. Diol **5** is collected by filtration, washed with water (2×1.3 L) and dried in a vacuum oven at 60 °C for not less than 12 h to afford 0.74 kg of a white solid (91%). The enantiomeric excess of the product was determined to be 99.2% by HPLC analysis using a Chiralpak AD column (4.6×250 mm; flow 1.0 mL/min; mobile phase 80:20 hexane/ethanol; 23 °C; 210 nm; 9.09 min (major enantiomer) and 12.66 min (minor enantiomer). Mp 186.0–186.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (dt, J=8.4, 1.8 Hz, 2H), 7.53 (dt, J=8.4, 1.8 Hz, 2H), 7.53 (s, 1H), 7.2 (d, J=1.0 Hz, 1H), 4.00 (d, J=11.3 Hz, 1H), 3.89 (d, J=11.1 Hz, 1H), 3.30 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.1, 140.3, 134.4, 132.6, 128.1, 127.4, 119.3, 111.7, 75.1, 70.2, 33.5 ppm. IR (MIC) 2220 cm^{-1}. $[\alpha]_D$=−145.4 (c=1.03, MeOH). Anal. Calcd for $C_{13}H_{13}N_3O_2$, C 64.19, H 5.39, N 17.27; found C 63.93, H 5.70, N 17.10. MS (ACPI) (M+1) 244.0.

3.1.5. 6-Fluoro-4′-(trifluoromethoxy)-[1,1′-biphenyl]-3-carbonitrile (4).[16] A suitable reaction vessel was charged with 3-bromo-4-fluorobenzonitrile **14** (2.63 kg, 12.9 mol), 4-trifluoromethoxyphenyl boronic acid **13** (3.06 kg, 14.7 mol, 1.1 equiv), bis(triphenylphosphine)-palladium(II) chloride (6.0 g, 8.4×10^{-3} mol, 0.06 mol%), $NaHCO_3$ (1.66 kg, 19.8 mol, 1.5 equiv), nitrogen-presparged toluene (6.6 L), and presparged water (6.8 L). The reaction mixture was heated to 75–85 °C until the aryl bromide was consumed (<1%), as determined by HPLC analysis (Zorbax Eclipse XDB-C8, 0.1% H_3PO_4/acetonitrile mobile phase) (about 2 h). *Note*. Carbon dioxide gas evolution is prominent as the reaction mixture is heated. Upon reaction completion, the reaction mixture was cooled to 60–65 °C, and the layers were separated above 45 °C. The organic layer was filtered through a pad of silica gel (2.6 kg pre-wet

with 5 L toluene), the silica gel pad was rinsed with toluene (12.8 L) and the filtrates were concentrated. Note: Small amounts of toluene are used to quantitate the transfers. Residual toluene was removed from the resulting oil by azeotropic distillation with ethanol–methanol (95:5; 3×6.4 L) until GC analysis showed that the percentage of toluene in alcohol solvent was under 0.5%. The resultant solid and/or solution was dissolved in ethanol–methanol (95:5; 6.4 L) and heated to about 40 °C. The homogeneous solution was removed from the heat, and water (6.4 L) was added dropwise while the solution was stirred and allowed to cool to room temperature. After cooling to room temperature, the slurry was then filtered. The solid was rinsed with 1:1 EtOH/water solution (12.8 L) at room temperature and then rinsed with water (6.4 L). The white solid was dried under nitrogen flow for approximately 1 h and then dried in a vacuum oven with N_2 stream at maximum of 50 °C (25–30 mm Hg) for approximately 90 h until the residual ethanol was minimized to afford 3.56 kg **4** (98% yield). Mp 62.2–62.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J=7.0, 2.1 Hz, 1H), 7.68 (ddd, J=8.4, 4.5, 2.2 Hz, 1H), 7.57 (m, 2H), 7.35 (m, 2H), 7.30 (dd, J=9.7, 8.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 149.5, 134.9, 133.5, 131.9, 130.4, 129.5, 121.2 (2), 120.4, 117.8, 117.7, 109.1 ppm. IR (KBr) 2230, 1516, 1490, 1265, 1256, 1222, 1161 cm^{-1}. HRMS (FAB): calcd for $C_{14}H_7F_4NO$ [M^+]: 281.0464, found 281.0466. Anal. Calcd for $C_{14}H_7F_4NO$, C 59.80, H 2.51, N 4.98; found C 59.74, H 2.56, N 4.90. ICP analysis: Pd <3 ppm, B <1 ppm, Na 2 ppm.

3.1.6. 6-[2-(4-Cyano-phenyl)-2-hydroxy-2-(3-methyl-3*H*-imidazol-4-yl)-ethoxy]-4′-trifluoromethoxy-biphenyl-3-carbonitrile (1). A suitable reaction vessel submersed in a cooling bath was charged with diol **5** (0.71 kg, 2.92 mol), biaryl fluoride **4** (1.07 kg, 3.81 mol, 1.3 equiv), and milled KOH (0.20 kg, 3.20 mol, 1.1 equiv). The bath temperature was adjusted to not more than 10 °C and THF (1.90 kg) was charged. The slurry was stirred and the internal temperature was adjusted to not more than −5 °C. Dimethylsulfoxide (2.48 kg) was charged slowly to the reaction mixture. Note: The reaction was slightly exothermic with the addition of DMSO. The milky solution was stirred for not less than 5 h at −2 °C. The reaction mixture was stirred for not less than 36 h at 14 °C. The reaction was judged to be complete if diol **5** peak area% was less than 3% by HPLC (Zorbax-C8 column 20 mM NH_4OAc/acetonitrile mobile phase). The internal temperature of the reaction mixture was lowered to not more than 0 °C and a 20% methanol in water solution (19 kg) was slowly charged keeping the temperature at not more than 20 °C. *Note*. The quench of reaction mixture was initially exothermic. The solid was collected by filtration and washed with methanol (6 kg) and distilled water (6 kg). The wet cake was allowed to dry under a N_2 flow for 1 h. The solid was washed with a 20% ethyl acetate in heptane solution (2×5 kg) and then heptane (10 kg). The solid as the crude free-base was allowed to dry under a N_2 flow for not less than 1 h. A suitable reaction vessel was charged with the crude solid and isopropanol (40 kg). The temperature was adjusted to 70 °C and the reaction mixture was stirred until most of the solids dissolved. The resulting solution was filtered into a suitable vessel through a 0.2 μm in-line filter, rinsing the reactor with isopropanol (3 kg). The internal temperature of the solution was adjusted to 60 °C and 1 M HCl (37% HCl, 0.29 kg) in isopropanol (1.83 kg) was added through the 0.2 μm in-line filter keeping the temperature at not more than 65 °C. The internal temperature of the reaction mixture was adjusted to 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The precipitated product was collected by filtration and washed with isopropanol (6 kg, filtered through the in-line filter). The solid was allowed to dry under a N_2 flow for not less than 1 h. To achieve suitable particle size properties, the salt was recrystallized from ethanol. The wet solid from the filter was transferred into a clean reactor. Ethanol (35 kg) was charged through a 0.2 μm in-line filter and the contents were heated to reflux to dissolve the solids. The contents of the reactor were distilled to a volume of approximately 20 L at atmospheric pressure and the reaction mixture was stirred with slow agitation at reflux for 3 h to help increase particle size. The temperature of the slurry was adjusted slowly to 0 °C at a rate of approximately 10 °C/h because slow cooling reduces the smaller size particle formation. The slurry was stirred at 0 °C for 3 h. The solid product was collected by filtration and dried under a N_2 flow for 1 h. The solid was dried in a dryer at 60±10 °C for 16 h under nitrogen to afford 1.13 kg of a white flocculent powder (75%) with 99.8% ee (HPLC, Chiralcel OD-RH column (150×4.6 mm, 5 μm; flow 1.0 mL/min; mobile phase 50:50 20 mM KH_2PO_4/acetonitrile; ambient temperature; 234 nm; 6 min (minor enantiomer) and 9.5 min (major enantiomer)). Mp 249.1–250.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 15.00 (s, 1H), 8.00 (d, J=1.5 Hz, 1H), 7.86 (dd, J=8.7, 2.3 Hz, 1H), 7.75 (d, J=2.3 Hz, 1H), 7.67 (m, 2H), 7.47 (d, J=8.9 Hz, 1H), 7.42 (m, 2H), 7.37 (m, 4H), 7.18 (s, 1H), 4.76 (d, J=10.1 Hz, 1H), 4.61 (d, J=10.1 Hz, 1H), 3.37 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.1, 147.7, 145.5, 137.4, 134.8, 134.2, 134.0, 133.9, 131.9, 131.3, 129.5, 127.3, 123.2 (CF_3), 121.1 (CF_3), 120.4, 119.1 (CF_3), 118.7, 118.4, 118.4, 117.0 (CF_3), 113.8, 110.6, 103.7, 74.1, 72.0, 34.8 ppm. IR (MIC) 3274, 3160, 2232, 1261 cm^{-1}. $[\alpha]_D$=−57.8 (c=1.02, MeOH). Anal. Calcd for $C_{27}H_{20}ClF_3N_4O_3$, C 59.95, H 3.73, N 10.36; found C 59.74, H 3.60, N 10.29. ICP <20 ppm for all metals.

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