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An Enantioselective Synthesis of the Key Intermediate for Triazole Antifungal Agents; Application to the Catalytic Asymmetric Synthesis of Efinaconazole (Jublia)

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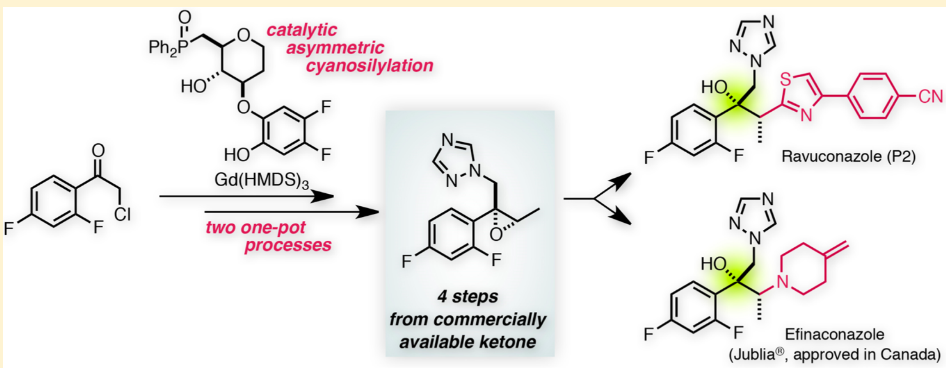
Supporting Information



ABSTRACT: A new synthetic route, the shortest reported to date, to access a key intermediate for the synthesis of various triazole antifungal agents was developed. The elusive tetrasubstituted stereogenic center that is essential in advanced triazole antifungal agents was constructed via the catalytic asymmetric cyanosilylation of a ketone. The subsequent transformations were performed in two one-pot operations, enhancing the overall synthetic efficiency toward the intermediate. This streamlined synthetic approach was successfully applied to efficient enantioselective syntheses of efinaconazole (Jublia) and ravuconazole.

Triazole antifungal agents have been in widespread clinical use for the treatment of various fungal infections, not only high-risk diseases such as acute invasive aspergillosis[1] but also low-risk pathological conditions such as nail infections.[2] Although fungal infections are generally regarded as nonfatal clinical conditions, immunocompromised patients with human immunodeficiency virus (HIV) infection or undergoing cancer chemotherapy are susceptible to life-threatening fungal diseases.[3] The representative triazole antifungal agent fluconazole (Figure 1), which was developed by Pfizer, is effective orally against a range of fungal infections.[4] However, it is poorly active against *Aspergillus* spp., which cause life-threatening infections in immunocompromised patients, and fluconazole resistance has been reported in patients receiving long-term treatment.[5] To address these issues, an advanced triazole antifungal agent, voriconazole (Vfend), was developed.[6] This agent is active against all *Candida* spp., including fluconazole-resistant *Candida albicans*, *Candida glabrata*, and *Candida krusei*, as well as several *Aspergillus* spp., including the amphotericin B-resistant *Aspergillus terreus*.[7] Therefore, voriconazole is a primary drug in the first-line treatment of invasive aspergillosis, as either an intravenous or oral formulation.[1a,7f,8] The high potency of voriconazole has inspired extensive efforts devoted to the development of a variety of synthetic derivatives.[9] The replacement of one of the triazole rings in fluconazole with heteroaromatics (e.g., 5-fluoropyrimidine for voriconazole) and the installation of a methyl group next to the tetrasubstituted stereogenic center have been proved to be beneficial structural modifications,[6a] leading to the identification of advanced triazole antifungal agents. As these modifications break the molecular symmetry of achiral fluconazole, the development of an efficient enantioselective synthetic route is in high demand.

Considering the common substructures that are shared in these antifungal agents, the enantiomerically pure epoxide **1** bearing 2,4-difluorobenzene, 1,2,4-triazole, and a methyl group is a rational intermediate for their divergent syntheses (Scheme 1). The enantioselective construction of the consecutive tetra- and trisubstituted stereogenic centers represents a formidable task in the synthesis of epoxide **1**. Because of the pivotal role of **1** in the efficient synthesis of these antifungal agents, various synthetic approaches toward epoxide **1** have been investigated.[10−12] Almost all of the synthetic routes rely on the use of D- or L-lactic acid as a chiral pool.[11a−c,12] In particular, Bristol-Myers Squibb has developed an excellent approach toward epoxide **1** in six steps in 25% overall yield, leading to the

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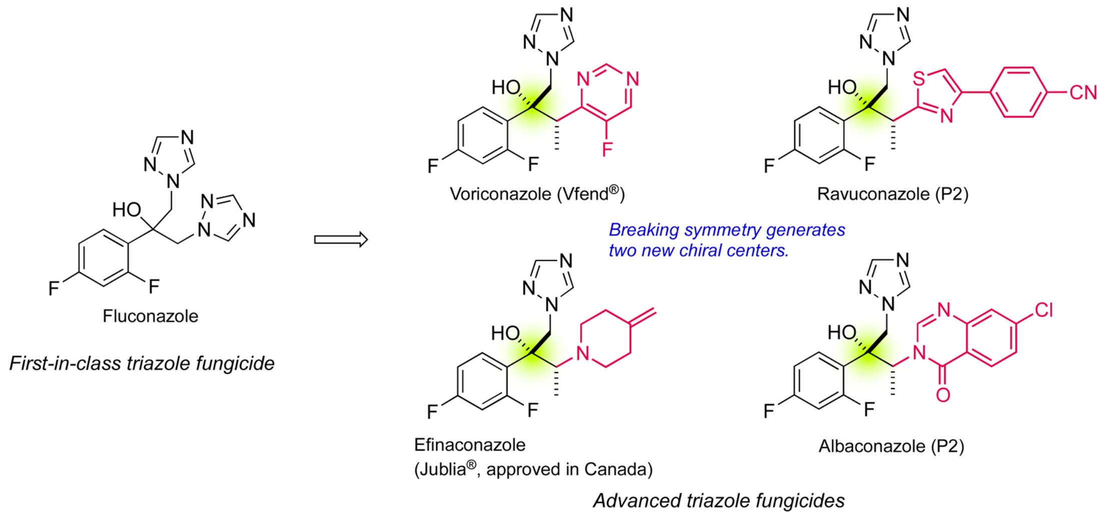
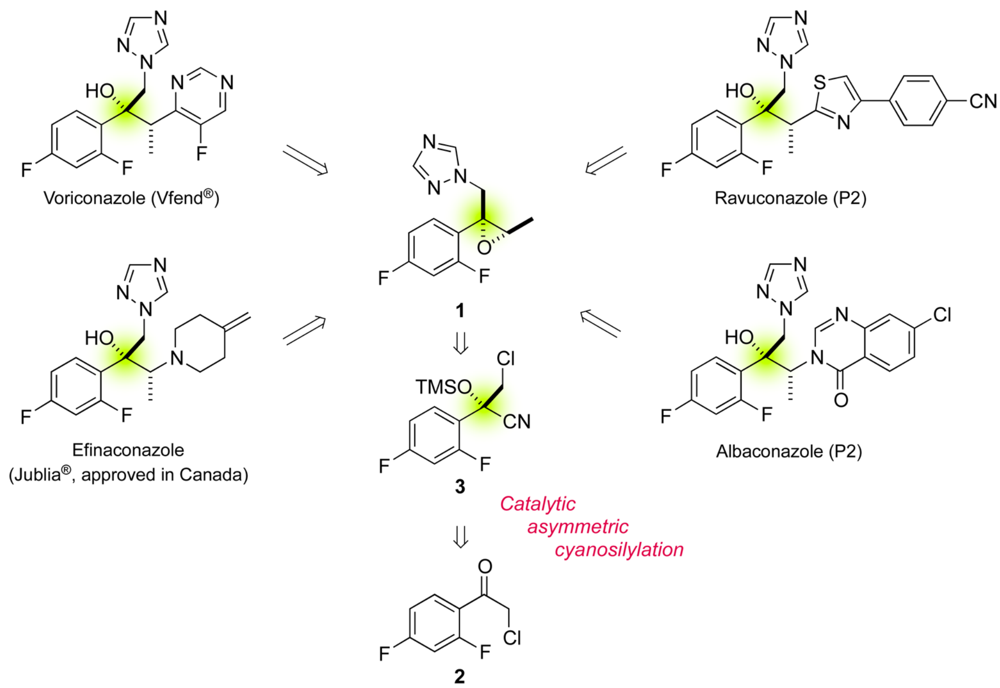


Figure 1. Structures of fluconazole and advanced triazole antifungal agents.

Scheme 1. Enantioselective Synthesis of Epoxide 1, a Key Intermediate for Various Antifungal Agents

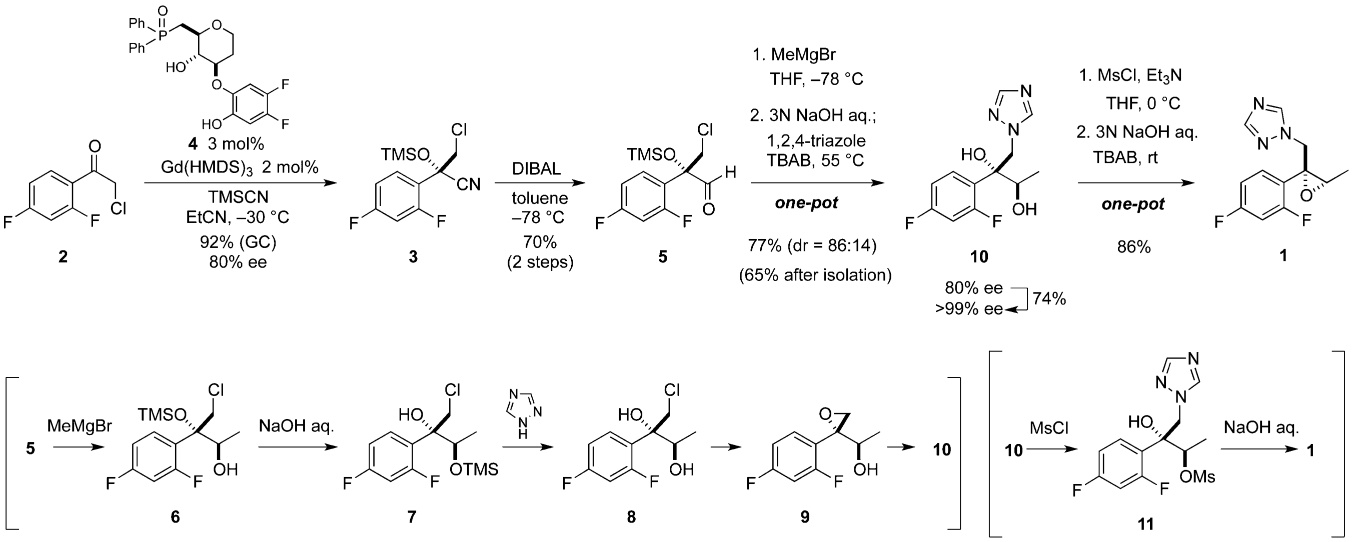


scalable synthesis of ravuconazole.[10] Although other approaches utilizing Sharpless asymmetric epoxidation[11e] or enzymatic resolution[11f] have been accomplished, there remains room for improvement in terms of the number of synthetic steps. The exploitation of a catalytic asymmetric C−C bond-forming reaction is a viable option for the integration of the construction of a molecular skeleton with a stereogenic center. We recently demonstrated that the catalytic asymmetric cyanosilylation of a ketone is particularly useful for the construction of the elusive tetrasubstituted stereogenic center, culminating in the enantioselective synthesis of voriconazole.[13]

Herein we report a new route, the shortest reported to date, to access epoxide **1** in four steps from commercially available ketone **2** in 29% yield. The key step features the catalytic asymmetric cyanosilylation to construct the tetrasubstituted stereogenic center of **3**. The utility of this synthetic approach has been demonstrated by the efficient syntheses of the significant antifungal agents ravuconazole[9b,10] and efinaconazole (Jublia).[9d,14] Ravuconazole, which bears a functionalized thiazole, features a broad antifungal spectrum as well as the longest half-life and has completed P2 clinical trials. Efinaconazol (Jublia), which possesses a 4-methylenepiperidine moiety and has recently received approval in Canada,[15] is the first external-use antifungal agent for the treatment of onychomycosis.[16]

Our synthesis commenced with the catalytic asymmetric cyanosilylation of ketone **2**, a key reaction promoted by a Gd-based asymmetric catalyst to construct the tetrasubstituted stereogenic center (Scheme 2).[17−19] A putative Gd-based polymetallic catalyst composed of Gd and the sugar-derived chiral ligand **4**[20,21] in a 2:3 ratio, as suggested by ESI-MS analysis in the presence of TMSCN,[17b] was generated by mixing $Gd(HMDS)_3$ and **4** in a 2:3 ratio at −30 °C. The polymetallic catalyst (2 mol% based on Gd) promoted the

Scheme 2. Short Synthesis of the Key Intermediate Epoxide 1

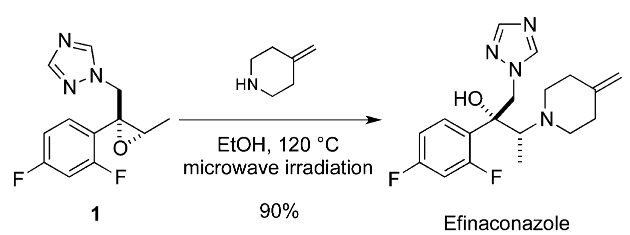


catalytic asymmetric cyanosilylation of **2** with TMSCN at −30 °C in propionitrile to afford the desired cyanohydrin **3** with TMS protection in 92% yield with 80% ee. Because of its instability under acidic and basic conditions and silica gel column chromatography, **3** was immediately submitted to DIBAL reduction to give corresponding aldehyde **5**. Our next focus was the diastereoselective installation of a methyl group and 1,2,4-triazole. Initially, we faced several undesired transformations. After the formation of secondary alcohol **6** using organometallic reagents, quenching with acidic or basic aqueous solutions led to partial migration of the TMS group to provide a complicated mixture of **6** and **7** and their diastereomers. The secondary TMS group of **7**[22] was prone to deprotection under either acidic or basic conditions as well as silica gel column chromatography. Even when **7** was isolated via laborious purification and subjected to 1,2,4-triazole introduction under basic conditions at room temperature, deprotection of the TMS group occurred and the subsequent formation of epoxide **9** proceeded partially. The suppression of these unwanted transformations was intractable, and the complicated reaction mixtures made the purification in each step fruitless. Given that all of the byproducts could be converted into diol **10**, we anticipated that the sequential manifestation of these undesired transformations in one-pot would allow direct access to **10**. After extensive manipulations of the reaction conditions, we found that the installation of the methyl group, the deprotection of the TMS group, the formation of epoxide **9**, and the installation of 1,2,4-triazole could be carried out in a one-pot operation. The initial Grignard addition to **5** gave secondary alcohol **6**. Other organometallic reagents resulted in low yield or low diastereoselectivity.[23] Treatment of the reaction mixture with a 3 N aqueous NaOH solution in the same flask converted **6** into tertiary alcohol **7** via intramolecular migration of the TMS group. Successive addition of 1,2,4-triazole and TBAB as a phase-transfer catalyst initially induced the removal of TMS to give diol **8**, which eventually cyclized to afford epoxide **9** under basic conditions. Ring opening of epoxide **9** proceeded slowly to furnish diol **10** in favor of the desired diastereomer in an 86:14 ratio. The diastereomers were easily separable using silica gel column chromatography to provide the requisite diol **10** as a single diastereomer in 65% yield from aldehyde **5**.

Diol **10** is a crystalline solid, and enantioenrichment was attempted at this stage. When a concentrated acetonitrile solution oversaturated at 60 °C was submitted to rapid nucleation with stirring at −20 °C, a nearly racemic solid (6.3% ee) appeared, and the filtrate was enriched to 97% ee.[24] The second cycle of an identical procedure (but with stirring at 0 °C) afforded the enantiopure diol **10** (>99% ee) in 74% recovery yield after two cycles.[25] With the optically pure diol **10** in hand, we examined its transformation to epoxide **1**. Regioselective mesylation of diol **10** proceeded smoothly at 0 °C to provide the transient intermediate **11**, which was subsequently treated with a 3 N aqueous NaOH solution and TBAB to afford the key intermediate epoxide **1** in 86% yield in one pot.

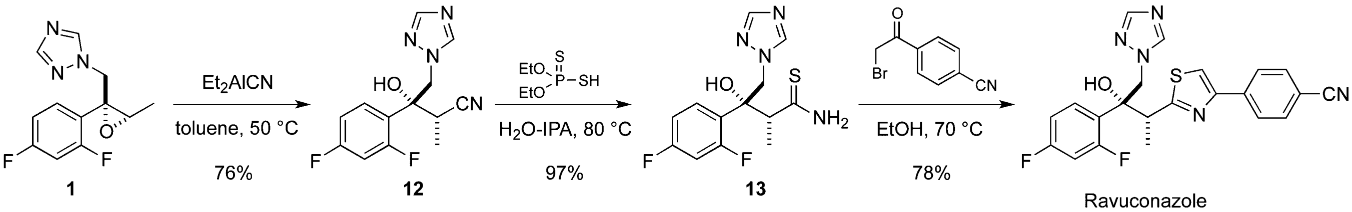
Next, we turned our attention to the synthesis of efinaconazole (Scheme 3). According to the literature

Scheme 3. Synthesis of Efinaconazole (Jublia)



procedure,[9d] epoxide **1** was subjected to a ring-opening reaction with 4-methylenepiperidine[26] at 80 °C. However, 51% of epoxide **1** remained unchanged after 24 h, and efinaconazole was isolated in 44% yield. Microwave irradiation at 120 °C solved this problem, affording efinaconazole in 90% yield.[27] The spectroscopic data of the synthesized sample were identical to those of the reported one.[9d] Moreover, we also demonstrated the synthesis of ravuconazole according to the literature procedure (Scheme 4).[9b,10] Ring opening of epoxide **1** using Et_2AlCN provided cyanide **12** in 76% yield. The nitrile functionality of **12** was transformed into a primary thioamide with diethyl dithiophosphate to give **13** in excellent yield. Treatment of **13** with 2-bromo-4′-cyanoacetophenone furnished ravuconazole in 78% yield.

Scheme 4. Synthesis of Ravuconazole



In conclusion, we have developed a new route, the shortest reported to date, to access the key intermediate epoxide **1** in 29% overall yield in four steps from the commercially available ketone **2**. The key step features a catalytic asymmetric cyanosilylation using Gd(HMDS)$_3$ and a sugar-derived chiral ligand to construct the tetrasubstituted stereogenic center that is essential in advanced triazole antifungal agents. This streamlined synthetic approach led us to demonstrate enantioselective efficient syntheses of two significant antifungal agents.

■ EXPERIMENTAL SECTION

General Procedures. The reactions were performed in a round-bottom flask with a Teflon-coated magnetic stirring bar and a three-way glass stopcock under an Ar atmosphere, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via a gastight syringe and a stainless steel needle. All workup and purification procedures were carried out using reagent-grade solvents under ambient atmosphere. Flash chromatography was performed using silica gel 60 (230−400 mesh). Chemical shifts (δ) for protons are reported in units of parts per million downfield from tetramethylsilane and are referenced to residual protons in the NMR solvent ($CDCl_3$, 7.24 ppm). For ^{13}C NMR, chemical shifts are reported on the scale relative to the NMR solvent ($CDCl_3$, 77.0 ppm) as an internal reference. For ^{19}F NMR, chemical shifts are reported on the scale relative to trifluoroacetic acid (76.5 ppm) as an external reference. NMR data are reported as follows: chemical shifts (multiplicity, coupling constant in Hz, integration). Multiplicities are denoted as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; sep, septet; m, multiplet; br, broad signal. Optical rotation was measured using a 2 mL cell with a 1.0 dm path length. Compounds **1**, **3**, **5**, **8**, **9**, **10**, **11**, **12**, and **13** are known compounds (CAS registry numbers 127000-90-2, 861718-83-4, 861718-85-6, 832151-94-7, 126918-35-2, 133775-25-4, 133775-26-5, 170862-36-9, and 170863-34-0, respectively).

(2*R*,3*S*)-4-Chloro-3-(2,4-difluorophenyl)-3-((trimethylsilyl)-oxy)butan-2-ol [(2*R*,3*S*)-6] and (2*S*,3*S*)-4-Chloro-3-(2,4-difluorophenyl)-3-((trimethylsilyl)oxy)butan-2-ol [(2*S*,3*S*)-6]. To a solution of **5** (1.24 g, 4.23 mmol) in THF (6.70 mL) was added 0.92 M MeMgBr solution in THF (6.44 mL, 5.92 mmol) at −78 °C, and the reaction mixture was stirred at the same temperature for 35 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the resulting mixture was warmed to room temperature and stirred for 20 min. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using silica gel column chromatography (*n*-hexane/EtOAc = 85:15) to give 740 mg of (2*R*,3*S*)-**6** (57% yield) as a colorless oil and 117 mg of (2*S*,3*S*)-**6** (9% yield) as a colorless oil. ^1H NMR for (2*R*,3*S*)-**6** (400 MHz, $CDCl_3$) δ 7.53−7.47 (m, 1H), 6.90−6.85 (m, 1H), 6.77−6.71 (m, 1H), 4.21 (d, *J* = 12.1 Hz, 1H), 4.20−4.15 (m, 1H), 4.12 (dd, *J* = 12.1, 1.1 Hz, 1H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.29 (s, 9H); ^{13}C NMR for (2*R*,3*S*)-**6** (100 MHz, $CDCl_3$) δ 162.4 (dd, *J* = 249, 13 Hz), 158.2 (dd, *J* = 246, 12 Hz), 131.0 (dd, *J* = 9.1, 6.2 Hz), 124.8 (dd, *J* = 13, 3.8 Hz), 111.0 (dd, *J* = 21, 3.4 Hz), 103.9 (dd, *J* = 29, 26 Hz), 83.2 (d, *J* = 6.7 Hz), 71.4 (d, *J* = 3.8 Hz), 50.1 (d, *J* = 6.7 Hz), 18.6, 2.41; ^{19}F NMR for (2*R*,3*S*)-**6** (376 MHz, $CDCl_3$) δ −108.7, −111.6; ^1H NMR for (2*S*,3*S*)-**6** (400 MHz, $CDCl_3$) δ 7.47−7.41 (m, 1H), 6.90−6.85 (m, 1H), 6.81−6.75 (m, 1H), 4.27 (d, *J* = 12.1 Hz, 1H), 3.97 (q, *J* = 6.3 Hz, 1H), 3.88 (dd, *J* = 12.1, 1.4 Hz, 1H), 1.10 (d, *J* = 6.3 Hz, 3H), 0.24 (s, 9H); ^{13}C NMR for (2*S*,3*S*)-**6** (100 MHz, $CDCl_3$) δ 162.5 (dd, *J* = 249, 13 Hz), 159.1 (dd, *J* = 248, 12 Hz), 131.3 (dd, *J* = 9.6, 5.8 Hz), 124.0 (dd, *J* = 13, 4.8 Hz), 110.8 (dd, *J* = 22, 4.3 Hz), 104.3 (dd, *J* = 29, 25 Hz), 83.2 (d, *J* = 4.8 Hz), 72.8 (d, *J* = 1.9 Hz), 48.6 (d, *J* = 7.7 Hz), 17.6, 2.33; ^{19}F NMR for (2*S*,3*S*)-**6** (376 MHz, $CDCl_3$) δ −107.1, −111.2; IR for (2*R*,3*S*)-**6** ($CHCl_3$, cm^{-1}) ν 3588, 3467, 2956, 1615, 1498, 1419, 1253; HRMS for (2*R*,3*S*)-**6** (ESI-TOF) calcd for $C_{13}H_{19}O_2ClF_2SiNa$ [M + Na]$^+$ *m*/*z* 331.0703, found 331.0702.

(2*S*,3*R*)-1-Chloro-2-(2,4-difluorophenyl)-3-((trimethylsilyl)-oxy)butan-2-ol (7). To a solution of (2*R*,3*S*)-**6** (21.4 mg, 0.0693 mmol) in THF (115 μL) was added 3 N NaOH (46.0 μL, 0.139 mmol) at room temperature, and the reaction mixture was stirred at the same temperature for 10 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using preparative TLC (*n*-hexane/EtOAc = 7:1) to give 12.4 mg of **7** (58% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72−7.65 (m, 1H), 6.92−6.87 (m, 1H), 6.78−6.72 (m, 1H), 4.31 (q, *J* = 6.2 Hz, 1H), 4.04 (d, *J* = 11.4 Hz, 1H), 3.84 (d, *J* = 11.4 Hz, 1H), 3.12 (s, 1H), 0.90 (d, *J* = 6.2 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (dd, *J* = 249, 13 Hz), 158.6 (dd, *J* = 247, 13 Hz), 130.7 (dd, *J* = 9.6, 6.7 Hz), 123.4 (dd, *J* = 13, 3.8 Hz), 111.3 (dd, *J* = 21, 3.4 Hz), 103.8 (dd, *J* = 27, 25 Hz), 77.9 (d, *J* = 5.8 Hz), 70.7 (d, *J* = 4.8 Hz), 51.5 (d, *J* = 5.8 Hz), 18.5, 0.21; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.7, −111.2; IR ($CHCl_3$, cm^{-1}) ν 3545, 2959, 1619, 1503, 1422, 1254; HRMS (ESI-TOF) calcd for $C_{13}H_{19}O_2ClF_2SiNa$ [M + Na]$^+$ *m*/*z* 331.0703, found 331.0703.

(2*S*,3*R*)-1-Chloro-2-(2,4-difluorophenyl)butane-2,3-diol (8). To a solution of (2*R*,3*S*)-**6** (31.7 mg, 0.103 mmol) in THF (343 μL) was added 1.0 M TBAF solution in THF (113 μL, 0.113 mmol) at 0 °C, and the reaction mixture was stirred at the same temperature for 15 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using preparative TLC ($CHCl_3$/MeOH = 10:1) to give 18.3 mg of **8** (75% yield) as a colorless crystal. Mp 86−87 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.57 (m, 1H), 6.93−6.88 (m, 1H), 6.81−6.75 (m, 1H), 4.27−4.14 (m, 3H), 3.09 (brs, 1H), 2.17 (brs, 1H), 0.96 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (dd, *J* = 250, 12 Hz), 158.6 (dd, *J* = 247, 12 Hz), 130.1 (dd, *J* = 9.6, 6.7 Hz), 123.8 (dd, *J* = 13, 3.8 Hz), 111.4 (dd, *J* = 21, 3.8 Hz), 104.2 (dd, *J* = 28, 25 Hz), 77.8 (d, *J* = 4.8 Hz), 70.0 (d, *J* = 4.8 Hz), 51.7 (d, *J* = 5.8 Hz), 18.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.2, −110.7; IR ($CHCl_3$, cm^{-1}) ν 3433, 3266, 2979, 1617, 1500, 1272; HRMS (ESI-TOF) calcd for $C_{10}H_{11}O_2ClF_2Na$ [M + Na]$^+$ *m*/*z* 259.0308, found 259.0310.

(*R*)-1-((*R*)-2-(2,4-Difluorophenyl)oxiran-2-yl)ethanol (9). To a solution of (2*R*,3*S*)-**6** (33.6 mg, 0.109 mmol) in THF (363 μL) was added 1.0 M TBAF solution in THF (272 μL, 0.272 mmol) at room temperature, and the reaction mixture was stirred at the same temperature for 23 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using preparative TLC ($CHCl_3$/MeOH = 15:1) to give 7.4 mg of **9** (34% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.36 (m, 1H), 6.89−6.84 (m, 1H), 6.81−6.76 (m, 1H), 4.07 (qd, J = 6.6, 1.6 Hz, 1H), 3.28 (d, J = 5.3 Hz, 1H), 2.78 (dd, J = 5.3, 0.5 Hz, 1H), 1.14 (dd, J = 6.6, 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (dd, J = 249, 13 Hz), 160.4 (dd, J = 249, 12 Hz), 130.6 (dd, J = 10, 6.2 Hz), 120.6 (dd, J = 15, 3.8 Hz), 111.4 (dd, J = 21, 3.8 Hz), 103.7 (dd, J = 25, 25 Hz), 68.4 (d, J = 1.9 Hz), 60.6, 51.9, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.6, −111.4; IR ($CHCl_3$, cm^{-1}) ν 3421, 2980, 2360, 1618, 1507, 1425, 1272; HRMS (ESI-TOF) calcd for $C_{10}H_{10}O_2F_2Na$ [M + Na]$^+$ m/z 223.0541, found 223.0543.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-butane-2,3-diol (10). To a solution of **5** (4.37 g, 14.9 mmol) in THF (24.9 mL) was added 0.92 M MeMgBr solution in THF (22.7 mL, 20.9 mmol) at −78 °C, and the reaction mixture was stirred at the same temperature for 40 min and then quenched with 3 N aqueous NaOH (50 mL, 150 mmol). The resulting mixture was warmed to room temperature and stirred for 20 min. Triazole (14.2 g, 206 mmol) and tetrabutylammonium bromide (2.40 g, 7.44 mmol) were added. After the reaction mixture was stirred at 55 °C for 28 h, H_2O was added. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give 3.09 g of **10** [77% yield, (2*R*,3*R*):(2*R*,3*S*) = 86:14 by ^{1}H NMR analysis] as a pale-yellow solid. The diastereomixture was purified again using silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give 2.60 g of **10** (65% yield, single isomer) as a colorless solid. A 467 mg sample of **10** (enantiomeric excess 80%) was taken up with MeCN (3.04 mL) at 60 °C, and the resulting solution was stirred at room temperature for 20 min. After additional stirring at −20 °C for 14 h, the resulting crystal was filtered and dried in vacuo to give 78.8 mg of **10** (enantiomeric excess 6.3%). The filtrate was concentrated under reduced pressure and dried in vacuo to give 376 mg of **10** (enantiomeric excess 97.1%). Next, 375 mg of **10** (enantiomeric excess: 97.1%) was taken up with MeCN (563 μL) at 60 °C, and the resulting solution was stirred at room temperature for 30 min. After additional stirring at 0 °C for 1.5 h, the resulting crystal was filtered. The filtrate was concentrated under reduced pressure and dried in vacuo to give 343 mg of **10** (74% recovery yield after two cycles, enantiomeric excess >99%) as a colorless crystal. Mp for enantiopure diol **10** (enantiomeric excess >99%), 114−117 °C; mp for racemic diol **10** (enantiomeric excess 1.6%), 159−160 °C; $[\alpha]_D^{24}$ −71.0 (c 1.06, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.81 (s, 1H), 7.42−7.36 (m, 1H), 6.77−6.70 (m, 2H), 4.84−4.76 (m, 2H), 4.30 (qd, J = 6.4, 2.8 Hz, 1H), 0.95 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7 (dd, J = 250, 12 Hz), 158.3 (dd, J = 246, 12 Hz), 152.0, 144.2, 130.0 (dd, J = 9.4, 6.5 Hz), 123.2 (dd, J = 14, 3.6 Hz), 111.8 (dd, J = 20, 2.9 Hz), 104.0 (dd, J = 27, 27 Hz), 78.3 (d, J = 5.8 Hz), 70.1 (d, J = 4.3 Hz), 55.4 (d, J = 5.8 Hz), 18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.4, −110.0; IR ($CHCl_3$, cm^{-1}) ν 3434, 3139, 2974, 2360, 1619, 1503, 1421, 1273, 1134; HRMS (ESI-TOF) calcd for $C_{12}H_{14}O_2N_3F_2$ [M + H]$^+$ m/z 270.1049, found 270.1046. The enantiomeric excess of **10** was determined by chiral HPLC analysis [DAICEL, CHIRALPAK AD-H, flow rate = 1.0 mL/min, n-hexane/EtOH = 85:15, detection at 254 nm, column temperature 23 °C, t_R = 11.4 min (*ent*-**10**), t_R = 18.4 min (**10**)].

1-(((2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methyloxiran-2-yl)-methyl)-1*H*-1,2,4-triazole (1). To a solution of **10** (1.97 g, 7.32 mmol) in THF (37 mL) were added Et_3N (4.50 mL, 32.2 mmol) and MsCl (1.25 mL, 16.2 mmol) at 0 °C, and the reaction mixture was stirred at the same temperature for 20 min. Next, 3 N NaOH aqueous (10 mL, 30.0 mmol) and tetrabutylammonium bromide (1.18 g, 3.66 mmol) were added. The resulting mixture was warmed to room temperature and stirred at this temperature for 14 h. Saturated aqueous NH_4Cl was added, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed three times with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give 1.59 g of **1** (86% yield) as a pale-yellow solid. Mp 91−92 °C; $[\alpha]_D^{24}$ −7.75 (c 1.06, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.78 (s, 1H), 7.00−6.95 (m, 1H), 6.77−6.66 (m, 2H), 4.85 (d, J = 14.7 Hz, 1H), 4.40 (d, J = 14.7 Hz, 1H), 3.16 (q, J = 5.6 Hz, 1H), 1.61 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (dd, J = 251, 12 Hz), 160.1 (dd, J = 249, 13 Hz), 151.9, 143.6, 129.3 (dd, J = 9.6, 5.8 Hz), 120.8 (dd, J = 14, 3.8 Hz), 111.6 (dd, J = 22, 3.4 Hz), 103.8 (dd, J = 25, 25 Hz), 60.5, 59.7, 51.6 (d, J = 1.9 Hz), 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.5, −112.6; IR ($CHCl_3$, cm^{-1}) ν 3113, 3096, 3084, 3003, 2969, 1618, 1508, 1424, 1269, 1137; HRMS (ESI-TOF) calcd for $C_{12}H_{12}ON_3F_2$ [M + H]$^+$ m/z 252.0943, found 252.0945. The enantiomeric excess of **1** was determined by chiral HPLC analysis [DAICEL, CHIRALCEL OD-H, flow rate = 1.0 mL/min, n-hexane/EtOH = 85:15, detection at 254 nm, column temperature 23 °C, t_R = 10.8 min (**1**), t_R = 12.6 min (*ent*-**1**)].

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (Efinaconazole). To a solution of **1** (54.2 mg, 0.216 mmol) in EtOH (217 μL) was added 4-methylenepiperidine (147 mg, 1.51 mmol), and the reaction mixture was stirred at 120 °C for 6 h under microwave irradiation. The reaction mixture was quenched with H_2O, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed three times with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give 67.6 mg of efinaconazole (90% yield) as a colorless amorphous solid. $[\alpha]_D^{20}$ −87.8 (c 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.76 (s, 1H), 7.51−7.45 (m, 1H), 6.78−6.68 (m, 2H), 5.50 (brs, 1H), 4.85 (d, J = 14.4 Hz, 1H), 4.78 (d, J = 14.4 Hz, 1H), 4.61 (s, 2H), 2.88 (q, J = 6.9 Hz, 1H), 2.66 (br s, 2H), 2.32 (br s, 2H), 2.21−2.17 (m, 4H), 0.93 (dd, J = 6.9, 2.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5 (dd, J = 250, 13 Hz), 158.5 (dd, J = 246, 12 Hz), 151.3, 145.9, 144.4, 130.6 (dd, J = 8.7, 5.8 Hz), 124.7 (dd, J = 14, 3.6 Hz), 111.4 (dd, J = 20, 2.9 Hz), 108.1, 104.1 (dd, J = 28, 25 Hz), 77.7 (d, J = 5.8 Hz), 64.4, 55.9 (d, J = 8.7 Hz), 52.4, 35.2, 7.63 (d, J = 2.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.8, −110.7; IR ($CHCl_3$, cm^{-1}) ν 3423, 3073, 2979, 2939, 2899, 2810, 1615, 1498, 1418, 1273, 1138; HRMS (ESI-TOF) calcd for $C_{18}H_{23}ON_4F_2$ [M + H]$^+$ m/z 349.1834, found 349.1828.

(2*S*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)butanenitrile (12). To a solution of **1** (415 mg, 1.65 mmol) in toluene (3.30 mL) was added a 1.0 M solution of Et_2AlCN in toluene (6.60 mL, 6.60 mmol) at room temperature, and the reaction mixture was stirred at 50 °C for 22 h. After the resulting mixture was cooled to 0 °C, H_2O and 1 N HCl were added. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give 349 mg of **12** (76% yield) as a colorless crystal. Mp 182−183 °C; $[\alpha]_D^{25}$ −28.1 (c 1.14, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.80 (s, 1H), 7.43−7.36 (m, 1H), 6.79−6.72 (m, 2H), 5.48 (s, 1H), 4.94 (d, J = 14.0 Hz, 1H), 4.79 (d, J = 14.0 Hz, 1H), 3.27 (q, J = 7.2 Hz, 1H), 1.14 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (dd, J = 253, 12 Hz), 157.8 (dd, J = 246, 11 Hz), 152.3, 143.9, 130.9 (dd, J = 9.6, 4.8 Hz), 121.2 (dd, J = 13, 3.4 Hz), 120.0, 112.1 (dd, J = 21, 3.4 Hz), 104.3 (dd, J = 28, 26 Hz), 75.8 (d, J = 4.8 Hz), 55.7 (d, J = 5.8 Hz), 33.4 (d, J = 4.8 Hz), 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.1, −109.6; IR ($CHCl_3$, cm^{-1}) ν 3140, 3003, 2951, 2864, 2246, 1618, 1502, 1422, 1269, 1136; HRMS (ESI-TOF) calcd for $C_{13}H_{13}ON_4F_2$ m/z [M + H]$^+$ 279.1052, found 279.1051.

(2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)butanethioamide (13). To a solution of **12** (151 mg, 0.543 mmol) in H_2O (242 μL) and isopropyl alcohol (302 μL) was added diethyl dithiophosphate (360 μL, 2.28 mmol) at room temperature, and the reaction mixture was stirred at 80 °C for 9 h. After the resulting mixture was cooled to room temperature, H_2O and 3 N NaOH were added. After the mixture was stirred at the same temperature for 30 min, EtOAc was added. The aqueous layer was

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extracted twice with EtOAc. The combined organic layers were washed three times with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give 164 mg of **13** (97% yield) as a colorless amorphous solid. $[\alpha]_D^{23}$ −137.9 (*c* 1.08, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (br s, 1H), 7.83 (s, 1H), 7.77 (s, 1H), 7.64 (br s, 1H), 7.45−7.39 (m, 1H), 6.78−6.69 (m, 2H), 5.75 (s, 1H), 5.06 (d, *J* = 14.2 Hz, 1H), 4.52 (d, *J* = 14.2 Hz, 1H), 3.70 (q, *J* = 7.0 Hz, 1H), 1.08 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 162.8 (dd, *J* = 251, 13 Hz), 157.9 (dd, *J* = 247, 13 Hz), 151.9, 144.0, 130.5 (dd, *J* = 9.1, 5.3 Hz), 122.9 (dd, *J* = 13, 3.8 Hz), 111.6 (dd, *J* = 21, 3.4 Hz), 104.3 (dd, *J* = 27, 25 Hz), 76.9, 55.5 (d, *J* = 6.7 Hz), 54.4 (d, *J* = 3.8 Hz), 15.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.2, −109.3; IR ($CHCl_3$, cm^{-1}) ν 3282, 3185, 1618, 1499, 1423, 1270, 1137; HRMS (ESI-TOF) calcd for $C_{13}H_{15}ON_4F_2S$ $[M + H]^+$ m/z 313.0929, found 313.0932.

4-(2-((2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butan-2-yl)thiazol-4-yl)benzonitrile (Ravuconazole). To a solution of **13** (45.8 mg, 0.147 mmol) in EtOH (458 μL) was added 2-bromo-4′-cyanoacetophenone (49.3 mg, 0.220 mmol) at room temperature, and the reaction mixture was stirred at 70 °C for 2 h. After the resulting mixture was cooled to room temperature, H_2O was added. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using preparative TLC (*n*-hexane/EtOAc = 50:50) to give 50.0 mg of ravuconazole (78% yield) as a colorless amorphous solid. $[\alpha]_D^{25}$ −26.6 (*c* 0.91, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (ddd, *J* = 8.2, 1.8, 1.7 Hz, 2H), 7.82 (s, 1H), 7.72 (ddd, *J* = 8.2, 1.8, 1.7 Hz, 2H), 7.66 (s, 1H), 7.62 (s, 1H), 7.50−7.46 (m, 1H), 6.81−6.76 (m, 2H), 5.71 (s, 1H), 4.89 (d, *J* = 14.4 Hz, 1H), 4.24 (d, *J* = 14.4 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 1H), 1.21 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 162.8 (dd, *J* = 251, 12 Hz), 158.3 (dd, *J* = 246, 12 Hz), 152.6, 151.5, 143.8, 137.9, 132.7, 130.6 (dd, *J* = 10, 5.8 Hz), 126.7, 123.4 (dd, *J* = 13, 4.3 Hz), 118.7, 116.0, 111.7 (dd, *J* = 20, 2.9 Hz), 111.6, 104.1 (dd, *J* = 27, 27 Hz), 77.3 (d, *J* = 5.8 Hz), 56.6 (d, *J* = 4.3 Hz), 44.1 (d, *J* = 2.9 Hz), 17.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.1, −109.7; IR ($CHCl_3$, cm^{-1}) ν 3400, 3109, 2981, 2226, 1608, 1499, 1273, 1139; HRMS (ESI-TOF) calcd for $C_{22}H_{18}ON_5F_2S$ $[M + H]^+$ m/z 438.1195, found 438.1192.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of synthesized compounds, HPLC charts for **10** and **1**, and characterization of intermediates en route to **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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