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An Enantioselective Synthesis of Voriconazole

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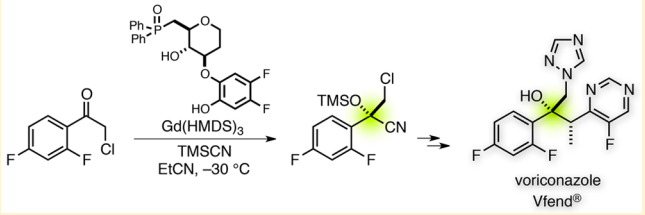
Supporting Information

ABSTRACT: A new seven-step sequence to access voriconazole, a clinically used antifungal agent, was developed. The initial catalytic asymmetric cyanosilylation is the key to constructing the consecutive tetra- and trisubstituted stereogenic centers. The fluoropyrimidine unit frequently triggered unexpected side reactions, but careful amendment of the reaction sequence allowed for the concise enantioselective synthesis.



INTRODUCTION

Invasive fungal diseases are life-threatening and devastating opportunistic infectious symptoms in immunocompromised patients.[1] Voriconazole (Vfend) is a clinically used triazole antifungal agent in both intravenous and oral formulations,[2] and a primary drug for invasive aspergillosis in first line treatment (Figure 1).[1b,3] Voriconazole is an advanced triazole

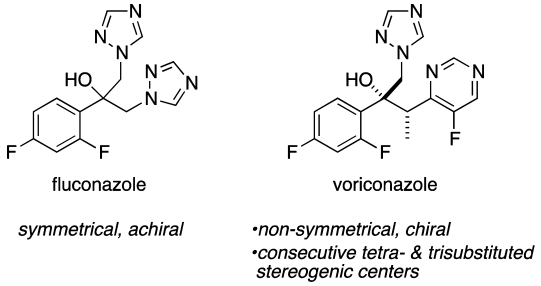


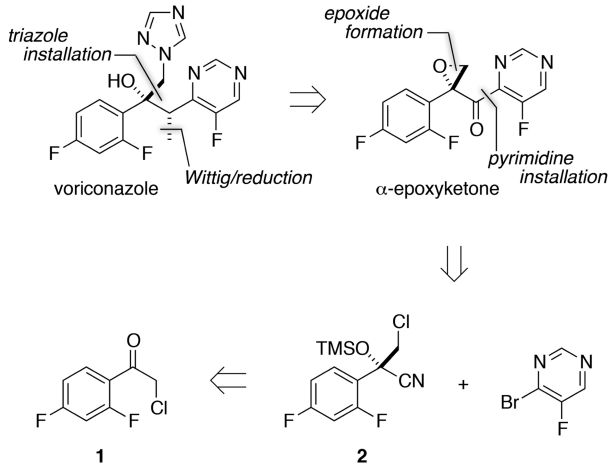
Figure 1. Structure of antifungal agents fluconazole and voriconazole.

fungicide with a very broad antifungal spectrum.[4] The structure of voriconazole is similar to a precedent triazole antifungal, fluconazole, sharing 2,4-difluorobenzene, 1,2,4-triazole, and tertiary alcohol substructures. However, the replacement of one of the two 1,2,4-triazole groups in fluconazole by fluoropyrimidine breaks the symmetry of the molecule, significantly increasing the molecular complexity together with an extra stereogenic center because of an additional methyl group. The original enantioselective synthetic route for voriconazole developed by Pfizer relied on optical resolution to construct the consecutive tetra- and trisubstituted stereogenic centers, although the overall synthesis is scalable for large-scale production.[2b,5] We envisioned applying our asymmetric catalyst designed for the enantioselective construction of stereogenic tertiary alcohols to the synthesis of voriconazole.[6] Herein, we report a seven-step sequence for enantioselective synthesis of voriconazole. Catalytic asymmetric cyanosilylation was the key as the initial chirality introduction step.

RESULTS AND DISCUSSION

Retrosynthesis of voriconazole is delineated in Scheme 1. 1,2,4-Triazole was planned to be installed at the last step, and the

Scheme 1. Retrosynthetic Analysis



pendant methyl group is to be formed by Wittig methylenation and diastereoselective hydrogenation. The precursor α-epoxyketone would be derived from cyanohydrin **2**. The epoxide ring was disconnected to α-chloromethylcarbinol, and metalated pyrimidine would be appended to the cyano group to furnish the requisite acylpyrimidine unit. The optically pure cyanohydrin **2** would be obtained from catalytic asymmetric cyanosilylation of commercially available functionalized ketone **1**.

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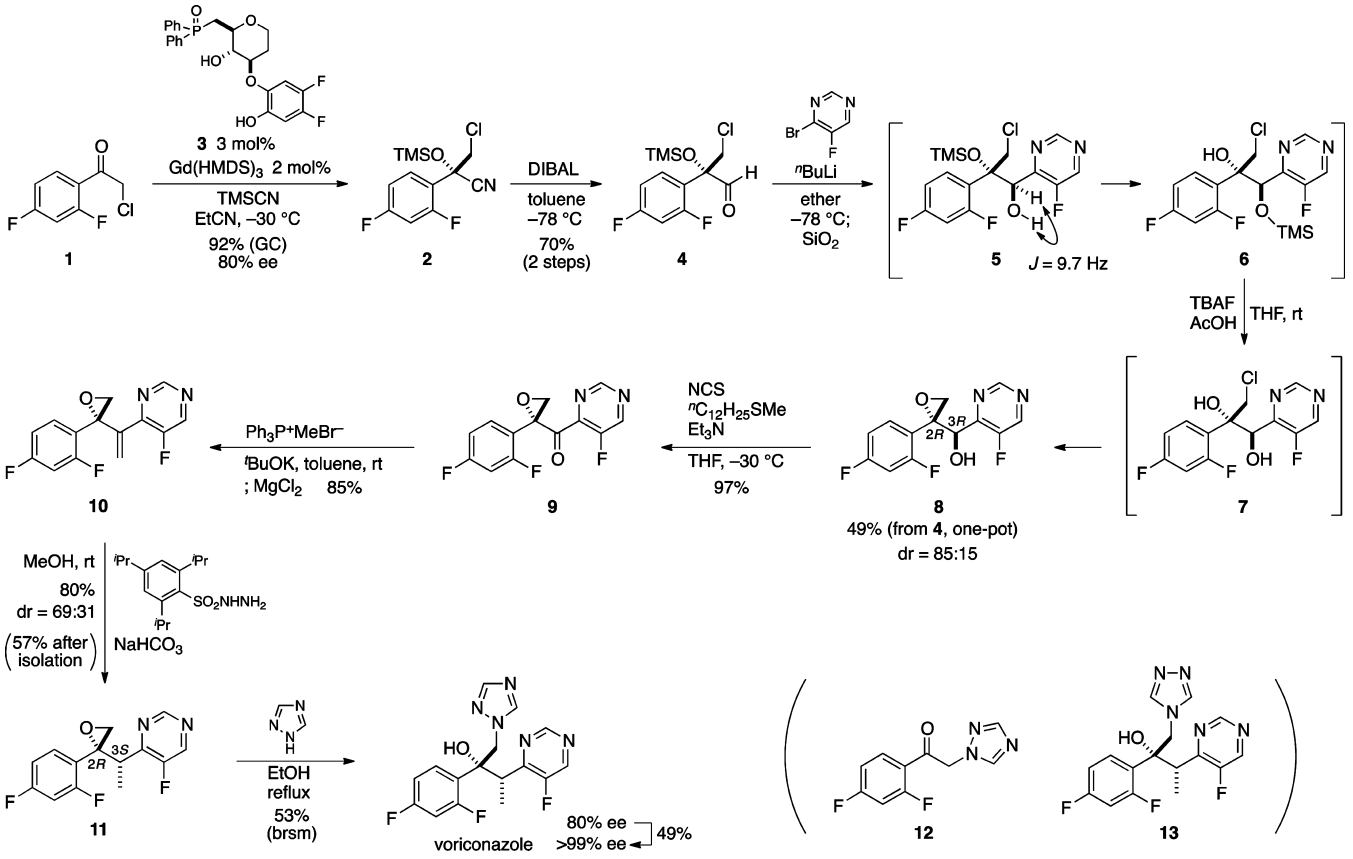
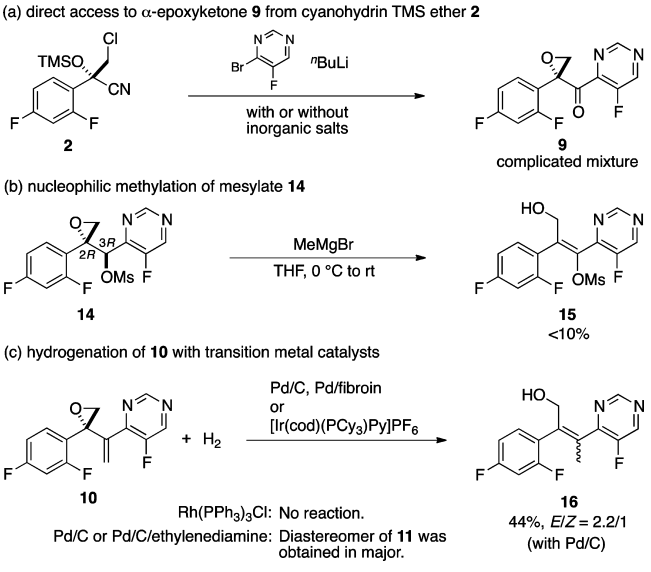
Scheme 2. Enantioselective Synthesis of Voriconazole

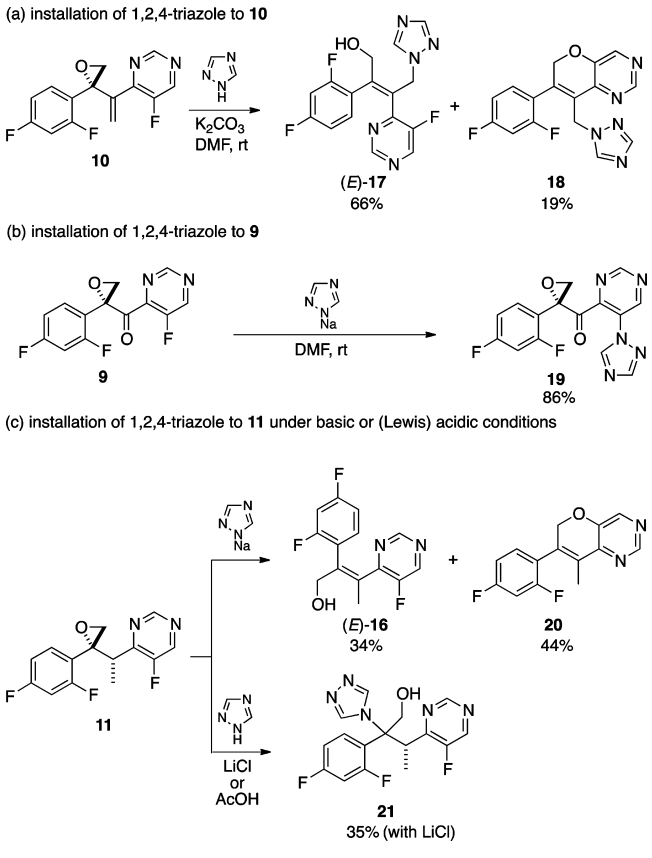


Scheme 2 outlines the seven-step synthetic route delivering voriconazole. Its associated unproductive transformations are summarized in Schemes 3 and 4, most of which were ascribed to the peculiar reactivity caused by the presence of the fluorine-substituted pyrimidine. The initial catalytic asymmetric cyanosilylation of ketone **1** was promoted by a Gd-based asymmetric catalyst.[7−9] $Gd(HMDS)_3$ and sugar-derived chiral ligand **3**[10,11] were mixed in a ratio of 2:3 at −30 °C, producing a putative polymetallic catalyst composed of Gd:**3** = 2:3,

Scheme 3. Unproductive Pathways



Scheme 4. Unfruitful Pathways for 1,2,4-Triazole Installation



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suggested by ESI-MS analysis in the presence of TMSCN.[7b] With 2 mol % of the catalyst (based on Gd), catalytic asymmetric cyanosilylation of **1** and TMSCN proceeded smoothly at −30 °C in propionitrile to afford the desired TMS-protected cyanohydrin **2** in 92% yield and 80% ee.[12] Because **2** was prone to retroreaction under acidic and basic conditions, **2** was immediately transformed into the corresponding aldehyde **4** by reduction with DIBAL. Installation of fluorine-substituted pyrimidine was effected with an aryllithium reagent prepared by selective lithiation of 4-bromo-5-fluoropyrimidine[13] with ^{n}BuLi in ether at −78 °C. Lithiation in THF led to significant decomposition of the reagent and barely produced the desired product.[14] The transient product **5** readily underwent silyl group transfer to give a mixture of tertiary and secondary TMS ethers **5** and **6**.[15] Subsequent treatment of the reaction mixture with TBAF and acetic acid at room temperature cleaved the TMS group to give diol **7**, and concomitant displacement of the terminal chloro leaving group by the adjacent tertiary alcohol produced α-epoxyalcohol **8**. Corey−Kim oxidation of the diastereomixture of **8** using odorless dodecyl methyl sulfide and *N*-chlorosuccinimide gave α-epoxyketone **9** in 97% yield.[16] Although the direct addition of lithiated fluoropyrimidine to cyanohydrin TMS ether **2** to obviate the reduction/oxidation sequence was attempted, extensive manipulations of reaction conditions resulted in the formation of complicated mixtures (Scheme 3a). Given the preferential formation of (2*R*,3*R*)-**8**, nucleophilic methylation of mesylate **14** via inversion of configuration was extensively investigated to introduce the requisite 3*S*-methyl group; however, all attempts were unproductive. The formation of unexpected byproducts was triggered by deprotonation of the benzylic proton, as exemplified by the formation of **15**,[17] which appeared impossible to suppress (Scheme 3b). This finding directed our attention to the introduction of the requisite methyl group by Wittig methylenation followed by diastereoselective hydrogenation. The exomethylene group of **10** was constructed using $Ph_3P^+MeBr^-$ and ^{t}BuOK at room temperature, and the resulting $Ph_3P{=}O$ was efficiently removed by the addition of $MgCl_2$ in toluene.[18] Despite an extensive investigation using transition metal catalysts, hydrogenation of **10** barely proceeded to afford the desired product **11**. Reactions using heterogeneous Pd catalysts[19] or homogeneous Crabtree's catalyst[20] gave an *E*,*Z*-mixture of allylic alcohol **16**, which was presumably produced by oxidative addition at the benzylic C−O bond and subsequent hydrogenolysis of the resulting π-allyl metal complex (Scheme 3c). Whereas **10** remained unchanged with Wilkinson's catalyst,[21] Pd/C and its modified variant with ethylenediamine promoted the hydrogenation to afford predominantly the undesired diastereomer of **11**.[22,23] To perturb the diastereoselectivity in the hydrogenation, prior installation of 1,2,4-triazole was attempted; however, an undesired S_N2'-type conjugate addition occurred to give (*E*)-**17** and **18**, which was produced from (*Z*)-**17** by the following *ipso* substitution of fluoride (Scheme 4a). The fluoropyrimidine unit was inherently reactive toward nucleophilic substitution, and an attempted epoxide-opening reaction of α-epoxyketone **9** with sodium 1,2,4-triazolide gave **19** (Scheme 4b). Eventually, we found that diimide reduction using 2,4,6-triisopropylbenzenesulfonylhydrazide under basic conditions produced **11** in 80% yield with preferential formation of the desired diastereomer (69:31).[24,25] Facile chromatographic separation allowed us to isolate the desired diastereomers in 57%, which was subjected to the final 1,2,4-triazole installation. The basic conditions using sodium 1,2,4-triazolide led to epimerization and epoxide opening to give (*E*)-**16** triggered by deprotonation at C3 (Scheme 4c). In contrast to hydrogenation conditions (Scheme 3c), (*Z*)-**16** readily underwent *ipso* substitution under basic conditions, and its cyclized compound **20** was isolated. The use of Lewis or protic acid favored the formation of **21**, which was presumably produced via S_N1-like addition of N4 of 1,2,4-triazole.[26] Regioselective epoxide opening at the less hindered site slowly proceeded with 1,2,4-triazole in refluxing ethanol to give voriconazole 40% (53% brsm) together with the production of a marginal amount of **12** and N4-adduct **13** in (27%).[27] Enantioenrichment of the thus obtained voriconazole (80% ee) from isopropanol afforded optically pure voriconazole (>99% ee) in 49% yield.

■ CONCLUSION

In conclusion, a seven-step enantioselective synthesis of voriconazole was achieved. Catalytic asymmetric cyanosilylation of a commercially available functionalized ketone was applied as the initial step to construct the tetrasubstituted stereogenic center. Although voriconazole is a relatively small chemical entity, unexpected undesired reactions frequently took place, partly because of the presence of the fluoropyrimidine unit. Further refinement of the synthetic route for large-scale production is currently under way.

■ EXPERIMENTAL SECTION

General Procedures. The reactions were performed in a round-bottom flask with a Teflon-coated magnetic stirring bar and a 3-way glass stopcock under 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 with reagent-grade solvents under ambient atmosphere. Flash chromatography was performed using silica gel 60 (230−400 mesh). Chemical shifts for protons are reported as δ in units of parts per million downfield from tetramethylsilane and are referenced to residual protons in the NMR solvent ($CDCl_3$ δ 7.24 ppm). For ^{13}C NMR, chemical shifts are reported in the scale relative to the NMR solvent ($CDCl_3$ 77.0 ppm) as an internal reference. For ^{19}F NMR, chemical shifts are reported in the scale relative to trifluoroacetic acid (76.5 ppm) as an external reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, sep: septet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. Optical rotation was measured using a 2 mL cell with a 1.0 dm path length. Compounds **2**, **4**, and **12** are known compounds (CAS Registry No. 861718-83-4, 861718-85-6, and 86404-63-9, respectively).

(S)-3-Chloro-2-(2,4-difluorophenyl)-2-((trimethylsilyl)oxy)-propanenitrile (2). To a flame-dried 10 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock was added ligand **3** (39.0 mg, 0.0847 mmol) in the glovebox. THF (1.8 mL) was added at 0 °C. To the resulting solution was added $Gd(HMDS)_3$ (0.175 M solution in THF, 0.305 mL, 0.0533 mmol) at the same temperature, and the resulting solution was stirred at 45 °C for 30 min. After cooling to room temperature, the solvent was removed under reduced pressure, and the resulting residue was dried in vacuo (2 mmHg) at 45 °C for 3 h. The complex was taken up with EtCN (1.7 mL), and the mixture was stirred at −30 °C. To the resulting mixture was added TMSCN (0.51 mL, 3.82 mmol), and the mixture was stirred at the same temperature for 20 min. To the solution was added ketone **1** (485 mg, 2.54 mmol), and the reaction mixture was stirred at the same temperature for 3 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **2**. Yield and enantioselectivity were determined to be 92% and 80% ee,

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respectively, by GC analysis (based on absolute calibration method). The spectroscopic data were consistent with the reported values.[7b]

*(S)-3-Chloro-2-(2,4-difluorophenyl)-2-((trimethylsilyl)oxy)-propanal (**4**).* The crude **2** (92% yield, 494 mg, 1.70 mmol) was taken up with toluene (1.7 mL), and the resulting solution was stirred at −78 °C. To the solution was added 1.0 M DIBAL in toluene (3.14 mL, 3.14 mmol), and the reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with a saturated NH_4Cl aq and 1 N HCl aq. To the resulting mixture was added Celite, and the mixture was stirred at room temperature for 30 min. The resulting slurry was filtered through a pad of Celite, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with H_2O and dried over $MgSO_4$. After removal of volatiles under reduced pressure, the resulting residue was purified using silica-gel column chromatography (*n*-hexane/EtOAc = 95:5) to give 351 mg of **4** (70% for 2 steps) as a colorless oil. The spectroscopic data were consistent with the reported values.[7b]

*(1R,2S)-3-Chloro-2-(2,4-difluorophenyl)-1-(5-fluoropyrimidin-4-yl)-2-((trimethylsilyl)oxy)propan-1-ol (**5**).* A flame-dried 10 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with Et_2O (0.3 mL). Then 2.69 M ^{n}BuLi solution in *n*-hexane (0.19 mL) was added via a gastight syringe with a stainless steel needle under an Ar atmosphere. To the resulting mixture was added 4-bromo-5-fluoropyrimidne (91.2 mg, 0.515 mmol) in Et_2O (0.7 mL) at −78 °C, and the mixture was stirred at the same temperature for 10 min. ZnI_2 (165 mg, 0.515 mmol) was added and then stirred for 20 min. To the resulting mixture was added aldehyde **4** (137 mg, 0.468 mmol) in Et_2O (1.3 mL) at −78 °C, and the solution was stirred at the same temperature for 30 min. The reaction mixture was quenched with H_2O. The aqueous layer was extracted two times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica-gel column chromatography (*n*-hexane/EtOAc = 70:30) gave 37.9 mg of **5** (21% yield, diastereomeric ratio was determined to be 93/7 by ^{1}H NMR analysis) as a colorless solid: mp 119−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, J = 2.8 Hz, 1H), 8.22 (d, J = 0.92 Hz, 1H), 6.96−6.90 (m, 1H), 6.83−6.78 (m, 1H), 6.71−6.66 (m, 1H), 5.32 (d, J = 9.7 Hz, 1H), 4.56 (d, J = 12.6 Hz, 1H), 4.45 (d, J = 9.7 Hz, 1H), 4.42 (d, J = 12.6 Hz, 1H), 0.250 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (dd, J = 250, 13 Hz), 159.5 (dd, J = 247, 13 Hz), 154.6 (d, J = 266 Hz), 153.8 (d, J = 7.2 Hz), 153.1−152.9 (m), 144.3 (d, J = 22 Hz), 130.2 (dd, J = 10, 5.8 Hz), 122.9 (dd, J = 13, 2.9 Hz), 110.8 (dd, J = 21, 3.6 Hz), 104.0 (dd, J = 28, 25 Hz), 83.7 (d, J = 5.8 Hz), 71.6, 49.7 (d, J = 8.7 Hz), 2.35; IR (neat, cm^{-1}) ν 3500, 3056, 2961, 1616, 1586, 1498, 1404; HRMS (ESI) Anal. Calcd. for $C_{16}H_{18}O_2N_2ClSiF_3Na$ m/z 413.0670 [M + Na]$^+$, found 413.0666.

*(1R,2S)-3-Chloro-2-(2,4-difluorophenyl)-1-(5-fluoropyrimidin-4-yl)-1-((trimethylsilyl)oxy)propan-2-ol (**6**).* A flame-dried 10 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with Et_2O (0.2 mL). Then 2.69 M ^{n}BuLi solution in *n*-hexane (0.21 mL) was added via a gastight syringe with a stainless steel needle under an Ar atmosphere. To the resulting mixture was added 4-bromo-5-fluoropyrimidne (99.3 mg, 0.515 mmol) in Et_2O (0.8 mL) at −78 °C, and the mixture was stirred at the same temperature for 10 min. To the resulting mixture was added aldehyde **3** (117 mg, 0.399 mmol) in Et_2O (1.0 mL) at −78 °C, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with H_2O. The aqueous layer was extracted two times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica-gel column chromatography (*n*-hexane/EtOAc = 70:30) gave 77.0 mg of **6** (49% yield, diastereomeric ratio was determined to be 72:28 by ^{1}H NMR analysis) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 2.5 Hz, 1H), 8.38 (d, J = 1.8 Hz, 1H), 7.35−7.28 (m, 1H), 6.77−6.71 (m, 1H), 6.69−6.64 (m, 1H), 5.51 (s, 1H), 4.62 (s, 1H), 4.27 (d, J = 11.2 Hz, 1H), 4.11 (dd, J = 11.2, 1.2 Hz, 1H), 0.046 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.8 (dd, J = 250, 13 Hz), 159.1 (dd, J = 247, 12 Hz), 155.1 (d, J = 267 Hz), 154.5 (d, J = 10 Hz), 153.8 (d, J = 7.2 Hz), 145.4 (d, J = 22 Hz), 130.5 (dd, J = 9.4, 6.5 Hz), 122.3 (dd, J = 13, 4.3 Hz), 111.3 (dd, J = 21, 3.6 Hz), 103.9 (dd, J = 28, 25 Hz), 78.5 (d, J = 5.8 Hz), 70.3, 50.4 (d, J = 7.2 Hz), −0.354; IR (neat, cm^{-1}) ν 3375, 2056, 2962, 1620; HRMS (ESI) Anal. Calcd. for $C_{16}H_{19}O_2N_2ClSiF_3$ m/z 391.0851 [M + H]$^+$, found 391.0853.

*(1R,2S)-3-Chloro-2-(2,4-difluorophenyl)-1-(5-fluoropyrimidin-4-yl)propane-1,2-diol (**7**).* To a solution of **6** (63.9 mg, 0.163 mmol) in EtOH (326 μL) was added 0.01 N HCl in EtOH (326 μL) at room temperature, and then the resulting mixture was stirred at the same temperature for 3 h. The reaction mixture was quenched with a saturated $NaHCO_3$ aq. The aqueous layer was extracted two times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica-gel column chromatography (*n*-hexane/EtOAc = 50:50) gave 45.8 mg of **7** (88% yield) as a colorless crystal: mp 154−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 2.5 Hz, 1H), 8.36 (d, J = 1.4 Hz, 1H), 7.26−7.20 (m, 1H), 6.81−6.69 (m, 2H), 5.50 (d, J = 10.6 Hz, 1H), 4.41 (d, J = 11.4 Hz, 1H), 4.26 (d, J = 11.4 Hz, 1H), 4.09 (d, J = 10.6 Hz, 1H), 4.02 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.0 (dd, J = 251, 12 Hz), 159.3 (dd, J = 248, 11 Hz), 154.7 (d, J = 276 Hz), 153.8 (d, J = 4.3 Hz), 153.6 (d, J = 8.7 Hz), 145.4 (d, J = 22 Hz), 130.0 (dd, J = 10, 5.8 Hz), 122.2 (dd, J = 13, 4.3 Hz), 111.4 (dd, J = 22, 2.9 Hz), 104.2 (dd, J = 28, 25 Hz), 78.6 (d, J = 5.8 Hz), 68.4, 50.2 (d, J = 7.2 Hz); IR (neat, cm^{-1}) ν 3473, 3201, 2850, 1617, 1498, 1409; HRMS (ESI) Anal. Calcd. for $C_{13}H_{10}O_2N_2ClF_3Na$ m/z 341.0275 [M + Na]$^+$, found 341.0279.

*(R)-((R)-2-(2,4-Difluorophenyl)oxiran-2-yl)(5-fluoropyrimidin-4-yl)methanol (**8**).* A flame-dried 10 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with Et_2O (0.3 mL). 2.69 M ^{n}BuLi solution in *n*-hexane (0.23 mL, 0.598 mmol) was added via a gastight syringe with a stainless steel needle under an Ar atmosphere. To the resulting mixture was added 4-bromo-5-fluoropyrimidine[13] (106 mg, 0.598 mmol) in Et_2O (0.8 mL) at −78 °C, and the mixture was stirred at the same temperature for 10 min. Aldehyde **4** (117 mg, 0.399 mmol) in Et_2O (0.9 mL) was added to the resulting mixture at −78 °C, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with silica gel. Then the resulting mixture was warmed to room temperature and stirred for 30 min. After cooling the reaction mixture to 0 °C, acetic acid (50.2 μL, 0.877 mmol) and 1.0 M TBAF solution in THF (1.76 mL, 1.76 mmol) were added. After stirring the resulting mixture at room temperature for 8 h, 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 silica-gel column chromatography (*n*-hexane/EtOAc = 70:30) to give 55.2 mg of diastereomixture of **8** (49% yield, (2*R*,3*R*):(2*R*,3*S*) = 85:15 by ^{1}H NMR analysis) as a colorless oil. Diastereomixture of **8** was submitted to the next reaction. Diastereomers were separable by silica-gel column chromatography (*n*-hexane/EtOAc = 70:30). Major isomer: colorless oil; $[\alpha]_D^{27}$ −2.94 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, J = 2.8 Hz, 1H), 8.45 (s, 1H), 7.17−7.11 (m, 1H), 6.76−6.67 (m, 2H), 5.34 (d, J = 9.6 Hz, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.44 (d, J = 5.3 Hz, 1H), 2.81 (d, J = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (dd, J = 247, 10 Hz), 160.5 (dd, J = 245, 9.6 Hz), 155.0 (d, J = 267 Hz), 153.9 (d, J = 7.7 Hz), 153.3 (d, J = 14 Hz), 144.6 (d, J = 21 Hz), 130.8 (dd, J = 9.6, 5.8 Hz), 119.1 (dd, J = 15, 3.8 Hz), 111.4 (dd, J = 22, 3.4 Hz), 103.6 (dd, J = 25, 25 Hz), 68.2, 59.0, 50.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.3, −112.0, −135.9; IR (neat, cm^{-1}) ν 3414, 3077, 2318, 1619, 1589, 1507, 1403; HRMS (ESI) Anal. Calcd. for $C_{13}H_9O_2N_2F_3Na$ m/z 305.0508 [M + Na]$^+$, found 305.0512. Minor isomer: white solid; mp 79−82 °C; $[\alpha]_D^{27}$ −16.5 (*c* 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, J = 2.8 Hz, 1H), 8.55 (d, J = 1.2 Hz, 1H), 7.27−7.21 (m, 1H), 6.83−6.78 (m, 1H), 6.75−6.69 (m, 1H), 5.31 (d, J = 7.4 Hz, 1H), 3.82 (d, J = 7.4 Hz, 1H), 3.20 (d, J = 4.6 Hz, 1H), 2.93 (d, J = 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2 (dd, J = 250, 12 Hz), 161.0 (dd, J = 250, 12 Hz), 155.5 (d, J = 269 Hz), 153.9 (d, J = 7.2 Hz), 153.1 (d, J = 13 Hz), 145.0 (d, J = 20 Hz), 131.3 (dd, J = 10, 5.8 Hz), 119.4−119.3 (m), 111.4 (dd, J = 22, 2.9 Hz), 103.9 (dd, J = 25, 25 Hz), 69.5, 59.3, 51.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.1, −111.1, −135.2; IR (neat, cm^{-1}) ν 3189, 3057, 280,

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2359, 1620, 1589, 1507, 1403; HRMS (ESI) Anal. Calcd. for $C_{13}H_9O_2N_2F_3Na$ m/z 305.0508 $[M + Na]^+$, found 305.0509.

*(R)-(2-(2,4-Difluorophenyl)oxiran-2-yl)(5-fluoropyrimidin-4-yl)-methanone (**9**).* To a suspension of *N*-chlorosuccinimide (2.18 g, 16.3 mmol) in THF (33.0 mL) was added *n*-dodecylmethylsulfide (4.85 mL, 19.0 mmol) at 0 °C, and the resulting mixture was stirred at the same temperature for 10 min. After cooling the reaction mixture to −30 °C, a solution of diastereomixtures of **8** (1.53 g, 5.44 mmol) in THF (40 mL) was added, and the reaction mixture was stirred at the same temperature for 1 h. To the resulting mixture was added Et_3N (4.55 mL, 32.6 mmol), and the mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with H_2O. The organic layer was washed twice 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 = 70:30) to give 1.48 g of **9** (97% yield) as a colorless oil: $[\alpha]_D^{27}$ 40.6 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 2.8 Hz, 1H), 8.73 (d, J = 1.4 Hz, 1H), 7.48−7.42 (m, 1H), 6.93−6.89 (m, 1H), 6.86−6.80 (m, 1H), 3.73 (d, J = 5.5 Hz, 1H), 3.32 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1 (d, J = 3.8 Hz), 163.6 (dd, J = 253, 11 Hz), 161.7 (dd, J = 250, 13 Hz), 154.8 (d, J = 275 Hz), 153.7 (d, J = 7.7 Hz), 148.1 (d, J = 8.6 Hz), 147 (d, J = 21 Hz), 130.6 (dd, J = 11, 5.8 Hz), 117.6 (dd, J = 16, 3.8 Hz), 111.8 (dd, J = 23, 4.3 Hz), 104.2 (dd, J = 25, 25 Hz), 59.6, 52.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.9, −110.0, −133.3; IR (neat, cm^{-1}) ν 3080, 2963, 2310, 1722, 1619, 1509, 1402, 1294; HRMS (ESI) Anal. Calcd. for $C_{13}H_8O_2N_2F_3$ m/z 281.0532 $[M + H]^+$, found 281.0535.

*(R)-4-(1-(2-(2,4-Difluorophenyl)oxiran-2-yl)vinyl)-5-fluoropyrimidine (**10**).* To a suspension of methyltriphenylphosphonium bromide (640 mg, 1.79 mmol) in toluene (2.0 mL) was added ^{t}BuOK (201 mg, 1.79 mmol), and the resulting mixture was stirred at 120 °C for 1 h. After cooling the reaction mixture to 0 °C, a solution of **9** (251 mg, 0.896 mmol) in toluene (7 mL) was added, and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with H_2O. The organic layer was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was taken up with toluene (4.5 mL), and then $MgCl_2$ (512 mg, 5.38 mmol) was added. The reaction mixture was stirred at 65 °C for 1 h. After cooling to room temperature, the resulting mixture was filtered, and concentrated under reduced pressure. The resulting residue was purified using silica-gel column chromatography (*n*-hexane/EtOAc = 70:30) to give 212 mg of **10** (85% yield) as a colorless crystal: mp 60−62 °C; $[\alpha]_D^{27}$ 65.8 (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 3.0 Hz, 1H), 8.50 (d, J = 3.2 Hz, 1H), 7.55−7.49 (m, 1H), 6.80−6.76 (m, 1H), 6.73−6.68 (m, 1H), 6.20 (br s, 1H), 6.16 (s, 1H), 3.33 (d, J = 5.3 Hz, 1H), 3.17 (d, J = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (dd, J = 250, 12 Hz), 161.5 (dd, J = 252, 13 Hz), 155.7 (d, J = 270 Hz), 153.9 (d, J = 8.6 Hz), 150.7 (d, J = 8.6 Hz), 145.5 (d, J = 24 Hz), 140.4 (d, J = 5.8 Hz), 131.6 (dd, J = 9.6, 4.8 Hz), 124.8 (dd, J = 9.6, 1.9 Hz), 121.5 (dd, J = 13, 3.8 Hz), 111.1 (dd, J = 21, 3.8 Hz), 104.1 (dd, J = 25, 25 Hz), 57.9, 54.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.9, −109.5, −131.7; IR (neat, cm^{-1}) ν 3062, 2997, 2374, 2352, 1894, 1617, 1579, 1507, 1403, 1283; HRMS (ESI) Anal. Calcd. for $C_{14}H_{10}ON_2F_3$ m/z 279.0740 $[M + H]^+$, found 279.0736.

*4-((S)-1-((R)-2-(2,4-Difluorophenyl)oxiran-2-yl)ethyl)-5-fluoropyrimidine (**11**).* To a solution of **10** (23.5 mg, 0.0845 mmol) in MeOH (84.5 μL) was added $NaHCO_3$ (9.2 mg, 0.110 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide (30.2 mg, 0.101 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for 18 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted three times 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 (*n*-hexane/EtOAc = 50:50) to give 18.9 mg of **11** as a diastereomixture (80% yield, (2*R*,3*S*):(2*R*,3*R*) = 69:31 by ^{1}H NMR analysis). Further purification of the diastereomixture of **11** using silica-gel column chromatography (*n*-hexane/diisopropyl ether =20:80) gave 13.4 mg of **11** (57% yield, single diastereomer) as a colorless oil: $[\alpha]_D^{28}$ −24.2 (*c* 0.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 2.8 Hz, 1H), 8.44 (d, J = 1.8 Hz, 1H), 7.16−7.10 (m, 1H), 6.77−6.69 (m, 2H), 3.90 (q, J = 7.3 Hz, 1H), 3.07 (d, J = 4.8 Hz, 1H), 2.86 (d, J = 4.8 Hz, 1H), 1.34 (d, J = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7 (dd, J = 248, 12 Hz), 160.7 (dd, J = 249, 12 Hz), 157.0 (d, J = 13 Hz), 156.4 (d, J = 266 Hz), 154.2 (d, J = 7.2 Hz), 144.3 (d, J = 22 Hz), 130.8 (dd, J = 8.7, 5.8 Hz), 122.1 (dd, J = 14, 4.3 Hz), 111.1 (dd, J = 21, 3.6 Hz), 103.9 (dd, J = 25, 25 Hz), 59.1, 51.0, 39.0, 13.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.1, −111.1, −135.7; IR (neat, cm^{-1}) ν 3069, 2975, 2943, 2377, 2353, 2310, 1585, 1507, 1402; HRMS (ESI) Anal. Calcd. for $C_{14}H_{12}ON_2F_3$ m/z 281.0896 $[M + H]^+$, found 281.0890.

*(2R,3S)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (Voriconazole), and (2R,3S)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(4H-1,2,4-triazol-4-yl)-butan-2-ol (**13**).* To a solution of **11** (373 mg, 1.33 mmol) in EtOH (1.5 mL) was added 1,2,4-triazole (2.76 g, 39.9 mmol) at room temperature, and the resulting mixture was stirred at 80 °C (bath temp.) for 18 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted three times 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 186 mg of voriconazole (40% yield, recovered **10**: 24%, 53% based on the recovered starting material) as a colorless crystal and **13** (125 mg, 27% yield) as a colorless crystal. 161 mg of voriconazole (enantiomeric excess: 80%) was taken up with isopropanol (483 μL) at 65 °C, and the resulting solution was stirred at room temperature for 1 h. After additional stirring at 0 °C for 1.5 h, the resulting crystal was filtered and dried in vacuo to give 85.7 mg of voriconazole (enantiomeric excess: 99.3%). 67.1 mg of voriconazole (enantiomeric excess: 99.3%) was taken up with isopropanol (168 μL) and *n*-hexane (168 μL) at 65 °C, and the resulting solution was stirred at room temperature for 1 h. After additional stirring at 0 °C for 12 h, the resulting crystal was filtered and dried in vacuo to give 61.5 mg of voriconazole (enantiomeric excess: >99%) as a colorless crystal: mp 134−136 °C; $[\alpha]_D^{27}$ −57.3 (*c* 1.0, MeOH, synthetic sample), $[\alpha]_D^{25}$ −62 (*c* 1.0, MeOH, reported in ref 2b); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 2.5 Hz, 1H), 8.59 (d, J = 1.4 Hz, 1H), 7.94 (s, 1H), 7.61−7.55 (m, 1H), 7.52 (s, 1H), 6.84−6.77 (m, 2H), 6.46 (s, 1H), 4.69 (d, J = 14.2 Hz, 1H), 4.29 (d, J = 14.2 Hz, 1H), 4.11 (q, J = 7.1 Hz, 1H), 1.08 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (dd, J = 250, 13 Hz), 159.3 (d, J = 12.5 Hz), 158.4 (dd, J = 248, 11 Hz), 155.7 (d, J = 267 Hz), 153.4 (d, J = 8.6 Hz), 150.9, 145.3 (d, J = 21 Hz), 143.9, 130.6 (dd, J = 9.6, 5.8 Hz), 123.5 (dd, J = 12, 3.8 Hz), 111.6 (dd, J = 20, 2.9 Hz), 104.1 (dd, J = 28, 26 Hz), 77.5 (d, J = 4.8 Hz), 57.3 (d, J = 4.8 Hz), 36.8 (d, J = 4.8 Hz), 16.1; IR (neat, cm^{-1}) ν 3197, 2994, 2979, 1619, 1587, 1496, 1451, 1408; HRMS (ESI) Anal. Calcd. for $C_{16}H_{14}ON_5F_3Na$ m/z 372.1043 $[M + Na]^+$, found 372.1037. The enantiometric excess of voriconazole was determined by chiral HPLC analysis (DAICEL, CHIRALCEL OD-H, flow rate =1.0 mL/min, *n*-hexane:EtOH = 85:25, detection at 254 nm, column temp. 23 °C, t_R = 17.7 min (voriconazole), t_R = 20.8 min (*ent*-voriconazole). **13**: mp 185−188 °C; $[\alpha]_D^{28}$ −46.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.62 (s, 1H), 7.84 (s, 2H), 7.51−7.45 (m, 1H), 6.81−6.74 (m, 2H), 6.46 (brs, 1H), 4.51 (d, J = 14.2 Hz, 1H), 4.02 (q, J = 6.9 Hz, 1H), 3.95 (d, J = 14.2 Hz, 1H), 1.04 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (dd, J = 251, 12 Hz), 159.1 (d, J = 13.0 Hz), 157.9 (dd, J = 246, 12 Hz), 155.6 (d, J = 266 Hz), 153.8 (d, J = 8.7 Hz), 146.0 (d, J = 22 Hz), 143.1, 131.2 (dd, J = 9.4, 5.1 Hz), 122.3 (dd, J = 12, 4.3 Hz), 112.3 (dd, J = 20, 2.9 Hz), 104.2 (dd, J = 27, 27 Hz), 77.7 (d, J = 4.3 Hz), 53.3 (d, J = 5.8 Hz), 36.4 (d, J = 4.3 Hz), 16.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.0, −110.3, −135.7; IR (neat, cm^{-1}) ν 3360, 3114, 2982, 2940, 2376, 1620, 1588, 1498, 1406; HRMS (ESI) Anal. Calcd. for $C_{16}H_{15}ON_5F_3$ m/z 350.1223 $[M + H]^+$, found 350.1228.

*(R)-((R)-2-(2,4-Difluorophenyl)oxiran-2-yl)(5-fluoropyrimidin-4-yl)methyl methanesulfonate (**14**).* To a solution of **8** (20.5 mg, 0.0726 mmol) in CH_2Cl_2 (363 μL) was added Et_3N (22.3 μL, 0.160 mmol) and MsCl (6.20 μL, 0.0799 mmol) at 0 °C, and the resulting mixture was stirred at the same temperature for 1 h. The reaction

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mixture was quenched with H_2O. The aqueous layer was extracted three times with $CHCl_3$. 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 26.7 mg of **14** (quantitative yield) as a colorless oil: $[\alpha]_D^{28}$ −12.8 (*c* 1.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.5 Hz, 1H), 8.58 (s, 1H), 7.38−7.32 (m, 1H), 6.87−6.83 (m, 1H), 6.74−6.69 (m, 1H), 6.03 (s, 1H), 3.40 (d, *J* = 4.6 Hz, 1H), 3.07 (s, 3H), 2.97 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (dd, *J* = 252, 11 Hz), 160.6 (dd, *J* = 250, 12 Hz), 155.3 (d, *J* = 270 Hz), 154.4 (d, *J* = 7.7 Hz), 149.1 (d, *J* = 11 Hz), 145.6 (d, *J* = 21 Hz), 131.5 (dd, *J* = 9.6, 4.8 Hz), 117.8 (dd, *J* = 14, 3.8 Hz), 111.8 (dd, *J* = 22, 3.8 Hz), 103.8 (dd, *J* = 25, 25 Hz), 76.9, 56.8, 51.0, 38.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.9, −111.1, −134.2; IR (neat, cm^{-1}) ν 3081, 3028, 2939, 1620, 1585, 1509, 1365; HRMS (ESI) Anal. Calcd. for $C_{14}H_{12}O_4N_2F_3S$ *m*/*z* 361.0465 $[M + H]^+$, found 361.0468.

*(E)-2-(2,4-Difluorophenyl)-1-(5-fluoropyrimidin-4-yl)-3-hydroxyprop-1-en-1-yl methanesulfonate (**15**).* Attmpts to obtain methylated product resulted in failure, and **15** was isolated from the complicated mixture. Tentative assignment was made with ^{1}H NMR, NOE, and HRMS. To a solution of **14** (24.6 mg, 0.0683 mmol) in THF (136 μL) was added 0.97 M MeMgBr in THF (0.21 mL, 0.205 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was quenched with 1 N HCl aq. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were dried over $MgSO_4$. After removal of volatiles under reduced pressure, the resulting residue was purified using preparative TLC ($CHCl_3$/MeOH = 10:1) to give 3.3 mg of **15** (ca. 13% yield, with some unidentified materials) as a yellow oil. **15**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.11 (d, *J* = 2.7 Hz, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 7.62−7.58 (m, 1H), 7.01−6.98 (m, 1H), 6.94−6.90 (m, 1H), 4.30 (s, 2H), 2.73 (s, 3H); HRMS (ESI) Anal. Calcd. for $C_{14}H_{12}O_4N_2F_3S$ *m*/*z* 361.0465 $[M + H]^+$, found 361.0469.

*(E)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)but-2-en-1-ol ((E)-**16**) and (Z)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)but-2-en-1-ol ((Z)-**16**).* To a solution of **10** (25.5 mg, 0.0917 mmol) in EtOH (917 μL) was added 10% Pd/C (20.8 mg) at room temperature under argon atmosphere. The resulting suspension was stirred at the same temperature under H_2 atmosphere for 1 h. After evacuation of H_2, argon was backfilled, and the resulting suspension was filtered and concentrated under reduced pressure. The resulting residue was purified using preparative TLC (*n*-hexane/EtOAc = 50:50) to give 11.1 mg of **16** (44% yield, *E*/*Z* = 2.2/1) as a colorless oil: ^{1}H NMR for *E* isomer (600 MHz, $CDCl_3$) δ 8.87 (d, *J* = 2.7 Hz, 1H), 8.26 (d, *J* = 2.1 Hz, 1H), 6.84−6.80 (m, 1H), 6.72−6.68 (m, 1H), 6.61−6.57 (m, 1H), 4.60 (s, 2H), 2.26 (s, 3H); ^{13}C NMR for *E* isomer (150 MHz, $CDCl_3$) δ 162.5 (dd, *J* = 250, 12 Hz), 160.0 (dd, *J* = 251, 13 Hz), 156.6 (d, *J* = 12 Hz), 154.2 (d, *J* = 7.2 Hz), 154.1 (d, *J* = 266 Hz), 144.8 (d, *J* = 23 Hz), 137.8, 132.2 (dd, *J* = 8.7, 5.8 Hz), 131.5 (d, *J* = 2.9 Hz), 122.8 (dd, *J* = 16, 4.3 Hz), 110.9 (dd, *J* = 21, 3.6 Hz), 104.0 (dd, *J* = 26, 26 Hz), 62.4, 17.9; ^{19}F NMR for *E* isomer (376 MHz, $CDCl_3$) δ −109.5, −109.7, −132.0; ^{1}H NMR for *Z* isomer (600 MHz, $CDCl_3$) δ 9.03 (d, *J* = 2.7 Hz, 1H), 8.64 (d, *J* = 2.1 Hz, 1H), 7.39−7.34 (m, 1H), 6.96−6.86 (m, 2H), 4.04 (s, 2H), 1.94 (s, 3H); ^{13}C NMR for *Z* isomer (150 MHz, $CDCl_3$) δ 162.7 (dd, *J* = 251, 11 Hz), 159.4 (dd, *J* = 248, 11 Hz), 155.4 (d, *J* = 267 Hz), 155.3 (d, *J* = 13 Hz), 154.0 (d, *J* = 7.2 Hz), 145.7 (d, *J* = 25 Hz), 138.4, 132.6 (d, *J* = 4.3 Hz), 131.2 (dd, *J* = 9.4, 5.1 Hz), 123.2 (dd, *J* = 17, 3.6 Hz), 111.7 (dd, *J* = 21, 3.6 Hz), 104.2 (dd, *J* = 26, 26 Hz), 64.1, 19.0 (d, *J* = 4.3 Hz); ^{19}F NMR for *Z* isomer (376 MHz, $CDCl_3$) δ −109.7, −110.1, −130.9; IR (*E*/*Z* mixture) (neat, cm^{-1}) ν 3378, 3063, 2924, 2876, 1614, 1583, 1503, 1402; HRMS (ESI) Anal. Calcd. for $C_{14}H_{12}ON_2F_3$ *m*/*z* 281.0896 $[M + H]^+$, found 281.0894.

*(E)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-4-(1H-1,2,4-triazol-1-yl)but-2-en-1-ol ((E)-**17**) and 8-((1H-1,2,4-Triazol-1-yl)-methyl)-7-(2,4-difluorophenyl)-6H-pyrano[3,2-d]pyrimidine (**18**).* To a solution of **10** (50.0 mg, 0.180 mmol) in DMF (500 μL) was added 1,2,4-triazole (124 mg, 1.80 mmol) and K_2CO_3 (248 mg, 1.80 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted three times 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 41.1 mg of (*E*)-**17** (66% yield) as a colorless amorphous and 11.3 mg of **18** (19% yield) as a colorless oil. (*E*)-**17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 2.7 Hz, 1H), 8.19 (d, *J* = 1.8 Hz, 1H), 8.08 (s, 1H), 7.87 (s, 1H), 7.00−6.94 (m, 1H), 6.70−6.62 (m, 2H), 5.50 (s, 2H), 4.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 252, 12 Hz), 159.4 (dd, *J* = 251, 12 Hz), 154.3 (d, *J* = 269 Hz), 154.3 (d, *J* = 7.7 Hz), 153.2 (d, *J* = 12 Hz), 152.1, 145.9 (dd, *J* = 1.9, 1.9 Hz), 145.4 (d, *J* = 23 Hz), 143.8, 131.8 (dd, *J* = 9.6, 4.8 Hz), 128.0 (d, *J* = 4.8 Hz), 122.6 (dd, *J* = 15, 3.4 Hz), 111.4 (dd, *J* = 22, 3.4 Hz), 104.3 (dd, *J* = 25, 25 Hz), 62.9 (d, *J* = 1.9 Hz), 48.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.9, −109.3, −129.9; IR (neat, cm^{-1}) ν 3369, 2352, 1614, 1580, 1504, 1272, 1141; HRMS (ESI) Anal. Calcd. for $C_{16}H_{12}ON_5F_3Na$ *m*/*z* 370.0886 $[M + Na]^+$, found 370.0884. **18**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.34 (s, 1H), 8.24 (s, 1H), 7.85 (s, 1H), 7.81−7.77 (m, 1H), 7.05−7.02 (m, 1H), 6.95−6.92 (m, 1H), 5.18 (br s, 2H), 5.08 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7 (dd, *J* = 253, 12 Hz), 160.0 (dd, *J* = 251, 13 Hz), 151.9, 151.4, 148.0, 146.6, 144.8, 144.0, 138.5, 132.0 (dd, *J* = 9.4, 5.1 Hz), 126.7, 118.0 (dd, *J* = 16, 4.3 Hz), 112.4 (d, *J* = 22 Hz), 104.9 (dd, *J* = 26, 26 Hz), 68.7 (d, *J* = 4.3 Hz), 44.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.1, −108.2; IR (neat, cm^{-1}) ν 3102, 3050, 2924, 2852, 1504, 1413; HRMS (ESI) Anal. Calcd. for $C_{16}H_{12}ON_5F_2$ *m*/*z* 328.1005 $[M + H]^+$, found 328.1006.; HRMS (ESI) Anal. Calcd. for $C_{16}H_{12}ON_5F_2$ *m*/*z* 328.1005 $[M + H]^+$, found 328.1006.

*(R)-(5-(1H-1,2,4-Triazol-1-yl)pyrimidin-4-yl)(2-(2,4-difluorophenyl)oxiran-2-yl)methanone (**19**).* To a solution of **9** (10.8 mg, 0.0385 mmol) in DMF (193 μL) was added 1,2,4-sodium triazolide (5.26 mg, 0.0578 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted three times 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 (*n*-hexane/EtOAc = 50:50) to give 10.9 mg of **19** (86% yield) as a colorless solid: $[\alpha]_D^{28}$ 27.4 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 9.05 (s, 1H), 8.60 (s, 1H), 8.11 (s, 1H), 7.47−7.41 (m, 1H), 6.94−6.89 (m, 1H), 6.88−6.83 (m, 1H), 3.70 (d, *J* = 5.7 Hz, 1H), 3.20 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 163.5 (dd, *J* = 252, 13 Hz), 161.6 (dd, *J* = 252, 12 Hz), 156.8, 154.5, 153.5, 150.0, 142.4, 130.6 (dd, *J* = 9.6, 4.8 Hz), 129.2, 117.4 (dd, *J* = 16, 2.9 Hz), 111.5 (dd, *J* = 22, 3.8 Hz), 104.1 (dd, *J* = 25, 25 Hz), 59.4, 52.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.2, −109.9; IR (neat, cm^{-1}) ν 3415, 3132, 3104, 2925, 2354, 1720, 1618, 1509, 1463, 1431; HRMS (ESI) Anal. Calcd. for $C_{15}H_{10}O_2N_5F_2$ *m*/*z* 330.0797 $[M + H]^+$, found 330.0802.

*7-(2,4-Difluorophenyl)-8-methyl-6H-pyrano[3,2-d]pyrimidine (**20**).* To a solution of **11** (26.5 mg, 0.0946 mmol) in DMF (265 μL) was added 1,2,4-sodium triazolide (86.1 mg, 0.946 mmol) at room temperature, and the resulting mixture was stirred at 60 °C for 1 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted three times 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 9.1 mg of (*E*)-**16** (34% yield) as a pale purple oil and 10.7 mg of **20** (44% yield) as a colorless crystal. Spectroscopic data of (*E*)-**16** is described above. **20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.22 (s, 1H), 7.25−7.19 (m, 1H), 6.97−6.88 (m, 2H), 4.97 (s, 2H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 251, 13 Hz), 159.9 (dd, *J* = 252, 13 Hz), 152.0, 149.2, 147.9, 143.2, 132.3, 131.2 (dd, *J* = 9.6, 4.8 Hz), 130.0, 119.9 (dd, *J* = 17, 6.2 Hz), 111.9 (dd, *J* = 21, 3.8 Hz), 104.8 (dd, *J* = 25, 25 Hz), 68.6 (d, *J* = 2.9 Hz), 12.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.0, 108.3; IR (neat, cm^{-1}) ν 3069, 2852, 1614, 1574, 1506, 1465, 1414; HRMS (ESI) Anal. Calcd. for $C_{14}H_{11}ON_2F_2$ *m*/*z* 261.0834 $[M + H]^+$, found 261.0828.

*(3R)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-2-(4H-1,2,4-triazol-4-yl)butan-1-ol (**21**).* To a solution of **11** (8.3 mg, 0.0296

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mmol) in EtOH (33.2 μL) was added 1,2,4-triazole (61.4 mg, 0.888 mmol) and LiCl (7.54 mg, 0.178 mmol) at room temperature, and the resulting mixture was stirred at 80 °C (bath temp.) for 5 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted three times 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 3.6 mg of **21** (35% yield) as a colorless amorphous: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.37 (s, 1H), 7.87 (s, 2H), 7.02−6.96 (m, 1H), 6.69−6.64 (m, 1H), 6.51−6.46 (m, 1H), 6.17 (br s, 1H), 4.55 (s, 2H), 4.24 (q, J = 6.9 Hz, 1H), 1.54 (d, J = 6.9 Hz, 3H) (in DMSO-d_6, doublet peak of OH proton was observed (J = 4.6 Hz), supporting that **21** is an isomeric primary alcohol formed by epoxide opening from the more congested carbon); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6 (dd, J = 251, 12 Hz), 158.9 (d, J = 13 Hz), 157.8 (dd, J = 244, 12 Hz), 154.6 (d, J = 266 Hz), 153.2 (d, J = 8.7 Hz), 145.4 (d, J = 22 Hz), 143.3, 130.0 (dd, J = 9.4, 5.1 Hz), 124.0 (dd, J = 13, 2.9 Hz), 111.9 (dd, J = 22, 2.9 Hz), 104.2 (dd, J = 27, 27 Hz), 76.8, 51.6 (d, J = 4.3 Hz), 36.7 (d, J = 5.8 Hz), 14.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.8, −109.5, −137.1; IR (neat, cm^{-1}) 3378, 3123, 2979, 2238, 1616, 1590, 1498, 1404; HRMS (ESI) Anal. Calcd. for $C_{16}H_{15}ON_5F_3$ m/z 350.1223 $[M + H]^+$, found 350.1222.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental procedures and ^{1}H and ^{13}C NMR spectra of new compounds. 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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