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Stereoselective synthesis of (+)-flutriafol

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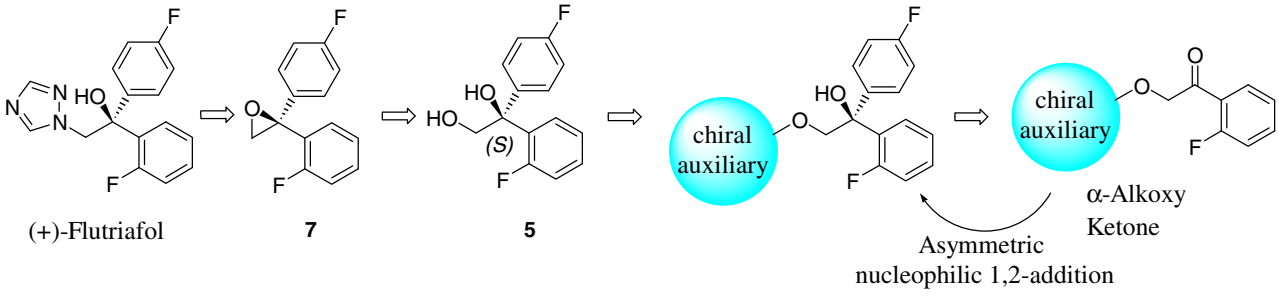
ABSTRACT

The stereoselective synthesis of (+)-flutriafol, a triazole fungicide, has been accomplished in seven linear steps from (1*S*)-[(4*R*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-(4-methoxyphenyl)methanol in 15% overall yield. Diastereoselective nucleophilic 1,2-addition was employed as a key step for constructing the requisite chiral 1,2-diol for flutriafol. A high degree of 1,4-asymmetric induction could be realized via a chelation-controlled mechanism during the key alkylation step.

1. Introduction

Flutriafol is a broad-spectrum triazole fungicide used for the control of important cereal diseases including powdery mildews, rusts, *Septoria* spp., and *Rhynchosporium secalis*.[1] It shares a common mode of action with other triazole fungicides by inhibiting the C-14α-demethylase enzyme involved in the biosynthesis of fungal sterols.[2] A characteristic structural feature of flutriafol is the tertiary alcohol with a 1,2,4-triazolylmethyl group and two differently substituted fluorophenyl groups. As shown in Scheme 1, flutriafol has one stereogenic center, but is marketed in the racemic form. Considering that the stereogenic center of flutriafol is located close to the 1,2,4-triazole ring, a key template in the binding of flutriafol to their target sites, chirality is expected to play a crucial role in the bioactivities of flutriafol. This has actually been proven by some bioassay results.[3] It was also reported that the (+)-isomer of flutriafol was more active than the (−)-isomer against both *Alternaria solani* and *Alternaria mali*.[4] Its absolute configuration has not yet been determined. However, optically active flutriafol has been separated only by a chromatographic method through enantiomeric or diastereomeric chiral separation.[5] The asymmetric synthesis of flutriafol has not yet been reported; therefore, the synthesis of flutriafol in enantiopure form is of interest. Our recent development of the chelation-controlled asymmetric alkylation process permitting efficient syntheses of chiral α-hydroxy esters prompted us to see if this process would be readily adaptable to the synthesis of chiral 1,2-diols.[6] If so, an efficient synthesis of (+)-flutriafol via chiral diol **5** would be feasible. Our synthetic strategy for (+)-flutriafol was based on the approach outlined in Scheme 1. A retrosynthetic analysis of (+)-flutriafol reveals the regioselective ring opening of epoxide **7** as a possible key step. As epoxide **7** shall be accessible from the corresponding diol **5**, we



Scheme 1. Retrosynthetic analysis of (+)-flutriafol.

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envisioned that the chelation-controlled asymmetric nucleophilic 1,2-addition to α-alkoxy ketone,[7] followed by removal of the chiral auxiliary would provide the requisite chiral diol **5**.

2. Results and discussion

Our synthesis began with the preparation of chiral auxiliary-conjugated α-alkoxy ketone as a substrate for the diastereoselective nucleophilic 1,2-addition reaction (Scheme 2). Chiral auxiliary **1**, readily prepared from (*R*)-glyceraldehyde diacetonide, was linked to the reaction template as its ether form, simply by an O-alkylative epoxide ring opening reaction.[6a,8] Alcohol **1** was converted to the corresponding alkoxide with KH in tetrahydrofuran (THF), followed by O-alkylation with 2-(2-fluorophenyl)oxirane in the presence of 18-crown-6 to afford ether **2** in 53% yield. Oxidation of the resulting alcohol was carried out with tetrapropylammonium perruthenate (TPAP) in the presence of *N*-methylmorpholine-N-oxide (NMO) to give ketone **3** in 65% yield. With key substrate **3** in hand, we undertook a short study to determine the optimum conditions for the asymmetric nucleophilic 1,2-addition reaction. As shown in Table 1, performing the reaction at a lower temperature in a less basic solvent led to better results. The addition of an additive to the reaction led to a dramatic breakthrough in stereoselectivity, with $MgBr_2$-etherate proving to be the best additive for the reaction. Thus, the optimum conditions involved performing the reaction in the presence of $MgBr_2$-etherate in dichloromethane (DCM) at −78 °C, to give the desired major product **4a** and its diastereomer **4b** in 95% chemical yield, in a 51:1 ratio of diastereomers. The absolute configuration of the newly created stereogenic center of **4a** could not be rigorously established at the present stage, but was assigned tentatively as (*S*) on the basis of our proposed chelation model as shown in Figure 1.[6a] The subsequent transformation of **4a** to (+)-flutriafol is outlined in Scheme 3. Alcohol **4a** was then converted to the corresponding diol **5** by treating with trimethylsilyl chloride

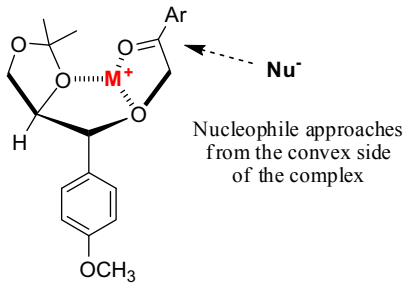
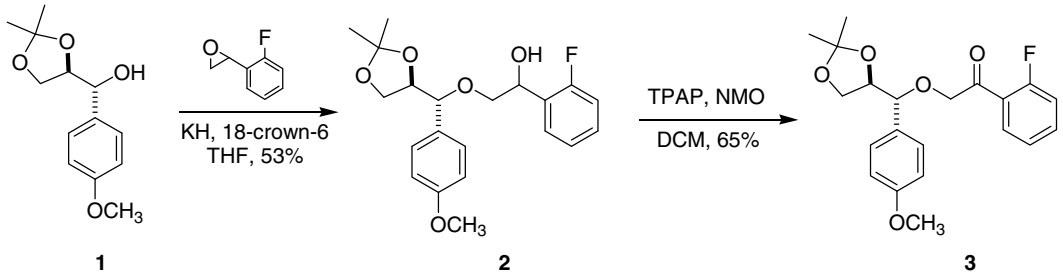
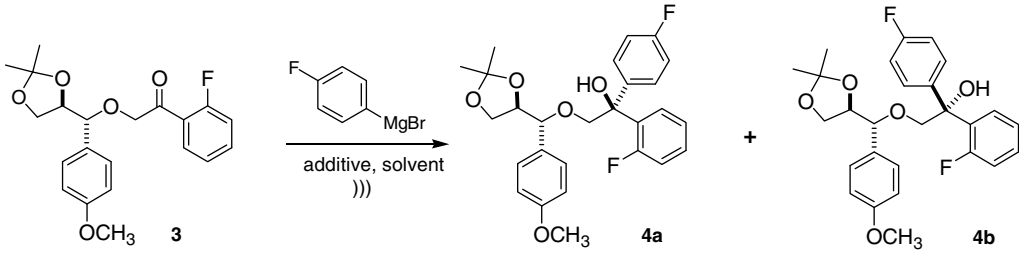


Figure 1. Possible chelation model for asymmetric nucleophilic 1,2-addition.



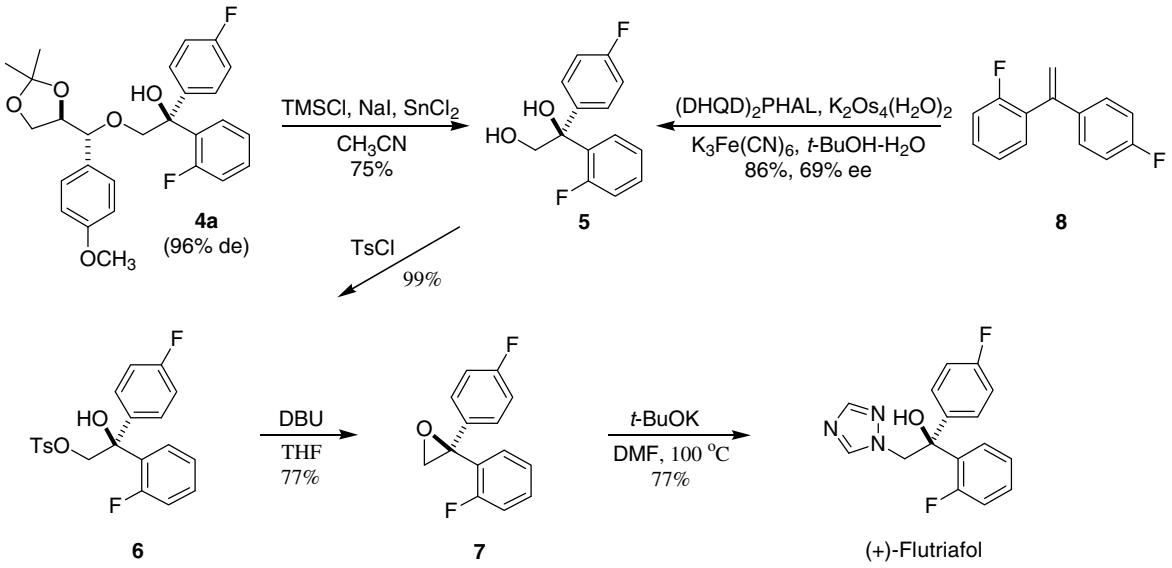
Scheme 2. Preparation of chiral auxiliary-conjugated α-alkoxy ketone.

Table 1
Asymmetric nucleophilic 1,2-addition



Entry	Solvent	Temperature (°C)	Additive	Yield (%)	Ratio[a] (**4a**:**4b**)
1	THF	rt	None	93	2:1
2	THF	−78	None	98	3:1
3	Ether	−78	None	95	4:1
4	DME	−78	None	94	1:1
5	DCM	−78	None	97	7:1
6	DCM	−78	LiBr	90	5:1
7	DCM	−78	$LiOCl_4$	96	6:1
8	DCM	−78	Ph_2Zn	80	4:1
9	DCM	−78	$MgCl_2$	93	15:1
10	DCM	−78	$MgBr_2{\cdot}OEt_2$	95	51:1

[a] The ratio (*R*/*S*) was determined by HPLC analysis (Chiralcel OD column).



Scheme 3. Synthesis of (+)-flutriafol.

(TMSCl) and NaI.[9] At this stage, the enantiomeric purity of the **4a** was reconfirmed by analyzing diol **5** by chiral HPLC (Chiralcel OD column). When treating **4a** with ceric ammonium nitrate; however, racemization occurred extensively, providing the diol with low enantiomeric purity. As chiral diols are generally readily available from the corresponding alkenes by Sharpless asymmetric dihydroxylation, we also prepared this chiral diol **5** from alkene **8** by Sharpless asymmetric dihydroxylation.[10] However, the enantioselectivity is not high enough (69% ee) due to the structural similarity between the two substituents around the double bond. Thus, diol **5** with high enantiomeric purity is needed for the asymmetric synthesis of flutriafol. In this sense, the asymmetric nucleophilic 1,2-addition to an α-alkoxy ketone can provide an alternative way to chiral diols not easily accessible by the Sharpless asymmetric dihydroxylation method. Selective tosylation of diol **5** with *p*-toluenesulfonyl chloride (TsCl) followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded epoxide **7** in 76% yield over two steps. Finally, treatment of 1,2,4-triazole with *t*-BuOK followed by a ring opening reaction with epoxide **7** at 100 °C in *N*,*N*-dimethylformamide (DMF) provided (+)-flutriafol in 77% yield. Spectral analyses of the synthetic (+)-flutriafol were found to be identical with those of commercially available (±)-flutriafol. The observed optical rotation of synthetic flutriafol was $[\alpha]_D$ = +21.8 (*c* 0.2, $CHCl_3$), in 96% ee by chiral HPLC analysis.

3. Conclusion

In conclusion, we have shown that (+)-flutriafol can be prepared efficiently from our chiral auxiliary via chelation-controlled diastereoselective nucleophilic 1,2-addition and an epoxide ring opening reaction. A high degree of 1,4-asymmetric induction has been realized during the key alkylation step via the chelation-controlled mechanism. Our synthetic method offers an alternative way to chiral diols not easily accessible from the Sharpless asymmetric dihydroxylation.

4. Experimental

4.1. General

The melting points were obtained using Büchi 535 melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP 1000 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Inova 400 spectrometer and the chemical shifts are reported as values in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. The infrared spectra (IR) were recorded on a JASCO FT/IR-430 spectrophotometer. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel glass plates ($60F_{254}$). Column chromatography was performed using the forced flow of indicated solvent on Merck Kieselgel 60 (230–400 mesh). Chiral HPLC was performed using a Shimadzu LC-10AS pumping system and Shimadzu SPD-10A UV detector with a chiral column (Chiralcel OD, 0.46 cm (Φ) × 25 cm, Daicel Chemical Ind., Ltd). (±)-Flutriafol was purchased from Fluka. Unless otherwise noted, the materials were obtained from commercially available sources and were used without further purification. THF was freshly distilled from sodium benzophenone ketyl under an argon atmosphere. Benzene, DCM, DMF, triethylamine (TEA) and toluene were freshly distilled under a nitrogen atmosphere with calcium hydride.

4.2. 2-{[(*R*)-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl](4-methoxyphenyl)methyl]oxy}-1-(2-fluorophenyl) ethanol 2

A solution of alcohol **1** (273 mg, 1.15 mmol) in THF (3 mL) was added to a suspension of KH (651 mg, 35% in oil, 5.75 mmol) in THF (7 mL). After being stirred at 55 °C for 30 min, 2-(2-fluorophenyl)oxirane (285 mg, 2.60 mmol) and 18-crown-6 (10 mg) were added at 0 °C and the mixture was gradually heated to refluxing temperature for 3 h. The reaction mixture was quenched with aq NH_4Cl (10 mL) and diluted with ethyl acetate (30 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The resulting crude residue was purified by column chromatography on silica gel (17% ethyl acetate in hexane) to give the title compound **2** as an oil (227 mg, 53%); $[\alpha]_D^{23} = -61.2$ (*c* 0.16, $CHCl_3$); IR (NaCl, neat): cm^{-1} 3444, 3069, 2986, 2934, 1512, 1455, 1244; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.16–7.12 (m, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.06 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.88 (ddd, *J* = 10.8, 7.6, 1.2 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.12 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.30–4.20 (m, 1H), 4.12 (d, *J* = 8.0 Hz, 1H), 3.73 (s, 3H), 3.66 (ddd, *J* = 11.2, 3.2, 1.2 Hz, 1H), 3.59 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.48 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.22 (dd, *J* = 11.2, 9.6 Hz, 1H), 2.60–2.50 (br s, 1H), 1.42(s, 3H), 1.33(s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 159.69, 159.41, 131.64, 128.74, 128.60, 128.06, 127.59, 124.15, 114.90, 114.68, 113.99, 113.88, 110.15, 82.98, 80.25, 79.05, 72.33, 66.02, 55.24, 27.02, 25.45; LRMS (FAB) *m*/*z* (rel intensity) 133 (7), 163 (86), 180 (100), 221 (15), 399 [69, (M+Na)]; HRMS (FAB^+) calcd for $C_{21}H_{25}FO_5Na$ (M+Na) 399.1584, found 399.1581.

4.3. 2-{[(*R*)-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl](4-methoxyphenyl)methyl]oxy}-1-(2-fluorophenyl)ethan-1-one 3

TPAP (16 mg, 0.046 mmol) was added to a mixture of alcohol **2** (172 mg, 0.46 mmol) and NMO (107 mg, 0.92 mmol) in dichloromethane (9 mL). After being stirred for 1 h at room temperature, the reaction mixture was quenched by the addition of saturated aqueous sodium sulfite solution (1 mL). The resulting mixture was diluted with dichloromethane. The organic layer was washed successively with brine, aqueous copper sulfate solution, water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The resulting crude residue was purified by column chromatography on silica gel (17% ethyl acetate in hexane) to give the title compound **3** as a white solid (111 mg, 65%); mp: 66–68 °C; $[\alpha]_D^{24} = -68.6$ (*c* 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.43 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.15 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.99 (dd, *J* = 11.0, 7.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 4.59 (dd, *J* = 18.4, 3.2 Hz, 1H), 4.45 (d, *J* = 7.2 Hz, 1H), 4.38 (m, 1H), 4.06 (dd, *J* = 18.0, 3.2 Hz, 1H), 3.73 (s, 3H), 3.60 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.52 (dd, *J* = 8.4, 7.2 Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.37, 161.70, 159.67, 134.65, 130.43, 128.92 (2C), 128.76, 124.44, 116.38, 116.15, 113.90 (2C), 110.03, 83.12, 78.94, 73.92, 66.01, 55.18, 26.60, 25.62; IR (KBr) cm^{-1} 2985, 2932, 1699, 1610, 1512, 1247; LRMS (FAB) *m*/*z* (rel intensity) 397 [100, (M+Na)], 398 (18), 399 (5); HRMS (FAB^+) calcd for $C_{21}H_{23}FO_5Na$ (M+Na) 397.1427, found 397.1428.

4.4. 2-{[(*R*)-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl](4-methoxyphenyl)methyl]oxy}-(1*S*)-1-(2-fluorophenyl)-1-(4-fluorophenyl)ethanol 4a

A mixture of ketone **3** (78.3 mg, 0.21 mmol) and $MgBr_2{\cdot}OEt_2$ (216 mg, 0.84 mmol) in CH_2Cl_2 (5 mL) was sonicated in ultrasonic cleaning water bath (Bransonic® 1210R-DTH) for 10 min, and then cooled to −78 °C. To the reaction mixture was added dropwise 4-fluorophenylmagnesium bromide (418 μL, 1.0 M solution in THF, 0.42 mmol) via syringe. The whole was stirred at −78 °C for 2 h and allowed to warm to room temperature. The reaction mixture was quenched with aqueous $NaHCO_3$ (1 mL) and diluted with dichloromethane (30 mL). The organic layer was stirred with aqueous NH_4Cl (10 mL) for 10 min. The layers were separated, and the aqueous layer was extracted twice with dichloromethane (15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The resulting crude residue was purified by column chromatography on silica gel (15% ethyl acetate in hexane) to give the title compound **4a** as pale yellow oil (70 mg, 97%): major (**4a**): R_f = 0.39 (*n*-hexane–EtOAc = 3:1); $[\alpha]_D^{23} = -32.9$ (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.30 (dd, *J* = 8.8, 6.0 Hz, 2H), 7.19–7.05 (m, 4H), 6.90–6.78 (m, 5H), 4.22 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.2–4.1 (m, 3H), 3.75 (d, *J* = 10.0 Hz, 1H), 3.72 (s, 3H), 3.66 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.43 (dd, *J* = 8.8, 6.0 Hz, 1H), 1.31 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 162.83, 160.39, 158.21, 139.83, 131.43, 131.32, 129.54, 129.19, 129.11, 128.50, 128.16, 128.07, 123.96, 115.97, 115.74, 114.60, 114.40, 113.96, 109.98, 85.39, 79.09, 76.11, 74.37, 65.89, 55.20, 22.66, 25.51; IR (NaCl, neat) cm^{-1} 3446, 3032, 2986, 1512, 1490, 1448, 1243; LRMS (FAB+) *m*/*z* (rel intensity) 163 (15), 181 (18), 221 (14), 493 [100, (M+Na)]; HRMS (FAB^+) calcd for $C_{27}H_{28}F_2O_5Na$ (M+Na) 493.1803, found 493.1805; HPLC (Chiralcel OD column, eluent = 0.5% isopropanol in hexane, flow rate = 0.5 mL/min) t_R of major (*S*) = 43.9 min; t_R of minor (*R*) = 50.2 min (*S*:*R* = 51:1). Minor (**4b**): R_f = 0.37 (*n*-hexane–EtOAc = 3:1); $[\alpha]_D^{23} = -28.17$ (*c* 0.66, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (t, *J* = 8.0 Hz, 1H), 7.28 (dd, *J* = 8.8, 6.4 Hz, 2H), 7.19–7.14 (m, 1H), 7.07 (d, *J* = 6.4 Hz, 1H), 7.04 (d, *J* = 6.4 Hz, 2H), 6.87–6.82 (m, 3H), 6.76 (d, *J* = 8.0 Hz, 2H), 4.28 (br s, 1H), 4.17–4.13 (m, 3H), 3.72–3.70 (m, 4H), 3.58–3.53 (m, 1H), 3.49–3.44 (m, 1H), 1.36 (s, 3H), 1.26 (s, 3H).

4.5. (*S*)-1-(2-Fluorophenyl)-1-(4-fluorophenyl)ethane-1,2-diol 5

Tin(II) chloride (1.9 mg, 0.01 mmol), chlorotrimethylsilane (37.8 μL, 0.30 mmol), and sodium iodide (44.7 mg, 0.30 mmol) were sequentially added to a stirred solution of **4a** (46.7 mg, 0.10 mmol) in acetonitrile (3 mL) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate solution (1 mL). The resulting mixture was diluted with ethyl acetate (30 mL). The organic layer was washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The resulting crude residue was purified by column chromatography on silica gel (17% ethyl acetate in hexane) to give the title compound **5** as a white solid (18.7 mg, 75%); mp: 66–67 °C; $[\alpha]_D^{22} = -25.6$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.30–7.10 (m, 3H), 7.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.97–6.80 (m, 3H), 4.18 (d, *J* = 11.2 Hz, 1H), 4.04 (d, *J* = 11.2Hz, 1H), 3.37 (br s, 1H), 2.09 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 163.20, 160.75, 138.97, 129.74, 129.69, 128.70, 127.71, 124.26, 116.37, 116.14, 115.15, 114.94, 68.52, 68.48; IR (KBr pellet, cm^{-1}): 3425, 2955, 2925,1604, 1486, 1225, 1160; HPLC (Chiralcel OD column) eluent = 5% isopropanol in hexane, flow rate = 0.5 mL/min; detection 254 nm light, t_R of (*S*)-major 38.6 min; t_R of (*R*)-minor 34.9 min (*S*:*R* = 51:1); MS (FAB^+) *m*/*z* (rel intensity) 227 (75), 233 (50), 260 (100), 273 [14, (M+Na)]; HRMS (FAB^+) calcd for $C_{14}H_{12}F_2O_2Na$ (M+Na) 273.0703, found 273.0696.

4.6. (*S*)-Toluene-4-sulfonic acid 2-(4-fluorophenyl)-2-(2-fluorophenyl)-2-hydroxy ethyl ester 6

To a solution of the diol **5** (29.5 mg, 0.12 mmol, 96% ee) in dichloromethane (3 mL) was added triethylamine (41 μL, 0.30 mmol) followed by 4-dimethylaminopyridine (2 mg). The solution was cooled to 0 °C and *p*-toluenesulfonyl chloride (33.7 mg, 0.12 mmol) was added, and then the mixture was allowed to warm to room temperature. After being stirred for 24 h, the reaction mixture was diluted with dichloromethane (30 mL). The organic layer was washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The resulting crude residue was purified by column chromatography on silica gel (12% ethyl acetate in hexane) to give the title compound **6** as a white solid (46.7 mg, 98%); mp: 134–135 °C; $[\alpha]_D$ = − 26.7 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.55 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.26–7.19 (m, 5H), 7.10 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.91–6.84 (m, 3H), 4.57 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.52 (d, *J* = 10.0 Hz, 1H), 3.13 (d, *J* = 2.4 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.51, 158.07, 145.05, 137.13, 132.07, 130.08, 129.99, 129.80 (2C), 128.13, 127.94, 127.88 (2C), 124.38, 116.26, 116.04, 115.18, 114.97, 75.53, 73.90, 21.71; IR (KBr pellet, cm^{-1}): 3530, 3434, 3069, 2932, 1373, 1164; LRMS (FAB+) (rel intensity) 233 (39), 264 (21), 427 [34, (M+Na)], 460 (100); HRMS (FAB^+) calcd for $C_{21}H_{18}F_2O_4SNa$ (M+Na) 427.0792, found 427.0796.

4.7. (*S*)-2-(2-Fluorophenyl)-2-(4-fluorophenyl)oxirane 7

To a solution of the tosylate **6** (35.7 mg, 0.10 mmol) in tetrahydrofuran (3 mL) was added 1,8-diazabicyclo[5,4,0]undec-7-ene (36.2 μL, 0.24 mmol). After the resulting mixture was stirred for 30 min at room temperature, the reaction mixture was diluted with ethyl acetate (30 mL). The organic layer was washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The resulting crude residue was purified by column chromatography on silica gel (3% ethyl acetate in hexane) to give the title compound **7** as a white solid (14.7 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.31–7.25 (m, 1H), 7.19–7.16 (m, 2H), 7.10 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.04–6.99 (m, 1H), 6.94–6.88 (m, 2H), 3.24 (dd, J = 5.2, 0.8 Hz, 1H), 3.13 (d, J = 5.2 Hz, 1H); IR (NaCl neat, cm^{-1}) 3050, 2986, 1606, 1509, 1453, 1220, 1159.

4.8. (*S*)-(+)-Flutriafol

To a solution of 1,2,4-triazole (8.3 mg, 0.12 mmol) in dimethylformamide (3 mL) was added potassium *tert*-butoxide (128.5 mg, 0.12 mmol). The reaction mixture was heated to 50 °C for 30 min, and then cooled to room temperature. The epoxide **7** (25.5 mg, 0.11 mmol) was then added and the mixture stirred for 24 h at 100 °C. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate (15 mL) and water (15 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were washed with brine. The solution was dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified over silica gel (50% ethyl acetate in hexane) to yield (+)-flutriafol as a syrup (24.7 mg, 77%); $[\alpha]_D^{23} = +21.8$ (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.69 (s, 1H), 7.56 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 7.35 (m, 2H), 7.16 (m, 1H), 7.02 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.97–6.89 (m, 3H), 5.36 (bs, 1H), 5.14 (dd, J = 14.0, 0.8 Hz, 1H), 4.72 (dd, J = 14.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 163.37, 160.91, 159.68, 157.27, 137.83, 130.09, 128.71, 127.71, 127.63, 124.72, 115.94, 115.70, 115.37, 115.16, 57.47, 57.41; IR (KBr pellet, cm^{-1}) 3423, 2925, 1604, 1509, 1483, 1226, 1162; HPLC (Chiralcel AD-H column) eluent = 7% isopropanol in hexane, flow rate = 0.5 mL/min; detection 254 nm light, t_R of (*S*)-major 29.5 min; t_R of (*R*)-minor 31.9 min (*S*:*R* = 51:1); LRMS (FAB$^+$) m/z (rel intensity) 233 (54), 302 [100, (M+H)]; HRMS (FAB+) calcd for $C_{16}H_{14}F_2N_3O$ (M+H) 302.1105, found 302.1106.

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