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

Keiji Tamura,† Naoya Kumagai,*† and Masakatsu Shibasaki*†‡

†Institute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan
‡ACT-C, Japan Science and Technology Agency (JST), 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan
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 eficonaonazole (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 but also low-risk pathological conditions such as nail infections. 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. The representative triazole antifungal agent fluconazole (Figure 1), which was developed by Pfizer, is effective orally against a range of fungal infections. 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. To address these issues, an advanced triazole antifungal agent, voriconazole (Vfend), was developed. 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. Therefore, voriconazole is a primary drug in the first-line treatment of invasive aspergillosis, as either an intravenous or oral formulation. The high potency of voriconazole has inspired extensive efforts devoted to the development of a variety of synthetic derivatives.

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, 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. Almost all of the synthetic routes rely on the use of D- or L-lactic acid as a chiral pool. In particular, Bristol-Myers Squibb has developed an excellent approach toward epoxide 1 in six steps in 25% overall yield, leading to the...
scalable synthesis of ravuconazole. Although other approaches utilizing Sharpless asymmetric epoxidation or enzymatic resolution 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.

Herein we report a new route, the shortest reported to date, to access epoxide in four steps from commercially available ketone in 29% yield. The key step features the catalytic asymmetric cyanosilylation to construct the tetrasubstituted stereogenic center (Scheme 2). A putative Gd-based polymetallic catalyst composed of Gd and the sugar-derived chiral ligand in a 2:3 ratio, as suggested by ESI-MS analysis in the presence of TMSCN, was generated by mixing Gd(HMDS) and 4 in a 2:3 ratio at −30 °C. The polymetallic catalyst (2 mol% based on Gd) promoted the significant antifungal agents ravuconazole and efinaconazole (Jublia) and efinaconazole (Jublia). 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-methyleneepiperidine moiety and has recently received approval in Canada, is the first external-use antifungal agent for the treatment of onychomycosis.

Our synthesis commenced with the catalytic asymmetric cyanosilylation of ketone in four steps from commercially available ketone 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 and efinaconazole (Jublia). 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-methyleneepiperidine moiety and has recently received approval in Canada, is the first external-use antifungal agent for the treatment of onychomycosis.

Our synthesis commenced with the catalytic asymmetric cyanosilylation of ketone in four steps from commercially available ketone 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
catalytic asymmetric cyanosilylation of 2 with TMSCN at $-30^\circ$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 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. 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 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 $^\circ$C was submitted to rapid nucleation with stirring at $-20^\circ$C, a nearly racemic solid (6.3% ee) appeared, and the filtrate was enriched to 97% ee.

The second cycle of an identical procedure (but with stirring at 0 $^\circ$C) afforded the enantiopure diol 10 (>99% ee) in 74% recovery yield after two cycles. With the optically pure diol 10 in hand, we examined its transformation to epoxide 1. Regioselective mesylation of diol 10 proceeded smoothly at 0 $^\circ$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 efnaconazole (Scheme 3). According to the literature procedure, epoxide 1 was subjected to a ring-opening reaction with 4-methylenepiperidine at 80 $^\circ$C. However, 51% of epoxide 1 remained unchanged after 24 h, and efnaconazole was isolated in 44% yield. Microwave irradiation at 120 $^\circ$C solved this problem, affording efnaconazole in 90% yield. The spectroscopic data of the synthesized sample were identical to those of the reported one. Moreover, we also demonstrated the synthesis of ravuconazole according to the literature procedure (Scheme 4). Ring opening of epoxide 1 using Et$_3$AlCN 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.
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), 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 NMR 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 (CDCl₃, 7.26 ppm) as an external reference. For ¹³C NMR, chemical shifts are reported on the scale relative to the NMR solvent (CDCl₃, 77.0 ppm) as an internal reference. For ¹⁹F NMR, chemical shifts are reported on the scale relative to trifluoroacetic acid (7.65 ppm) as an external reference. NMR data are reported as follows: chemical shifts (multiplicity, coupling constant in Hz, number of protons); 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, 123151-94-7, 126918-35-2, 133775-25-4, 861718-83-4, 861718-85-6, 832151-94-7, 103981-14-4, respectively).

(2R,3S)-4-Chloro-2-(2,4-difluorophenyl)-3-((trimethylsilyl)oxy)butan-2-ol (7). To a solution of (2R,3S)-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 NH₄Cl, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over MgSO₄, 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 (85% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 158.6 (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 = 13.8, 11.3 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; ¹⁹F NMR (376 MHz, CDCl₃) δ −109.7, −111.3; IR (CHCl₃, cm⁻¹) ν 3545, 2959, 1619, 1503, 1422, 1524; HRMS (ESI-TOF) calcd for C₁₂H₁₄O₂F₂Na [M + Na]⁺ m/z 331.0703, found 331.0702.

(25S,R)-1-Chloro-2-(2,4-difluorophenyl)butan-2,3-diol (8). To a solution of (2R,3S)-6 (317 mg, 1.013 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 NH₄Cl, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified using preparative TLC (CHCl₃/MeOH = 10:1) to give 18.3 mg of 8 (75% yield) as a colorless crystal. Mp 86–88 °C; ¹H NMR (400 MHz, CDCl₃) 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), ¹³C NMR (100 MHz, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) δ −109.2, −110.7; IR (CHCl₃, cm⁻¹) ν 3433, 3266, 2979, 1617, 1500, 1272; HRMS (ESI-TOF) calcd for C₁₃H₁₂O₂F₂SiNa [M + Na]⁺ m/z 359.0308, found 359.0310.

(2R,3S)-1-Chloro-2-(2,4-difluorophenyl)oxiran-2-yl)ethanol (9). To a solution of (2R,3S)-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 NH₄Cl, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified using preparative TLC (CHCl₃/MeOH = 15:1)
to give 7.4 mg of 9 (34% yield) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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 (dd, $J$ = 5.3, 1.3 Hz, 1H), 2.78 (dd, $J$ = 5.3, 0.5 Hz, 1H), 1.14 (dd, $J$ = 6.6, 1.1 Hz, 3H); $^1$C NMR (100 MHz, CDCl$_3$) $\delta$ 162.8 (dd, $J$ = 249, 13 Hz), 160.4 (dd, $J$ = 249, 12 Hz), 130.6 (dd, $J$ = 10.2, 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$_3$) $\delta$ −109.6, −111.4; IR (CHCl$_3$, cm$^{-1}$) 3424, 3190, 2930, 2898, 2810, 1615, 1498, 1418, 1273, 1138; HRMS (ESI-TOF) calc for C$_7$H$_8$F$_2$O$_2$Na [M + Na]$^+$ m/z 223.0543, found 223.0543.

(2R,3R)-2-(2,4-Difluorophenyl)-1-(1H,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. Tetrabutylammonium bromide (2.40 g, 7.44 mmol) were added. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with H$_2$O, 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 2.34 mg of 10 (65% yield, single isomer) as a colorless solid. A 467 mg sample of 10 (enantimeric 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 (enantimeric excess 62%). The filtrate was concentrated under reduced pressure and dried in vacuo to give 376 mg of 10 (enantimetric excess 97%). Next, 357 mg of 10 (enantimetric excess: 97%) was taken up with MeCN (563 mL) 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 434 mg of 10 (74% recovery yield after two cycles, enantiomeric excess >99%) as a colorless crystal. Mp for enantiopure diol 10 (enantimetric excess >99%), 114–117 °C; mp for racemic diol 10 (enantimetric excess 1.6%), 159–160 °C; [α]$_D^{20}$ = −71.0 (c 1.06, MeOH); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); $^1$C NMR (150 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ −109.4, −110.0; IR (CHCl$_3$, cm$^{-1}$) v 3434, 3134, 2974, 2360, 1619, 1503, 1421, 1273, 1134; HRMS (ESI-TOF) calc for C$_9$H$_8$F$_2$ON$_2$F$_2$ [M + H]$^+$ m/z 270.1049, found 270.1046. The enantiomeric excess of 10 was determined by chiral HPLC analysis (DAICEL, CHIRAL-PK 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$_S$ = 18.4 min [ent-10]).

1-(((2R,3R)-2-(2,4-Difluorophenyl)-3-methyloxiran-2-yl)-methyl)-1H-1,2,4-triazole (1). To a solution of 10 (1.97 g, 7.32 mmol) in THF (37 mL) were added Et$_3$N (4.50 mL, 32.2 mmol) and MeCl$_2$ (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$_4$Cl was added, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed three times with H$_2$O, 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 1.51 mg of 10 (86% yield) as a pale-yellow solid. Mp 91–92 °C; [α]$_D^{20}$ = −7.5 (c 1.06, MeOH); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.79 (s, 1H), 7.78 (s, 1H), 7.06–6.95 (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); $^1$C NMR (100 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ −108.5, −112.6; IR (CHCl$_3$, cm$^{-1}$) ν 3131, 3096, 3084, 3003, 2969, 1618, 1508, 1424, 1269, 1137; HRMS (ESI-TOF) calc for C$_8$H$_6$F$_2$ON$_2$ [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, t$_S$ = 12.6 min [ent-1]).
extracted twice with EtOAc. The combined organic layers were washed three times with H2O, dried over MgSO4, filtered, and concentrated under reduced pressure. The resulting residue was purified using silica gel column chromatography (CHCl3/MeOH = 10:1) to give 164 mg of I3 (97% yield) as a colorless amorphous solid. [α]D23 +137.9 (c 1.08, MeOH); 1H NMR (400 MHz, CDCl3) 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), 1.67~6.69 (m, 2H), 5.75 (s, 1H), 5.06 (d, J = 14.2 Hz, 1H), 4.52 (d, J = 14.2 Hz, 1H), 3.70 (d, J = 7.0 Hz, 1H), 1.08 (d, J = 7.0 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 210.2, 152.6, 151.5, 143.8, 137.9, 132.7, 127.3, 113.9; HRMS (ESI-TOF) calcd for C12H10NO3F2S [M + H]+ m/z 348.1195, found 348.1192.

■ ASSOCIATED CONTENT

S Supporting Information
1H and 13C 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.

■ AUTHOR INFORMATION

Corresponding Authors
E-mail: nkumagai@bikaken.or.jp.
E-mail: mshibasa@bikaken.or.jp.

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by JST, ACT-C, and KAKENHI (25713002). Dr. Ryuchi Sawa and Ms. Yumiko Kubota are gratefully acknowledged for technical assistance with the NMR analysis.

■ REFERENCES


(22) Compound 7 was claimed in WO2005007658. However, no spectroscopic data were reported.

(23) The reaction with MeLi (LiBr complex) in THF (−78 °C, 10 min) afforded 7 in 32% yield with dr = 73:27. The use of MeMgBr with ZnI2 (−78 °C, 30 min) afforded 6 in 31% yield with dr = 69:31.


(25) The melting points of racemic 10 and enantiopure 10 were 159 and 114 °C, respectively. This might be due to strong intermolecular interactions in the heteroconium mixture of 10 through hydrogen bonding.
