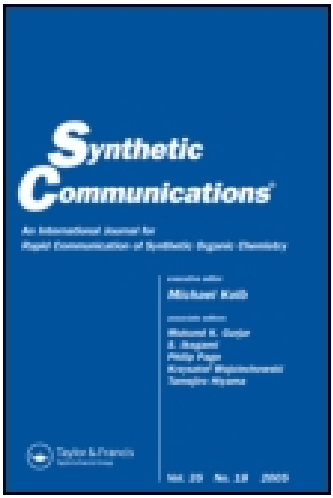


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Improved Chiral Synthesis of Ravuconazole

Lin Xu [a b], Marc R. Muller [c], Xiong Yu [b] & Bao-Quan Zhu [b]

[a] Basilea Pharmaceutica China Ltd., Haimen, Jiangsu, China

[b] Shanghai Institute of Pharmaceutical Industry, Shanghai, China

[c] Basilea Pharmaceutica International AG, Basel, Switzerland

Published online: 02 Apr 2009.

To cite this article: Lin Xu, Marc R. Muller, Xiong Yu & Bao-Quan Zhu (2009) Improved Chiral Synthesis of Ravuconazole, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:9, 1611-1625, DOI: 10.1080/00397910802563420

To link to this article: http://dx.doi.org/10.1080/00397910802563420

Synthetic Communications®, 39: 1611–1625, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802563420

Taylor & Francis
Taylor & Francis Group

Improved Chiral Synthesis of Ravuconazole

Lin Xu,[1,2] Marc R. Muller,[3] Xiong Yu,[2] and Bao-Quan Zhu[2]
[1]Basilea Pharmaceutica China Ltd., Haimen, Jiangsu, China
[2]Shanghai Institute of Pharmaceutical Industry, Shanghai, China
[3]Basilea Pharmaceutica International AG, Basel, Switzerland

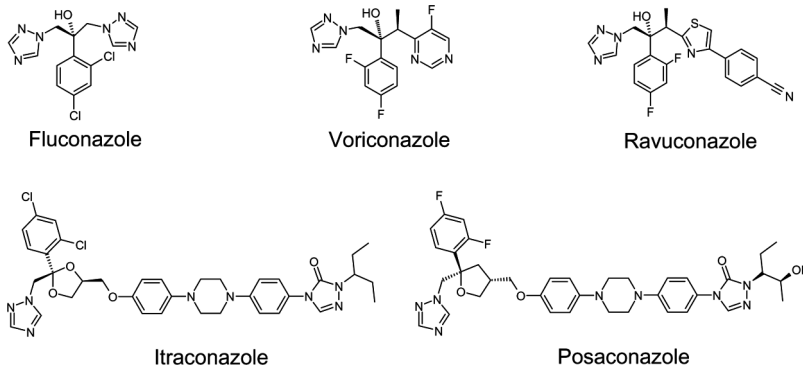
Abstract: A short, elegant, and high yielding synthesis of ravoconazole is presented. The key step of this synthesis is an enantioselective palladium-catalyzed chiral zinc-allene addition reaction. The starting materials are 2-chloro-1-(2, 4-difluorophenyl)-ethanone and (R)-4-phenylbutyn-2-ol obtained from enzymatic resolution of its racemate.

Keywords: Azoles, enantioselective addition reaction, enzymatic resolution, Pd catalysis, propargylic alcohol, zinc-allene derivative

INTRODUCTION

The first azole with antifungal activity was reported in 1944, and the first azole made available for clinical use in 1958 was chlormidazole.[1] Currently, the azoles are the most widely used and studied class of antifungal agent. Fluconazole, itraconazole, voriconazole, and posaconazole are the most prominent marketed representatives. Ravuconazole is a new molecule in this class and is currently in phase II clinical trials. This compound is a particular challenge for every organic chemist: it contains two contiguous chiral centers, one being quaternary and the other tertiary.

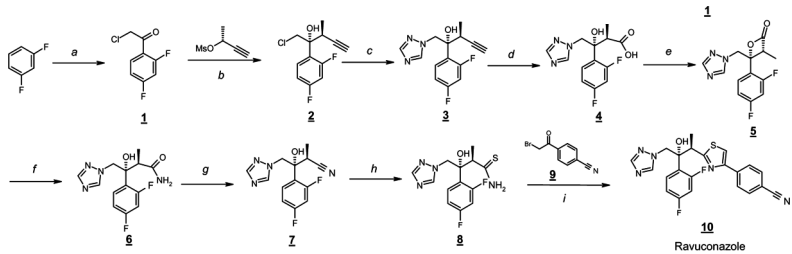
Received September 8, 2008.
Address correspondence to Marc R. Muller, Core Chemistry, Basilea Pharmaceutica International AG, Grenzacherstrasse 487, Postfach, CH 4005 Basel, Switzerland. E-mail: marc.muller@basilea.com



RESULTS AND DISCUSSION

The medicinal interest and the synthetic challenge prompted various approaches to this type of molecule or advanced intermediates thereof.[2–6] In this context, M. Soukup from Hoffmann-La Roche developed also a new convergent synthesis of ravuconazole.[7] The key step of this synthesis is based on a chiral allene addition reaction catalyzed by palladium, where a zinc–allene derivative generated from a chiral propargylic mesylate is reacted with a benzophenone derivative (Scheme 1).

Tamaru et al.[8] described the formation of allylic zinc derivatives obtained after transmetallation starting from the palladium (π-allyl species. These allylic zinc species react nicely with carbonyl or thiocarbonyl partners to form adducts with high diastereoselectivity. Later,

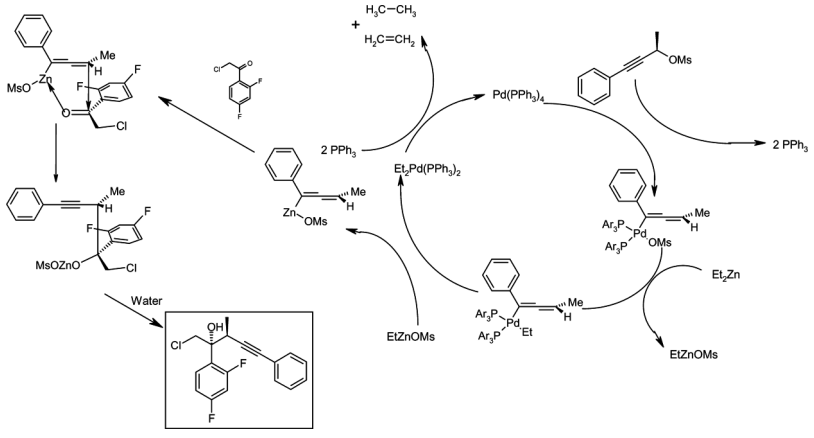


Scheme 1. (a) Chloroacetyl chloride, $AlCl_3$, 80%; (b) $PdCl_2(CH_3CN)_2$, Et_2Zn, 3 equivalents, THF/toluene, rT, 77%; 90% ee; (c) triazole, NaOH/DMSO, 40%; (d) $NaIO_4$, Ru_2O, acetic acid, 88%; (e) carbonyl diimidazole, 74%; (f) aqueous ammonia, quant. (g) $POCl_3$, 74%; (h) $(EtO)_2PSSH$, 78%; (i) 86%.

Marshall, Adams, and Wallace[9–10] adapted this approach to propargylic mesylates. Indeed, their treatment with diethyl zinc produces the zinc–allene derivative via the palladium allene complex (Scheme 2). These zinc–allene derivatives react readily and in a diastereoselective fashion with carbonyl partners (anti/syn ratio ranging from 95:5 to 68:32), and when chiral propargylic mesylates are used, ee values up to 95% for the main diastereoisomer are observed.

Proposed Reaction Mechanism of the Allene Addition

For the Soukup synthesis of ravuconazole, 2-chloro-1-(2,4-difluoro-phenyl)-ethanone **1** was reacted with the allene derivative obtained by the treatment of methanesulfonic acid 1-methyl-prop-2-ynyl ester with diethyl zinc in presence of palladium(II) catalyst. The adduct **2** was obtained in a diastereoselective and enantioselective manner. The anti syn ratio was about 70:30, and the ee was 90%, which are in line with the Adams and Marshall publications. This primary adduct **2** was then reacted with triazole to give the stable compound **3**. Oxidative cleavage of the triple bond[11] using sodium periodate in presence of catalytic amounts of ruthenium dioxide gave the acid **4**. The cyano-derivative **7** was obtained via activation of the acid **4** as the β-lactone **5**, followed by ammonia addition to **6** and then dehydration. The thioamide **8** was obtained in classical fashion and was then submitted to a Hantzsch reaction with the bromo acetophenone **9** to give ravuconazole **10** in an 8% overall yield in high purity.



Scheme 2.

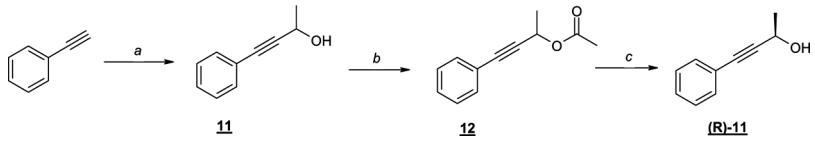
The beauty of this synthesis is the simultaneous construction of the two contiguous chiral centers, one being quaternary and the other tertiary, in a diastereoselective and enantioselective manner.

The scarce availability of the chiral (R)-2-butynol in large quantities and its price are nevertheless problematic. It can be obtained by chiral reduction of butynone, a compound that is prone to polymerize very easily and therefore is delicate to handle. The enzymatic resolution of a racemic 2-butynol ester despite extensive efforts was not successful. The reason for this failure is that the triple bond has to be substituted by a bulky group (for instance, trimethylsilyl) to get a good enzymatic resolution.

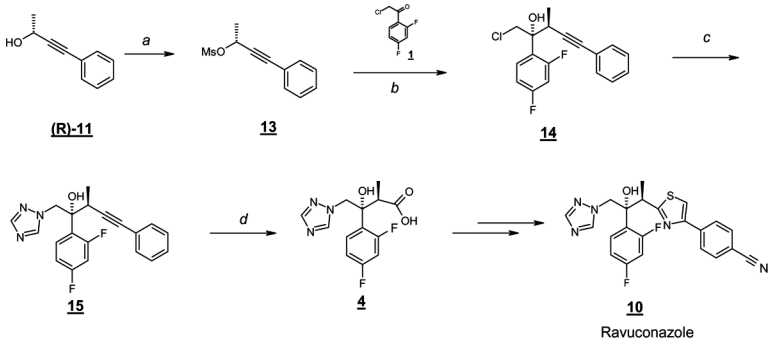
This prompted us to use easily accessible racemic 4-phenyl-3-butyn-2-ol **11** as starting material in our synthesis. This compound **11** was synthesized from phenyl-acetylene and acetaldehyde. The chiral resolution was performed via enzymatic esterification using the lipase AK. After transesterification with vinyl acetate catalyzed by lipase AK, the formed chiral ester (***R*)-11** was isolated and subsequently hydrolyzed. The ee of the obtained (*R*)-4-phenyl-3-butyn-2-ol (***R*)-11** was up to 96% (Scheme 3), and the overall yield starting from phenyl-acetylene was 35%.

(*R*)-4-Phenyl-3-butyn-2-ol (***R*)-11** was easily converted to the corresponding mesylate **13**. Based on the proposed mechanism (see Scheme 2), we did not anticipate that the presence of the phenyl group in the 4-position would have a negative impact on the allene addition reaction because no steric interactions were expected from this extra phenyl group in the transition state. Indeed, the reaction proceeded smoothly, and the yield and enantioselectivity of the reaction were in the same range as those of unsubstituted butynol. Merely the diastereoselectivity (determined by NMR to be 16:1) seemed better.

As expected, the chloro-alcohol **14** was not very stable and therefore converted directly to the triazole derivative **15**, which was purified by chromatography to afford the desired compound with an ee of 93%. Simple recrystallization in ethanol improves the optical purity of compound 15



Scheme 3. (a) n-BuLi, CH_3CHO, 81%; (b) lipase AK, vinyl acetate, 47.8%; and (c) NaOH, 92%; 96% ee.



Scheme 4. (a) MsCl, Et_3N, 83%, 92% ee; (b) $PdCl_2$ $(CH_3CN)_2$, Et_3Zn, 3 equivalents, THF/toluene, Rt, 87%; 85% ee; (c) triazole, NaOH/DMSO, 72.5%; and (d) $NaIO_4$, Ru_2O, acetic acid, 71%.

up to 99%. Despite the higher steric congestion, the oxidative cleavage of the triple bond worked quite smoothly; interestingly about 30% of the corresponding tertiary benzoyl ester was obtained (Scheme 4). This ester could be converted to the acid **4** by simple hydrolysis under basic conditions. The overall yield of this step was 71%. This acid **4** was then converted to ravuconazole in the way previously described (Scheme 1).

CONCLUSIONS

4-Phenyl-3-butyn-2-ol proved to be a suitable starting material for the synthesis of ravuconazole. The overall yield of this eight-step synthesis was 12.5%. The purity of the obtained product is 99%, and the ee was more than 99.5%.

The chiral 4-phenyl-3-butyn-2-ol (***R*)-11** was obtained by enzymatic resolution in an easy and efficient fashion.

EXPERIMENTAL

General Methods

Starting materials and solvents were obtained from commercial suppliers and used without further purifications unless otherwise stated. Lipase AK was purchased from Amano Co.

NMR spectra were recorded on a Varian Mercury Plus 400. Chemical shifts are reported as δ ppm relative to tetramethylsilane (TMS) in $CDCl_3$ ($\delta = 0$), used as internal standard for ^1H NMR. For ^{13}C NMR spectra, the solvent peak of dimethyl sulfoxide (DMSO-d_6) ($\delta = 39.52$ ppm) is used as the internal standard. Mass spectral analysis (ESI-MS) were recorded on a Varian 1200 L Quadrupole. GC/MS were recorded Varian CP-3800 GC system fitted with a Varian Saturn 2200 mass selective detector (El, 70 ev) and a DB-17MS column (30 m × 250 μm). [T_{GC}(injector) = 250 °C, time program (oven): $T_{0min} = 80$ °C, $T_{1min} = 80$ °C, $T_{6min} = 250$ °C (20 °C, (min), $T_{15.5min} = 250$ °C]. Analytical high-performance liquid chromatography (HPLC) was performed on an Agilent 1100 series using Chiralcel OJ-H, Chiralcel OD-H, Chiralpak AS-H, and Chiralpak AD-H (each 4.6 × 250 mm, Daicel Chem. Ind.) as chiral columns. IR spectra were taken on a Shimadzu FTIR-8400S. Optical rotations were measured on a PE341 polarimeter. Melting points were measured on a Büchi B-540 melting-point apparatus and are uncorrected. Elemental analyses were performed on a CarloErba-1106.

Synthesis of 4-Phenyl-3-butyn-2-ol 11

Phenyl acetylene (89.6 mL, 817 mmol) was dissolved in dry ether (300 mL). The mixture was cooled to − 20 °C and a butyl lithium solution (509 mL, 1.6 M solution in hexane, 814 mmol) was added slowly. The reaction mixture was warmed to 0 °C, and acetaldehyde (40 g, 870 mmol) was added. The reaction was stirred at 0 °C for 2 h, then the mixture was quenched with a saturated aqueous ammonium chloride solution (120 mL). The mixture was extracted three times with ethyl acetate (3 × 200 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure to give 4-phenyl-3-butyn-2-ol **11** (100.2 g, 686 mmol, yield 83%) as light yellow liquid. IR (film): 3329, 1599, 1489, 1105, 756, 690 cm^{-1}. ^1H NMR (DMSO-d6) δ: 7.40–7.33 (m, 5H), 5.44 (d, $J = 5.2$ Hz, 1H), 4.57 (q, $J = 6.4$ Hz, 1H), 1.36 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (DMSO-d6) δ: 131.89, 129.34, 129.06, 123.20, 94.11, 82.80, 57.36, 25.29. GC/MS: $R_t = 6.34$ min: m/z (%) = 145 (94.4) [$M^+ - 1$].

Synthesis of (1*R*)-acetic Acid 1-Methyl-3-phenyl-prop-2-ynyl Ester 12

4-Phenyl-3-butyn-2-ol **11** (30 g, 187 mmol) was dissolved in hexane (600 mL). Vinyl acetate (52.8 mL, 561 mmol, 3.0 equiv.) and lipase AK

(0.5 mass equiv.) were added at room temperature, and the reaction mixture was stirred for 7 h. The solids were filtered off, and the solvent was evaporated. The residue was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate = 20:1) to give (1*R*)-acetic acid 1-methyl-3-phenyl-prop-2-ynyl ester **12** (17.9 g, 95 mmol, yield: 47.8%) as a light yellow liquid. Enantiomeric excess: 98.5% as determined by HPLC on a Chiralcel OD-H column (n-hexane/2-propanol, 98:2), R_t=5.32 min. $[\alpha]_D^{23} = 171.8°$ (c = 1, MeOH). IR (film): 2989, 1747, 1490, 1232, 758, 692 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.41–7.43 (m, 2 H), 7.26–7.28 (m, 3 H), 5.67 (q, J = 6.4 Hz, 1H), 2.06 (3H, s), 1.56 (d, J = 6.8 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ: 170.14, 132.08, 128.81, 21.73, 128.47, 122.49, 87.65, 84.78, 61.03, 29.92, 21.33. GC/MS: R_t = 7.44 min; min; m/z (%) = 188 (23.9) [M^+].

Synthesis of (*R*)-4-Phenyl-3-butyn-2-ol (*R*)-11

(1*R*)-Acetic acid 1-methyl-3-phenyl-prop-2-ynyl ester **12** (17.8 g, 88.8 mmol) was dissolved in a potassium hydroxide solution in (6.37 g, 113 mmol) in methanol (100 mL) at −10 °C. The reaction mixture was stirred at 0 °C for 1 h, and then water (30 mL) was added. The mixture was extracted with methylene chloride (100 mL × 3). The combined organic phases were washed with brine and dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure to give (*R*)-4-phenyl-3-butyn-2-ol (***R*)-11** (12.4 g, 84.4 mmol, yield 95.0%) as a light yellow liquid. The enantiomeric excess was determined to be 94.0% by HPLC on Chiralpak OD-H (n-hexane/2-propanol, 95:5).

R_t=13.32 min. $[\alpha]_D^{23} = 31.9°$ (c = 1, MeOH). IR (film): 3329, 1599, 1490, 1103, 756, 690 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 7.33–7.40 (m, 5 H), 5.44 (s, 1 H), 4.57 (q, J = 6.4 Hz, 1H), 1.36 (d, J = 6.4 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ: 131.89, 129.34, 129.06, 123.20, 94.11, 82.80, 57.36, 25.29. GC/MS: R_t = 6.29 min; m/z (%) = 145 (68.2) [$M^+ - 1$].

Methanesulfonic Acid 1(*R*)-Methyl-3-phenyl-prop-2-ynyl Ester 13

(*R*)-4-Phenyl-3-butyn-2-ol (***R*)-11** (3.00 g, 20.2 mmol) and triethylamine (5.76 mL, 40.4 mmol) were dissolved in dichloromethane (30 mL) at − 78 °C. Mesylchloride (2.40 mL, 30.4 mmol) was added slowly. The reaction mixture was stirred at − 78 °C for 1 h and then warmed to room temperature slowly. The mixture was quenched with saturated aqueous sodium bicarbonate solution (50 mL). The organic phase was separated,

and the aqueous layer was extracted with methylene chloride (30 mL × 3). The combined organic phases were washed with water and dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure to give methanesulfonic acid 1(*R*)-methyl-3-phenyl-prop-2-ynyl ester **13** (4.23 g, 84.4 mmol, yield: 89.3%) as a light brown liquid. Enantiomeric excess was 91.5% as determined by HPLC on Chiralpak AS-H column (n-hexane/2-propanol, 95:5); R_t=19.01 min. min. IR (film): 2939, 2233, 1490, 1175, 760, 692 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 7.39–7.48 (m, 5H), 5.62 (q, J = 6.6 Hz, 1 H), 3.28 (s, 3 H), 1.64 (d, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ: 132.25, 130.12, 129.43, 121.55, 87.28, 87.01, 68.83, 39.04, 23.17.

Synthesis of (2*R*,3*S*)-1-chloro-2-(2,4-difluorophenyl)-3-methyl-5-phenyl-pent-4-yn-2-ol 14

Bis-acetonitrile palladium chloride (0.27 g, 1.03 mmol) and triphenylphosphine (0.67 g, 2.57 mmol) were suspended in THF (80 mL). The mixture was stirred at 20 °C for 1 h. Methanesulfonic acid 1(*R*)-methyl-3-phenyl-prop-2-ynyl ester **13** (10.4 g, 46.3 mmol) and 2-chloro-1-(2,4-difluorophenyl)-ethanone (5.0 g, 25.7 mmol) in THF (50 mL) were added in sequence. A diethyl zinc solution in toluene (70.1 mL, 1.1 M, 77.1 mmol) was added slowly to the reaction mixture, and the temperature of the reaction mixture was kept between 35 °C and 38 °C. After 40 min, the mixture was quenched with cold brine (50 mL). Ethyl acetate (25 mL) and concentrated hydrochloric acid (10 mL) were added. The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (50 ml × 3). The combined organic phases were washed with a saturated aqueous sodium bicarbonate solution (30 mL × 3) and water (30 mL) and dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure to give the crude product, which was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate = 25:1) to give (2*R*,3*S*)-1-chloro-2-(2,4-difluorophenyl)-3-methyl-5-phenyl-pent-4-yn-2-ol **14** (6.48 g, 20.2 mmol, yield 78.6%). White solid, melting point: 62.8 to 63.8 °C. Enantiomeric excess: 85.0% as determined by HPLC on Chiralcel OD-H column (n-hexane/2-propanol, 99.5:0.5, R_t=14.46 min. $[\alpha]_D^{20} = 35.3°$ (c = 1, MeOH). IR (KBr): 1616, 1500, 1138, 756, 690 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 7.64–7.71 (m, 1H), 7.42–7.44 (m, 2 H), 7.33–7.35 (m, 3 H), 7.17–7.23 (m, 1 H), 7.09–7.13 (m, 1 H), 6.01 (s, 1 H), 4.30 (d, J = 12 Hz, 1H), 4.17 (d, J = 12 Hz, 1H), 3.23 (q, J = 6.8 Hz, 1H), 0.98 (d, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ: 162.47 (dd, $^1J_{CF}$ = 244 Hz, $^3J_{CF}$ = 12.1 Hz), 158.91 (dd, $^1J_{CF}$ = 245 Hz, $^3J_{CF}$ = 12.1 Hz), 132.33, 132.09, 129.20, 128.87,

125.89, 123.56, 111.66 (d, $^2J_{CF} = 21.3$ Hz), 104.62 (t, $^2J_{CF} = 26$ Hz), 90.99, 83.66, 77.20 (d, $^3J_{CF} = 5$ Hz), 52.61, 35.78, 16.70. M/S (ESI) (real intensity) m/z 321. Anal. calcd. for $C_{18}H_{15}ClF_2O$: C, 67.40; H, 4.71; Cl, 11.05; F,11.85. Found: C, 67.50; H, 4.55; Cl, 11.01; F, 11.90.

Synthesis of (2*R*,3*S*)-2-(2,4-difluoro-phenyl)-3-methyl-5-phenyl-1-[1,2,4]-triazol-1-yl-pent-4-yn-2-ol 15

1,2,4-Triazole (6.65 g, 96.3 mmol) and sodium hydroxide (3.85 g, 96.3 mmol) were dissolved in DMSO (25 mL). The mixture was heated at 70 °C for 30 min and then cooled to room temperature. Compound **14** (15.0 g, 30.4 mmol) dissolved in DMSO (5 mL) was added slowly over a period of 20 min. The resulting solution was stirred at 70 °C for 3 h. After cooling to room temperature, the reaction mixture was quenched with water (100 mL) and extracted with toluene (50 mL × 4). The combined organic phases were washed with an aqueous 2 N HCl solution (25 mL) and water (25 mL) and dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure; the residue was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate = 5:1) to give (2*R*,3*S*)-2-(2,4-difluoro-phenyl)-3-methyl-5-phenyl-1-[1,2,4] triazol-1-yl-pent-4-yn-2-ol **15** (8.2 g, 22.0 mmol, yield 72.5%). White solid, melting point: 111.2 to 112.2 °C. Enantiomeric excess over 99.5% as determined by HPLC on Chiralpak OD-H column (n-hexane/2-propanol, 90:10, $R_t = 20.76$ min. $[\alpha]_D^{20} = 25.1°$ (c = 1, MeOH). IR (KBr): 1499, 1420, 1138, 758 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 8.34 (s, 1 H), 7.66 (s, 1 H), 7.64–7.71 (m, 1 H), 7.42–7.44 (m, 2 H), 7.33–7.35 (m, 3 H), 7.13–7.17 (m, 1 H), 6.90-6.94 (m, 1 H), 5.97 (s, 1 H), 4.30 (d, $J = 12$ Hz, 1 H), 4.86 (d, $J = 12$ Hz, 2 H), 3.43 (q, $J = 6.8$ Hz, 1 H), 0.99 (d, $J = 6.8$ Hz, 3 H). ^{13}C NMR (DMSO-d_6) δ: 162.55 (dd, $^1J_{CF} = 246$ Hz, $^3J_{CF} = 12.1$ Hz), 159.27 (dd, $^1J_{CF} = 246$ Hz, $^3J_{CF} =$ 12.1Hz), 151.12, 145.45, 132.21, 131.31 (m), 129.19, 128.90, 124.86 (d, $^2J_{CF} = 12.0$ Hz), 123.64, 111.49 (d, $^2J_{CF} = 21.3$ Hz), 104.56 (t, $^2J_{CF} =$ 27.3 Hz), 91.06, 84.05, 76.62 (d, $^3J_{CF} = 4.6$ Hz), 56.99, 34.72, 16.28. MS(ESI) m/z (real intensity) 354. Anal. calcd. for $C_{20}H_{17}F_2N_3O$: C, 67.98; H, 4.85; F, 10.75; N, 11.89. Found: C, 67.86; H, 4.84; F, 10.86; N, 11.84.

Synthesis of (2*R*,3*R*)-3-(2,4-difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]-triazol-1-yl-butyric Acid 4

Ruthenium (IV) oxide hydrate (0.188 mmol) and sodium periodate (9.68 g, 45.3 mmol) were dissolved in water (160 mL). After addition of

adogene 464 (0.2 mL), compound **15** (4.00 g, 11.3 mmol) dissolved in acetic acid (100 ml) and water (20 ml) was added slowly at 5° to 10 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. After addition of 2-propanol (25 mL), the reaction mixture was stirred for an additional 30 min at room temperature. Then the pH of the reaction mixture was adjusted to pH4 by the addition of aqueous sodium hydroxide solution (4 N, 80 mL). The resulting solution was diluted with water (100 mL) and extracted with ethyl acetate (30 mL × 6). The combined organic phases were dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography (eluent: ethyl acetate/petroleum ether = 5:1) to give (2*R*,3*R*)-3-(2,4-difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4] triazol-1-yl-butyric acid **4** (1.56 g, 5.20 mmol, yield 46%) and the corresponding tertiary benzylated ester **4a** (1.32 g, yield 29%).

Ester **4**, white solid, melting point: 215.0 to 215.6 °C. Enantiomeric excess: 98.5% as determined by HPLC on Chiralpak AS-H column [n-hexane (0.1% TFA)/ethanol, 87:13], $R_t = 6.50$ min. $[\alpha]_D^{20} = -50.9°$ (c = 1, MeOH). IR (KBr): 2920, 1657, 1497, 1421, 1128 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 12.77 [s (br), 1H], 8.29 (s, 1 H), 7.58 (s, 1 H), 7.11–7.21 (m, 2 H), 6.84–6.88 (m, 1 H), 5.84 [s (br), 1 H], 4.77 (d, $J = 14.4$ Hz, 1 H), 4.69 (d, $J = 14.4$ Hz, 1 H), 3.08 (q, $J = 6.8$ Hz, 1 H), 0.82 (d, $J = 6.8$ Hz, 3 H). ^{13}C NMR (DMSO-d_6) δ: 175.49, 162.42 (dd, $^1J_{CF} = 245$ Hz, $^3J_{CF} = 12.1$ Hz), 159.12 (dd, $^1J_{CF} = 244$ Hz, $^3J_{CF} = 12.1$ Hz), 150.91, 145.42, 130.60, 125.17 (d, $^2J_{CF} = 12.2$ Hz), 111.35 (d, $^2J_{CF} = 19.8$ Hz), 104.45 (t, $^2J_{CF} = 27.4$ Hz), 76.21 (d, $^3J_{CF} = 4.6$ Hz), 56.58, 45.65, 13.19. MS(ESI) m/z (real intensity) 298. Anal. calcd. for $C_{13}H_{13}F_2N_3O$: C, 52.53; H, 4.41; F, 12.78; N, 14.14. Found: C, 52.74; H, 4.44; F, 12.83; N, 14.08.

(2*R*,3*R*)-3-(2,4-difluoro-phenyl)-3-benzoyloxy-2-methyl-4-[1,2,4]-triazol-1-yl-butyric Acid 4a

White solid, melting point: 162.6–164.6 °C. IR (KBr): 3435, 1728, 1716, 1275, 1109, 878, 712 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 12.54 [s(br), 1H], 8.30 (s, 1 H), 7.90–7.92 (m, 3H), 7.63–7.67 (m, 1H), 7.48–7.52 (m, 2H), 7.41–7.47 (m, 1H), 7.10–7.23 (m, 2H), 5.53 (d, J = 14.8 Hz, 1H), 5.32 (d, J = 14.8, 1H), 3.24 (q, J = 6.8 Hz, 1H), 1.09 (d, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ: 173.76, 165.04, 162.58 (dd, $^1J_{CF} = 245.9$ Hz, $^3J_{CF} = 13.6$ Hz), 160.16 (dd, $^1J_{CF} = 248.7$ Hz, $^3J_{CF} = 11.8$ Hz), 152.30, 146.38, 134.25, 130.61, 130.29, 130.09, 129.37, 121.06 (d, $^2J_{CF} = 10.1$ Hz), 111.65 (d, $^2J_{CF} = 21.9$ Hz), 105.27 (t, $^2J_{CF} = 25.2$ Hz), 84.40 (d,

$^3J_{CF} = 3.3$ Hz), 50.68, 45.59, 12.86. MS(ESI) m/z (real intensity) 402. The ester **4a** (1.32 g, 3.29 mmol) was hydrolyzed in aqueous sodium hydroxide solution (4 N, 10 mL) under reflux temperature for 3 h. The pH of the reaction solution was adjusted to pH4 by the addition of hydrochloric acid (4 N, 9.3 mL). The resulting solution was extracted with ethyl acetate (30 mL × 6). The combined organic phases were dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography (eluent: ethyl acetate/petroleum ether = 5:1) to give the corresponding acid **4** (0.83 g, 2.79 mmol, yield 85%).

The overall yield of the alkyne cleavage reaction (directly formed acid combined with the acid obtained after hydrolysis of the benzoyl group) was 70.7%.

Synthesis of (3*R*,4*R*)-4-(2,4-difluoro-phenyl)-3-methyl-4-[1,2,4]-triazol-1-ylmethyl-oxetan-2-one 5

Compound **4** (1.6 g, 5.17 mmol) and 1,1̀-carbonyl diimidazole (1.13 g, 6.72 mmol) were dissolved in THF (30 mL). The reaction mixture was heated at 60 °C for 3 h and then cooled to room temperature. The solvent was partially evaporated. The residue was poured into a 0.5 N hydrochloric acid solution (50 mL). The aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with water (30 mL × 2) and saturated aqueous sodium bicarbonate solution (30 mL × 3) and dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate = 2:1) to give (3*R*,4*R*)-4-(2,4-difluoro-phenyl)-3-methyl-4-[1,2,4]triazol-1-ylmethyl-oxetan-2-one **5** (1.36 g, 4.77 mmol, yield 92.2%). White solid, melting point: 61.3 to 63.5 °C. Enantiomeric excess: 98.3% as determined by HPLC on Chiralpak AS-H column (n-hexane/2-propanol, 90:10), R_t=25.72 min. $[\alpha]_D^{20} = 44.9$ ° (c = 1, MeOH). IR (KBr): 1832, 1504, 1276 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 1.11 (d, $J = 7.6$ Hz, 3 H), 3.96 (q, $J = 7.6$ Hz, 1 H), 4.85 (s, 2H), 4.85 (d, $J = 12$ Hz, 2 H), 6.91–6.96 (m, 2 H), 7.32–7.37 (m, 1 H), 7.85 (s, 1 H), 8.13 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ: 168.64, 163.83 (dd, $^1J_{CF} = 251$ Hz, $^3J_{CF} = 12.1$ Hz), 158.95 (dd, $^1J_{CF} = 246$ Hz, $^3J_{CF} = 12.1$ Hz), 152.20, 144.92, 129.32 (m), 118.05 (d, $^2J_{CF} = 13.7$ Hz), 112.68 (d, $^2J_{CF} = 21.3$ Hz), 104.92 (t, $^2J_{CF} = 25.1$ Hz), 80.95, 54.94 (d, $^3J_{CF} = 3.1$ Hz), 52.41, 9.83. MS(ESI) m/z (real intensity) 280.0. Anal. calcd. for $C_{13}H_{11}F_2N_3O_2$: C, 55.92; H, 3.97; F,13.61; N, 15.05. Found: C, 56.08; H, 3.99; F, 13.70; N, 15.01.

Synthesis of (2*R*,3*R*)-3-(2,4-difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]-triazol-1-yl-butyramide 6

Compound **5** (0.62 g, 2.21 mmol) and 4-dimethyl-aminopyridine (19.9 mg, 0.16 mmol) were dissolved in 25% aqueous ammonium hydroxide solution (70 mL). The reaction mixture was stirred for 5 h at room temperature. The solution was evaporated, and the residue was taken up in methylene chloride. The organic phase was dried over magnesium sulfate, the solids were filtered off, and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography (eluent: ethyl acetate/petroleum ether = 2:1) to give (2*R*,3*R*)-3-(2,4-difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyramide **6** (0.64 g, 2.12 mmol, yield: 96.7%). White solid, melting point: 161.3 to 162.7°C. Enantiomeric excess: 99.5% as determined by HPLC on Chiralpak AD-H column [n-hexane (0.1% TFA)/ethanol], R_t= 17.68 min. $[\alpha]_D^{20} = -74.8°$ (c = 0.42, MeOH). IR (KBr): 3339, 3300, 1666, 1618, 1500, 1417, 1136 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 8.28 (s, 1 H), 8.15 [s (br), 1 H], 7.59 [s (br), 1 H], 7.57 (s, 1 H), 7.12–7.24 (m, 1 H), 6.84–6.88 (m, 1 H), 6.64 (s, 1 H), 4.70 (d, J = 14 Hz, 1 H), 4.40 (d, J = 14 Hz, 1 H), 3.12 (q, J = 6.8 Hz, 1 H), 0.81 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (DMSO-d_6) δ: 178.58, 161.96 (dd, $^1J_{CF}$ = 243 Hz, $^3J_{CF}$ = 12.1 Hz), 158.65 (dd, $^1J_{CF}$ = 260 Hz, $^3J_{CF}$ = 12.1 Hz), 144.97, 130.31, 124.10 (d, $^2J_{CF}$ = 12 Hz), 111.03 (d, $^2J_{CF}$ = 18.3 Hz), 104.03 (t, $^2J_{CF}$ = 26.6 Hz), 75.85 (d, $^3J_{CF}$ = 3 Hz), 56.72, 41.79, 13.89. MS (ESI) m/z (real intensity) 297.0. Anal. calcd. for $C_{13}H_{14}F_2N_4O_2$: C, 52.70; H, 4.76; F, 12.82; N, 18.91. Found: C, 52.51; H, 4.71; F, 13.11; N, 18.61.

Synthesis of (2*S*,3*R*)-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]-triazol-1-yl-butyronitrile 7

(2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]-triazol-1-yl-butyramide **6** (1 g, 3.38 mmol) was dissolved in phosphorous oxychloride (1.26 mL, 13.5 mmol). The mixture was stirred at 40 °C for 3 h. After cooling the mixture to room temperature, excess of phosphorous oxychloride was removed under high vacuum. The oily residue was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate = 1:1) to give (2*S*,3*R*)-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]-triazol-1-yl-butyronitrile **7** (0.89 g, 3.20 mmol, yield 94.6%). White solid, melting point: 182.9 to 184.2 °C. Enantiomeric excess: >99.5% as determined by HPLC on Chiralpak AD-H [n-hexane column (0.1%

TFA)/ethanol], 80:20, R_t =11.41 min. $[\alpha]_D^{20} = 28.8°$ (c = 1, MeOH). IR (KBr): 2245, 1502, 1421, 1136, 1070 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 8.32 (s, 1 H), 7.71 (s, 1 H), 7.29–7.35 (m, 1 H), 7.16–7.21 (m, 1 H), 6.95–7.00 (m, 1 H), 6.63 (s, 1 H), 4.78 (d, J = 14.0 Hz, 1 H), 4.66 (d, J = 14.0 Hz, 1 H), 3.59 (q, J = 7.2 Hz, 1 H), 1.02 (d, J = 7.2 Hz, 3 H). ^{13}C NMR (DMSO-d_6) δ: 162.92 (dd, $^1J_{CF}$ = 246 Hz, $^3J_{CF}$ = 13.7 Hz), 159.22 (dd, $^1J_{CF}$ = 246 Hz, $^3J_{CF}$ = 13.7 Hz), 151.43, 145.79, 131.15 (d, $^3J_{CF}$ = 13.7 Hz), 123.17 (d, $^2J_{CF}$ = 13.7 Hz), 121.39, 111.93 (d, $^2J_{CF}$ = 21.3 Hz), 104.76 (t, $^2J_{CF}$ = 26.6 Hz), 75.54 (d, $^3J_{CF}$ = 4.6 Hz), 56.40, 134.26, 3.63. MS(API-ES) m/z 279.1. Anal. calcd. for $C_{13}H_{12}F_2N_4O$: C, 56.11; H, 4.35; F, 13.65; N, 20.13. Found: C, 55.96; H, 4.31; F, 13.62; N,19.95.

Synthesis of (2*R*,3*R*)-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]-triazol-1-yl-thiobutyramide 8

(2*S*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]-triazol-1-yl-butyronitrile **7** (1.0 g, 3.41 mmol) was dissolved in ethanol (20 mL). The mixture was stirred at room temperature for 10 min, and aqueous ammonium sulfide solution (48 wt.%, 14.6 mL, 85.4 mmol) was added. The mixture was stirred at 50 °C for 7 h. The reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic phases were washed with water (30 mL × 3) and dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography (eluent: ethyl acetate/petroleum ether = 2:1) to give (2*R*,3*R*)-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]-triazol-1-yl-thiobutyramide **8** (0.76 g, 2.43 mmol, yield 70.4%). White solid, melting point: 131.5° to 133.6 °C. Enantiomeric excess: >99.5% as determined by HPLC on Chiralpak AD-H column [n-hexane (0.1% TFA)/ethanol]. $[\alpha]_D^{20} = -145.8°$ (c = 1.0, MeOH). IR (KBr): 1500, 1423, 1136, 1101 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 10.11 (s (br), 1 H), 9.95 [s (br), 1 H], 8.27 (s, 1 H), 7.57 (s, 1 H), 7.23–7.27 (m, 1 H), 7.15–7.20 (m, 1 H), 6.84–6.89 (m, 1 H), 6.53 (s, 1 H), 4.80 (d, J = 14.4 Hz, 1 H), 4.49 (d, J = 14.4 Hz, 1 H), 3.56 (q, J = 6.8 Hz, 1 H), 0.89 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (DMSO-d_6) δ: 209.03, 162.47 (dd, $^1J_{CF}$ = 246 Hz, $^3J_{CF}$ = 12 Hz), 159.13 (dd, $^1J_{CF}$ = 246 Hz, $^3J_{CF}$ = 12 Hz), 150.89, 145.32, 131.06, 124.50 (d, $^2J_{CF}$ = 12 Hz), 111.50 (d, $^2J_{CF}$ = 19.7 Hz), 104.69 (t, $^2J_{CF}$ = 26.6 Hz), 76.11 (d, $^3J_{CF}$ = 5 Hz), 56.70, 50.19,16.73. MS (API-ES) m/z 313.0. Anal. calcd. for $C_{13}H_{14}F_2N_4OS$: C, 49.99; H, 4.52; F, 12.17; N, 17.94; S, 10.27. Found: C, 49.96; H, 4.54; F, 12.20; N, 17.72; S, 10.23.

Synthesis of 4-[2-[(1*R*,2*R*)-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1,2,4-triazol-1-yl)propyl]thiazol-4-yl]benzonitrile (Ravuconazole)

(2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-[1,2,4]-triazol-1-yl-thiobutyramide **8** (100 mg, 0.32 mmol) and 2-bromo-4-cyanoacetophenone (789 mg, 0.35 mmol) were dissolved in ethanol (10 mL). The mixture was heated under reflux for 3 h. After cooling to room temperature, water (10 mL) was added. The mixture was extracted with ethyl acetate (30 mL × 3). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution (10 mL × 3) and brine (10 mL × 3) and dried over sodium sulfate. The solids were filtered off, and the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography (eluent: petroleum ether/ethyl acetate = 1:1) to give 4-[2-[2(*R*)-(2,4-difluorophenyl)-2-hydroxy-1(*R*)-methyl-3-(1,2,4-triazol-1-yl)propyl]thiazol-4-yl]benzonitrile (ravuconazole) (0.11 g, 0.25 mmol, yield: 79.5%). White solid; melting point: 161.6 to 163 °C. Enantiomeric excess: >99.5% as determined by HPLC on Chiralpak AD-H column [n-hexane (0.1% TFA)/ethanol]. $[\alpha]_D^{20} = -30.2°$ (c = 1, MeOH). IR (KBr): 2226, 1608, 1500, 1138 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 8.41 (s, 1 H), 8.20 (s, 1 H), 8.18 (d, $J = 8.4$ Hz, 2 H), 7.91 (d, $J = 8.4$ Hz, 2 H), 7.61 (s, 1 H), 7.26–7.30 (m, 1 H), 7.18–7.23 (m, 1 H), 6.91–6.95 (m, 1 H), 6.07 (s, 1 H), 4.85 (d, $J = 14.4$ Hz, 1 H), 4.35 (d, $J = 14.4$ Hz, 1 H), 4.07 (q, $J = 7.2$ Hz, 1 H), 1.12 (d, $J = 7.2$ Hz, 3 H). ^{13}C NMR (DMSO-d_6) δ: 172.45, 162.57 (dd, $^1J_{CF} = 245$ Hz, $^3J_{CF} = 12.1$ Hz), 159.33 (dd, $^1J_{CF} = 245$ Hz, $^3J_{CF} = 12.1$ Hz), 152.02, 151.12, 138.99, 145.41, 133.58, 130.90, 127.39, 125.30 (d, $^2J_{CF} = 14$ Hz), 119.61, 119.09, 111.57 (d, $^2J_{CF} = 19.7$ Hz), 110.78, 104.70 (d, $^3J_{CF} = 6$ Hz), 76.89 (d, $^2J_{CF} = 26.6$ Hz), 56.64, 45.21,17.25. MS (API-ES) m/z 438.0. Anal. calcd. for $C_{22}H_{17}F_2N_5OS$: C, 60.40; H, 3.92; F, 8.69; N, 16.01; S, 7.33. Found: C, 60.56; H, 3.93; F, 8.76; N, 15.76; S, 7.36.

ACKNOWLEDGMENTS

We are grateful for the important contribution of the analytical services of Basilea China, especially to Xianzheng Liang and Jianxia Zhou for the determinations of the ee of the produced compounds. Skillful technical assistance by other analytic chemists in Basilea China is greatly acknowledged.

REFERENCES

1. Sheehan, D. J.; Hitchcock, C. A.; Sibley, C. M. Current and emerging azole antifungal agents. *Clin. Microbiol. Rev.* **1999**, *12* (1), 40–79.

2. Saji, I.; Tamoto, K.; Tanaka, Y.; Miyauchi, H.; Fujimoto, K.; Ohashi, N. Stereoselective synthesis of antifungal agents *threo*-2-(2,4-difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (SM-8668). *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1427–1433.
3. Tasaka, A.; Tamura, N.; Matsushita, Y.; Kitazaki, T.; Hayashi, R.; Okonogi, K.; Itoh, K. Optically active antifungal azoles, IV: Synthesis and antifungal activity of (2R,3R)-3-azoyl-2-(substituted phenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols. *Chem. Pharm. Bull.* **1995**, *43* (3), 432–440.
4. Gala, D.; DiBenedetto, D. J.; Mergelsberg, I.; Kugelman, M. Total chiral synthesis of azole antifungals via α-hydroxylation of ketones. *Tetrahedron Lett.* **1996**, *37* (43), 8117–8120.
5. Kaku, Y.; Tsuruoka, A.; Kakinuma, H.; Tsukuda, I.; Yanagisawa, M.; Naito, T. A novel route for chiral synthesis of triazole antifungal ER-30346. *Chem. Pharm. Bull.* **1998**, *46* (7), 1125–1129.
6. Bennet, F.; Ganguly, A. K.; Girijavallabhan, V. M.; Pinto, P. A an enantioselective synthesis of the antifungal agent (2R,3R)-(2,4-difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (Sch 42427; SM-8668). *Synlett.* **1995**, 1110–1113.
7. Soukup, M. Intermediate halophenyl derivatives and their use in a process for preparing azole derivatives. Patent PTC WO03/002498A1, **2003**.
8. Tamaru, Y.; Tanaka, A.; Yasui, K.; Goto, S.; Tanaka, S. Highly stereoselective allylation of benzaldehyde: Generation of a stereochemically defined allylzinc species from a π-allypalladium intermediate and diethylzinc. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 787.
9. Marshall, J. A., Adams, N. D. Synthesis of Chiral Enantioenriched Homopropargylic Mesylates Via Chiral Allylzinc Intermediates. *J. Org. Chem.* **1998**, *63*, 3812–3813.
10. Marshall, J. A.; Wolf, M. A.; Wallace, E. M. Synthetic routes to allenic acids and esters and their stereospecific conversion to butenolides. *J. Org. Chem.* **1997**, *62*, 367.
11. Sato, F.; An, D. K.; Okamoto, S. Synthetic routes to allyltitaniums having axial chirality by the reaction of optically active propargylic compounds with $Ti(O\text{-}i\text{-}Pr)_4/2\text{-}i\text{-}PrMgCl$ reagent. *Tetrahedron Lett.* **1998**, *39*, 4555–4558.