A Novel Route for Chiral Synthesis of the Triazole Antifungal ER-30346

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A novel synthetic route to (2S,3S)-2-[(2,4-difluorophenyl)-3-hydroxy-2-methyl-4-(1,1,2,4-triazolyl)]butyronitrile (2), an intermediate for the orally active triazole antifungal agent ER-30346, was developed from methyl S-(+)-3-hydroxy-2-methylpropionate, a commercially available chiral compound. The second chiral center was constructed with 6:4:1 diastereoselectivity via osmium tetroxide catalyzed dihydroxylation.

Key words: ER-30346; triazole antifungal; diastereoselective synthesis; methyl S-(+)-3-hydroxy-2-methylpropionate

ER-30346 is a novel, orally active antifungal agent with potent activity against a wide range of fungi, including Candida species, Aspergillus fumigatus, and Cryptococcus neoformans.1) During structure–activity relationship studies, we found that the activity of this compound is dependent on the stereochemistry: among the four possible stereoisomers, the (2R,3R) form is the most active against major pathogenic fungi.2)

We have previously synthesized ER-30346 in optically active form using the nitrile 2 as a key chiral intermediate (Chart 1).3,4) In this route, 2 was synthesized by the reaction of diethylaluminum cyanide,3) or lithium cyanide4) with the known epoxide 1.5) Herein, we present an alternative route to 2 that does not involve the use of metal cyanide.

We selected commercially available methyl S-(+)-3-hydroxy-2-methylpropionate6) as the chiral starting material. A retrosynthetic analysis is shown in Chart 2.

Thus, one of the chiral centers is derived from the starting material and the other results from stereoselective oxirane ring formation at the C=O group. For the latter step, several types of reactions are available, including oxirane formation with dimethylsulfoxonium methyliide, as was applied for the synthesis of compound 1.5a)

In order to introduce the second carbon functionality with high stereoselectivity, selection of an appropriate protecting group for the alcoholic hydroxyl group was deemed important. Thus protecting group should be bulky enough to induce face-selective attack of the carbon nucleophile on the carbonyl group, should be stable to nucleophilic reagents, and be easy to remove under mild conditions. We thus selected the triphenylmethyl (trityl) group.

The starting material was first converted to trityl-protected 2-pyridylthioester (5) using a conventional method. Difluorophenyl magnesium bromide was then
coupled with 5 to form the ketone (6) in 62% yield. The optical yield of this compound was at least 90%, based on the optical yield of the deprotected product (7).

The ketone (6) was next subjected to epoxide formation reaction using dimethylsulfonium methylyde according to a known method. However, only unidentified decomposition products were obtained and no epoxide was detected.

Next, we investigated methylene insertion to the carbonyl bond of 6 with chloromethylolithium, as shown in Chart 4. As the results, the epoxide (8) was obtained in 96% yield with 0.4:1 diastereoselectivity. Thus, epoxide mixture was then reacted with 1,2,4-triazole sodium salt, and the two diastereomers of 1,2,4-triazole trityl alcohol (9) separated using silica gel column chromatography. The major diastereomer, obtained in 29% yield, was then deprotected under acidic conditions. The $^1$H-NMR spectrum of this product showed peaks corresponding to the structure of a triazole diol, but was not identical with an authentic sample of the desired diol. We characterized this compound as 10, the diastereoisomer of the desired product.

We applied this process to several ketones corresponding to 6 with different protecting groups, but the diastereoselectivity was not reversed.

We assume that these reactions proceeded as illustrated in Chart 5. According to this model, the preferred conformation of the ketone 6 minimizes steric repulsion between the phenyl moiety and the bulky protecting group is minimized, and the carbon nucleophile then approaches from the less-hindered side of the carbonyl group.

One possible way to reverse the stereochemistry of the
major product is to exchange the roles of the carbon and oxygen atoms at the second chiral center. Thus, if exo-methylene compound (11) is chosen as the starting material instead of 6 and allowed to react with an appropriate oxidizing agent, the product of the desired stereocchemistry should be obtained (Chart 6). Considering the bulkiness of the reagent and compatibility with the protecting group, we selected osmium-catalyzed dihydroxylation as the oxidation method.

Based on this new strategy, the construction of the second chiral center was successfully carried out (Chart 7). exo-Methylene compound (11) was synthesized by standard Wittig reaction of ketone 6 in 85% yield. This compound was then dihydroxylated with N-methylmorpholine-N-oxide and a catalytic amount of osmium tetroxide. Two diastereomers of the diol (12 and 13) were obtained 58% and 9% yields, respectively. The major diastereomer was converted to 1,2,4-triazolyl diol derivative 15 via the mesylate and trityloxy alcohol 14, and was identical with an authentic sample.

Conversion of diol 15 to the known intermediate 2 was accomplished using conventional chemistry. Thus, 15 was first converted to the aldehyde 16 by Swern oxidation, followed by conversion to the nitrile using hydroxylamine O-sulfonic acid. The resulting compound was identical with an authentic sample of 2 obtained by the previous method.

In conclusion, we have found a novel synthetic route to compound 2, a key intermediate for the novel antifungal triazole ER-50346, starting from commercially available methyl S-(+)-3-hydroxy-2-methylpropionate.

**Experimental**

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (1H-NMR) spectra were recorded on a Varian Unity 400 (400MHz) spectrometer with chloroform-d as the solvent, and chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as an internal reference. Infrared (IR) spectra were recorded on a Nicolet 205 FT-IR spectrometer. Fast atom bombardment mass spectra (FAB-MS) were recorded on a JEOL JMS-HX100 spectrometer. Elemental analysis (C, H, N) was carried out on a Yanaco CHN corder MT-5. The optical rotations were recorded with a JASCO DIP 1000 digital polarimeter.

Commercially available reagents and organic solvents were used without purification. Silica gel (Kieselgel 60, Merck) was used for column chromatography.

**Methyl (S)-2-Methyl-3-triphenylmethoxypropionate (3)** Triphenylchloromethane (18.1g, 1.5eq) was added to a solution of methyl (S)-3-hydroxy-2-methylpropionate (6.6ml, 60mmol) in pyridine (33ml) and the mixture heated at 80°C for 1h. After cooling to room temperature, the mixture was slowly added to water. The resulting crystals were collected by filtration, washed with water, dried under vacuum, and recrystallized from ethanol to afford 3 (18.3g, 85%), mp 84-85°C. IR (CHCl3) cm⁻¹: 1733, 1602, 1471, 1303, 1216. FAB-MS m/z: 360 (M + H)⁺. 1H-NMR δ: 1.15 (d, 3H, J = 7.1Hz, CH2CH3), 2.69-2.77 (m, 1H, CH2CH3), 3.17 (dd, J = 5.6, 8.8Hz, 1H, CH2), 3.29 (dd, 1H, J = 5.6, 8.8Hz, CH2), 3.70 (s, 3H, CO2CH3), 7.20-7.44 (m, 15H, Ar-H). [x]D² +14.9° (c = 0.21, MeOH). Anal. Calcd. For C28H23O2: C, 79.79; H, 6.71. Found: C, 79.77; H, 6.76.

**Methyl (S)-2-Methyl-3-triphenylmethoxypropionic Acid (4)** Lithium hydroxide monohydrate (2.52g, 60.0mmol) in water (54ml) was added to a solution of 3 (10.8g, 30.0mmol) in a mixture of tetrahydrofuran (108ml) and methanol (54ml) over 15 min with stirring and cooling in an ice-bath. After complete addition, the ice-bath was removed and stirring continued for 4h. Glacial acetic acid (3.6ml) was then added and organic solvent removed by evaporation. The residual aqueous solution was then extracted with ethyl acetate, and the combined organic layers washed with water, dried over magnesium sulfate, and evaporated in vacuo. The resulting compound (10.4g, quantitative yield) was used for subsequent reactions without further purification. A sample for elemental analysis was obtained by recrystallization from dichloromethane-hexane, mp 99-102°C. IR (CHCl3) cm⁻¹: 1712, 1602, 1471, 1386, 1217. FAB-MS m/z: 347 (M + H)⁺. 1H-NMR δ: 1.18 (d, 3H, J = 7.2Hz, CH2CH3), 2.69-2.78 (m, 1H, CH2CH3), 3.25 (dd, 1H, J = 5.6, 8.8Hz, CH2), 3.32 (dd, 1H, J = 5.6, 8.8Hz, CH2), 7.15-7.45 (m, 15H, Ar-H). [x]D² +8.7° (c=0.11, MeOH). Anal. Calcd. For C27H21O2: C, 79.74; H, 6.49. Found: C, 79.59; H, 6.47.

**S-(2-Pyridyl) (S)-2-Methyl-3-triphenylmethoxypropanoate (5)** Compound 4 (10.3g, 29.8mmol) was dissolved in dichloromethane
(50 ml) and 2-mercaptoypyridine (3.64 g, 32.7 mmol), 4-diethylamino-pyridine (364 mg, 2.98 mmol), and dicyclohexylcarbodiimide (6.76 g, 32.8 mmol) were added with cooling in an ice-bath. The mixture was then stirred for 3.5 h at the same temperature, and at room temperature for 2 h. The precipitate was removed by filtration and the filtrate was diluted with ethyl acetate. This solution was washed with water (2 x) and brine, then dried over magnesium sulfate. Solvent was evaporated in vacuo, and the residue purified by column chromatography on silica gel with ethyl acetate/hexane to obtain 5 (11.9 g, 91%), IR (CHCl₃ cm⁻¹): 1712, 1621, 1486, 1385, 1217. ¹H-NMR δ: 1.21 (d, 3H, J = 7.2 Hz, CH₃), 2.99–3.09 (m, 1H, CH₂), 3.21 (dd, 1H, J = 5.6, 9.2 Hz, CH₂), 3.44 (dd, 1H, J = 7.6, 9.2 Hz, CH₂), 7.21–7.33 (m, 10H, Ar-H), 7.43–7.47 (m, 6H, Ar-H), 7.63 (d, 1H, J = 8.0 Hz, Ar-H), 7.73 (t, 1H, J = 8.0 Hz, Ar-H), 8.63 (d, 1H, J = 4.8 Hz, Ar-H). [x] D² = +8.0° (c = 0.13, MeOH). Anal. Calc'd for C₂₄H₂₂NO₂: C 75.88; H 5.78; N 3.16. Found: C 75.70; H 6.00; N 3.10.

(2S,3S)-3-(2,4-Difluorophenyl)-2-methyl-4-[1-(1,2,4-triazolyl)-1,3-butan-1-ol (10) A solution of 9 (72 mg, 0.137 mmol) in acetic acid (0.3 ml) was treated with 25% HBr/AcOH at room temperature for 5 min. The mixture was quenched with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane to obtain 10 (17 mg). ¹H-NMR δ: 1.35 (d, 3H, J = 7.2 Hz, CH₃), 2.30–2.38 (m, 1H, CH₂), 2.67 (t, 1H, J = 4.4 Hz, CH₂ O), 3.46–3.57 (m, 2H, CH₂ O), 4.57 (d, 1H, J = 14.0 Hz, CH₂ Ar), 4.82 (d, 1H, J = 14.0 Hz, CH₂ Ar), 5.17 (s, 1H, C=OH), 6.70–6.78 (m, 2H, Ar-H), 7.36–7.43 (m, Ar-H), 7.69 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H).

(2S,3S)-3-(2,4-Difluorophenyl)-3-methyl-4-(3-oxobenzylidene)pyrrolidine-1,2-butanediol (11) A solution of 4 (16.6 mg in 0.5 ml), 12 (11.2 ml, 17.92 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (6.43 g, 18.0 mmol) in tetrahydrofuran (64 ml) under an ice cooling. The mixture was stirred 2 h at room temperature and a solution of 6 (6.63, 15.0 mmol) in tetrahydrofuran (30 ml) was added dropwise and the mixture was stirred for another 30 min. Hexane (500 ml) and water (300 ml) were added and insoluble material was removed by filtration. The organic layer was separated, washed with water (3 x) and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with ethyl acetate/hexane to afford an oily product (5.4 g, 85%). IR (CHCl₃ cm⁻¹): 1614, 1562, 1471, 1384, 1168. ¹H-NMR δ: 1.16 (d, 3H, J = 7.0 Hz, CH₃), 2.81–2.89 (m, 1H, CH₂CH₂), 2.99 (dd, 1H, J = 6.0, 9.2 Hz, OCH₂), 3.30 (dd, 1H, J = 6.0 Hz, 9.2 Hz, OCH₂), 5.11 (s, 1H, C=CH), 5.21 (s, 1H, C=O), 7.19–7.22 (m, 8H, Ar-H), 7.35–7.39 (5H, 6H, Ar-H). [x] D² = +9.6° (c = 0.13, MeOH). Anal. Calc'd for C₂₃H₂₃O₂: C 81.79; H 5.95. Found: C 81.54; H 6.00.

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-4-(3-oxobenzylidene)pyrrolidine-1,2-butanediol (12) and (2S,3S)-2-(2,4-Difluorophenyl)-3-methyl-4-(3-oxobenzylidene)pyrrolidine-1,2-butanediol (13) A 4% aqueous solution of sodium tetroxide (36 ml, 5.61 mmol) and 0.5 mol of acetone (2.54 ml) were added to a mixture of 50% aqueous N-methylmorpholine oxide (144 ml, 0.617 mmol), water (0.5 ml) and acetone (2.5 mol). The solution was stirred overnight, and further 4% aqueous tetroxide solution (100 ml, 3.90 mol) was added. The reaction mixture was then stirred for a further 24 h at room temperature, quenched with 10% aqueous sodium hydrogen sulfite and extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate, and evaporated in vacuo the residue purified by column chromatography on silica gel with hexane/ethyl acetate to afford 12 (153 mg, 58%) and 13 (23 mg, 9%).

12: IR (CHCl₃ cm⁻¹): 3155, 1644, 1602, 1471, 1383. FAB-MS m/z: 473 (M + H)⁺. ¹H-NMR δ: 0.75 (d, 3H, J = 8.8 Hz, CH₃CH₂), 2.44–2.53 (m, 1H, CH₂CH₂), 2.77 (dd, 1H, J = 3.6, 8.4 Hz, CH₂OH), 3.21 (dd, 1H, J = 8.4, 14.0 Hz, CH₂OH), 3.32 (dd, 1H, J = 8.4, 14.0 Hz, CH₂OH), 3.63 (ddd, 1H, J = 8.4, 11.2 Hz, CH₂OCH₂), 3.96 (dd, 1H, J = 2.8, 5.6, 11.2 Hz, CH₂OCH₂), 4.39 (s, 1H, C=CH), 6.69–6.76 (m, 1H, Ar-H), 6.79–6.84 (m, 1H, Ar-H), 7.22–7.30 (m, 3H, Ar-H), 7.32–7.37 (m, 6H, Ar-H), 7.43–7.47 (m, 6H, Ar-H), 7.52–7.58 (m, 5H, Ar-H). [x] D² = +4.6° (c = 0.12, MeOH).

13: IR (CHCl₃ cm⁻¹): 3155, 1644, 1601, 1478. FAB-MS m/z: 475 (M + H)⁺. ¹H-NMR δ: 1.35 (d, 3H, J = 7.2 Hz, CH₃), 2.34–2.44 (m, 1H, CH₂CH₂), 2.93 (dd, 1H, J = 3.6, 9.6 Hz, CH₂OH), 3.19 (dd, 1H, J = 3.6, 9.6 Hz, CH₂OH), 3.82 (dd, 1H, J = 6.8, 10.6 Hz, CH₂OH), 3.96 (dd, 1H, J = 5.2, 10.6 Hz, CH₂OCH₂), 4.50 (s, 1H, C=O), 6.57–6.64 (m, 4H, Ar-H), 6.70–6.75 (m, 1H, Ar-H), 7.18–7.31 (m, 1H).
The solution was extracted with two portions of dichloromethane. The organic phase was washed with water and brine, dried over magnesium sulfate, and solvent was removed in vacuo, and the residue purified by column chromatography on silica gel with methanol/dichloromethane to afford 16 (106 mg, 75%). Spectral data were identical with those of an authentic sample obtained by the reported method.  

References and Notes


6) Available from Aldrich Chemical Co., Inc. or Tokyo Kasei Kogyo Co., Ltd.


9) An authentic sample of 14 was synthesized by reduction of the aldehyde corresponding to 16, obtained by the method described in reference 3.

10) The protecting groups we examined in addition to trityl were tert-butyldiphenylylmethyl, methoxymethyl, tetrahydropyranyl, and benzyl.

11) In general, osmium-catalyzed dihydroxylation reactions are known to proceed mainly from the less-hindered side of the double bond. See Schröder M., *Chem. Rev.*, 80, 187—223 (1980) and references cited therein.