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

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A novel synthetic route to (2*S*,3*S*)-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 (2*R*,3*R*) 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).[2,3] In this route, **2** was synthesized by the reaction of diethylaluminum cyanide,[3] or lithium cyanide[4] 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-methylpropionate[6] 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 methylide, 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

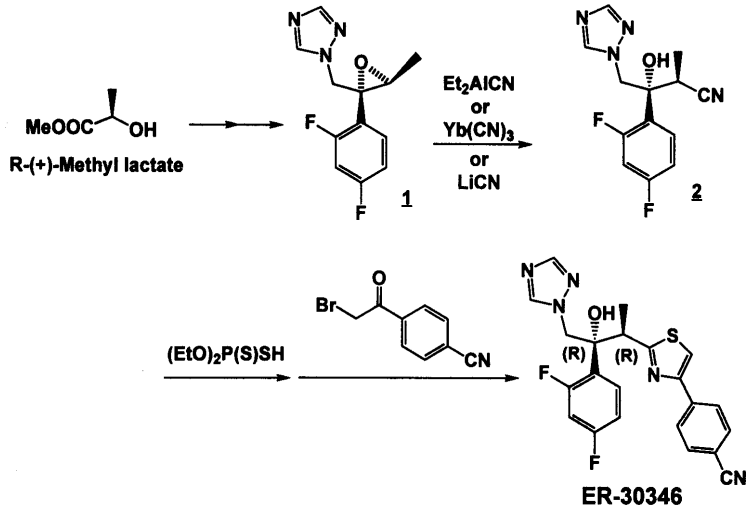

Chart 1

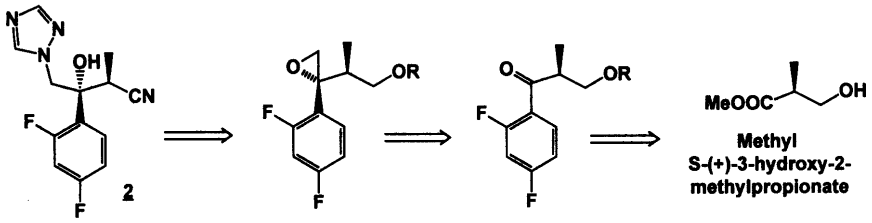

Chart 2

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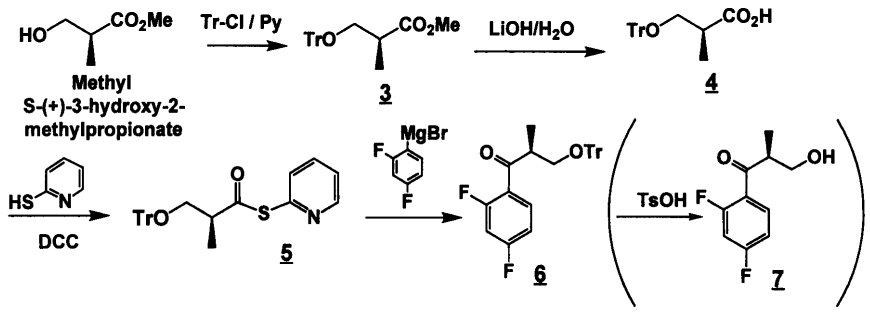

Chart 3

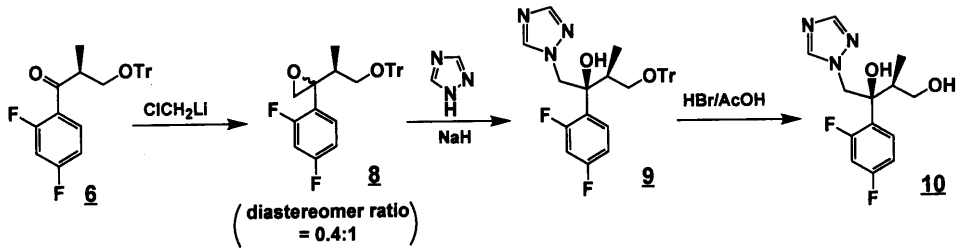

Chart 4

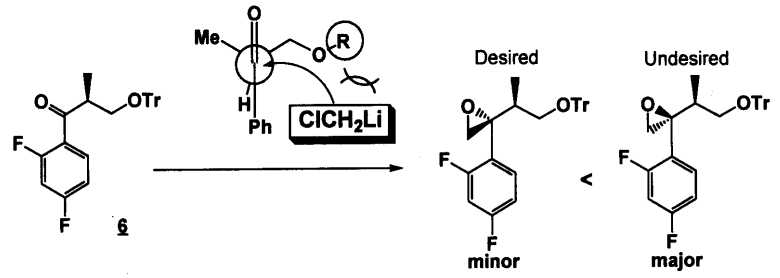

Chart 5

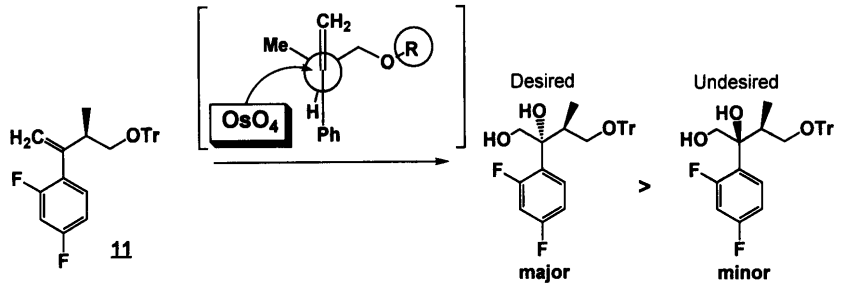

Chart 6

coupled with **5** to form the ketone (**6**) in 62% yield.[7] 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 dimethylsulfoxonium methylide according to a known method.[5a] However, only unidentified decomposition products were obtained and no epoxide was detected.

Next, we investigated methylene insertion to the carbonyl bond of **6** with chloromethyllithium,[8] 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 triazolyl 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 triazolyl diol, but was not identical with an authentic sample of the desired diol.[9] 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.[10]

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

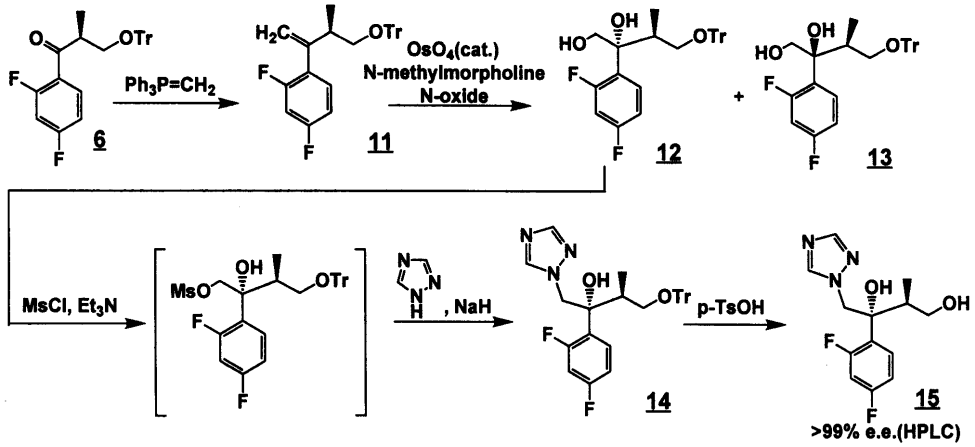

Chart 7

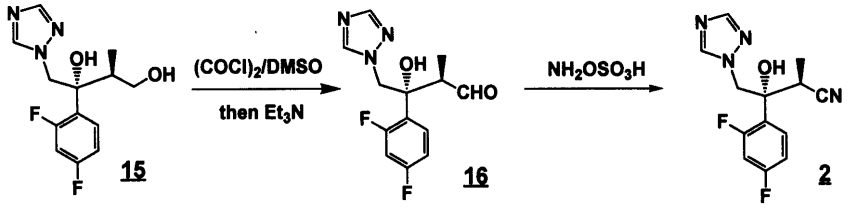

Chart 8

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 stereochemistry should be obtained (Chart 6). Considering the bulkiness of the reagent and compatibility with the protecting group, we selected osmium-catalyzed dihydroxylation[11] 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.[9]

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.[3]

In conclusion, we have found a novel synthetic route to compound **2**, a key intermediate for the novel antifungal triazole ER-30346, 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 (^{1}H-NMR) spectra were recorded on a Varian Unity 400 (400 MHz) 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-triphenylmethyloxypropionate (3) Triphenylchloromethane (18.1 g, 1.5 eq) was added to a solution of methyl (*S*)-3-hydroxy-2-methylpropionate (6.6 ml, 60 mmol) in pyridine (33 ml) and the mixture heated at 80 °C for 1 h. 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** (18.3 g, 85%), mp 84—85 °C. IR ($CHCl_3$) cm^{-1}: 1733, 1602, 1471, 1383, 1216. FAB-MS *m/z*: 360 $(M+H)^+$. ^{1}H-NMR δ: 1.15 (d, 3H, J=7.1 Hz, $CHC\underline{H}_3$), 2.69—2.77 (m, 1H, $CHCH_3$), 3.17 (dd, J=5.6, 8.8 Hz, 1H, CH_2), 3.29 (dd, 1H, J=5.6, 8.8 Hz, CH_2), 3.70 (s, 3H, CO_2CH_3), 7.20—7.44 (m, 15H, Ar-H). $[\alpha]_D^{22}$ +14.9° (c= 0.21, MeOH). *Anal.* Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.77; H, 6.76.

(*S*)-2-Methyl-3-triphenylmethyloxypropionic Acid (4) Lithium hydroxide monohydrate (2.52 g, 60.0 mmol) in water (54 ml) was added to a solution of **3** (10.8 g, 30.0 mmol) in a mixture of tetrahydrofuran (108 ml) and methanol (54 ml) over 15 min with stirring and cooling in an ice-bath. After complete addition, the ice-bath was removed and stirring continued for 4 h. Glacial acetic acid (3.6 ml) was then added and organic solvent removed by evaporation. The residul 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 (10.4 g, 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 ($CHCl_3$) cm^{-1}: 1712, 1602, 1471, 1386, 1217. FAB-MS *m/z*: 347 $(M+H)^+$. ^{1}H-NMR δ: 1.18 (d, 3H, J=7.2 Hz, $CHC\underline{H}_3$), 2.69—2.78 (m, 1H, $C\underline{H}CH_3$), 3.25 (dd, 1H, J=5.6, 8.8 Hz, CH_2), 3.32 (dd, 1H, J=5.6, 8.8 Hz, CH_2), 7.15—7.45 (m, 15H, Ar-H). $[\alpha]_D^{22}$ +8.7° (c=0.11, MeOH). *Anal.* Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.59; H, 6.47.

***S*-(2-Pyridyl) (*S*)-2-Methyl-3-triphenylmethyloxypropanothioate (5)** Compound **4** (10.3 g, 29.8 mmol) was dissolved in dichloromethane

(50 ml) and 2-mercaptopyridine (3.64 g, 32.7 mmol), 4-dimethylaminopyridine (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×) 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 ($CHCl_3$) cm^{-1}: 1712, 1621, 1486, 1385, 1217. ^{1}H-NMR δ: 1.21 (d, 3H, J=7.2 Hz, $CHCH_3$), 2.99—3.09 (m, 1H, $CHCH_3$), 3.21 (dd, 1H, J=5.6, 9.2 Hz, CH_2), 3.44 (dd, 1H, J=7.6, 9.2 Hz, CH_2), 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). $[\alpha]_D^{22}$ +8.0° (c= 0.13, MeOH). *Anal.* Calcd for $C_{28}H_{25}NO_2S$ +0.2H_2O: C, 75.88; H, 5.78; N, 3.16. Found: C, 75.70; H, 6.00; N, 3.10.

(*S*)-2-Methyl-3-triphenylmethyloxy-2′,4′-propiophenone (6) Magnesium turnings (780 mg, 14.3 mmol) were suspended in tetrahydrofuran (7.8 ml), and 1 drop of 2,4-difluorobromobenzene and a small piece of iodine were added and the whole was stirred vigorously under a nitrogen stream. 2,4-Difluorobromobenzene (3.67 ml, 14.3 mmol) in tetrahydrofuran (17 ml) was then added dropwise at a rate sufficient to maintain the temperature of the mixture at 40—60 °C. Further tetrahydrofuran (20 ml) was then added, and the mixture chilled to −30 °C. A solution of **5** (11.9 g, 27.1 mmol) in tetrahydrofuran (90 ml) was added dropwise while the temperature was maintained between −25 °C and −30 °C. The resulting mixture was stirred for 15 min at −30 °C and then for 2 h at room temperature. The mixture was quenched with a saturated aqueous solution of ammonium chloride, then ethyl acetate and water were added. The organic phase was washed with water (2×) and brine, dried over magnesium sulfate, and solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel with ethyl acetate/hexane and the crude product recrystallized from methanol to obtain pure **6** (7.46 g, 62%), mp 94—97 °C. IR ($CHCl_3$) cm^{-1}: 1689, 1611, 1471, 1385, 1217. FAB-MS m/z: 442 $(M+H)^+$. ^{1}H-NMR δ: 1.21 (d, 3H, J=6.8 Hz, $CHCH_3$), 3.21 (dd, 1H, J=5.2, 8.8 Hz, CH_2), 3.42 (dd, 1H, J=6.4, 8.8 Hz, CH_2), 3.56 (m, 1H, $CHCH_3$), 6.80 (m, 1H, Ar-H), 6.94 (m, 1H, Ar-H), 7.17—7.31 (m, 15H, Ar-H), 7.77—7.83 (m, 1H, Ar-H). $[\alpha]_D^{22}$ +1.3° (c=0.11, MeOH). *Anal.* Calcd for $C_{29}H_{24}F_2O_2$: C, 78.7; H, 5.47. Found: C, 78.73; H, 5.48.

(*S*)-3-Hydroxy-2-methyl-(2,4-difluoropropiophenone) (7) A solution of **6** (110 mg, 0.25 mmol) in methanol (1.1 ml) was treated with *p*-toluenesulfonic acid monohydrate (53 mg) and the mixture was stirred for 20 min at 40 °C. Water and ethyl acetate were added and the organic phase separated, washed with brine, and dried over magnesium sulfate. Solvent was removed *in vacuo* and the residue purified by silica gel column chromatography with ethyl acetate/hexane to obtain **7** (32 mg, 64%). HPLC analysis of this product (column, Chiralcel OB® (4 mm i.d. × 250 mm); eluent, isopropanol : hexane = 1 : 9 v/v; flow rate, 0.5 ml/min; UV at 254 nm; temperature, ambient) showed that its optical purity was 90%. IR ($CHCl_3$) cm^{-1}: 3156, 1602, 1471, 1384, 1167. FAB-MS m/z: 201 $(M+H)^+$. ^{1}H-NMR δ: 1.18 (d, 3H, J=6.8 Hz, $CHCH_3$), 2.50 (t, 1H, J=6.0 Hz, CH_2OH), 3.45—3.54 (m, 1H, $CHCH_3$), 3.72—3.79 (m, 1H, CH_2OH), 3.84—3.92 (m, 1H, CH_2OH), 6.82—6.88 (m, 1H,), 6.92—6.98 (m, 1H, Ar-H), 7.83—7.90 (m, 1H, Ar-H). $[\alpha]_D^{22}$ +8.7° (c=0.04, MeOH).

(2*RS*,3*S*)-2-(2,4-Difluoro)phenyl-3-methyl-4-triphenylmethyloxy-1,2-epoxybutane (8) A solution of **6** (221 mg, 0.50 mmol) and chloroiodomethane (44 μl, 0.60 mmol) in tetrahydrofuran (2.2 ml) was treated with 1.6 M *n*-butyllithium solution (0.34 ml, 0.55 mmol) at −70 °C under a nitrogen stream. The mixture was stirred for 5 min and then for 1 h at ambient temperature. Aqueous ammonium chloride solution was added and the whole was extracted with ethyl acetate. The organic phase was washed with water and brine, dried over magnesium sulfate and evaporated to afford a residue that was purified by column chromatography on silica gel with ethyl acetate/hexane to give compound **8** (219 mg, 96%) as a 0.4 : 1 mixture of two diastereomers (^{1}H-NMR). It was used in the next reaction without further purification.

(2*S*,3*S*)-2-(2,4-Difluorophenyl)-3-methyl-1-[1-(1,2,4-triazolyl)]-4-(triphenylmethyloxy)-2-butanol (9) Sodium hydride (60% dispersion in mineral oil, 38 mg, 0.956 mmol) was suspended in dimethylformamide (1 ml), and 1,2,4-triazole (99 mg, 1.43 mmol) was added with cooling in an ice-bath. A solution of **8** (219 mg, 0.478 mmol), obtained by the procedure described above, in dimethylformamide (2 ml) was added. The reaction mixture was stirred overnight at 60 °C, then cooled to room temperature, and extracted with ethyl acetate/water. The organic phase was washed with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with methanol/dichloromethane to afford the title compound (72 mg, 29% from the starting material) and a 1 : 1 diastereomeric mixture (5 mg). IR ($CHCl_3$) cm^{-1}: 1616, 1471, 1385, 1217. ^{1}H-NMR δ: 1.48 (d, 3H, J=7.6 Hz, $CHCH_3$), 2.47—2.56 (m, 1H, $CHCH_3$), 2.92 (dd, 1H, J=3.2, 9.6 Hz, CH_2OCPh_3), 3.19 (dd, 1H, J=3.2, 9.6 Hz, CH_2OCPh_3), 4.56 (d, 1H, J=14.0 Hz, CH_2Ar), 4.69 (d, 1H, J=14.0 Hz, CH_2Ar), 4.78 (s, 1H, C–OH), 6.49—6.61 (m, 2H, Ar-H), 7.01—7.09 (m, 1H, Ar-H), 7.16—7.37 (m, 15H, Ar-H), 7.63 (s, 1H, Ar-H), 7.88 (s, 1H, Ar-H). *Anal.* Calcd for $C_{32}H_{29}F_2N_3O_2$: C, 73.13; H, 5.56; N, 7.99. Found: C, 73.13; H, 5.48; N, 7.93.

(2*S*,3*S*)-3-(2,4-Difluorophenyl)-2-methyl-4-[1-(1,2,4-triazolyl)]-1,3-butanediol (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* and the residue purified by column chromatography on silica gel to afford **10** (17 mg). ^{1}H-NMR δ: 1.35 (d, 3H, J=7.2 Hz, $CHCH_3$), 2.30—2.38 (m, 1H, $CHCH_3$), 2.67 (t, 1H, J=4.4 Hz, CH_2OH), 3.46—3.57 (m, 2H, CH_2OH), 4.57 (d, 1H, J=14.0 Hz, CH_2Ar), 4.82 (d, 1H, J=14.0 Hz, CH_2Ar), 5.17 (s, 1H, C–OH), 6.70—6.78 (m, 2H, Ar-H), 7.36—7.43 (m, 1H, Ar-H), 7.69 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H)

(*S*)-2-(2,4-Difluorophenyl)-3-methyl-4-(triphenylmethyloxy)-1,2-butene (11) A 1.6 M solution of *n*-butyllithium in hexane (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 cooling in an ice bath. The mixture was stirred 2 h at room temperature and a solution of **6** (6.63 g, 15.0 mmol) in tetrahydrofuran (30 ml) added dropwise and the mixture was stirred a further 30 min. Hexane (500 ml) and water (300 ml) were added and insoluble material removed by filtration. The organic layer was separated, washed with water (3×) 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 ($CHCl_3$) cm^{-1}: 1614, 1562, 1471, 1384, 1168. ^{1}H-NMR δ: 1.16 (d, 3H, J=7.0 Hz, $CHCH_3$), 2.81—2.89 (m, 1H, $CHCH_3$), 2.99 (dd, 1H, J=6.0, 9.2 Hz, OCH_2), 3.06 (dd, J=6.0 Hz, 1H, 9.2 Hz, OCH_2), 5.11 (s, 1H, C=CH_2), 5.21 (s, 1H, C=CH_2), 6.68—6.75 (m, 2H, Ar-H), 7.00—7.06 (m, 1H, Ar-H), 7.18—7.28 (m, 9H, Ar-H), 7.35—7.39 (m, 6H, Ar-H). $[\alpha]_D^{22}$ −9.6° (c=0.13, MeOH). *Anal.* Calcd for $C_{30}H_{26}O$: C, 81.79; H, 5.95. Found: C, 81.54; H, 6.00.

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methyl-4-triphenylmethyloxy-1,2-butanediol (12) and (2*S*,3*S*)-2-(2,4-Difluorophenyl)-3-methyl-4-triphenylmethyloxy-1,2-butanediol (13) A 4% aqueous solution of osmium tetroxide (36 μl, 5.61 μmol) and a solution of compound **11** (247 mg, 0.561 mmol) in acetone (2.54 ml), were added to a mixture of 50% aqueous *N*-methylmorpholine oxide (144 μl, 0.617 mmol), water (0.5 ml) and acetone (2.5 ml). The solution was stirred overnight, and further 4% osmium tetroxide solution (100 μl, 3.90 μmol) 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 brine, 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 ($CHCl_3$) cm^{-1}: 3155, 1644, 1602, 1471, 1383. FAB-MS m/z: 473 $(M+H)^+$. ^{1}H-NMR δ: 0.75 (d, 3H, J=8.8 Hz, $CHCH_3$), 2.44—2.53 (m, 1H, $CHCH_3$), 2.77 (dd, 1H, J=5.6, 8.4 Hz, CH_2OH), 3.21 (dd, 1H, J=8.4, 14.0 Hz, CH_2OH), 3.32 (dd, 1H, J=2.8, 14.0 Hz, CH_2OH), 3.63 (dd, 1H, J=8.4, 11.2 Hz, CH_2OCPh_3), 3.96 (ddd, 1H, J=2.8, 5.6, 11.2 Hz, CH_2OCPh_3), 4.39 (s, 1H, C–OH), 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, 1H, Ar-H). $[\alpha]_D^{22}$ +6.9° (c=0.12, MeOH).

13: IR ($CHCl_3$) cm^{-1}: 3156, 1644, 1601, 1471, 1384. FAB-MS m/z: 473 $(M+H)^+$. ^{1}H-NMR δ: 1.35 (d, J=7.2 Hz, 3H, $CHCH_3$), 2.34—2.44 (m, 1H, $CHCH_3$), 2.93 (dd, 1H, J=3.6, 9.6 Hz, CH_2OH), 3.19 (dd, 1H, J=3.6, 9.6 Hz, CH_2OH), 3.82 (dd, 1H, J=6.8, 10.6 Hz, CH_2OCPh_3), 3.96 (dd, 1H, J=5.2, 10.6 Hz, CH_2OCPh_3), 4.50 (s, 1H, C–OH), 6.57—6.64 (m, 1H, Ar-H), 6.70—6.75 (m, 1H, Ar-H), 7.18—7.31 (m,

15H, Ar-H), 7.39—7.45 (m, 1H, Ar-H). $[\alpha]_D^{22}$ −5.5° (c=0.14, MeOH).

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methyl-1-[1-(1,2,4-triazolyl)]-4-(triphenylmethyloxy)-2-butanol (14) Triethylamine (54 μl, 0.388 mmol) and methanesulfonyl chloride (28 μl, 0.355 mmol) were added to a solution of **12** (153 mg, 0.323 mmol) in dichloromethane (1.5 ml). The mixture was stirred for 1 h, then ethyl acetate and water were added. The organic phase was washed with water and brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was diluted with dimethylformamide (1.5 ml), and added to a suspension of sodium hydride (59 mg, 1.46 mmol) and 1,2,4-triazole (150 mg, 2.17 mmol) in dimethylformamide (0.5 ml). The mixture was stirred for 15.5 h at 80 °C, then cooled to room temperature, and ethyl acetate and water were added. The organic phase was washed with water and brine and dried over magnesium sulfate, then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with dichloromethane/methanol to afford **14** (98 mg, 60%). IR ($CHCl_3$) cm^{-1}: 1616, 1471, 4686. ^{1}H-NMR δ: 0.87 (d, 3H, J=7.6 Hz, $CHC\underline{H}_3$), 2.37—2.45 (m, 1H,), 3.40 (dd, 1H, J=3.2, 10.0 Hz, $C\underline{H}_2OCPh_3$), 3.55 (dd, 1H, J=5.6, 10.0 Hz, $C\underline{H}_2OCPh_3$), 4.19 (d, 1H, J=14.4 Hz, $C\underline{H}_2Ar$), 4.65 (d, 1H, J=14.4 Hz, $C\underline{H}_2Ar$), 4.88 (s, 1H,), 6.64—6.72 (m, 2H, Ar-H), 7.22—7.30 (m, 4H, Ar-H), 7.32—7.37 (m, 6H, Ar-H), 7.46—7.50 (6H, m, Ar-H), 7.64 (s, 1H, Ar-H), 7.84 (s, 1H, Ar-H). $[\alpha]_D^{22}$ −9.6° (c=0.13, MeOH). *Anal.* Calcd for $C_{32}H_{29}F_2N_3O_2$: C, 73.13; H, 5.56; N, 7.99. Found: C, 73.04; H, 5.69; N, 7.69.

(2*S*,3*R*)-3-(2,4-Difluorophenyl)-2-methyl-4-[1-(1,2,4-triazolyl)]-1,3-butanediol (15) *p*-Toluenesulfonic acid (295 mg, 1.55 mmol) was added to a solution of **14** (740 mg, 1.41 mmol) in methanol (7.4 ml), and the resulting solution was stirred for 1 h at room temperature. Additional *p*-toluenesulfonate (225 mg, 0.427 mmol) was added and stirring was continued for a further 3 h. Ethyl acetate and saturated aqueous sodium hydrogen carbonate were added to the mixture, and the organic phase washed with water and brine, dried over magnesium sulfate, and solvent evaporated *in vacuo*. The residue was then purified by column chromatography on silica gel with dichloromethane/methanol. The enantiomeric excess of this compound measured by HPLC analysis on a 4 mm i.d. × 250 mm Chiralcel OD column (hexane : ethanol = 9 : 1; flow rate, 0.5 ml/min) was 90%. The crude product was recrystallized from dichloromethane–isopropanol. Yield 190 mg (48%), mp 134—135 °C. IR ($CHCl_3$) cm^{-1}: 3156, 1652, 1499, 1386, 1278. ^{1}H-NMR δ: 0.84 (d, 3H, J=7.2 Hz, $CHC\underline{H}_3$), 2.30—2.39 (m, 1H, $C\underline{H}CH_3$), 2.67—2.77 (1H, br s), 3.83 (dd, 1H, J=5.4, 11.2 Hz, $C\underline{H}_2OCPh_3$), 3.99 (dd, 1H, J=3.2, 11.2 Hz, $C\underline{H}_2OCPh_3$), 4.76 (d, 1H, J=14.0 Hz, $C\underline{H}_2Ar$), 4.97 (d, 1H, J=14.0 Hz, $C\underline{H}_2Ar$), 5.28 (s, 1H, C–OH), 6.69—6.78 (m, 2H,), 7.36—7.43 (m, 1H, Ar-H), 7.75 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H). $[\alpha]_D^{22}$ −66.4° (c=0.12, MeOH). *Anal.* Calcd for $C_{13}H_{15}F_2N_3O_2$: C, 55.12; H, 5.34; N, 14.83. Found: C, 55.09; H, 5.33; N, 14.93.

(2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-[1-(1,2,4-triazolyl)]butanal (16) Dimethyl sulfoxide (185 μl, 2.40 mmol) in dichloromethane (0.9 ml) was added dropwise to a solution of oxalyl chloride (96 μl, 1.10 mmol) in dichloromethane (3.3 ml) chilled in a dry ice-acetone bath under a nitrogen stream. The mixture was stirred for 5 min, then a solution of **15** (142 mg, 0.50 mmol) in dichloromethane (4.2 ml) was added dropwise. The resulting mixture was stirred for a further 30 min, then triethylamine (350 μl, 2.50 mmol) was added, and the cooling bath was removed. After reaching room temperture, water was added, and the solution was extracted with two portions of dichloromethane. The organic phase was washed with water and brine, dried over magnesium sulfate, 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.[3]

(2*S*,3*S*)-2-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-[1-(1,2,4-triazolyl)]butyronitrile (2) Compound **16** (36 mg, 0.128 mmol) was suspended in water (0.36 ml) and hydroxylamine *O*-sulfonic acid (17 mg, 1.2 eq) was added. The reaction mixture was heated at 50 °C for 1.5 h. Additional hydroxylamine *O*-sulfonic acid (21 mg) was added and heating continued for a further 40 min. Ethyl acetate and sodium hydrogen sulfate were added to the mixture, the organic phase separated, washed with water and brine, dried over magnesium sulfate, and solvent removed *in vacuo*. Column chromatography of the residue on silica gel with dichloromethane/methanol afforded **2** (12 mg). Spectral data for this compound were identical to those of an authentic sample obtained by the known method.[3]

References and Notes

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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*-butyldiphenylsilyl, 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 Shröder M., *Chem. Rev.*, **80**, 187—223 (1980) and references cited therein.