Triazole Antifungals. III.¹⁾ Stereocontrolled Synthesis of an Optically Active Triazolymethyloxirane Precursor to Antifungal Oxazolidine Derivatives

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Stereocontrolled synthesis of an optically active triazolymethyloxirane 2, an important intermediate for the preparation of antifungal oxazolidine compounds 1, was achieved by two methods using L-lactic acid as a starting material. The key intermediate ketone 6 used in the procedures also served for the synthesis of the enantiomer of 2 and the corresponding diastereomeric epoxide.

Keywords stereocontrolled synthesis; triazole antifungal; L-lactic acid; chiral epoxide; (triazolymethyl)oxirane; stereoselective epoxidation; (dimethylisopropoxysilyl)methylmagnesium chloride; Mitsunobu reaction

In a previous paper¹⁾ we reported the synthesis and antifungal activities of 3-acyl-5-aryl-4-methyloxazolidines (**1**), which were designed as potential inhibitors of the fungal cytochrome P-450 14 α -demethylase. These compounds exhibited remarkably potent activity against a mouse systemic *Candida albicans* infection after oral or parenteral administration. Comparison of the activities of both enantiomers of the 2,4-dichlorophenyl analog (**1**: X = 2,4-Cl₂) revealed that the antifungal activity resides mainly in the (4*R*,5*R*) enantiomer. The potent activity of these triazoles was hypothesized to be a consequence of a structural similarity between (4*R*,5*R*)-**1** and lanosterol, a substrate of the cytochrome P-450 14 α -demethylase. The above-described optically active 2,4-(dichlorophenyl)oxazolidines were obtained *via* optical resolution of the racemic intermediate using *d*- or *l*-10-camphorsulfonic acid as a resolving agent. In order to extend our evaluation studies on this series of compounds, we needed the corresponding (2,4-difluorophenyl)oxazolidines in optically active forms. However, several attempts to resolve the racemic 2,4-difluorophenyl analogs in a practical manner have failed.²⁾ In this paper we report stereoselective synthesis of an optically active triazolymethyloxirane (2*R*,3*S*)-**2** and related stereoisomers from a common starting material. The epoxide **2** is an important intermediate to prepare the (4*R*,5*R*)-(2,4-difluorophenyl)oxazolidines (**1**: X = 2,4-F₂) *via* another key intermediate, the azidoalcohol (2*R*,3*R*)-**3**.

Stereoselective synthesis of (2*R*,3*S*)-**2** and its enantiomer was performed as shown in Chart 2 starting from (*S*)-2-acetoxypropionic acid (**4**), which was readily provided by acetylation of L-lactic acid according to the literature procedure.³⁾ Friedel–Crafts reaction of the acyl chloride, derived from (*S*)-**4**, and 1,3-difluorobenzene afforded a 1 : 1 mixture of α -acetoxy- and α -hydroxy-propiophenone, (*S*)-**5** and (*S*)-**6**, which, on acid treatment in methanol (MeOH), gave the pure alcohol (*S*)-**6**, [α]_D²⁵ – 67.1° (*c* = 1.17, CHCl₃),

in 67% yield from (*S*)-**4**. The optical purity of (*S*)-**6** was determined to be >99.5% ee by high-performance liquid chromatographic (HPLC) analysis using a chiral stationary phase column. For the synthesis of (2*R*,3*S*)-**2**, inversion at the asymmetric center in (*S*)-**6** was required. Tosylation of (*S*)-**6** with *p*-toluenesulfonyl chloride in pyridine at –10 °C afforded the crude solid, which was purified by recrystallization to give the optically pure tosylate (*S*)-**7** in 60% yield. In this reaction, a racemic α -chloropropiophenone derivative was obtained as a by-product. To avoid the formation of this by-product, *p*-toluenesulfonyl anhydride was used instead of *p*-toluenesulfonyl chloride, and the yield of (*S*)-**7** was improved to 76%. On the other hand, mesylation of (*S*)-**6** with methanesulfonyl chloride and triethylamine in CH₂Cl₂ resulted in the competing formation of the sultone⁴⁾ **10** in 25% yield along with a 63% yield of the mesylate (*S*)-**8**. The S_N2 displacement reaction of the tosylate (*S*)-**7** to (*R*)-**6** was conducted by slow addition (over a period of 2 h) of an aqueous solution of 1 eq of lithium hydroxide to (*S*)-**7** in *N,N*-dimethylformamide (DMF) at –15 °C. The enantiomeric hydroxyketone (*R*)-**6**, [α]_D²⁵ + 64.2° (*c* = 0.74, CHCl₃), was obtained in 73% yield. The product was partially racemized (determined by HPLC to be 94.5% ee). Faster addition of lithium hydroxide or a higher reaction temperature brought about appreciable racemization and lowered the optical purity of the product.

Protection of the hydroxy group of (*R*)-**6** with the tetrahydropyranyl group yielded (*R*)-**9**, which was stereoselectively transformed into the chiral epoxide (2*R*,3*S*)-**2** according to the procedure described in the previous paper for the preparation of (±)-**2** from (±)-**9**.¹⁾ The ketone (*R*)-**9** was treated with the Grignard reagent [(dimethylisopropoxysilyl)methylmagnesium chloride] developed by Tamao and Ishida,⁵⁾ and the resulting silyl alcohol **11** was oxidatively desilylated⁵⁾ and then hydrolyzed to the optically pure triol

Chart 1

Chart 2

Chart 3

(2*R*,3*R*)-**12**, after recrystallization, in 77% overall yield from (*R*)-**9**. Mesylation of (2*R*,3*R*)-**12** gave the dimesylate **13**, which was then treated with excess sodium triazolidate to afford the epoxide (2*R*,3*S*)-**2**, mp 88–89.5 °C, $[\alpha]_D^{25} -7.55^\circ$ ($c=1.06$, CHCl_3), in 76% yield from (2*R*,3*R*)-**12**. This reaction is known to proceed *via* an intermediate ep-

oxymesylate **14**, which affords the epoxide **2** through ring-opening and recyclization by an attack of the triazolidate ion.¹⁾ The epoxide (2*R*,3*S*)-**2** gave the azidoalcohol (2*R*,3*R*)-**3** by reaction with sodium azide in a usual manner.

The enantiomeric epoxide (2*S*,3*R*)-**2** was also prepared starting from (*S*)-**6**, *via* (*S*)-**9** and (2*S*,3*S*)-**12**, following the

same reaction sequence as described for the (2*R*,3*S*) epoxide **2**. This epoxide was transformed into the azidoalcohol enantiomer (2*S*,3*S*)-**3**.

Alternative synthesis of the epoxide (2*R*,3*S*)-**2** from the ketone (*S*)-**6** was achieved as shown in Chart 3. As can be seen from the above results, the epoxymesylate **14**, a reaction intermediate in the transformation of **13** to (2*R*,3*S*)-**2**, should be a useful synthetic intermediate. Stereoselective synthesis of the corresponding epoxyalcohol (2*R*,3*R*)-**19** from (*S*)-**9** was carried out by means of a reaction sequence including the silyl-Wittig olefination, stereoselective epoxidation and Mitsunobu reaction. The Grignard reaction of (*S*)-**9** with (trimethylsilyl)methylmagnesium chloride⁶ afforded the silylalcohol **15**, which, on treatment with a catalytic amount of *p*-toluenesulfonic acid in MeOH, underwent β -elimination and deprotection to afford the allylic alcohol (*S*)-**16** in 92% yield from (*S*)-**9**. Epoxidation of (*S*)-**16** with *m*-chloroperbenzoic acid gave an inseparable 4:1 mixture of the epoxyalcohols (2*S*,3*R*)-**17** and (2*S*,3*S*)-**19**, whereas the reaction of (*S*)-**16** with *tert*-butyl hydroperoxide and a catalytic amount of oxyvanadium acetylacetonate⁷ proceeded with higher stereoselectivity to provide a *ca.* 20:1 mixture of (2*S*,3*R*)-**17** and (2*S*,3*S*)-**19** in 87% yield. The latter mixture was subjected to Mitsunobu reaction,⁸ and the resulting benzoate **18** (96% yield) was solvolyzed in MeOH in the presence of a catalytic amount of MeONa to give (2*R*,3*R*)-**19** (85% yield). This product was contaminated with a small amount (<5%) of the diastereoisomer (2*R*,3*S*)-**17**. Mesylation of this epoxyalcohol followed by treatment of the resulting mesylate **14** with sodium triazolidine afforded the epoxide (2*R*,3*S*)-**2**, in 77% yield (after recrystallization) from (2*R*,3*R*)-**19**; this product was identical with the aforementioned optically pure (2*R*,3*S*) epoxide.

The diastereomeric epoxide (2*R*,3*R*)-**21** was also obtained as an oil in a similar manner from the epoxymesylate **20**, which was prepared by mesylation of the epoxyalcohol (2*S*,3*R*)-**17**. This oily epoxide was transformed into the crystalline azidoalcohol (2*R*,3*S*)-**22**.

A different approach to the azidoalcohol (2*R*,3*R*)-**3** from the above-described epoxyalcohol **17** was also examined. Recently, Sharpless and coworkers reported the usefulness of vicinal diol cyclic sulfates,⁹ which act as reactive epoxide equivalents. Thus, the (2*S*,3*R*) epoxyalcohol **17** was treated with sodium triazolidine to afford the diol **23**, which was converted to **24**, then to the cyclic sulfate **25** according to the Sharpless procedure. Treatment of **25** with sodium azide in DMF, followed by hydrolysis of the resulting sulfate ester, gave the desired azidoalcohol (2*R*,3*R*)-**3**. The yield, however, was unsatisfactory (<30%).

Conversion of the above-mentioned optically active triazolylmethyloxiranes and azidoalcohols to new aminoalcohol derivatives with antifungal activity will be reported in a forthcoming paper.

Experimental

Melting points are uncorrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer and proton magnetic resonance spectra (¹H-NMR) on a Varian EM-360L spectrometer in CDCl₃ using Me₄Si as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS D300 spectrometer. Optical rotations were determined on a Perkin-Elmer 141 spectrometer. Thin-layer chromatography (TLC) was performed on TLC plates, Silica gel 60 F₂₅₄ precoated, layer thickness 0.25 mm (E.

Merck), and spots were made visible by ultraviolet (UV) irradiation, by spraying with vanadic acid-sulfuric acid followed by heating, or by iodine treatment. Chromatography columns were prepared with silica gel (60–110 mesh, Kanto Chemical Co., Inc.) and preparative TLC was carried out on TLC plates, Silica gel 60 F₂₅₄ precoated, layer thickness 2 mm (E. Merck). The amount of silica gel and the developing solvents are shown in parentheses. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, triplet of doublets; q, quartet; qd, quartet of doublets; m, multiplet; br, broad.

(*S*)-2-Hydroxy-2',4'-difluoropropiophenone [(*S*)-**6**] Oxalyl chloride (16.9 ml, 0.197 mol) and then DMF (1.0 ml) was added to a solution of (*S*)-2-acetoxypropionic acid (**4**) [$[\alpha]_D^{25} -49.0^\circ$ (*c*=1.35, CHCl₃), lit.,³) [$[\alpha]_D^{25} -49.3^\circ$ (*c*=7.3, CHCl₃); 20.0 g, 0.15 mol] in CH₂Cl₂ (100 ml). The mixture was stirred at room temperature for 1.5 h. At the end of this time, the solvent was distilled off under reduced pressure. To the oily residue, 1,3-difluorobenzene (25.9 g, 0.227 mol) and aluminum chloride (50.5 g, 0.379 mol) were added, with stirring at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. The mixture was diluted with CH₂Cl₂ (60 ml), and poured into ice-water with stirring, then the separated oil was extracted with AcOEt (400 ml). The extract was washed, in turn, with aqueous NaHCO₃ and with brine. Evaporation of the solvent *in vacuo* afforded a *ca.* 1:1 mixture (36 g) of (*S*)-**5** [¹H-NMR (CDCl₃) δ : 1.48 (3H, dd, *J*=7, 1.5 Hz), 2.10 (3H, s), 5.76 (1H, qd, *J*=7, 1.5 Hz), 6.7–7.2 (2H, m), 7.7–8.2 (1H, m)] and (*S*)-**6**. The mixture was dissolved in cold MeOH (180 ml), 45% (v/v) H₂SO₄ (30 ml) was added, and the whole was allowed to stand at room temperature overnight. The mixture was concentrated under reduced pressure to 1/3 the initial volume, and partitioned between AcOEt and water. The organic layer was washed successively with aqueous NaHCO₃ and brine. Evaporation of the solvent and distillation of the product gave (*S*)-**6** (18.6 g, 67%), bp 65–67°C (3 mmHg), [$\alpha]_D^{25} -67.1^\circ$ (*c*=1.17, CHCl₃). The optical purity was >99.5% ee, as determined by HPLC using a chiral stationary phase column, Chiralcel OJ[®] (4.6 mm i.d. $\times$ 250 mm, Daicel Chemical Industries, Tokyo, Japan) (column temperature, 23°C; mobile phase, hexane-isopropanol, 99:1, v/v; flow rate, 1.0 ml/min; detection, UV at 254 nm). Retention times of the enantiomers are as follows: (*S*)-**6**, 13.2 min; (*R*)-**6**, 14.4 min. *Anal.* Calcd for C₉H₈F₂O₂: C, 58.07; H, 4.33; F, 20.41. Found: C, 58.18; H, 4.35; F, 20.32. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3510, 1678, 1615. ¹H-NMR (CDCl₃+D₂O) δ : 1.42 (3H, dd, *J*=6.5, 2 Hz), 5.00 (1H, qd, *J*=6.5, 2 Hz), 6.7–7.3 (2H, m), 7.8–8.2 (1H, m).

(*S*)-2-(*p*-Toluenesulfonyloxy)-2',4'-difluoropropiophenone [(*S*)-**7**] i) *p*-Toluenesulfonyl chloride (10.24 g, 53.7 mmol) was added to a solution of (*S*)-**6** (5.00 g, 26.9 mmol) in pyridine (25 ml) at –10°C and the whole was stirred at the same temperature for 6 h. The mixture was partitioned between AcOEt and aqueous NaHCO₃. The organic layer was washed with brine, dried and concentrated *in vacuo* to give a crystalline residue, which was recrystallized from acetone-cyclohexane to give (*S*)-**7** (5.49 g, 60%), mp 88–90°C, [$\alpha]_D^{25} -19.3^\circ$ (*c*=0.92, CHCl₃). *Anal.* Calcd for C₁₆H₁₄F₂O₄S: C, 56.47; H, 4.15; S, 9.42. Found: C, 56.74; H, 4.06; S, 9.63. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 1695 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.53 (3H, dd, *J*=7, 2 Hz), 2.42 (3H, s), 5.67 (1H, q, *J*=7 Hz), 6.7–7.1 (2H, m), 7.27 (2H, d, *J*=9 Hz), 7.78 (2H, d, *J*=9 Hz), 7.6–8.1 (1H, m).

The mother liquor was concentrated and chromatographed. Elution with benzene afforded 2-chloro-2',4'-difluoropropiophenone (380 mg, 7%) as an oil, whose optical rotation was 0°. MS *m/z*: 206, 204 (M⁺). IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 1690, 1610. ¹H-NMR (CDCl₃) δ : 1.70 (3H, d, *J*=6.5 Hz), 5.15 (1H, q, *J*=6.5 Hz), 6.7–7.2 (2H, m), 7.75–8.25 (1H, m).

ii) A solution of (*S*)-**6** (340 mg, 1.83 mmol) and *p*-toluenesulfonic anhydride (895 mg, 2.74 mmol) in pyridine (1.4 ml) was allowed to stand at 0°C for 30 min. The mixture was diluted with AcOEt and washed, in turn, with aqueous NaHCO₃ and with brine. Evaporation of the solvent under reduced pressure and purification of the product by column chromatography (10 g, benzene) afforded a crystalline mass, which was recrystallized from acetone-hexane to furnish (*S*)-**7** (472 mg, 76%), mp 88–90°C.

Methanesulfonylation of (*S*)-6**** Methanesulfonyl chloride (95 mg, 0.83 mmol) was added, with stirring at 0°C, to a solution of (*S*)-**6** (118 mg, 0.63 mmol) and triethylamine (84 mg, 0.83 mmol) in CH₂Cl₂ (3.5 ml). After 10 min, the mixture was diluted with AcOEt, washed with brine and dried. Evaporation of the solvent under reduced pressure followed by column chromatography (AcOEt-benzene, 1:15, v/v) of the product gave the mesylate (*S*)-**8** (105 mg, 63%) as an oil. ¹H-NMR (CDCl₃) δ : 1.61 (3H, dd, *J*=7, 1.5 Hz), 3.15 (3H, s), 5.87 (1H, qd, *J*=7, 1 Hz), 6.7–7.2 (2H, m), 7.8–8.2 (1H, m). Further elution afforded a more polar product **10** (38 mg, 25%), mp 119–121°C (colorless prisms from AcOEt-hexane). IR

$\nu_{\text{max}}^{\text{KBr}}$: 3490 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.33 (3H, d, $J=6.5$ Hz), 3.61 (1H, dd, $J=14$, 1.5 Hz), 3.98 (1H, s), 4.15 (1H, d, $J=14$ Hz), 5.16 (1H, q, $J=6.5$ Hz), 6.7–7.2 (2H, m), 7.79 (1H, td, $J=9$, 6 Hz).

(R)-2-Hydroxy-2',4'-difluoropropiophenone [(R)-6] A solution of lithium hydroxide (352 mg, 14.7 mmol) in H_2O (20 ml) was added, with stirring at -15°C , to a solution of (S)-7 (5.00 g, 14.7 mmol) in DMF (50 ml) over a period of 2 h. The mixture was stirred at the same temperature for 1 h, then a 5% aqueous solution of NH_4Cl (20 ml) was added. The whole was extracted with AcOEt, washed with brine and concentrated *in vacuo* to leave an oil, which was purified by column chromatography on silica gel (50 g, benzene–AcOEt, 20:1, v/v) to give (R)-6 (2.00 g, 73%) as an oil, $[\alpha]_D^{25} + 64.2^\circ$ ($c=0.74$, CHCl_3), whose $^1\text{H-NMR}$ and TLC behavior were identical with those of (S)-6 described above. The optical purity was determined as 94.5% ee by HPLC in the same manner as described for (S)-6.

(R)-2-(2-Tetrahydropyranyloxy)-2',4'-difluoropropiophenone [(R)-9] A solution of (R)-6 (2.00 g, 10.7 mmol) obtained above, 2,3-dihydropyran (1.17 g, 13.9 mmol) and pyridinium *p*-toluenesulfonate (135 mg, 0.54 mmol) in CH_2Cl_2 (20 ml) was stirred overnight at room temperature. The mixture was washed successively with aqueous NaHCO_3 and brine, dried, and concentrated under reduced pressure to give an oily residue, which was chromatographed (40 g, benzene–hexane, 5:1, v/v) to provide (R)-9 (2.54 g, 87%) as an oil, $[\alpha]_D^{25} + 53.4^\circ$ ($c=1.24$, CHCl_3). IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 1695 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (1.5H, dd, $J=6.5$, 3 Hz), 1.45 (1.5H, dd, $J=6.5$, 1.5 Hz), 1.3–2.0 (6H, m), 3.1–4.1 (2H, m), 4.6–4.8 (1H, m), 4.86 (0.5H, qd, $J=6.5$, 2 Hz), 5.10 (0.5H, dq, $J=6.5$, 2 Hz), 6.7–7.2 (2H, m), 7.7–8.2 (1H, m).

(2S,3R)-2-(2,4-Difluorophenyl)-1-(dimethylisopropoxysilyl)-3-(2-tetrahydropyranyloxy)-2-butanol (11) A suspension of a small amount of magnesium activated with methyl iodide in ether was added, under an N_2 atmosphere, to a refluxing mixture of magnesium (0.50 g, 20.6 mmol), chloromethyldimethylisopropoxysilane⁵⁾ (3.03 g, 18.2 mmol) and ether (60 ml) to initiate the reaction. The mixture was heated under reflux for 3 h and then cooled to 0°C . A solution of (R)-9 (2.62 g, 9.70 mmol) in tetrahydrofuran (THF) (15 ml) was added dropwise, with stirring at 0°C , to the above mixture over a period of 10 min. The whole was warmed to room temperature, stirred for 15 min and again cooled to 0°C . A saturated aqueous solution of NH_4Cl was added to the mixture, which was extracted with AcOEt. The extract was washed with brine and concentrated *in vacuo* to give 11 (4.02 g) as an oil, which was used without further purification for the next reaction. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3425 cm^{-1} .

(2R,3R)-2-(2,4-Difluorophenyl)-1,2,3-butanetriol [(2R,3R)-12] Sodium hydrogen carbonate (0.70 g, 8.33 mmol) and 35% aqueous H_2O_2 (7.0 ml) were added to a solution of 11 (4.54 g, 11.28 mmol) in THF–MeOH (1:1, v/v, 50 ml), and the whole was heated at 70°C for 1.5 h. The mixture was cooled, diluted with AcOEt (100 ml) and washed with brine. Evaporation of the solvent under reduced pressure gave an oily product (4.50 g), whose IR and $^1\text{H-NMR}$ spectra were identical with those of the corresponding racemate.¹⁾ The crude product (2.85 g) was treated with *p*-toluenesulfonic acid (120 mg, 0.63 mmol) in MeOH (40 ml) at room temperature for 30 min. After the addition of triethylamine (0.071 g, 0.70 mmol), the mixture was concentrated under reduced pressure to give a crystalline mass, which was recrystallized from acetone–cyclohexane to yield (2R,3R)-12 [1.58 g, 77% yield from (R)-9], mp 81 – 82°C , $[\alpha]_D^{25} + 11.4^\circ$ ($c=1.11$, CHCl_3). Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{F}_2\text{O}_3$: C, 55.04; H, 5.55; F, 17.42. Found: C, 55.08; H, 5.66; F, 17.21. IR $\nu_{\text{max}}^{\text{KBr}}$: 3430 (br), 3370 (br). The $^1\text{H-NMR}$ spectrum of (2R,3R)-12 was identical with that of the corresponding racemate.¹⁾

(2R,3R)-2-(2,4-Difluorophenyl)-1,3-bis(methanesulfonyloxy)-2-butanol (13) Methanesulfonyl chloride (1.51 ml, 19.5 mmol) was added, with stirring at 0°C , to a solution of (2R,3R)-12 (1.54 g, 7.06 mmol) in pyridine (6 ml). Stirring was continued at the same temperature for 30 min, then the solvent was distilled off under reduced pressure to leave an oil, which was dissolved in AcOEt. This solution was washed, in turn, with aqueous NaHCO_3 and with brine. Evaporation of the solvent *in vacuo* gave 13 (2.69 g, 96%) as an oil, which was used without further purification for the next reaction. The $^1\text{H-NMR}$ spectrum of 13 was identical with that of the corresponding racemate.¹⁾

(2R,3S)-2-(2,4-Difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)-methyl]oxirane [(2R,3S)-2] 1H-1,2,4-Triazole (1.95 g, 28.2 mmol) was slowly added to a suspension of sodium hydride (55% mineral oil dispersion, 1.08 g, 24.7 mmol, washed with hexane) in DMF (30 ml), with stirring at 0°C . When hydrogen gas ceased to evolve, a solution of 13 (2.62 g, 7.05 mmol) in DMF (5 ml) was added. After being stirred at 65 – 70°C for 2 h, the mixture was concentrated under reduced pressure and the residue was partitioned between benzene and water. The organic

layer was washed with brine and dried. Evaporation of the solvent under reduced pressure gave a crude product, which was purified by column chromatography (30 g, benzene–AcOEt, 2:1, v/v) to give a crystalline mass. Recrystallization of this from benzene–hexane gave (2R,3S)-2 (1.40 g, 76% yield from (2R,3R)-12), mp 88 – 89.5°C , $[\alpha]_D^{25} - 7.55^\circ$ ($c=1.06$, CHCl_3). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{F}_2\text{N}_3\text{O}$: C, 57.37; H, 4.11; N, 16.73. Found: C, 57.43; H, 4.37; N, 16.86. The IR and $^1\text{H-NMR}$ spectra were identical with those of the corresponding racemate.¹⁾

(2R,3R)-3-Azido-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol [(2R,3R)-3] A mixture of (2R,3S)-2 (30.0 g, 119 mmol), sodium azide (23.5 g, 360 mmol), ammonium chloride (10.6 g, 195 mmol) and DMF (400 ml) was stirred at 105°C for 4 h. The mixture was concentrated under reduced pressure and the residue was partitioned between benzene and water. The organic layer was washed with brine, dried, and evaporated *in vacuo*. The crystalline residue was recrystallized from benzene–hexane to give (2R,3R)-3 (25.8 g, 73%), mp 139 – 140°C , $[\alpha]_D^{25} - 88^\circ$ ($c=1.12$, CHCl_3). Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{F}_2\text{N}_6\text{O}$: C, 48.98; H, 4.11; F, 12.91; N, 28.56. Found: C, 48.92; H, 4.08; F, 13.02; N, 28.47. The IR and $^1\text{H-NMR}$ spectra were identical with those of the corresponding racemate.¹⁾

(S)-2-(2-Tetrahydropyranyloxy)-2',4'-difluoropropiophenone [(S)-9] According to a procedure similar to that described for (R)-9, (S)-9 (13.0 g, 90%) was prepared as an oil from (S)-6 (10.0 g). $[\alpha]_D^{25} - 56.3^\circ$ ($c=1.11$, CHCl_3). The IR and $^1\text{H-NMR}$ spectra were identical with those of (R)-9.

(2S,3S)-2-(2,4-Difluorophenyl)-1,2,3-butanetriol [(2S,3S)-12] According to a procedure similar to that described for (2R,3R)-12, (2S,3S)-12 was prepared in 79% yield from (S)-9 as crystals, mp 81 – 82°C , $[\alpha]_D^{25} - 11.2^\circ$ ($c=0.97$, CHCl_3).

(2S,3R)-2-(2,4-Difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)-methyl]oxirane [(2S,3R)-2] According to a procedure similar to that described for (2R,3S)-2, (2S,3R)-2 was prepared in 80% yield from (2S,3S)-12 as crystals, mp 88 – 88.5°C , $[\alpha]_D^{25} + 7.53^\circ$ ($c=1.33$, CHCl_3).

(2S,3S)-3-Azido-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol [(2S,3S)-3] According to a procedure similar to that described for (2R,3R)-3, (2S,3S)-3 was prepared in 75% yield from (2S,3R)-2 as crystals, mp 139 – 140°C , $[\alpha]_D^{25} + 88^\circ$ ($c=0.95$, CHCl_3).

(S)-3-(2,4-Difluorophenyl)-3-buten-2-ol [(S)-16] A solution of (S)-9 (11.2 g, 41.4 mmol) in ether (50 ml) was added dropwise to a stirred solution of (trimethylsilyl)methylmagnesium chloride⁶⁾ [prepared from chloromethyltrimethylsilane (10.0 g, 82.9 mmol) and magnesium (2.01 g, 82.6 mmol) in ether (150 ml)] over a period of 10 min at 0°C . The mixture was stirred at the same temperature for 1 h, then quenched with a saturated aqueous solution of NH_4Cl , and extracted with benzene. The extract was washed with brine and evaporated *in vacuo* to give an oily product 15 (15.0 g), which was treated with *p*-toluenesulfonic acid (0.50 g) in MeOH (100 ml) at room temperature for 12 h. The mixture was concentrated under reduced pressure to ca. 1/4 the initial volume, and partitioned between benzene and water. The organic layer was washed with brine and dried. Evaporation of the solvent and distillation of the product under reduced pressure gave (S)-16 (7.00 g, 92%), bp 49 – 51°C (1.5 mmHg), $[\alpha]_D^{25} + 49^\circ$ ($c=1.22$, CHCl_3). Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{F}_2\text{O}$: C, 65.21; H, 5.47; F, 20.63. Found: C, 65.44; H, 5.28; F, 20.51. MS m/z : 184 (M^+), 169, 141 (100%), 140, 139, 127, 119, 114, 101, 63, 45, 43. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3600, 3430 (br). $^1\text{H-NMR}$ (CDCl_3) δ : 1.28 (3H, d, $J=6.5$ Hz), 2.1 (1H, br), 4.69 (1H, brq, $J=6.5$ Hz), 5.17 (1H, brs), 5.54 (1H, t, $J=1.5$ Hz), 6.6–7.6 (3H, m).

(2S,3R)-3-(2,4-Difluorophenyl)-3,4-epoxy-2-butanol [(2S,3R)-17] i) A solution of (S)-16 (7.00 g, 38.0 mmol), *tert*-butyl hydroperoxide (70% purity, 9.80 g, 76.0 mmol) and oxovanadium acetylacetonate (140 mg) in benzene (35 ml) was stirred at room temperature overnight. The mixture was washed with brine, dried and concentrated *in vacuo* to give an oily residue, which was chromatographed on silica gel (100 g, AcOEt–hexane, 1:3, v/v) to afford (2S,3R)-17 (6.58 g, 87%) as an oil, $[\alpha]_D^{25} - 26.4^\circ$ ($c=1.25$, CHCl_3). This product contained a small amount of the inseparable diastereoisomer (2S,3S)-19; the diastereomeric ratio determined from the $^1\text{H-NMR}$ spectrum was ca. 20:1. MS m/z : 200 (M^+), 183, 170, 156, 155, 141, 127 (100%), 114, 101, 63, 45, 43. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3560, 3500 (br). $^1\text{H-NMR}$ (CDCl_3) δ : 1.19 (3H, dd, $J=6.5$, 1.5 Hz), 2.4 (1H, br), 2.89 (1H, d, $J=5$ Hz), 3.26 (1H, d, $J=5$ Hz), 4.10 (1H, q, $J=6.5$ Hz), 6.6–7.1 (2H, m), 7.2–7.6 (1H, m).

ii) A solution of (S)-16 (26 mg, 0.14 mmol) and *m*-chloroperbenzoic acid (85% purity, 40 mg, 0.20 mmol) in CH_2Cl_2 (1 ml) was stirred at room temperature overnight. The mixture was treated with aqueous Na_2SO_3 and extracted with AcOEt. The organic layer was washed successively with aqueous NaHCO_3 and brine. Evaporation of the solvent followed by purification of the crude product by preparative TLC (AcOEt–hexane, 1:3, v/v) afforded a mixture of diastereoisomers (2S,3R)-17 and (2S,3S)-19

(13 mg, 46%), whose ratio was determined as 4:1 on the basis of the $^1\text{H-NMR}$ spectrum.

(2R,3R)-3-(2,4-Difluorophenyl)-3,4-epoxy-2-butyl Benzoate [(2R,3R)-18] Diethyl azodicarboxylate (8.48 g, 49.0 mmol) was added, with stirring at 0°C , to a solution of triphenylphosphine (12.78 g, 48.8 mmol), benzoic acid (7.94 g, 65.0 mmol) and (2S,3R)-17 (6.50 g, 32.5 mmol), prepared as described above by procedure i), in THF (90 ml) over a period of 5 min. The mixture was then warmed to room temperature, stirred for 1 h, and partitioned between benzene and water. The organic layer was washed with brine and dried. Evaporation of the solvent under reduced pressure gave an oily residue, which was chromatographed on silica gel (200 g, AcOEt-hexane, 1:10, v/v) to afford (2R,3R)-18 (10.0 g, 96%) as an oil, $[\alpha]_D^{25} -52.6^\circ$ ($c=1.33$, CHCl_3). This product contained a small amount (<5% by $^1\text{H-NMR}$) of the (2R,3S) diastereoisomer, possibly derived from (2S,3S)-19. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ 1716 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.35 (3H, dd, $J=6.5$, 1.5 Hz), 2.88 (1H, d, $J=4.5$ Hz), 3.22 (1H, d, $J=4.5$ Hz), 5.44 (1H, q, $J=6.5$ Hz), 6.6–7.1 (2H, m), 7.2–7.8 (4H, m), 7.9–8.2 (2H, m).

(2R,3R)-3-(2,4-Difluorophenyl)-3,4-epoxy-2-butanol [(2R,3R)-19] The benzoate (2R,3R)-18 (8.40 g, 26.2 mmol) obtained above was added to a 0.5% solution of MeONa in MeOH (85 ml). The mixture was allowed to stand at room temperature for 6 h, then diluted with AcOEt, washed with brine and dried. The solvent was evaporated off *in vacuo* to give an oil, which was purified by column chromatography (100 g, AcOEt-hexane, 1:4, v/v) to yield (2R,3R)-19 (4.47 g, 85%) as an oil. $[\alpha]_D^{25} -54.9^\circ$ ($c=1.45$, CHCl_3). This product was contaminated with a small amount (<5% by $^1\text{H-NMR}$) of the diastereoisomer (2R,3S)-17. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3590, 3470 (br). $^1\text{H-NMR}$ (CDCl_3) δ : 1.15 (3H, dd, $J=6.5$, 1.5 Hz), 2.2 (1H, br), 2.79 (1H, d, $J=5$ Hz), 3.28 (1H, d, $J=5$ Hz), 4.15 (1H, br), 6.6–7.1 (2H, m), 7.2–7.7 (1H, m).

(2R,3R)-3-(2,4-Difluorophenyl)-3,4-epoxy-2-butyl Methanesulfonate (14) Triethylamine (3.40 g, 33.6 mmol) and then methanesulfonyl chloride (3.35 g, 29.2 mmol) were added to a stirred solution of (2R,3R)-19 (4.50 g, 22.5 mmol) in CH_2Cl_2 (45 ml) at -15°C . Stirring was continued for 10 min at the same temperature, then the mixture was partitioned between AcOEt and water. The organic layer was dried and concentrated *in vacuo* to give 14 (6.33 g, 100%) as an oil, which was used without further purification for the next reaction. The $^1\text{H-NMR}$ data were identical with that of the racemic compound described previously.¹⁾

Transformation of the Epoxymesylate 14 into the Triazolymethyloxirane (2R,3S)-2 The mesylate 14 (5.80 g, 20.8 mmol) in DMF (25 ml) was added to a solution of sodium triazolidine, prepared from triazole (5.05 g, 73.1 mmol) and sodium hydride (55% mineral oil dispersion, 2.74 g, 62.8 mmol, washed with hexane) in DMF (50 ml), and the mixture was stirred at 60°C for 3 h. After cooling, the mixture was diluted with benzene and washed with brine. The solvent was then distilled off under reduced pressure to give an oily residue, which was purified by column chromatography (80 g, AcOEt-hexane, 2:1, v/v) to afford a crystalline product (4.22 g), $[\alpha]_D^{25} -6.95^\circ$ ($c=1.41$, CHCl_3). Recrystallization from benzene-hexane provided the pure triazolymethyloxirane (2R,3S)-2 [4.01 g, 77% yield from (2R,3R)-19], mp $88-89.5^\circ\text{C}$, $[\alpha]_D^{25} -7.52^\circ$ ($c=1.21$, CHCl_3).

(2S,3R)-3-(2,4-Difluorophenyl)-3,4-epoxy-2-butyl Methanesulfonate (20) Methanesulfonyl chloride (90 mg, 0.79 mmol) was added to a stirred solution of (2S,3R)-17 (110 mg, 0.55 mmol), obtained by procedure i) above, and triethylamine (85 mg, 0.85 mmol) in CH_2Cl_2 (2 ml) at -10°C . After 10 min, the mixture was treated with aqueous NaHCO_3 and extracted with AcOEt. The extract was washed with brine, dried and concentrated *in vacuo* to dryness to give the crude mesylate 20 (155 mg, ca. 100%) as a solid, which was used without further purification for the next reaction. $^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (3H, dd, $J=6.5$, 1 Hz), 2.90 (1H, d, $J=5$ Hz), 2.93 (3H, s), 3.21 (1H, d, $J=5$ Hz), 4.99 (1H, q, $J=6.5$ Hz), 6.6–7.7 (3H, m).

(2R,3R)-2-(2,4-Difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)-methyl]oxirane [(2R,3R)-21] The mesylate 20 (155 mg, 0.55 mmol) in DMF (1 ml) was added to a solution of sodium triazolidine, prepared from sodium hydride (55% mineral oil dispersion, 50 mg, 1.15 mmol) and triazole (90 mg, 1.30 mmol) in DMF (2 ml) as described for (2R,3S)-2, and the mixture was stirred at 60°C for 3 h under an N_2 atmosphere. The cooled mixture was partitioned between benzene and brine. The organic layer was dried, and concentrated *in vacuo*, then the residue was purified by preparative TLC (AcOEt-hexane, 3:1, v/v) to afford (2R,3R)-21 (86 mg, 62% yield from 17) as an oil, $[\alpha]_D^{25} -5.0^\circ$ ($c=0.96$, CHCl_3), which was contaminated with a small amount (ca. 5% content determined by $^1\text{H-NMR}$) of the diastereomeric epoxide (2S,3R)-2, which could have originated from the minor epoxyalcohol (2S,3S)-19 in (2S,3R)-17. MS

m/z : 252, 251 (M^+), 236, 188, 169, 153, 141, 119, 110, 96 (100%), 69. The $^1\text{H-NMR}$ spectrum of (2R,3R)-21 was identical with that of the racemic material.¹⁾

(2R,3S)-3-Azido-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol [(2R,3S)-22] A mixture of (2R,3R)-21 (74 mg, 0.29 mmol) obtained above, sodium azide (90 mg, 1.38 mmol), ammonium chloride (20 mg, 0.37 mmol) and DMF (1.5 ml) was stirred at 110°C for 2.5 h. After cooling, the mixture was partitioned between AcOEt and brine. The organic layer was washed with brine, dried and concentrated *in vacuo*. Preparative TLC (AcOEt-hexane, 7:1, v/v) of the residue gave a crystalline mass (62 mg), mp $115-120^\circ\text{C}$, $[\alpha]_D^{25} +31.3^\circ$ ($c=0.72$, CHCl_3), which was recrystallized from benzene-hexane to yield (2R,3S)-22 (55 mg, 63%) as prisms, mp $126-127.5^\circ\text{C}$, $[\alpha]_D^{25} +33.5^\circ$ ($c=0.93$, CHCl_3). The IR and $^1\text{H-NMR}$ spectra were identical with those of the racemic material.¹⁾

(2R,3S)-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol (23) The epoxyalcohol 17 (125 mg, 0.63 mmol), prepared as described above by procedure i), was dissolved in a solution of sodium triazolidine, prepared from sodium hydride (55% mineral oil dispersion, 55 mg, 1.25 mmol) and triazole (97 mg, 1.4 mmol) in DMF (2.5 ml) as described above. The mixture was stirred at 65°C for 2 h. After cooling, the mixture was diluted with AcOEt and washed with brine. Evaporation of the solvent followed by column chromatography (3 g, AcOEt) afforded 23 (117 mg, 70%) as an oil, $[\alpha]_D^{25} -66^\circ$ ($c=1.30$, CHCl_3). MS m/z : 270 ($\text{M}^+ + 1$), 224 (100%), 182, 156, 141, 127, 113, 82, 70. $^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (3H, dd, $J=6.5$, 1.5 Hz), 3.99 (1H, qd, $J=6.5$, 1 Hz), 4.57 (1H, dd, $J=14$, 1.5 Hz), 5.04 (1H, dd, $J=14$, 2 Hz), 6.5–7.0 (2H, m), 7.55 (1H, td, $J=9$, 7 Hz), 7.75 (1H, s), 8.12 (1H, s).

(4R,5S)-4-(2,4-Difluorophenyl)-5-methyl-4-[(1H-1,2,4-triazol-1-yl)-methyl]-1,3,2-dioxathiolane 2-Oxide (24) A solution of SOCl_2 (485 mg, 4.07 mmol) in CH_2Cl_2 (2 ml) was added dropwise to a solution of 23 (1.00 g, 3.72 mmol) and triethylamine (825 mg, 8.15 mmol) in CH_2Cl_2 (10 ml), with stirring at 0°C . The mixture was stirred at the same temperature for 15 min and then partitioned between AcOEt and ice-water. The organic layer was washed with brine and dried. Evaporation of the solvent under reduced pressure gave an oily residue, which was chromatographed (15 g, AcOEt-benzene, 1:1–2:1, v/v) to yield 24 (1.18 g, 100%) as an oil. This product was a 5:4 mixture of diastereoisomers, A and B, as determined from the $^1\text{H-NMR}$ spectrum. MS m/z : 316 ($\text{M}^+ + 1$), 251, 233, 169, 141 (100%), 127, 113, 86, 82. $^1\text{H-NMR}$ (CDCl_3) δ : for A; 1.87 (3H, dd, $J=6.5$, 1.5 Hz), 5.00 (1H, q, $J=6.5$ Hz), 5.05 (2H, s), 6.6–7.5 (3H, m), 7.64 (1H, s), 8.21 (1H, s); for B; 1.78 (3H, dd, $J=6.5$, 1.5 Hz), 4.59 (1H, d, $J=14$ Hz), 4.91 (1H, d, $J=14$ Hz), 5.20 (1H, q, $J=6.5$ Hz), 7.74 (1H, s), 8.05 (1H, s).

(4R,5S)-4-(2,4-Difluorophenyl)-5-methyl-4-[(1H-1,2,4-triazol-1-yl)-methyl]-1,3,2-dioxathiolane 2,2-Dioxide (25) A solution of 24 (900 mg, 2.85 mmol), $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (9 mg) and NaIO_4 (920 mg, 4.30 mmol) in acetonitrile (13.5 ml)–water (20 ml) was stirred at room temperature for 40 min, after which AcOEt was added and the mixture was washed with brine. Evaporation of the solvent followed by purification of the product by column chromatography (20 g, AcOEt-benzene, 1:1–2:1, v/v) afforded 25 (786 mg, 83%) as a solid. Recrystallization from benzene-hexane gave a pure specimen, mp $127-128^\circ\text{C}$, $[\alpha]_D^{25} -25.9^\circ$ ($c=1.19$, CHCl_3). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{F}_2\text{N}_3\text{O}_4\text{S}$: C, 43.50; H, 3.35; N, 12.68. Found: C, 43.66; H, 3.38; N, 12.55. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1612, 1605, 1510. $^1\text{H-NMR}$ (CDCl_3) δ : 1.84 (3H, d, $J=6.5$, 2 Hz), 5.03 (2H, s), 5.21 (1H, q, $J=6.5$ Hz), 6.7–7.5 (3H, m), 7.69 (1H, s), 8.15 (1H, s).

Reaction of 25 and Sodium Azide A mixture of 25 (50 mg, 0.15 mmol), sodium azide (30 mg, 0.46 mmol) and DMF (1 ml) was stirred at 50°C for 2 h. Then, 20% sulfuric acid (1 ml) was added and the whole was stirred at the same temperature for 4 h. After cooling, the mixture was made alkaline (pH 9) by the addition of a diluted aqueous solution of NaHCO_3 and concentrated under reduced pressure. Acetone was added to the residue and insoluble materials that emerged were filtered off. The filtrate was concentrated and the residue was purified by preparative TLC (AcOEt-benzene, 4:1, v/v) to give (2R,3R)-3 (13 mg, 29%) as a solid. Recrystallization from benzene-hexane afforded a pure specimen, mp $139-140^\circ\text{C}$, $[\alpha]_D^{25} -88^\circ$ ($c=0.58$, CHCl_3), which was identical with the sample obtained above by the reaction of (2R,3S)-2 and sodium azide.

References and Notes

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