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Stereoselective Syntheses of (+)- and (-)-Terconazole

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Abstract: The recently described *cis*-benzoates (2*R*,4*R*)- and (2*S*,4*S*)-**2** were transformed into (+)- and (-)-terconazole, respectively, by reaction with 1*H*-1,2,4-triazole followed by hydrolysis to give alcohols (+)- and (-)-**3** which were mesylated and reacted with phenol **5**. The ee's of (+)- and (-)-terconazole determined by HPLC on the CSP Chiralcel OD-H were > 99%.

Terconazole is a potent orally active, broad-spectrum antifungal azolic agent[1] which is marketed as a racemic mixture of *cis*-1-[4-[[2-(2,4-dichlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl] methoxy]phenyl]-4-(1-methylethyl)piperazine, (±)-**1**. To the best of our knowledge, syntheses of the enantiomers of terconazole have not been described yet, and thus no information is available about the antifungal activity of both enantiomers.

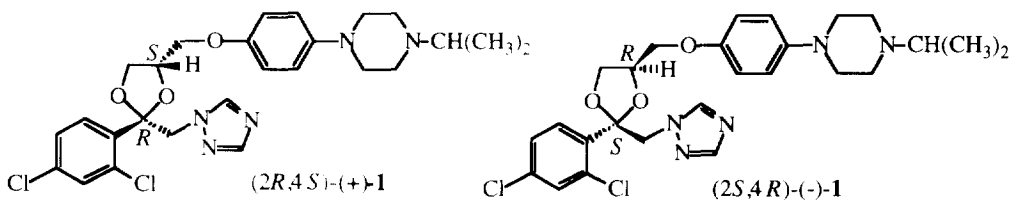
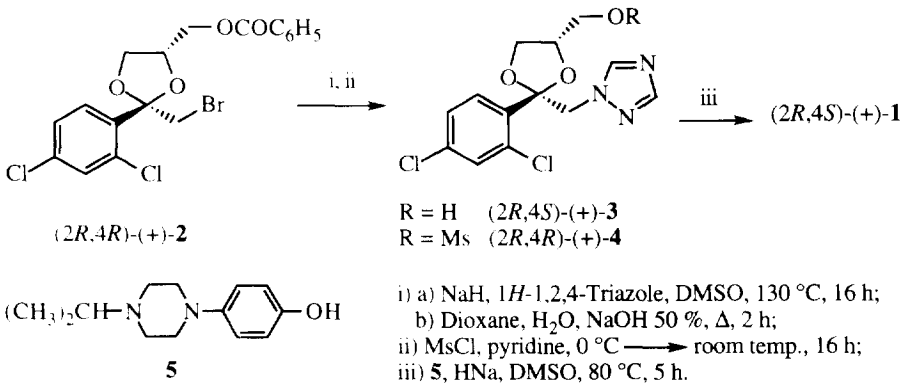


Figure 1. Enantiomers of terconazole

We have recently described[2] the preparation of both enantiomers of (+)- and (-)-ketoconazole from bromobenzoates (2*R*,4*R*)-(+)-**2** and (2*S*,4*S*)-(-)-**2**, respectively. The syntheses of both enantiomers of terconazole from these intermediates should be straightforward, following the procedures[3] described for the preparation of (±)-**1** from (±)-**2**. As shown in Scheme 1, reaction of (2*R*,4*R*)-(+)-**2** with the sodium salt of 1*H*-1,2,4-triazole in dimethylsulfoxide (DMSO) followed by alkaline hydrolysis gave the corresponding alcohol (2*R*,4*S*)-(+)-**3**. Esterification of this alcohol with methanesulfonyl chloride gave the corresponding mesylate (2*R*,4*R*)-(+)-**4** which on reaction with the sodium phenolate derived from 4-[4-(1-methylethyl)piperazin-1-yl]phenol in DMSO afforded (+)-terconazole, (2*R*,4*S*)-(+)-**1**, in yields comparable with those described for the racemic compound.

The same sequence of transformations, starting from (2*S*,4*S*)-(-)-**2** led to (2*S*,4*R*)-(-)-**1** via the corresponding alcohol (2*S*,4*R*)-(-)-**3** and mesylate (2*S*,4*S*)-(-)-**4**.

The ee's of (+)- and (-)-**1** were established to be > 99% by chiral HPLC, using the CSP Chiralcel OD-H and a mixture of hexane / ethanol in a ratio of 1 / 1 containing 0.1% of diethylamine, as eluent.



Scheme 1. Synthesis of (+)-terconazole.

All new compounds were fully characterized through their spectroscopic data (IR, ^{1}H- and ^{13}C-NMR) and elemental analyses. Since the spectra of the enantiomers are identical, only the spectra for one member of each pair is given in the experimental. Assignment of the NMR spectra of these compounds could be easily carried out on the basis of COSY ^{1}H / ^{1}H and ^{1}H / ^{13}C experiments and by comparison with published data.[2,4] It is worth noting that the m.p.'s of the single enantiomers of terconazole and its precursors **3** and **4**, are about 20 to 26 °C lower than those of the corresponding racemic mixture.

The stereoselective syntheses of (+)- and (-)-terconazole herein described, open the way for future activity studies.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting-point apparatus, model MFB 595010M. IR spectra were recorded on a FT/IR Perkin-Elmer spectrometer, model 1600. NMR spectra were taken on Varian Gemini 300 and VXR 500 spectrometers. The chemical shifts are given in ppm (δ scale) relative to internal TMS. COSY ^{1}H / ^{1}H experiments were performed using standard procedures while for COSY ^{1}H / ^{13}C experiments the HMQC sequence with an indirect detection probe was used. Coupling constants are expressed in Hertz. Optical rotations were measured in a 1-dm cell on a Perkin-Elmer, model 241 polarimeter. HPLC analyses were carried out on a Waters model 600 liquid chromatograph, provided with variable λ detector, using the chiral column Chiracel OD-H (25 x 0.46 cm; Daicel Chem. Ind., Ltd.), a mixture of ethanol / hexane in a ratio of 1 / 1, containing 0.1% diethylamine, as eluent, flow 0.5 ml / min, λ = 235 nm, temp 25°C. Column chromatography was carried out by using silica gel SDS 60 A CC (70-230 mesh), 50 g silica gel per gram of product. Mycroanalyses were carried out at the Microanalysis Service of the Centro de Investigación y Desarrollo, CID, Barcelona, Spain.

(2*R*,4*S*)-(+)-2-(2,4-Dichlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolane-4-methanol (2*R*,4*S*)-(+)-**3**. 1*H*-1,2,4-Triazole (358 mg, 5.17 mmol) was added to a suspension of NaH (60-65% in mineral oil, 230 mg, ca. 5.7 mmol) in anhydrous DMSO (5.5 ml) and the mixture was stirred at room temp. for 1 h. Then, (2*R*,4*R*)-(+)-**2** [$[\alpha]_D^{20}$ = + 24.7 (c = 0.5, $CHCl_3$), 1.55 g, 3.47 mmol] was added and the solution was heated at 130 °C for 16 h. The reaction mixture was allowed to cool to room temp., diluted with water (30 ml) and extracted with CH_2Cl_2 (4 x 40 ml). The combined organic extracts were washed with brine (3 x 40 ml), dried with Na_2SO_4 and concentrated at reduced pressure to dryness to give an oily residue (1.46 g). To a solution of this residue in dioxane (7.8 ml) containing water (1.5 ml), 50% aqueous solution of NaOH (10.3 ml) was added and

the mixture was heated at the reflux temp. for 2 h. The reaction mixture was allowed to cool to room temp., diluted with water (30 ml) and extracted with CH_2Cl_2 (4 x 40 ml). The combined organic extracts were washed with water (3 x 75 ml), dried with Na_2SO_4 and concentrated at reduced pressure to dryness to give an oily residue which was submitted to column chromatography (silica gel, $CHCl_3$ / methanol in a ratio of 98 / 2 as eluent) and it was cristallized from a mixture of ethyl acetate / diethyl ether affording pure (2*R*,4*S*)-(+)-**3** (448 mg, 39% yield) as a white solid, m.p. 117-119 °C [lit.[3] (±)-**3**, m. p. 138.2 °C], $[\alpha]_D^{20}$ = + 20.1 (c = 0.5, $CHCl_3$). IR (KBr) ν: 3195, 2921, 2868, 1585, 1558, 1520, 1468, 1430, 1379, 1278, 1220, 1168, 1135, 1104, 1058, 1026, 971, 872, 833, 794, 736, 672 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.2-2.8 (broad, 1 H, CH_2OH), 3.26 (dd, J = 12.0 Hz, J' = 4.5 Hz, 1 H) and 3.68 (dd, J = 12.0 Hz, J' = 3.5 Hz, 1 H) (CH_2-OH), 3.72 (dd, J = 8.0 Hz, J' = 6.5 Hz, 1 H) and 3.87 (dd, J = 8.0 Hz, J' = 7.0 Hz, 1 H) (5-H_2), 4.17 (m, 1 H, 4-H), 4.78 (s, 2 H, CH_2-N), 7.28 (dd, J = 8.5 Hz, J' = 2.0 Hz, 1 H, 5-H of $C_6H_3Cl_2$), 7.49 (d, J = 2.0 Hz, 1 H, 3-H of $C_6H_3Cl_2$), 7.59 (d, J = 8.5 Hz, 1 H, 6-H of $C_6H_3Cl_2$), 7.97 (s, 1 H, 3-H of triazole), 8.17 (s, 1 H, 5-H of triazole). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 53.4 (CH_2, CH_2-N), 61.5 (CH_2, CH_2-OH), 66.3 (CH_2, C5), 76.8 (CH, C4), 107.2 (C, C2), 127.2 (CH, C5 of $C_6H_3Cl_2$), 129.6 (CH, C6 of $C_6H_3Cl_2$), 131.3 (CH, C3 of $C_6H_3Cl_2$), 132.9 (C, C2 of $C_6H_3Cl_2$), 134.1 (C, C1 of $C_6H_3Cl_2$), 136.0 (C, C4 of $C_6H_3Cl_2$), 145.1 (CH, C5 of triazole), 151.4 (CH, C3 of triazole). $C_{13}H_{13}Cl_2N_3O_3$ (330.19): calcd. C 47.29% H 3.98% N 12.73% Cl 21.48%. Found: C 47.16% H 3.95% N 12.68% Cl 21.46%.

(2*R*,4*R*)-(+)-[2-(2,4-Dichlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyl methanesulfonate (2*R*,4*R*)-(+)-**4.** To a cold (ice-bath) solution of (2*R*,4*S*)-(+)-**3** (400 mg, 1.21 mmol) in anhydrous pyridine (5 ml), methanesulfonyl chloride (98%)(0.19 ml, 2.42 mmol) was added and the mixture was stirred for 16 h allowing the reaction mixture to warm slowly to room temp. The mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic phases were washed with water (3 x 40 ml), dried with Na_2SO_4 and concentrated at reduced pressure to dryness to give an oily residue which was crystallized from a mixture of ethyl acetate / diethyl ether affording pure (2*R*,4*R*)-(+)-**4** (470 mg, 95% yield) as a white solid, m.p. 71-73 °C [lit.[3] (±)-**4**, m. p. 98.0 °C], $[\alpha]_D^{20}$ = + 22.2 (c = 0.5, $CHCl_3$). IR (KBr) ν: 3120, 3020, 2959, 2934, 2896, 1587, 1558, 1509, 1466, 1425, 1352, 1273, 1216, 1174, 1136, 1104, 1051, 1026, 1007, 966, 858, 831, 812, 794, 675 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 3.08 (s, 3 H, SO_3-CH_3), 3.74 (dd, J = 8.5 Hz, J' = 5.0 Hz, 1 H) and 3.89 (dd, J = 8.5 Hz, J' = 7.0 Hz, 1 H) (5-H_2), 3.90 (dd, J = 11.0 Hz, J' = 5.0 Hz, 1 H) and 4.00 (dd, J = 11.0 Hz, J' = 6.0 Hz, 1 H) (CH_2OMs), 4.32 (m, 1 H, 4-H), 4.77 (d, J = 14.5 Hz, 1 H) and 4.82 (d, J = 14.5 Hz, 1 H) (CH_2-N), 7.25 (dd, J = 8.5 Hz, J' = 2.0 Hz, 1 H, 5-H of $C_6H_3Cl_2$), 7.47 (d, J = 2.0 Hz, 1 H, 3-H of $C_6H_3Cl_2$), 7.51 (d, J = 8.5 Hz, 1 H, 6-H of $C_6H_3Cl_2$), 7.90 (s, 1 H, 3-H of triazole) and 8.15 (s, 1 H, 5-H of triazole). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 37.7 (CH_3, CH_3SO_3), 53.4 (CH_2, CH_2-N), 66.2 (CH_2, C5), 67.4 (CH_2, CH_2OMs), 73.8 (CH, C4), 108.0 (C, C2), 127.3 (CH, C5 of $C_6H_3Cl_2$), 129.5 (CH, C6 of $C_6H_3Cl_2$), 131.5 (CH, C3 of $C_6H_3Cl_2$), 133.0 (C, C2 of $C_6H_3Cl_2$), 133.3 (C, C1 of $C_6H_3Cl_2$), 136.3 (C, C4 of $C_6H_3Cl_2$), 144.9 (CH, C5 of triazole), 151.3 (CH, C3 of triazole). $C_{14}H_{15}Cl_2N_3O_3S$ (408.26): calcd. C 41.19% H 3.71% N 10.29% S 7.85% Cl 17.37%. Found: C 41.20% H 3.76% N 10.33% S 7.97% Cl 17.30%.

(2*R*,4*S*)-(+)-1-[4-[[2-(2,4-diclorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl] methoxy]phenyl]-4-(1-methylethyl)piperazine (2*R*,4*S*)-(+)-**1.** To a suspension of NaH (60-65% dispersion in mineral oil, 100 mg, 2.5 mmol) in anhydrous DMSO (8 ml), phenol **5** (474 mg, 2.15 mmol) was added and the mixture was stirred at room temp. for 1 h. Then, (2*R*,4*R*)-(+)-**4** (440 mg, 1.08 mmol) was added and the mixture was heated at 80 °C for 5 h with stirring. The reaction mixture was allowed to cool to room temp., diluted with water (40 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were washed with aqueous 5 N NaOH (3 x 50 ml) and water (3 x 50 ml), dried with Na_2SO_4 and concentrated at reduced pressure to dryness. The oily residue was dissolved in ethyl acetate (30 ml), decoloured with charcoal and crystallized from diisopropyl ether affording (2*R*,4*S*)-(+)-**1** (295 mg, 51% yield) as a white solid m.p. 106°-107°C [lit.[3] (±)-**1**, m. p. 126.3 °C], $[\alpha]_D^{20}$ = + 15.6 (c = 0.4, $CHCl_3$). The ee was shown to be > 99% by chiral HPLC, r.t. 18.00 min. IR (KBr) ν: 3125, 3070, 2962, 2818, 1586, 1559, 1513, 1464, 1380, 1272, 1245, 1178, 1134, 1104, 1049, 1028, 978, 918, 868, 817, 795, 736, 675 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.09 [d, J = 6.5 Hz, 6 H, $CH(CH_3)_2$],

2.68 [t, J = 5.0 Hz, 4 H, Ar-N(CH_2-)$_2$ of piperazine], 2.70 [m, 1 H, C*H*(CH_3)$_2$], 3.10 [t, J = 5.0, 4 H, *i*-Pr-N(CH_2-)$_2$ of piperazine], 3.49 (dd, J = 10.0 Hz, J' = 6.0 Hz, 1 H, CH_A-OAr), 3.80 (m, 2 H, CH_B-OAr and 5-H_A), 3.91 (dd, J = 8.5 Hz, J' = 6.5 Hz, 1 H, 5-H_B), 4.34 (m, 1 H, 4-H), 4.75 (d, J = 14.5 Hz, 1 H) and 4.83 (d, J = 14.5 Hz, 1 H) (CH_2-N), 6.77 [d, J = 9.0 Hz, 2 H, N-C(CH)$_2$ of OC_6H_4N], 6.88 [d, J = 9.0 Hz, 2 H, O-C(CH)$_2$ of OC_6H_4N], 7.24 (dd, J = 8.5 Hz, J' = 2.0 Hz, 1 H, 5-H of $C_6H_3Cl_2$), 7.46 (d, J = 2.0 Hz, 1 H, 3-H of $C_6H_3Cl_2$), 7.55 (d, J = 8.5 Hz, 1 H, 6-H of $C_6H_3Cl_2$), 7.88 (s, 1 H, 3-H of triazole) and 8.19 (s, 1 H, 5-H triazole). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 18.6 [CH_3, CH(CH_3)$_2$], 48.7 [2 CH_2, *i*-Pr-N(CH_2-)$_2$ of piperazine], 50.6 [2 CH_2, Ar-N(CH_2-)$_2$ of piperazine], 53.5 (CH_2, CH_2-N), 54.4 [CH, *C*H(CH_3)$_2$], 67.3 (CH_2, C5), 67.5 (CH_2, CH_2O), 74.6 (CH, C4), 107.5 (C, C2), 115.0 [CH, N-C(*C*H)$_2$ of OC_6H_4N], 117.9 [CH, O-C(*C*H)$_2$ of OC_6H_4N], 127.1 (CH, C5 of $C_6H_3Cl_2$), 129.5 (CH, C6 of $C_6H_3Cl_2$), 131.3 (CH, C3 of $C_6H_3Cl_2$), 133.0 (C, C2 of $C_6H_3Cl_2$), 134.0 (C, C1 of $C_6H_3Cl_2$), 135.9 (C, C4 of $C_6H_3Cl_2$), 144.8 (CH, C5 of triazole), 146.2 (C, N-*C*(CH)$_2$ of OC_6H_4N], 151.2 (CH, C3 of triazole), 152.0 (C, O-*C*(CH)$_2$ of OC_6H_4N]. $C_{26}H_{31}Cl_2N_5O_3$ (532.49): calcd. C 58.65% H 5.87% N 13.15% Cl 13.32%. Found: C 58.69% H 5.89% N 13.06% Cl 13.65%.

(2*S*,4*R*)-(-)-2-(2,4-Dichlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolane-4-methanol (2*S*,4*R*)-(-)-**3**. This compound was prepared as described above for (2*R*,4*S*)-(+)-**3**. From (2*S*,4*S*)-(-)-**2** [$[\alpha]_D^{20}$ = - 26.6 (c = 0.5, $CHCl_3$),1.55 g, 3.47 mmol] and 1*H*-1,2,4-triazole (358 mg, 5.17 mmol), (2*S*,4*S*)-(-)-**3** (485 mg, 42% yield) was obtained, after column chromatography and crystallization from a mixture of diethyl ether / ethyl acetate, as a white solid, m.p. 117-119 °C, $[\alpha]_D^{20}$ = - 21.5 (c = 0.5, $CHCl_3$). $C_{13}H_{13}Cl_2N_3O_3$ (330.19): calcd. C 47.29% H 3.98% N 12.73% Cl 21.48%. Found: C 47.23% H 4.01,% N 12.71% Cl 21.54%.

(2*S*,4*S*)-(-)-[2-(2,4-Dichlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyl methanesulfonate (2*S*,4*S*)-(-)-**4.** This compound was prepared as described above for (2*R*,4*R*)-(+)-**4**. From (2*S*,4*R*)-(-)-**3** (400 mg, 1.21 mmol) and methanesulfonyl chloride (0.19 ml, 98%, 2.42 mmol), after crystallization from a mixture of ethyl acetate / diethyl ether, (2*S*,4*S*)-(-)-**4** (460 mg, 93% yield) was obtained as a white solid, m.p. 74-76 °C, $[\alpha]_D^{20}$ = - 23.0 (c = 0.5, $CHCl_3$). $C_{14}H_{15}Cl_2N_3O_3S$ (408.26): calcd. C 41.19% H 3.71% N 10.29% S 7.85% Cl 17.37%. Found: C 41.25% H 3.77% N 10.22% S 7.77% Cl 17.45%.

(2*S*,4*R*)-(-)-1-[4-[[2-(2,4-diclorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-4-yl] methoxy]phenyl]-4-(1-methylethyl)piperazine (2*S*,4*R*)-(-)-**1.** This compound was prepared as described above for (2*R*,4*S*)-(+)-**1**. From (2*S*,4*S*)-(-)-**4** (420 mg, 1.03 mmol), phenol **5** (455 mg, 2.06 mmol), (2*S*,4*S*)-(-)-**1** (275 mg, 50% yield), was obtained, after crystallization from diisopropyl ether, as a white solid m.p. 105°-106 °C, $[\alpha]_D^{20}$ = - 15.5 (c = 0.4, $CHCl_3$) The ee was shown to be > 99% by chiral HPLC, r.t. 20.61 min. $C_{26}H_{31}Cl_2N_5O_3$ (532.49): calcd. C 58.65% H 5.87% N 13.15% Cl 13.32%. Found: C 58.78% H 5.90% N 13.07% Cl 13.32%.

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