Pergamon

Tetrahedron Letters, Vol. 38, No. 45, pp. 7839-7842, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10129-0

Efficient Stereoselective Synthesis of *cis,syn*-Hydroxyitraconazole Isomers

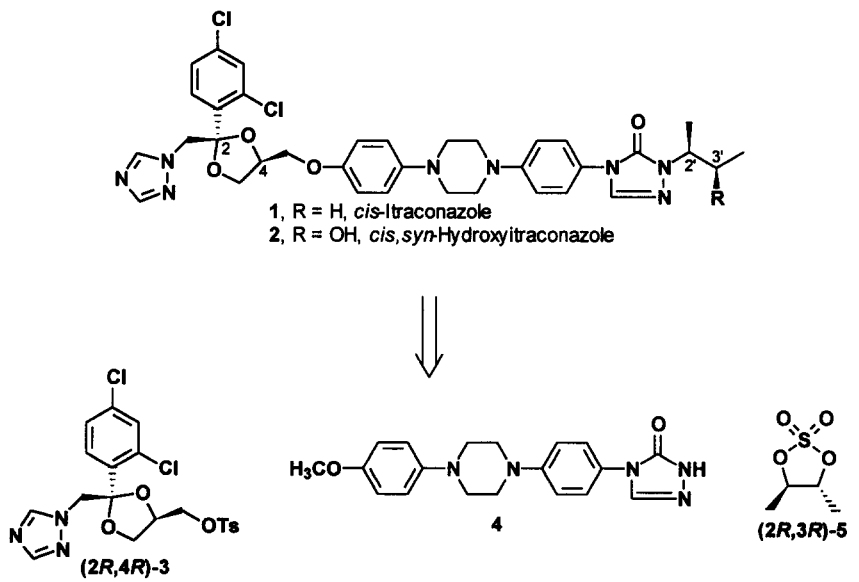
Gerald J. Tanoury,* Chris H. Senanayake,*,[1] Robert Hett, Yaping Hong, and Stephen A. Wald

Department of Chemical Research and Development, Sepracor Inc., 111 Locke Drive, Marlborough, MA 01752, USA

Abstract: The first stereoselective synthesis of *cis,syn*-hydroxyitraconazole isomers via a tricomponent coupling strategy is described. The isomers are prepared from two chiral subunits and connected via an achiral linker. A highly stereoselective route to the *cis,syn*-isomers is presented. © 1997 Elsevier Science Ltd.

Racemic *cis*-itraconazole (**1**) (SPORANOX) is a highly functionalized and widely used anti-fungal and anti-yeast agent.[1] Compound **1** has two chiral subunits attached to a linear aromatic chain. The subunits contain three stereogenic centers, affording four *cis*-stereoisomers. Itraconazole is hydroxylated on the *sec*-butyl sidechain by cytochrome P450 3A4 (CYP3A4) to give the active metabolite hydroxyitraconazole (**2**).[2] The added hydroxyl group could afford improved chemical and pharmacological characteristics to **2** suitable for the development of new anti-fungal/anti-yeast agents. Due to an interest in understanding the biological and medicinal properties of the isomers of **2** and its analogs, the first stereoselective synthesis of *cis,syn*-hydroxyitraconazole isomers has been developed. Disclosed here is a highly stereoselective route to the *cis,syn*-isomers of **2**.

Scheme I

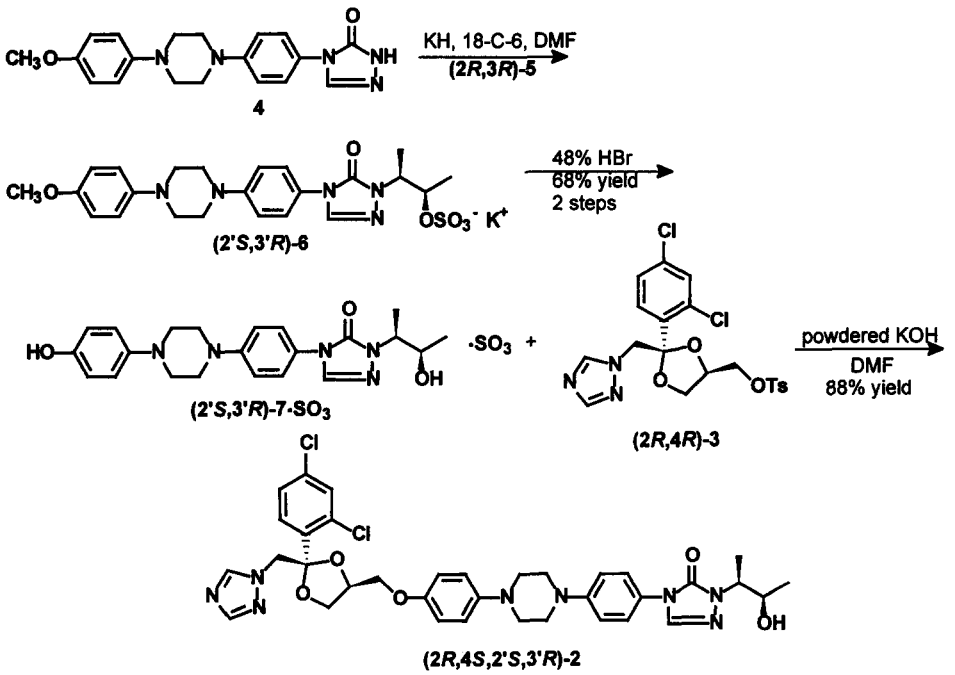


A retrosynthetic analysis for one isomer of hydroxyitraconazole is shown in Scheme I. The molecule can be disconnected into three basic fragments: a central achiral aromatic linker (**4**),[3] a chiral *cis*-dioxolane unit (**3**) and a chiral 3-hydroxy-2-butyl precursor (**5**). The chiral *cis*-dioxolyl tosylate **3** has been reported previously, and its coupling to phenols has been shown to occur in high yield for similar itraconazoles.[4] However, stereoselective formation of the secondary alcohol unit remains to be demonstrated.

N-Alkylation of triazolone **4** with an appropriate chiral cyclic sulfate **5** should be a facile method for generation of the chiral 3-hydroxy-2-butyl moiety.[5] The key intermediates for the synthesis of the *syn*-(2′*S*,3′*R*) and *syn*-(2′*R*,3′*S*) hydroxybutyl units are, respectively, the (2*R*,3*R*)- and (2*S*,3*S*)-cyclic sulfates **5**, available from the corresponding chiral 2,3-butanediols. The four *syn* isomers of **2**, therefore, should be available in high enantiomeric purity by using all combinations of (2*R*,3*R*)-/(2*S*,3*S*)-**5** and (2*R*,4*R*)-/(2*S*,4*S*)-**3**.

Scheme II details the total synthesis for one enantiomer of *cis,syn*-hydroxyitraconazole (**2**). According to literature methods,[4] (2*R*,3*R*)-2,3-butanediol (98% ee) was converted to the corresponding cyclic sulfate (2*R*,3*R*)-**5** in 96% yield. Alkylative ring-opening of (2*R*,3*R*)-**5** by triazolone **4** was performed with KH in DMF in the presence of 18-crown-6 at 0 °C over 1 hr to give diastereomerically-pure (2′*S*,3′*R*)-**6** via an exclusive S_N2 displacement.[6,7] Without the 18-crown-6 present, 51% recovery of the starting triazolone was obtained after reaction at 80 °C for 18 h; only 40% product formation was observed by HPLC analysis. Attempts to hydrolyze alkyl sulfate **6** directly from the reaction mixture by addition of 20% aqueous sulfuric acid were met with great difficulty: little or no hydrolysis occurred, even with four volume equivalents of 20% sulfuric acid at 80°C for 15 hr. However, exposure of the isolated adduct to 48% HBr at 50 °C for 20 min provided the hydrolyzed product. Continued warming at 110-120 °C for 6 hr resulted in demethylation to give phenol (2′*S*,3′*R*)-**7**•SO_3 in 68% yield for two steps, >98% de, with no observable dehydration of the secondary alcohol.[8] The crude phenol was coupled to optically-pure (2*R*,4*R*)-**3** with powdered KOH in DMF at 55 °C for 3.5 hr to give (2*R*,4*S*,2′*S*,3′*R*)-hydroxyitraconazole (**2**) in 88% yield.[9] The reaction was completely chemoselective: no coupling to the alkyl hydroxyl group was observed. The identical methodology was followed for all combinations of both *trans*-cyclic sulfate enantiomers of **5** and both *cis*-dioxolane enantiomers of **3** to prepare all four *cis,syn* isomers in >98% de.[10]

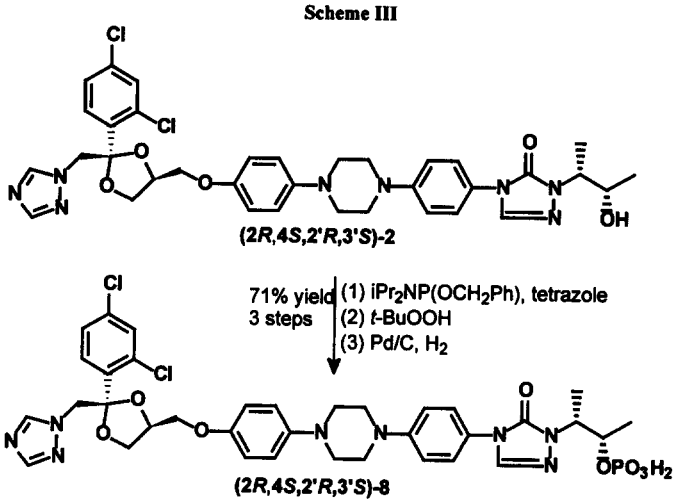
Scheme II



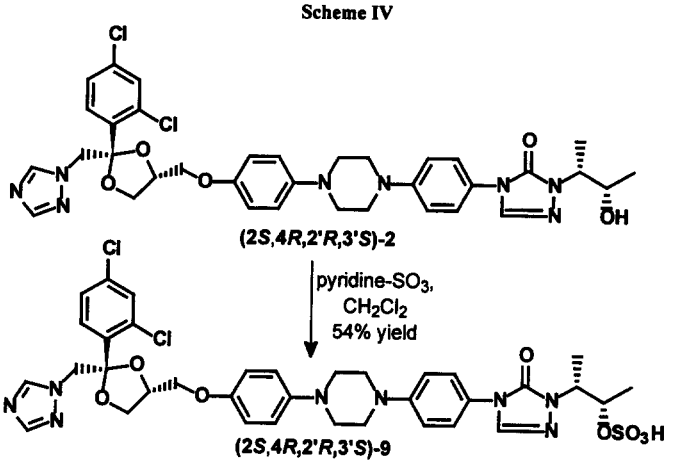
With the stereoselective synthesis of **2** and its isomers established, the phosphate and sulfate derivatives were prepared. Synthesis of the phosphate analog followed literature procedures, as shown in Scheme III.[11] Reaction of (2*R*,4*S*,2′*R*,3′*S*)-**2** with dibenzyl diisopropylphosphoramidite in dichloromethane in the presence of tetrazole, followed by oxidation with *t*-BuOOH gave the crude dibenzyl phosphate. Hydrogenolysis with Pd/C under a H_2 (50 psig) atmosphere afforded the desired phosphate analog (2*R*,4*S*,2′*R*,3′*S*)-**8** in 71 % yield from (2*R*,4*S*,2′*R*,3′*S*)-**2**.

Synthesis of the sulfate analog proceeded well. Reaction of (2*S*,4*R*,2′*R*,3′*S*)-**2** with pyridine-sulfur trioxide complex in dichloromethane at room temperature for 24 hr provided sulfate analog (2*S*,4*R*,2′*R*,3′*S*)-**9** in 54% yield (Scheme IV).[12,13]

Scheme III



Scheme IV



In conclusion, the first stereoselective synthesis of antifungal *cis,syn*-hydroxyitraconazole isomers in high diastereomeric excess has been demonstrated, and the hydroxyl group has shown to be a suitable handle for analog preparation. The key to the success of the synthesis via a tricomponent coupling strategy was the highly stereoselective and stereospecific alkylation of the triazolone moiety. This methodology should be applicable to other pharmacologically important triazolone molecules. Further work in this area is currently in progress.

References and Notes

‡Dedicated to Professor Carl R. Johnson on the occasion of his 60th birthday.

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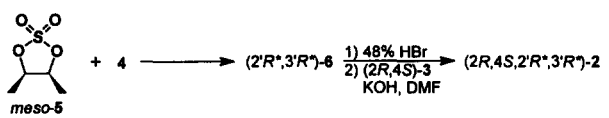
6. (a) The diastereoselectivity was determined by comparison of the methyl resonances in the 300 MHz ^{1}H-NMR spectra of (2′*R*,3′*R*)-**6** and (2′*S*,3′*R*)-**6**. (b) **Preparation of 2,4-Dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2-[(1*S*,2*R*)-(2-hydroxy-1-methylpropyl)]-3H-1,2,4-triazol-3-one ((2′*S*,3′*R*)-6).** To potassium hydride (825 mg, 7.2 mmol, 35 wt% dispersion in oil), [Note: KH was used as a dispersion in oil, no prewashing was done] at room temperature was added 18-crown-6 (2.38 g, 9.0 mmol) and 2,4-dihydro-4-[4-[4-(4-methoxyphenyl)-1-piperazinyl]pheny]-3H-1,2,4-triazol-3-one (**6**) (2.11 g, 6.0 mmol). *N,N*-Dimethylformamide (60 ml) was added slowly (gas evolution). The solution was warmed to 80-85 °C for 1 hr, then cooled in an ice-water bath to 0 °C. To this solution was added (4*R*,5*R*)-4,5-dimethyl-1,2,3-dioxathiolane 2,2-dioxide (**5a**) (1.19 g, 7.8 mmol). The reaction mixture warmed from 1.0 °C to 5.5 °C upon addition over 1 min. The reaction mixture was stirred at 0 °C for 1 hr, then warmed to room temperature. The reaction mixture was poured into 300 ml of methyl *t*-butyl ether, cooled to 0 °C and stirred for 1 hr. The white solid product was collected by filtration, rinsed with methyl *t*-butyl ether (3X) and dried *in vacuo* at 60 °C to give 4.03 g (quantitative mass balance) of potassium (2*R*,3*S*)-3-[2,4-Dihydro-4-[4-[4-(4-methoxyphenyl)-1-piperazinyl]phenyl]-3H-1,2,4-triazol-3-on-2-yl]but-2-yl sulfate (**6**). ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.36 (s, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 1H), 6.97 (d, *J* = 9.1 Hz, 1H), 6.85 (d, *J* = 9.1 Hz, 1H), 4.32 (dq, *J* = 8,5 6.2 Hz, 1H), 4.00 (dq, *J* = 8.5, 6.8 Hz, 1H), 3.74 (s, 3H), 3.28 (m, 8H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, d_6-DMSO): δ 153.2, 151.5, 149.9, 145.3, 135.4, 125.4, 123.0 (2C), 117.8 (2C), 115.8 (2C), 114.3 (2C), 73.9, 55.2, 54.5, 49.7 (2C), 48.3 (2C), 17.9, 16.1. IR (KBr): 1696, 1509, 1242, 1228 cm^{-1}. MS (CI) *m/z* 502 (M^+). HPLC purity: 99.0 A%. (HPLC Symmetry C_{18}, 5 µm, 150 x 3.9 mm; 0.05 M NaH_2PO_4 - 0.1% TEA (pH 3.0)/acetonitrile (55:45), 1.0 mL/min, 260 nm, 1.9 min).
7. (a) Alkylative ring-opening of the corresponding cyclic thionocarbonate under identical reaction conditions at 80-85 °C for 16 hr resulted in no observable product formation. For the use of thionocarbonates in ring-opening reactions, see: Ko, S. Y. *J. Org. Chem.* **1995**, *60*, 6250. (b) Alkylative ring-opening of (2*R*,3*R*)-**5** by triazolone **4** with Cs_2CO_3/18-crown-6 in DMF provided a mixture of isomers.
8. The structure of the diol (2′*S*,3′*R*)-**7•SO$_3$** was established by ^{1}H NMR, ^{13}C NMR and mass spectral.
9. **Spectral Data for (2*R*,4*S*,2′*S*,3′*R*)-2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.89 (s, 1H), 7.64 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.25 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 4.85 (d_{AB}, *J* = 14.7 Hz, 1H), 4.75 (d_{AB}, *J* = 14.7 Hz, 1H), 4.36 (m, 1H), 4.27 (m, 1H), 4.21 (m, 1H), 3.92 (t, *J* = 6.7 Hz, 1H), 3.79 (m, 2H), 3.67 (d, *J* = 2.5 Hz, 1H), 3.48 (dd, *J* = 9.8, 6.5 Hz, 1H), 3.36 (m, 4H), 3.24 (m, 4H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.6, 152.0, 151.3, 150.7, 145.9, 144.9, 136.0, 134.3, 134.0, 133.1, 131.4, 129.6, 127.2, 125.3, 123.7 (2C), 118.4 (2C), 116.6 (2C), 115.2 (2C), 107.6, 74.7, 69.8, 67.6, 67.4, 57.3, 53.5, 50.5 (2C), 49.1 (2C), 19.4, 12.4. MS (CI) *m/z* 721 (MH^+). Anal. Calcd for $C_{35}H_{38}Cl_2N_4O_5$: C, 58.25; H, 5.32; Cl, 9.83; N, 15.53. Found: C, 57.80; H, 5.39; Cl, 9.56 ; N, 15.55. $[\alpha]_D^{25}$ = 12.7° (c = 0.1, MeOH). HPLC purity: 99.0 A%. (HPLC Symmetry C_{18}, 5 µm, 150 x 3.9 mm; 0.05 M NaH_2PO_4 - 0.1% TEA (pH 3.0)/acetonitrile (55:45), 1.0 mL/min, 260 nm, 9.7 min).
10. Rapid access was gained to the *cis,anti* isomers of **2** for biological evaluation from the *meso* isomer of **5** and each *cis*-dioxolane enantiomer of **3**. As outlined below, using *meso*-**5** and (2*R*,4*R*)-**3** gave a 1:1 mixture of (2*R*,4*S*,2′*R**,3′*R**)-hydroxyitraconazole isomers, and using (2*S*,4*S*)-**3** gave the other pair of *cis,anti* isomers, (2*S*,4*R*,2′*R**,3′*R**)-hydroxyitraconazole.



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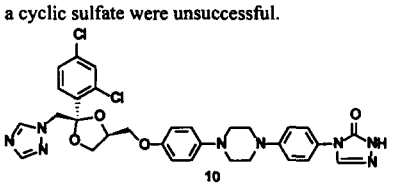
13. Attempts to directly alkylate **10** with a cyclic sulfate were unsuccessful.



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(*Received in USA* 15 *August* 1997; *revised* 8 *September* 1997; *accepted* 9 *September* 1997)