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Total synthesis of (2*R*,4*S*,2′*S*,3′*R*)-hydroxyitraconazole: implementations of a recycle protocol and a mild and safe phase-transfer reagent for preparation of the key chiral units

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Abstract—A convergent total synthesis of enantiomerically-pure (2*R*,4*S*,2′*S*,3′*R*)-hydroxyitraconazole **1b** is described. The left dioxolane portion of the molecule was prepared in good yield by the conversion of (*S*)-**10** to the corresponding enantiomerically and diastereomerically-pure acetonide (2*R*,4*R*)-**3** by a recycle protocol involving diastereoselective crystallization of the tosylate salt, followed by re-equilibration of the mother liquor and crystallization. The right-hand triazolone moeity (2*S*,3*R*)-**4** was generated by alkyaltion of triazolone **6** with enantiomerically pure cyclic sulfate (4*R*,5*R*)-**7** under mild and essentially non-hazardous reaction conditions (TDA-1, K_2CO_3, acetonitrile).

1. Introduction

Itraconazole **1a** (Sporanox) and its active metabolite, hydroxyitraconazole **1b**, are members of a large class of azole antifungal compounds.[1] In addition to having a high molecular weight in comparison to other pharmaceutical agents, **1a** and **1b** contain a high degree of chemical complexity. Efficient syntheses of enantiomerically-pure *cis*,*syn*-hydroxyitraconazole isomers have been previously reported.[2] The key steps in these syntheses were an alkylative ring-opening of an enantiomerically-pure cyclic sulfate, and a Buchwald–Hartwig[3] type Pd-catalyzed aromatic amination of two highly functionalized subunits to give **1b**. While these approaches provided solutions to our synthetic needs, several synthetic improvements were required: (1) a practical synthesis of the *cis*-dioxolane moiety in enantiomerically pure form; and (2) an economic and safe process for the triazolone alkylation step. In this paper, we summarize our previous synthetic work and provide critically important process solutions to our requirements for the synthesis of (2*R*,4*S*,2′*S*,3′*R*)-hydroxyitraconazole **1b**.

2. Results and discussion

A synthetic analysis of **1b** is outlined in Scheme 1. Paramount to the success of this strategy are the preparations of dioxolane (2*R*,4*R*)-**3** and triazolone (2*S*,3*R*)-**4** in high diastereomeric and enantiomeric purities. The use of (2*R*,4*R*)-**3** for the preparation of left chiral portion of **1b** has been described,[2] but a practical and high yielding synthesis of this fragment has not been reported. Preparation of (2*S*,3*R*)-**4** by alkylation of **6** with (4*R*,5*R*)-**7** has been previously performed using KH/18-crown-6 in DMF.[2] A safe and cost-effective procedure which obviates the uses of KH and 18-crown-6 was needed.

Development of a synthetic route for the preparation of (2*R*,4*R*)-**3** in high diastereomeric and enantiomeric purities is outlined in Scheme 2. The key transformation involved a diastereoselective ketalization of **9** with *R*-**12**, consisting of four steps: (1) formation of ketotriazole **9**; (2) tosylation of (*S*)-isopropylideneglycerol **10**; (3) deprotection of the isopropylidene ketal *R*-**11**; and (4) ketal formation to generate (2*R*,4*R*)-**3**. In accord

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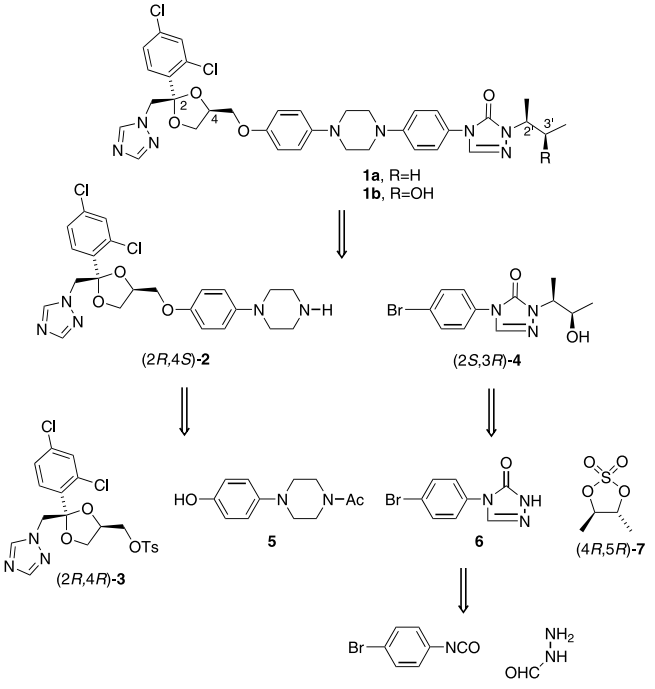
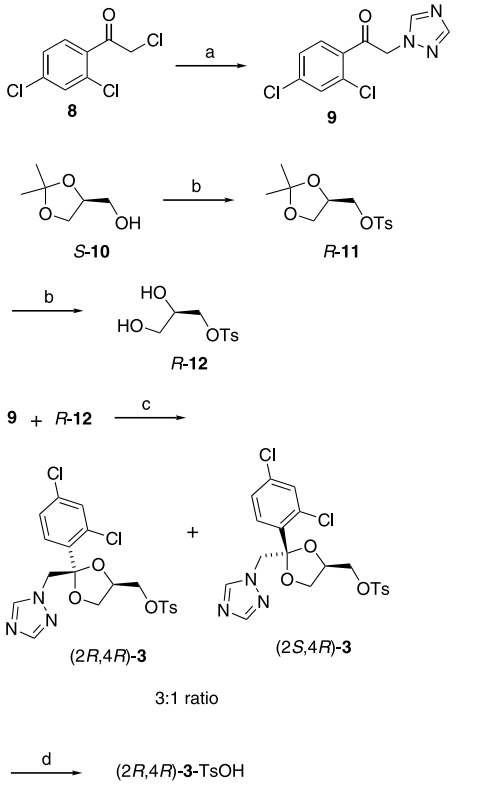


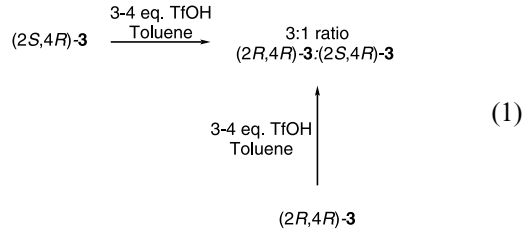
Scheme 1.



Scheme 2. *Reagents and conditions*: (a) 4-amino-4H-1,2,4-triazole, CH_2Cl_2; Aq. HCl, $NaNO_2$ (Ref. 3); (b) TsCl, pyridine, 0°C; acetone, HCl, reflux (Ref. 4); (c) 3 equiv. TfOH, toluene, rt, 24-36 h; (d) TsOH, MIBK; CH_3CN, recrystallize, 51% yield from *R*-**12**.

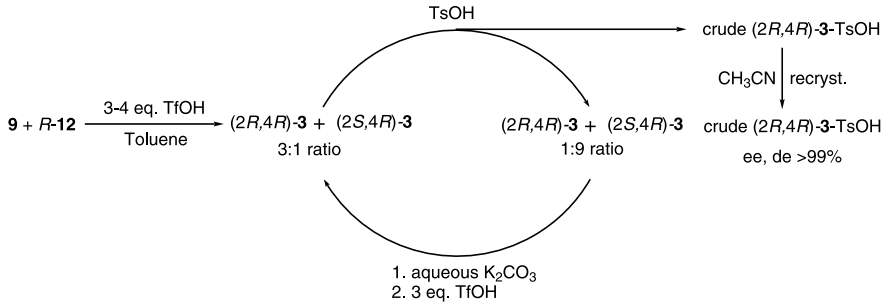
with literature precedence,[4] reaction of α-chloroketone **8** with 4-amino-1,2,4-triazole followed by treatment with nitrous acid ($NaNO_2$, HCl) gave **9**. Tosylation of (*S*)-isopropylideneglycerol *S*-**10** by a standard protocol (tosyl chloride in pyridine at 0°C), and hydrolysis with 1 M HCl in acetone gave (*R*)-glyceryl tosylate *R*-**12**.[5] Condensation of (*R*)-glyceryl tosylate with **9** was challenging. Initial efforts on the ketalization resulted in long reaction times (days) and low yields. In the presence of 30 equivalents of MsOH in refluxing toluene for 7 days (2*R*,4*R*)-**3** was isolated in 18% yield.[6] After extensive experimentation and optimization, the use of 3 equivalents of TfOH in toluene at room temperature for 24–36 h provided a 3:1 mixture of (2*R*,4*R*)-**3** and (2*S*,4*R*)-**3**. After neutralization and work-up, the crude product was dissolved in *iso*-butyl methyl ketone and treated with tosic acid. A solid crystallized from the solution as a 95:5 mixture of (2*R*,4*R*)-**3**:(2*S*,4*R*)-**3** as the tosylate salts. The crude solid product was purified to a single stereoisomer of (2*R*,4*R*)-**3** by recrystallization from acetonitrile, and was isolated in 51% yield from **9**.

The observation that a diastereomerically-pure product could be obtained from the crude 3:1 mixture of isomers by isolation as the tosylate salt, followed by recrystallization from acetonitrile, led to the development of a recycle protocol to obtain (2*R*,4*R*)-**3** in high yield and high diastereomeric purity. Initially, to ensure thermodynamic equilibrium was attained at a 3:1 mixture of isomers, a solution of diastereomerically-pure (2*R*,4*R*)-**3** was converted to the free-base and treated with triflic acid (3 equiv.) in toluene. A 3:1 mixture of diastereomers was obtained (Eq. (1)). Analogously, when diastereomerically-pure (2*S*,4*R*)-**3** was subjected to the identical procedure a 3:1 mixture of diastereomers was obtained. Having confirmed that equilibrium was reached during formation and isolation of (2*R*,4*R*)-**3**, a recycle protocol was developed.



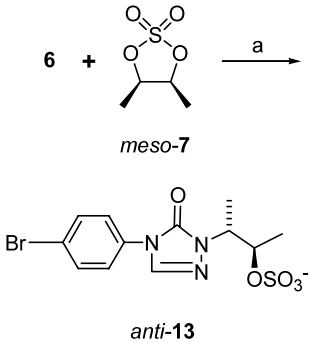
(1)

Scheme 3 shows the recycle process for generation of (2*R*,4*R*)-**3** from the reaction of **9** and *R*-**12**. As described above, addition of TsOH to the 3:1 mixture of diastereomers followed by two recrystallizations of the crude solid from acetonitrile gave diastereomerically and enantiomerically-pure (2*R*,4*R*)-**3**. Collection and assay of the mother liquor from the crude reaction showed a 1:9 mixture of (2*R*,4*R*)-**3**:(2*S*,4*R*)-**3** tosylate salts. The solution was neutralized with aqueous K_2CO_3, dried, and concentrated. Addition of MIBK and 3 equivalents of triflic acid effected equilibration to a 3:1 mixture of isomers. Addition of tosic acid, and isolation and purification of the crude solid provided diastereomerically and enantiomerically-pure (2*R*,4*R*)-**3**. Using the recycle procedure, (2*R*,4*R*)-**3** was obtained in 73% total yield after two recycles.



Scheme 3.

Turning our attention to the triazolone moeity, preliminary investigations were performed using the less costly *meso*-**7** (prepared from *meso*-2,3-butanediol). The initial approach entailed the reaction of **6** with KH/18-crown-6 in DMF, followed by addition of the cyclic sulfate (Eq. (2)) to give the sulfate intermediate *anti*-**13**.[7] *Anti*-**13** was converted to the alcohol by reaction with 48% HBr at 45–50°C for 30–45 min. These reaction conditions were suitable for the initial synthetic studies of hydroxyitraconazole isomers, but other approaches were sought to preclude the use of 18-crown-6 due to its toxicity and cost, and the use of KH due to its high reactivity and flammability.



(2)

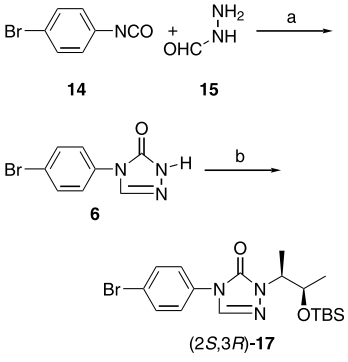
a. KH, 18-crown-6, DMF, 0 °C to RT, 1h, 72% yield

The replacement of 18-crown-6 was examined by considering alternative chelating additives. Since cost, low toxicity, and availability were paramount, tris-[2-(methoxyethoxy)ethyl]amine [tris(3,6-dioxaheptyl)-amine, TDA-1] was selected for study.[8] To address the issues associated with KH, easily-handled carbonate salts were chosen as replacements. Table 1 shows the results from a series of experiments comparing TDA-1 and 18-C-6 as additives for the alkylation of **6** with *meso*-**7** using lithium, sodium, and potassium carbonates as base in acetonitrile at 40°C. From the data, TDA-1 and 18-C-6 behaved comparably as phase transfer reagents. With lithium and sodium salts, the rates of reaction were identical or similar (entries 1 and 2 versus 4 and 5). With potassium carbonate,

Table 1. Effect of TDA-1 and 18-C-6 on the reaction of *meso*-**7** with **6** in the presence of base[a]

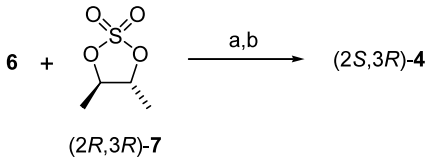
Entry	Base	Additive	Reaction time (h)	Reaction completion[b](%)
1	Li_2CO_3	TDA-1	16	11
2	Na_2CO_3	TDA-1	16	31
3	K_2CO_3	TDA-1	16	98
4	Li_2CO_3	18-C-6	16	11
5	Na_2CO_3	18-C-6	16	50
6	K_2CO_3	18-C-6	8	99
7	K_2CO_3	None	16	34

[a] Reaction conditions: 0.15 M solution of **6**, 2.0 equiv. carbonate base, 1.0 equiv. additive, acetonitrile, 40°C.
[b] Determined by HPLC analysis.



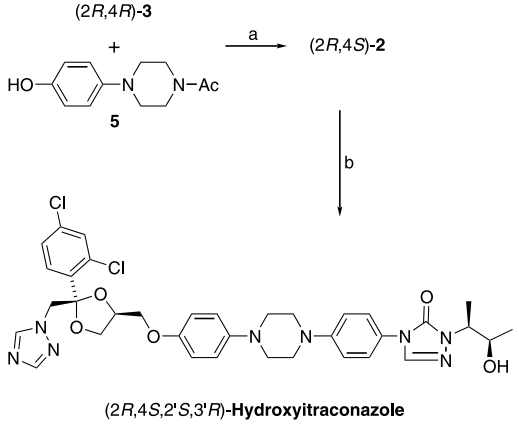
Scheme 4. *Reagents and conditions*: (a) *n*-BuOH, 0°C, 1 h; KOH, reflux, 3 h; HCl, 49% yield from **14**; (b) Eq. (3); TBSCl, imidazole, DMF, rt, 48 h, 75% yield.

however, the alkylation was 2–4 times faster with 18-C-6 than TDA-1 (entries 3 and 6). When compared to the result with no additive present (potassium carbonate as base), TDA-1 provided a substantial accelerating effect (entries 3 versus 7). The data indicated that TDA-1 would be an excellent phase transfer reagent for the reaction in Eq. (2), using K_2CO_3 as base in acetonitrile. The reaction was performed on (4*R*,5*R*)-**7** to provide (2*R*,3*R*)-**4** in 79% yield for two steps (Eq. (3)).



(3)

a. TDA-1 (1 eq.), K_2CO_3 (2 eq.), CH_3CN, 40 °C, 16 h. b. 48% HBr, 50 °C, 30 min, 79% (2 steps)



Scheme 5. *Reagents and conditions*: (a) NaH, DMF, rt, 4 h; KOH, IPA, reflux, 16 h, 85%; (b) (2*R*,4*S*)-**17**, Pd_2dba_3, NaO^{t}Bu, BINAP, toluene, 100°C, 4 h; Bu_4NF, THF, 74% for 2 steps.

Incorporation of the improvements in the synthetic methodology provided a practical and efficient approach to the total synthesis of (2*R*,4*S*,2′*S*,3′*R*)-hydroxyitraconazole, as outlined in Schemes 4 and 5. Isocyanate **14** was converted to triazolone **6** in two steps by condensation with **15** followed by ring closure and dehydration using KOH in n-butanol at reflux. Compound **6** was converted to (2*S*,3*R*)-**4** according to Eq. (3), followed by silylation of the hydroxyl group by standard methods to give (2*S*,3*R*)-**17**. Tosylate (2*R*,4*R*)-**3** was condensed with 4-(4-hydroxyphenyl)-1-acetylpiperazine to give intermediate (2*R*,4*S*)-**2**. Palladium-catalyzed coupling of amine (2*R*,4*S*)-**2** with bromide (2*S*,3*R*)-**17** gave the silylated penultimate product (2*R*,4*S*,2′*S*,3′*R*)-**18**. Subsequent desilylation provided enantio- and diastereopure (2*R*,4*S*,2′*S*,3′*R*)-hydroxyitraconazole in 13% yield via a 13-step convergent synthesis from **9**, (*R*)-**12**, 4-bromophenyl isocyanate and (2*R*,3*R*)-2,3-butanediol.

3. Conclusion

A practical and safe route for the total synthesis of enantiopure and diastereopure (2*R*,4*S*,2′*S*,3′*R*)-hydroxyitraconazole has been described. The route has provided an improvement to previous syntheses. The difficulty in preparing the *cis*-dioxolane intermediate in high de and ee was addresssed by taking advantage of the practicality of an equilibration/recycle method to generate the thermodynamically more stable *cis* stereochemistry. Recrystallization provided the intermediate in 73% yield after two recycles and >99% de and ee. The safety issues associated with the use of toxic 18-crown-6 and the high reactivity of the combination of KH with DMF in the alkylation of **6** were solved by replacement of 18-crown-6 with non-carcinogenic TDA-1 and the use of K_2CO_3/acetonitrile in the place of KH/DMF. The combined improvements offered a cost-effective and safe solution for the total synthesis of *cis*,*syn*-hydroxyitraconazole.

4. Experimental

4.1. General

Flash chromatography was performed on EM Science silica gel 60. Thin layer chromatography was performed using silica gel 60 F_{254} plates. All reactions were carried out in oven-dried glassware under an argon atmosphere. NMR spectra were recorded on a Varian Inova 300 operating at 300 MHz and 75 MHz for ^1H and ^{13}C, respectively, and referenced to internal standards. Mass spectra were performed by M-Scan Mass Spectral Analysis. Elemental analyses were conducted by Galbriath Laboratories, Inc., 2323 Sycamore Drive, PO Box 1610, Knoxville, TN 37950-1610. (*S*)-2,2-Dimethyl-1,3-dioxolane-4-methanol, p-toluenesulfonylchloride, p-toluenesulfonic acid, 4-amino-4H-1,2,4-triazolone, sodium nitrite, triflic acid, (2*R*,3*R*)-(+)-2,3-butanediol, *meso*-2,3-butanediol, thionyl chloride, $RuCl_3$–H_2O, $NaIO_4$, potassium hydride, 18-crown-6, formic hydrazine, 4-bromophenylisocyanate, TDA-1, imidazole, *tert*-butyldimethylchlorosilane, hydrobromic acid, *N*-acetyl-*N*′-(4-hydroxyphenyl)piperazine, tris(dibenzylideneacetone)-dipalladium, (*R*)-BINAP, sodium *tert*-butoxide, and tetra-*n*-butylammonium fluoride were purchased from the Aldrich Chemical Company and used without further purifications. Potassium carbonate and potassium hydroxide were purchased from Fisher Scientific and used without further purification. All solvents were purchased as anhydrous from Aldrich Chemical Company and used without further purification. 1-(2,4-Dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (**9**) was prepared according to the method of Astelford et al.[3] (*R*)-3-Tosyloxy-1,2-propanediol (*R*)-**12** was prepared according to the method of Pirrung et al.[4]

4.2. Preparation of (2*R*,4*R*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-4-tosyloxymethyl-1,3-dioxolane tosylate (2*R*,4*R*)-3, tosylate salt

A suspension of (*R*)-tosyloxy-1,2-propanediol (*R*)-12 (10.0 g, 40 mmol) and 1-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone **9** (10.0 g, 39 mmol) in toluene

(50 mL) was cooled to 5°C. Triflic acid (15 mL, 160 mmol) was slowly added so that the temperature stayed below 15°C. After complete addition, the reaction mixture (2 phases) was stirred at 25°C for 60 h. The mixture was diluted with EtOAc (200 mL) and slowly dropped into a solution of K_2CO_3 (50 g, 36.2 mmol) in water (400 mL) at 5°C. The organic layer was separated and the aqueous layer was extracted with EtOAc (150 mL). The combined organic extracts were dried over Na_2SO_4 (10 g) and filtered. A solution of TsOH monohydrate (7.6 g, 40 mmol) in EtOAc (50 mL) was slowly added at 25°C. The white solid product was filtered after 30 min, washed and dried to give (2*R*,4*R*)-**3**, tosylate salt containing 5% of the (2*R*,4*S*)-isomer. Two crystallizations from CH_3CN (400 mL) gave 13.5 g of pure (2*R*,4*R*)-**3**, tosylate salt (50% yield). ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.98 (s, 1H), 8.29 (s, 1H), 7.80 (d, $J=8.4$ Hz, 1H), 7.66 (br s, 1H), 7.50 (d, $J=8.1$ Hz, 4H), 7.40 (br s, 2H), 7.12 (d, $J=8.1$ Hz, 2H), 4.82 (br s, 2H), 4.23 (m, 1H), 3.97 (dd, $J=11$ Hz, 3.4 Hz, 1H), 3.80 (m, 2H), 3.62 (dd, $J=8.7$ Hz, 5.5 Hz, 1H), 2.42 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, d_6-DMSO): δ 148.0, 145.3, 145.1, 144.6, 138.1, 134.8, 134.1, 132.5, 132.0, 130.7, 130.3, 130.1, 128.2, 127.8, 127.4, 125.5, 107.1, 73.7, 69.5, 65.7, 53.5, 21.2, 20.9. MS (CI) m/z (M+1, $C_{20}H_{19}Cl_2N_3O_5S$) 484.05. HPLC purity = 99.8 A% (μ-bondapack C18 column, 220 nm, CH_3CN: 0.05 M NaH_2PO_4 (pH = 3, 0.1% NEt_3) 50: 50, 1 ml/min; trans 13 min, cis 14 min) $[\alpha]_D^{25}=+16.6$ ($c=1$, MeOH) ee = 99.6% (HPLC Chiracel OD-H, EtOH:$HNEt_2$ 100:0.1, 0.25 mL/min, 254 nm, 23 min).

4.3. Preparation of (4*R*,5*R*)-4,5-dimethyl-1,2,3-dioxathiolane 2,2-dioxide (4*R*,5*R*)-7

According to the procedure of Sharpless and Gao and a known prep,[7] a three-necked 500 ml RBF fitted with a reflux condenser and a calcium chloride drying tube was charged with (2*R*,3*R*)-(+)-2,3-butanediol (10.0 g, 10.1 ml, 0.11 mol) and carbon tetrachloride (120 ml). Thionyl chloride (16.0 g, 9.8 ml, 0.13 mol) was added dropwise at room temperature. Rapid gas evolution (HCl) began. The reaction mixture was stirred at room temperature for 10 min, then warmed to reflux for 30 min to insure complete removal of HCl gas. The reaction mixture was cooled to 0°C in an ice-water bath and acetonitrile (120 ml), $RuCl_3$–H_2O (14 mg, 0.07 mmol), $NaIO_4$ (35.6 g, 0.17 mol) and water (180 ml) were added, respectively. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The mixture was poured into methyl *t*-butyl ether (900 ml), and water was added to dissolve the remaining $NaIO_4$ (ca. 600 ml). The phases were separated and the aqueous phase was extracted with methyl *t*-butyl ether (2×100 ml). The combined organic phases were washed with water (1×50 ml), saturated aqueous sodium bicarbonate (2×50 ml) and saturated aqueous sodium chloride (1×50 ml). The organic solution was dried over anhydrous magnesium sulfate and filtered through a bed of silica gel to give a clear and colorless solution. The solvent was removed in vacuo to give 16.01 g (95% yield) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.70 (m, 1H), 1.55 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 85.5, 16.5.

4.4. Preparation of 2,4-dihydro-4-bromophenyl-3H-1,2,4-triazol-3-one 6

To formic hydrazine (8.34 g, 0.139 mol) in 1-butanol (600 ml) at 0–5°C was added 4-bromophenylisocyanate (25.00 g, 0.126 mol) portion-wise to maintain the reaction temperature below 15°C. The reaction mixture was cooled to 0–5°C, stirred for 15 min, warmed to room temperature and stirred for another 15 min. Potassium hydroxide (7.79 g, 0.139 mol) was added, a Dean Stark trap was added and the reaction mixture was warmed to reflux for 3 h. After cooling to room temperature, the solvent was removed to give a white solid. Water (500 ml) was added to the solid and the mixture was stirred for 1 h to give a slightly beige solution with a white precipitate. After filtration, the pH of the filtrate was lowered to 7, and the white solid product was isolated by filtration and dried in vacuo to give 12.28 g of the title compound. The above white precipitate was suspended in water (200 ml) by rapid stirring for 48 h. Filtration of this mixture and neutralization of the filtrate to pH 7 gave more solid white product which was dried in vacuo to give 2.63 g of the title compound. The combined yield was 14.91 g (49% yield). ^{1}H NMR (300 MHz, d_6-DMSO): δ 12.05 (s, 1H), 8.40 (s, 1H), 7.65 (s, 4H). ^{13}C NMR (75 MHz, d_6-DMSO): δ 152.76, 135.96, 133.43, 132.16, 123.20, 119.22. MS (CI, $C_8H_6BrN_3O$) m/z 242.21 (M^+), 240.21 (M^+), 161.46.

4.5. Preparation of 2,4-dihydro-4-bromophenyl-2-[(2*S*,3*R*)-(3-hydroxy-2-butyl)]-3H-1,2,4-triazol-3-one (2*S*,3*R*)-4

To a round-bottomed flask was added potassium carbonate (5.80 g, 42 mmol) and 2,4-dihydro-4-bromophenyl-3H-1,2,4-triazol-3-one (**6**) (5.00 g, 21 mmol). Acetonitrile was added (65 mL), followed by TDA-1 (6.79 g, 6.7 mL, 21 mmol). (4*R*,5*R*)-4,5-Dimethyl-1,2,3-dioxathiolane-2,2-dioxide ((4*R*,5*R*)-**7**) (4.12 g, 27.11 mmol) was added, and the mixture was warmed to 40°C for 16 h. The mixture was cooled to rt and filtered. The solid was rinsed with methanol, and the combined filtrates were concentrated in vacuo. To the crude intermediate was added 48% HBr (40 mL) and the reaction mixture was warmed to 50°C for 45 min. The solution was poured into water (100 mL) and neutralized with saturated aqueous potassium carbonate to pH 7. The aqueous solution was extracted with MTBE (3×25 mL), and the combined organic phases dried over anhydrous magnesium sulfate, filtered, and the solvent was removed in vacuo to give the crude. The crude material was purified by flash chromatography (chloroform/1% methanol) to give 5.15 g (79% yield) of the desired product (2*S*,3*R*)-**4**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.60 (d, $J=8.9$ Hz, 2H), 7.47 (d, $J=8.9$ Hz, 2H), 4.28 (dq, $J=3.3$, 6.8 Hz, 1H), 4.17 (dq, $J=3.2$, 6.4 Hz, 1H), 1.42 (d, $J=7.0$ Hz, 3H), 1.23 (d, $J=6.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.43, 133.25, 132.75, 123.40, 121.28, 69.82, 57.14, 19.32, 12.56. MS (CI, $C_{12}H_{14}BrN_3O_2$) m/z 296.15 (M^+-H_2O), 294.15 (M^+-H_2O), 242.21, 240.21.

4.6. Preparation of 2,4-dihydro-4-bromophenyl-2-[(2*S*,3*R*)-[3-(1,1-dimethylethyl)dimethylsiloxy-butyl]]-3H-1,2,4-triazol-3-one (2*S*,3*R*)-17

To 2,4-dihydro-4-bromophenyl-2-[(1*S*,2*R*)-(2-hydroxy-1-methylpropyl)]-3H-1,2,4-triazol-3-one (2*S*,3*R*)-**4b** (320 mg, 1.0 mmol), imidazole (163 mg, 2.4 mmol), and *tert*-butyldimethylchlorosilane (166 mg, 1.1 mmol) at room temperature was added DMF (1.0 ml). The reaction mixture was stirred at room temperature for 48 h. Ethyl acetate (3 ml) and water (3 ml) were added, and the phases were separated. The organic phase was washed with water, 1.2 N HCl, water, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent in vacuo, the crude material was purified by flash chromatography (10:1 hexane:ethyl acetate) to give 436 mg (>99% yield) of the desired product (2*S*,3*R*)-**26**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.60 (d, $J=8.9$ Hz, 2H), 7.47 (d, $J=8.9$ Hz, 2H), 4.19 (p, $J=6.9$ Hz, 1H), 4.06 (q, $J=6.1$ Hz, 1H), 1.44 (d, $J=6.7$ Hz, 3H), 1.12 (d, $J=6.0$ Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.41, 132.99, 132.65 (2C), 123.20 (2C), 120.86, 70.12, 57.00, 25.74 (3C), 20.62, 17.91, 15.03, −4.43, −5.00. MS (CI, $C_{18}H_{28}BrN_3O_2Si$) m/z 428.06 (M^+), 426.09 (M^+), 412.06, 410.06, 296.16, 294.16, 242.21, 240.21. HPLC: Chiralpak AD, 10 μm, 4.6 mm×25 cm, Hexane/IPA (97:3), 1.0 ml/min, 220 nm. (2*S*,3*R*)-**26**: 7.1 min, (2*R*,3*S*)-**26**: 8.2 min, *meso*-**26**: 7.0 min.

Desired enantiomer	Isomer % area (ret time)		
	(2*S*,3*R*)-**17**	(2*R*,3*S*)-**17**	*meso*-**17**
(2*S*,3*R*)-**17**	99.89	0.11	–

4.7. Preparation of (2*R*,4*S*)-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-piperazine (2*R*,4*S*)-2

To a separatory funnel containing 10% aqueous potassium carbonate (150 ml) was added (2*R*,4*R*)-**3b**-TsOH (15.00 g, 22.8 mmol). Dichloromethane (150 ml) was added and the mixture was shaken vigorously with venting. The organic phase was decanted and the procedure was continued until the organic and aqueous phases were clear. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and the solvent was removed in vacuo to give 11.35 g of (2*R*,4*R*)-**3b** as a clear sticky material. To (2*R*,4*R*)-**3b** was added *N*-acetyl-*N*′-(4-hydroxyphenyl)piperazine **5** (5.06 g, 23.0 mmol) and DMF (100 ml). To the clear solution was added sodium hydride (1.50g of a 60% dispersion in oil, 37.5 mmol) in portions. Gas evolution occurred and a precipitate began to form immediately. After the addition was complete, the reaction mixture was warmed to 50°C for 15 h. After cooling to room temperature, water (300 ml) was added and the mixture was extracted with dichloromethane (3×200 ml). The solvents were removed in vacuo and the crude material was dissolved in ethyl acetate (600 ml) and extracted with water (4×50 ml). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvents were removed in vacuo to give a brown foam. To this crude product was added potassium hydroxide (16.18 g, 289 mmol), *iso*-propyl alcohol (40 ml), and water (10 ml). The reaction mixture was warmed to reflux for 14 h, cooled to room temperature and concentrated in vacuo. The crude material was purified by flash chromatography eluting with a gradient from 3% methanol in chloroform to 5% triethylamine:3% methanol: chloroform by increasing the triethylamine concentration in 1% portions to give 9.45 g (85% yield) of (2*R*,4*S*)-**2**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.89 (s, 1H), 7.58 (d, $J=8.4$ Hz, 1H), 7.47 (d, $J=2.0$ Hz, 1H), 7.25 (dd, $J=8.9$, 2.0 Hz, 1H), 6.88 (d, $J=9.0$ Hz, 2H), 6.78 (d, $J=9.0$ Hz, 2H), 4.80 (d_{AB}, $J=14.7$ Hz, 1H), 4.36 (m, 1H), 3.92 (t, $J=6.7$ Hz, 1H), 3.79 (m, 2H), 3.48 (dd, $J=9.8$, 6.5 Hz, 1H), 3.06 (s, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.2, 151.2,146.4, 144.8, 135.9, 133.9, 133.0, 131.2, 129.5, 127.1, 118.1 (2C), 115.1 (2C), 107.4, 74.6, 67.5, 67.3, 53.4, 51.1(2C), 45.8 (2C).

4.8. Preparation of (2*R*,4*S*)-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-[(2*S*,3*R*)-(3-[(1,1-dimethylethyl)dimethylsiloxy-2-butyl]]-3H-1,2,4-triazol-3-one (2*R*,4*S*,2′*S*,3′*R*)-18

(2*R*,4*S*)-4-[4-[[2-(2,4-Dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-piperazine (2*R*,4*S*)-2 (110 mg, 0.28 mmol), 2,4-dihydro-4-bromophenyl-2-[(2*S*,3*R*)-[3-(1,1-dimethylethyl)-dimethylsiloxy-2-butyl]]-3H-1,2,4-triazol-3-one (2*S*,3*R*)-**17** (110 mg, 0.25 mmol), tris(dibenzylideneacetone)dipalladium (2.3 mg, 0.0025 mmol), *R*-BINAP (4.7 mg, 0.0075 mmol) and sodium *tert*-butoxide (34 mg, 0.35 mmol) were combined in a dry flask. The contents were vacuum purged with argon (3×). To this was added degassed toluene (1.25 ml), and the entire solution was purged by bubbling argon through it. The reaction mixture was warmed to 85°C for 3 h, cooled to room temperature, and ethyl acetate and water were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (3×). After drying the combined organic phases over anhydrous magnesium sulfate, filtering and removing the solvent in vacuo, the crude material was purified by flash chromatography (98:2 chloroform:methanol) followed by purification on a Chromatotron (the plate wetted with chloroform and eluted with 98:2 chloroform:methanol) to give 171 mg (81% yield) of the desired product (2*R*,4*S*,2′*S*,3′*R*)-**18**. ^{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), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 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.

4.9. Preparation of (2*R*,4*S*)-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-[(2*S*,3*R*)-(3-hydroxy-2-butyl)]-3H-1,2,4-triazol-3-one (2*R*,4*S*,2′*S*,3′*R*)-hydroxyitraconazole

To (2*R*,4*S*)-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-[(2*S*,3*R*)-(3-(1,1-dimethylethyl)dimethylsiloxy-2-butyl)]-3H-1,2,4-triazol-3-one (2*R*,4*S*,2′*S*,3′*R*)-**18** (171 mg, 0.20 mmol) in THF (0.6 ml) at room temperature was added tetra-*n*-butylammonium fluoride (0.3 ml of a 1.0 M solution in THF, 0.3 mmol). The reaction mixture was stirred at room temperature for 17 h. Water and chloroform were added, and the phases were separated. The aqueous phase was extracted with chloroform (2X), dried over anhydrous magnesium sulfate, filtered, and the solvent was removed in vacuo. The crude material was purified by flash chromatography (95:5 chloroform:methanol) to give 131 mg (91% yield) of the desired product (2*R*,4*S*,2′*S*,3′*R*)-hydroxyitraconazole. ^{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. Anal. Calcd for $C_{35}H_{38}Cl_2N_8O_5$: 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 μ Bondapak C_{18}, 300×3.9 mm; 0.1 M $NaClO_4$-0.01 M NaH_2PO_4 (pH 3.0)/acetonitrile (50:50), 1.0 mL/min, 254 nm, 12.3 min).

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