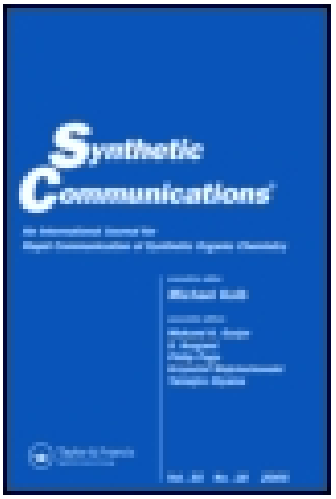

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Synthesis of 2[(1R,2R)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-yl)propyl]-4-[4-tetrafluoropropoxy)phenyl]-3-(2H,4H)-1,2,4-triazol-3-thione—A Novel and Potent Azole Antifungal Agent

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SYNTHESIS OF 2[(1*R*,2*R*)-2-(2,4-DIFLUOROPHENYL)-2-HYDROXY-1-METHYL-3-(1*H*-1,2,4-TRIAZOL-YL)-PROPYL]-4-[4-TETRAFLUOROPROPOXY)PHENYL]-3-(2*H*,4*H*)-1,2,4-TRIAZOL-3-THIONE—A NOVEL AND POTENT AZOLE ANTIFUNGAL AGENT

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A simple approach involving refluxing appropriately disubstituted thiosemicarbazide* 8 *in presence of formic acid for the synthesis of* 1*, a potent azole antifungal agent, has been described.

Keywords: Azole antifungal; thiosemicarbazide; 1,2,4-triazol-3-thione

BACKGROUND

Incidences of systemic fungal infections have increased significantly over the past three decades. This has been attributed[1] to a marked increase in the population of immunocompromised patients with HIV infection or undergoing immunosuppressant therapy following organ transplant or chemotherapy. This has led to significant morbidity and mortality. As a consequence, there has been a concerted effort by the pharmaceutical industry and academic laboratories to find safe, potent, and orally bioavailable antifungal agents.

During the course of our research, we discovered 2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy) phenyl]-3-(2*H*,4*H*)-1,2,4-triazol-3-thione **(1)** has potent and broad-spectrum activity against yeast and filamentous fungi.[2] The *in vitro* activity correlated well with *in vivo* protection, indicating adequate pharmacokinetic properties in mice. The initial synthesis of **1** involved Lawesson's[3a,b] (or modified Lawesson's[3c]) reagent–mediated transformation (Scheme 1) of the corresponding triazolone **2**[4] to the desired thio analog.[5] However, we faced several challenges when this transformation was carried out on a large scale. This reaction did not proceed to completion, and because the

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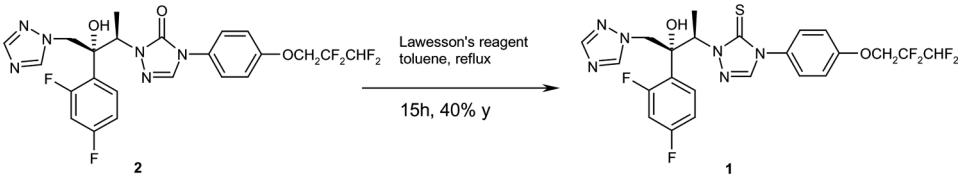


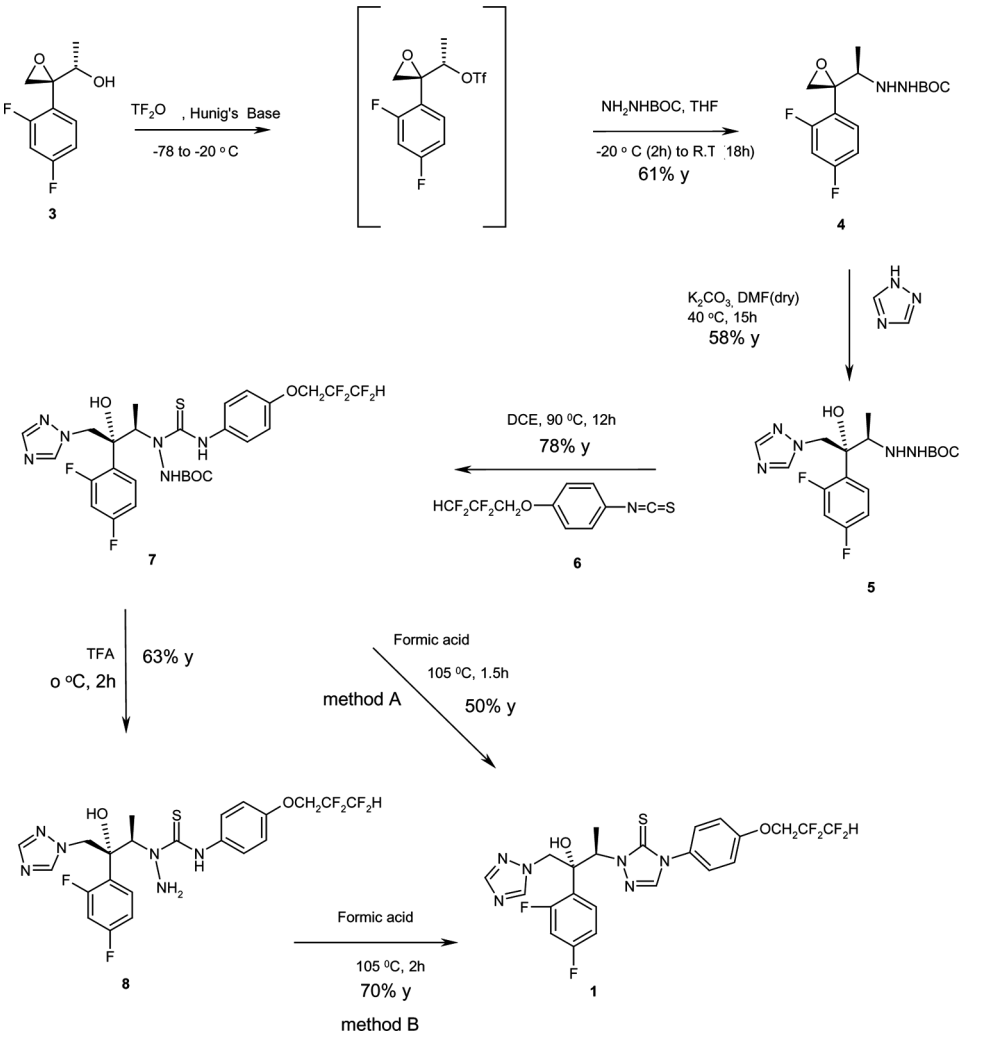
Scheme 1. Synthesis of **1** using Lawesson's reagent.

Rf values of the starting material and the product were similar, column chromatography often failed to purify the product. Additionally, the Lawesson's reagent and its by-product had very foul odors. Therefore, there was a need to develop a robust and simple synthesis for **1** that would facilitate its generation in multigram quantities.

PRESENT WORK

The construction of the 1,2,4-triazol-3-thione ring system previously reported involved the cyclization of 2,4-disubstituted thiosemicarbazides in the presence of a carbon source such as triethylorthoester, formic acid, or formamidine acetate.[6] In this article, we describe the synthesis of compound **1** based on this protocol. Thus, in the first step, the epoxy alcohol **3** was converted to the corresponding triflate derivative with trifluoromethanesulphonic anhydride (Tf_2O) in the presence of Hunig's base at $-78°C$ (Scheme 2). The triflate, without any purification, was subjected to nucleophilic substitution with *tert*-butyl carbazate in dry tetrahydrofuran (THF) at $-20°C$ to afford 2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2,3-epoxy-1-methylpropyl-1-*tert*-butylcarbazate **(4)** in 61% yield. The epoxy carbazate **4** was treated with 1,2,4-triazole in the presence of potassium carbonate at 70°C in dry dimethylformamide (DMF) to give the ring-opened product 2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1-*tert*-butylcarbazate **(5)** as a pale yellow solid in 58% yield. Compound **5**, on heating with 4-(2,2,3,3-tetrafluoropropoxy)phenylisothiocyanate **(6)** in 1,2-dichloroethane at 90°C, gave 1-*tert*-butoxycarbonyl-2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl] thiosemicarbazide **(7)** in 63% yield. Removal of the *tert*-butoxycarbonyl (BOC) group in compound **7** was accomplished by stirring it with trifluoroacetic acid (TFA) in dichloromethane (DCM) at 0°C for 2 h to give Boc-deprotected amine 2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-l-methyl-3-(l*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]thiosemicarbazide **(8)** in 63% yield.

Cyclization of the thiosemicarbazide **8** was the most crucial step in the synthetic strategy. Initial attempts to cyclize **8** under several conditions, such as refluxing in the presence of propionic acid/NaOMe in methanol (MeOH) or heating with formamidine acetate in acetic acid at 80°C, resulted in complex mixtures. However, when **8** was heated for 2 h in formic acid, the final compound **1** was obtained in 70% yield. Furthermore, as the Boc group is known to be cleaved under strongly acidic conditions (pH < 1.0; 90°C), we attempted to convert **7** into **1** directly through an *in situ* deprotection followed by cyclization in one step. As anticipated, the reaction led to the formation of compound **1**, but the yield obtained from **8** was slightly better than that obtained from **7** (i.e., 70% vs 50%).



Scheme 2. Formic acid mediated cyclization to **1**.

In conclusion, we have developed a new synthetic strategy for the synthesis of the potent azole antifungal **2** in multigram quantities.

EXPERIMENTAL

Preparation of 2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2,3-epoxy-1-methylpropyl-1-*tert*-butylcarbazate (4)

(1*S*)-1-[(2*R*)-2-(2,4-Difluorophenyl)oxiran-2-yl]ethanol[7] **(3)** (62.1 g, 0.265 mol), Hunig's base (*N*,*N*-diisopropylethylamine) (119 ml, 0.645 mol), and dichloromethane

(DCM) (300 mL) were placed in a dry, 500-mL, three-neck, round-bottom flask equipped with a nitrogen inlet, guard tube, addition funnel, and a septum. The mixture was cooled to −78°C, and trifluoromethanesulphonic anhydride (55.6 mL, 330.5 mol) was added dropwise. After the completion of addition, the reaction mixture was stirred at −78°C for 30 min and at −20°C for a further 30 min. A solution of *tert*-butyl carbazate (80.73 g, 0.611 mol) in dry tetrahydrofuran (THF) (150 mL) was then added. The reaction mixture was stirred at −20°C for 2 h followed by stirring at room temperature for 18 h. THF was evaporated *in vacuo*, and the residue was dissolved in DCM (150 mL). The organic layer was washed with water and brine and dried over sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography (silica gel, 100–200 mesh, 6:4 DCM–hexane) to afford the title compound. Yield: 59.6 g (61%). ^{1}H NMR (300 MHz, $CDCI_3$): δ 1.07 (d, $J = 6.7$ Hz, 3H), 1.46 (s, 9H), 2.79 (d, $J = 5$ Hz, 1H), 3.08 (d, $J = 5$ Hz, 1H), 3.22 (q, $J = 6.7$ Hz, 1H), 5.97 (s, 1H), 6.19 (s, 1H), 6.76–6.90 (m, 2H), 7.35–7.43 (m, 1H). MS m/z (rel. int.): 337.2 [M + 23, 100%].

Preparation of 2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1-*tert*-butylcarbazate (5)

Anhydrous K_2CO_3 (45.3 g, 0.328 mol) was added to a solution of epoxy carbazate **4** (52.0 g, 0.165 mol) and 1,2,4-triazole (22.6 g, 0.327 mol) in dry DMF (250 ml) under a nitrogen atmosphere. The reaction mixture was stirred at 40°C for 15 h and then at 70°C for 4 h. The reaction mixture was poured into ice-cold water (1000 mL) and extracted with ethyl acetate (EtOAc) (3 × 200 mL). The combined organic layers were washed with water and brine and dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (silica gel, 100–200 mesh, 1:5 EtOAc–DCM) to afford the title compound. Yield: 37.0 g (58%). ^{1}H NMR (300 MHz, $CDC1_3$): δ 0. 91 (d, $J = 6.7$ Hz, 3H), 1.48 (s, 9H), 3.52 (q, $J = 6.7$ Hz, 1H), 4.75–4.90 (m, 3H), 6.2 (s, 1H), 6.70–6.77 (m, 2H), 7.33–7.41 (m, 1H), 7.73 (s, 1H), 7.90 (s, 1H). MS m/z (rel. int.): 384.0 [MH^+, 70%].

Preparation of 1-*tert*-Butoxycarbonyl-2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]thiosemicarbazide (7)

4-[2,2,3,3-Tetrafluoropropoxy]phenylisothiocyanate **6** (37.92 g, 0.142 mol) was added to a solution of **5** (36.31 g, 0.095 mol) in 1,2-dichloroethane (170 mL), and the mixture was heated under reflux for 12 h. The solvent was evaporated, and the residue was purified by column chromatography (silica gel, 100–200 mesh, 1:10 EtOAc–DCM) to afford the title compound. Yield: 40 g (78%). ^{1}H NMR (300 MHz, $CDC1_3$): δ 1.05 (d, $J = 6.6$ Hz, 3H), 1.51 (s, 9H), 4.35 (t, $J = 11.7$ Hz, 2H), 4.44 (d, $J = 14.5$ Hz, 1H), 5.55 (d, $J = 14.3$ Hz, 1H), 5.82 (s, 1H), 6.07 (tt, $J = 53.1$ and 4.9 Hz, 1H), 6.74–6.79 (m, 3H), 6.93–6.96 (d, $J = 8.$ 8 Hz, 2H), 7.36–7.39 (d, $J = 8.8$ Hz, 2H), 7.79 (s, 1H), 7.81 (s, 1H), 8.51 (brs, 1H). MS m/z (rel. int.): 648 [MH^+, 100%].

Preparation of 2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-l-methyl-3-(l*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)-phenyl]thiosemicarbazide (8)

A solution of TFA (18 ml.) in dry DCM (60 ml, 30% v/v) was added slowly to a solution of 1-*tert*-butoxycarbonyl-2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl] thiosemicarbazide **(7)** (3.5 g, 5.4 mmol) in dry DCM (30 ml) at 0°C, and the reaction mixture was stirred at 0°C for 2 h. The solvents were evaporated *in vacuo*, and the residue was dissolved in DCM. The organic layer was washed with 5% aq. $NaHCO_3$ until effervescence ceased. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (silica gel, 100–200 mesh, 1:10 EtOAc–DCM) to afford the title compound. Yield: 1.82 g (62.7%), mp 72–76.5°C. ^{1}H NMR ($CDC1_3$, 300 MHz): δ 1.12 (d, $J = 7.0$ Hz, 3H), 4.35 (t, $J = 11.8$ Hz, 2H), 4.48 (d, $J = 14.6$ Hz, 1H), 4.55 (s, 2H), 5.60 (d, $J = 14.6$ Hz, 1H), 5.65 (s, 1H), 6.06 (tt, $J = 53.1$ and 4.9 Hz, 1H), 6.64 (q, $J = 6.6$ Hz, 1H), 6.73–6.80 (m, 2H), 6.94 (d, $J = 8.9$ Hz, 2H), 7.33–7.36 (m, 1H), 7.46 (d, $J = 8.9$ Hz, 2H), 7.79 (s, 1H), 7.83 (s, 1H), 9.94 (s, 1H). MS m/z (rel. int.): 549.3 [MH^+, 100%].

Preparation of 2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3-(2*H*,4*H*)-1,2,4-triazol-3-thione (1)

Method A: From butoxycarbonylthiosemicarbazide 7. A solution of 1-*tert*-butoxycarbonyl-2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]thiosemicarbazide **(7)** (38 g, 0.2 mol) in formic acid (582 mL) was heated under reflux for 1.5 h, poured into ice-cold water, and neutralized with 5% aq. $NaHCO_3$. The organic layer was extracted with EtOAc, washed with water, and dried over sodium sulfate. Solvent was removed *in vacuo*, and the residue was purified by column chromatography (silica gel, 100–200 mesh, 1:1 EtOAc–DCM) to afford the title compound. Yield: 15.31 g (50%), mp: 76.8–84.3°C. ^{1}H NMR (300 MHz, $CDCI_3$): δ 1. 33 (d, $J = 6.9$ Hz, 3H), 4.34–4.46 (m, 3H), 5.13 (d, $J = 14.4$ Hz, 1H), 5.21 (s, 1H), 5.88–5.96 (m, 1H), 6.06 (tt, $J = 48.5$ and 4.6 Hz, 1H), 6.82–6.88 (m, 2H), 7.09–7.12 (m, 2H), 7.53–7.65 (m, 3H), 7.74 (s, 1H), 7.93 (s, 1H); MS m/z (rel. int.): 559 [MH^+, 100%].

Method B: From thiosemicarbazide 8. A solution of 2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-l-methyl-3-(l*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]thiosemicarbazide **(8)** (1.5 g, 2.73 mmol) in formic acid (3.0 ml) was heated under reflux for 2 h, poured in ice-cold water, and neutralized with 5% aq. $NaHCO_3$. The organic layer was extracted with EtOAc, washed with water, and dried over $NaSO_4$. Solvent was removed *in vacuo*, and the residue was purified by column chromatography (silica gel, 100–200 mesh, 1:1 EtOAc–DCM) to afford the title compound. Yield: 1.021 g (70%).

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