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A Concise Process of Terbinafine Synthesis

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Among relatively few known therapeutic agents against fungal infections, terbinafine **1** has been developed as an extremly effective and almost non-toxic antimycotic agent even with oral administration[1] through intensive studies on structural-activity relationships since the accidental discovery of naftifine.[2]

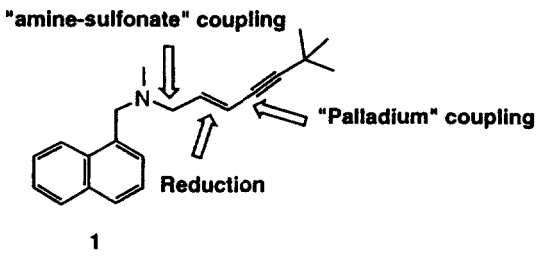
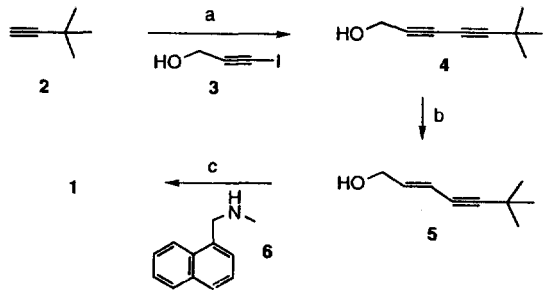


Figure 1.



Regents : (a) **3**, $Pd(PPh_3)_4$, CuI, iPr_2NH (b) Sodium bis(2-methoxyethoxy) aluminium hydride , THF (c) MsCl, Et_3N, DMAP, CH_2Cl_2 ; **6**, K_2CO_3, DMF

Scheme 1.

Terbinafine is an allylamine derivative with an (*E*)-1,3-enyne functionality. Several attempts to synthesize **1**, e.g. condensation of an allylic bromide with the secondary amine, elimination of hydroxyl group, and DIBAL reduction of **1**, 3-diyne, suffered from a lack of stereoselectivity at the olefin.[1,3] Only Stille's vinyl iodide-stannane coupling could furnish the desired stereochemistry stereoselectively, although the notorious toxicity of stannane compound should remain problematic.[4]

In this note we describe a concise, efficient route to the the synthesis of **1** from readily available materials. We envision that palladium coupling for the 1,3-diyne synthesis, stereospecific aluminium hydride reduction to the (*E*)-1,3-enyne functional group, and sulfonate-secondary amine coupling would provide the desired compound (Figure 1).

Commercially available *t*-butyl acetylene **2** was coupled with iodopropargyl alcohol **3**[5] in the presence of $Pd(PPh_3)_4$, CuI, and diisopropylamine to produce a 38% yield of **4**.[6] In order to prepare the desired (*E*)-olefinic alcohol **5**, compound **4** was reduced regio and stereospecifically by sodium bis(2-methoxyethoxy)aluminium hydride[7] in THF solution in a quantitative yield. For the final coupling reaction, compound **5** was first converted to the corresponding methanesulfonate by reaction with methanesulfonyl chloride at 0° within 5 mins., and the crude sulfonate was readily reacted with N-methyl-1-naphthalene-methylamine in DMF solution with K_2CO_3 to afford **1**. Prolonged stirring at the mesylation step yielded allylic chloride as a by-product, which provided a much less yield of **1** in the following coupling reaction with the amine. More practically, terbinafine hydrochloride was obtained as a white solid in 77% yield by HCl-salt formation

from the crude mixture followed by recrystallization in EtOAc. As the overall route is concise and efficient, a practical scale-up process for terbinafine **1** is in progress.

In summary, terbinafine hydrochloride was prepared concisely *via* 4 steps in 27% overall yield.

Experimental

General. All commercial chemicals were used as obtained without further purification, and all solvents were carefully dried and distilled by standard methods prior to use. Column chromatography was carried out on silica gel 60 (E. Merck, 230-400 mesh) with the flash technique. Melting points were determined on a Thomas-Hoover melting point apparatus and uncorrected. Nuclear magnetic resonance spectra were determined on a Bruker ARX 300 spectrometer. Chemical shifts are reported in δ ppm relative to $(CH_3)_4Si$ for ^1H and ^{13}C NMR. Coupling constants, J are reported in Hz. Infrared spectra (cm^{-1}) were obtained on a Nicolet 710 FT-IR spectrometer. GC-mass analysis was performed on a Hewlet-Packard MSD 5890 series equipped with a capillary column(HP 1, 25 m).

6,6-dimethyl-2,4-diheptyn-1-ol (4). To a solution of 3-hydroxy-1-iodopropyne **3** (1.82 g, 10 mmol), *t*-Butyl acetylene **2** (1.5 mL, 12 mmol), $Pd(PPh_3)_4$ (350 mg), CuI (60 mg) in THF (40 mL) under a nitrogen atmosphere was added diisopropylamine (3.0 mL). After 3 hrs at room temperature the mixture was dilluted with ether, washed with saturated ammonium chloride solution and brine, then dried over $MgSO_4$. After concentration, the crude product was purified by column chromatography on silica gel (Hex : EtOAc = 5 : 1) to yield **4** (517 mg, 38%): ^1H NMR ($CDCl_3$) δ 4.32 (s, 2H), 1.85 (br, 1H), 1.24 (S, 9H); ^{13}C NMR ($CDCl_3$) δ 89.30, 75.01, 70.43, 63.04, 51.21, 30.21, 27.80; MS ($M^+ + 1$) : 137.04; IR (film) ν 2970, 2252, 1022 cm^{-1}

6,6-dimethyl-2E-hepten-4-yn-1-ol (5). To a solution of compound **4** (350 mg, 2.57 mmol) in THF (1.5 mL) was added sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al from Aldrich, 65 wt% 1.27 g, 4.1 mmol) at 0 ℃. The reaction mixture was warmed to room temperature and stirred for 1 hr. The reaction mixture was quenched with 1.0 N sulfuric acid solution (1.5 mL), and the white solid was filtered off. Dilution with ether was followed by washing the organic phase with water twice and with brine once. The organic solution was dried over $MgSO_4$. Evaporation of solvent under reduced pressure provided compound **5** quantitatively: ^1H NMR ($CDCl_3$) δ 6.20 (dt, J = 15.9, 5.5, 1H), 5.84 (dt, J = 15.9, 1.5, 1H), 4.21 (dd, J = 5.5, 1.5, 2H), 1.64 (s, 1H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 140.0, 112.0, 99.0, 63.0, 60.5, 31.0, 28.0; MS ($M^+ + H$): 139.04; IR (film) ν 2960, 2287, 1265 cm^{-1}.

Terbinafine (1), Terbinafine HCl salt. To a solution of compound **4** (300 mg, 2.17 mmol), Et_3N (1 mL), a catalytic amount of DMAP in methylene chloride (3.0 mL) was added methanesulonyl chloride (0.336 mL, 4.34 mmol) at 0 ℃. After 5 mins. at 0 ℃, the reaction was quenched with water (2 mL) and stirred for 1 hr. Dilution with methylene chloride was followed by washing with water and drying over $MgSO_4$. Evaporation of solvent on the rotatory evaporator afforded an oily compound. This crude product was added to a reaction mixture of N-methyl-1-naphthalenemethylamine (342.4 mg, 2.0 mmol), K_2CO_3 (1.5 g, 10.8 mmol) in DMF (1.5 mL). The reaction mixture was stirred for 6 hrs. at room temperature and then quenched with water. Extraction with EtOAc, washing with water, drying over $MgSO_4$, and evaporation followed by separation by column chromatography afforded an oily compound **1**. For the more practical separation, the crude product was treated with HCl in methanol and evaporated to obtain a crude salt, and then the crude salt was treated with EtOAc to yield a white solid (448.1 mg, 77.0%): **terbinafine 1**; ^1H NMR ($CDCl_3$) δ 8.31 (m, 1H), 7.81 (m, 2H), 7.51 (m, 4H), 6.23 (dt, J = 15.9, 6.6, 1H), 5.70 (dt, J = 15.9, 1.4, 9H), 3.94 (S, 2H), 3.10 (dd, J = 6.6, 1.4, 2H), 2.22 (S, 3H), 1.31 (S, 9H). Spectrum matches that reported in *J. Med. Chem.* **1984**, *27*, 1539. **terbinafine hydrochloride**; mp 191-192 ℃ (lit.,[3a] mp 195-198 ℃); ^1H NMR (DMSO) δ 10.9 (s, 1H), 8.4 (d, J = 15.9, 1H), 8.1 (m, 2H), 7.9 (d, J = 15.9, 1H), 7.6 (m, 3H), 6.2 (m, 1H), 6.0 (bd, 1H), 4.9 (m, 1H), 4.8 (m, 1H), 3.9 (m, 2H), 3.4 (S, 3H), 1.1 (s, 9H).

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Stereoselective Synthesis of (*E*)-Silyl Ketene Acetal from 2-Pyridyl Thioester[1]

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Over the past decade, the stereoselective formation of ester and thioester enolates in aldol-type reactions has been the subject of intense investigation.[2] This is also the case for their related silyl ketene acetal,[3] since Mukaiyama's disclosure[4] for Lewis acid-mediated aldol condensation. During recent work[5] on stereocontrolled Mukaiyama's aldol condensation, we have become interested in using the silyl ketene acetal of 2-pyridyl thioesters as aldol precursors.

Although aldol reaction with silyl ketene acetal of thioester is generally stereoconvergent regardless of the geometry of silyl ketene acetal,[3,6] we needed the stereoselective synthesis