mp 74-75 °C).

2,6-Di(azidomethyl)pyridine, 7. A mixture of dichloride **6** (1.8 g, 10 mmol), sodium azide (3.3 g, 50 mmol) and triethylbenzylammonium chloride (0.2 g, 0.5 mmol) in acetonitrile (50 mL) was heated at reflux for 30 min. The solvent was removed by a rotary evaporator. To the residue was added methylene chloride (50 mL) and the insoluble material was removed by filtration. The filtrate was washed with brine, dried over $MgSO_4$. The solution was concentrated and then dried under vacuum to give **7** (1.55 g, 82%) as a pale brown liquid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (t, *J*=7.8 Hz, 1H, Ar-*H*), 7.29 (d, *J*=7.8 Hz, 2H, Ar-*H*) and 4.47 (s, 4H, ArCH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6 (*C2, C6* of Ar), 137.7 (*C4* of Ar), 120.8 (*C3, C5* of Ar) and 55.1 (ArCH_2); IR (neat) 3068 w, 2928 m, 2877 w, 2099 vs, 1594 s, 1458 s, 1279 s, 800 m, 760 m and 656 m cm $^{-1}$.

2,6-Di(aminomethyl)pyridine, 4

Synthesis from 3. A mixture of dinitrile **3** (2.6 g, 20 mmol) and Raney nickel (2 g) in ethanol (30 mL) was charged in an autoclave. The autoclave was closed, evacuated, flushed with hydrogen three time and then pressurized to 10 atm. The autoclave was stirred with a magnetic stirrer at room temperature for 12 hours. The catalyst was removed by filtration and washed with water. The filtrate was concentrated *in vacuo*. The residue was distilled under vacuum (70 °C, 2 mmHg) to give **4** (1.78 g, 65%) as an icy solid:

Synthesis from 7. Under same reaction condition as above, diazide **7** (0.41 g, 2.17 mmol) afforded 0.21 g of **4** (70%): mp 29-31 °C (lit.[5] mp 30 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (t, *J*=7.8 Hz, 1H, Ar-*H*), 7.13 (d, *J*=7.8 Hz, 2H, Ar-*H*), 3.96 (s, 4H, ArCH_2), 1.72 (s, 4H, NH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.1 (*C2, C6* of Ar), 136.8 (*C4* of Ar), 118.9 (*C3, C5* of Ar) and 47.4 (ArCH_2); IR (neat) 3348 m, 3292 m, 3063 w, 2920 m, 1604 vs, 1577 vs, 1459 s, 1372 m, 1313 s, 795 s cm $^{-1}$; mass spectrum, m/z (rel intensity). 138 (M+1, 25), 137 (M^+, 11), 122 (10), 121 (100), 120 (26); Anal. Calcd for $C_7H_{11}N_3$: C, 61.29; H, 8.08; N, 30.63. Found: C, 60.96; H, 8.42; N, 30.27.

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A New Route to the Synthesis of Terbinafine

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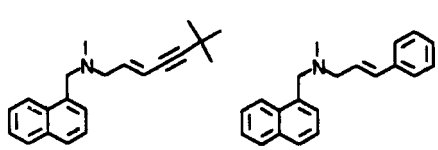
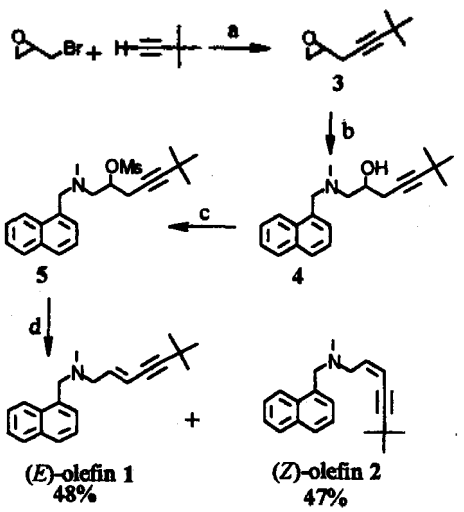
Terbinafine **1**, one of an antifungal agents selectively inhibiting fungal squalene epoxidase, exhibits strong antimycotic activity and is currently used for the treatment of skin mycoses.[1] Terbinafine is an allylamine derivative with an (*E*)-1,3-enyne structural moiety that has developed from studies on structural-activity relationships since the accidental discovery of naftifine[2] (Figure 1).

To date, various synthetic methods for terbinafine **1** have been reported as follows: 1) condensation[3] of an allylic bromide with the secondary amine, 2) DIBAL-H reduction[4] of 1,3-diyne, and 3) palladium catalyzed cross coupling.[5]



Terbinafine 1 Naftifine

Figure 1.



Scheme 1. Reagents: (a) *n*-BuLi, THF; (b) N-methyl-1-naphthalenemethylamine hydrochloride, Et_3N, toluene; (c) MsCl, Et_3N, CH_2Cl_2; (d) K^+-OBu^t, DMF.

In this paper we describe a new route to the synthesis of terbinafine **1** by β-elimination of secondary methanesulfonate **5** with potassium *t*-butoxide in dimethylformamide (DMF) as shown in Scheme 1.

Lithiation of 3,3-dimethyl-1-butyne using 1.1 equimolar amount of *n*-butyllithium at −20 °C, followed by addition of epibromohydrin, led to the formation of the coupling product **3** in 95% yield. The epoxide ring opening of **3** with N-methyl-1-naphthalenemethylamine hydrochloride in the presence of triethylamine gave the secondary alcohol **4** in 72% yield. Methanesulfonylation of **4** in the presence of methanesulfonylchloride and triethylamine gave the desired compound **5** in 98% yield. From the epibromohydrin and 3,3-dimethyl-1-butyne, **5**, a key intermediate of **1**, was prepared *via* three steps in 67% yield.

Finally, β-elimination of **5** with potassium *t*-butoxide in DMF at 0 °C gave a mixture of *ca.* 1:1 ratio of two stereoisomers (*E*)-olefin **1** and (*Z*)-olefin **2** in 95% yield. Then, the ratio and stereochemistry of double bonds were determined by ^{1}H NMR spectrum analysis. Separation of the crude mixture of **1** and **2** was accomplished by flash column chromatography to give (*E*)-olefin **1** (48% yield) as an oil and by-product (*Z*)-olefin **2** (47% yield) as an oil. Study of stereocontrol of (*E*)-olefin **1** and (*Z*)-olefin **2** through β-elimination of **5** under various basic conditions is in progress.

In summary, terbinafine was synthesized *via* four steps in 32% overall yield. We think that the newly developed process for terbinafine **1** is worth noting because all of the reaction conditions are mild, and reagents used are cheap and commercially available.

Experimental

^{1}H NMR (nuclear magnetic resonance) spectra were recorded on a Bruker DPX 300 (300 MHz) instrument. Chemical shifts are reported in δ ppm relative to $(CH_3)_4Si$. Coupling constants, *J* are reported in Hz. Column chromatography was carried out on silica gel 60 (E. Merck, 230-400 mesh) with the flash technique. Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (0.25 mm layer thickness, 60F-254, E. Merck) with UV (254 nm) light and/or a solution of ethanol (675 mL), *p*-anisaldehyde (175 mL), sulfuric acid (25 mL), and acetic acid (7.5 mL)-heat gun as a developing agent.

6,6,-Dimethyl-1,2-epoxy-4-heptyne (3). To a solution of 3,3-dimethyl-1-butyne (2.9 mL, 23.4 mmol) in tetrahydrofuran (30 mL) was added dropwise *n*-butyllithium (12.3 mL, 2.1 M in hexane) by syringe under an nitrogen atmosphere at −20 °C. After being stirred for 30 min, a solution of epibromohydrin (3.2 g, 23.4 mmol) in tetrahydrofuran (5 mL) was added by cannula. The reaction mixture was allowed to warm to 0 °C and stirred for 8 h. The resulting solution was quenched with saturated aqueous $NH_4^+Cl^-$ solution, extracted with diethyl ether, and dried over $MgSO_4$. Evaporation of solvent by rotary evaporator at low temperature (5 °C) provided the coupling product **3** (3.1 g, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.09-3.08 (m, 1H), 2.79 (dd, *J*=4.9, 4.0 Hz, 1H), 2.68 (dd, *J*=4.9, 2.6 Hz, 1H), 2.47-2.40 (m, 2H), 1.22 (s, 9H).

N-(6,6-Dimethyl-2-hydroxy-4-heptynyl)-N-methyl-1-naphthalenemethylamine (4). To a stirred mixture of the epoxy compound **3** (2.50 g, 18.1 mmol) and N-methyl-1-naphthalenemethylamine hydrochloride (3.76 g, 18.1 mmol) in toluene was added triethylamine (5.1 mL, 36.2 mmol) at room temperature. The reaction mixture was warmed to 80 °C and stirred for 8 h, and then followed by cooling to room temperature. The resulting mixture was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated by rotary evaporator. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/hexane, 1:4) to give the desired product **4** (4.03 g, 72%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.24-8.23 (m, 1H), 7.89-7.79 (m, 2H), 7.55-7.49 (m, 2H), 7.43-7.41 (m, 2H), 4.10 (d, *J*=12.8 Hz, 1H), 3.93 (d, *J*=12.8 Hz, 1H), 3.83-3.78 (m, 1H), 2.61-2.59 (m, 2H), 2.40 (dd, *J*=16.5, 5.3 Hz, 1H), 2.32 (s, 3H), 2.25 (dd, *J*=16.5, 6.9 Hz, 1H), 1.20 (s, 9H).

N-(6,6-Dimethyl-2-methanesulfonyloxy-4-heptynyl)-N-methyl-1-naphthalenemethylamine (5). To a solution of the alcohol **4** (1.25 g, 4.04 mmol) and triethylamine (0.85 mL, 6.06 mmol) in methylene chloride (10 mL) was added methanesufonyl chloride (0.34 mL, 4.44 mmol) at 0 °C. After being stirred for 20 min, the reaction mixture was diluted with methylene chloride (20 mL), washed with water, and dried over $MgSO_4$. Evaporation of solvent on the rotary evaporator afforded the desired compound **5** (1.53 g, 98%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.29-8.28 (m, 1H), 7.89-7.80 (m, 2H), 7.55-7.52 (m, 2H), 7.43-7.41 (m, 2H), 4.73-4.62 (m, 1H), 4.02 (d, *J*=12.8 Hz, 1H), 3.94 (d, *J*=12.8 Hz, 1H), 2.93 (s, 3H), 2.88-2.78 (m, 2H), 2.58-2.52 (m, 2H), 2.35 (s, 3H), 1.20 (s, 9H).

(E)-N-(6,6-Dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethylamine (1) and its (Z)-olefin (2). To a solution of **5** (1.12 g, 2.89 mmol) in dimethylformamide (6 mL) was added potassium *t*-butoxide (357 mg, 3.18 mmol) at −20 °C. After being stirred for 30 min, the resulting solution was cooled to 0 °C, quenched with saturated aqueous $NH_4^+Cl^-$ solution, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated by rotary eva-

porator. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/hexane, 1 : 20) to give the desired compound, (*E*)-olefin **1** (404 mg, 48%) as an oil and by-product, (*Z*)-olefin **2** (396 mg, 47%) as an oil. The stereochemistry and ratio (*ca.* 1 : 1) of two isomers, (*E*)-olefin **1** and (*Z*)-olefin **2**, were determined by ^{1}H NMR spectrum analysis: (*E*)-olefin **1**: R_f=0.53 (ethyl acetate/hexane, 1 : 9); ^{1}H NMR ($CDCl_3$) δ 8.31-8.28 (m, 1H), 7.88-7.85 (m, 1H), 7.81-7.78 (m, 1H), 7.54-7.41 (m, 4H), 6.18 (dt, *J*= 15.7, 6.6 Hz, 1H), 5.70 (dt, *J*=15.7, 1.4 Hz, 1H), 3.92 (s, 2H), 3.15 (dd, *J*=6.6, 1.4 Hz, 2H), 2.25 (s, 3H), 1.26 (s, 9H): (*Z*)-olefin **2**: R_f=0.42 (ethyl acetate/hexane, 1 : 9); ^{1}H NMR ($CDCl_3$) δ 8.31-8.28 (m, 1H), 7.88-7.85 (m, 1H), 7.81-7.78 (m, 1H), 7.54-7.41 (m, 4H), 6.05 (dt, *J*=10.2, 6.5 Hz, 1H), 5.69 (dt, *J*=10.2, 1.4 Hz, 1H), 3.95 (s, 2H), 3.39 (dd, *J*=6.5, 1.4 Hz, 2H), 2.28 (s, 3H), 1.29 (s, 9H). Spectrum matches that in *J. Med. Chem.* **1984**, *27*, 1539.

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Synthesis and Conformational Properties of 1,2-Dibenzoester Calix[4]arene

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Selective derivatization of calixarene has greatly widened the area of calixarenes in Host-Guest chemistry.[1-3] Several synthetic procedures for selective alkylation have been developed such as 1,3-dialkylation,[4] 1,2-dialkylation,[5] monoalkylation,[6] and trialkylation.[7] Also a few selective acylation techniques has been reported.[8] Unlike alkyl moiety, acyl groups at the lower rim of calixarenes not only can control the reactivity of the *para* position of upper rim, but be utilized as useful protecting groups. Thus selective acylation can provide the quite useful intermediate compounds for the developing of important calixarene host. Gutsche and Lin[8a] found that calix[4]arene is only tribenzoylated when it is treated with excess benzoyl chloride in pyridine. They also reported[8] that when *t*-butylcalix[4]arene was treated with 3,5-dinitrobenzoyl chloride in the presence of bases, various substitution patterns were observed such as triester, 1,3-diester, 1,2-diester, and monoester compounds depending on reaction conditions. But these substitution patterns were only applied to *t*-butylcalix[4]arene with 3,5-dinitrobenzoyl chloride. Here we developed a selective indirect acylation procedure providing specifically 1,2-dibenzoester by removing benzyl group selectively from trisubstituted calix[4]arene. Trisubstituted calix[4]arene was obtained from benzoylation of monobenzylcalix[4]arene in pyridine. 1,2-Dibenzoester of calix[4]arene never has been prepared and it could provide the excellent building block for the useful host calix[4]arenes.

Direct 1,2-substitution of calix[4]arene with benzoyl groups was attempted by varying the reaction conditions, but failed to obtain any significant amounts of 1,2-dibenzoester products. Always 1,3-dibenzoylated calix[4]arene and/or tribenzoylated calix[4]arene was obtained as a major products depending on the reaction conditions.[8] After direct 1,2-dibenzoylation failed, a three step procedure was sought. It is known[8] that calix[4]arene **1** produces only tribenzoylated products in pyridine when treated with excess benzoyl chloride. If this selective benzoylation occurred with monoalkylcalix[4]arenes, it is possible to get 1,2-benzoester from this reaction. Thus, we treated monobenzyl ether calix[4]arene **2** prepared by the reported procedure[6] with excess benzoyl chloride in pyridine to obtain the asymmetrically substituted calix[4]arene **3**. As expected, only two benzoyl groups were introduced exclusively, one at the opposite and the other at the adjacent position relative to the present benzyl group, to give so called ABBH type[10] chiral calix[4]arenes as shown in Scheme 1. Two benzoyl group might end up at both adjacent positions relative to alkyl group, which can be described as a ABHB type, but we observed none of this product. It can be rationalized by the order of benzoylation. If we assume that two benzoylation do not occur simultaneously, first benzoyl group could prefer to be introduced at the opposite side of the existing alkyl group due to steric crowd. Then the second benzoyl group will end up either side to finish a ABBH type calix[4]arene. The ^{1}H NMR spectrum of **3** shows the typical chiral calix[4]arene characteristics such as four pairs of doublet at 3.2-4.1 ppm for the eight bridge methylene protons and the very complicated aromatic signals around 6.2-8.0 ppm. The diastereotopic protons of benzylic methylene appear as a pair of doublets at 4.3 ppm as expected.