Synthesis and Structure–Activity Relationships of Side-Chain-Substituted Analogs of the Allylamine Antimycotic Terbinafine Lacking the Central Amino Function

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Terbinafine is a therapeutically used inhibitor of fungal squalene epoxidase that has prompted extensive derivatization programs for structure–activity relationship studies. In the present study, derivatives of terbinafine were synthesized that lack the central tertiary amino group but have polar substituents at the *tert*-butyl residue of the side chain. Evaluation of the antifungal potential revealed that representatives of this novel structural type can also exhibit broad antifungal activity, indicating that the central amino function of allylamine antimycotics is not essential for inhibition of fungal growth. Potency appears to correlate with the polarity of the introduced functional groups, while broad antifungal activity seems to be restricted to compounds with basic substituents. The dimethylamino-substituted "carba-analog" of terbinafine (**8k**) showed the best antimycotic profile within the whole series.

Introduction

The allylamine derivatives are a class of synthetic antifungal agents[1] that selectively inhibit fungal squalene epoxidase.[2] Presently, two allylamine antimycotics are on the market: naftifine (Exoderil) for topical[3] and terbinafine (**1**, Lamisil; Figure 1) for both oral and topical treatment of mycoses.[4,5] The discovery of terbinafine was the result of intensive structure–activity relationship (SAR) studies within the allylamines,[6] particularly concentrating on modification of the allylamine side chain.[7] Further SAR explorations revealed that antifungal activity against yeasts was increased when halogen substituents were introduced in the naphthalene moiety of **1** at appropriate positions[8] (5-fluoro, 5-chloro, 5,7-difluoro) or when naphthalene was replaced by 3-halo-7-benzo[*b*]thiophenes.[9–11] Extensive variations of the allylamine side chain of **1** led to the identification of two additional potent antifungal classes, the benzylamines[11–13] and the homopropargylamines.[11,14] All these findings together led to the hypothesis that the structural requirements for high activity of allylamine, homopropargylamine, and benzylamine antimycotics can be characterized by the pharmacophoric model A (Figure 1), in which two lipophilic domains (e.g., L1 = 1-naphthalene and L2 = *tert*-butylacetylene in **1**) are linked by a spacer of appropriate length containing a polar center (P = NMe) at a defined position.[14]

Initial studies with the "carba-analog"[11,15] of terbinafine (**2**; Figure 1) indicated that the allylamine nitrogen is not essential for enzyme inhibition per se but is required for penetration of the fungal cell envelope. The present study was designed in order to explore whether high antifungal potency is restricted to compounds of the general formula A (Figure 1) or whether efficient cell penetration and, hence, antifungal activity can also be attained by introducing a polar substituent at one of the two lipophilic domains. Previous studies had shown that substituents other than fluorine were tolerated only at position 5 of the naphthalene moiety (L1) in **1**,[8] whereas increase in bulkiness of L2 even resulted in compounds with enhanced antifungal activity.[13,14] Therefore, analogs of general structure B (Figure 1, P = polar group) were synthesized, and their antifungal potential evaluated.

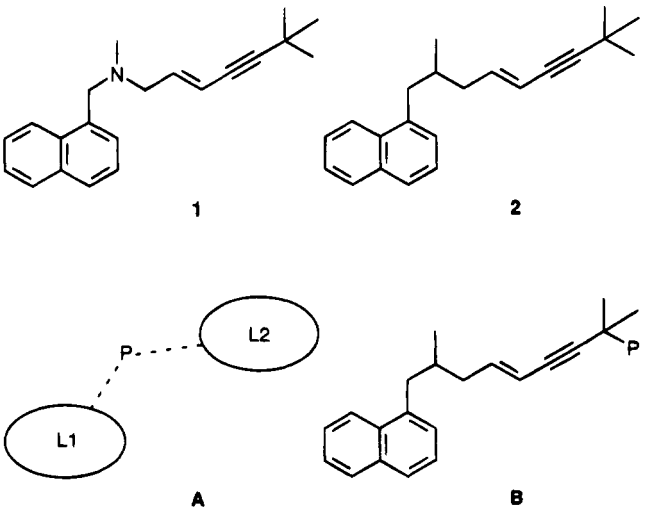

Figure 1. Structural comparison of terbinafine (**1**), its "carba-analog" (*E*)-**2**, the hypothesized general formula for highly active allyl/benzyl/homopropargylamine antimycotics (A), and the general structure for the target compounds (B).

Chemistry

Scheme 1 summarizes the synthesis of the terbinafine carba-analog **2**.[11] The key step was the Wittig reaction of the aldehyde **3** and the propargylic phosphonium bromide **4** to generate the enyne structural element. In general, the reaction yielded a mixture of (*E*)-**2**, (*Z*)-**2**, and the cumulene **5** (*E*/*Z* = 1/1) with ratios depending on the reaction conditions. When sodium hydride in tetrahydrofuran at ambient temperature was used, the 1,2,3-triene **5** was the predominating product. Performing the reaction in the same solvent at −70 °C with lithium diisopropylamide as base, the product ratio was about 6/3/1 for (*E*)-**2**, (*Z*)-**2**, and **5**. Separation of the three products was achieved by chromatography on silica gel.

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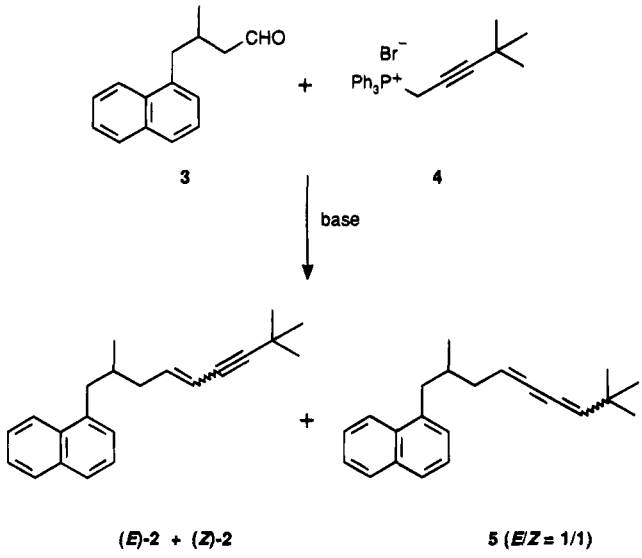
Scheme 1. Synthesis of the "Carba-Analog" of Terbinafine



The substituted analogs **8** were synthesized according to Scheme 2 as racemic mixtures. The aldehyde **3** was first converted to the *E*-iodoolefin **6** by treatment with triiodomethane/chromous chloride.[16] The following Pd(0)-catalyzed coupling of **6** with alkynes failed in several cases, possibly due to residual chromium impurities. This problem could be solved using the following procedure: iodo compound **6** was stirred with triethylamine and catalytic amounts of tetrakis(triphenylphosphine)palladium and cuprous iodide for 2 h in toluene and chromatographed again. The repurified vinylic iodide **6** then reacted with acetylenes **7a–f** in the presence of Pd(0)/Cu(I) catalysts to produce the corresponding enynes **8**. In agreement with the literature, the *E*-stereochemistry of the starting material **6** was maintained under the reaction conditions leading exclusively to *E*-enyne products, and the method proved to be compatible with the functional groups present in the alkynes **7a–f**. As outlined in Scheme 2, additional analogs bearing different substituents (R) were prepared from compounds **8a,e,i,h** following standard procedures for functional group transformations.

Results and Discussion of Biological Activities

The pharmacophoric model A (Figure 1) summarizes the extensive SAR studies on allylamine antimycotics performed so far[1,6,17] and describes the minimum structural requirements for high potency in this compound class. The model features two lipophilic domains (L1 = bicyclic aromatic ring system, L2 = preferentially *tert*-alkylacetylene or 4-*tert*-alkylbenzene) connected by a spacer of appropriate length containing a polar center, P (usually the methylamino group), at a defined position. Initial studies with terbinafine analog **2** (Figure 1), in which the polar center was replaced by the CHMe group, revealed that although **2** was a quite potent inhibitor of *Candida albicans* ergosterol biosynthesis in a cell-free system (IC_{50} = 0.24 μM), it was unable to inhibit the growth of the intact microorganism.[11,15] This suggested that the polar amino function of allylamine antimycotics is not essential for enzyme inhibition but is required for penetration through the fungal cell envelope. The crucial role of the polar amino function in **1** for potent cellular antifungal activity is evident when comparing the in vitro spectrum of **1** and its carba-analog (*E*)-**2** (Table 1). With the exception of moderate activity against dermatophytes (*Trichophyton mentagrophytes*, *Microsporum canis*), compound (*E*)-**2** is inactive. On the basis of these findings, we wanted to know if the cell penetration-enhancing effect is restricted to the *N*-methyl group and its particular location in the center of the molecule (model A, Figure 1) or whether introduction of polar groups at other positions of the molecule would lead to sufficient penetration as reflected in antifungal activity. Therefore, we synthesized and evaluated the antimycotic potential of analogs of (*E*)-**2** in which polar substituents were introduced at the *tert*-butyl region (general structure B, Figure 1). The substituents in the new compounds **8a–m** were chosen to cover a broad range of polarity and explore the effect of introducing neutral, basic, acidic, and ionic functionalities in the molecule. The full length of the carbon skeleton of **2** is maintained in compounds **8a–g**, whereas it is one carbon atom shorter in compounds **8h–m**. All compounds were prepared and tested as racemic mixtures (with respect to the asymmetric center created by replacing the nitrogen with a CH group), thus enabling rapid verification of the hypothesis.

The antifungal activities of the new compounds **8a–m** against those of a panel of human pathogenic fungi are listed in Table 1. The methyl ester derivative **8a** showed moderate potency against dermatophytes and was inactive against the other strains tested. Thus, although **8a** was slightly more active than the parent compound (*E*)-**2** (Table 1) against dermatophytes, the activity profile of the two substances was very similar. Hydrolysis of the ester to the corresponding carboxylic acid analog **8b** caused a drastic increase in polarity of the molecule, accompanied by loss of activity. The hydroxymethyl compound **8c** and the methylamide derivative **8d** (derived from the carboxylic acid **8b**) had polarities lying between those of the methyl ester analog **8a** and the carboxylic acid **8b** and showed only poor to moderate activity against dermatophytes. Introduction of a primary amide functionality (**8e**) resulted in loss of activity against all strains tested. Replacement of the methyl ester in **8a** by a cyano group (almost equivalent to the ester group in terms of polarity) led to **8f** and an antimycotic profile similar to those of (*E*)-**2** and **8a**. Analog **8g** with the methylamino function as polar substituent was the first compound out of the series that demonstrated activity against *Aspergillus fumigatus* and *Sporothrix schenckii* in addition to dermatophytes. Although the MIC values were generally quite high (6.25–50 mg/L), the activity spectrum of the amino compound **8g** was considerably broader than those of (*E*)-**2** and **8a,d,f**.

The carbon skeleton of compounds **8h–m** is shorter by one atom. Here the heteroatoms of the functional groups are directly attached to the terminal propargylic carbon. The tertiary alcohol **8h** was expected to be less polar relative to its homolog, the primary alcohol **8c**. Nevertheless, both compounds were inactive against nearly all fungal strains. Replacement of the hydroxy group in **8h** by the amino function yielded **8i**, which demonstrated increased potencies against dermatophytes, *A. fumigatus*, and *S. schenckii*. The improvement of the MIC values (1.56–25 mg/L) and the activity

Scheme 2 Synthesis of Target Compounds **8a–m**

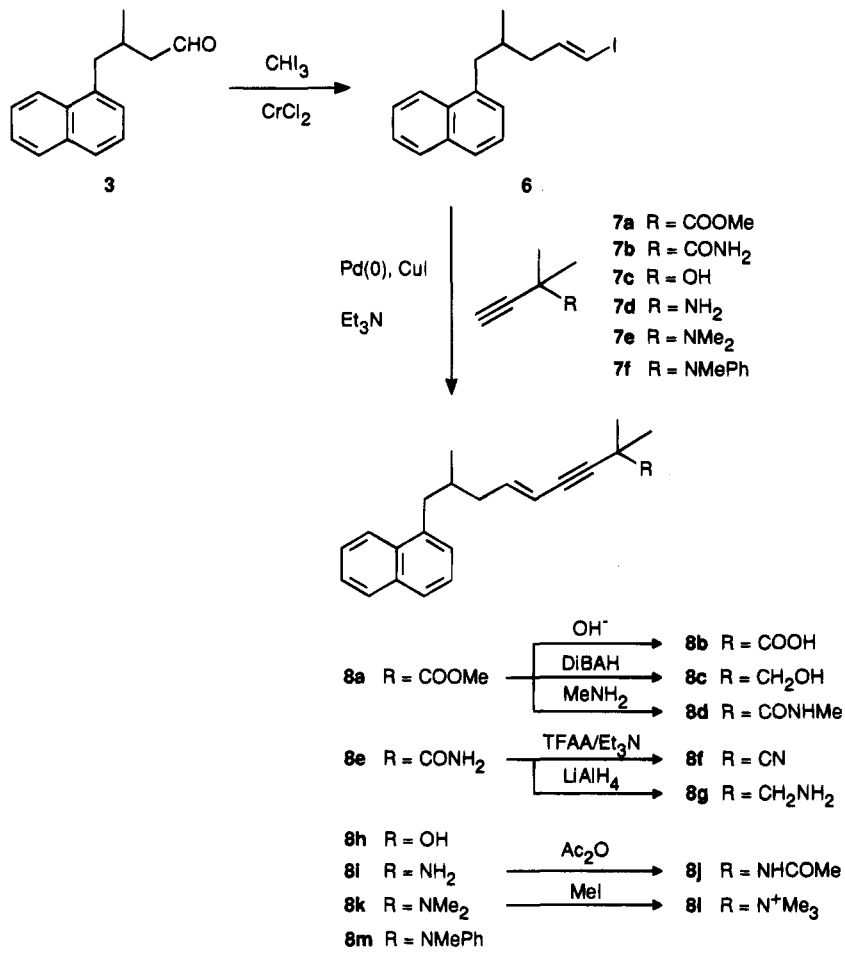


Table 1. In Vitro Activity (MIC, mg/L) of Compounds **8a–m** in Comparison with Naftifine, Terbinafine (**1**), and Carba-Analog (*E*)-**2**

		organisms[a]					
no.	R	*T. ment.*	*M. canis*	*A. fum.*	*S. sch.*	*C. a. 124*	*C. par. 39*
naftifine		0.05	0.1	12.5	1.6		1.6
1		0.003	0.006	0.8	0.4	25	0.8
(*E*)-**2**		0.4	3.1	>100	>100	>100	>100
8a	-COOMe	0.1	0.8	>100	>100	>100	>100
8b	-COOH	>100	>100	>100	>100	>100	>100
8c	$-CH_2OH$	3.1	100	>100	>100	>100	>100
8d	-CONHMe	0.4	1.6	>100	>100	>100	>100
8e	$-CONH_2$	>100	>100	>100	>100	>100	>100
8f	-CN	0.4	12.5	>100	>100	>100	>100
8g	$-CH_2NH_2$	6.25	25	50	25	>50	>50
8h	-OH	3.1	>100	>100	>100	>100	>100
8i	$-NH_2$	1.6	3.1	25	12.5	>100	100
8j	-NHAc	>50	>50	>50	>50	>50	>50
8k	$-NMe_2$	0.1	0.2	12.5	3.1	50	6.25
8l	$-N^+Me_3$	>100	>100	100	12.5	25	100
8m	-NMePh	>100	>100	>100	>100	>100	>100

[a] Abbreviations: *Trichophyton mentagrophytes*, *T. ment.*; *Microsporum canis*, *M. canis*; *Aspergillus fumigatus*, *A. fum.*; *Sporothrix schenckii*, *S. sch.*; *Candida albicans* Δ124, *C. a. 124*; *Candida parapsilosis* Δ39, *C. par. 39*.

spectrum was even more pronounced than for compound **8g**. Thus, the antimycotic profile of the terbinafine carba-analog (*E*)-**2** could be substantially broadened by introducing an amino residue at its bulky lipophilic domain L2. Acetylation of the amino function in **8i** generated the amide derivative **8j**, which was completely inactive up to concentrations of 50 mg/L. In contrast, analog **8k** bearing a dimethylamino substituent, which is less polar than the corresponding primary amino groups in **8g,i**, demonstrated improved antifungal potency relative to **8g,i**. With MIC values of 0.1–0.2 mg/L for dermatophytes, 3.13 mg/L for *S. schenckii*, 12.5 mg/L for *A. fumigatus*, and 6.25–50 mg/L for *Candida* strains, compound **8k** displayed a spectrum of activity very similar to that of naftifine (Table 1), the first clinically used allylamine antimycotic. Substitution of **8k** by one extra methyl group produced the quaternary ammonium salt **8l**, which showed only weak inhibitory potency (MIC = 12.5–100 mg/L) against *S. schenckii* and yeasts. Substance **8l** thus exhibited an activity profile contrasting the selective antidermatophytic activity of many compounds of the present series (**8a,c,d,f**). In **8m** one methyl group of the dimethylamino function of **8k** was replaced by a phenyl residue

to achieve further reduction in polarity. A similar increase in side-chain bulkiness within the allylamine, benzylamine, and homopropargylamine antimycotics led to highly active derivatives.[13,14] Unexpectedly, however, compound **8m** was found to be inactive.

Previous studies showed that the activity of terbinafine against a panel of human pathogenic fungi is lost upon replacing the N-CH_3 by a CH-CH_3 group in (*E*)-**2**. The results presented here demonstrate that activity can be partially regained by introducing polar functionalities at another site of the molecule. However, simple considerations of polarity are not sufficient to explain the observed biological activities of compounds **8a–m**. For example, whereas antifungal activity seems to correlate with decreasing polarity for the analogs **8g,i,k**, the relatively nonpolar methyl ester **8e** nd nitrile **8f** do not show substantial improvement of activity as compared with the parent compound (*E*)-**2**. Therefore, it is tempting to conclude that high antifungal activity requires the presence of functional groups having not only a certain degree of polarity but also basic character (amino groups). Interestingly, in the most active compound of the present series (**8k**), the amino group is very similar in terms of polarity and basicity to the central amino function of the highly potent allylamine antimycotic terbinafine (**1**).

In summary, the results of the present study indicate that, for the present series of terbinafine-derived compounds, antifungal activity strongly depends on both overall lipophilicity of the molecule and a fine balance between lipophilic and polar moieties. This agrees well with previous SAR findings within the allylamine antimycotics. For example, introduction of hydroxy or carboxyl groups at the *tert*-butyl moiety of terbinafine led to either a drastic decrease or complete loss of activity, whereas the corresponding methyl ester analog showed high antifungal potency in vitro.[11] Although the exact requirements for optimal antifungal activity of compounds characterized by general formula B (Figure 1) have not yet been determined, basicity was identified as being an important factor for high potency in addition to substituent polarity. Although having a much lower absolute activity than many of the allylamine derivatives, the profile obtained for analog **8k** shows that compounds of general structure B can exhibit broad antifungal activity.

Experimental Section

Chemistry. Materials and Methods. 2-Methyl-3-butyn-2-ol (**7c**) and 2-methyl-3-butyn-2-amine (**7d**) were purchased from Aldrich. 2,2-Dimethyl-3-butynoic acid,[18] *N,N*,2-trimethyl-3-butyn-2-amine[19] (**7e**), *N*-methyl-*N*-(2-methyl-3-butyn-2-yl)-aniline[20] (**7f**), 1-bromo-4,4-dimethyl-2-pentyne,[21] and 3-methyl-4-(1-naphthalenyl)butanal[22] (**3**) were prepared according to published procedures.

Melting points were determined on a Reichert Thermovar microscope and are not corrected. The temperature is given in Celsius units. Thin-layer chromatography was performed using silica gel F_{254} plates (Merck), and bands were visualized with UV, iodine vapor, or potassium permanganate. Column chromatography was performed using silica gel 60 (0.040–0.063 mm; Merck), pressure 3–5 bar. ^{1}H-NMR spectra were recorded at 250 MHz (Bruker WM 250) usually in $CDCl_3$ with $(CH_3)_4Si$ as internal standard. Chemical shifts are given as δ units. Elemental analyses were performed by Mag. J. Theiner, Microanalytical Laboratory at the University of Vienna, Institute of Physical Chemistry.

Synthesis of Enyne Compounds 8. Pd(0)-Coupling Reaction. General Procedure: (*E*)-9-(1-Naphthalenyl)-2,2,8-trimethyl-5-nonen-3-ynoic Acid Methyl Ester (8a). In a typical procedure, argon was bubbled through a solution of (*E*)-1-iodo-4-methyl-5-(1-naphthalenyl)-1-pentene (**6**; 930 mg, 2.8 mmol) in dry toluene (50 mL) for 15 min. Tetrakis-(triphenylphosphine)palladium (160 mg, 0.14 mmol), cuprous iodide (42 mg, 0.2 mmol), 2,2-dimethyl-3-butynoic acid methyl ester (**7a**; 520 mg, 4.1 mmol), and triethylamine (1.2 mL) were added, and the mixture was stirred overnight under an argon atmosphere. Then the mixture was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate, 95/5) to give **8a** (388 mg, 42%) as a colorless oil: NMR δ 7.14–8.11 (m, 7H), 6.15 (dt, J = 16.5 + 6.5 Hz, 1H), 5.50 (d, J = 16.5 Hz, 1H), 3.73 (s, 3H), 2.64–3.30 (m, 2H), 1.86–2.41 (m, 3H), 1.49 (s, 6H), 0.92 (d, J = 6 Hz, 3H). Anal. ($C_{23}H_{26}O_2$) C, H.

The following compounds were prepared using the procedure described for **8a**, starting from the appropriately substituted alkynes **7b–f** and iodoolefin **6** (Scheme 2).

(*E*)-9-(1-Naphthalenyl)-2,2,8-trimethyl-5-nonen-3-ynoic amide (8e): 70%, colorless oil; NMR δ 7.94–8.03 (m, 1H), 7.84–7.91 (m, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.44–7.57 (m, 2H), 7.40 (dd, J = 8 + 8.5 Hz, 1H), 7.30 (dd, J = 8 + 1.5 Hz, 1H), 6.59 (br s, 1H), 6.17 (dt, J = 16 + 7 Hz, 1H), 5.60 (br s, 1H), 5.53 (dt, J = 16 + 1 Hz, 1H), 3.09 (dd, J = 14 + 6.5 Hz, 1H), 2.85 (dd, J = 14 + 7.5 Hz, 1H), 2.18–2.32 (m, 1H), 2.00–2.15 (m, 2H), 1.49 (s, 6H), 0.95 (d, J = 6.5 Hz, 3H); MS *m/e* 319, 305, 304, 277, 275, 233, 232, 195, 191, 169, 153. Anal. ($C_{22}H_{25}NO$) C, H, N.

(*E*)-2,8-Dimethyl-9-(1-naphthalenyl)-5-nonen-3-yn-2-ol (8h): 27%, yellowish oil; NMR δ 7.95–8.04 (m, 1H), 7.81–7.90 (m, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.34–7.56 (m, 3H), 7.27 (d, J = 7.5 Hz, 1H), 6.17 (dt, J = 16 + 7.5 Hz, 1H), 5.52 (dt, J = 16 + 1 Hz, 1H), 3.10 (dd, J = 14 + 7 Hz, 1H), 2.83 (dd, J = 14 + 7.5 Hz, 1H), 1.99–2.32 (m, 3H), 1.95 (s, 1H), 1.55 (s, 6H), 0.93 (d, J = 7 Hz, 3H). Anal. ($C_{21}H_{24}O$) C, H.

(*E*)-2,8-Dimethyl-9-(1-naphthalenyl)-5-nonen-3-yn-2-amine (8i): 72%, greenish oil; NMR δ 7.95–8.04 (m, 1H), 7.81–7.91 (m, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.42–7.56 (m, 2H), 7.39 (dd, J = 7.5 + 7 Hz, 1H), 7.28 (dd, J = 7.5 + 1 Hz, 1H), 6.11 (dt, J = 16 + 7 Hz, 1H), 5.53 (br d, J = 16 Hz, 1H), 3.11 (dd, J = 14.5 + 7 Hz, 1H), 2.82 (dd, J = 14.5 + 7.5 Hz, 1H), 2.15–2.32 (m, 1H), 1.96–2.15 (m, 2H), 1.73 (br s, 2H), 1.44 (s, 6H), 0.93 (d, J = 7 Hz, 3H). Anal. ($C_{21}H_{25}N$) C, H, N.

(*E*)-9-(1-Naphthalenyl)-*N,N*,2,8-tetramethyl-5-nonen-3-yn-2-amine (8k): 48%, yellowish oil; NMR δ 7.96–8.05 (m, 1H), 7.81–7.90 (m, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.42–7.56 (m, 2H), 7.38 (dd, J = 7.5 + 7 Hz, 1H), 7.28 (dd, J = 7.5 + 1 Hz, 1H), 6.14 (dt, J = 16 + 7 Hz, 1H), 5.56 (dt, J = 16 + 1 Hz, 1H), 3.13 (dd, J = 14.5 + 6 Hz, 1H), 2.82 (dd, J = 14.5 + 7.5 Hz, 1H), 2.31 (s, 6H), 2.15–2.29 (m, 1H), 1.96–2.15 (m, 2H), 1.73 (br s, 2H), 1.40 (s, 6H), 0.94 (d, J = 6 Hz, 3H). Anal. ($C_{23}H_{29}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-[2,8-dimethyl-9-(1-naphthalenyl)-5-nonen-3-yn-2-yl]aniline (8m): 67%, colorless oil; NMR δ 7.96–8.06 (m, 1H), 7.81–7.91 (m, 1H), 7.73 (d, J = 8 Hz, 1H), 7.22–7.56 (m, 8H), 7.08–7.22 (m, 1H), 6.15 (dt, J = 16 + 7 Hz, 1H), 5.57 (dt, J = 16 + 1 Hz, 1H), 3.13 (dd, J = 13.5 + 6 Hz, 1H), 2.85 (s, 3H), 2.82 (dd, J = 13.5 + 7.5 Hz, 1H), 1.96–2.36 (m, 3H), 1.41 (s, 6H), 0.95 (d, J = 6 Hz, 3H). Anal. ($C_{28}H_{31}N$) C, H, N.

Synthesis of (*E*)-9-(1-Naphthalenyl)-2,2,8-trimethyl-5-nonen-3-ynoic Acid (8b). An aqueous sodium hydroxide solution (2 N, 1 mL) was added to a solution of **8a** (160 mg, 0.5 mmol) in methanol (12 mL), and the mixture was stirred overnight at room temperature. After evaporation of the solvent, the residue was taken up in water and washed two times with ether. Then the aqueous layer was acidified with 0.1 N aqueous hydrochloric acid and extracted with ether. The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo to yield **8b** as a viscous oil (136 mg, 89%): NMR δ 10.60 (s, 1H), 7.95–8.04 (m, 1H), 7.81–7.90 (m, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.40–7.56 (m, 4H), 6.18 (dt, J = 16 + 7.5 Hz, 1H), 5.52 (dt, J = 16 + 1 Hz, 1H), 3.11 (dd, J = 14 + 6.2 Hz, 1H), 2.82 (dd, J = 14 + 7.5 Hz, 1H),

2.15–2.31 (m, 1H), 1.95–2.15 (m, 2H), 1.55 (s, 6H), 0.93 (d, J = 6.2 Hz, 3H). Anal. ($C_{22}H_{24}O_2$) C, H.

Synthesis of (*E*)-9-(1-Naphthalenyl)-2,2,8-trimethyl-5-nonen-3-yn-1-ol (8c). Diisobutylaluminum hydride (0.42 mL, 0.5 mmol, 1.2 M solution in toluene) was added to **8a** (80 mg, 0.24 mmol) in dry toluene (10 mL) under argon at −40 °C. The mixture was stirred for 1 h at this temperature and then treated with a saturated aqueous ammonium chloride solution at 0 °C and stirred again vigorously for 30 min. Filtration, extraction with ethyl acetate, and purification by chromatography on silica gel (hexane/ethyl acetate, 9/1) yielded **8c** (74%, yellowish oil): NMR δ 7.92–8.06 (m, 1H), 7.78–7.91 (m, 1H), 7.73 (d, J = 8 Hz, 1H), 7.40–7.57 (m, 2H), 7.38 (dd, J = 8 + 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 6.13 (dt, J = 16 + 7 Hz, 1H), 5.51 (dt, J = 16 + 1Hz, 1H), 3.42 (d, J = 6.5 Hz, 2H), 3.11 (dd, J = 14.5 + 6.2 Hz, 1H), 2.83 (dd, J = 14.5 + 7.5 Hz, 1H), 2.14–2.32 (m, 1H), 1.93–2.13 (m, 2H), 1.79 (br t, J = 6.5 Hz, 1H), 1.23 (s, 6H), 0.93 (d, J = 6.2 Hz, 3H). Anal. ($C_{22}H_{26}O$) C, H.

Synthesis of (*E*)-9-(1-Naphthalenyl)-*N*,2,2,8-tetramethyl-5-nonen-3-ynamide (8d). Methylamine (0.5 mL, 4 mmol, 8 M solution in ethanol) was added to a solution of **8a** (95 mg, 0.3 mmol) in dry ethanol (5 mL). The mixture was stirred for 3 d at room temperature. The solvent was distilled off in vacuo, and the residue was subjected to silica gel chromatography (hexane/ethyl acetate, 1/1) to give **8d** (69 mg, 73%) as a colorless oil: NMR δ 7.96–8.05 (m, 1H), 7.83–7.91 (m, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.44–7.57 (m, 2H), 7.41 (dd, J = 8 + 7.5 Hz, 1H), 7.28 (dd, J = 7.5 + 1 Hz, 1H), 6.67 (br s, 1H), 6.18 (dt, J = 16 + 7 Hz, 1H), 5.54 (dt, J = 16 + 1 Hz, 1H), 3.10 (dd, J = 14 + 6.2 Hz, 1H), 2.86 (dd, J = 14 + 7.5 Hz, 1H), 2.84 (d, J = 5 Hz, 3H), 2.19–2.33 (m, 1H), 1.99–2.16 (m, 2H), 1.46 (s, 6H), 0.96 (d, J = 6.2 Hz, 3H). Anal. ($C_{23}H_{27}NO$) C, H, N.

Synthesis of (*E*)-9-(1-Naphthalenyl)-2,2,8-trimethyl-5-nonen-3-ynenitrile (8f). Pyridine (100 μL, 1.3 mmol) and trifluoroacetic anhydride (52 μL, 0.4 mmol) were added successively to a solution of **8e** (100 mg, 0.32 mmol) in dry dichloromethane (5 mL) at 5 °C. The mixture was stirred for 2 h at room temperature, poured into water, and extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 3/1) to give **8f** (88 mg, 93%) as a colorless oil: NMR δ 7.95–8.04 (m, 1H), 7.82–7.90 (m, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.35–7.57 (m, 3H), 7.28 (dd, J = 7.5 + 1Hz, 1H), 6.21 (dt, J = 16 + 7.5 Hz, 1H), 5.84 (dt, J = 16 + 1 Hz, 1H), 3.09 (dd, J = 15 + 7 Hz, 1H), 2.85 (dd, J = 15 + 7.5 Hz, 1H), 2.16–2.31 (m, 1H), 1.98–2.14 (m, 2H), 1.66 (s, 6H), 0.94 (d, J = 7 Hz, 3H). Anal. ($C_{22}H_{23}N$) C, H, N.

Synthesis of (*E*)-9-(1-Naphthalenyl)-2,2,8-trimethyl-5-nonen-3-yn-1-amine (8g). **8e** (120 mg, 0.38 mmol) was dissolved in dry ether (6 mL) and treated with lithium aluminum hydride (0.4 mL, 0.4 mmol, 1 M solution in ether; Aldrich). The mixture was stirred for 4 h at room temperature, poured cautiously into water, and extracted with ether. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by chromatography on silica gel (ethyl acetate) to yield **10g** (59 mg, 51%) as a colorless oil: NMR δ 7.96–8.07 (m, 1H), 7.81–7.91 (m, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.45–7.56 (m, 2H), 7.40 (dd, J = 7.5 + 7 Hz, 1H), 7.28 (dd, J = 7.5 + 1Hz, 1H), 6.10 (dt, J = 16 + 7.5 Hz, 1H), 5.51 (dt, J = 16 + 1Hz, 1H), 3.12 (dd, J = 14 + 6 Hz, 1H), 2.83 (dd, J = 14 + 7.5 Hz, 1H), 2.58 (s, 2H), 2.14–2.33 (m, 1H), 1.95–2.14 (m, 2H), 1.52 (s, 2 H), 1.20 (s, 6 H), 0.94 (d, J = 7 Hz, 3H). Anal. ($C_{22}H_{27}N$) C, H, N.

Synthesis of (*E*)-*N*-[2,8-Dimethyl-9-(1-naphthalenyl)-5-nonen-3-yn-2-yl]acetamide (8j). Acetic anhydride (150 μL) was added to a solution of **8i** (60 mg, 0.2 mmol) in dry pyridine (3 mL). The mixture was stirred for 2 h at room temperature and concentrated in vacuo. The residue was partitioned between ethyl acetate and 0.5 N HCl. After separation the organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. Chromatography of the residue on silica gel (hexane/ethyl acetate, 2/1) produced **8j** (42 mg, 61%) as yellowish crystals: mp 92–96 °C; NMR δ 7.94–8.03 (m, 1H), 7.81–7.90 (m, 1H), 7.73 (d, J = 8 Hz, 1H), 7.43–7.56 (m, 2H), 7.39 (dd, J = 7.5 + 7 Hz, 1H), 7.27 (dd, J = 7.5 + 1 Hz, 1H), 6.16 (dt, J = 16 + 7.5 Hz, 1H), 5.63 (br s, 1H), 5.52 (dt, J = 16 + 1 Hz, 1H), 3.10 (dd, J = 14 + 6.2 Hz, 1H), 2.82 (dd, J = 14 + 7.5 Hz, 1H), 2.14–2.32 (m, 1H), 1.98–2.14 (m, 2H), 1.95 (s, 3H), 1.66 (s, 6H), 0.92 (d, J = 6.2 Hz, 3H). Anal. ($C_{23}H_{27}NO$) C, H, N.

Synthesis of (*E*)-9-(1-Naphthalenyl)-*N*,*N*,*N*,2,8-pentamethyl-5-nonen-3-yn-2-ylammonium Iodide (8l). A solution of **8k** (32 mg, 0.1 mmol) in ethanol (4 mL) was treated with methyl iodide (0.2 mL) and refluxed for 2 h. The solvent was distilled off, and the residue was crystallized from ethanol/ether to yield **8l** (36 mg, 78%) as colorless crystals: mp 153 °C, NMR δ 7.94–8.04 (m, 1H), 7.82–7.92 (m, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.35–7.58 (m, 3H), 7.29 (d, J = 7 Hz, 1H), 6.19–6.37 (m, 1H), 5.49 (d, J = 15.5 Hz, 1H), 3.52 (s, 9H), 2.86–3.23 (m, 2H), 2.20–2.39 (m, 1H), 2.01–2.19 (m, 2H), 1.83 (s, 6H), 0.97 (d, J = 7 Hz, 3H). Anal. ($C_{24}H_{32}IN$) C, H, N, I.

Synthesis of 2. Lithium diisopropylamide was prepared by adding *n*-butyllithium (2.96 mL, 4.73 mmol, 1.6 M solution in hexane) to diisopropylamine (478 mg, 4.73 mmol) in dry tetrahydrofuran (7 mL) at −40 °C under argon. The solution was stirred for 30 min at this temperature and then added under argon to a suspension of (4,4-dimethyl-2-pentynyl)-triphenylphosphonium bromide (**4**; 2.06 g, 4.71 mmol) in dry tetrahydrofuran (15 mL) precooled to −70 °C whereupon the color of the suspension became orange. This mixture was stirred for an additional 20 min. Upon addition of 3-methyl-4-(1-naphthalenyl)butanal (**3**; 1 g, 4.71 mmol), which was prepared according to the published synthesis of 3-methyl-4-phenylbutanal,[22] at −70 °C the color changed to light yellow. The mixture was stirred for 1.5 h at this temperature and then treated with water. The layers were separated, and the aqueous phase was extracted with ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was stirred vigorously with *n*-hexane (30 mL) for 1 h at ambient temperature. After filtration, the collected crystalline material (triphenylphosphine oxide) was washed with hexane. The filtrate and the washings were combined and evaporated in vacuo. The residue was chromatographed on silica gel (hexane) to yield cumulene **5** [E/Z = 1/1; 41 mg, 3%; NMR δ 7.98–8.09 (m, 1H), 7.80–7.88 (m, 1H), 7.72 (d, J = 7.5 Hz, 1 H), 7.42–7.54 (m, 2H), 7.38 (dd, J = 7 + 7.5 Hz, 1H), 7.29 (d, J = 7 Hz, 1H), 5.47–5.65 (m, 2H), 3.13–3.29 (m, 1H), 2.74–2.92 (m, 1H), 2.10–2.42 (m, 3H), 1.11 + 1.09 (2 s, 9H), 0.98 + 0.95 (2 d, J = 7 Hz, 3H)] followed by (*Z*)-**2** [138 mg, 10.1%; NMR δ 7.99–8.11 (m, 1H), 7.83–7.89 (m, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.47–7.59 (m, 2H), 7.43 (dd, J = 7 + 7.5 Hz, 1H), 7.34 (dd, J = 7 + 1 Hz, 1H), 5.96 (dt, J = 10.5 + 7.5 Hz, 1H), 5.62 (dt, J = 10.5 + 1 Hz, 1H), 3.22 (dd, J = 14 + 6.5 Hz, 1H), 2.87 (dd, J = 14 + 8 Hz, 1H), 2.28–2.53 (m, 2H), 2.04–2.19 (m, 1H), 1.29 (s, 9H), 1.01 (d, J = 7 Hz, 3H)] and (*E*)-**2** (278 mg, 20.3%) as a colorless oil: NMR δ 7.98–8.10 (m, 1H), 7.87–7.95 (m, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.50–7.61 (m, 2H), 7.45 (dd, J = 7 + 7.5 Hz, 1H), 7.33 (dd, J = 7 + 1 Hz, 1H), 6.17 (dt, J = 16 + 7.5 Hz, 1H), 5.61 (dt, J = 16 + 1 Hz, 1H), 3.17 (dd, J = 14 + 6.5 Hz, 1H), 2.86 (dd, J = 14 + 7.5 Hz, 1H), 2.01–2.35 (m, 3H), 1.32 (s, 9H) 0.98 (d, J = 7 Hz, 3H). Anal. ($C_{22}H_{25}$) C, H.

Starting Materials. Synthesis of 2,2-Dimethyl-3-butynoic Acid Methyl Ester (7a). 2,2-Dimethyl-3-butynoic acid[18] (8.9 g, 79 mmol) was dissolved in dry methanol (50 mL) and treated with *p*-toluenesulfonic acid (120 mg). At 40 °C 2,2-dimethoxypropane (14 mL, 114 mmol) was added slowly, and the mixture was heated to reflux overnight. The solvent was carefully distilled off under normal pressure using a Vigreux column. Vacuum distillation of the residue yielded pure **7a** (4.89 g, 61%) as a light yellow oil: bp 70–72 °C/120 mbar; NMR δ 3.80 (s, 3H), 2.35 (s, 1H), 1.53 (s, 6H).

Synthesis of 2,2-Dimethyl-3-butynamide (7b). 2,2-Dimethyl-3-butynoic acid[18] (2.24 g, 20 mmol) was mixed with thionyl chloride (5 mL) and heated to reflux for 4 h. The excess thionyl chloride was distilled off by Kugelrohr distillation. The residual acid chloride was dropped into an ice-cooled saturated

aqueous ammonium hydroxide solution (15 mL), and the mixture was stirred for 1 h at room temperature. Continuous extraction with ether gave **7b** (1.8 g, 81%) as a colorless crystals: mp 66–67 °C; NMR δ 6.62 (br s, 1H), 6.00 (br s, 1H), 2.45 (s, 1H), 1.47 (s, 6H).

Synthesis of (4,4-Dimethyl-2-pentynyl)triphenylphosphonium Bromide (4). Hydrobromic acid (4.4 mL, 47% aqueous solution) was added dropwise at room temperature to a solution of triphenylphosphine (10 g, 38.3 mmol) in dioxane (25 mL). Then 1-bromo-4,4-dimethyl-2-pentyne[21] (6.7 g, 38.3 mmol) in dioxane (10 mL) was added slowly. The mixture was heated to reflux for 5 min and stirred for an additional 2 h without heating for complete crystallization of the product. The crystals were filtered, washed with dioxane, and recrystallized from ethanol to produce **4** (10.45 g, 62.5%) as colorless crystals: mp 235–240 °C; NMR δ 7.62–8.10 (m, 15H), 4.99 (d, J = 15 Hz, 2H), 0.98 (s, 9H).

Synthesis of (*E*)-1-Iodo-4-methyl-5-(1-naphthalenyl)-1-pentene (6). Chromous chloride (7 g, 57 mmol) was suspended in dry tetrahydrofuran (30 mL) under argon atmosphere. To this was added a solution containing 3-methyl-4-(1-naphthalenyl)butanal[22] (**3**; 2 g, 9.42 mmol) and triiodomethane (4.6 g, 11.7 mmol) in dry tetrahydrofuran (20 mL) slowly at 0 °C. The mixture was stirred for 3 h at 0 °C, poured into water, and extracted with ether. The combined organic extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was stirred vigorously with n-hexane (35 mL) for 20 min and filtered. The filtrate was concentrated and the residue chromatographed immediately on silica gel (toluene) to give **6** (2.4 g 76%, ≥ 95% E-configuration) as a yellow oil: NMR δ 7.93–8.02 (m, 1H), 7.81–7.91 (m, 1H), 7.73 (d, J = 8 Hz, 1H), 7.35–7.57 (m, 3H), 7.26 (dd, J = 7.5 + 1 Hz, 1H), 6.56 (dt, J = 15 + 7.5 Hz, 1H), 6.02 (dt, J = 15 + 1 Hz, 1H), 3.09 (dd, J = 13.5 + 6 Hz, 1H), 2.84 (dd, J = 13.5 + 7.5 Hz, 1H), 1.93–2.03 (m, 3H), 0.94 (d, J = 6 Hz, 3H).

The subsequent Pd(0) coupling of the vinylic iodide **6** with alkynes failed in several cases, possibly due to residual chromium impurities. The highest yields of enyne products were obtained when **6** was reisolated from the failed coupling reaction, rechromatographed, and then used again. Therefore, **6** was routinely stirred with triethylamine in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium and cuprous iodide for 2 h in toluene before being used in subsequent reactions.

Mycology. The in vitro antifungal activity of the allylamine derivatives was investigated against isolates of *T. mentagrophytes*, *M. canis*, *S. schenckii*, *A. fumigatus*, *Candida albicans* Δ124, and *Candida parapsilosis* Δ39. Minimum inhibitory concentrations (MIC) were determined for dermatophytes, aspergilli, and S. *schenckii* grown in Sabouraud's dextrose broth (pH 6.5) and for yeasts grown in glass tubes in malt extract broth (pH 4.8). The test compounds were dissolved in DMSO and serially diluted with the growth media. The growth control was read after incubation at 30 °C for 48 h (yeasts), 72 h (molds), or 7 d (*S. schenckii* and dermatophytes). The MIC is defined as the lowest substance concentration at which fungal growth is macroscopically undetectable.

The fungal strains were obtained from the following centers: the American Type Culture Collection, Rockville, MD; the Centraalbureau voor Schimmelcultures, Baarn, The Netherlands; the Hygiene-Institut, Würzburg, FRG; or the II. Universitäts-Hautklinik, Vienna, Austria. Filamentous fungi were harvested with a spatula from cultures grown on Kimmig agar (E. Merck AG, Darmstadt, FRG) at 30 °C for 21 d. Yeast blastospores were taken from cultures shaken at 37 °C for approximately 30 h in yeast nitrogen base (Difco Laboratories, Detroit, MI).

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