Synthesis and Structure–Activity Relationships of Naftifine-Related Allylamine Antimycotics

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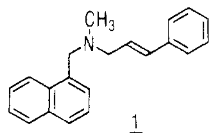
Naftifine (1) is the first representative of the new antifungal allylamine derivatives. Its biological activity is strictly bound to specific structural requirements that are unrelated to those of known antifungals. A tertiary allylamine function seems to be a prerequisite for activity against fungi. By systematic variation of the individual structural elements in 1, detailed structure–activity relationships are defined in which the phenyl ring is the structural feature permitting the widest variations. Versatile synthetic routes to allylamine derivatives and comparative biological data are presented.

Naftifine (1) is the first representative of a novel structural class of antimycotics, the allylamine derivatives,[1,2] and was identified as such largely by chance. It



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is active against a wide range of pathogenic fungi both in vitro[3] and in vivo.[4] In various clinical studies 1 has shown high efficacy as a topical agent against various types of dermatomycoses.[5] Biochemical studies have shown a specific inhibitory effect on sterol biosynthesis in *Candida albicans*, *Candida parapsilosis*, and *Trichophyton mentagrophytes*.[6-8] In particular, the epoxidation of squalene in *Candida albicans* is strongly inhibited,[6] a mode of action differing from that of the azole antimycotics, which inhibit ergosterol synthesis at the level of 14α-demethylation.[9,10]

In comparison with other classes of antimycotics,[11] 1 appears to be quite different with respect to characteristic structural features. For example, it contains neither an imidazole nor a triazole ring typical of the azoles[12,13] (miconazole, clotrimazole, ketoconazole etc.) and lacks the thiocarbamate function characteristic of tolnaftate and tolciclate.[14,15] Aliphatic tertiary amines[16] with fungicidal activity, among them substituted morpholines and piperidines,[17,18] are well known, but they all appear to be structurally unrelated to 1.

In view of the structural novelty of this clinically useful drug, it was pertinent to study to what extent the antifungal activity of 1 is specifically linked with its molecular structure and to define structure–activity relationships as a preliminary step toward designing even more potent representatives of this new type of antifungal.

Chemistry. The following versatile routes have been worked out for synthesizing allylamine derivatives (Scheme I).

1. The Schiff base was prepared by conventional methods. Reduction with $NaBH_4$ yielded secondary amines, which were then reductively methylated by means of CH_2O and excess $NaBH_4$[19] or NaH_2PO_3.[20] Use of $NaBH_4$ permits a one-pot reaction to give, e.g., 1 in 94% overall yield.

2. Mannich condensation of the appropriately substituted acetophenones, secondary amines, and paraformaldehyde yielded β-aminocarbonyl compounds, which were reduced with $NaBH_4$ and then dehydrated under strongly acidic conditions.

3. Mannich condensation of 1-alkynes, paraformaldehyde, and secondary amines under CuCl or $ZnCl_2$ catalysis in refluxing dioxane gave the tertiary 2-alkynylamines. The latter were stereoselectively reduced to the corresponding (*E*)-2-alkenylamines with diisobutylaluminum hydride (Dibal), a reaction recently described in detail.[21,22]

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(1) Berney, D.; Schuh, K. *Helv. Chim. Acta* 1978, 1262.
(2) Petranyi, G.; Ryder, N. S.; Stütz, A. *Science* 1984, *224*, 1239.
(3) Georgopoulos, A.; Petranyi, G.; Mieth, H.; Drews, J. *Antimicrob. Agents Chemother.* 1981, *19*, 386.
(4) Petranyi, G.; Georgopoulos, A.; Mieth, H. *Antimicrob. Agents Chemother.* 1981, *19*, 390.
(5) For example, see: (a) Ganzinger, U.; Stephen, A.; Gumhold, G. *Clin. Trials J.* 1982, 342; *Biol. Abstr.* 1983, *15*, 86150. (b) Hantschke, D.; Reichenberger, M. *Mykosen* 1980, *23*, 657. (c) Zaun, H.; Luszpinski, P. *Z. Hautkr.* 1984, *59*, 1209. (d) Klaschka, F.; Gartmann, H.; Weidinger, G. *Z. Hautkr.* 1984, *59*, 1218. (e) Meinincke, K.; Striegel, C.; Weidinger, G. *Mykosen* 1984, *27*, 608. (f) Haas, P. J.; Tronnier, H.; Weidinger, G. *Myokosen* 1985, *28*, 33. (g) Nolting, S.; Weidinger, G. *Mykosen* 1985, *28*, 69.
(6) (a) Ryder, N. S.; Seidl, G.; Troke, P. F. *Antimicrob. Agents Chemother.* 1984, *25*, 483. (b) Ryder, N. S. In "Microbial Cell Wall Synthesis and Autolysis"; Nombala, C., Ed.; Elsevier: Amsterdam, 1984; p 313.
(7) Paltauf, F.; Daum, G.; Zuder, G.; Högenauer, G.; Schulz, G.; Seidl, G. *Biochem. Biophys. Acta* 1982, *712*, 268.
(8) Meingassner, J. G.; Sleytr, U.; Petranyi, G. *J. Invest. Dermatol.* 1981, *77*, 444.
(9) Van den Bossche, H.; Willemsens, G.; Cools, W.; Lauwers, W. F.; Le Jeune, L. *Chem.-Biol. Interact.* 1978 *21*, 59.
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(11) For recent reviews, see: (a) Riley, J. F.; Wilson, R. G.; Gravestock, M. B.; Poyser, J. P. *Adv. Pharmacol. Chemother.* 1981, *18*, 49. (b) Gravestock, M. B.; Ryley, J. F. In "Annual Reports in Medicinal Chemistry"; Academic Press: New York, 1984; pp 19, 127.
(12) Reference 11a, pp 81–86.
(13) Fromtling, R. A. *Med. Actual.* 1984, *20*, 325; *Chem. Abstr.* 1984, *101*, 143395.
(14) Weinstein, M. J.; Oden, E. M.; Moss, E. *Antimicrob. Agents Chemother.* 1964, 595.
(15) (a) de Carnieri, I.; Monti, G.; Bianchi, A.; Castellino, S.; Meinardi, G.; Mandelli, V. *Arzneim.-Forsch.* 1976, *26*, 769. (b) Melloni, P.; Metelli, R.; Vecchietti, V.; Logemann, W.; Castellino, S.; Monti, G.; de Carneri, I. *Eur. J. Med. Chem.-Chim. Ther.* 1974, *9*, 26.
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(17) Himmele, W.; Pommer, E. H. *Angew. Chem.* 1980, *92*, 176.
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(19) Sondengam, B. L.; Hentchoya, Hêmo, J.; Charles, G. *Tetrahedron Lett.* 1973, *3*, 261.
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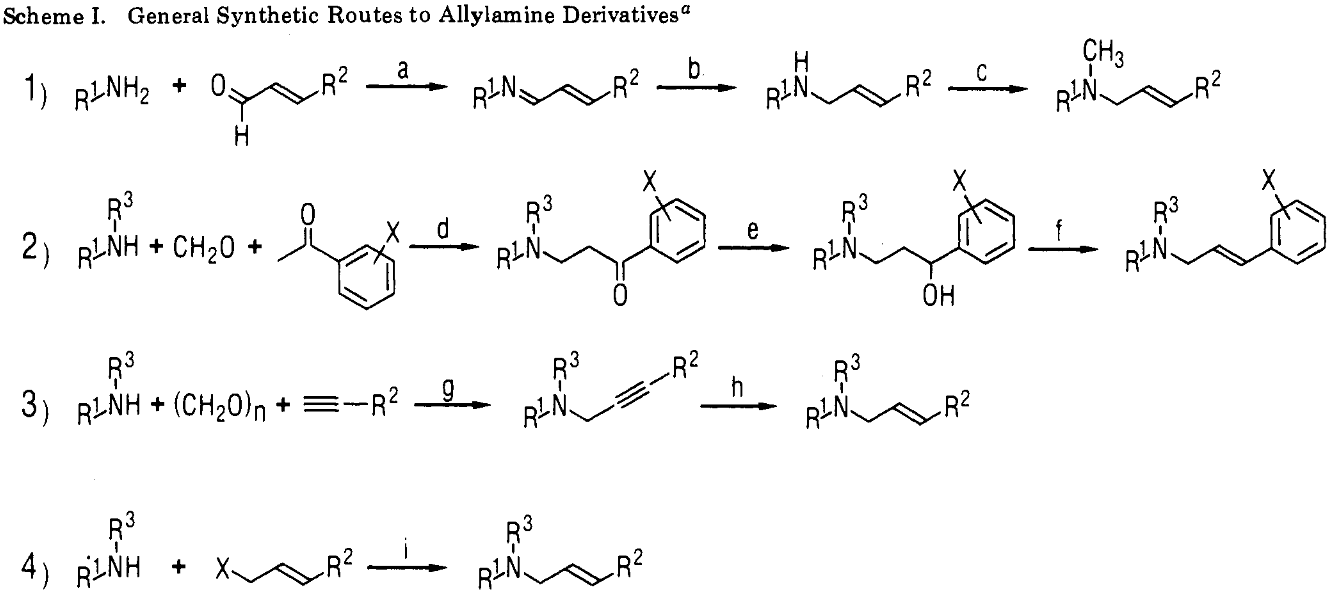
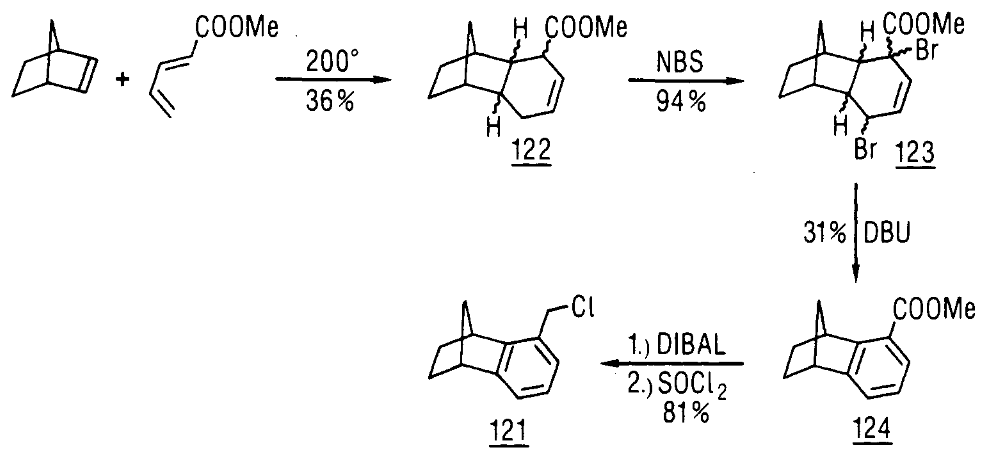
Scheme I. General Synthetic Routes to Allylamine Derivatives[a]



[a] (a) Azeotrop H_2O removal or molecular sieves, (b) $NaBH_4$, (c) $NaBH_4/CH_2O$[19] or NaH_2PO_3/CH_2O,[20] (d) reflux HCl/H_2O/EtOH, (e) $NaBH_4$, (f) 5 N HCl, (g) CuCl or $ZnCl_2$ catalysis in refluxing dioxane, (h) Dibal in toluene, 40 °C,[21,22] (i) Na_2CO_3 in DMF.

Scheme II. Synthesis of 5-(Chloromethyl)-1,2,3,4-tetrahydro-1,4-methanonaphthalene (121)



4. The N-alkylation of secondary amines with allyl halides is best performed in dimethylformamide at room temperature in the presence of Na_2CO_3.

The precursor for the synthesis of **23**, a bridged tetrahydronaphthalene with a carbon substituent at position 5, was synthesized according to Scheme II: Diels–Alder reaction of 1,3-butadiene-1-carboxylic acid methyl ester and bicyclo[2.2.1]hept-2-ene at 200 °C furnished **122**, which was dibrominated with *N*-bromosuccinimide to give **123**. Dehydrobromination with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) yielded the aromatic ester **124**, which was reduced with Dibal and converted to the chloride **121**.

Syntheses that do not fit into the above general routes are described in the Experimental Section.

Mycology. Antifungal activity was investigated in vitro against isolates of *Trichophyton mentagrophytes* (*Trich. ment.*), *Epidermophyton floccosum* (*Epid. fl.*), *Microsporum canis* (*Micr. can.*), *Sporothrix schenckii* (*Spor. sch.*), *Aspergillus fumigatus* (*Asp. fum.*), and *Candida parapsilosis* (*Cand. par.*). Minimal inhibitory concentrations (MIC) were determined with use of Sabouraud's dextrose broth (pH 6.5) in tests tubes. The test compounds were dissolved in dimethyl sulfoxide and serially diluted with the growth media. The growth assessment for yeasts was made after 48 h, for molds after 72 h, and for dimorphic fungi and all dermatophytes after 7 days of incubation at 30 °C. The MIC was defined as that substance concentration at which no macroscopic signs of fungal growth were detectable.

Activity in vivo was determined by topical treatment of experimental guinea pig dermatophytosis caused by *Trichophyton mentagrophytes*. The tests were carried out with 8–10 guinea pigs at each dose level. The backs (lumbar region) of the animals were shorn and then inoculated with 0.1 mL of Sabouraud's 2% dextrose broth containing 10^6 cfu of *Trich. ment.* over a circular area 3.5 cm in diameter. A 0.4-mL sample of the test compound solution (PEG 400/ethanol = 75/25, v/v) was spread over the infected skin area of the animals, which were treated once daily for 7 consecutive days, starting 48 h after inoculation. Mycological status was assessed on the third day after the last treatment, by culturing hairs from the infected lesions. Following incubation, cultures were evaluated microscopically for fungal growth in the region of hair roots.[23]

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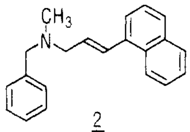
(22) Granitzer, W.; Stütz, A. *Tetrahedron Lett.* **1979**, *34*, 3145.
(23) Petranyi, G.; Leitner, J.; Mieth, H. *Sabouraudia* **1982**, *20*, 101.

Table I. In Vitro Antimycotic Activity Compounds 1-11

No.	MIC (μg/ml) Trich. ment.	Epid. fl.	Micr. can.	Asp. fum.	Spor. sch.	Cand. par.
1	0.05	0.1	0.1	12.5	1.6	1.6
2	100	100	100	>100	100	>100
3	>100	>100	>100	>100	>100	>100
4	25	25	50	>100	100	>100
5	12.5	>100	>100	>100	>100	>100
6	3.1	>100	>100	>100	>100	>100
7	6.2	>100	>100	>100	>100	>100
8	12.5	25	50	100	25	50
9	3.1	6.2	3.1	100	100	>100
10	50	50	50	>100	>100	>100
11	1.6	12.5	12.5	>100	>100	>100

Results and Discussion

In order to clarify the basic structural requirements for antifungal activity of 1, compounds 2–4 have been prepared and found to be inactive (Table I). Thus the phenyl and the naphthyl groups must not be exchanged and naphthalene has to bear the side chain in α-position.



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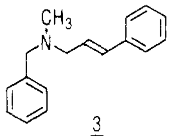

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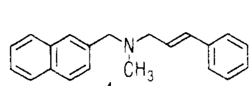

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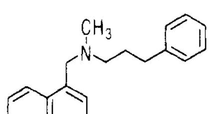
The saturated analogue 5 and the allyl ether 6 were again found to be inactive apart from residual activity against *Trich. mentagrophytes* (Table I). Both the amino function and the double bond thus seem to be essential for biological activity.



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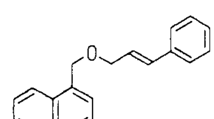

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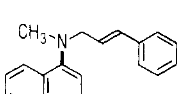
We therefore studied whether the distance between the individual functional groups and the aromatic systems could be extended or shortened without attenuation or loss of activity (compounds 7–11). Although these compounds are active to some extent, they fall far short of 1 (Table I).



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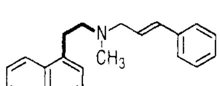

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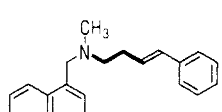

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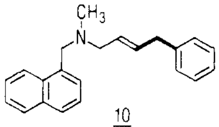

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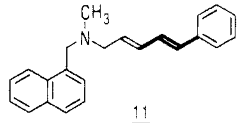

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With these findings it was evident that the antifungal activity of 1 is indeed bound to specific structural requirements. Systematic variation of individual structural elements was then undertaken to gain deeper insight into these structure–activity relationships.

Systematic Variation of the Individual Structural Elements in Naftifine. 1. Modifications of the Naphthalene System. Substituents in position 4 of the naphthalene nucleus such as CH_3 (**12**), Cl (**13**), or OCH_3 (**14**) cause a slight loss of activity in vitro and in vivo. A CH_3O group in position 6 (**15**) and especially in position 2 (**16**) has a much more pronounced negative effect. An analogue with OH in position 2 (**17**) is only weakly active (Table II).

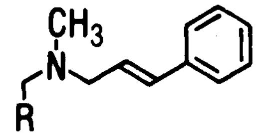
The dihydro derivative **21** is still quite active in vitro. Of the three tetrahydronaphthalenes (**18–20**), only the 5,6,7,8-tetrahydro derivative (**18**) retains a fair degree of antimycotic activity. The indene **22** is active but inferior to 1. The benzonorbornadiene **23**, a bridged tetrahydronaphthalene compound, is only weakly active. Compound **24**, a compound in which the naphthylmethyl moiety is replaced by a diphenylmethane group, is no longer active. The tricyclic analogues **25** and **26**, though still quite active in vitro, show slight activity after topical application only at a high concentration. The phenanthrene analogue **27** however is inactive.

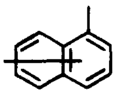
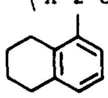
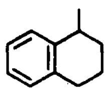
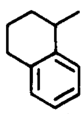
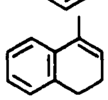
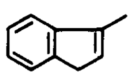
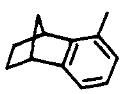
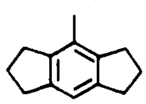
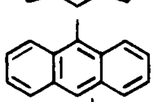
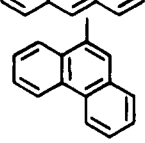
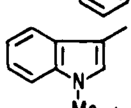
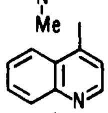
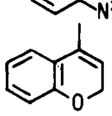
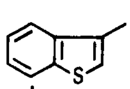
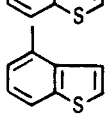
Replacement of naphthyl by a condensed heterocyclic ring system leads to compounds active in vitro. For good activity in vivo, however, a polar heterocycle like indole or quinoline, especially the latter, seems not to be allowed (compounds **28, 29**). The highly lipophilic benzo[*b*]thiophene derivatives **31** and **32** however are roughly comparable to 1 in vitro and on topical application. A somewhat lower activity is observed with the benzo[*b*]furan **33** and the chromene **30**.

2. Modifications at the Amino Group. The amino group must be tertiary as the corresponding N-demethylated **34** and the quaternary compound **35** are almost inactive, as are the imine **36** and the hydroxylamine **37**. The size of the alkyl group seems to be limited to C_1 and C_2, because the *N*-ethyl derivative **38** is the only such analogue that is still highly active in vitro and in vivo. The *N*-isopropyl and the *N*-allyl compounds **39** and **40** have a curtailed spectrum that lacks activity against *Cand. parapsilosis*. The *N*-cinnamyl (**41**), the *N*-cyclohexyl (**42**), the *N*-phenyl (**43**), and the *N*-benzyl analogues (**44**) are completely devoid of activity.

Introduction of a methyl group at the carbon atom between naphthalene and the nitrogen (**45**) is tolerated

Table II. Antimycotic Activity of Naftifine Derivatives Modified at the Naphthalene System



No.	R	MIC (μg/ml) Trich. ment.	Epid. fl.	Micr. can.	Asp. fum.	Spor. sch.	Cand. par.	TOPICAL ACTIVITY (% myc. cure) 0.1%	0.5%	2%
1	X=H	0.05	0.1	0.1	13.5	1.6	1.6	35	88	100
12	X=4-CH_3	0.1	0.2	0.4	>100	3.1	12.5			
13	X=4-Cl	0.05	0.1	0.1	>100	3.1	1.6	18	44	88
14	X  X=4-OCH_3	≤1.6	≤1.6	≤1.6	>100	50	50		41	65
15	X=6-OCH_3	1.6	12.5	12.5	>100	25	>100			
16	X=2-OCH_3	50	50	100	>100	>100	>100			
17	X=2-OH	25	50	50	>100	100	>100			
18		0.4	0.8	0.8	>100	3.1	50	0	22	50
19		6.2	50	50	>100	100	>100			
20	R = 	12.5	50	50	>100	100	>100			
21		≤1.6	≤1.6	≤1.6	>100	12.5	25			
22		1.6	12.5	3.1	>100	>100	>100			
23		6.2	12.5	50	>100	100	>100			
24	R = $(Ph)_2CH$	>100	>100	>100	>100	>100	>100			
25		1.6	3.1	1.6	>100	6.25	>100			
26		0.8	0.4	0.8	100	50	100	0	0	38
27		100	100	100	100	100	100			
28		≤1.6	≤1.6	≤1.6	>100	≤1.6	25	0	0	88
29		1.6	1.6	1.6	>100	12.5	2.5	0	0	3
30		0.2	0.4	0.4	50	6.2	6.2			82
31		0.1	0.2	0.2	25	1.6	3.1	0	54	97
32		0.1	0.1	0.1	12.5	1.6	1.6		75	100
33		1.6	12.5	1.6	>100	100	25			

without significant loss of activity. A methyl group between the double bond and the nitrogen (**46**) however is detrimental to biological activity.

Of the three possible amides (**47–49**), only **49** is active in vitro and to a somewhat lesser extent in vivo.

Replacement of the amino function by a thio ether (**50**), sulfoxide (**51**), or sulfone group (**52**) did not result in compounds with antimycotic activity (Table III).

3. Modifications at the Double Bond. The cis isomer (**53**) of **1** is the only structural modification at this site to retain significant antimycotic efficacy in vitro and in vivo. Compounds in which the double bond system is replaced by a triple bond (**54**), cyclopropane ring (**55**), $CH_2C{=}O$ (**56**), or, with one less carbon, by C=O (**58**) or CH_2 (**59**) are still active but only weakly so. An analogue with CH_2CHOH instead of the double bond (**57**) is inactive (Table IV). The olefinic protons in **1** may not be substituted by methyl (**60** and **61**).

4. Modifications at the Phenyl Ring. Analogues with fluorine at positions 4 (**62**) and 2 (**63**) of the phenyl ring have antimycotic activities similar to that of **1**. The corresponding 4-Cl and 2-Cl analogues (**64** and **65**) and the 4-methyl derivative **66** are slightly less active. In contrast to its effect in the naphthalene system, a 4-methoxy substituent in the phenyl ring (**67**) causes loss of most of the antimycotic activity.

Replacement of the phenyl ring by monocyclic heteroaromatic ring systems gives good results (comparable to **1**) with the 2- and 3-thiophene analogues **68** and **69**, respectively, and to a somewhat lesser extent with the furan derivative **70**. Polar heterocycles like *N*-methylpyrrole (**71**) or pyridine (**72** and **73**) have a marked negative effect on biological activity. 1-Naphthyl instead of phenyl (compound **74**) results in almost total loss of activity with the exception of *Trich. mentagrophytes*.

Cyclohexane (compound **75**) and a cyclohexene with the double bond in position 3 (nonconjugated, **76**) are not acceptable substitutes for phenyl. When the cyclohexenyl group (compound **77**) is conjugated, however, a highly active compound is obtained, which is at least as potent as **1** both in vitro and also on topical application in the guinea pig dermatophytosis model. Of similar efficacy are the cycloheptenyl and the cyclopentenyl analogues **77** and **78** and the 2,4-alkadienylamine **80**, which can be considered as an acyclic analogue of **77**.

Replacement of the phenyl ring by H (**81**), CH_3 (**82**), CN (**83**), CH_2OH (**84**), and COOH (**85**) leads to inactive compounds. The carboxylic ester analogues **86–89** are particularly active in vitro but not in vivo (Table V).

Summary

The studies described here show that the antifungal activity of **1** is strictly bound to specific structural requirements, which are unrelated to those of known antifungals. A tertiary allylamine function seems to be irreplaceable for antifungal activity. We have therefore suggested the name *allylamine* derivatives for this new structural class in antimycotic chemotherapy.[2] Many compounds of this type with considerable antimycotic activity have already been synthesized. The naphthalene ring system, which must bear the side chain in α-position, may be replaced by other condensed (but not too polar) heterocyclic systems. The phenyl ring is the structural feature permitting the widest variation. Cycloalkenes and alkene chains are at least equivalent substitutes for phenyl and open possibilities for further variations that may lead to compounds superior to **1** in antimycotic activity. Aspects of this work and the resulting compounds, including some with oral activity superior to that of clinical standards, have been reported elsewhere.[24]

Experimental Section

Melting points were determined on a Reichert Thermovar microscope and are not corrected. The temperature is given in Celsius units. The purity of the compounds was checked by GLC (Siemens Sichromat 1) using quartz capillaries (stat. phase OV-101) or high-performance liquid chromatography (pump: Waters M 6000) on a column of RP 18, 10 μm (Partisil ODS-10), with a water/acetonitrile gradient and a Schoeffel SF 770 UV detector (270 nm).

Thin-layer chromatography was performed on silica gel F_{254} (Merck), and the spots were made visible by a UV lamp or iodine vapor. Column chromatography was done on silica gel 60 (0.040–0.063 mm, Merck) under pressure of 3–5 bars.[25] If not otherwise stated, the following eluants were used: toluene/ethyl acetate = 9/1 (A), toluene/ethyl acetate = 4/1 (B).

IR spectra were recorded on a Perkin-Elmer spectrophotometer 298. ^{1}H NMR spectra were recorded at 90 MHz (Bruker WH 90) in $CDCl_3$ with $(CH_3)_4Si$ as internal standard. Chemical shifts are reported in δ units. The 1-naphthalenemethanamine derivatives usually show the aromatic signals at δ 8.2–8.4 (m, 1 H), 7.7–7.9 (m, 2 H), and 7.2–7.6 (m, 4 H) and are not routinely given. Mass spectra were recorded on a MAT 311A instrument with EI ion source (70 eV and 250 °C) and direct inlet system by Dr. A. Nikiforov at the Institute of Organic Chemistry, University of Vienna. Elemental analyses were performed by Dr. O. Zak, microanalytical laboratory at the University of Vienna, Institute of Organic Chemistry.

Standard workup was as follows: extraction of the aqueous phase with methylene chloride, ethyl acetate, and diethyl ether or partition of the residue between saturated aqueous $NaHCO_3$ and these organic solvents, drying of the organic phase with anhydrous Na_2SO_4, and evaporation to dryness.

The following abbreviations are used: Et_2O (diethyl ether), EtOH (ethanol), MeOH (methanol), THF (tetrahydrofuran), DMF (dimethylformamide), rt (room temperature), h (hour), min (minute).

Synthesis of the Allylamines. 1. Via Schiff Base/Reductive Methylation. (a) *N*-(3-Phenyl-2-propenylidene)-1-naphthalenemethanamine (36). A solution of cinnamaldehyde (8.41 g, 63.6 mmol) and 1-naphthalenemethanamine (10 g, 63.6 mmol) in benzene was boiled in a Dean–Stark apparatus until the calculated amount of water had separated. After removal of solvent the residue was directly used in the next step. For analytical purpose, **36** was crystallized from Et_2O: mp 96–98 °C. Anal. ($C_{20}H_{17}N$) C, H, N.

(b) *N*-(3-Phenyl-2-propenyl)-1-naphthalenemethanamine (34). The Schiff base **36** (5.42 g, 20 mmol) was taken up in methanol, treated with solid $NaBH_4$ (0.75 g, 20 mmol) at 40 °C, and stirred for 20 min at this temperature. This reaction mixture was used directly for reductive methylation following the procedure of Sondengam.[19] For isolation of **34** the reaction mixture was evaporated, and after usual workup an oil (5.4 g, quant) was obtained, which after treatment with HCl/EtOH and recrystallization from EtOH/Et_2O gave analytically pure hydrochloride: mp 155–157 °C. Anal. ($C_{20}H_{19}N{\cdot}HCl$) C, H, N, Cl.

The following secondary amines were prepared as described for **34** via steps 1a,b, starting from the appropriately substituted carbonyl compounds and amines.

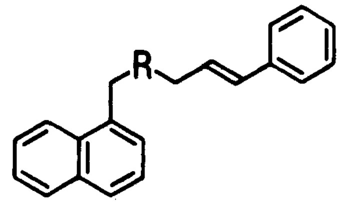
***N*-Methyl-2-methoxy-1-naphthalenemethanamine (91):** 27%; mp (hydrochloride) 141–144 °C.

(*E*)-*N*-Methyl-2-methyl-3-phenyl-2-propenylamine (92). Starting from α-methylcinnamaldehyde (10 g, 100 mmol) and methylamine, **92** was obtained as the hydrochloride in 82% yield (16.3 g): mp 175–178 °C (EtOH/Et_2O).

***N*-Cyclohexyl-1-naphthalenemethanamine (93):**[26] 85%.

(24) Stütz, A.; Petranyi, G. *J. Med. Chem.* 1984, *27*, 1539.
(25) Loibner, H.; Seidl, G. *Chromatographia* 1979, *12*, 600.
(26) Hutton, R. C.; Salam, S. A.; Stephen, W. I. *J. Chem. Soc. A.* 1966, 1573.
(27) Lazar, J.; Matkovics, B.; Foldeak, S.; Porszasz, J. *Acta Phys. Chem.* 1963, *9*, 148; *Chem. Abstr.* 1964, *61*, 11965e.

Table III. Antimycotic Activity of Naftifine Derivatives Modified at the Amino Group



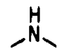
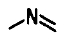
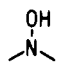
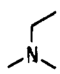
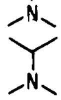
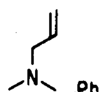
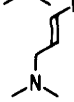
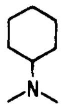
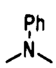
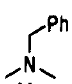
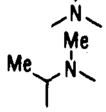
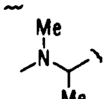
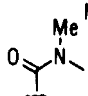
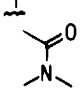
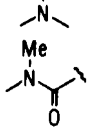
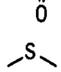
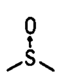
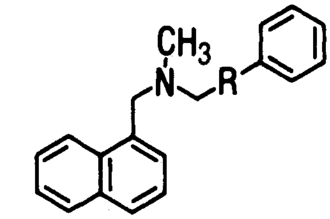
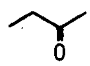
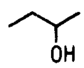
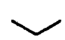
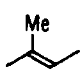
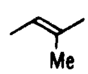
No.	R	MIC (µg/ml) Trich. ment.	Epid. fl.	Micr. can.	Asp. fum.	Spor. sch.	Cand. par.	TOPICAL ACTIVITY (% myc. cure) 0.1%	0.5%	2%
34		12.5	100	100	>100	100	>100			
35		25	>100	>100	>100	>100	>100			
36		100	100	>100	>100	100	>100			
37		12.5		50	>100	>100	>100			
38		≤1.6	≤1.6	≤1.6	100	12.5	12.5	19	25	81
39		≤1.6	≤1.6	3.1	>100	50	100			
40		≤1.6	3.1	≤1.6	100	6.25	>100			
41		>100	>100	>100	>100	>100	>100			
42		>100	>100	>100	>100	>100	>100			
43		>100	>100	>100	>100	50	>100			
44		>100	>100	>100	>100	>100	>100			
45		0.1	0.2	0.4	50	3.1	3.1	15	75	100
46		≤1.6	12.5	25	>100	25	>100			
47		≤1.6	≤1.6	≤1.6	12.5	25	>100	0	0	60
48		>100	>100	>100	>100	>100	>100			
49		>100	>100	>100	>100	>100	>100			
50		25	>100	>100	>100	>100	>100			
51		>100	>100	>100	>100	>100	>100			
52		>100	>100	>100	>100	>100	>100			

Table IV. Antimycotic Activity of Naftifine Derivatives Modified at the Double Bond



No.	R	MIC (µg/ml) Trich. ment.	Epid. fl.	Micr. can.	Asp. fum.	Spor. sch.	Cand. par.	TOPICAL ACTIVITY (% myc. cure) 0.1%	0.5%	2%
53		0.1	0.2	0.2	25	3.1	3.1	34	47	100
54		3.1	50	3.1	>100	100	100			
55		12.5	25	12.5	>100	100	>100			
56		6.2	6.2	6.2	>100	50	>100			
57		>100	>100	>100	>100	>100	>100			
58		3.1	12.5	6.2	>100	>100	>100			
59		12.5	100	100	>100	>100	>100			
60		12.5	100	100	>100	100	>100			
61		50	100	100	>100	100	>100			

***N*-Phenyl-1-naphthalenemethanamine (94)** (60%): NMR δ 4.7 (d, $J = 5$ Hz; after treatment with D_2O, s, 2 H), 3.9 (br, NH).

(c) **(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenemethanamine (1).**[1] To the reaction mixture obtained in step 1b was added aqueous 35% formaldehyde solution (16 mL, ~200 mmol) and the mixture was refluxed for 30 min. The mixture was then treated with ice cooling with solid $NaBH_4$ (7.6 g, 200 mmol) in several portions and stirred at rt for 3 h. After concentration in vacuo and usual workup, 1 was obtained as an oil (5.7 g, quant.) with a GC purity of 94%: mp 177–179 °C (2-propanol).

For reductive methylation of **34** using NaH_2PO_3 as reducing agent, see ref 20.

The following compounds were prepared as described for 1 via steps 1a–c, starting from the appropriate amines and aldehydes.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenamine (7). In this case the N-methylation of the secondary amine (3 g, 11.5 mmol, mp 80–83 °C) was done by treatment with dimethyl sulfate (5.5 mL, 56 mmol) in benzene at rt for 6 days. After evaporation, usual workup, and chromatography (hexane/toluene = 4/1), 7 (1.1 g, 35%) was obtained as an oil: NMR δ 6.2–6.8 (AB part of ABX_2 system, $J_{AB} = 16$ Hz, $J_{BX2} = 6$ Hz, 2 H), 3.85 (d, $J = 6$ Hz, 2 H), 2.88 (s, 3 H); MS, *m/e* 273. Anal. ($C_{20}H_{19}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1-naphthalene-2-ethanamine (8). With use of 2-(1-naphthyl)ethanamine (5 g, 29 mmol) as the starting material, the Schiff base was prepared by stirring with cinnamaldehyde (3.83 g, 29 mmol) and molecular sieves (4 Å) in Et_2O for 6 h. Compound 8 was obtained in 38% overall yield (3.31 g) after chromatography (eluant B): NMR δ 6.1–6.6 (AB part of ABX_2 system, $J_{AB} = 16$ Hz, $J_{AX2} = 6$ Hz, 2 H), 3.1–3.4 (m and d, $J = 6$ Hz, 4 H), 2.65–2.9 (m, 2 H), 2.4 (s, NCH_3); MS, *m/e* 301; bp 175 °C (10^{-3} mm) (Kugelrohr). Anal. ($C_{22}H_{23}N$) C, H, N.

(*E*,*E*)-*N*-Methyl-*N*-(5-phenyl-2,4-pentadienyl)-1-naphthalenemethanamine (11). With use of 5-phenyl-2,4-pentadienal[28] (4.3 g, 27 mmol) as the starting material, 11 was prepared in 90% overall yield (7.25 g): NMR δ 5.8–7.0 ($J_1 = 15$, $J_2 = 10.5$, $J_3 = 15.5$, $J_4 = 6.8$ Hz, 4 olef H), 3.9 (s), 3.2 (d, $J = 6.8$ Hz, 2 H), 2.24 (s, 3 H); MS, *m/e* 313; mp (hydrochloride) 170–174 °C. Anal. ($C_{23}H_{23}N{\cdot}HCl$) C, H, N, Cl.

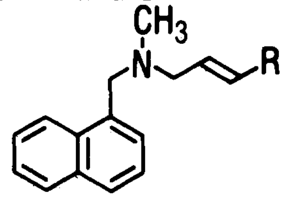
(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-6-methoxy-1-naphthalenemethanamine (15). With use of 6-methoxy-1-naphthalenemethanamine (0.95 g, 5.1 mmol) [prepared by $LiAlH_4$ reduction of 6-methoxynaphthalene-1-carbonitrile[29] in refluxing THF for 2 h and isolated as hydrochloride (2.35 g, 38%), mp 265–270 °C (EtOH)] and cinnamaldehyde (0.67 g, 5.1 mmol) as the starting material, 15 was obtained in 80% overall yield (1.30 g) after chromatography (eluant B): NMR δ 8.25 (d, $J = 8$ Hz, 1 H), 7.65 (dd, $J = 7$ and 2.5 Hz, 1 H), 7.0–7.5 (m, 10 H), 6.2–6.7 (AB part of ABX_2 system, $J_{AB} = 16$ Hz and $J_{AX2} = 6$ Hz, 2 H), 3.9 (s, OCH_3 and Ar CH_2N), 3.25 (d, $J = 6$ Hz, 2 H), 2.26 (s, NCH_3).

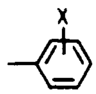
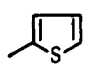
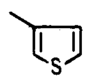
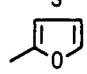
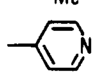
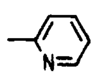
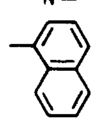
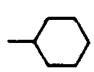
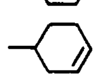
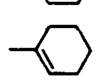
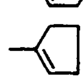
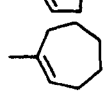
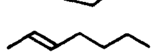
(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1,2,3,4-tetrahydro-1-naphthalenemethanamine (19). With use of 1,2,3,4-tetrahydro-1-naphthalenemethanamine[30] (5 g, 31 mmol) as the starting material, oily 19 was obtained in 50% overall yield (4.5 g) after chromatography (eluant $CHCl_3$): NMR δ 7.0–7.4 (m, 9 H), 6.0–6.6 (AB part of ABX_2 system, $J_{AB} = 16$ Hz and $J_{AX2} = 6$ Hz, 2 H), 2.2–3.4 (m, 7 H), 2.35 (s, NCH_3), 1.6–2.1 (m, 4 H); MS, *m/e* 291.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1,2,3,4-tetrahydro-1-naphthalenamine (20). With use of 1,2,3,4-tetrahydro-1-naphthaleneamine[27] (3 g, 20 mmol) and cinnamaldehyde (2.57 mL, 20 mmol) as the starting material, 20 was prepared in 50% overall yield (2.75 g): NMR δ 7.65–7.85 (m, 1 H), 6.9–7.5 (m, 8 H), 6.1–6.7 (AB part of ABX_2 system, $J_{AB} = 16$ Hz, 2 H), 3.8–4.1 (br m, 1 H), 3.0–3.4 (AB part of ABX_2 system, $J_{AB_{gem}}$ =

(28) Marshall, D.; Whiting, M. C. *J. Chem. Soc.* **1956**, 4082.
(29) Jacobs, S. A.; Harvey, R. G. *J. Org. Chem.* **1983**, *48*, 5134.
(30) Glennon, R. A.; Liebowitz, S. M. *J. Med. Chem.* **1982**, 393.

Table V. Antimycotic Activity of Naftifine Derivatives Modified at the Phenyl Ring



No.	-R	MIC (μg/ml) Trich. ment.	Epid. fl.	Micr. can.	Asp. fum.	Spor. sch.	Cand. par.	TOPICAL ACTIVITY (% myc. cure) 0.1%	0.5%	2.0%
62	 X=4-F	0.1	0.1	0.2	25	1.6	3.1	21	82	100
63	X=2-F	≤1.6	≤1.6	≤1.6	100	6.25	12.5	0	59	94
64	X=4-Cl	0.2	0.4	0.4	>100	3.1	100	0	25	44
65	X=2-Cl	≤1.6	3.1	≤1.6	>100	25	>100			
66	X=4-CH_3	≤1.6	≤1.6	≤1.6	>100	12.5	50	7	22	50
67	X=4-OCH_3	6.2	50	50	>100	>100	>100			
68		0.1	0.2	0.2	100	3.1	6.2	13	56	96
69		0.1	0.1	0.2	50	3.1	6.2	7	47	100
70		≤1.6	6.2	6.2	>100	100	>100			
71		25	25	50	>100	50	>100			
72		≤1.6	25	25	>100	100	>100			
73		≤1.6	12.5	12.5	>100	100	>100	0	0	7
74		1.6	100	100	>100	100	>100			
75		1.6	12.5	12.5	>100	>100	>100			
76		25	25	25	>100	100	>100			
77		0.05	0.1	0.1	12.5	0.8	0.8	41	97	100
78		0.1	0.2	0.2	50	3.1	6.2	30	91	100
79		0.05	0.1	0.05	25	0.8	1.6	29	85	100
80		0.05	0.2	0.1	25	3.1	1.6	40	69	100
81	-H	>100	>100	>100	>100	>100	>100			
82	-CH_3	>100	>100	>100	>100	>100	>100			
83	-CN	100	100	100	>100	>100	>100			
84	-CH_2OH	>100	>100	>100	>100	>100	>100			
85	-COOH	≤100	≤100	≤100	≤100	≤100	≤100			
86	-$COOC_2H_5$	≤1.6	3.1	6.25	>100	12.5	>100	0	0	16
87	-$COOC_5H_{11}$	≤1.6	≤1.6	≤1.6	50	≤1.6	25	0	0	10
88	-$COOCH_2Ph$	≤1.6	≤1.6	≤1.6	>100	12.5	>100	0	0	8
89	$COOC_2H_5$	≤1.6	3.1	3.1	>100	100	>100			

14 Hz, $J_{AX} = J_{BX}$ = 6 Hz, NC*H*HCH=), 2.6–2.8 (m, 2 H), 2.25 (s, NCH_3), 1.4–2.2 (m, 4 H); bp 125 °C (10^{-3} mm) (Kugelrohr). Anal. ($C_{20}H_{23}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-3,4-dihydro-1-naphthalenemethanamine (21). With use of *3,4-dihydronaphthalene-1-carboxaldehyde* (100 mg, 0.63 mmol) [prepared in 40% yield by Dibal reduction of 3,4-dihydronaphthalene-1-carbonitrile[31] and acidic workup] and (*E*)-3-phenyl-2-propenylamine (84 mg, 0.63 mmol) as the starting material, **21** was obtained as oil in 40% overall yield (75 mg) after chromatography (eluant B): NMR δ 7.0–7.6 (m, 9 H), 6.1–6.7 (AB part of ABX_2 system, J_{AB} = 16 Hz and J_{AX2} = 6 Hz, 2 H), 6.0 (t, *J* = 5 Hz, 1 H), 3.3 (s, 2 H), 3.2 (d, *J* = 6 Hz, 2 H), 2.6–2.9 (m, 2 H), 2.1–2.4 (m, 2 H), 2.22 (s, 3 H); MS, *m/e* 289.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)diphenylmethanamine (24). With use of diphenylmethanamine (4.0 g, 21.8 mmol) as the starting material, **24** was obtained in 80% overall yield after crystallization of the crude reaction product from MeOH (5.45 g, mp 63–65 °C): NMR δ 7.0–7.6 (m, 15 H), 6.1–6.6 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 5 Hz, 2 H), 4.43 (s, 1 H), 3.15 (d, *J* = 5 Hz, 2 H), 2.18 (s, 3 H); MS, *m/e* 313. Anal. ($C_{23}H_{23}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-9-anthracenemethanamine (26). With use of anthracene-9-carboxaldehyde (7.94 g, 38.5 mmol) as the starting material, **26** was obtained as yellow crystals in 53% overall yield (6.87 g) after chromatography (eluant A): mp 93 °C (EtOH). Anal. ($C_{25}H_{23}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-9-phenanthrenemethanamine (27). With use of phenanthrene-9-carboxaldehyde (5 g, 24.2 mmol) as the starting material, **27** was obtained as yellow crystals in 65% overall yield (5.3 g) after chromatography (eluant B): mp 140–143 °C (EtOH). Anal. ($C_{25}H_{23}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1-methyl-3-indolemethanamine (28). With use of 1-methylindole-3-carboxaldehyde (2 g, 12.5 mmol) as the starting material, oily **28** was obtained in 46% overall yield (1.65 g) after chromatography (eluant $CHCl_3$/EtOH = 9/1): NMR δ 8.0 (m, 1 H), 7.0–7.4 (m, 8 H), 6.6 (s, 1 H), 6.2–6.6 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 5 Hz, 2 H), 3.86 (s, 2 H), 3.18 (d, *J* = 5 Hz, 2 H), 3.02 (s, 3 H), 2.28 (s, 3 H); MS, *m/e* 290.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-4-quinolinemethanamine (29). With use of chinoline-4-carboxaldehyde (1.57 g, 10 mmol) as the starting material, **29** was obtained as oil in 60% overall yield (1.72 g) after chromatography (eluant $CHCl_3$/EtOH = 97/3): NMR δ 8.55 (d, 1 H), 8.2 (m, 2 H), 7.1–7.8 (m, 9 H), 6.2–6.7 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 6 Hz, 2 H), 3.9 (s, 2 H), 3.25 (d, *J* = 6 Hz, 2 H), 2.3 (s, 3 H); MS, *m/e* 288; bp 150 °C (10^{-3} mm) (Kugelrohr). Anal. ($C_{20}H_{20}N_2$) C, H, N.

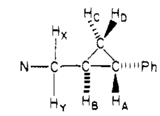
(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-3-benzo[*b*]thiophenemethanamine (31). With use of 3-benzo[*b*]thiophenemethanamine[32] (3 g, 18 mmol) as the starting material, **31** was obtained as oil in 41% overall yield (2.15 g) after chromatography (eluant A): NMR δ 7.8–8.0 (m, 2 H), 7.2–7.5 (m, 8 H), 6.2–6.7 (m, AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 6 Hz, 2 H), 3.8 (s, 2 H), 3.25 (d, *J* = 6 Hz, 2 H), 2.3 (s, 3 H); MS, *m/e* 293; bp 150 °C (10^{-3} mm) (Kugelrohr). Anal. ($C_{19}H_{19}NS$) C, H, N, S.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-4-benzo[*b*]thiophenemethanamine (32). With use of **4-benzo[*b*]thiophenemethanamine (95)** (0.65 g, 4 mmol) as the starting material, **32** was prepared in 60% overall yield (0.7 g) after chromatography (eluant B): oil; NMR δ 7.8 (m, 1 H), 7.65 (d, *J* = 5.5 Hz, 1 H), 7.1–7.5 (m, 9 H), 6.1–6.7 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 6 Hz), 3.84 (s, 2 H), 3.25 (d, *J* = 6 Hz, 2 H), 2.26 (s, 3 H); MS, *m/e* 293.

Compound **95** was prepared by Curtius reaction of 4-benzo-[*b*]thiophenacetic acid (1 g, 5.2 mmol) according to a modified procedure,[33] yielding the amine (77%, 0.65 g): NMR δ 7.8 (qui, *J* = 5 Hz, 1 H), 7.46 (s, 2 H), 7.3 (d, *J* = 5 Hz, 2 H), 4.2 (s, 2 H), 1.6 (s, NH_2).

_N_-Methyl-_N_-(4-phenyl-3-buten-2-yl)-1-naphthalenemethanamine (46). With use of benzalacetone (146 mg, 1 mmol) and naphthalene-1-methanamine (156 mg, 1 mmol) as the starting material, oily **46** was obtained in 45% overall yield (135 mg) after chromatography (eluant B): MS, *m/e* 301. Anal. ($C_{22}H_{23}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-(2-phenylcyclopropylmethyl)-1-naphthalenemethanamine (55). With use of *trans*-2-phenylcyclopropanecarboxaldehyde (0.74 g, 5 mmol) and 1-naphthalenemethanamine (0.78 g, 5 mmol) as the starting material, oily **55** was obtained in 60% overall yield (0.9 g) after chromatography (eluant $CHCl_3$): NMR δ 3.92 (s, 2 H); for



H_Y 2.60, H_X 2.45, H_A 1.70, H_B 1.30, H_C 0.99, H_D 0.83 [J_{AB} 4.86, J_{AC} 4.97, J_{AD} 8.61, J_{BC} 8.52, J_{BD} 5.57, J_{BX} 6.98, J_{BY} 6.06, J_{CD} −5.01, J_{XY} −12.7 Hz]; MS, *m/e* 301.

The starting *trans*-2-phenylcyclopropanecarboxaldehyde[34] was prepared by reduction of 2-phenyl-1-carbethoxycyclopropane[35] (1 g, 5.2 mmol) with Dibal (1.4 equiv) in hexane at −75 °C for 1 h. After addition of aqueous $NaHCO_3$ and usual workup, the crude aldehyde (0.64 g, 85%) was obtained and used directly in the next step [NMR δ 9.15 (d, *J* = 5 Hz) and 8.6 (d, *J* = 6 Hz), Σ 1 H, CHO)].

_N_-Methyl-_N_-(2-phenylethyl)-1-naphthalenemethanamine (59). With use of 1-naphthalenecarboxaldehyde (1 g, 6.4 mmol) and 2-phenylethylamine (0.77 g, 6.4 mmol) as the starting material, oil **59** was obtained in 45% overall yield (0.79 g): NMR δ 8.1–8.3 (m, 1 H), 7.65–7.9 (m, 2 H), 7.1–7.5 (m, 9 H), 3.9 (s, 2 H), 2.6–3.0 (m, 4 H), 2.26 (s, 3 H); MS, *m/e* 275.

(*E*)-*N*-Methyl-*N*-[3-(2-thienyl)-2-propenyl]-1-naphthalenemethanamine (68). With use of (*E*)-3-(2-thienyl)-2-propenal[36] (1.38 g, 10 mmol) as the starting material, oily **68** was obtained in 48% overall yield (1.4 g) after chromatography (eluant A): NMR δ 8.25–8.45 (m, 1 H), 7.7–7.9 (m, 2 H), 7.1–7.6 (m, 5 H), 6.9–7.1 (m, 2 H), 6.95 (d, *J* = 16 Hz, 1 H), 6.22 (dt, *J* = 16 and 2 × 6.5 Hz, 1 H), 3.94 (s, 2 H), 3.25 (dd, *J* = 6.5 and 1.5 Hz, 2 H), 2.28 (s, 3 H); MS, *m/e* 293; mp (hydrochloride) 175–180 °C (2-propanol/Et_2O). Anal. ($C_{19}H_{19}NS{\cdot}HCl$) C, H, N, S, Cl.

(*E*)-*N*-Methyl-*N*-[3-(3-thienyl)-2-propenyl]-1-naphthalenemethanamine (69). With use of (*E*)-3-(3-thienyl)-2-propenal[37] (0.52 g, 3.8 mmol) as the starting material, **69** was obtained as oil in 56% overall yield (0.63 g) after chromatography (eluant A): NMR δ 6.7 (d, *J* = 16 Hz, 1 H), 6.2 (dt, *J* = 16 and 2 × 6 Hz, 1 H), 3.94 (s, 2 H), 3.24 (d, *J* = 6 Hz, 2 H), 2.3 (s, 3 H); MS, *m/e* 293.

(*E*)-*N*-Methyl-*N*-[3-(2-furyl)-2-propenyl]-1-naphthalenemethanamine (70). With use of (*E*)-3-(2-furyl)-2-propenal[38] (0.12 g, 1 mmol) as the starting material, **70** was obtained as oil in 40% overall yield (0.11 g) after chromatography (eluant B): NMR δ 8.25–8.4 (m, 1 H), 7.7–7.95 (m, 2 H), 7.25–7.6 (m, 5 H), 6.1–6.6 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 6 Hz, 2 H), 6.38 (m, 2 H_{fur}), 3.94 (s, 2 H), 3.25 (d, *J* = 6 Hz, 2 H), 2.26 (s, 6 H); MS, *m/e* 277.

(*E*)-*N*-Methyl-*N*-[3-(1-methylpyrrol-2-yl)-2-propenyl]-1-naphthalenemethanamine (71). With use of (*E*)-3-(1-methylpyrrol-2-yl)-2-propenal[39] (4.35 g, 32 mmol) as the starting material, **71** was obtained as oil in 23% overall yield (2.1 g) after chromatography (eluant $CHCl_3$/acetone = 4/1): NMR δ 6.6 (t,

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(39) Ullrich, F. W.; Breitmaier, E. *Synthesis* **1983**, 641.

J = 2 Hz, 1 H_{pyrr}), 6.5 (d, J = 16 Hz, 1 H), 6.46 (t, J = 2 Hz, 1 H_{pyrr}), 6.1 (dt, J = 16 and 2 × 6.5 Hz, 1 H), 6.1 (m, 1 H_{pyrr}), 3.94 (s, 2 H), 3.62 (s, 3 H), 3.25 (d, J = 6.5 Hz, 2 H), 2.26 (s, 3 H); MS, m/e 290.

(*E*)-*N*-Methyl-*N*-[3-(4-pyridyl)-2-propenyl]-1-naphthalenemethanamine (72). With use of (*E*)-3-(4-pyridyl)-2-propenal[40] (1.33 g, 10 mmol) as the starting material, **72** was obtained as oil in 68% overall yield (1.95 g) after chromatography (eluant $CHCl_3$/acetone = 7/3): NMR δ 8.5 (m, 2 H), 8.2–8.4 (m, 1 H), 7.1–7.9 (8 H), 6.35–6.7 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX} = 6 Hz, 2 H), 3.96 (s, 2 H), 3.3 (d, J = 6 Hz, 2 H), 2.3 (s, 3 H); MS, m/e 288; mp (dihydrochloride) 172–178 °C (EtOH). Anal. ($C_{20}H_{20}N_2$·2HCl) C, H, N, Cl.

(*E*)-*N*-Methyl-*N*-[3-(2-pyridyl)-2-propenyl]-1-naphthalenemethanamine (73). With use of (*E*)-3-(2-pyridyl)-2-propenal[40] (2.66 g, 20 mmol) as the starting material, **73** was prepared in 30% overall yield (1.72 g) after chromatography (eluant $CHCl_3$/acetone = 95/5): NMR δ 8.55 (m, 1 H), 8.2–8.4 (m, 1 H), 7.0–8.0 (m, 9 H), 6.5–7.0 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 5.5 Hz, 2 H), 4.0 (s, 2 H), 3.35 (d, J = 5.5 Hz, 2 H), 2.3 (s, 3 H); MS, m/e 288.

(*E*)-*N*-Methyl-*N*-[3-(3-cyclohexenyl)-2-propenyl]-1-naphthalenemethanamine (76). With use of **(*E*)-3-(3-cyclohexenyl)-2-propenal (96)** (2.72 g, 20 mmol) as the starting material, **76** was obtained as oil in 28% overall yield (1.62 g) after chromatography (eluant A): NMR δ 5.4–5.8 (m, 4 olef H), 3.85 (s, 2 H), 3.05 (d, J = 6 Hz, 2 H), 2.2 (s, 3 H), 1.2–2.7 (m, 6 H); MS, m/e 291.

The aldehyde **96** was prepared by reaction of 3-cyclohexene-1-carboxaldehyde with (formylmethylene)triphenylphosphorane following the procedure reported in ref 40: 65%, oil; NMR δ 9.45 (d, J = 7 Hz, 1 H), 6.8 (dd, J = 16 and 6 Hz, 1 H), 6.05 (dd, J = 16 and 7 Hz, 1 H), 5.6 (br 2 H), 0.8–3.0 (m, 7 H).

(*E*,*E*)-*N*-Methyl-*N*-(2,4-nonadienyl)-1-naphthalenemethanamine (80) was prepared in 67% overall yield as has been previously reported.[24]

(*E*,*E*)-6-[*N*-Methyl-*N*-(naphthylmethyl)amino]-2,4-hexenoic Acid Ethyl Ester (89). With use of (*E*,*E*)-5-carbethoxy-2,4-pentadienal[41] (1.53 g, 10 mmol) as the starting material, **89** was obtained in 62% overall yield (1.91 g) after chromatography (eluant A): NMR δ 8.2–8.4 (m, 1 H), 7.6–7.9 (m, 2 H), 7.15–7.6 (m, 4 arom H + 1 olef H), 6.1–6.5 (m, J_1 = 16 Hz, J_2 = 5.5 Hz, 2 olef H), 5.84 (d, J = 16 Hz, 1 olef H), 4.2 (qua, J = 7 Hz, 2 H), 3.9 (s, 2 H), 3.2 (d, J = 5.5 Hz, 2 H), 2.24 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H); MS, m/e 309.

2. Mannich Condensation with Acetophenones/Dehydration. (a) 3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-phenyl-1-propanone (56). Compound **90** (20.8 g, 0.12 mol) was dissolved in EtOH (50 mL), treated with concentrated aqueous HCl (12.2 g), 35% aqueous formaldehyde solution (10 g, 0.12 mmol), and acetophenone (14.7 g, 0.12 mmol), and refluxed for 1 h. Then paraformaldehyde (5.5 g, 0.18 mmol) was added and the reaction mixture again refluxed for 1 h. After cooling, H_2O (400 mL) and 30% NaOH (25 g) were added and worked up as usual. The oily residue was dissolved in hot hexane and after cooling crystalline **56** (20.3 g, 55%) was obtained: mp 88–90 °C (methanol). Anal. ($C_{21}H_{21}NO$) C, H, N.

The following compounds were prepared in the same way as **56** starting from the appropriately substituted acetophenones and secondary amines.

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(4-fluorophenyl)-1-propanone (97) (60%): mp 80–87 °C (hexane).

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(2-fluorophenyl)-1-propanone (98) (83%): mp ($^1/_2$1,5-naphthalenedisulfonate) 288–291 °C (EtOH).

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(4-chlorophenyl)-1-propanone (99) (80%): oil, used crude for the next step.

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(2-chlorophenyl)-1-propanone (100) (65%): mp (hydrochloride) 146–150 °C (EtOH/Et_2O).

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(4-methylphenyl)-1-propanone (101) (25%): mp 92–95 °C (hexane).

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(4-methoxyphenyl)-1-propanone (102) (55%): mp (hydrochloride) 171–173 °C (EtOH/Et_2O).

3-[*N*-Methyl-*N*-(2-naphthylmethyl)amino]-1-phenyl-1-propanone (103) (65%): mp (hydrochloride) 231–234 °C (EtOH/Et_2O).

3-[*N*-Methyl-*N*-(1-naphthyl-1-ethyl)amino]-1-phenyl-1-propanone (104) (49%): mp (oxalate) 200 °C dec (EtOH/Et_2O).

(b) **3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-phenyl-1-propanol (57).**[1] To a solution of **56** (7.5 g, 24.7 mmol) in MeOH (400 mL) was added $NaBH_4$ (1 g, 26 mmol) in portions at rt. After stirring for 15 min, the solvent was evaporated and the residue worked up as usual. The oily **57** (7.5 g, quant) was directly used in the next step. For analytical purpose, **57** was converted to its hydrochloride, mp 155–158 °C (EtOH/Et_2O).

The following compounds were prepared in the same way as **57**, starting from the appropriately substituted β-amino ketones **97–104**.

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(4-fluorophenyl)-1-propanol (105) (80%): mp (oxalate) 120–124 °C (EtOH/Et_2O). Anal. ($C_{21}H_{22}FNO·C_2H_2O_4$) C, H, N.

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(2-fluorophenyl)-1-propanol (106) (90%): oil, used crude for the next step.

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(4-chlorophenyl)-1-propanol (107) (90%): oil, used crude for the next step.

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(2-chlorophenyl)-1-propanol (108) (90%): oil, used crude for the next step.

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(4-methylphenyl)-1-propanol (109) (79%): mp ($^1/_2$1,5-naphthalenedisulfonate·$^1/_2H_2O$) 145–151 °C (MeOH/Et_2O). Anal. ($C_{22}H_{25}NO·C_5H_4O_3S·^1/_2H_2O$) C, H, N.

3-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-1-(4-methoxyphenyl)-1-propanol (110) (88%): mp ($^1/_2$1,5-naphthalenedisulfonate) 180–183 °C (MeOH/Et_2O). Anal. ($C_{22}H_{25}NO_2·C_5H_4O_3S$) C, H, N.

3-[*N*-Methyl-*N*-(2-naphthylmethyl)amino]-1-phenyl-1-propanol (111) (90%): oil, used crude for the next step.

3-[*N*-Methyl-*N*-(1-naphthyl-1-ethyl)amino]-1-phenyl-1-propanol (112) (90%): oil, used crude for the next step.

(c) Compound 1. Compound **57** (7.5 g, 24.7 mmol), obtained in step 2b, was heated to reflux in 5 N HCl (300 mL) for 2 h. After cooling, the solution was made alkaline with 30% NaOH (250 g) and worked up as usual. The oily residue was dissolved in EtOH and treated with HCl/Et_2O, and after addition of Et_2O (100 mL), **1** (6.55 g, 82%) was obtained as the hydrochloride.

The following compounds were prepared in the same way as **1**, starting from the appropriately substituted β-amino alcohols **105–112**.

(*E*)-*N*-[3-(4-Fluorophenyl)-2-propenyl]-*N*-methyl-1-naphthalenemethanamine (62) (87%): mp (hydrochloride) 196–206 °C (EtOH/Et_2O). Anal. $C_{21}H_{20}FN·HCl$) C, H, N, Cl.

(*E*)-*N*-[3-(2-Fluorophenyl)-2-propenyl]-*N*-methyl-1-naphthalenemethanamine (63) (40%): mp (hydrochloride) 176–181 °C (EtOH/Et_2O). Anal. $C_{21}H_{20}FN·HCl$) C, H, N, Cl.

(*E*)-*N*-[3-(4-Chlorophenyl)-2-propenyl]-*N*-methyl-1-naphthalenemethanamine (64) (95%): mp (hydrochloride) 209–212 °C (EtOH/Et_2O). Anal. $C_{21}H_{20}ClN·HCl$) C, H, N, Cl.

(*E*)-*N*-[3-(2-Chlorophenyl)-2-propenyl]-*N*-methyl-1-naphthalenemethanamine (65) (30%): mp (hydrochloride 178–181 °C (EtOH/Et_2O). Anal. ($C_{21}H_{20}ClN·HCl$) C, H, N, Cl.

(*E*)-*N*-[3-(4-Methylphenyl)-2-propenyl]-*N*-methyl-1-naphthalenemethanamine (66) (82%): mp (hydrochloride) 207–211 °C (EtOH/Et_2O). Anal. ($C_{22}H_{23}N·HCl$) C, H, N, Cl.

(*E*)-*N*-[3-(4-Methoxyphenyl)-2-propenyl]-*N*-methyl-1-naphthalenemethanamine (67) (85%): mp (hydrochloride) 193–196 °C (EtOH). Anal. ($C_{22}H_{23}NO·HCl$) C, H, N, Cl.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-2-naphthalenemethanamine (4) (65%): mp (hydrochloride) 175–179 °C (EtOH/Et_2O). Anal. ($C_{21}H_{21}N·HCl$) C, H, N, Cl.

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(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1-naphthalene-1-ethanamine (45) (37%): mp (1/2 1,5-naphthalenedisulfonate) 213–215 °C ($EtOH/Et_2O$). Anal. ($C_{22}H_{23}N \cdot C_5H_4O_3S$) C, H, N.

3. Mannich Condensation with Alkynes/Trans-Reduction with Dibal. (a) ***N*-[3-(1-Cyclohexenyl)-2-propynyl]-*N*-methyl-1-naphthalenemethanamine (113).** Compound **113** was prepared as described in ref 21 by $ZnCl_2$-catalyzed condensation of 1-ethynylcyclohexene, paraformaldehyde, and **90** in refluxing dioxane (90%).

The following compounds were prepared in the same way as **113**, starting from the appropriately substituted 1-alkynes.

***N*-(3-Cyclohexyl-2-propynyl)-*N*-methyl-1-naphthalenemethanamine (114)** (65%): NMR δ 3.96 (s, 2 H), 3.45 (d, J = 2 Hz, 2 H), 2.4–2.7 (br, 1 H), 2.35 (s, 3 H), 1.2–2.1 (m, 10 H).

***N*-[3-(1-Cyclopentenyl)-2-propynyl]-*N*-methyl-1-naphthalenemethanamine (115):** 85%.[21]

***N*-[3-(1-Cycloheptenyl)-2-propynyl]-*N*-methyl-1-naphthalenemethanamine (116):** 75%.[21]

***N*-Methyl-*N*-(3-phenyl-2-propynyl)-1-naphthalenemethanamine (54)** (65%): mp 215–224 °C (1/2 1,5-naphthalenedisulfonate·1/2 H_2O. Anal. ($C_{21}H_{19}N \cdot C_5H_4O_3S \cdot {}^1/_2H_2O$) C, H, N.

(b) **(*E*)-*N*-[3-(1-Cyclohexenyl)-2-propenyl]-*N*-methyl-1-naphthalenemethanamine (77).** Compound **77** was prepared by trans-hydroalumination with Dibal in toluene as is described in ref 21.

The following compounds were prepared in the same way as **77**, starting from **114–116**.

(*E*)-(3-Cyclohexyl-2-propenyl)-*N*-methyl-1-naphthalenemethanamine (75) (60%): NMR δ 5.4–5.8 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 5.5 Hz, 2 H), 3.88 (s, 2 H), 3.05 (d, J = 5.5 Hz, 2 H), 2.2 (s, 3 H), 0.8–2.3 (m, 11 Hz); MS, m/e 293.

(*E*)-*N*-[3-(1-Cycloheptenyl)-2-propenyl]-*N*-methyl-1-naphthalenemethanamine (79): 87%.[21]

(*E*)-*N*-[3-(1-Cyclopentenyl)-2-propenyl]-*N*-methyl-1-naphthalenemethanamine (78): 77%.[21]

4. N-Alkylation of Secondary Amines. (*E*)-*N*-Methyl-*N*-[3-(1-naphthyl)-2-propenyl]-1-naphthalenemethanamine (74). A mixture of **90** (3.56 g, 20 mmol), Na_2CO_3 (2.12 g, 20 mmol), and **(*E*)-3-(1-naphthyl)-2-propenyl Bromide (117)** (5.15 g, 20 mmol) in dimethylformamide (50 mL) was stirred overnight at rt. Most of the solvent was removed in vacuo and the residue partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. After usual workup crude **74** (7.0 g, quant) was obtained which was chromatographed over silica gel (eluant A) to give pure **74** (3.8 g, 54%) as an oil: NMR δ 8.25–8.45 (m, 1 H), 8.0–8.2 (m, 1 H), 7.15–7.9 (m, 12 arom H + 1 olef H), 6.4 (dt, J = 16 and 2 × 7 Hz, 1 olef H), 4.0 (s, 2 H), 3.38 (dd, J = 7 and 1.5 Hz, 2 H), 2.35 (s, 3 H); MS, m/e 337.

The starting bromide **117**[42] was prepared as follows. (a) Wittig–Horner reaction of 1-naphthaldehyde (20 g, 128 mmol) and triethyl phosphonoacetate (28 g, 128 mmol) with NaH (4.6 g [80%], 144 mmol) in benzene, 1 h rt, 3 h 60 °C, gave crude **(*E*)-ethyl 3-(1-naphthyl)prop-2-enoate (118)** (28.5 g, quant): NMR δ 8.4 (d, J = 16 Hz, 1 olef H), 6.4 (d, J = 16 Hz, 1 olef H), 4.3 (qua, J = 7 Hz, 2 H), 1.3 (t, J = 7 Hz, 3 H).

(b) Reduction of **118** (8.5 g, 37 mmol) with Dibal (94 mL of 1.2 M solution, 113 mmol) in toluene at −20 °C, hydrolysis, and basic workup gave **(*E*)-3-(1-naphthyl)-2-propen-1-ol (120)** (7 g, quant) as oil: NMR δ 6.3 (dt, J = 16 and 2 × 5 Hz, 1 olef H), 4.35 (d, J = 5 Hz, 2 H), 2.3 (s, OH).

(c) Treatment of **120** (4.77 g, 26 mmol) with CBr_4 (9.5 g, 28.6 mmol) and Ph_3P (7.5 g, 28.6 mmol) in acetonitrile at rt for 3 h, evaporation, and chromatography (eluant A) gave **117** (5.15 g, 81%): NMR δ 6.4 (dt, J = 16 and 2 × 7 Hz, 1 olef H), 4.2 (d, J = 7 Hz, 2 H).

The following compounds were prepared in the same way as **74**, starting from the appropriately substituted amines and halides.

(*E*)-*N*-Methyl-*N*-[3-(1-naphthyl)-2-propenyl]-1-benzylamine (2). Compound **2** (800 mg, 35%) was obtained as oil after chromatography (B) using *N*-methylbenzylamine (0.98 g, 8.1 mmol) and **117** (2 g, 8.1 mmol) as starting materials: NMR δ 8.0–8.2 (m, 1 H), 7.15–7.9 (m, 11 arom H + 1 olef H), 7.3 (dt, J = 16 and 2 × 7 Hz, 1 H), 3.6 (s, 2 H), 3.28 (dd, J = 7 and 1.5 Hz, 2 H), 2.3 (s, 3 H); MS, m/e 287.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)benzylamine (3):[43] 75%.

***N*-Methyl-*N*-(3-phenylpropyl)-1-naphthalenemethanamine (5).** Compound **5** was obtained by using 3-bromo-1-phenylpropane (2.19 g, 11 mmol), **90** (1.95 g, 11 mmol), and a reaction time of 5 h at 70 °C. After the usual workup the crude base was treated with 1,5-naphthalenedisulfonic acid to give the corresponding salt, which was recrystallized from ethanol (3.25 g, 68%): mp (1/2 naphthalenedisulfonic acid) 160–164 °C. Anal. ($C_{21}H_{23}N \cdot C_5H_4O_3S$) C, H, N.

(*E*)-*N*-Methyl-*N*-(-4-phenyl-3-butenyl)naphthalenemethanamine (9). With use of 1-bromo-4-phenyl-3-butene[44] (0.81 g, 4.7 mmol) as the starting material and a temperature of 60 °C for 4 h, **9** was obtained as oil in 45% yield (635 mg) after chromatography (eluant B): NMR δ 6.05–6.6 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 6 Hz, 2 H), 3.92 (s, 2 H), 2.3–2.8 (m, 4 H), 2.26 (s, 3 H); MS, m/e 301.

***N*-Methyl-*N*-(4-phenyl-2-butenyl)-1-naphthalenemethanamine (10).** With use of 1-iodo-4-phenyl-2-butene[45] (3 g, 11.6 mmol) as the starting material, oily **10** was obtained as an E/Z mixture in 52% yield (1.8 g): NMR δ 5.4–6.0 (m, 2 olef H), 3.84 (s, 2 H), 2.35 (m, 2 H), 3.05 (d, J = 6 Hz, 2 H), 2.18 (s, 3 H); MS, m/e 301.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-4-methyl-1-naphthalenemethanamine (12). With use of **126** as the starting material, **12** was obtained as the hydrochloride in 45% yield: mp 197–201 °C (2-propanol/Et_2O). Anal. ($C_{22}H_{23}N \cdot HCl$) C, H, N, Cl.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-4-chloro-1-naphthalenemethanamine (13). With use of **127** as the starting material, **13** was obtained as the hydrochloride in 60% yield: mp 198–208 °C ($EtOH/Et_2O$). Anal. ($C_{21}H_{20}ClN \cdot HCl$) C, H, N, Cl.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-4-methoxy-1-naphthalenemethanamine (14). With use of *N*-methyl-4-methoxy-1-naphthalenemethanamine[46] as the starting material, **14** was obtained as the hydrochloride in 70% yield: mp 211–214 °C ($EtOH/Et_2O$). Anal. ($C_{22}H_{23}NO \cdot HCl$) C, H, N, Cl.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-2-methoxy-1-naphthalenemethanamine (16). With use of **91** as the starting material, **16** was obtained in 85% yield: mp (1/2 1,5-naphthalenedisulfonate) 248–250 °C (H_2O/EtOH). Anal. ($C_{22}H_{23}NO \cdot C_5H_4O_3S$) C, H, N.

Treatment of **16** (2.21 g, 7 mmol) with BBr_3 (5.25 g, 21 mmol) in CH_2Cl_2 at 0 °C (1 h), dilution with MeOH, addition of 1,5-naphthalenedisulfonic acid in MeOH, and Et_2O resulted in the crystalline salt of **(*E*)-*N*-methyl-*N*-(3-phenyl-2-propenyl)-2-hydroxy-1-naphthalenemethanamine (17)** (57%, 1.8%): mp (1/2 1,5-naphthalenedisulfonate) 197–199 °C ($MeOH/Et_2O$). Anal. ($C_{21}H_{21}NO \cdot C_5H_4O_3S$) C, H, N.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-5,6,7,8-tetrahydro-1-naphthalenemethanamine (18). With use of *N*-methyl-5,6,7,8-tetrahydro-1-naphthalenemethanamine (5.9 g, 33 mmol)[47] [prepared by high-pressure hydrogenation (140 atm) of **90** over PtO_2 in glacial acetic acid for 6 h at 30 °C; bp 82–83 °C (0.1 mm), 72% yield] as the starting material, **18** was obtained as oil in 39% yield (3.7 g) after chromatography (eluant A) and Kugelrohr distillation: NMR δ 6.9–7.5 (m, 8 H), 6.1–6.7 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 6 Hz, 2 H), 3.45 (s, 2 H), 3.2 (d, J = 6 Hz, 2 H), 2.7–2.9 (m, 4 H), 2.2 (s, 3 H), 1.6–1.9 (m, 4 H); MS, m/e 291; bp 150 °C (10^{-3} mm) (Kugelrohr). Anal. ($C_{21}H_{25}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-3-indenemethanamine (22). With use of 3-(chloromethyl)indene (165 mg, 1 mmol) [prepared by treatment of 3-(hydroxymethyl)indene[48] with excess $SOCl_2$ at 0 °C] and (*E*)-*N*-methyl-3-phenyl-2-propenylamine (147

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mg, 1 mmol) as the starting material, **22** was obtained as oil in 25% yield (70 mg) after chromatography (eluant A): NMR δ 7.1–7.7 (m, 9 H), 6.4 (br s, 1 H), 6.15–6.7 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 6 Hz, 2 H), 3.55 (s, 2 H), 2.38 (s, 2 H), 3.25 (d, *J* = 6 Hz, 2 H), 2.32 (s, 3 H); MS, *m/e* 275.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1,2,3,4-tetrahydro-1,4-methano-5-naphthalenemethanamine (23). With use of **5-(chloromethyl)-1,2,3,4-tetrahydro-1,4-methanonaphthalene (121)** (470 mg, 2.43 mmol) and (*E*)-*N*-methyl-3-phenyl-2-propenylamine (357 mg, 2.43 mmol) as the starting material, **23** was obtained as oil in 48% yield (350 mg) after chromatography (eluant B): NMR δ 6.9–7.4 (m, 8 H), 6.1–6.6 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 6 Hz, 2 H), 3.6 (br, 1 H), 3.55 (AB system, J_{AB} = 11 Hz, Ar C*HH*N), 3.3 (br, 1 H), 3.18 (d, *J* = 6 Hz), 2.22 (s, 3 H), 1–2 (m, 6 H); MS, *m/e* 303, 302, 262, 212, 157, 146, 129, 117, 115, 91, 42.

The starting material **121** was prepared as follows. (a) 2,4-Pentadienoic acid methyl ester (10 mL, 85.6 mmol) and bicyclo[2.2.1]hept-2-ene (28.2 g, 300 mmol) were heated in dioxane at 200 °C in an autoclave overnight. After evaporation and chromatography (eluant toluene/ethyl acetate = 95/5), **1,2,3,4,4a,5,8,8a-octahydro-1,4-methanonaphthalene-5-carboxylic acid methyl ester) (122)** (6.35 g, 36%) was obtained: NMR δ 5.6–6.1 (m, 2 olef H + C*H*COOMe), 3.75 (s, 3 H), 2.6 (d, *J* = 9 Hz, 1 H), 0.8–2.4 (m, 11 H); MS, *m/e* 206 (M), 178 (M – 28), 147 (M – $COOCH_3$).

(b) A mixture of **122** (4.5 g, 21.8 mmol), NBS (8.5 g, 48 mmol), and catalytic α,α′-azobis(isobutyronitrile) was heated in CCl_4 under reflux for 1 h. After filtration, crude 5,8-dibromo-1,2,3,4,4a,5,8,8a-octahydro-1,4-methanonaphthalene-5-carboxylic acid methyl ester (**123**) (7,43 g, 94%) was obtained and directly used in the next step.

(c) Crude **123** (7.3 g, 20 mmol) was dissolved in benzene, DBU (8.8 mL, 60 mmol) was added, and the mixture was stirred at rt overnight. The reaction mixture was poured onto cooled 1 N H_2SO_4, extracted with benzene, and worked up as usual. The residue was chromatographed (eluant toluene) and **1,2,3,4-tetrahydro-1,4-methanonaphthalene-5-carboxylic acid methyl ester (124)** (1.24 g, 31%) was obtained as oil: NMR δ 7.7 (dd, *J* = 8 and 1 Hz, 1 H), 7.3 (br d, *J* = 7 Hz, 1 H), 7.1 (t, *J* = 7 Hz, 1 H), 4.2 (br, 1 H), 3.9 (s, 3 H), 3.4 (br s, 1 H), 1–2.2 (m, 6 H); MS, *m/e* 202, *174*.

(d) Compound **124** (0.6 g, 3 mmol) was reduced to the corresponding alcohol by Dibal in toluene (3 equiv) at -10 °C (410 mg, 81%) and converted to the chloride **121** by treatment with excess $SOCl_2$ (570 mg, quant): **NMR** δ 7.0–7.25 (m, 3 H), 4.6 (AB system, J_{AB} = 11.Hz, Ar C*HH*Cl), 3.58 (br, 1 H), 3.36 (br, 1 H), 1–2 (m, 6 H).

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-4-*s*-hydrindacenemethanamine (25). With use of 4-(chloromethyl)-*s*-hydrindacene[49] (1.5 g, 7.26 mmol) and (*E*)-*N*-methyl-3-phenyl-2-propenylamine (1.07 g, 7.26 mmol) as the starting material, **25** was obtained as oil in 83% yield (1.98 g) after chromatography (eluant B): NMR δ 7.2–7.4 (5 H), 7.04 (s, 1 H), 6.55 (d, *J* = 16 Hz, 1 H), 6.28 (dt, *J* = 16 and 2 × 6 Hz, 1 H), 3.48 (s, 2 H), 3.18 (d, *J* = 6 Hz, 2 H), 2.92 (qua, *J* = 7 Hz, 8 H), 2.21 (s, 3 H), 2.07 (qui, *J* = 7 Hz, 4 H); MS, *m/e* 317.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-2*H*-1-benzopyran-4-methanamine (30). With use of (4-chloromethyl)-2*H*-1-benzopyran[50] and (*E*)-*N*-methyl-3-phenyl-2-propenylamine as the starting material, **30** was obtained as oil in 40% yield after chromatography (eluant B): NMR δ 6.7–7.5 (m, 9 H), 6.5 (d, *J* = 16 Hz, 1 H), 6.2 (dt, *J* = 16 and 2 × 6 Hz, 1 H), 5.8 (m, 1 H), 4.68 (m, 2 H), 3.22 (m, 2 H), 3.13 (d, *J* = 6 Hz, 2 H), 2.2 (s, 3 H). Anal. ($C_{20}H_{21}NO$) C, H, N.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-3-benzo[*b*]furanmethanamine (33). With use of *N*-methyl-3-benzo[*b*]-furanmethanamine[51] (0.28 g, 1.74 mmol) as the starting material, **33** was obtained as oil in 47% yield (0.23 g) after chromatography ($CHCl_3$/EtOH = 95/5): NMR δ 7.65–7.8 (m, 1 H), 7.55 (s, 1 H), 7.2–7.5 (m, 4 H), 6.15–6.7 (AB part of ABX_2 system, J_{AB} = 17 Hz, J_{AX2} = 6 Hz, 2 H), 3.68 (s, 2 H), 3.23 (d, *J* = 6 Hz, 2 H), 2.29 (s, 3 H); MS, *m/e* 277.

(*E*)-*N*-(3-Phenyl-2-propenyl)-*N*-hydroxy-1-naphthalenemethanamine (37). With use of *N*-hydroxy-1-naphthalenemethanamine (125) (0.2 g, 1.15 mmol) as the starting material, **37** was obtained in crystals (mp 92–96 °C) and 78% yield (0.26 g), after chromatography (eluant A): NMR δ 6.2–6.7 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX2} = 6 Hz, 2 H), 5.6 (br, NOH), 4.24 (s, 2 H), 3.55 (d, *J* = 6 Hz, 2 H); MS, *m/e* 289; mp 92–96 °C. Anal. ($C_{20}H_{19}NO$) C, H, N.

The hydroxylamine **125** was prepared by $NaCNBH_3$ reduction of naphthalene-1-carboxaldehyde oxime (5.0 g, 29 mmol) in MeOH in pH 3 according to a standard procedure.[52] After recrystallization from benzene/hexane (1/1) pure **125** (3.1 g, 61%) was obtained: mp 82–85 °C. Anal. ($C_{11}H_{11}NO$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenemethanamine (38). With use of *N*-ethyl-1-naphthalenemethanamine (5.5 g, 24.8 mmol) as the starting material, **38** was obtained as the hydrogen fumarate (7.25 g, 70%): mp 127–129 °C (acetone/Et_2O). Anal. ($C_{22}H_{23}N{\cdot}C_4H_4O_4$) C, H, N.

(*E*)-*N*-Isopropyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenemethanamine (39). Treatment of **34** with isopropyl iodide (1 equiv) furnished **39** (30%): mp ($^1/_2$ 1,5-naphthalenedisulfonate) 225–230 °C (EtOH/Et_2O). Anal. ($C_{23}H_{25}N{\cdot}C_5H_4O_3S$) C, H, N.

(*E*)-*N*-(3-Phenyl-2-propenyl)-*N*-2-propenyl-1-naphthalenemethanamine (40). Treatment of **34** with allyl bromide (1 equiv) gave **40** (30%), isolated as the hydrochloride: mp 95–103 °C (acetone/Et_2O). Anal. ($C_{23}H_{23}N{\cdot}HCl$) C, H, N, Cl.

(*E*)-*N*,*N*-Bis(3-phenyl-2-propenyl)-1-naphthalenemethanamine (41). Treatment of **34** with (*E*)-1-bromo-3-phenyl-2-propene (1 equiv) gave **41** (56%) after chromatography (eluant A): mp 90–91 °C (EtOH); MS, *m/e* 389. Anal. ($C_{29}H_{27}N$) C, H, N.

(*E*)-*N*-Cyclohexyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenemethanamine (42). With use of **93** (3 g, 12.5 mmol) as the starting material, **42** was obtained in 52% yield (2.3 g) after chromatography (toluene): mp 73–75 °C (EtOH); MS, *m/e* 355. Anal. ($C_{26}H_{29}N$) C, H, N.

(*E*)-*N*-Phenyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenemethanamine (43). With use of **94** (2 g, 8.6 mmol) as the starting material and heating at 70 °C for 4 h gave **43** in 40% yield (1.3 g) after chromatography: mp 84–86 °C (MeOH); MS, *m/e* 349. Anal. ($C_{26}H_{23}N$) C, H, N.

(*E*)-*N*-Benzyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenemethanamine (44). Treatment of **34** (3 g, 11 mmol) with benzyl chloride (1.4 g, 11 mmol) gave after chromatography (toluene/hexane = 8/2) **44** as oil in 59% yield (2.36 g): MS, *m/e* 363. Anal. ($C_{27}H_{25}N$) C, H, N.

***N*-Methyl-*N*-phenacyl-1-naphthalenemethanamine (58).** Treatment of **90** (0.5 g, 2.9 mmol) with phenacyl bromide (0.58 g, 2.9 mmol) gave after chromatography (eluant A) **58** in 57% yield (0.45 g): NMR δ 4.1 (s, 2 H), 3.8 (s, 2 H), 2.42 (s, 3 H); MS, *m/e* 289.

(*E*)-*N*-Methyl-*N*-(2-methyl-3-phenyl-2-propenyl)-1-naphthalenemethanamine (60). With use of **92** and 1-(chloromethyl)naphthalene as the starting material, **60** was obtained in 77% yield: mp (hydrochloride) 183–191 °C (EtOH/Et_2O). Anal. ($C_{22}H_{23}N{\cdot}HCl$) C, H, N, Cl.

***N*-Methyl-*N*-2-propenyl-1-naphthalenemethanamine (81).** After reaction of **90** (10 g, 58 mmol) with allyl bromide (7.1 g, 5.8 mmol) **81** was obtained in 46% yield (5.6 g) after distillation: bp 92 °C (10^{-3} mm); MS, *m/e* 211. Anal. ($C_{15}H_{17}N$) C, H, N.

(*E*)-*N*-Methyl-*N*-2-butenyl-1-naphthalenemethanamine (82). After reaction of **90** (10 g, 58 mmol) with crotyl bromide (7.8 g, 58 mmol) **82** was obtained in 75% yield (9.78 g) after chromatography (eluant B): NMR δ 5.5–5.8 (m, 2 H), 3.88 (s, 2 H), 3.0–3.2 (m, 2 H), 2.2 (s, 3 H), 1.7 (m, 3 H); MS, *m/e* 225.

(*E*)-*N*-Methyl-*N*-(3-cyano-2-propenyl)-1-naphthalenemethanamine (83). After reaction of **90** with 3-bromoacrylo-

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nitrile, 83 was obtained as an E/Z mixture (~1:1) in 82% yield after chromatography (eluant B): NMR [6.7 (dt, J = 16 and 2 × 6 Hz) and 6.45 (dt, J = 11 and 2 × 7 Hz) Σ 1 H], [5.56 (dt, J = 16 and 2 × 2 Hz) and 5.38 (dt, J = 11 and 2 × 2 Hz) Σ 1 H], 3.95 (s, 2 H); [3.42 (dd, J = 7 and 2 Hz) and 3.2 (dd, J = 6 and 2 Hz) Σ 2 H], [2.30 (s) and 2.28 (s) Σ 3 H].

(*E*)-4-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-2-butenoic Acid Ethyl Ester (86). After reaction of **90** (3 g, 17.5 mmol) with 4-bromocrotonic acid ethyl ester (3.3 g, 17.5 mmol), chromatography (eluant A) and Kugelrohr distillation [bp 170 °C (10^{-3} mm)] 86 (3.4 g, 70%) was obtained: NMR δ 7.0 (dt, J = 16 and 2 × 6 Hz, 2 H), 6.0 (dt, J = 16 and 2 × 1.5 Hz, 1 H), 4.2 (qua, J = 7 Hz, 2 H), 3.9 (s, 2 H), 3.2 (dd, J = 6 and 1.5 Hz, 2 H), 2.25 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H); MS, m/e 283. Anal. ($C_{18}H_{21}NO_2$) C, H, N.

By hydrolysis of 86 with excess NaOH in EtOH (48 h, rt) and acidic workup, **(*E*)-4-[*N*-methyl-*N*-(1-naphthylmethyl)amino]-2-butenoic acid (85)** [quant, mp 65–66 °C (benzene). Anal. ($C_{16}H_{17}NO_2$) C, H, N] was obtained.

(*E*)-4-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-2-butenoic Acid *n*-Pentyl Ester (87). After reaction of **90** with 4-bromocrotonic acid *n*-pentyl ester[53] [prepared by bromination of crotonic acid *n*-pentyl ester with NBS in CCl_4] and chromatography (eluant A), 87 was obtained as oil in 40% yield: NMR δ 7.0 (dt, J = 16 and 2 × 6 Hz, 1 H), 6.0 (dt, J = 16 and 2 × 1.5 Hz, 1 H), 4.1 (qua, J = 7 Hz, 2 H), 3.9 (s, 2 H), 3.2 (dd, J = 6 and 1.5 Hz, 2 H), 2.24 (s, 3 H), 1.1–1.8 (m, 6 H), 0.9 (t, J = 7 Hz, 3 H); MS, m/e 325. Anal. ($C_{21}H_{27}NO_2$) C, H, N.

(*E*)-4-[*N*-Methyl-*N*-(1-naphthylmethyl)amino]-2-butenoic Acid Benzyl Ester (88). After reaction of **90** with 4-bromocrotonic acid benzyl ester [prepared by bromination of crotonic acid benzyl ester with NBS in CCl_4] and chromatography (eluant A), 38% 88 was obtained as oil: NMR δ 7.1 (dt, J = 16 and 2 × 6 Hz, 1 H), 6.05 (dt, J = 16 and 2 × 1.5 Hz, 1 H), 5.18 (s, 2 H), 3.9 (s, 2 H), 3.22 (dd, J = 6 and 1.5 Hz, 2 H), 2.3 (s, 3 H); MS, m/e 345.

Synthesis of Other Compounds. (*E*)-3-Phenyl-2-propenyl 1-Naphthylmethyl Ether (6). A solution of 1-(hydroxymethyl)naphthalene (1.84 g, 11.6 mmol) in THF was dropped to a suspension of NaH [0.35 g (80%), 11.6 mmol] in THF and stirred for 30 min at rt. then (*E*)-1-bromo-3-phenyl-2-propene (2.3 g, 11.6 mmol), dissolved in DMF was added and the mixture stirred overnight. After evaporation and usual workup, crude **6** was obtained and chromatographed (eluant: hexane/ethyl acetate = 9/1) to give pure **6** (1.6 g, 50%) as oil: NMR δ 6.2–6.8 (AB part of ABX_2 system, J_{AB} = 16 Hz, J_{AX_2} = 5 Hz, 2 H), 4.04 (s, 2 H), 3.3 (d, J = 5 Hz, 2 H); MS, m/e 274. Anal. ($C_{20}H_{18}O$) C, H.

(*E*)-*N*,*N*-Dimethyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenemethanammonium Iodide (35). Treatment of **1** (2.7 g, 10 mmol) with CH_3I (1.42, 10 mmol) in acetone for 4 h, filtration of the crystals, and drying gave **35** (3.75 g, 93%): mp 185–187 °C. Anal. ($C_{22}H_{24}NI$) C, H, N, I.

(*E*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1-naphthamide (47). To a solution of (*E*)-*N*-methyl-3-phenyl-2-propenylamine (7.7 g, 52 mmol) in pyridine was added at 0 °C 1-naphthoyl chloride (10 g, 52 mmol) dissolved in THF. After the mixture was stirred for 1 h at rt, the solvent was removed in vacuo. After acidification and usual workup, crystalline **47** was obtained (71%, 11.15 g) and recrystallized from cyclohexane: mp 69–71 °C. Anal. ($C_{21}H_{19}NO$) C, H, N.

(*E*)-*N*-Acetyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenemethanamine (48). Treatment of **34** with excess acetic anhydride, evaporation, and usual workup furnished oily 48 (79%, 250 mg) after chromatography ($CHCl_3$/EtOH = 9/1): IR 1630 cm^{-1}; NMR, mixture of rotational isomers [2.24 (s) and 2.15 (s), 3 H, $NCOCH_3$]; MS, m/e 315.

(*E*)-*N*-(3-Phenyl-2-propenoyl)-*N*-methyl-1-naphthalenemethanamine (49). Compound **49** was prepared as is described for **47**, starting from **89** (5 g, 29 mmol) and cinnamoyl chloride (4.87 g, 29 mmol). After chromatography (eluant B), **47** was obtained crystalline in 90% yield (7.8 g): mp 97 °C (cyclohexane); MS, m/e 301. Anal. ($C_{21}H_{19}NO$) C, H, N.

(*E*)-3-Phenyl-2-propenyl 1-Naphthylmethyl Sulfide (50). 1-(Mercaptomethyl)naphthalene (7.5 g, 43 mmol) was converted to its sodium salt by NaOEt (1 equiv) in EtOH, then treated with (*E*)-1-bromo-3-phenyl-2-propene (8.4 g, 43 mmol), and stirred for 2 h. After evaporation, usual workup, and crystallization from hexane, pure **50** (7.6 g, 61%) was obtained: mp 58–60 °C; MS, m/e 290. Anal. ($C_{20}H_{18}S$) C, H, S.

(*E*)-3-Phenyl-2-propenyl 1-Naphthylmethyl Sulfoxide (51) and (*E*)-3-Phenyl-2-propenyl 1-Naphthylmethyl Sulfone (52). Compound **50** (1 g, 3.4 mmol) was treated with *m*-chloroperbenzoic acid (1.4 g, 3.4 mmol) at 0 °C in $CHCl_3$ and stirred overnight. After usual workup the residue was chromatographed ($CHCl_3$). First was obtained **52** (850 mg, 38%): mp 40–142 °C; MS, m/e 322. Anal. ($C_{20}H_{18}SO_2$) C, H, S. Then **51** (300 mg, 14%) was eluted: mp 158–160 °C; MS, m/e 306. Anal. ($C_{20}H_{18}SO$) C, H, S.

(*Z*)-*N*-Methyl-*N*-(3-phenyl-2-propenyl)-1-naphthalenemethanamine (53). Compound **54** (3 g, 10.4 mmol) was dissolved in pyridine and hydrogenated over $Pd/BaSO_4$ (5%, 150 mg) until theoretical H_2 uptake. After filtration and evaporation, the crude product was chromatographed (eluant A) to give 44% **53** (1.3 g) as oil: NMR δ 6.6 (dt, J = 12 and 2 × 2 Hz, 1 H), 5.9 (dt, J = 12 and 2 × 7 Hz, 1 H), 3.9 (s, 2 H), 3.35 (dd, J = 7 and 2 Hz, 2 H), 2.24 (s, 3 H); MS, m/e 287; mp (hydrochloride) 155–170 °C ($EtOH/Et_2O$). Anal. ($C_{21}H_{21}N{\cdot}HCl$) C, H, N, Cl.

(*E*)-*N*-Methyl-*N*-(3-methyl-3-phenyl-2-propenyl)-1-naphthalenemethanamine (61). Compound **56** (4.5 g, 14.8 mmol) was dissolved in Et_2O and cooled to 0 °C. A 2 M solution of CH_3Li (15 mL, 30 mmol) was added and the reaction mixture was brought to rt. After 30 min, H_2O was added and worked up as usual. The residue was crystallized from hexane to give **4-[methyl(1-naphthylmethyl)amino]-2-phenyl-2-butanol** (2.75 g, 59%): mp 75–78 °C. Dehydration as is described for **1** in step 2c gave **61** in 65% yield (1.74 g): mp (hydrochloride) 190–193 °C. Anal. ($C_{22}H_{23}N{\cdot}HCl$) C, H, N, Cl.

(*E*)-*N*-(4-Hydroxy-2-butenyl)-*N*-methyl-1-naphthalenemethanamine (84). Compound 84 was prepared as described previously.[21]

***N*-Methyl-1-naphthalenemethanamine (90).** A solution of 1-(chloromethyl)naphthalene (17.6 g, 0.1 mmol) in EtOH was dropped to a 33% solution of methylamine in EtOH (33%, 100 mL) with ice cooling and stirred at rt overnight. After evaporation and usual workup, the oily residue was distilled in vacuo to give **90** in 78% yield (13.3 g): bp 85–87 °C (0.01 mm).

The following compounds were prepared in the same way, starting from the appropriately substituted halides.

***N*-Methyl-4-methyl-1-naphthalenemethanamine (126):** 27%; mp (hydrochloride) 202–208 °C.

***N*-Methyl-4-chloro-1-naphthalenemethanamine (127):** 32%; mp (hydrochloride) 223–236 °C.

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Registry No. 1, 65472-88-0; 2, 98977-52-7; 3, 98977-53-8; 4, 98977-54-9; 5, 98977-55-0; 6, 98977-56-1; 7, 98977-57-2; 8, 98977-58-3; 9, 98977-59-4; (*E*)-10, 98977-60-7; (*Z*)-10, 98978-56-4; 11, 98977-61-8; 12, 79482-57-8; 13, 79416-76-5; 14, 79416-77-6; 15, 98977-62-9; 16, 65473-05-4; 17, 65472-94-8; 18, 98977-63-0; 19, 98977-64-1; 20, 98977-65-2; 21, 98977-66-3; 22, 98977-67-4; 23, 98977-68-5; 24, 98977-69-3; 25, 98977-70-9; 26, 98977-71-0; 27, 98977-72-1; 28, 98977-73-2; 29, 98977-74-3; 30, 83554-66-9; 31, 98977-75-4; 32, 98977-76-5; 33, 98977-77-6; 34, 92610-10-1; 34·HCl, 98978-52-0; 35, 98990-51-3; 36, 98977-78-7; 37, 98977-79-8; 38, 65503-09-5; 39, 65472-96-0; 40, 79416-78-7; 41, 98977-80-1; 42, 98977-81-2; 43, 98977-82-3; 44, 98977-83-4; 45, 65503-07-3; 46, 98977-84-5; 47, 98977-85-6; 48, 98977-86-7; 49, 98977-87-8; 50, 98977-88-9; 51, 98977-89-0; 52, 98977-90-3; 53, 65473-08-7; 54, 98977-91-4; 55, 98977-92-5; 56, 98977-93-6; 57, 98977-94-7; 58, 98977-95-8; 59, 98977-96-9; 60, 98977-97-0; 61, 98977-98-1; 62,

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Synthesis of Alkyl-Substituted Arecoline Derivatives as γ-Aminobutyric Acid Uptake Inhibitors

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A series of *N*-methyltetrahydropyridine-3-carboxylic acids and methyl esters have been synthesized and biologically evaluated. Arecoline (**6**) was lithiated with LDA in THF to give **7**, which was treated with various alkyl halides to afford exclusively the α-substituted products **8a–g**. Thermodynamic reaction of **7** with carbonyl compounds gave the corresponding 5-substituted arecoline derivatives **10a–q**. When phenyldiazonium tetrafluoroborate was used as electrophile, **8h** and **9** were obtained. The relative stereochemistry of **10j–o** was established by ^1H NMR spectroscopy. Compound **12** was obtained by condensation of the silylketene acetal **11** with *N*-acetylindoxyl. Dehydration of **10a–c** yielded **14a–c**, respectively. Deprotection of the esters **14a**, **14c**, and **15** followed by chromatography on an ion-exchange resin gave the amino acids **16a**, **16c**, and **16d**. The alcohol **17** was obtained by $LiAlH_4$ reduction of the corresponding ester **14c**. The amino acid **16c** displayed a marked inhibitory effect on the synaptosomal uptake of γ-amino[^3H]butyric acid ([^3H]GABA). The type of inhibition was competitive with a K_i of 12.9 μM. Compound **16d** also inhibited [^3H]GABA uptake but was about 10 times weaker than **16c**. None of the biologically tested compounds (**8a–g**, **9**, **10a–q**, **12**, **14a–c**, **16a–d**, **17**) showed any effect in binding studies using [^3H]GABA as ligand.

Growing interest in the pharmacology of GABA (γ-aminobutyric acid) has been stimulated by findings linking this amino acid to certain psychiatric and neurological diseases.[2-4] Therefore, particular interest has been directed to compounds that interact with the neuronal and glial GABA-uptake system or the postsynaptic GABA receptors.[5-7]

For instance, (*RS*)-piperidine-3-carboxylic acid (nipecotic acid) (**1**) and 1,2,5,6-tetrahydropyridine-3-carboxylic acid (guvacine) (**2**) have been shown to be potent inhibitors of the GABA-uptake process,[6,8,9] whereas the isomeric compounds piperidine-4-carboxylic acid (isonipecotic acid) (**3**)

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