(Aryloxy)methylsilane Derivatives as New Cholesterol Biosynthesis Inhibitors: Synthesis and Hypocholesterolemic Activity of a New Class of Squalene Epoxidase Inhibitors

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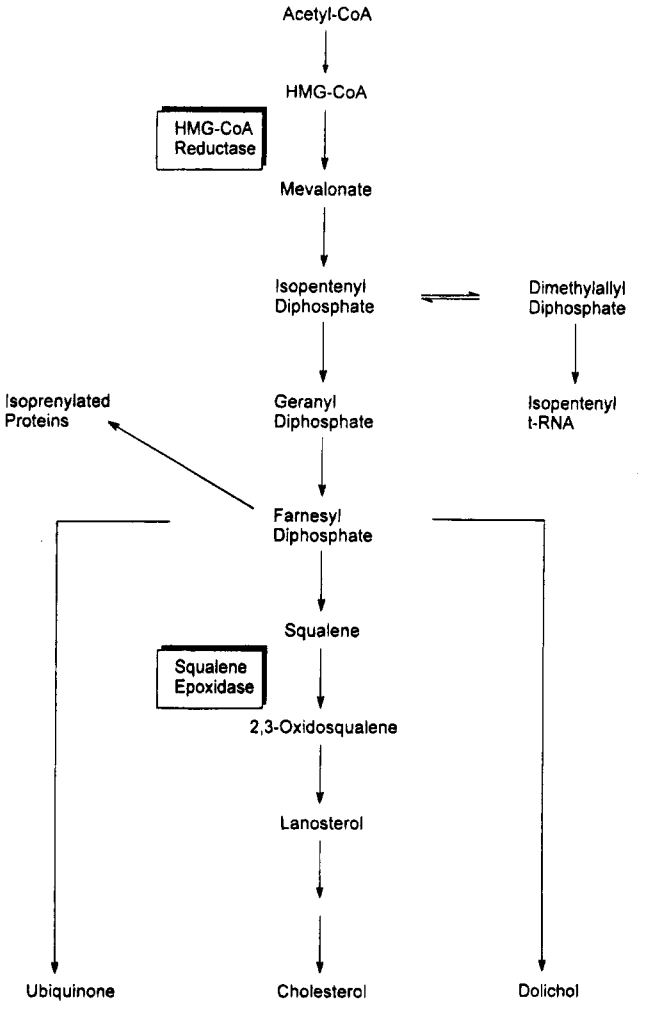
A series of 3-substituted (aryloxy)silane derivatives of benzylamine (**4**, **4′**, or **4″**) was synthetized and evaluated for hypocholesterolemic activity. Most of the new silane derivatives were identified as potent inhibitors of pig liver squalene epoxidase with IC_{50} values in the submicromolar range. *In vitro* inhibition of cholesterol biosynthesis in Hep-G_2 cells was observed with a very good potency for the ene–yne derivatives **4a**, **4i**, **4n**, **4q**, and **4u** as well as for the yne–yne compound **4″**. *In vivo*, **4i**, **4u**, **4′**, and **4″** were found to decrease cholesterol biosynthesis in rats upon oral administration with ED_{50} values in the range of 2–7 mg/kg. Therefore, these new (aryloxy)methylsilane derivatives of benzylamine represent a new class of potent squalene epoxidase inhibitors with promising hypocholesterolemic properties.

Introduction

Raised plasma low-density lipoprotein (LDL)-cholesterol levels are widely accepted to be a major risk factor for coronary artery disease as well as other atherosclerotic diseases and thus lowering plasma LDL-cholesterol levels in hypercholesterolemic patients represents an important clinical objective.[1,2] Currently, the most effective approach to lower serum LDL-cholesterol concentrations is by inhibiting sterol biosynthesis which leads to an up-regulation of hepatic LDL receptors and consequently removal of LDL-cholesterol from the blood plasma.[3] Many attempts have been made to produce hypolipidemic agents that inhibit enzymes in the cholesterol synthetic pathway. This has been widely illustrated by the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors as cholesterol-lowering drugs with proven clinical efficacy.[4] However, HMG-CoA reductase inhibitors block mevalonate production, which occurs at an early stage in the cholesterol synthetic pathway (Chart 1). Therefore, these compounds are thought to inhibit the synthesis of other biologically important substances derived from mevalonate such as ubiquinones, the dolichols, isopentenyl ^{t}RNA, and isoprenylated proteins. For instance, the levels of ubiquinone (coenzyme Q_{10}), demonstrated recently as being indispensable for cardiac function, decreased in rats and in humans upon treatment by lovastatin.[5,6] Moreover, HMG-CoA reductase inhibitors like simvastatin or pravastatin may enhance respiratory impairment of liver mitochondria under pathophysiological conditions such as ischemia[7] (ubiquinone is essential for the production of energy through oxidative phosphorylation). A more selective inhibition of cholesterol biosynthesis may be achieved by inhibiting steps beyond farnesyl pyrophosphate, the common intermediate for all prenylation processes (Chart 1). The enzymes squalene synthase (SS) (EC 2.5.1.21), squalene epoxidase (SE) (EC 1.14.99.7), and 2,3-oxidosqualene cyclase (OSC) (EC 5.4.99.7) are, therefore, attractive targets[8] for hypolipidemic drug design since inhibition of one of these three enzymes, which are specifically committed to sterol biosynthesis, should not interfere with essential

Chart 1. Cholesterol Biosynthesis



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Scheme 1. Conversion of Squalene to 2,3-Oxidosqualene

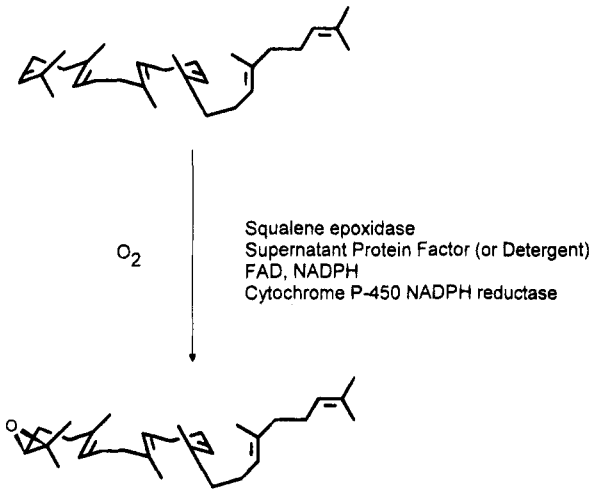
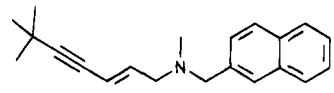
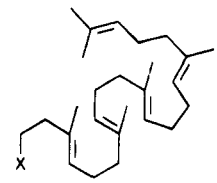


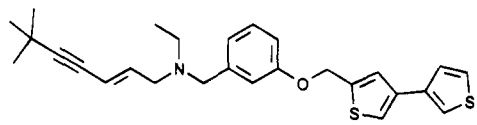
Chart 2. Squalene Epoxidase Inhibitors



Terbinafine, 1



2a, X = CH_2OH
2b, X = CH_2NH(cyclopropyl)
2c, X = $CH{=}CF_2$



NB-598, 3

non-sterol pathways and moreover, will not result in the accumulation of steroidal precursors.

SE catalyses the conversion of squalene to 2,3-oxidosqualene (Scheme 1), an essential step in the biosynthesis of sterols in mammals, plants, and microorganisms. This enzymatic reaction is known to be the first step among oxygenase-catalyzed reactions in cholesterol biosynthesis requiring O_2, NADPH, and FAD for full activity. Recent studies have shown that SE, an important regulatory enzyme, plays an important role in the maintenance of cholesterol homeostasis in both Hep-G_2 cells and rat liver.[9] Moreover, squalene, which is expected to accumulate upon SE inhibition,[10] has been reported to be a safe substance in humans.

Most squalene epoxidase inhibitors have been known as antifungal agents. Among them, terbinafine (**1**) (Chart 2) has recently emerged as a marketed drug which is used both topically and orally as an antimycotic agent.[11] It is noteworthy that terbinafine (**1**) as well as many other benzylamine analogues are very potent inhibitors of fungal SE but inhibit the mammalian enzyme only very slightly. Recently, several groups have reported a number of squalene analogues as mammalian SE inhibitors.[8] These include some acetylene, allene, and diene analogues (inhibition of rat liver SE with IC_{50} values from 50 to 200 μM) and many carboxyl, hydroxy, or amine derivatives. Among them, trisnorsqualene alcohol **2a** (Chart 2) (K_i = 4 μM for pig liver SE) and trisnorsqualene cyclopropylamine **2b** (K_i = 2 μM for pig liver SE) were shown to be the most potent inhibitor of the series. Interestingly, the cyclopropylamine derivative of squalene **2b** was identified as a slow, tight-binding inhibitor of vertebrate SE. This inhibitor was successfully used on an affinity resin for purification of pig liver SE.[12] A time-dependent, irreversible mechanism-based enzyme inactivation of SE was recently reported[13] by using the terminal difluoroolefin analogue of squalene **2c** (K_i = 8 μM; k_{inact} = 0.12 min^{-1} for rat liver SE).

Although benzylamine derivatives of terbinafine were known as selective fungal SE inhibitors, chemical modifications around the aromatic moiety resulted in the identification of the first potent inhibitor of vertebrate SE from compounds of this class. NB-598, **3** (Chart 2), was found to be a highly potent, competitive, and specific inhibitor of vertebrate SE (IC_{50} = 4.4 nM for rat liver SE) showing no antifungal activity.[14,15] This bis(thienyl) derivative strongly inhibited cholesterol biosynthesis from [^{14}C]acetate both in Hep-G_2 cells and *in vivo* in the rat. Chronic administration of oral doses of NB-598 decreased serum total and LDL-cholesterol levels in dogs[16] with a similar potency to simvastatin. From these observations, an SE inhibitor is expected to be highly effective in the treatment of hypercholesterolaemia.

In this paper, we report the synthesis and biological activity of the (aryloxy)methylsilane derivatives of benzylamine **4**, **4'**, and **4''** (see Tables 4 and 5) as a new class of potent mammalian squalene epoxidase inhibitors which inhibit cholesterol biosynthesis in Hep-G_2 cells and show oral activity in rats.

Chemistry

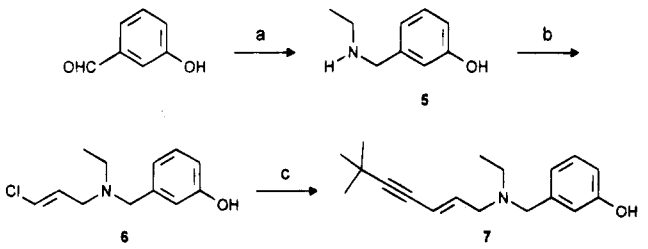
To explore the potential of the silyl group in compounds **4** substituting for the 3,3'-bis(thienyl) group found in NB-598 as a pharmacophore recognized by SE, we first studied substitution around the silicon atom (R_1) in benzylamine derivatives **4a**–**x** (see Table 4).

The (aryloxy)methylsilane derivatives of ene–yne benzylamines **4a**–**k** were prepared from the key phenol intermediate **7** which was obtained in three steps from 3-hydroxybenzaldehyde by (1) reductive amination with ethylamine, (2) alkylation with pure (*E*)-1,3-dichloropropene using potassium carbonate, and (3) Stephens–Castro coupling with 3,3-dimethylbutyne,[17] as illustrated in Scheme 2.

Condensation of the phenol derivative **7** with appropriate (chloromethyl)dimethylarylsilanes **8a**–**k**[18] in the presence of potassium carbonate and a stoichiometric amount of potassium iodide in dimethyl sulfoxide at 80 °C allowed the preparation of the expected products **4a**–**k** in a one-step procedure as shown in Table 1.

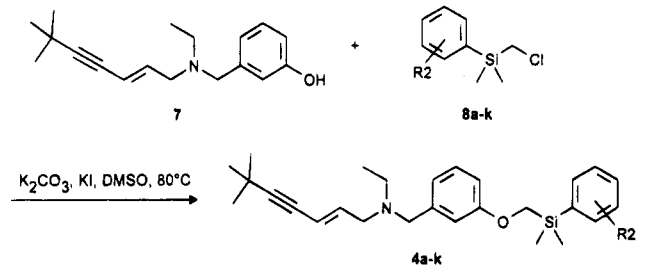
Compounds **4l**–**p** were synthesized by a lithium-bromine exchange reaction starting from the 4-(bromophenyl) silane derivative **4d**, followed by condensation with an appropriate electrophile according to Table 2. Thus, treatment with trimethylsilyl isocyanate,[19] di-

Scheme 2[a]



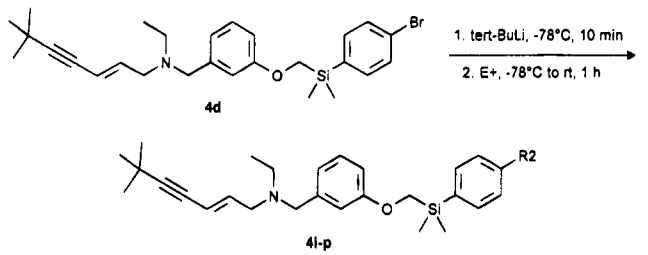
[a] (a) (i) $EtNH_2$, EtOH, 20 °C; (ii) $NaBH_4$, EtOH, 20 °C; (b) (*E*)-1,3-dichloropropene, K_2CO_3, DMSO, 50 °C; (c) 3,3-dimethylbutyne, $Pd(PPh_3)_4$, CuI, $nBuNH_2$, THF, 20 °C.

Table 1. General Method



compd	R2	yield, %	compd	R2	yield, %
4a	H	80	**4g**	4-CH_3S	53
4b	4-F	52	**4h**	3-CH_3	63
4c	4-Cl	70	**4i**	2-CH_3	80
4d	4-Br	60	**4j**	2-CH_3O	57
4e	4-CH_3	65	**4k**	2-CF_3	20
4f	4-CH_3O	67			

Table 2. Bromide–Lithium Exchange Method



compd	E+	R2	yield, %
4l	$B(OMe)_3$[a]	OH[b]	70
4m	S_8	SH	35
4n	Me_2NCHO	CHO	60
4o	TMS–N=C=O	$CONH_2$	40
4p	CF_3CO_2Et	$COCF_3$	45

[a] *n*BuLi was used in place of *t*-BuLi. [b] Alcohol was isolated after subsequent treatment of the intermediate borane with *N*-methylmorpholine-*N*-oxide.

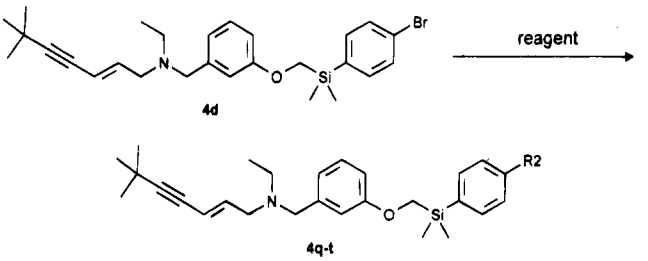
methylformamide, elemental sulfur,[20] or trifluoromethyl acetate[21] respectively yielded the silanes **4m**, **4n**, **4o**, and **4p**.

In the particular case of the preparation of phenol **4l**, the aryllithium intermediate was first quenched with trimethylboronate[22] and the so-formed boronate was then oxidized with an excess of *N*-methylmorpholine *N*-oxide. This oxidizing agent appears to be a reagent of choice to selectively oxidize a boronate intermediate in the presence of a tertiary amine, an ene–yne residue, and a silicon group, especially when compared to hydrogen peroxide, which is usually described for such type of transformation.[22]

4-Bromo-substituted (aryloxy)silane **4d** was also used to prepare a variety of other compounds, as reported in Table 3. Thus, the 4-cyano group (**4q**) was introduced with potassium cyanide and palladium diacetate;[23] the 4-vinyl group (**4r**) with vinyltributyltin and tetrakis(triphenylphosphine)palladium;[24] the 4-ethynyl group (**4s**) with (trimethylsilyl)acetylene, bis(triphenylphosphine)palladium(II), and copper chloride;[25] and the 3-thienyl group (**4t**) by a Suzuki coupling with 3-thienylboronic acid.[26]

The general method disclosed in Table 1 to prepare compounds of formula **4** (condensation of the (chloromethyl)arylsilanes **8** with phenol derivative **7**) was found not to be efficient when the arylsilane portion was

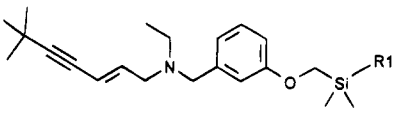
Table 3. Palladium Cross-Coupling Method



compd	reagent	R2	yield, %
4q	potassium cyanide $Pd(OAC)_2$, PPh_3, $Ca(OH)_2$, DMF	CN	45
4r	vinyltributyltin $Pd(PPh_3)_4$, toluene	$CH=CH_2$	84
4s	(trimethysilyl)acetylene $PdCl_2(PPh_3)_2$, CuI, $nBuNH_2$, THF[a]	CCH	40
4t	3-thienylboronic acid $Pd(PPh_3)_4$, Na_2CO_3, DME	3-C_4H_3S	70

[a] Yield is given after deprotection of the trimethylsilyl group using potassium fluoride dihydrate in dimethyl sulfoxide.

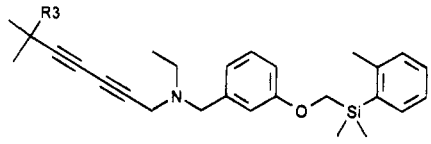
Table 4



compd	R1	IC_{50} pig liver (μM)	IC_{50} HepG2 cells (μM)[a]	ED_{50}: rat (mg/kg)
4a	Ph	0.15	0.5 (0.8)	20
4b	C_6H_4-(4-F)	0.06	5	>40
4c	C_6H_4-(4-Cl)	0.4	>10	>40
4d	C_6H_4-(4-Br)	0.21	>10	>40
4e	C_6H_4-(4-CH_3)	0.12	5	ND
4f	C_6H_4-(4-OCH_3)	0.87	>10	ND
4g	C_6H_4-(4-SCH_3)	1	>10	ND
4h	C_6H_4-(3-CH_3)	3	>10	ND
4i	C_6H_4-(2-CH_3)	0.03	0.12 (0.15)	3.80
4j	C_6H_4-(2-OCH_3)	0.15	5	>40
4k	C_6H_4-(2-CF_3)	0.07	1.48	20
4l	C_6H_4-(4-OH)	8	ND	ND
4m	C_6H_4-(4-$CONH_2$)	5	1	ND
4n	C_6H_4-(4-CHO)	0.10	0.14 (0.15)	20
4o	C_6H_4-(4-SH)	8	10	ND
4p	C_6H_4-(4-$COCF_3$)	5	ND	ND
4q	C_6H_4-(4-CN)	0.02	0.06 (0.07)	>40
4r	C_6H_4-(4-$CH=CH_2$)	0.07	1.32	>40
4s	C_6H_4-(4-$C\equiv CH$)	1	ND	ND
4t	C_6H_4-[2-(3-C_4H_3S)]	10	ND	ND
4u	C_6H_4-(2-CN)	0.03	0.08 (0.08)	7.0
4v	$PhCH_2$	0.13	>10	>40
4w	$PhCH_2CH_2$	>10	>10	ND
4x	C_6H_{11}	20	ND	ND

[a] Values given for inhibition of cholesterol biosynthesis from [^{14}C]mevalonate; values in parentheses indicate IC_{50} values obtained when [^{14}C]acetate is used as cholesterol precursor.

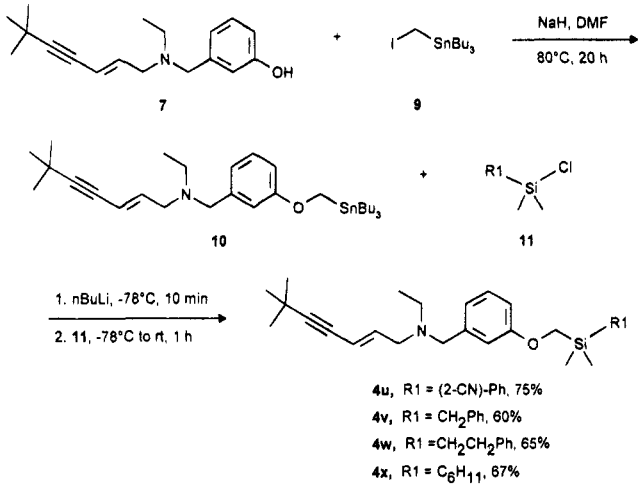
Table 5



compd	R3	IC_{50} pig liver (μM)	IC_{50} HepG2 cells (μM)[a]	ED_{50}: rat (mg/kg)
4′	CH_3	0.09	0.78	5
4″	OCH_3	0.07	0.29 (0.12)	1.80
NB-598		0.02	0.02 (0.02)	2.5
pravastatin		>10	>10 (0.43)	0.9

[a] Values given for inhibition of cholesterol biosynthesis from [^{14}C]mevalonate; values in parentheses indicate IC_{50} values obtained when [^{14}C]acetate is used as cholesterol precursor.

Scheme 3. Tin–Lithium Exchange Method

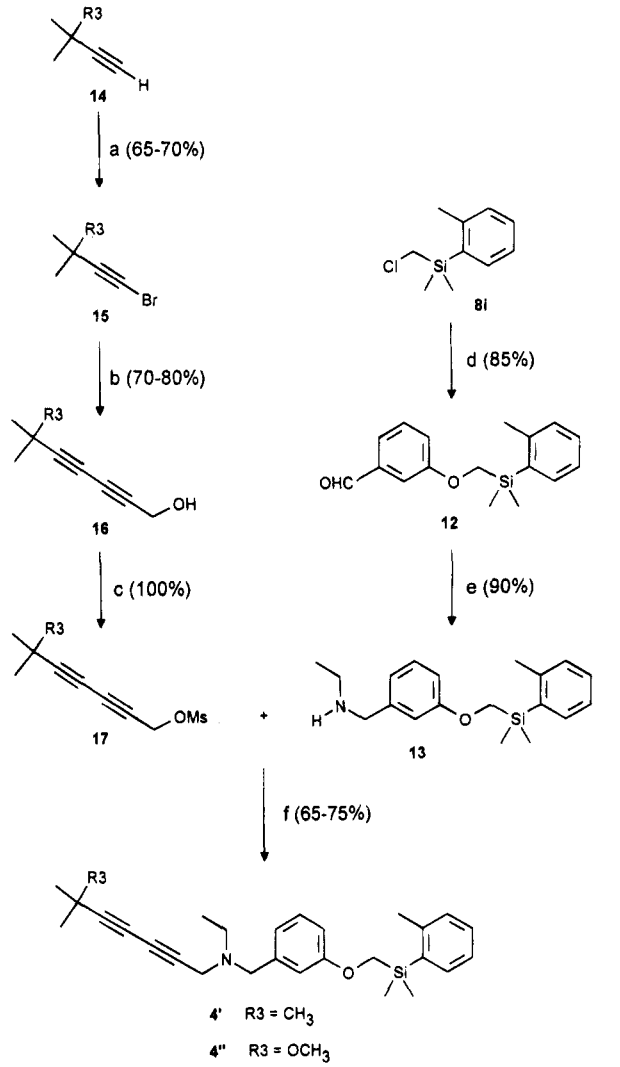


substituted with ortho-electron-withdrawing groups. For example, the yield of condensation product **4k** was only 20% in the case of chloromethyl(2-(trifluoromethyl)-phenyl)dimethylsilane. Moreover, this method was limited by the availability of the starting (chloromethyl)-silanes **8** due to their method of preparation involving highly basic and nucleophilic *n*-butyllithium. In order to solve this problem, another synthetic approach was studied in which the silane moiety was introduced by the formation of a carbon–silicon bond. This was achieved by condensing the appropriate α-lithio ether with a chlorosilane derivative **11** in tetrahydrofuran according to Scheme 3. The nucleophilic α-lithio ether intermediate was generated *in situ* by a tin–lithium exchange reaction triggered by treating the tributyltin derivative **10** with *n*-butyllithium in tetrahydrofuran at −78 °C. The preparation of **10** was readily achieved by alkylation of phenol **7** with iodotributyltin[27] and sodium hydride (Scheme 3).

Although the ene–yne part of NB-598 and derivatives is known to be very important for binding to mammalian squalene epoxidase, its replacement by an yne–yne moiety as well as the introduction of a terminal methoxy group was reported to give potent enzyme inhibitors with altered physicochemical properties.[8] In order to examine the role of this region of molecules in compounds of type **4**, the diynes **4′** and **4″** were synthesized by a convergent strategy depicted in Scheme 4.

The key step in the preparation of the diyne part (R = Me or R = OMe) was a Cadiot–Chodkiewicz coupling[28] between the bromoalkyne **15** and propargyl alcohol, affording **16** in a very straightforward manner. The arylsilane part was readily obtained starting from silane **8i** and 3-hydroxybenzaldehyde using a high yield alkylation-reductive amination sequence. Finally, coupling of the two parts was carried out through the mesylate **17** (R = Me or R= OMe) with triethylamine in dimethylformamide to result in the formation of **4′** and **4″**.

Scheme 4[a]



[a] (a) (i) *n*BuLi, Et_2O, −78 °C; (ii) Br_2, −70 °C to room temperature; (b) propargyl alcohol, $EtNH_2$ (70% H_2O), CuCl, NH_2OH·HCl, MeOH, 30–40 °C; (c) MsCl, Et_3N, THF, 0 °C (d) 3-hydroxybenzaldehyde, K_2CO_3, KI, DMSO, 80 °C; (e) (i) $EtNH_2$, EtOH, 20 °C; (ii) $NaBH_4$, EtOH, 20 °C; (f) Et_3N, DMF, room temperature.

Biological Results and Discussion

The compounds **4**, **4′**, and **4″** listed in Tables 4 and 5, respectively, were tested *in vitro* for their inhibitory activity against pig liver microsomal squalene epoxidase (conversion of [^{14}C]squalene to [^{14}C]squalene oxide) and for their ability to inhibit cholesterol biosynthesis in Hep-G_2 cells in culture from [^{14}C]mevalonate (and from [^{14}C]acetate for some of them). In addition, some of the most interesting compounds have also been evaluated *in vivo* as inhibitors of cholesterol biosynthesis from [^{14}C]acetate after a single oral administration in female rats. As indicated in Table 5, NB-598 and pravastatin

(a potent HMG-CoA reductase inhibitor) have also been evaluated in the same procedures for comparison purposes.

As expected, NB-598 was found to be a potent inhibitor of pig liver squalene epoxidase and cholesterol biosynthesis both in Hep-G_2 cells and *in vivo* in the rat. On the other hand, pravastatin was completely devoid of activity against squalene epoxidase and cholesterol biosynthesis in Hep-G_2 cells when [^{14}C]mevalonate was used as a radiolabeled precursor. According to previous reports, pravastatin was found to inhibit cholesterol biosynthesis from [^{14}C]acetate both in Hep-G_2 cells and *in vivo* in the rat. These results are in agreement with the reported mechanisms of action of these two inhibitors, since cholesterol biosynthesis starting from [^{14}C]-mevalonate can be reduced by a squalene epoxidase inhibitor but is not affected by an HMG-CoA reductase inhibitor. However, both types of inhibitors can be compared by using [^{14}C]acetate as a precursor of cholesterol biosynthesis. This is particularly interesting in the rat model in order to evaluate the therapeutic potential of squalene epoxidase inhibitors compared to clinically useful drugs like pravastatin. Data of Tables 4 and 5 clearly indicate that most of the newly reported (aryloxy)methylsilane derivatives of benzylamine **4**, **4′**, and **4″** are potent inhibitors of pig liver squalene epoxidase and offer some interesting indications concerning the substructural requirements around the silicon atom. For example, comparison of IC_{50} values at the enzymatic level (Table 4) between the silane derivatives **4a** and **4x** (where R_1 is respectively phenyl and cyclohexyl) as well as the results obtained with the benzyl- (**4v**) and phenethyl- (**4w**) substituted derivatives indicate the importance of an aromatic moiety directly attached to silicon. Introduction of substituents on the silicon-attached phenyl ring of the prototype compound **4a** was also found to affect the inhibitory properties of these compounds at the pig liver enzyme level. For example, 4-substitution with methoxy (**4f**), thiomethyl (**4g**), hydroxy (**4l**), thiol (**4o**), carbamoyl (**4m**), trifluoroacetyl (**4p**), ethynyl (**4s**), or 3-thienyl (**4t**) residues dramatically decreases the inhibitory potential of the parent derivative while, on the other hand, 4-substitution with fluorine (**4b**), methyl (**4e**), formyl (**4n**), cyano (**4q**), or vinyl (**4r**) residues results in an improvement of their inhibitory potential. An increase in activity is also observed with the introduction of methyl, methoxy, trifluoromethyl, or cyano substituents in the 2 position, as demonstrated with compounds **4i**, **4j**, **4k**, and **4u**.

It is noteworthy that while the introduction of a methyl group in 2 or 4 position of the phenyl silicon ring results in an increase of affinity, the 3-methyl substitution leads to an almost complete loss of activity (compare **4a**, **4e**, **4i**, and **4h** as inhibitors of pig liver SE).

Results recorded in Table 5 show that the yne−yne derivatives **4′** and **4″** (in which the silicon-attached phenyl ring is substituted in ortho position by a methyl group) are also very potent inhibitors of the enzyme, showing that the ene−yne nitrogen substituent can be replaced by an yne−yne side chain. In conclusion, the (aryloxy)methylsilane derivatives **4i**, **4q**, and **4u** are almost equipotent to NB-598 as inhibitors of microsomal pig liver squalene epoxidase.

Results obtained in Hep-G_2 cells when evaluating the silyl derivatives **4a−x**, **4′**, and **4″** indicate that some of the potent inhibitors of pig liver squalene epoxidase are also very good inhibitors of cholesterol biosynthesis from [^{14}C]mevalonate. In particular, the cyano derivatives **4q** and **4u** in the ene−yne series (Table 4) emerge as among the best compounds tested with IC_{50} values lower than 100 nM. Surprisingly, some potent pig liver squalene epoxidase inhibitors (compounds **4b**, **4k**, **4r**, or **4v**) were found to be modest inhibitors of cholesterol biosynthesis in Hep-G_2 cells. Moreover, in order to compare the potential of the (aryloxy)methylsilanes as inhibitors of cholesterol biosynthesis in Hep-G_2 cells with pravastatin, some of them have also been evaluated in the same model, but using [^{14}C]acetate as a precursor of radiolabeled cholesterol. Under these conditions, the squalene epoxidase inhibitors **4a**, **4i**, **4n**, **4q**, **4u**, and **4″** were found to inhibit strongly cholesterol biosynthesis, with IC_{50} values (Tables 4 and 5, values in brackets) which are remarkably close to the IC_{50} values obtained when [^{14}C]mevalonate is used as cholesterol precursor. These results show the high reliability of the cellular model to evaluate cholesterol biosynthesis inhibitors but also demonstrate that the (aryloxy)methylsilane derivatives have no direct effect at the HMG-CoA reductase level. Moreover, the IC_{50} values obtained with squalene epoxidase inhibitors compare very favorably with the potency observed for pravastatin (IC_{50} = 0.43 μM).

Interestingly enough, compounds **4i**, **4u**, **4′**, and **4″**, which have been identified as potent inhibitors of pig liver squalene epoxidase *in vitro* as well as potent inhibitors of cholesterol biosynthesis in Hep-G_2 cells, were also found capable of controlling *in vivo* cholesterol biosynthesis in rat upon oral administration. The ED_{50} values found for these new silane derivatives are very close to the ED_{50} values found for NB-598 and pravastatin, demonstrating that these new types of squalene epoxidase inhibitors are promising candidates for further studies as hypolipidemic agents. On the contrary, compound **4q**, a potent pig liver SE inhibitor (IC_{50} = 0.02 μM) with good activity in Hep-G_2 cells (IC_{50} = 0.06 μM), appeared to be very modest as inhibitor of *in vivo* cholesterol biosynthesis in the rat. Although comparisons between *in vitro* and *in vivo* data have to be considered carefully since we do not know the bioavailibility of these compounds, this could also be explained by differences between species like pig and rat in squalene epoxidase binding sites, as has been previously suggested.[29] Monitoring the formation of radiolabeled metabolites from [^{14}C]mevalonate in Hep-G_2 cells or [^{14}C]acetate in rats shows that (aryloxy)-methylsilane derivatives like **4i**, **4u**, **4′**, and **4″** as well as NB-598 can decrease the formation of cholesterol but at the same time lead to a concomitant increase of squalene (data not shown). This observation is in very good agreement with the hypothesis that these derivatives are able to control cholesterol biosynthesis by inhibiting squalene epoxidase. This, of course, differs totally from what is observed with pravastatin which does not lead to any accumulation of squalene or any intermediary metabolite between acetate and cholesterol.

Conclusions

We have described the synthesis and activity of a new class of squalene epoxidase inhibitors exemplified by the (aryloxy)methylsilane derivatives **4**, **4′**, and **4″**. Among

them, compounds **4i**, **4u**, **4'**, and **4''** were also identified as very potent inhibitors of cholesterol biosynthesis as demonstrated by the results obtained in Hep-G_2 cells and after oral administration of these compounds in rats.

Further studies concerning the hypolipidemic activity of these new squalene epoxidase are in progress in order to evaluate their therapeutic potential.

Experimental Section

General Experimental Methods—Procedures. All reactions were performed under a positive pressure of nitrogen or argon. Air or moisture sensitive compounds were introduced via syringe or cannula through a rubber septum.

Physical Data. Melting point were measured with a Kofler apparatus or a Electrothermal 9200 apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-200 (200 MHz) spectrometer. Data were reported as follows: chemical shift in ppm using residual proton solvent as internal standard (7.24 for $CDCl_3$, 2.50 for DMSO-d_6) on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet), coupling constant(s) in hertz, and integration. Elemental analyses were performed on a Erba Science 11108 CHN analyzer.

Chromatography. Analytical thin layer chromatography (TLC) was performed using silica gel F254 plates (Merck). Compounds were visualized by illumination with ultraviolet light (254 nm) or with iodine or by staining with one of the following reagents: *p*-anisaldehyde in ethanol–sulfuric acid or 7% phosphomolybdic acid in ethanol. Column chromatography (flash,[30] pressure 0.5–1 bar) was performed using silica gel 60 (0.040–0.063 mm, SDS).

Solvents and Reagents. Solvents were distilled and/or stored over 4 Å molecular sieves prior to use. Unless otherwise noted, all the reagents used were commercially available. Silanes **8a–k** were all prepared according to published procedures.[18]

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-hydroxybenzylamine (7). A mixture of 3-hydroxybenzaldehyde (20 g, 0.164 mol), an ethanol solution of ethylamine (1.9 M, 220 mL, 0.410 mol, 2.5 equiv), and 3 Å molecular sieves was stirred for 20 h at room temperature. After filtration over Celite and evaporation of the solvent, the resulting Schiff base was dissolved in ethanol (150 mL) and sodium borohydride (7.44 g, 0.2 mol, 1.2 equiv) was added by small portions. Stirring was continued for 2 h, and ethanol evaporated under reduced pressure. The residue was extracted with ethyl acetate and a saturated aqueous sodium chloride solution. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH 90/9/1 then 80/18/2) afforded *N-ethyl-3-hydroxybenzylamine* (**5**) as a white powder (19.8 g, 80%): ^{1}H NMR ($CDCl_3$) δ 7.12 (t, J = 7.5 Hz, 1H), 6.78–6.65 (m, 3H), 6.12 (brs, 1H, NH), 3.69 (s, 2H), 2.70 (q, J = 7.0 Hz, 2H), 1.15 (t, J = 7.0 Hz, 3H).

To a solution of **5** (15 g, 0.1 mol) in dimethyl sulfoxide (200 mL) were added (*E*)-1,3-dichloropropene (11.1 g, 0.1 mol, 1 equiv) and ground potassium carbonate (13.8 g, 0.1 mol, 1 equiv) under ice cooling. The mixture was stirred for 6 h at 50°C, and after cooling, diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2, 50/50 petroleum ether/ether) to provide *(E)-N-(3-chloropropenyl)-N-ethyl-3-hydroxybenzylamine* (**6**) as a yellow oil (16.9 g, 75%): ^{1}H NMR ($CDCl_3$) δ 7.12 (t, J = 7.5 Hz, 1H), 6.90–6.68 (m, 3H), 6.14 (d, J = 14 Hz, 1H), 6.00 (dt, J = 14.0, 6.2 Hz, 1H), 4.60 (brs, 1H), 3.54 (s, 2H), 3.10 (d, J = 6.2 Hz, 2H), 2.55 (q, J = 7.0 Hz, 2H), 1.06 (t, J = 7 Hz, 3H).

A suspension of palladium diacetate (198 mg, 0.088 mmol, 2%), copper iodide (420 mg, 2.2 mmol, 5%), and triphenylphosphine (464 mg, 1.76 mmol, 4%) in tetrahydrofuran (80 mL) was stirred at room temperature for a few minutes and to the resulting mixture was added amine **6** (10 g, 44.2 mmol) in tetrahydrofuran (80 mL). The reaction mixture was stirred for 1.5 h, then 3,3-dimethylbutyne (7.1 mL, 52.8 mmol, 1.2 equiv) was introduced and butylamine (8.5 mL, 88.8 mmol, 2 equiv) was added dropwise at 0°C. The reaction mixture was stirred for 24 h at room temperature and concentrated *in vacuo*. The resulting crude oil was purified by column chromatography on silica gel (hexanes/ethyl acetate 80/20 then 50/50) to afford **7** as a dark orange oil (9.6 g, 80%): ^{1}H NMR ($CDCl_3$) δ 7.17 (t, J = 8 Hz, 1H), 6.90–6.70 (m, 3H), 6.10 (dt, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.53 (s, 2H), 3.09 (d, J = 6.2 Hz, 2H), 2.50 (q, J = 7.0 Hz, 2H), 1.25 (s, 9H), 1.04 (t, J = 7.0 Hz, 3H).

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(phenyldimethylsilyl)methoxy]benzylamine (4a). A mixture of phenol **7** (500 mg, 1.84 mmol), and finely ground potassium carbonate (1.02 g, 7.36 mmol, 4 equiv) in dimethyl sulfoxide (10 mL) was heated at 90 °C for 30 min. After cooling, potassium iodide (458 mg, 2.76 mmol, 1.5 equiv) and (chloromethyl)phenyldimethylsilane (510 mg, 2.76 mmol, 1.5 equiv) in dimethyl sulfoxide (10 mL) were successively added. The reaction was stirred for 5 h at 90 °C and then, after cooling, partitioned between ethyl acetate and water. Separation of the layers and washing of the ethyl acetate layer with water was continued until the aqueous phase reached pH = 7. The aqueous fractions were extracted with ethyl acetate (×2) and the combined organic layers dried over magnesium sulfate. Filtration and solvent removal *in vacuo* gave the crude product which was purified by column chromatography (SiO_2, 95/5 petroleum ether/ether) to afford the title compound as a colorless oil (618 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 7.65–7.60 (m, 2H), 7.41–7.36 (m, 3H), 7.19 (m, 1H), 6.95–6.77 (m, 3H), 6.01 (dt, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.79 (s, 2H), 3.53 (s, 2H), 3.09 (d, J = 6.2 Hz, 2H), 2.50 (q, J = 7.0 Hz, 2H), 1.25 (s, 9H), 1.04 (t, J = 7.0 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{27}H_{37}NOSi$) C, H, N.

The following compounds were prepared in the same way as described for **4a**, starting from the appropriately substituted silanes **8**.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-fluorophenyl)dimethylsilyl)methoxy]benzylamine (4b). This compound was obtained from **7** (500 mg, 1.84 mmol) and (chloromethyl)(4-fluorophenyl)dimethylsilane (560 mg, 2.76 mmol, 1.5 equiv). Column chromatography over silica gel (95/05 petroleum ether/ether) gave **4b** as a colorless oil (425 mg, 52%): ^{1}H NMR ($CDCl_3$) δ 7.65–7.54 (m, 2H), 7.29–6.82 (m, 6H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.50 (q, J = 7.0 Hz, 2H), 2.38 (s, 3H), 1.28 (s, 9H), 1.05 (t, J = 7.0 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{27}H_{36}FNOSi$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-chlorophenyl)dimethylsilyl)methoxy]benzylamine (4c). This compound was obtained from **7** (500 mg, 1.84 mmol) and (chloromethyl)(4-chlorophenyl)dimethylsilane (605 mg, 2.76 mmol, 1.5 equiv). Column chromatography over silica gel (90/10 hexanes/ether) gave **4c** as a colorless oil (585 mg, 70%): ^{1}H NMR ($CDCl_3$) δ 7.60–7.42 (A_2B_2, 4H), 7.20 (t, J = 7.8 Hz, 1H), 7.00–6.80 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.50 (q, J = 7.0 Hz, 2H), 2.38 (s, 3H), 1.28 (s, 9H), 1.05 (t, J = 7.0 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{27}H_{36}ClNOSi$) C, H, N, Cl.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-bromophenyl)dimethylsilyl)methoxy]benzylamine (4d). This compound was obtained from **7** (500 mg, 1.84 mmol) and (chloromethyl)(4-bromophenyl)dimethylsilane (730 mg, 2.76 mmol, 1.5 equiv). Column chromatography over silica gel (90/10 hexanes/ether) gave **4d** as a colorless oil (550 mg, 60%): ^{1}H NMR ($CDCl_3$) δ 7.61–7.53 (A_2B_2, 4H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.77 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.50 (q, J = 7.0 Hz, 2H), 2.38 (s, 3H), 1.28 (s, 9H), 1.05, (t, J = 7.0 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{27}H_{36}BrNOSi$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-methylphenyl)dimethylsilyl)methoxy]benzylamine (4e).

This compound was obtained from **7** (500 mg, 1.84 mmol) and (chloromethyl)(4-methylphenyl)dimethylsilane (550 mg, 2.76 mmol, 1.5 equiv). Column chromatography over silica gel (90/10 hexanes/ether) provided **4e** as a colorless oil (519 mg, 65%): ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 2H), 7.18 (m, 3H), 7.02–6.80 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.11, (d, 2H, J = 6.2 Hz), 2.50 (q, J = 7.0 Hz, 2H), 2.38 (s, 3H), 1.28 (s, 9H), 1.05, (t, J = 7.0 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{39}NOSi$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(4-methoxyphenyl)dimethylsilyl)methoxy]benzylamine (4f). This compound was obtained from **7** (500 mg, 1.84 mmol) and (chloromethyl)(4-methoxyphenyl)dimethylsilane (593 mg, 2.76 mmol, 1.5 equiv). Column chromatography over silica gel (90/10 petroleum ether/ether) gave **4f** (554 mg, 67%): ^{1}H NMR ($CDCl_3$) δ 7.61–7.53 (m, 2H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 5H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.76 (s, 3H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.50 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05, (t, J = 7.0 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{39}NO_2Si$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(4-(thiomethyl)phenyl)dimethylsilyl)methoxy]benzylamine (4g). This compound was obtained from **7** (500 mg, 1.84 mmol) and (chloromethyl)(4-(thiomethyl)phenyl)dimethylsilane (636 mg, 2.76 mmol, 1.5 equiv). Column chromatography over silica gel (90/10 hexanes/ether) provided **4g** as a colorless oil (455 mg, 53%): ^{1}H NMR ($CDCl_3$) δ 7.58–7.48 (m, 2H), 7.31–7.15 (m, 3H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.76 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.58–2.45 (m, 5H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{39}NOSSi$) C, H, N, S.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3-methylphenyl)dimethylsilyl)methoxy]benzylamine (4h). This compound was obtained from **7** (500 mg, 1.84 mmol) and (chloromethyl)(3-methylphenyl)dimethylsilane (543 mg, 2.76 mmol, 1.5 equiv). Column chromatography over silica gel (90/10 hexanes/ether) gave **4h** (502 mg, 63%): ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 2H), 7.18 (m, 3H), 7.02–6.80 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.11 (d, 2H, J = 6.2 Hz), 2.50 (q, J = 7.0 Hz, 2H), 2.42 (s, 3H), 1.28 (s, 9H), 1.05, (t, J = 7.0 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{39}NOSi$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(2-methylphenyl)dimethylsilyl)methoxy]benzylamine (4i). This compound was obtained from **7** (500 mg, 1.84 mmol) and (chloromethyl)(2-methylphenyl)dimethylsilane (550 mg, 2.76 mmol, 1.5 equiv). Column chromatography over silica gel (95/05 hexanes/ether) afforded **4i** as a colorless oil (640 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 7.59–7.51 (m, 1H), 7.38–7.14 (m, 4H), 7.02–6.80 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.88 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.50 (q, J = 7.0 Hz, 2H), 2.50 (s, 3H), 1.28 (s, 9H), 1.05, (t, J = 7.0 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{39}NOSi$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(2-methoxyphenyl)dimethylsilyl)methoxy]benzylamine (4j). This compound was obtained from **7** (500 mg, 1.84 mmol) and (chloromethyl)(2-methoxyphenyl)dimethylsilane (550 mg, 2.76 m mol, 1.5 equiv). Column chromatography over silica gel (90/10 hexanes/ether) provided **4j** as a colorless oil (470 mg, 57%): ^{1}H NMR ($CDCl_3$) δ 7.61–7.53 (m, 2H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 5H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.76 (s, 3H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{39}NO_2Si$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((2-(trifluoromethyl)phenyl)dimethylsilyl)methoxy]benzylamine (4k). This compound was obtained from **7** (500 mg, 1.84 mmol) and (chloromethyl)(2-(trifluoromethyl)phenyl)-dimethylsilane (698 mg, 2.76 mmol, 1.5 equiv). Column chromatography over silica gel (90/10 hexanes/ether) afforded **4k** as a slightly yellow oil (178 mg, 20%): ^{1}H NMR ($CDCl_3$) δ 7.82–7.65 (m, 2H), 7.54–7.43 (m, 2H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{36}F_3NOSi$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-hydroxyphenyl)dimethylsilyl)methoxy]benzylamine (4l). A solution of **4d** (400 mg, 0.8 mmol) in tetrahydrofuran (10 mL) was treated at −78 °C with *n*-butyllithium (1.6 M in hexanes, 600 μL, 0.96 mmol, 1.2 equiv). The mixture is stirred at −78 °C for 30 min, treated with trimethylborate (268 μL, 2.4 mmol, 3 equiv) and allowed to warm to room temperature over a period of 2 h. An excess of *N*-methylmorpholine *N*-oxide (280 mg, 2.4 mmol, 3 equiv) was then added to the solution under a positive pressure of argon and the resulting suspension was refluxed for 4 h. After dilution in ether, the reaction mixture was hydrolyzed with water and the organic phase washed with water to reach pH = 7. The aqueous phases were extracted with ether and the combined etheral phases dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Column chromatography over silica gel (80/20 petroleum ether/ether) provided **4l** as a colorless oil (260 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 7.50–7.40 (m, 2H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H) 5.68 (d, J = 16.1 Hz, 1H), 3.69 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{27}H_{37}NO_2Si$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-thiophenyl)dimethylsilyl)methoxy]benzylamine (4m). A solution of **4d** (1g, 2 mmol) in tetrahydrofuran (10 mL) was treated at −78 °C with *tert*-butyllithium (2.58 mL of a 1.7 M in pentane, 4.4 mmol, 2.2 equiv). The mixture was stirred at −78°C for 30 min and treated with sulfur (28 mg, 0.88 mmol, 1.1 equiv). The reaction mixture was allowed to warm to room temperature over a period of 2 h and partitioned between ether and an aqueous solution of 1 N hydrochloric acid. The organic layer was washed with water until pH = 8, dried over magnesium sulfate, and concentrated *in vacuo*. Column chromatography over silica gel (80/20 petroleum ether/ether) gave **4m** (35%): ^{1}H NMR ($CDCl_3$) δ 7.65–7.32 (m, 4H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.77 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{27}H_{37}NOSiS$) C, H, N.

The following compounds were prepared in the same way as described for **4m**, starting from the appropriate electrophiles.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-formylphenyl)dimethylsilyl)methoxy]benzylamine (4n). This compound was obtained from **4d** (400 mg, 0.8 mmol) and dimethylformamide (770 μL, 10 mmol, 5 equiv). The crude oil obtained was purified by column chromatography over silica gel (90/10 hexanes/ether) to provide **4n** (510 mg, 54%): ^{1}H NMR ($CDCl_3$) δ 10.05 (s, 1H), 7.87 (A_2B_2, 4H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H) 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{37}NO_2Si$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-acetamidophenyl)dimethylsilyl)methoxy]benzylamine (4o). This compound was obtained from **4d** (400 mg, 0.8 mmol) and trimethylsilyl isocyanate (160 μL, 1.2 mmol, 1.5 equiv). Column chromatography over silica gel (95/4.5/0.5 CH_2Cl_2/MeOH/NH_4OH) gave **4o** as a white powder (144 mg, 40%): mp = 118 °C, ^{1}H NMR (CD_2Cl_2) δ 7.77 (A_2B_2, 4H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.80 (s, 2H), 3.50 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{38}N_2O_2Si$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-(trifluoroacetyl)phenyl)dimethylsilyl)methoxy]benzylamine (4p). This compound was obtained from **4d** (400 mg, 0.8 mmol) and ethyl trifluoroacetate (114 μL, 0.96 mmol, 1.1 equiv). Column chromatography over silica gel (75/25 hexanes/ether) gave **4p** (180 mg, 44%): ^{1}H NMR (CD_2Cl_2) δ 8.02 (A_2B_2, 4H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.76 (s, 3H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz,

2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{29}H_{36}NO_2SiF_3$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-cyanophenyl)dimethylsilyl)methoxy]benzylamine (4q). To a mixture of potassium cyanide (78 mg, 1.2 mmol, 1.5 equiv), calcium hydroxide (59 mg, 0.8 mmol, 1 equiv), palladium diacetate (2.7 mg, 0.12 mmol, 15%) and triphenylphosphine (63 mg, 0.24 mmol, 30%) was added a solution of **4d** (400 mg, 0.8 mmol) in dimethyformamide (5 mL). The mixture was heated to 140 °C for 1 h and on cooling, diluted in ether. The organic phase was washed with aqueous sodium bicarbonate solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography over silica gel (85/15 then 70/30 petroleum ether/ether) provided the title compound as an oil (160 mg, 45%): ^{1}H NMR ($CDCl_3$) δ 7.65 (A_2B_2, 2H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{36}N_2OSi$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-vinylphenyl)dimethylsilyl)methoxy]benzylamine (4r). A stirred mixture of **4d** (400 mg, 0.8 mmol), tetrakis(triphenylphosphine)palladium (20 mg, 2%), vinyltributyltin (258 μL, 0.88 mmol, 1.1 equiv), and toluene (8 mL) was heated under reflux for 3 h. After cooling, toluene was evaporated and the crude oil was purified by column chromatography over silica gel (100% petroleum ether then 75/25 petroleum ether/ether) to afford **4r** as a colorless oil (300 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 2H), 7.38 (AB, 2H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.68 (dd, J = 15.9, 10.9 Hz, 1H), 6.10 (td, 16.1/6.2 Hz, 1H), 5.76 (dd, J = 15.9, 0.8 Hz, 1H), 5.68 (d, J = 16.1 Hz, 1H), 5.24 (dd, J = 10.9, 0.8 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{29}H_{39}NOSi$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-ethynylphenyl)dimethylsilyl)methoxy]benzylamine (4s). To a solution of **4d** (500 mg, 1.0 mmol) and (trimethylsilyl)-acetylene (170 μL, 1.2 mmol, 1.2 equiv) in diethylamine (5 mL) were added copper iodide (20 mg, 1%) and bis(chloro)bis-(triphenylphosphine)palladium (140 mg, 2%). The mixture was stirred 20 h at room temperature, diluted in ether, and filtered through Celite. The etheral solution was concentrated in vacuo, and the crude product obtained (homogeneous by TLC) was treated with potassium fluoride (177 mg, 5 equiv) in dimethyl sulfoxide (10 mL) for 2 h at room temperature. The mixture was then diluted in ether and washed with water until neutral pH. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Column chromatography over silica gel (90/10 petroleum ether/ether) gave **4s** (110 mg, 40%): ^{1}H NMR ($CDCl_3$) δ 7.54 (A_2B_2, 47H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.11 (s, 1H), 3.08 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{29}H_{37}$-NOSi) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((4-(3-thienyl)phenyl)dimethylsilyl)methoxy]benzylamine (4t). To a suspension of tetrakis(triphenylphosphine)palladium (42 mg, 3%) in anhydrous dimethoxyethane (2 mL) was added a solution of aryl bromide **4d** (600 mg, 1.2 mmol) in dimethoxyethane (10 mL) and the mixture was stirred 10 min at room temperature. To this solution was added sequentially 3-thienylboronic acid (230 mg, 1.8 mmol, 1.5 equiv) and aqueous 2 M bicarbonate solution (1.2 mL, 2.4 mmol, 2 equiv). The mixture was refluxed for 5 h, cooled, diluted in ether, and washed with saturated aqueous sodium chloride solution to reach neutral pH. Drying over magnesium sulfate, filtration, and concentration *in vacuo* afforded a crude oil which was subjected to a column chromatography over silica gel (90/10 petroleum ether/ether) to lead to the title compound **4t** as an orange oil (404 mg, 67%): ^{1}H NMR ($CDCl_3$) δ 7.66 (A_2B_2, 4H), 7.48 (dd, J = 2.8, 2.10 Hz, 1H), 7.40–7.37 (m, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.08 (d, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{31}H_{39}NOSSi$) C, H, N, S.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-((tributylstannyl)methoxy)benzylamine (10). (Iodomethyl)-zinc iodide was prepared according to a slight modification of the Seyferth[27b] procedure.

To a zinc suspension (zinc foil, 10 g, 154 mmol) in tetrahydrofuran (12 mL) was added 1,2-dibromoethane (600 mg, 3 mmol), and the reaction mixture was heated to reflux for 1 min. After the mixture was cooled to 25 °C, chlorotrimethylsilane (0.3 mL, 2.4 mmol) was added and the activated zinc was stirred for 5 min. A THF solution (45 mL) of diiodomethane (40.1 g, 150.0 mmol) was added at room temperature within 15 min. Stirring was then continued for 6 h at this temperature and a solution of tributyltin chloride (23.1 mL, 85 mmol) in tetrahydrofuran was added within 30 min. The resulting mixture was stirred 18 h at 25 °C, diluted with petroleum ether, and washed with water. After drying over sodium sulfate, the solvent was removed at reduced pressure and vacuum distillation gave *(iodomethyl)tributyltin* (**9**) as a stable, colorless oil (30 g, 82%) (bp = 110 °C/0.10 mmHg).

To a solution of phenol **7** (10 g, 37 mmol) in dimethylformamide (150 mL) was added sodium hydride (1.8 g, 44.2 mmol, 1.2 equiv) portionwise at 0 °C. Stirring was continued for 1 h at room temperature and the resulting solution was treated with (iodomethyl)tributyltin (**9**) (17.5 g, 40.5 mmol, 1.1 equiv) in dimethylformamide (50 mL). The mixture was heated at 100 °C for 24 h and, after cooling, diluted in ether, washed with water to reach pH = 7, and dried over magnesium sulfate. Filtration and concentration *in vacuo* afforded a crude oil which was subjected to column chromatography (90/10 petroleum ether/ether) to provide **10** as an oil (9.5g, 45%): ^{1}H NMR ($CDCl_3$) δ 7.22 (t, J = 7.5 Hz, 1H), 6.95–6.75 (m, 3H), 6.10 (dt, J = 16.1, 6.2 Hz, 1H), 5.68 (d, J = 16.1 Hz, 1H), 4.15 (s, 2H), 3.53 (s, 2H), 3.09 (d, J = 6.2 Hz, 2H), 2.50 (q, J = 7.0 Hz, 2H), 1.65–1.27 (m, 12H), 1.25 (s, 9H), 1.04 (t, J = 7.0 Hz, 3H), 1.00–0.78 (m, 15H). Anal. ($C_{31}H_{53}NOSn$), C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[((2-cyanophenyl)dimethylsilyl)methoxy]benzylamine (4u). A solution of **10** (500 mg, 0.85 mmol) in tetrahydrofuran (10 mL) was treated at −78 °C with *n*-butyllithium (1.6 M in hexanes, 690 μL, 1.10 mmol, 1.3 equiv). The mixture was stirred at −78 °C for 15 min and chloro(2-cyanophenyl)dimethylsilane (200 mg, 1.02 mmol, 1.2 equiv) was then added. The resulting solution was allowed to warm up to room temperature in 1 h diluted with ether and extracted with water. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Column chromatography over silica gel (90/10 petroleum ether/ether) gave **4u** (160 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 7.70–7.44 (m, 4H), 7.28–7.15 (m, 1H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.94 (s, 2H), 3.55 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.56 (s, 6H). Anal. ($C_{28}H_{36}N_2OSi$) C, H, N.

The following compounds were prepared in the same way as described for **4u**, starting from the appropriate commercially available chlorosilanes **11**.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(benzyldimethylsilyl)methoxy]benzylamine (4v). This compound was obtained from **10** (500 mg, 0.85 mmol) and benzyldimethylchlorosilane (188 mg, 1.02 mmol, 1.2 equiv). Column chromatography over silica gel (90/10 petroleum ether/ether) afforded **4v** as a colorless oil (227 mg, 60%): ^{1}H NMR ($CDCl_3$) δ 7.23–7.07 (m, 6H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.52 (s, 4H), 3.11 (d, J = 6.2 Hz, 2H), 2.52 (q, J = 7.0 Hz, 2H), 2.24 (s, 2H), 1.28 (s, 9H), 1.05 (t, J = 7 Hz, 3H), 0.1 (s, 6H). Anal. ($C_{28}H_{39}$-NOSi) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(phenethyldimethylsilyl)methoxy]benzylamine (4w). This compound was obtained from **10** (500 mg, 0.85 mmol) and phenethyldimethylchlorosilane (260 mg, 1.3 mmol, 1.5 equiv). Column chromatography over silica gel (95/5 petroleum ether/ether) afforded **4w** as a colorless oil (150 mg, 65%): ^{1}H NMR ($CDCl_3$) δ 7.30–7.13 (m, 6H), 6.98–6.72 (m, 3H), 6.10 (dt, J = 16.1, 6.2 Hz, 1H), 5.68 (d, J = 16.1 Hz, 1H), 3.55 (s, 2H), 3.51

(s, 2H), 3.09 (d, J = 6.2 Hz, 2H), 2.75–2.66 (m, 2H), 2.50 (q, J = 7.0 Hz, 2H), 1.25 (s, 9H), 1.10–0.99 (m, 5H), 0.12 (s, 6H). Anal. ($C_{29}H_{41}NOSi$) C, H, N.

(*E*)-*N*-Ethyl-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(cyclohexyldimethylsilyl)methoxy]benzylamine (4x). This compound was obtained from **10** (500 mg, 0.85 mmol) and cyclohexyldimethylchlorosilane (200 mg, 1.13 mmol, 1.3 equiv). Column chromatography over silica gel (95/5 petroleum ether/ether) afforded **4x** as a colorless oil (147 mg, 67%): ^{1}H NMR ($CDCl_3$) δ 7.22 (t, J = 7.5 Hz, 1H), 6.95–6.75 (m, 3H), 6.10 (dt, J = 16.1, 6.2 Hz, 1H), 5.68 (d, J = 16.1 Hz, 1H), 3.56 (s, 2H), 3.50 (s, 2H), 3.09 (d, J = 6.2 Hz, 2H), 2.50 (q, J = 7.0 Hz, 2H), 1.82–1.55 (m, 6H), 1.35–1.10 (m, 15H), 1.04 (t, J = 7.0 Hz, 3H), 0.90–0.82 (m, 1H), 0.05 (s, 6H). Anal. ($C_{27}H_{43}NOSi$) C, H, N.

Representative procedures are given below for the preparation of **4''** (R_3 = OMe) and are identical for **4'** (R_3 = Me).

1-Bromo-3-methoxy-3-methylbutyne (15). To a solution of 3-methoxy-3-methylbutyne (**14**) (105 g, 1.07 mol) prepared according to a published procedure[31] in anhydrous ether (750 mL) was added *n*-butyllithium (10 M in hexanes, 128 mL, 1.28 mol, 1.2equiv) at −78 °C. The reaction mixture was then stirred for 1 h at this temperature and addition of bromine (56 mL, 1.07 mol, 1 equiv) was carried out between −78 and −50 °C by maintaining the inner temperature by cooling with a liquid nitrogen bath. The resulting orange solution was allowed to warm to room temperature and hydrolyzed with water. The organic layer was washed with water to reach pH = 7, and the aqueous phases were extracted with ether. The etheral phases were dried over magnesium sulfate, filtered, and concentrated *in vacuo* (~40 mmHg) at room temperature to remove the volatils. Further distillation of the residue under reduce pressure (50 °C/25 mmHg) provided the title compound (120 g, 65%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3H), 1.45 (s, 6H).

3-Methoxy-3-methyl-2,4-heptadiyn-1-ol (16). Cadiot coupling was carried out by dissolving sequentially ethylamine (70% in water, 200 mL, 3.1 mol, 7 equiv), anhydrous copper chloride (1 g, 10 mmol, 0.024 equiv), hydroxylamine hydrochloride (5 g, 72 mmol, 0.17 equiv), and propargyl alcohol (26.5 mL, 0.446 mol, 1.1 equiv) in methanol (500 mL) to produce a yellow suspension. Dropwise addition of 1-bromo-3-methoxy-3-methylbutyne (**14**) (74 g, 0.42 mol) in methanol (100 mL) between 20 and 40 °C in 1 h resulted in a homogeneous solution. Stirring was then continued for 1 h at room temperature and the solvent evaporated. Water and ethyl acetate were added, and the insoluble material was removed by filtration. The aqueous layer separated was extracted with ethyl acetate, and the combined organic phases were dried over magnesium sulfate. Filtration and evaporation *in vacuo* afforded an oil which was purified by vacuum distillation (93–97 °C/2 mmHg) to give the expected alcohol as a colorless oil (53 g, 81%): ^{1}H NMR ($CDCl_3$) δ 4.28 (s, 2H), 3.31 (s, 3H), 3.10 (brs, 1H), 1.42 (s, 6H).

3-Methoxy-3-methyl-2,4-heptadiynyl-1-methanesulfonate (17). To a 0 °C cooled solution of alcohol **16** (7.3 g, 47.6 mmol) and triethylamine (15 mL, 110 mmol, 2.25 equiv) in tetrahydrofuran (150 mL) was added dropwise methanesulfonyl chloride (5.14 mL, 52.3 mmol, 1.1 equiv). The reaction mixture was stirred 1 h at room temperature and then filtered over silica gel (fast plug) eluting with ether in order to remove the precipitate and triethylamine. Evaporation of the solvent *in vacuo* afforded the title compound as an orange oil (12 g, 100%) pure enough to be used in the next step without further purification.

(*E*)-*N*-Ethyl-3-[((2-methylphenyl)dimethylsilyl)methoxy]benzylamine (13). 3-Hydroxybenzaldehyde (2 g, 16.4 mmol), finely ground potassium carbonate (8.16 g, 59.1 mmol, 3 equiv), potassium iodide (3.27 g, 19.7 mmol, 1.2 equiv), and dimethyl sulfoxide (50 mL) were mixed and heated to 80 °C. Addition of (chloromethyl)phenyldimethylsilane (3.9 g, 19.7 mmol, 1.2 equiv) in one portion was then carried out. The reaction was stirred for 2 h at 80 °C, and after cooling, the mixture was partitioned between ethyl acetate and water. Separation of the layers and washing of the ethyl acetate layer with water was continued to reach pH = 7. The aqueous fractions were extracted with ethyl acetate (×2) and the combined organic layers dried over magnesium sulfate. Filtration and solvent removal *in vacuo* gave the crude product which was purified by column chromatography (SiO_2, 80/20 petroleum ether/ether) to afford **12** as a colorless oil (4.2 g, 90%): ^{1}H NMR ($CDCl_3$) δ 9.98 (s, 1H), 7.55–7.12 (m, 3H), 3.91 (s, 2H), 2.52 (s, 3H), 0.50 (s, 6H).

Aldehyde **12** (3.8 g, 13.4 mmol), ethylamine (1.9 M, 50 mL) and 3 Å molecular sieves were mixed, the resulting mixture was stirred for 20 h at room temperature and filtered over Celite, and the solvent was evaporated in vacuo. The resulting oil was dissolved in ethanol (100 mL) and treated with sodium borohydride (1 g, 26.4 mmol, 2 equiv). Stirring was continued for 2 h, and ethanol was evaporated under reduced pressure. The residue was extracted with ethyl acetate and a saturated aqueous sodium chloride solution. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH 90/9/1) afforded **13** as a colorless oil (4.16 g, 95%): ^{1}H NMR ($CDCl_3$) δ 7.56–7.51 (m, 1H), 7.37–7.15 (m, 4H), 6.98–6.85 (m, 3H), 3.88 (s, 2H), 3.78 (s, 2H), 2.68 (q, J = 7.0 Hz, 2H), 2.52 (s, 3H), 1.41 (brs, 1H), 1.15 (t, J = 7.0 Hz, 3H), 0.49 (s, 6H). Anal. ($C_{19}H_{27}NOSi$) C, H, N.

Compounds **4'** and **4''** were prepared according to the same following procedure.

To a solution of amine **13** (1.5 g, 4.78 mmol) and triethylamine (1.33 mL, 9.6 mmol, 2 equiv) in dimethylformamide (20 mL) was added a solution of mesylate **17** (R = Me or OMe), (7.2 mmol, 1.5 equiv) in dimethyformamide (10 mL). The reaction mixture was stirred for 15 h at room temperature, diluted with ether, and washed with water (x2). The aqueous phases were extracted with ether and the combined organic layers dried over magnesium sulfate. Filtration and solvent removal *in vacuo* gave the crude product which was purified by column chromatography (SiO_2, 90/10 petroleum ether/ether) to afford **4'** or **4''**.

***N*-Ethyl-*N*-(6,6-dimethyl-2,4-heptadiynyl)-3-[((2-methylphenyl)dimethylsilyl)methoxy]benzylamine (4'):** white powder, mp = 69 °C: ^{1}H NMR ($CDCl_3$) δ 7.51–7.47 (m, 1H), 7.28–7.15 (m, 4H), 7.01–6.82 (m, 3H), 3.84 (s, 2H), 3.59 (s, 2H), 3.40 (s, 2H), 2.60 (q, J = 7.0 Hz, 2H), 2.50 (s, 3H), 1.26 (s, 6H), 1.10 (t, J = 7.0 Hz, 3H), 0.47 (s, 6H). Anal. ($C_{28}H_{37}NOSi$) C, H, N.

***N*-Ethyl-*N*-(6-methoxy-6-methyl-2,4-heptadiynyl)-3-[((2-methylphenyl)dimethylsilyl)methoxy]benzylamine (4''):** ^{1}H NMR ($CDCl_3$) δ 7.51–7.47 (m, 1H), 7.28–7.15 (m, 4H), 7.01–6.82 (m, 3H), 6.10 (td, J = 16.1, 6.2 Hz, 2H), 5.68 (d, J = 16.1 Hz, 1H), 3.82 (s, 2H), 3.55 (s, 2H), 3.40 (s, 2H), 3.35 (s, 3H), 2.58 (q, J = 7.0 Hz, 2H), 2.50 (s, 3H), 1.28 (s, 6H), 1.05 (t, J = 7 Hz, 3H), 0.45 (s, 6H). Anal. ($C_{28}H_{37}NO_2Si$) C, H, N.

Squalene Epoxidase Activity in Pig Liver. The microsomal squalene epoxidase activity was assayed according to a published procedure[32] with some modifications.

The microsomes from pig liver were solubilized with 10% Triton X-100 in 0.1 M Tris-HCL buffer, pH 7.5. The standard assay mixture consisted of a total volume of 1 mL containing 955 μL of solubilized microsomes (1 mg/mL protein containing 1 mM EDTA and 1 mM DTT); *N*,*N*-dimethyldodecylamine *N*-oxide, an inhibitor of oxidosqualene cyclase (0.1 mM), FAD (0.1 mol); NADPH (2 mM); and [^{14}C]squalene (0.16 μM) dispersed with the aid of Tween 80. Compounds were dissolved in dimethyl sulfoxide (final 0.1%). The enzyme reaction was started by adding NADPH. Assays were performed at 37 °C for 60 min. The reaction was terminated by adding 1 mL of methanolic KOH. The mixture was saponified for 1 h at 22 °C, and nonsaponifiable materials were extracted with petroleum ether and chromatographed on silica gel TLC plates using hexanes/ethyl acetate (97/3). After developing the plate with a TLC linear analyzer (Berthold), the squalene epoxide is quantified and the test compound activity (IC_{50}) is calculated as the concentration of compound giving 50% inhibition of squalene epoxide synthesis relative to the control assay.

Inhibition of Cholesterol Biosynthesis in Hep-G_2 Cells. Hep-G_2 cells in culture are used as described previously[15] with slight modifications. Cells are cultured in 12-well plates in DMEM with 10% fetal calf serum until they become subcon-

fluent and then are transfered into DMEM plus ultroser G 2% for a further 48 h. After a 1 h incubation period with various selective modulators of the cholesterol synthesis or their respective vehicles (DMSO 0.1%), [^{14}C]mevalonate (1 μCi/mL) is added for 4 h. Then, the cells are washed with a cold phosphate buffer and dissolved in aqueous KOH, and the cell lysate is saponified in ethanolic KOH at 75 °C for 1 h. The nonsaponifiable lipids are extracted, separated by TLC (solvent system composed by hexanes/ethyl ether/acetic acid 85/15/4), and the plate is read with a linear analyzer (Berthold).

The inhibition of cholesterol biosynthesis was determined by comparing the percentage of [^{14}C]cholesterol formed in drug-treated cells with that in control cells. Respective inhibitory concentrations 50% were calculated.

Acute Inhibition of Cholesterol Synthesis in Rats. Studies of cholesterol biosynthesis *in vivo* were carried out as described previously[14] with some modifications.

Female SD rats weighing 60–80 g were obtained from IFFA CREDO. Rats were kept for 11 days in an environment of reversed light cycle (i.e., dark between 5:00 a.m. and 5 p.m.). The rats were allowed to take a solid diet and water freely. At 9:00 a.m., rats were given a single dose of compounds suspended in an aqueous solution containing 2% of dimethyl sulfoxide and 5% Tween 80. The volume of administration was 1 mL/100 g of body weight. One hour after drug administration, the rats were injected intraperitoneally with [^{14}C]acetate at 80 μCi/kg of weight. One hour later, animals were sacrified and livers were removed, washed, homogenized, and hydrolyzed with methanolic KOH. Nonsaponified materials were extracted with petroleum ether and spotted on silica TLC plate. The plate was developed with a solvent system composed of hexanes/ethyl ether/acetic acid (85/15/4) and analyzed with a linear analyzer (Berthold). The inhibition of cholesterol biosynthesis was determined by comparing the percentage of [^{14}C]cholesterol biosynthesized in the test group with that in the control group. Mean ED_{50} values (level of drug required to suppress cholesterol synthesis *in vivo* by 50%) were calculated from at least two experiments.

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