Zwitterionic Sulfobetaine Inhibitors of Squalene Synthase

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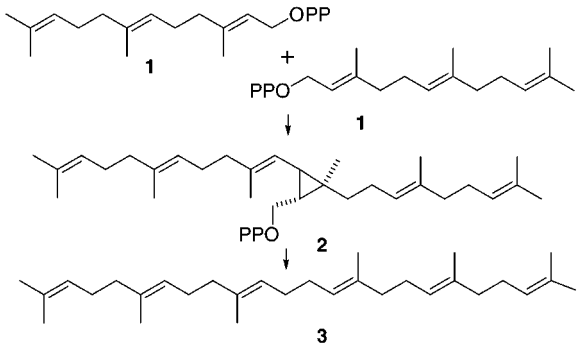
Received August 7, 1998

A substantial number of sulfobetaines (e.g., **10**) have been synthesized and evaluated as inhibitors of squalene synthase (SS) on the basis of the idea that their zwitterionic structure would have properties conducive both to binding in the active site and to passage through cell membranes. When the simple sulfobetaine moiety is incorporated into compounds containing hydrophobic portions like those in farnesyl diphosphate (**1**) or presqualene diphosphate (**2**), inhibition of SS in a rat liver microsomal assay was indeed observed. For example, farnesylated sulfobetaine **10** has $IC_{50} = 10\ \mu M$ and aromatic derivative **35** has $IC_{50} = 2\ \mu M$ for SS inhibition. A wide variety of structural modifications, exemplified by compounds **43**, **52**, **76**, **85**, **91**, **99**, **111**, and **115**, was investigated. Unfortunately, no inhibitors in the submicromolar range were discovered, and exploration of a different type of zwitterion seems necessary if this appealing approach to inhibition of SS is going to provide a potential antihypercholesterolemic agent.

In recent years, there have been extensive efforts directed toward development of inhibitors of squalene synthase (SS),[1] the enzyme that catalyzes the remarkable reductive dimerization of two farnesyl diphosphates (FPP, **1**) via presqualene diphosphate (PSP, **2**) to form squalene (**3**) (Scheme 1). These efforts have been prompted by the possible need for SS inhibitors as an alternative to the statin class of HMG-CoA reductase inhibitors as cholesterol lowering agents. The latter class of drugs has to date been notably successful in clinical practice,[2] but, because they are inhibitors of the rate-limiting step in the isoprenoid biosynthetic pathway, they have the potential for depletion of essential nonsterol isoprenoid metabolites.[3] As the catalyst of the first step in cholesterol biosynthesis committed exclusively to sterol formation, SS presents an attractive target for inhibition that does not present this potential drawback.

An impressive array of structurally diverse inhibitors of SS has been reported, and these have recently been authoritatively reviewed.[1] Extensive modifications of both the hydrophobic and polar portions of **1** and **2** have been explored in analogues. Among the most impressive of these have been FPP analogues developed at Bristol-Myers Squibb containing modified diphosphate moieties, including the first highly potent such compound **4**[4] and the more recent **5**, which is active in vivo (Scheme 2).[5] Natural product screening revealed the extremely potent

Scheme 1



zaragozic acids (squalestatins), e.g., zaragozic acid A (**6**).[6] Compounds containing ammonium ions have been successfully used as mimics of putative carbocation intermediates in the conversions of both **1** to **2** and **2** to **3**.[1] Incorporation of an appropriate surrogate for the diphosphate group has been essential in the design of SS inhibitors, because compounds containing that moiety are labile to esterases and have difficulty crossing cell membranes due to their strong charge.[1] On the other hand, it has been suggested that anionic character is necessary for binding to SS.[7] We have been exploring a new approach to incorporation of these requisite at-

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‡ Uniformed Services University of the Health Sciences.

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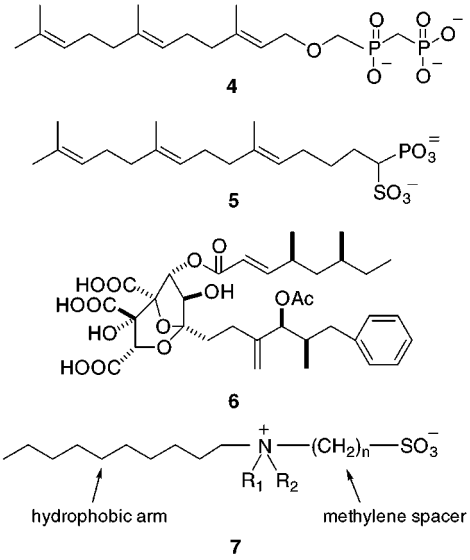
10.1021/jo981617q CCC: $18.00
Published on Web 01/20/1999

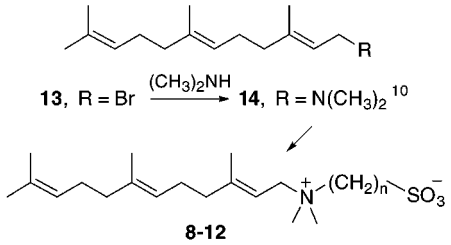
Scheme 2



tributes in SS inhibitors by use of simple zwitterionic sulfobetaines of the type shown schematically in **7**. This paper describes the preparation and preliminary biological evaluation of a number of zwitterionic sulfobetaines designed to mimic either FPP (**1**) or PSP (**2**).[8]

Sulfobetaines, which are zwitterions containing an ammonium cation and a sulfonate anion, are well-known for their surfactant properties and have a variety of commercial uses.[9] Our initial efforts were directed at determining whether sulfobetaines such as **7** would, in fact, inhibit SS and, if so, what the optimum separation between the ionic centers would be. To this end, zwitterions **8**−**12**, containing connectors of two to six methylene groups between the ammonium and sulfonate ions, were synthesized as outlined in Scheme 3. Two standard methods were employed throughout these studies for preparing the sulfobetaine zwitterionic moieties from the appropriate amine precursor, such as farnesyldimethylamine (**14**).[10] The procedure of Barnhurst,[11] consisting in successive treatment of the amine with an excess of α,ω-dibromoalkane and then sodium sulfite, is suitable for construction of **7** with a methylene spacer of any length. Sulfobetaines with three or four methylene units separating the charges (**7**, $n = 3$ or 4) can alternatively be prepared by treatment of the appropriate amine with 1,3-propane sultone or 1,4-butane sultone (**15**), respectively.[12] During application of these methods, it was found that purification of the various sulfobetaines could usually be best effected by reversed-phase flash chromatography. However, the purified sulfobetaines were generally quite hygroscopic and seldom gave good combustion analyses.

Scheme 3



Reagents Used with **14**	Compound Produced	IC_{50} (μM)
1) $BrCH_2CH_2Br$; 2) Na_2SO_3	**8**, n = 2	200
	**9**, n = 3	200
 **15**	**10**, n = 4	15
1) $Br(CH_2)_5Br$; 2) Na_2SO_3	**11**, n = 5	200
1) $Br(CH_2)_6Br$; 2) Na_2SO_3	**12**, n = 6	200

Compounds **8**−**12** were evaluated as SS inhibitors in a standard microsomal assay.[13] The results, indicated in Scheme 3 as IC_{50} values, show that this type of zwitterion indeed can inhibit the action of SS and that a separation of four methylene groups between the charges, as in **10**, clearly provides the most effective inhibition. Interestingly, the total chain length of **10** is one atom longer than that in Biller's potent inhibitor **4**[4] and two atoms longer than FPP (**1**).

Encouraged that farnesyl sulfobetaines did indeed have potential as SS inhibitors, we explored modifications in structure to try to establish the requirements for increased effectiveness. First, to determine if the methyl substituents on **10** were undesirably bulky, zwitterion **18** was prepared (Scheme 4) from farnesylamine (**17**),[14] but it was found to be inferior to **10** as an SS inhibitor. Previous observations that similar substitution on the ammonium ion in this type of SS inhibitor is actually advantageous have been made,[15] although the reasons for this remain obscure. Next, the sulfonate anion in **10** was replaced by a carboxylate group in **19**, prepared by alkylation of **14** with ethyl 5-bromovalerate (Scheme 4), but **19** also proved to be inferior to **10** as an SS inhibitor.

Changing the size of the hydrophobic farnesyl moiety was then explored. By use of geranyl or prenyl bromide instead of **13** in the standard sulfobetaine synthetic sequences, compounds **20**−**22** were prepared. These compounds were poor SS inhibitors, as might have been anticipated on the basis of analogous changes in other types of SS inhibitors.[16] The farnesyl moiety was also shortened by one carbon atom in **24**, to place the ammonium ion at the same relative position as the terminus of the putative allylic carbocation formed from

(7) (a) Magnin, D. R.; Biller, S. A.; Dickson, J. K., Jr.; Logan, J. V.; Lawrence, R. M.; Chen, V.; Sulsky, R. B.; Ciosek, C. P., Jr.; Harrity, T. W.; Jolibois, K. G.; Kunselman, L. K.; Rich, L. C.; Slusarchyk, D. A. *J. Med. Chem.* **1995**, *38*, 2596. (b) Castro, A.; Erickson, S. K.; Shechter, I.; Spencer, T. A. *Bioorg. Chem.* **1996**, *24*, 242.

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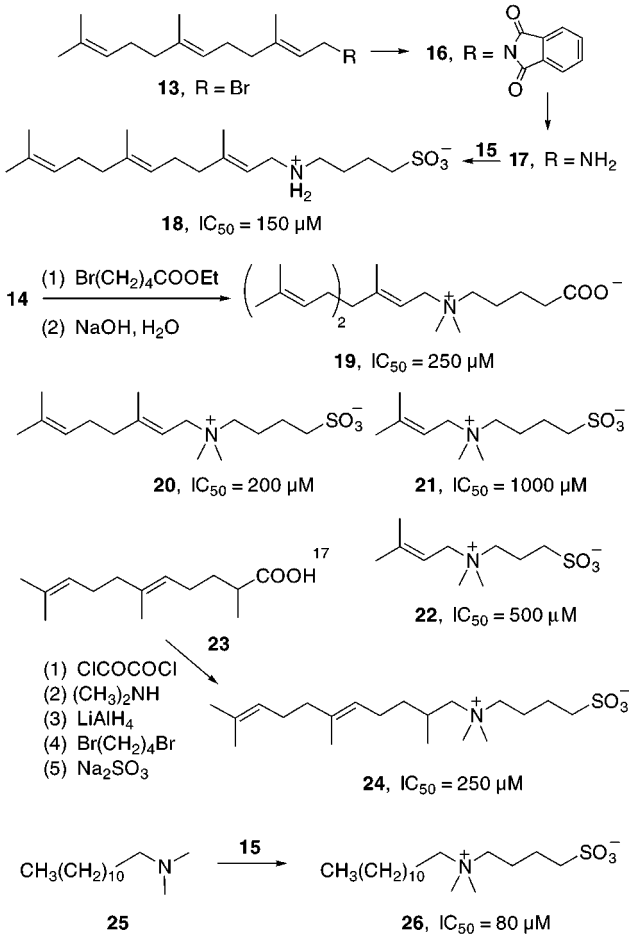
Scheme 4



FPP (**1**). Compound **24** was prepared from known carboxylic acid **23**[17] by the steps shown in Scheme 4, but it exhibited distinctly disappointing SS inhibition.

Introduction of aromatic rings into the hydrophobic portion of a variety of SS inhibitors has proved effective,[1] and aromatic rings are found at the ends of at least one of the side chains in the zaragozic acids (e.g., **6**). It was therefore decided to incorporate a phenyl group at the end of the hydrocarbon portion of zwitterionic sulfobetaine inhibitors. Since it would be easiest to prepare such compounds in which the phenyl group was connected to the sulfobetaine moiety by a straight-chain alkyl group, the effect of replacing the farnesyl group in **10** by a dodecyl group, as in **26** (Scheme 4), was examined first. Compound **26** was readily prepared from dimethyldodecylamine (**25**) and was found to have $IC_{50} = 80\ \mu M$, reduced only by a factor of about 5 relative to **10**. This result suggested that we proceed with a study of compounds such as **31**−**36**, having methylene connectors of varied length between the ammonium ion moiety and a phenyl group, and these were synthesized, as shown in Scheme 5, by reaction of **15** with the appropriate ω-phenylalkyldimethylamine, prepared in the case of **27**−**30** via monophenylation of the appropriate α,ω-dibromide. Evaluation of **31**−**36** in the microsomal SS assay gave the IC_{50} values indicated and showed that **35**, with a connector of nine carbons, is the best inhibitor, having $IC_{50} = 2\ \mu M$, almost 1 order of magnitude more potent than **10**.

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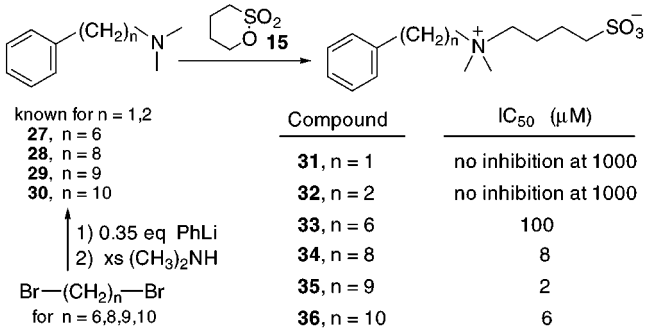
Scheme 5



Compound	IC_{50} (μM)
31, n = 1	no inhibition at 1000
32, n = 2	no inhibition at 1000
33, n = 6	100
34, n = 8	8
35, n = 9	2
36, n = 10	6

Since introduction of one aromatic ring had afforded the best zwitterionic SS inhibitor developed so far, the effect of incorporation of a second phenyl group was explored next with compounds **40**, **43**, **47**, and **52**. The syntheses of these compounds are outlined in Scheme 6. Preparation of **40** proceeded from the known **37**, prepared via Friedel−Crafts acylation,[18] and synthesis of **52** followed an analogous sequence, starting from biphenylmethylene. Preparation of **43** and **47** was based on work by Lee et al.,[19] who had previously prepared bromide **41**, which could be transformed in standard manner to **42** and **43**. Analogous alkyne coupling led to homologue **44**, which was carried on to **47**. Biological evaluation of **40**, **43**, **47**, and **52** showed that **43**, with five methylene groups between the phenyl group and the nitrogen, is the best SS inhibitor, with an IC_{50} value of 5 μM, almost as good as that of **35**.

Further variations of **35**, the best SS inhibitor thus far prepared, were also undertaken to try to achieve IC_{50} values in the nM range. The presence of electronegative atoms in the otherwise hydrophobic chains of previously described effective SS inhibitors[20] prompted synthesis of **54** and **56**, which proceeded smoothly as described in Scheme 7. However, these compounds were somewhat less effective than **35**. Introduction of some of the unsaturation of the farnesyl group into the hydrocarbon chain of **35** was then explored with **63**. The previously reported 7-phenyl-1-heptanol[21] (**57**) was converted through the series of steps shown in Scheme 7 via ester **59** to **63**, which likewise was not as effective as **35**.

Incorporation of both a terminal phenyl group and as much of the farnesyl moiety as possible into a prospective zwitterionic inhibitor was then explored. Synthesis of the phenylgeranyl derivative **64** (Scheme 8) was approached via the well-known SeO_2 ω oxidation of geranyl acetate **65** to form **67**[22] and of the analogous TBDMS derivative **66** to form **68**. A variety of attempts to convert **67** or **68** to the corresponding bromide for use in coupling reactions with metallobenzenes were unrewarding, so **67** was oxidized with MnO_2 to **69**,[23] which, upon reaction with

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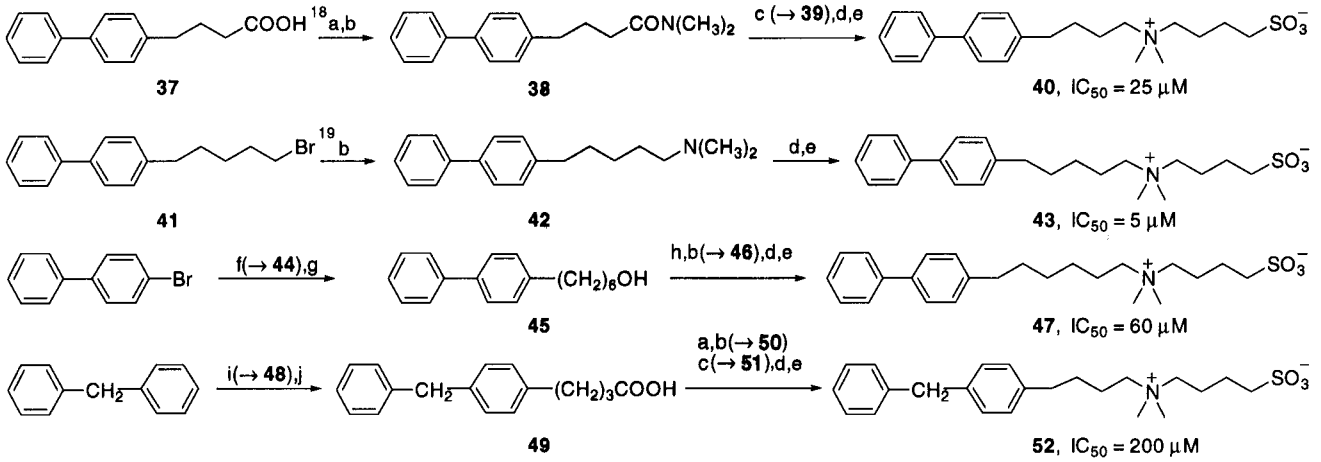
Scheme 6[a]

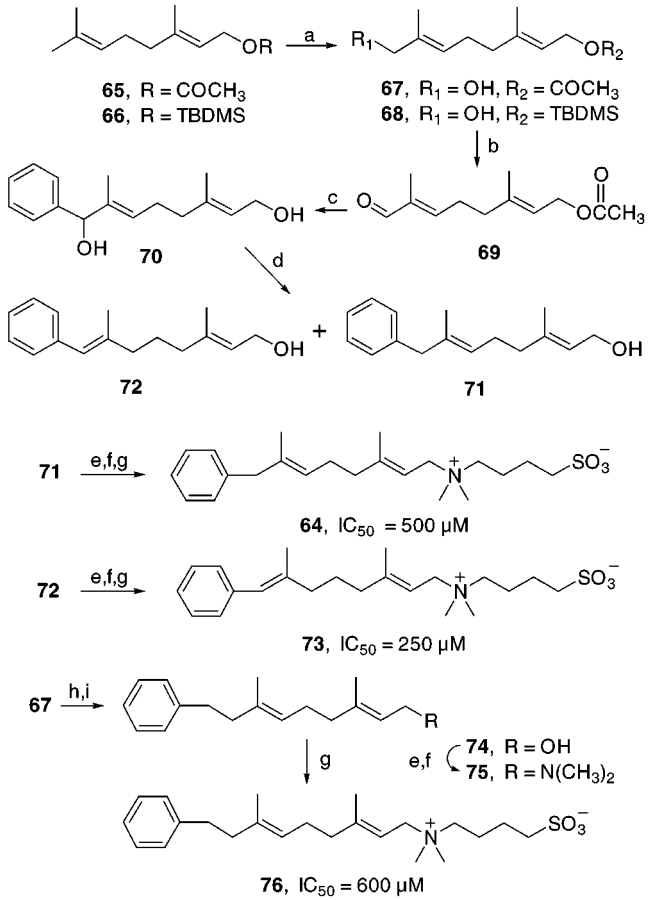


[a] Reagents: (a) ClCOCOCl; (b) $(CH_3)_2NH$; (c) $LiAlH_4$; (d) $Br(CH_2)_4Br$; (e) Na_2SO_3; (f) $(Ph_3)Pd$, CuI, Et_3N, $HCC(CH_2)_3CH_2OH$; (g) H_2, Pd/C; (h) PBr_3; (i)[7] , $AlCl_3$; (j) H_2NNH_2, KOH, 180 °C.

Scheme 7[a]

[a] Reagents: (a) NaOH, H_2O, CH_2Cl_2, TBABr, $Br(CH_2)_8Br$; (b) $(CH_3)_2NH$; (c) **15**; (d) 2 equiv BuLi; (e) 2 equiv $Br(CH_2)_9Br$; (f) Swern; (g) NaH, $(EtO)_2POCH_2COOEt$; (h) DIBALH; (i) PBr_3; (j) $Br(CH_2)_4Br$; (k) Na_2SO_3.

Scheme 8[a]



[a] Reagents: (a) SeO_2; (b) MnO_2; (c) 5 equiv of PhMgBr; (d) $ZnBr_2$, $NaBH_3CN$; (e) PBr_3; (f) $(CH_3)_2NH$; (g) **15**; (h) MsCl; (i) 5 equiv of $PhCH_2Cl$.

phenyl Grignard reagent, efficiently afforded **70**. Selective removal of the secondary allylic and benzylic hydroxyl group of **70** was effected by treatment with $ZnBr_2$ and $NaBH_3CN$[24] to afford a 2:1 mixture of **71** and **72**. Reduction of **70** with other Lewis acids and hydride donors failed to change the isomeric product ratio significantly, so **71** and **72** were separated by argentation chromatography[25] and individually carried forward to **64** and its isomer **73** by the series of steps indicated in Scheme 8. Subsequently, it was found that **67** could be selectively converted to **71** via careful mesylation and

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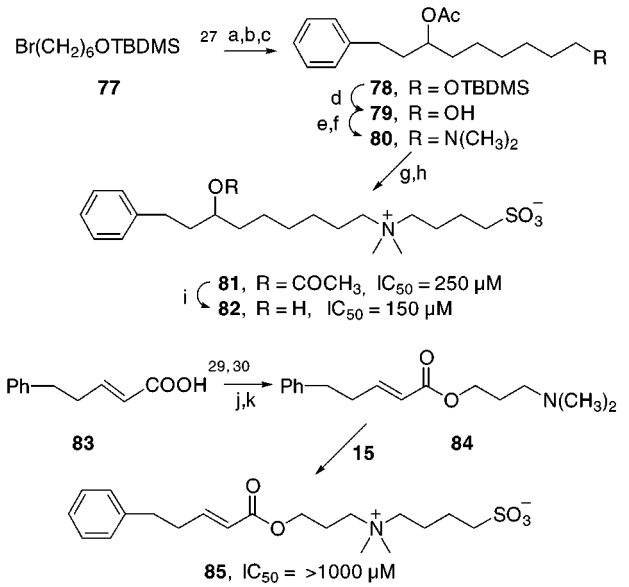
Scheme 9[a]



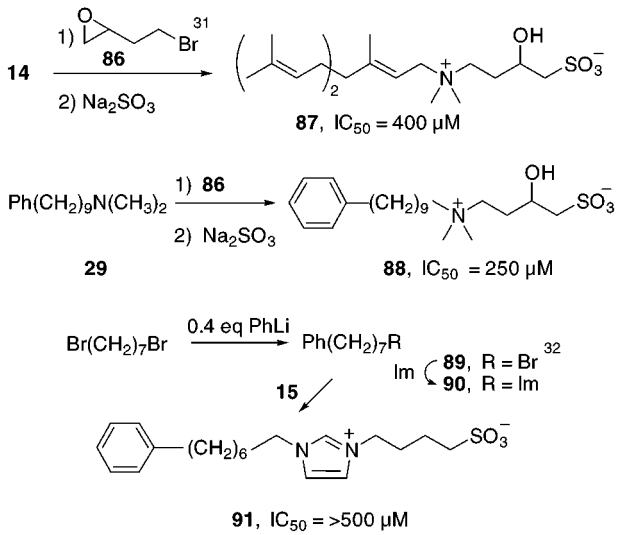
[a] Reagents: (a) Mg; (b) $Ph(CH_2)_2CHO$; (c) Ac_2O; (d) nBu_4NF; (e) PBr_3; (f) $(CH_3)_2NH$; (g) $Br(CH_2)_4Br$; (h) Na_2SO_3; (i) KOH, CH_3OH; (j) ClCOCOCl; (k) $NaO(CH_2)_3N(CH_3)_2$.

coupling with phenyllithium. Very recently, an interesting alternative synthesis of **71** was reported,[26] involving Cu(I)-mediated coupling of phenylmagnesium bromide with the C8 tetrahydropyranyloxy derivative of geraniol. Homologue **76** of **71** was also prepared by mesylation and reaction with phenyllithium, via intermediates **74** and **75**. It was disappointing that compounds **64**, **73**, and **76** all proved to be very poor SS inhibitors.

Attention was then turned to introduction of polar functional groups into the hydrocarbon chain of **35**, guided by the nature and location of groups in the side chains of the zaragozic acids. As indicated in Scheme 9, compounds **81** and **82** were prepared by reaction of the Grignard reagent derived from **77**[27] with hydrocinnamaldehyde to afford, after acetylation, compound **78**. Deprotection afforded **79**, which was carried on to the zwitterions by the usual steps, via **80**. Unfortunately, both **81** and **82** were distinctly less effective SS inhibitors than **35**. Because zaragozic acid A (**6**) has been shown to lead slowly to irreversible inactivation of SS,[28] an effect ascribed to the presence of the electrophilic α,β-unsaturated ester group in a side chain, an analogous functionality was incorporated into zwitterion **85**, which was prepared as indicated in Scheme 9 from unsaturated acid **83**,[29,30] via **84**. Regrettably, **85** was an extremely poor inhibitor of SS, and detection of any relatively slow irreversible inactivation[28] was clearly not feasible.

Changes in the structure of the zwitterionic end of this type of inhibitor were also briefly explored. Increased polarity in the connector between the ammonium and sulfonate ions, to simulate better the polarity of the diphosphate moiety of FPP (**1**), was examined with compounds **87** and **88**. These were prepared via reaction of the appropriate previously used tertiary amines **14** and

Scheme 10



29 with bromoepoxide **86**[31] as shown in Scheme 10, but they proved to be disappointingly poor inhibitors. The nature of the positively charged center was modified to make it resemble more closely the allylic carbocation derived from FPP (**1**) by construction of imidazolium zwitterion **91**, via **89**[32] and **90**, as outlined in Scheme 10. Amidonium ions have previously been used with some success as mimics of the delocalized farnesyl carbocation,[33] but this appears to be the first trial of an imidazolium ion for this purpose. However, **91** turned out to be an extremely weak inhibitor of SS.

All of the zwitterions prepared thus far were intended as surrogates for FPP (**1**). The intermediate presqualene diphosphate (**2**) in the SS-catalyzed reaction of course presents another target for simulation that has been employed[1] and that seemingly occurs naturally in the zaragozic acids (e.g., **6**).[6] To test this approach in the context of zwitterionic sulfobetaines, compounds **93**, **97**, and **99**, containing two hydrophobic chains of the types found to afford most effective inhibition, were synthesized as outlined in Scheme 11. Introduction of the second large chain to form intermediates **92**, **96**, and **98** was more difficult than the previous formation of analogous, less bulky tertiary amines. Particularly when **94**[34] was combined with **95** to form **96** vigorous conditions were required. Two additional zwitterions, **101** and **103**, containing an *N*-benzyl group were also prepared, via **100** and **102** as outlined in Scheme 11, prompted by Prashad's finding that *N*-benzyl-substituted tertiary amine **104** is a particularly effective SS inhibitor.[35] Compounds **93**, **97**, **99**, **101**, and **103** all did indeed inhibit SS in the microsomal assay, but none approached **35** in effectiveness.

Finally, the idea of combining two zwitterionic units in a single inhibitor was tested, since the capacious SS active site for formation of squalene (**3**) is able to bind, in addition to two farnesyl diphosphates (**1**) or their combination in presqualene diphosphate (**2**), a divalent

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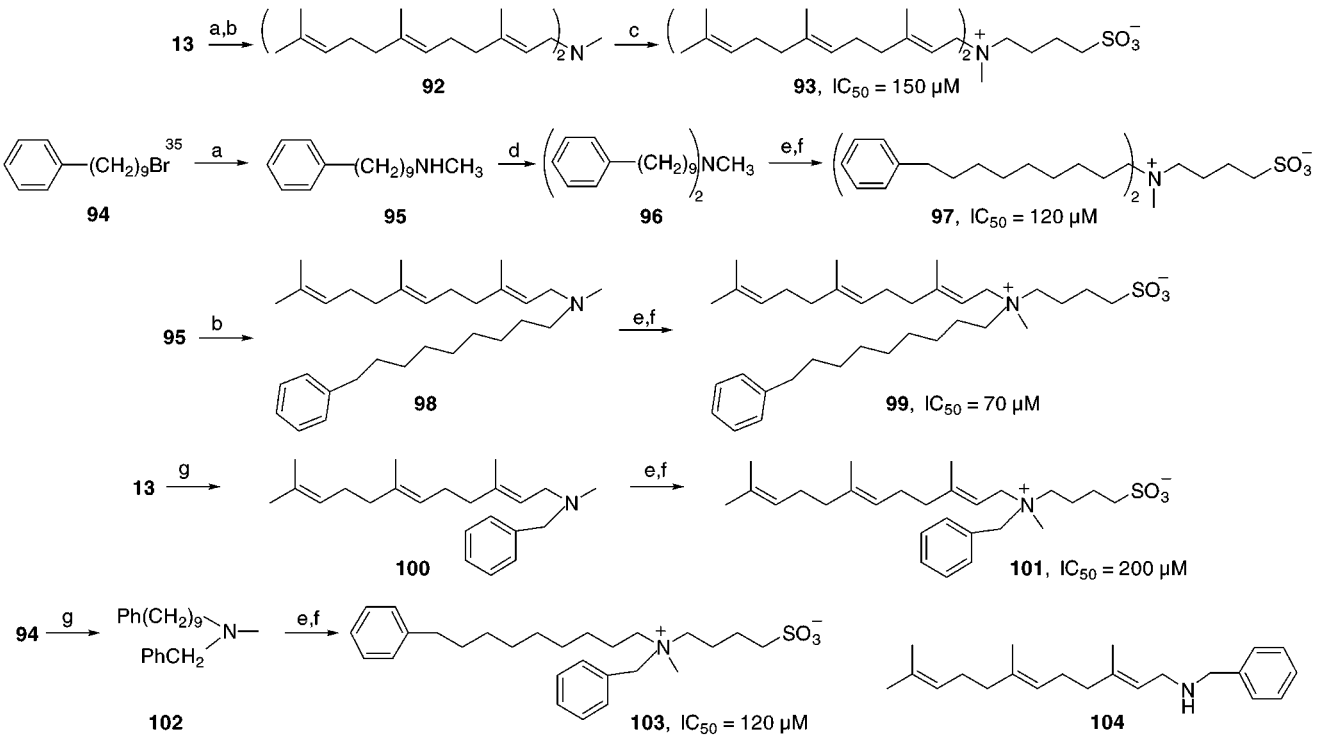
Scheme 11[a]



[a] Reagents: (a) CH_3NH_2; (b) **13**; (c) **15**; (d) **94**; (e) $Br(CH_2)_4Br$; (f) Na_2SO_3; (g) $PhCH_2NHCH_3$.

metal cation and an $NADP^+ \rightleftarrows NADPH$ coenzyme unit.[36] This approach was first tested with biszwitterion **106** because this compound was easily accessible via **105**[37] by reaction with **15**, as indicated in Scheme 12. In view of the relatively simple structure of the hydrocarbon moiety of **106**, its modest effectiveness as an SS inhibitor encouraged examination of more complex biszwitterions. Accordingly, compounds **109** and **111** were prepared as shown in Scheme 12, by reaction of **107**[38] or **95** with about 0.5 equiv of ethylene dibromide. Unfortunately, **109** and **111** were less effective inhibitors than **106**. Incorporation of one hydrocarbon chain of the most effective type, that found in **35**, into a biszwitterion was also evaluated with compound **115**, which was prepared from diethyl malonate, via alkylation with **89**, reduction to **112**, and conversion to dibromide **113** and diamine **114** (Scheme 12). Disappointingly once again, **115** proved to be a very poor inhibitor.

The initial results with compounds such as **10** had made the idea of using sulfobetaine zwitterions as inhibitors of SS seem quite promising and led to the synthesis of the variety of structural modifications described in this paper. However, none of the many inhibitors tested has an IC_{50} value lower than the 2 μM obtained early on with the phenylnonyl derivative **35**. Exploration of a different type of zwitterion would seem to be the next logical step toward determining if this appealing approach to inhibition of SS can provide compounds with IC_{50} values in the desired nanomolar range.

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Experimental Section

General Procedures. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. The symbols ^1H and ^{13}C indicate that the NMR data are included in the Supporting Information. Elemental microanalyses were performed by Atlantic Microlabs Inc., Norcross, GA. The elemental symbols (e.g., C, H, N) indicate that the analytical data are included in the Supporting Information. Electron ionization (EI) and fast atom bombardment (FAB) high-resolution mass spectra (HRMS) were obtained at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois; the symbols (e.g., EI-HRMS) indicate that the data are in the Supporting Information.

Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone. 1,2-Dichloroethane, dimethylformamide (DMF), hexamethylformamide (HMPA), and *tert*-butyl alcohol were distilled from barium oxide. Acetic acid was distilled from P_4O_{10}. All reactions were magnetically stirred. Flash column chromatography was carried out on EM Reagent silica gel 60 (230−400 mesh), Brockmann I activated aluminum oxide (150 mesh) (normal phase), or Bakerbond Octadecyl (C_{18}) 40 μm preparative LC packing (reversed phase) from J. T. Baker, Inc. Thin-layer chromatography (TLC) was conducted on EM plastic sheets precoated with silica gel 60 F-254, Baker-flex plastic sheets precoated with aluminum oxide IB, or Whatman $MKC_{18}F$ glass-backed reversed-phase plates. Visualization was obtained by exposure to iodine vapors, UV radiation, $KMnO_4$, or ceric ammonium sulfate solution. Dimethylamine (bp = 7 °C) and methylamine (bp = −8 °C) were obtained from commercial aqueous solutions by an adaptation of the method of Overberger et al.,[39] by dripping the aqueous amine onto KOH pellets, passing the resulting gas through a KOH drying tube, and condensing it by means of a dry ice−acetone trap. Ion-exchange resins used were Dowex 50W-X12 (H^+) cation-exchange resin 200−400 mesh from J. T. Baker, Inc., and Amberlite IRA-402 (OH^-) anion-exchange resin 16−50 mesh from Sigma Chemical Co. All reagents, unless otherwise noted, were obtained from Aldrich Chemical Co.

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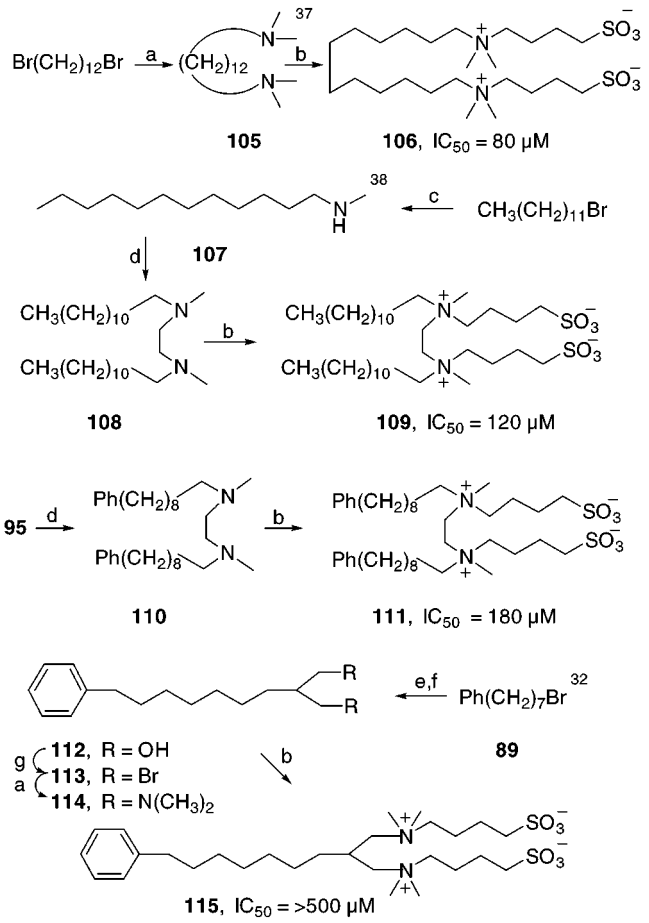
Scheme 12[a]



[a] Reagents: (a) $(CH_3)_2NH$; (b) **15**; (c) CH_3NH_2; (d) $Br(CH_2)_2Br$; (e) $NaCH(COOEt)_2$; (f) $LiAlH_4$; (g) PBr_3.

Standard abbreviations used: usual workup (solvent), "the mixture was extracted with the solvent indicated and the organic extracts were dried over $MgSO_4$ and evaporated"; NPC (solvents), "this material was purified by normal-phase chromatography using the solvents indicated"; RPC (solvents), "this material was purified by reversed-phase chromatography using the solvents indicated".

***N,N*-Dimethyl-1-(3,7,11-trimethyl-2,6,10-dodecatrienyl)amine (Farnesyldimethylamine, 14).** According to the procedure of Edstrom,[40] *E,E*-farnesol was converted with PBr_3 to **13** which had bp and ^1H NMR consistent with the literature.[41,42] In a slight modification of a procedure by Norman and co-workers,[10] to a cold (0 °C) solution of 50 mL of $(CH_3)_2NH$ in 100 mL of Et_2O was added a solution of 3.21 g (11.2 mmol) of **13** in 7.0 mL of Et_2O. The mixture was allowed to warm to room temperature over 4 h, stirred for 15 h, washed with 2 M NaOH (3 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and evaporated to give 2.72 g (97%) of **14** as a clear oil: ^1H; ^{13}C.

***N,N*-Dimethyl-1-(3,7,11-trimethyl-2,6,10-dodecatrienyl)ammonium-1-(2-ethylsulfonate) (8).** According to a procedure by Barnhurst,[11] a solution of 0.628 g (2.52 mmol) of **14** in 2.20 mL (25.5 mmol) of 1,2-dibromoethane was stirred at 30 °C for 105 h. The excess 1,2-dibromoethane was then removed over 1 h at 40 °C under vacuum to give 0.844 g (77%) of bromoethyl derivative as a waxy solid. Recrystallization from EtOAc gave 0.53 g (48%) of this colorless salt: mp 117−120 °C. This material and 0.16 g (1.3 mmol) of Na_2SO_3 in 10.0 mL of H_2O was stirred at 80−85 °C for 10 h. The mixture was then evaporated to give 0.52 g of waxy residue, which was redissolved in 10.0 mL of H_2O and treated with a mixture of ~3 g of cation-exchange resin (H^+) and ~3 g of anion-exchange resin (OH^-), filtered, and evaporated to give 0.22 g (51%) of colorless **8**. An analytical sample was prepared by recrystallization from H_2O and then CH_3CN/EtOAc: mp 260−263 °C; ^1H; ^{13}C; FAB-HRMS.

Compound **8** was also prepared according to the procedure of Downing and Johnson[43] by reaction of 2-bromoethanesulfonate[44] with **14**, but the yield was poor.

***N,N*-Dimethyl-1-(3,7,11-trimethyl-2,6,10-dodecatrienyl)ammonium-1-(3-propylsulfonate) (9).** According to a procedure by Linfield, Abend, and David,[12] to a solution of 0.98 g (3.9 mmol) of **14** in 5.0 mL of 1,2-dichloroethane was added 0.50 g (4.0 mmol) of 1,3-propane sultone. The mixture was stirred at room temperature for 24 h and concentrated under vacuum to give 1.6 g (108%) of crude **9** as a waxy solid. Crystallization from 2:3 CH_3CN/EtOAc gave 0.98 g (67%) of colorless **9**: mp 205−207 °C; ^1H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-1-(3,7,11-trimethyl-2,6,10-dodecatrienyl)ammonium-1-(4-butylsulfonate) (10).** Similarly,[12] to a solution of 0.72 g (2.9 mmol) of **14** in 5.0 mL of 1,2-dichloroethane was added 0.30 mL (2.9 mmol) of **15** dropwise, and the mixture was stirred for 43 h at room temperature. Processing as in the preparation of **9** gave 0.57 g (51%) of **10**: mp 244−247 °C (after recrystallization from CH_3CN:EtOAc); ^1H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-1-(3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatrienyl)ammonium-1-(5-pentylsulfonate) (11).** According to a procedure by Barnhurst,[11] a solution of 0.40 g (1.6 mmol) of **14** in 3.09 g (16.1 mmol) of 1,5-dibromopentane was wrapped in aluminum foil and stirred for 192 h at room temperature. The resulting yellow solution was diluted with hexane and washed with 3 × 20 mL of 4:1 H_2O/CH_3OH solution. The aqueous layer was concentrated to give 0.52 g (68%) of clear burnt-orange oily bromopentyl derivative: ^1H; ^{13}C. A mixture of 0.72 g (1.5 mmol) of this compound and 0.29 g (1.9 mmol) of Na_2SO_3 in 20 mL of H_2O was stirred for 66 h at room temperature and concentrated to give 1.2 g of waxy residue. RPC (4:1 MeOH/H_2O) gave 0.491 g (82%) of white amorphous gummy **11**: ^1H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-1-(3,7,11-trimethyl-2*E*,6*E*,10-dodecatrienyl)ammonium-1-(6-hexylsulfonate) (12).** As for **11**, **14** and 1,6-dibromohexane gave 71% of bromohexyl derivative: ^1H; ^{13}C. This compound was treated with Na_2SO_3 to give 55% of white amorphous gummy **12**: ^1H; ^{13}C; FAB-HRMS.

3,7,11-Trimethyl-2(*E*),6(*E*),10-dodecatrienylamine (Farnesylamine, 17). According to a procedure of Stang and Fox,[45] to a solution of 2.63 g (9.23 mmol) of **13** and 1.86 g (9.23 mmol) of potassium phthalimide in 30 mL of dry toluene was added 2.53 g (9.57 mmol) of 18-crown-6. The mixture was stirred at room temperature for 18 h under N_2, washed with 3 × 40 mL of 1 N $NaHCO_3$ and 3 × 50 mL of 2 N KOH, dried over $MgSO_4$, and evaporated to give 2.90 g (82%) of tan oily farnesyl phthalimide (**16**): ^1H; ^{13}C; C, H. To a solution of 2.50 g (7.11 mmol) of **16** in 50 mL of EtOH was added 2.8 g (80 mmol) of hydrazine hydrate. The reaction mixture was stirred at reflux for 10 h, treated with 12 mL (0.12 mol) of 10 N HCl, diluted to 250 mL with H_2O, and made alkaline with concentrated NaOH solution. Usual workup (EtOAc) gave 1.55 g (100%) of tan oily **17**: ^1H (lit.[14] ^1H); ^{13}C.

1-(3,7,11-Trimethyl-2(*E*),6(*E*),10-dodecatrienyl)ammonium-1-(4-butylsulfonate) (18). As for **10**, 1.51 g (6.83 mmol) of **17** and 0.817 g (6.00 mmol) of **15** gave 2.54 g of product that was treated with 100 mL of 5% $NaHCO_3$ solution and extracted using a continuous extraction apparatus for 24 h with CH_2Cl_2, which was evaporated to afford 1.09 g of tan oil. RPC (4:1 MeOH/H_2O) gave 0.40 g, which was crystallized from

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MeOH/H_2O to give 0.251 g (12%) of colorless **18**: mp 136−137 °C; ^{1}H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-1-(3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatrienyl)ammonium-1-(5-pentylcarboxylate) (19).** To a solution of 0.371 g (1.49 mmol) of **14** in 15 mL of MeOH was added 0.237 g (1.50 mmol) of ethyl 5-bromovalerate, and the resulting mixture was heated at reflux for 36 h under N_2. The solution was cooled to room temperature, treated with 0.620 g (15.5 mmol) of powdered NaOH, and reheated at reflux for 18 h. The mixture was evaporated, treated with 10 mL of EtOH, filtered, and poured into 40 mL of Et_2O to give 0.62 g of white gummy solid. RPC (4:1 MeOH/H_2O) gave 0.220 g (31%) of white gummy **19**: ^{1}H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-1-(3,7-dimethyl-2(*E*),6-octadienyl)ammonium-1-(4-butylsulfonate) (20).** A solution of 0.789 g (4.39 mmol) of geranyldimethylamine[46] in 20 mL of 1,2-dichloroethane was treated with 0.440 mL (4.30 mol) of **15**, stirred for 20 h, and evaporated to give 1.12 g of residue, which was recrystallized three times from EtOH/isopropyl ether to afford 0.094 g (8%) of colorless **20**: mp 286−289 °C; ^{1}H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-1-(3-methyl-2-butenyl)ammonium-1-(4-butylsulfonate) (21).** As for **20**, a solution of 0.707 g (6.18 mmol) of prenyldimethylamine[47] and 0.84 g (6.2 mmol) of **15** in 10.0 mL of 1,2-dichloroethane gave, after recrystallization from EtOH/Et_2O, 0.54 g (35%) of colorless **21**: mp 254−256 °C; ^{1}H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-1-(3-methyl-2-butenyl)ammonium-1-(3-propylsulfonate) (22).** As for **20**, a solution of 0.401 g (3.55 mmol) of prenyldimethylamine[47] and 0.450 mL (3.68 mmol) of 1,3-propanesultone in 4.0 mL of 1,2-dichloroethane gave, after recrystallization from EtOH/Et_2O, 0.191 g (23%) of colorless **22**: mp 231−236 °C; ^{1}H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-*N*-(2,6,10-trimethyl-5(*E*)-undecadienyl)-ammonium-1-(4-butylsulfonate) (24).** According to the procedure of Pfeffer,[17] **23** was prepared in 84% yield from homogeranyl iodide, which had been prepared according to the procedures of Kocienski and Wadman[48] from 2,3-dihydrofuran and 1-iodo-4-methyl-3-pentene, which in turn had been prepared from methylcyclopropyl ketone by the procedure of Biernacki and Gdula.[49] A solution of 0.292 g (1.30 mmol) of **23** and 0.113 g (1.43 mmol) of pyridine in 4.22 mL of CH_2Cl_2 was treated with 0.198 g (1.56 mmol) of oxalyl chloride at 0 °C under N_2. The bright yellow, cloudy mixture was stirred at room temperature for 13 h and evaporated, and the residue was dissolved in dry THF. The mixture was cooled to −78 °C, treated with excess $(CH_3)_2NH$, allowed to warm to room temperature, stirred for 16.5 h, cooled to 0 °C, stirred for 20 min exposed to the atmosphere, evaporated, and diluted with saturated $NaHCO_3$. Usual workup (ether) gave 0.310 g of residue. NPC (1:1 EtOAc/hexane) gave 0.300 g (90%) of colorless, oily tertiary amide: ^{1}H; ^{13}C. This amide (1.41 g, 5.54 mmol) was added at 0 °C under N_2 to a suspension of 0.704 g (17.6 mmol) of $LiAlH_4$ in 24.5 mL of dry THF. The mixture was stirred at 0 °C for 15 min, refluxed for 18 h, cooled to room temperature, and treated with 225 mL of 1 M NaOH. Usual workup (ether) gave 1.29 g of residue. NPC (15:83:2 Et_2O/hexane/NH_4OH) gave 1.028 g (78%) of clear, oily tertiary amine, which was converted into its hydrochloride with anhydrous HCl in Et_2O: ^{1}H. A mixture of 0.369 g (1.54 mmol) of the tertiary amine and 3.74 mL (31.4 mmol) of 1,4-dibromobutane was stirred for 5 d at room temperature under N_2. The reaction mixture was distilled to remove excess dibromobutane. RPC (3:1 CH_3OH/H_2O) gave a yellow oil to which was added a solution of 0.267 g (2.14 mmol) of Na_2SO_3 in 18.5 mL of H_2O, the mixture was heated at room temperature for 18 h and treated with 110 mL of methanol, and the resulting precipitate was removed by filtration. The filtrate was evaporated to give 0.97 g of oil. RPC (3:1 CH_3OH/H_2O) gave after dissolution in EtOH and precipitation with Et_2O 0.228 g (39%) of colorless **24**: ^{1}H.

***N,N*-Dimethyldodecylamine (25).** Reaction[10] of excess $(CH_3)_2NH$ in Et_2O with 5.02 g (20.1 mmol) of dodecylbromide afforded 4.21 g (98%) of oily **25**: ^{1}H; ^{13}C; EI-HRMS.

***N,N*-Dimethyl-1-dodecylammonium-1-(4-butylsulfonate) (26).** As for **20**, a solution of 1.31 g (6.14 mmol) of **25** and 0.836 g (6.14 mmol) of **15** in 6 mL of 1,2-dichloroethane gave, after recrystallization from EtOH/Et_2O, 1.17 g (55%) of colorless **26**: mp 267−268 °C dec; ^{1}H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-*N*-benzylammonium-1-(4-butylsulfonate) (31).** As for **20**, a solution of 2.0 mL (13.3 mmol) of benzyldimethylamine and 1.43 mL (14.0 mmol) of **15** in 20 mL of 1,2-dichloroethane gave, after recrystallization from EtOH, 2.55 g (70%) of colorless **31**: mp 285−6 °C; ^{1}H; ^{13}C; C, H, N.

***N,N*-Dimethyl-*N*-2-phenylethylammonium-1-(4-butylsulfonate) (32).** Reaction[10] of excess $(CH_3)_2NH$ in Et_2O with 4.8 g (26 mmol) of 2-phenethyl bromide afforded 3.67 g (95%) of colorless oily *N*,*N*-dimethyl-2-phenethylamine: ^{1}H (cf. ref 50); ^{13}C. By the procedure used for **20**, a solution of 2.00 g (13.4 mmol) of this amine and 1.83 g (13.4 mmol) of **15** in 20 mL of 1,2-dichloroethane gave, after recrystallization from EtOH, 1.46 g (38%) of colorless **32**: mp 274−275 °C; ^{1}H; ^{13}C; C, H, N.

***N,N*-Dimethyl-6-phenylhexylamine (27).** To a solution of 7.50 mL (30.7 mmol) of 1,6-dibromohexane in 20 mL of THF was added 5.69 mL (10.2 mmol) of PhLi as a 1.8 M solution in ether. The mixture was stirred at −10 °C under N_2 for 30 min, cooled to −78 °C, treated with 20 mL of $(CH_3)_2NH$, stirred at room temperature for 50 h, diluted with 100 mL of Et_2O, washed with 3 × 75 mL of 2.0 N NaOH, dried over $MgSO_4$, filtered, and evaporated to give 7.42 g of tan oil. NPC (18:2:1 EtOAc/MeOH/concd NH_4OH) gave 1.04 g (51% based on PhLi) of colorless oily **27**: ^{1}H; ^{13}C.

***N,N*-Dimethyl-1-(6-phenylhexyl)ammonium-1-(4-butylsulfonate) (33).** As for **20**, 0.196 g (0.954 mmol) of **27** and 0.102 mL (1.00 mmol) of **15** gave, after recrystallization from CH_2Cl_2/Et_2O, 0.114 g (35%) of colorless **33**: mp 222−224 °C dec; ^{1}H; ^{13}C; C, H, N.

***N,N*-Dimethyl-8-phenyloctylamine (28).** As for **27**, 6.00 mL (32.5 mmol) of 1,8-dibromooctane afforded 2.84 g (94% based on PhLi) of **28**, which by treatment with methanolic HCl was converted to its hydrochloride: mp 47−48 °C; ^{1}H; ^{13}C; C, H, N.

***N,N*-Dimethyl-1-(8-phenyloctyl)ammonium-1-(4-butylsulfonate) (34).** As for **20**, 0.752 g (3.22 mmol) of **28** and 0.443 g (3.25 mmol) of **15** gave, after recrystallization twice from EtOH/Et_2O, 0.761 g (65%) of colorless **34**: mp 222−224 °C dec: ^{1}H; ^{13}C; C, H, N.

***N,N*-Dimethyl-9-phenylnonylamine (29).** As for **27**, 12.1 mL (59.5 mmol) of 1,9-dibromooctane afforded 3.26 g (73% based on PhLi) of **29**): ^{1}H; ^{13}C; EI-HRMS.

***N,N*-Dimethyl-1-(9-phenylnonyl)ammonium-1-(4-butylsulfonate) (35).** As for **20**, 0.842 g (3.40 mmol) of **29** and 0.327 mL (3.21 mmol) of **15** gave, after recrystallization from EtOH/Et_2O, 0.454 g (38%) of **35**: mp 188−191 °C; ^{1}H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-10-phenyldecylamine (30).** As for **27**, 9.23 mL (30.7 mmol) of 1,10-dibromodecane afforded 2.2 g (82% based on PhLi) of **30**: ^{1}H; ^{13}C; C, H, N.

***N,N*-Dimethyl-1-(10-phenyldecyl)ammonium-1-(4-butylsulfonate) (36).** As for **20**, 0.796 g (0.305 mmol) of **30** and 0.304 mL (3.01 mmol) of **15** gave 0.742 g (62%) of **36**, which was recrystallized three times from EtOH/Et_2O to give 0.132 g (11%) of **36**: mp 249−251 °C dec; ^{1}H; ^{13}C; FAB-HRMS.

4-(1,1′-Biphenyl)butanoic Acid (37). Biphenyl was converted by the procedure of Hey and Wilkinson[18] in 68% yield to 4-(1,1′-biphenyl)-4-oxobutanoic acid: mp 187−188 °C (lit.[18] mp 185 °C). According to the procedure of Katritsky and Marson,[51] this acid was converted in 99% yield to **37**: mp 113.5−114.2 °C (lit.[51] mp 116 °C); ^{1}H; ^{13}C.

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***N,N*-Dimethyl-4-(1,1′-biphenyl)butanamide (38).** By successive treatment with oxalyl chloride and $(CH_3)_2NH$, **37** was converted in 78% yield to **38**: mp 65.4−66.3 °C; ^1H; ^{13}C; C, H, N.

***N,N*-Dimethyl-4-(1,1′-biphenyl)butanamine (39).** According to the procedure of Dokuzovic et al.,[52] a suspension of 0.72 g (18 mmol, 3.17 equiv) of $LiAlH_4$ in 25 mL of THF at 0 °C was treated with a solution of 1.51 g (5.66 mmol, 1 equiv) of **38** in 15 mL of THF. The mixture was stirred at 0 °C for 15 min, allowed to warm to room temperature, heated at reflux (85 °C) for 23 h, and cooled to room temperature, and the excess $LiAlH_4$ was destroyed with 230 mL of 1 M aqueous NaOH solution. Usual workup (ether) and NPC (30:68:2 CH_3OH/EtOAc/concd NH_4OH) gave 1.20 g (84%) of **39** as a pale yellow oil: ^1H; ^{13}C; C, H, N.

***N,N*-Dimethyl-*N*-1-[4-(1,1′-biphenyl)butyl]ammonium-1-(4-butylsulfonate) (40).** As for **11**, **39** was converted in 39% yield to **40**: ^1H; ^{13}C; FAB-HRMS.

4-(5-Bromopentyl)-1,1′-biphenyl (41). By the procedures of Lee et al.,[19] 4-bromobiphenyl was converted in 61% overall yield to 4-(5-hydroxypentyl)-1,1′-biphenyl: mp 74−75 °C. A solution of 0.60 g (2.5 mmol) of this alcohol in 32 mL of Et_2O at 0 °C was slowly treated with 96 μL (1 mmol) of PBr_3. The mixture was allowed to warm to room temperature, stirred for 17 h, treated with 10 mL of 5% $NaHCO_3$, and extracted with 3 × 10 mL of Et_2O, and the Et_2O layers were evaporated. NPC (1:19 Et_2O/hexane) gave 0.35 g (46%) of colorless oily **41**: ^1H; ^{13}C.

***N,N*-Dimethyl-4-(5-pentanamine)-1,1′-biphenyl (42).** A solution of 0.35 g (1.16 mmol) of **41** in 14.5 mL of THF at −78 °C was treated with excess $(CH_3)_2NH$, stirred at −78 °C for 30 min, allowed to warm to room temperature, tightly stoppered, stirred for 17 h at room temperature, and evaporated. The residue was dissolved in 30 mL of Et_2O and washed with 20 mL of 5% aqueous NaOH solution. Usual workup (ether) and NPC (10:88:2 CH_2OH/EtOAc/concd NH_4OH) gave 0.29 g (95%) of **42** as a pale yellow oil: ^1H; ^{13}C; C, H, N.

***N,N*-Dimethyl-*N*-1-[5-(1,1′-Biphenyl)-*n*-pentyl]ammonium-1-(4-butylsulfonate) (43).** As for **40**, 0.219 g (0.82 mmol) of **42** was converted in 55% yield to **43**: ^1H; ^{13}C; FAB-HRMS.

6-(1,1′-Biphenyl)-5-hexyn-1-ol (44). By the procedure of Lee et al.,[19] 4.19 g (18.0 mmol) of 4-bromobiphenyl was converted by reaction with 5-hexyn-1-ol in 87% yield to **44**: mp 67−68 °C; ^1H; ^{13}C; C, H.

6-(1,1′-Biphenyl)hexan-1-ol (45). By the procedure of Lee et al.,[19] 2.62 g (10.5 mmol) of **44** was converted in 90% yield to **45**: ^1H; ^{13}C; C, H.

4,4-Dimethyl-4-(6-hexanamine)-1,1′-biphenyl (46). As for **41**, 2.24 g (8.82 mmol) of **45** was converted in 40% yield to the corresponding bromide: ^1H; ^{13}C. By the procedure used for **42**, 1.04 g (3.8 mmol) of this bromide was converted in 92% yield to **46**: ^1H; ^{13}C; C, H, N.

***N,N*-Dimethyl-*N*-1-[6-1,1′-biphenyl-*n*-hexyl]ammonium-1-(4-butylsulfonate) (47).** As for **40**, 0.79 g (2.8 mmol) of **46** was converted in 51% yield to **47**: ^1H; ^{13}C; FAB-HRMS.

4-(Diphenylmethylene)-4-oxobutanoic Acid (48). By the procedure of Hey and Wilkinson,[18] 6.12 g (36.4 mmol) of biphenylmethylene was converted in 53% yield to **48**: mp 124−125 °C; ^1H; ^{13}C; FAB-HRMS.

4-(Diphenylmethylene)-*n*-butanoic Acid (49). As for **37**, 1.64 g (6.17 mmol) of **48** gave, after recrystallization from hexane, 81% of **49**: mp 94.0−94.5 °C; ^1H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-4-(diphenylmethylene)-*n*-butanamide (50).** As for **38**, 1.00 g (3.94 mmol) of **49** was converted in 92% yield to **50**: ^1H; ^{13}C; C, H, N.

***N,N*-Dimethyl-4-(diphenylmethylene)-*n*-butanamine (51).** As for **39**, 0.95 g (3.4 mmol) of **50** was converted in 94% yield to **51**: ^1H; ^{13}C; C, H, N.

***N,N*-Dimethyl-*N*-1-[4-(diphenylmethylene)butyl]ammonium-1-(4-butylsulfonate) (52).** As for **40**, 0.78 g (2.92 mmol) of **51** was converted in 49% yield to **52**: ^1H; ^{13}C; C, H, N, S.

***N,N*-Dimethyl-8-phenoxy-*N*-octylamine (53).** A solution of 0.50 g (5.3 mmol) of phenol and 0.15 g (0.46 mmol) of tetrabutylammonium bromide in 5 mL of 2 M NaOH was treated with 3.99 g (14.8 mmol) of 1,8-dibromooctane in 5 mL of CH_2Cl_2. The mixture was heated at reflux (oil bath temperature 80−90 °C) with rapid stirring for 12 h. The layers were separated, and the aqueous layer was extracted with 2 × 25 mL of CH_2Cl_2. The combined organic layers were dried and evaporated to give 3.45 g (99%) of crude 1-bromo-8-phenoxyooctane,[53] which was dissolved in 25 mL of THF, cooled to −78 °C, and treated with excess $(CH_3)_2NH$ as in the preparation of **42** to give 2.38 g of residue. NPC (10:78:2 CH_3OH/EtOAc/concd NH_4OH) gave 0.45 g (38%) of yellow oily **53**: ^1H; ^{13}C.

***N,N*-Dimethyl-1-(8-phenoxyoctyl)ammonium-1-(4-butylsulfonate) (54).** A mixture of 450 mg (1.80 mmol) of **53** and 27.3 mg (2.00 mmol) of **15** in 5 mL of 1,2-dichloroethane was stirred at room temperature for 10 d and evaporated to give 563 mg of residue. RPC (3:17 H_2O/CH_3OH) gave 105 mg, which was dissolved in absolute EtOH (∼0.5 mL) and precipitated by addition of Et_2O to afford 92.0 mg (13%) of **54**: mp 248−250 °C; ^1H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-9-(4-methoxyphenyl)nonylamine (55).** To a solution of 10 mL of 2 M *n*-butyllithium (20 mmol) in 80 mL of THF at −100 °C was added 1.87 g (10 mmol) of *p*-bromoanisole. The mixture was stirred at −100 °C for 40 min, treated with 5.77 g (20 mmol) of 1,9-dibromononane, warmed to 0 °C, stirred for 12 h, quenched with 10 mL of 10% NH_4Cl solution, and evaporated. The residue (7.97 g) was dissolved in 50 mL of ether and washed with 2 × 25 mL of 2 M NaOH solution. The ether was evaporated to give 6.37 g of residue. NPC (hexane) gave 3.14 g of a mixture of 9-(4-methoxyphenyl)nonyl bromide and *p*-butylanisole, which was dissolved in 30 mL of THF, cooled to −78 °C, and treated with 28.7 g (586 mmol) of $(CH_3)_2NH$ as in the preparation of **42** to give 2.04 g of residue. NPC (10:88:2 CH_3OH/EtOH/concd NH_4OH) gave 714 mg (26%) of yellow oily **55**: ^1H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-1-[9-(4-methoxyphenyl)nonyl]ammonium-1-(4-butylsulfonate) (56).** As for **54**, 714 mg (2.58 mmol) of **55** was converted in 19% yield to **56**: mp 241−242 °C; ^1H; ^{13}C; C, H, N.

7-Phenyl-1-heptanol (57).[21] According to the procedure of Chapman et al.,[54] 1,7-heptanediol was converted in 42% yield to 7-bromoheptan-1-ol, which in turn was converted in 91% yield to its *tert*-butyldimethyl silyl derivative.[55] A solution of 7.97 g (25.8 mmol) of this material in 60 mL of ether at 0 °C was slowly treated with 16.2 mL (29.2 mmol) of a 1.8 M solution of phenyllithium in cyclohexane/Et_2O. The mixture was stirred at 0 °C for 35 min, allowed to warm to room temperature, stirred at room temperature for 19 h, and diluted with 40 mL of saturated aqueous NH_4Cl solution. Usual workup (ether) gave 6.69 g of crude 7-phenyl-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]heptane, which was dissolved in 150 mL of THF, cooled to 0 °C, and slowly treated with 26.2 mL (26.2 mmol) of 1M $(^nBu)_4NF$ in THF. The mixture was allowed to warm to room temperature, stirred for 17 h, and evaporated, and the residue was diluted with 50 mL of H_2O. Usual workup (ether) and NPC (1:1 EtOAc/hexane) gave 4.04 g (82%) of **57**: ^1H; ^{13}C.

7-Phenyl-1-heptanal (58). Swern oxidation[56] of 2.76 g (14.4 mmol) of **57** afforded 85% of **58**: ^1H; ^{13}C; FAB-HRMS.

Ethyl (*E*)-9-Phenylnon-2-enoate (59). According to the method of Schmidt et al.,[57] a suspension of 0.81 g (20.3 mmol) of 60% sodium hydride in THF was cooled to 0 °C and slowly treated with 3.47 mL (20.1 mmol) of triethylphosphonoacetate. The mixture was allowed to warm to room temperature, stirred for 1.5 h, treated with a solution of 1.91 g (10.1 mmol) of **58** in

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6 mL of THF, stirred for 19 h, and diluted with 200 mL of icy H_2O. Usual workup (ether) and NPC (6:94 Et_2O/hexane) gave 1.89 g (72%) of **59**: ^1H; ^{13}C; EI-HRMS.

(*E*)-9-Phenylnon-2-en-1-ol (60). According to the method of Nagaoka and Kishi,[58] a solution of 0.51 g (1.96 mmol) of **59** in 13 mL of CH_2Cl_2 and 26 mL of hexane at −78 °C was slowly treated with 7.87 mL (7.87 mmol) of a solution of DIBALH in THF. The mixture was stirred for 4 h, treated with 2 mL of MeOH, allowed to warm to room temperature, treated with 4 mL of brine and 10 g of $MgSO_4$, stirred for 1 h, filtered, and evaporated. NPC (3:7 ether/hexane) gave 0.26 g (61%) of **60**: ^1H; ^{13}C; FAB-HRMS.

1-Bromo-9-phenylnon-2-ene (61). As for **41**, 0.25 g (1.15 mmol) of **60** was converted in 87% yield to **61**: ^1H; ^{13}C; FAB-HRMS.

(*E*)-*N*,*N*-Dimethyl-9-phenylnon-2-en-1-amine (62). As for **42**, 0.27 g (0.96 mmol) of **61** was converted in 93% yield to **62**: ^1H; ^{13}C; FAB-HRMS.

***N*,*N*-Dimethyl-N-1-(9-phenylnon-2(*E*)-enyl)ammonium-1-(4-butylsulfonate) (63).** As for **40**, 0.21 g (0.86 mmol) of **62** was converted in 55% yield to **63**: ^1H; ^{13}C; FAB-HRMS.

(1,1-Dimethylethyl)[(3,7-dimethyl-2(*E*),6-octadienyl)-oxy]dimethylsilane (66). By the procedure of Corey and Venkateswarlu,[59] 5.00 g (58.1 mmol) of geraniol was converted in 83% yield to **66**: ^1H (lit.[60] ^1H); ^{13}C; C, H.

8-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,6-dimethyl-2(*E*),6(*E*)-octadien-1-ol (68). According to a procedure by Umbreit and Sharpless,[22] to a solution of 11.3 mL (0.113 mol) of 90% *tert*-butyl hydroperoxide and 0.55 g (0.0050 mol) of selenium dioxide in 100 mL of CH_2Cl_2 was added 4.60 g (14.4 mol) of **66.** The mixture was stirred at room temperature for 8 h, stored over 11 g of activated alumina for 24 h, filtered, and evaporated to give 16.1 g of oil, which was diluted with 100 mL of ether, washed with 3 × 50 mL of 1 N NaOH and 2 × 50 mL of brine, dried over $MgSO_4$, filtered, and evaporated to give 12.4 g of colorless oil. NPC (1:19 EtOAc/hexane) gave 3.09 g (19%) of oily **68**: ^1H; ^{13}C; C, H.

8-Acetoxy-3,7-dimethyl-2(*E*),6(*E*)-octadienal (69). Similar oxidation[22] of **65** prepared in 94% yield from geraniol by treatment with Ac_2O in pyridine gave 40% of **67**: ^1H; ^{13}C. According to a procedure of Mashraqui and Keehn,[61] 0.072 g (0.34 mmol) of **67** was converted in 96% yield to **69**: ^1H (lit.[62] ^1H); ^{13}C.

1,8-Dihydroxy-2,6-dimethyl-1-phenyl-2(*E*),6(*E*)-octadiene (70). To a solution of 4.32 g (20.6 mmol) of **69** in 50 mL of THF at 0 °C was added 35.0 mL (0.098 mol) of a 2.8 M solution of PhMgBr in ether. The mixture was stirred at 0 °C for 1 h under N_2, treated with 200 mL of 1.0 N HCl, and extracted with 3 × 75 mL of Et_2O. The organic layer was washed with 3 × 100 mL of 1.0 N HCl, dried over $MgSO_4$, filtered, and evaporated to give 7.26 g of yellow/orange oil. NPC (2:3 EtOAc/hexane) gave 4.87 g (96%) of yellow oily **70**: ^1H; ^{13}C; C, H.

3,7-Dimethyl-8-phenyl-2(*E*),6(*E*)-octadienol (71) and 3,7-Dimethyl-8-phenyl-2(*E*),7(*E*)-octadienol (72). According to a procedure by Lau et al.[63] to a solution of 0.323 g (1.31 mmol) of **70** in 30 mL of 1,2-dichloroethane was added 0.627 g (1.97 mmol) of $ZnBr_2$ and 0.438 g (9.38 mmol) of $NaBH_3CN$. The mixture was stirred at room temperature, and when **70** was no longer detected by TLC, the mixture was filtered through Celite that was then was washed with 150 mL of CH_2Cl_2. The filtrate was dried over $MgSO_4$, filtered, and evaporated to give 0.294 g (96%) of a mixture of **71** and **72**: ^1H; ^{13}C; EI-HRMS.

3,7-Dimethyl-8-phenyl-2(*E*),6(*E*)-octadienol (71). According to a procedure by Raucher and Klein,[64] to a solution of 3.81 g (18.0 mmol) of **67** in 50 mL of THF was added 1.55 mL (20.0 mmol) of freshly distilled methanesulfonyl chloride and 2.80 mL (20.0 mmol) of Et_3N at 0 °C under N_2. The mixture was stirred for 0.5 h, treated with 30.0 mL (90.0 mmol) of a solution of 3.0 M PhMgBr in ether, stirred for 1 h, warmed to room temperature, washed with 3 × 100 mL of 1.0 N HCl, dried over $MgSO_4$, filtered, and evaporated to give 8.0 g of oil. NPC (1:1 EtOAc/hexane) gave 2.21 g (54%) of colorless oily **71**: ^1H; ^{13}C; EI-HRMS.

3,7-Dimethyl-8-phenyl-2(*E*),7(*E*)-octadienol (72). The 0.294 g of a mixture of **71** and **72** described above was chromatographed on 10% $AgNO_3$-impregnated silica gel[25] (1:9 EtOAc/hexane) to give 0.103 g (35%) of oily colorless **72**: ^1H; ^{13}C; EI-HRMS; C, H.

***N*,*N*-Dimethyl-1-(3,7-dimethyl-8-phenyl-2(*E*),6(*E*)-octadienyl)ammonium-1-(4-butylsulfonate) (64).** As for **13**, 1.04 g (4.70 mmol) of **71** afforded 81% of 3,7-dimethyl-8-phenyl-2(*E*),6(*E*)-octadienyl bromide: ^1H; ^{13}C. As for **14**, 1.46 g (5.00 mmol) of this bromide afforded 73% of *N*,*N*,3,7-tetramethyl-8-phenyl-2(*E*),6(*E*)-octadienylamine: ^1H; ^{13}C. As for **20**, 0.824 g (3.21 mmol) of this amine was converted to crude **64**. RPC (90:9.5:0.5 MeOH/H_2O/NH_4OH) gave 0.274 g (22%) of **64**: mp 286−289 °C; ^1H; ^{13}C; FAB-HRMS.

***N*,*N*-Dimethyl-1-(3,7-dimethyl-8-phenyl-2(*E*),7(*E*)-octadienyl)ammonium-1-(4-butylsulfonate) (73).** As for **13**, 0.126 g (0.538 mmol) of **72** afforded 92% of 3,7-dimethyl-8-phenyl-2(*E*),7(*E*)-octadienyl bromide: ^1H; ^{13}C. As for **14**, 0.146 g (0.495 mmol) of this bromide afforded 97% of *N*,*N*,3,7-tetramethyl-8-phenyl-2(*E*),7(*E*)-octadienylamine: ^1H; ^{13}C. As for **20**, 0.124 g (0.480 mmol) of this amine afforded crude **73**. RPC (90:9.5:0.5 MeOH/H_2O/NH_4OH) gave 0.274 g (22%) of **73**: mp 281−282 °C; ^1H; ^{13}C; FAB-HRMS.

3,7-Dimethyl-9-phenyl-2(*E*),6(*E*)-nonadienol (74). As for **71**, a solution of 0.36 g (1.7 mmol) of **67** in 20 mL of THF was treated with 0.151 mL (1.95 mmol) of methanesulfonyl chloride and 0.273 mL (1.96 mmol) of Et_3N and then with 6.8 mL (6.8 mmol) of a 1.0 M solution of $PhCH_2MgCl$ to give 0.4 g of oil. NPC (1:4 EtOAc/hexane) gave 0.251 g (61%) of colorless viscous oily **74**: ^1H; ^{13}C; EI-HRMS.

***N*,*N*,3,7-Tetramethyl-9-phenyl-(2(*E*),6(*E*)-nonadienyl)-amine (75).** As for **13**, 1.30 g (5.32 mmol) of **74** afforded 92% of 3,7-dimethyl-9-phenyl-2(*E*),6(*E*)-nonadienyl bromide: ^1H; ^{13}C. As for **14**, 1.30 g (4.23 mmol) of this bromide afforded 57% of **75**: ^1H; ^{13}C; EI-HRMS.

***N*,*N*,3,7-Tetramethyl-9-phenyl-(2(*E*),6(*E*)-nonadienyl)-ammonium-1-(4-butylsulfonate) (76).** As for **20**, 0.508 g (1.86 mmol) of **75** afforded 0.155 g (21%) of hygroscopic colorless **76**: mp 273−275 °C; ^1H; ^{13}C; FAB-HRMS.

7-Acetoxy-9-phenyl-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-*n*-nonane (78). A solution of 2.63 g (14.5 mmol) of 6-bromo-1-hexanol in 182 mL of CH_2Cl_2 at 0 °C was treated with 2.30 mL (16.7 mmol) of Et_3N, 2.40 g (16.0 mmol) of *tert*-butyldimethylsilyl chloride, and 70.9 mg (0.58 mmol) of DMAP. The mixture was stirred at 0 °C for 20 min and at room temperature for 8 h and evaporated. The residue was treated with 50 mL of Et_2O and extracted with 3 × 20 mL of 10% aqueous HCl solution, followed by 30 mL of brine, and the organic layer was dried ($MgSO_4$) and evaporated. NPC (2.5:97.5 EtOAc/hexane) gave 3.83 g (89%) of **77**:[27] ^1H; ^{13}C. A suspension of 0.41 g (17.1 mmol, 1.4 equiv) of Mg turnings and 5.05 g (17.1 mmol) of **77** in 70 mL of THF was heated at 90 °C until all the Mg was consumed (3.5 h). A solution of 1.96 g (14.6 mmol) of 3-phenylpropanal in 10 mL of THF was added, and the mixture was stirred at 70 °C for 3 h and diluted with 30 mL of 5% aqueous HCl. Usual workup (ether) gave a residue that was treated with 30 mL of Et_2O, 16 mL of Ac_2O, 32 mL of pyridine, and 47 mg of DMAP. The mixture was stirred at room temperature for 17 h and diluted with 50 mL of saturated aqueous $NaHCO_3$ solution. Usual workup (ether) and NPC (1:9 EtOAc/hexane) gave 4.42 g (92%) of **78**: ^1H; ^{13}C; FAB-HRMS.

7-Acetoxy-9-phenyl-*n*-nonan-1-ol (79). A solution of 1.49 g (3.80 mmol) of **78** in 48 mL of THF at 0 °C was slowly treated with 4.2 mL (4.18 mmol) of a 1.0 M solution of $(n\text{Bu})_4NF$ in THF, stirred at 0 °C for 20 min, allowed to warm to room

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temperature, stirred for 2.5 h, and evaporated, and the residue was treated with 50 mL of H_2O. Usual workup (ether) and NPC (2:3 EtOAc/hexane) gave 0.99 g (93%) of **79**: ^1H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-7-(acetyloxy)-9-phenyl-*n*-nonanamine (80).** As for **41** (in hexane), 0.20 g (0.72 mmol) of **79** afforded, after NPC (1:4 EtOAc/hexane), 0.17 g (50%) of 7-(acetyloxy)-1-bromo-9-phenylnonane: ^1H; ^{13}C. As for **42**, 0.21 g (0.62 mmol) of this bromide gave, after NPC (10:88:2 MeOH/EtOAc/concd NH_4OH), 0.19 g (100%) of **80**: ^1H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-*N*-1-(7-acetoxy-9-phenyl-*n*-nonyl)ammonium-1-(4-butylsulfonate) (81).** By procedures similar to those used in the preparation of **24**, 0.75 g (2.46 mmol) of **80** was converted by successive treatment with 1,4-dibromobutane and Na_2SO_3 in 49% yield to **81**: ^1H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-*N*-1-(7-hydroxy-9-phenyl-*n*-nonyl)ammonium-1-(4-butylsulfonate) (82).** According to a procedure of Rapoport,[65] 0.73 g (1.66 mmol) of **81** was methanolyzed to give 92% of **82**: ^1H; ^{13}C; FAB-HRMS.

1-[3-(*N,N*-Dimethylamino)propyl]-5-phenyl-2(*E*)-pentenoamide (84). The procedure of Schmidt et al.[57] was used to convert 3-phenylpropanal in 95% yield to ethyl 5-phenyl-2(*E*)-pentenoate, which was saponified to give 88% of **83**: mp 101−102 °C (lit.[29] mp 101−103 °C; lit.[30] mp 103−104 °C): ^1H; ^{13}C. A solution of 1.21 g (6.89 mmol) of **83** and 0.61 g (7.56 mmol) of pyridine in 23.3 mL of CH_2Cl_2 was treated with 1.06 g (8.25 mmol) of oxalyl chloride in 0 °C under N_2. The mixture was stirred at room temperature for 20 h and evaporated. The residue was dissolved in 23 mL of dry THF and added to a solution of 0.53 g (5.30 mmol) of 3-(*N,N*-dimethylamino)-1-propanol and 0.127 g (5.30 mmol) of NaH in 15 mL of dry THF at 0 °C under N_2. The mixture was stirred for 24 h at room temperature, evaporated, dissolved in $CHCl_3$, extracted with cold 10% Na_2CO_3, dried over $MgSO_4$, filtered through K_2CO_3, and evaporated to afford 2.38 g of residue. NPC (15:83:2 CH_3OH/EtOAc/concd NH_4OH) gave 1.24 g (90%) of oily **84**, which was converted into its hydrochloride with anhydrous HCl (1M) in Et_2O: mp 131.5−132.5 °C; ^1H; ^{13}C; C, H, N.

***N,N*-Dimethyl-N-1-[3-(5-phenyl-2(*E*)-pentenoate)propyl]-ammonium-1-(4-butylsulfonate) (85).** A mixture of 0.867 g (3.32 mmol) of **84** and 0.572 g (31.4 mmol) of **15** in 25 mL of DMF was heated at reflux under N_2 for 2 d and evaporated to yield 2.11 g of residue. RPC (35:65 H_2O/methanol) gave 0.856 g (65%) of crude **85**, which was dissolved in EtOH and precipitated with Et_2O to afford 0.526 g (40%) of **85**: mp 201−203 °C; ^1H; ^{13}C; C, H, N.

1-Bromo-3,4-epoxybutane (86). By the procedure of Thanei-Wyss and Waser,[31] 2.18 g (16.1 mmol) of 1-bromo-3-butene was epoxidized to give 84% of **86**: ^1H; ^{13}C.

***N,N*-Dimethyl-*N*-1-(3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatrienyl)ammonium-1-(3-hydroxy-4-butylsulfonate) (87).** By the procedure described next for preparation of **88**, 0.42 g (1.69 mmol) of **14** was converted in 45% yield to **87**: ^1H; ^{13}C; FAB-HRMS.

***N,N*-Dimethyl-*N*-1-(9-phenyl-*n*-nonyl)ammonium-1-(3-hydroxy-4-butylsulfonate) (88).** A solution of 0.350 g (2.32 mmol) of **86** in 5 mL of anhydrous Et_2O was treated with 0.284 g (1.15 mmol) of **29** in 4 mL of ether, the mixture was heated at reflux (60 °C) for 19 h and evaporated, and the residue was dissolved in a minimum amount of EtOH. Addition of ether precipitated the ammonium salt, which was collected, dissolved in 1.5 mL of MeOH, and treated with 0.22 g (1.73 mmol) of Na_2SO_3 in 6 mL of H_2O. The mixture was heated at 70 °C for 6 h and evaporated, and the residue was mixed with 30 mL of CH_3OH, which was filtered and evaporated. RPC (3:7 H_2O/MeOH) gave 0.28 g (61%) of **88**, which was dissolved in a minimum amount of 95% EtOH, precipitated with Et_2O, and dried in vacuo at 50 °C to afford 0.22 g (48%) of **88**: ^1H; ^{13}C; FAB-HRMS.

1-Bromo-7-phenylheptane (89).[32] A solution of 18.0 g (70.3 mmol) of 1,7-dibromoheptane in 80 mL of THF was cooled to −78 °C and treated with 2.35 g (28.0 mmol) of 1.8 M phenyllithium in cyclohexanes−ether. The mixture was stirred for 30 min, warmed to room temperature, stirred for 24 h, quenched with 20 mL of saturated NH_4Cl solution, and evaporated to give 17.3 g of residue. NPC (hexane) gave a fraction (5.97 g, $R_f \approx 0.8$) containing **89**, 1,7-dibromoheptane, and 1,7-diphenylheptane. The 1,7-dibromoheptane was removed by distillation at 47 °C (0.25 mm) to yield 2.23 g (82%) of colorless oily **89** containing a trace of 1,7-diphenylheptane: ^1H (lit.[32] ^1H); ^{13}C (lit.[32] ^{13}C).

1-(7-Phenylheptyl)imidazole (90). To a solution of 0.27 g (3.9 mmol) of imidazole in 10 mL of acetone was added 1.1 g (20 mmol) of KOH with vigorous stirring. After 5 min, 0.5 g (2.0 mmol) of **89** was added dropwise. The mixture was stirred for 72 h and evaporated. The residue was redissolved in 20 mL of CH_2Cl_2, and 15 mL of H_2O was added. The aqueous layer was washed with 15 mL of CH_2Cl_2. The combined organic layers were diluted with 20 mL of hexane and washed with 20 mL of 10% hydrochloric acid. The aqueous layer was made basic with 1 N sodium hydroxide and extracted with 2 × 15 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated to yield 0.29 g (61%) of **90**. A 0.35 g sample of **90** was treated with a saturated solution of HCl in Et_2O. Evaporation and two recrystallizations from EtOH/Et_2O gave 0.32 g (79%) of off-white flaky hydrochloride: ^1H; ^{13}C.

1-(7-Phenylheptyl)imidazolium-3-(4-butylsulfonate) (91). A solution of 0.29 g (1.2 mmol) of **90** and 0.12 mL (1.2 mmol) of **15** in 20 mL of acetone was heated at reflux for 4 d, after which time TLC showed unreacted **90**. DMF (20 mL) was added, the mixture was heated at reflux for 3 d and concentrated in vacuo, and Et_2O was added to precipitate 0.76 g of residue. RPC (2:3 H_2O/CH_3OH) gave 0.38 g (83%) of **91**, which was recrystallized from EtOH/Et_2O to afford fluffy white solid **91**: mp 142−143 °C; ^1H; ^{13}C; C, H, N.

***N*-Methylbis(3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatrienyl)amine (Difarnesylmethylamine, 92).** As for **14**, 2.50 g (10.7 mmol) of **13** and 30 mL of methylamine gave 2.37 g (95%) of farnesylmethylamine: ^1H (lit.[66] ^1H); ^{13}C (lit.[66] ^{13}C). To a solution of 2.00 g (8.54 mmol) of farnesylmethylamine in 10 mL of Et_2O was added 2.40 g (8.40 mmol) of **13**. The mixture was stirred for 48 h at room temperature under N_2, washed with 3 × 50 mL of 2.0 N NaOH, dried over $MgSO_4$, and evaporated to give 4.14 g of residue. NPC (1:19 CH_3OH/EtOAc) gave 0.91 g (25%) of tan oily **92**: ^1H; ^{13}C; C, H. N.

***N*-Methyl-1-bis(3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatrienyl)ammonium-1-(4-butylsulfonate) (93).** To a solution of 0.461 g (1.05 mmol) of **92** in 10.0 mL of 1,2-dichloroethane was added 1.36 g (1.00 mmol) of **15**. The mixture was stirred at 40 °C for 36 h, diluted with CH_2Cl_2 to 40 mL, washed with 3 × 50 mL of H_2O, dried over $MgSO_4$, and evaporated to give 2.0 g of brown residue. NPC (gradient hexane to EtOAc; then 1:9 CH_3OH/EtOAc) gave 0.088 g (15%) of tan oily **93**: ^1H; ^{13}C; FAB-HRMS.

9-Phenyl-1-bromononane (94).[34] By the procedure used in the preparation of **27**, 12.4 g (43.4 mmol) of 1,9-dibromononane afforded 53% of **94**, bp 135−141 °C (0.3 mmHg). Alternatively, a solution of 1.01 g (4.59 mmol) of 9-phenyl-1-hydroxynonane (Lancaster Synthesis, Inc.) in 50 mL of ether at 0 °C was treated with 0.17 mL (1.84 mmol) of PBr_3, and the mixture was allowed to warm to room temperature, stirred for 3 d, and treated with 20 mL of 5% aqueous $NaHCO_3$ solution. Usual workup and NPC (3:9 EtOH/hexane) gave 0.97 g (75%) of **94**: ^1H (lit.[34] ^1H); ^{13}C.

***N*-Methyl-9-phenyl-*n*-nonylamine (95).** Crude **94** was treated with excess CH_3NH_2 to afford, after NPC (10:88:2 CH_3OH/EtOAc/concd NH_4OH), 53% of **95**: ^1H; ^{13}C; C, H, N.

***N*-Methyl,*N*-(9-phenyl-*n*-nonyl)-9-phenyl-*n*-nonylamine (96).** According to the procedure of Amundsen and Sanderson,[67] a solution of 0.45 g (1.59 mmol) of **94** in 6 mL of xylene was treated with a solution of 0.77 g (3.30 mmol) of **95**

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in 3.0 mL of xylene. The mixture was heated at reflux (oil bath, 170−185 °C) for 16 h. The xylene was removed under reduced pressure, and the residue was diluted with 20 mL of ether. The precipitate which formed was removed by filtration, and the residue was washed several times with ether, which was then evaporated. NPC (1:9 MeOH/EtOAc) gave 0.49 g (70%) of **96**: ^{1}H; ^{13}C; FAB-HRMS.

***N*-Methyl-*N*,*N*-bis(9-phenyl-*n*-nonyl)ammonium-1-(4-butylsulfonate) (97).** As for **81** (except a reaction time of 4 d), 0.18 g (0.41 mmol) of **96** gave 0.11 g (46%) of **97**, which was precipitated from EtOH with Et_2O and dried at 50 °C in vacuo overnight to afford the off-white solid **97**: ^{1}H; ^{13}C; FAB-HRMS.

***N*-Methyl-*N*-(3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatrienyl)-9-phenyl-*n*-nonamine (98).** A mixture of 0.50 g (2.15 mmol, 1 equiv) of **95** and 0.89 g (10.8 mmol, 5 equiv) of $NaHCO_3$ in 26 mL of THF was treated with a solution of 0.61 g (2.14 mmol, 1 equiv) of **13** in 8 mL of THF. The mixture was stirred at room temperature for 39 h, washed with 3 × 12 mL of 2 M aqueous NaOH solution and 15 mL of brine, dried ($MgSO_4$), and evaporated. NPC (1:19 MeOH/EtOAc) gave 0.31 g (33%) of **98**: ^{1}H; ^{13}C; FAB-HRMS.

***N*-Methyl-*N*-(3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatrienyl)-*N*-1-(9-phenyl-*n*-nonanyl)ammonium-1-(4-butylsulfonate) (99).** As for **81** (except a reaction time of 4.5 d), 0.24 g (0.55 mmol) of **98** gave, after precipitation from EtOH with Et_2O, 0.14 g (44%) of **99**: ^{1}H; ^{13}C; FAB-HRMS.

***N*-Methyl-*N*-(3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatrienyl)benzylamine (100).** To a solution of 2.21 g (7.75 mmol) of **13** in 31 mL of THF was added a solution of 1.94 g (16.03 mmol) of *N*-methylbenzylamine in 5 mL of THF. The mixture was heated at 85 °C for 16 h and evaporated, and the residue was mixed with 70 mL of ether, which was filtered, and the filtrate was evaporated. NPC (3:17 MeOH/EtOAc) gave 1.72 g (68%) of **100**: ^{1}H; ^{13}C; FAB-HRMS.

***N*-Methyl-*N*-(3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatrienyl)-*N*-benzylammonium-1-(4-butylsulfonate) (101).** As for **97**, 1.54 g (4.74 mmol) of **100** afforded 52% of **101**: ^{1}H; ^{13}C; FAB-HRMS.

***N*-Benzyl-*N*-methyl-9-phenyl-*n*-nonylamine (102).** As for **100**, 0.95 g (3.36 mmol) of **94** and 0.84 g (6.94 mmol) of *N*-methylbenzylamine afforded 84% of **102**: ^{1}H; ^{13}C; FAB-HRMS.

***N*-Benzyl-*N*-methyl-*N*-1-(9-phenyl-*n*-nonyl)ammonium-1-(4-butylsulfonate) (103).** As for **97**, 0.39 g (1.21 mmol) of **102** afforded 35% yield of **103**: ^{1}H; ^{13}C; FAB-HRMS.

1,12-Bis(*N*,*N*-dimethylamino)dodecane (105).[37] A solution of 1.01 g (3.08 mmol) of 1,12-dibromododecane in 25 mL of THF was cooled to −78 °C and treated with 28.7 g (586 mmol) of $(CH_3)_2NH$. The mixture was stirred at −78 °C for 30 min, allowed to warm to room temperature, tightly stoppered, stirred for 24 h at room temperature, and evaporated. The residue (847 mg) was dissolved in 50 mL of ether, washed with 3 × 25 mL of 2 M NaOH solution, dried ($MgSO_4$), and evaporated to yield 787 mg (99%) of yellow oily **105**: ^{1}H; ^{13}C; FAB-HRMS.

***N*,*N*′-Bis[dimethylammonium-1-(4-butylsulfonyl)]dodecane (106).** A mixture of 787 mg (3.07 mmol) of **105** and 1.26 g (9.22 mmol) of **15** in 20 mL of MeOH was stirred at room temperature for 14 d and then evaporated to give 2.04 g of residue. RPC (1:9 H_2O/CH_3OH) gave 345 mg of **106**, which was crystallized from EtOH and dried for 12 h in vacuo at 50 °C to yield 283 mg (18%) of colorless **106**: mp 288−289 °C; ^{1}H; ^{13}C; FAB-HRMS.

***N*-Methyldodecylamine (107).**[38] As for **105**, 10.0 g (40.0 mmol) of 1-bromododecane gave 8.66 g of residue. NPC (10:88:2 CH_3OH/EtOAc/concd NH_4OH) gave 5.17 g (65%) of yellow oily **107**: ^{1}H; ^{13}C; C, H, N.

***N*,*N*′-Bis(methyldodecyl)ethylenediamine (108).** A mixture of 3.29 g (16.5 mmol) of **107**, 1.32 g (7.03 mmol) of 1,2-dibromoethane, and 2.00 g (14.0 mmol) of K_2CO_3 in 45 mL of 95% EtOH was heated at reflux (oil bath, 78−82 °C) with rapid stirring for 48 h and evaporated. A solution of the 6.61 g of residue in 50 mL of ether was washed with 3 × 30 mL of 2 M NaOH, dried ($MgSO_4$), and evaporated to give 4.08 g of residue. Chromatography on basic alumina (EtOAc) gave 1.73 g (58%) of yellow oily **108**: ^{1}H; ^{13}C; C, H, N.

1,2-Bis[*N*-methyldodecylammonium-1-(4-butylsulfonyl)]-ethane (109). A mixture of 400 mg (1.65 mmol) of **108** and 250 mg (1.84 mmol) of **15** in 20 mL of DMF was heated at reflux (oil bath, 152−158 °C) for 24 h and evaporated to give 650 mg of residue. RPC (3:7 H_2O/MeOH) gave 98.0 mg of **109**, which was dissolved in absolute EtOH and precipitated by addition of Et_2O to yield 77.0 mg (11%) of colorless **109**: mp 166−167 °C; ^{1}H; ^{13}C; FAB-HRMS.

***N*,*N*′-Bis(methyl-9-phenylnonyl)ethylenediamine (110).** As for **108** (except a reaction time of 24 h), 1.22 g (5.47 mmol) of **95** gave 2.59 g of residue. Chromatography on basic alumina (EtOAc) gave 509 mg (40%) of yellow oily **110**: ^{1}H; ^{13}C; FAB-HRMS.

1,2-Bis[*N*-methyl-1-(9-phenylnonyl)ammonium-1-(4-butylsulfonyl)]ethane (111). As for **109** (except a reaction time of 48 h), 407 mg (0.827 mmol) of **110** was converted in 12% yield to **111**: mp 131.5−134.5 °C; ^{1}H; ^{13}C; FAB-HRMS.

2-(Hydroxymethyl)-9-phenylnonanol (112). A solution of 510 mg (22.2 mmol) of Na in 20 mL of absolute EtOH was treated with 3.52 g (22.0 mmol) of diethyl malonate. This mixture was added dropwise to a solution of 5.00 g (22.2 mmol) of **89** in 50 mL of absolute EtOH over 15 min. The mixture was stirred for 15 min at room temperature, heated at reflux (oil bath, 80−85 °C) for 4 h, and evaporated, and the residue (9.10 g) was dissolved in 50 mL of ether, washed with 30 mL of 10% NH_4Cl solution, and evaporated to give 6.63 g of residue. A mixture of 6.56 g of this residue and 4.17 g (101 mmol) of $LiAlH_4$ in 80 mL of THF was heated at reflux (oil bath, 65−70 °C) for 3 d. The mixture was quenched with 20 mL of H_2O, followed by 30 mL of 10% HCl solution, and the THF was evaporated. The aqueous layer was extracted with 3 × 25 mL of CH_2Cl_2. The combined organic layers were washed with 3 × 25 mL of saturated $NaHCO_3$ solution and evaporated to give 5.30 g of residue. NPC (1:1 EtOAc/hexane) gave 2.23 g (40%) of colorless oily **112**: ^{1}H; ^{13}C.

2-(Bromomethyl)-9-phenylnonyl Bromide (113). According to a modification of a procedure by Nampalli,[68] a solution of 646 mg (2.58 mmol) of **112** in 25 mL of DMF at 0 °C was treated dropwise with 1.40 g (5.17 mmol) of PBr_3. The mixture was stirred overnight at room temperature, poured over ice, extracted with 3 × 25 mL of CH_2Cl_2, and evaporated to give 1.01 g of residue. NPC (hexane) gave 753 mg (77%) of colorless oily **113**: ^{1}H; ^{13}C; C, H.

2-(*N*′,*N*′-Dimethylmethylamino)-*N*,*N*-(dimethylamino)-9-phenylnonane (114). As for **105**, 676 mg (1.80 mmol) of **113** gave 572 mg of residue. NPC (10:88:2 MeOH/EtOAc/concd NH_4OH) gave 340 mg (62%) of yellow oily **114**: ^{1}H; ^{13}C; FAB-HRMS.

2-(*N*′,*N*′-Dimethylmethylammonium)-1′-(4′-butylsulfonyl)-*N*,*N*-dimethyl-1-(9-phenylnonyl)ammonium-1-(4-butylsulfonate) (115). As for **109**, 340 mg (1.12 mmol) of **114** was converted in 11% yield to **115**: mp 266−268 °C; ^{1}H; ^{13}C; C, H, N.

Inhibition Assays. Rat liver microsomal SS assays were conducted as previously described.[13]

Acknowledgment. This research was partially supported by NIH Grant No. HL50628 to I.S.

Supporting Information Available: Additional experimental details for preparation of some compounds and ^{1}H and ^{13}C NMR data and combustion or HRMS analytical data for all new compounds (26 pages). See any current masthead page for ordering and Internet access information.

JO981617Q

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