Synthesis of Inhibitors of 2,3-Oxidosqualene-lanosterol Cyclase: Conjugate Addition of Organocuprates to *N*-(Carbobenzyloxy)-3-carbomethoxy-5,6-dihydro-4-pyridone

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Received November 20, 1991

Synthesis of ammonium ion analogues of the first cationic intermediate, **5**, presumed to be formed during the cyclization of 2,3-oxidosqualene by 2,3-oxidosqualene-lanosterol cyclase are reported. The required 2,3-substituted-4-piperidinols are prepared by conjugate addition of higher order alkyl (2-thienyl)(cyano)cuprates to 1-(carbobenzyloxy)-3-carbomethoxy-5,6-dihydro-4-pyridone. The nitrogen protecting group (carbobenzyloxy) is key to the synthesis in that it allows the conjugate addition to proceed in high yield and is easily converted to the required *N*-methyl group in the final products. The key terpenoid side chain appended to C-2 of the piperidinols was constructed from homofarnesyl bromide and 1,5-difunctionalized homoisopentenyl derivatives prepared by zirconium-catalyzed carboalumination of protected 1-butyn-4-ol.

Introduction

The reaction mediated by 2,3-oxidosqualene-lanosterol cyclase[1,2] is one of the most complex in nature. This enzyme catalyzes the sequential formation of four new carbon–carbon bonds leading to protosterol (**1**), as well as the backbone rearrangement of this intermediate to lanosterol (**2**). The mechanism of the cyclization of (3*S*)-2,3-oxidosqualene (**3**) to lanosterol (**2**) by this enzyme has long been a subject of debate. The initial cyclization could proceed either via a "synchronous" process,[3] whereby no discrete intermediates are generated in the formation of **1**, or via a "stepwise" mechanism. The latter, as advanced by van Tamelen,[4,5b,d-f] involves generation of a series of conformationally rigid carbocationic intermediates during the initial cyclization (Scheme I).

The entropic requirement to fold 2,3-oxidosqualene in a conformation resembling the chair-boat-chair five-membered ring topology of **1** renders the "synchronous" process unlikely. Furthermore, acceptance of unnatural modified 2,3-oxidosqualenes and partially cyclized substrate analogues[5,6,7] by the cyclase reveals the lack of a perfect "lock and key" requirement and suggests that entropic control by this enzyme may be minimal. As well, chemical,[3,4b,8,9] theoretical,[10] and biological[11] evidence strongly suggests that the "stepwise" cyclization involving enzymatically stabilized carbocationic intermediates is the most likely process. Recent work suggests that a sulfhydral group may be involved in stabilizing the carbocationic intermediates.[2e]

The only direct evidence for the "stepwise" mechanism in the enzyme-mediated process has been presented by Boar et al.,[11] who isolated bicyclic triterpenoid **8** (Figure 1), which arises from the interception of the presumptive carbocation intermediate **6** by water. The equatorial geometry of the C-8 hydroxyl group (steroid numbering) is that expected if **6** undergoes a chair-boat to chair-chair conformational change prior to reaction with water from the least hindered α-face.[6]

An incisive approach to the question of the involvement of carbocation intermediates in the cyclization of 2,3-oxidosqualene is the study of the inhibition of 2,3-oxidosqualene-lanosterol cyclase by cationic heteroatom mimics of the presumptive intermediates. If the initial formation of ring A leading to intermediate **5** is the rate-limiting step in the enzymatic cyclization, as observed by van Tamelen for the biomimetic cyclizations,[4b] then the cyclase might achieve this kinetic result by stabilization of the first-formed cationic intermediate **5**. If this is the case, then mechanism-based inhibition by analogues of **5** would be expected to be significant.

Inhibition[1c,7] of 2,3-oxidosqualene cyclases from plant, animal, and fungal sources has been achieved by ammonium ion mimics of the presumptive intermediate **6**. Thus, azadecalins, possessing a 1,5-polyene terpenoid chain and

(1) (a) Schroepfer, G. J., Jr. *Ann. Rev. Biochem.* **1982**, *51*, 555. (b) Poulter, C. D.; Rilling, H. J. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; John Wiley and Sons: New York, 1981; Vol. 1. (c) Oehlschlager, A. C.; Czyzewska, E. In *Emerging Targets in Antibacterial and Antifungal Chemotherapy*; Sutcliffe, J., Georgopapadakou, N. H., Eds.; Routledge, Chapman & Hall, Inc.: New York, 1992.

(2) (a) For purification of 2,3-oxidosqualene-lanosterol cyclase, see: Cory, E. J.; Matsuda, S. P. T. *J. Am. Chem. Soc.* **1991**, *113*, 8172 and references cited therein. (b) For partial purifications, see: Hoshino, T.; Williams, H. J.; Chung, Y.; Scott, A. I. *Tetrahedron* **1991**, *47*, 5925. (c) For purification of the cyclases from plants, see: Abe, I.; Ebizuka, Y.; Sankawa, U. *Chem. Pharm. Bull. Jpn.* **1988**, *36*, 5031 and (d) Abe, I.; Ebizuka, Y.; Seo, S.; Sankawa, U. *FEBS Lett.* **1989**, *249*, 100. (e) Duriatti, A.; Schuber, F. *Biochem. Biophys. Res. Commun.* **1988**, *151*, 1378. (f) Sen, S. E.; Prestwich, G. D. *J. Med. Chem.* **1989**, *32*, 2152 from animal source.

(3) (a) For a thorough review on this topic, see: Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9. (b) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. See also refs 9a,b for leading sources.

(4) (a) van Tamelen, E. E. *J. Am. Chem. Soc.* **1982**, *104*, 6480 and references cited therein. (b) van Tamelen, E. E.; James, D. R. *J. Am. Chem. Soc.* **1977**, *99*, 950.

(5) (a) Corey, E. J.; Lin, K.; Jautelat, M. *J. Am. Chem. Soc.* **1968**, *90*, 2724. (b) van Tamelen, E. E.; Sharpless, K. B.; Willett, J. D.; Clayton, R. B.; Burlingame, A. L. *J. Am. Chem. Soc.* **1967**, *89*, 3920. (c) Corey, E. J.; Gross, S. K. *J. Am. Chem. Soc.* **1967**, *89*, 4561. (d) van Tamelen, E. E.; Sharpless, K. B.; Hanzlik, R. P.; Clayton, R. B.; Burlingame, A. L.; Wszolek, P. C. *J. Am. Chem. Soc.* **1967**, *89*, 7150. (e) van Tamelen, E. E.; Hopla, R. E. *J. Am. Chem. Soc.* **1979**, *101*, 6112. (f) van Tamelen, E. E.; Leopold, E. J.; Marson, S. A.; Waespe, H. R. *J. Am. Chem. Soc.* **1982**, *104*, 6479. (g) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 4025. (h) Corey, E. J.; Virgil, S. C.; Sarshar, S. *J. Am. Chem. Soc.* **1991**, *113*, 8171.

(6) (a) Medina, J. C.; Guajardo, R.; Kyler, K. S. *J. Am. Chem. Soc.* **1989**, *111*, 2310. (b) Medina, J. C.; Kyler, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 4818. This group has found that the structural features that perturb the β-face but not the α-face of the modified 2,3-oxidosqualene substrates folded in the chair-boat-chair conformation interfere with the enzymatic cyclization.

(7) For a complete up-to-date set of references on the inhibitors of 2,3-oxidosqualene-lanosterol cyclase, see: Xiao, X.-Y.; Prestwich, G. D. *J. Am. Chem. Soc.* **1991**, *113*, 9673.

(8) Johnson, W. S; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517.

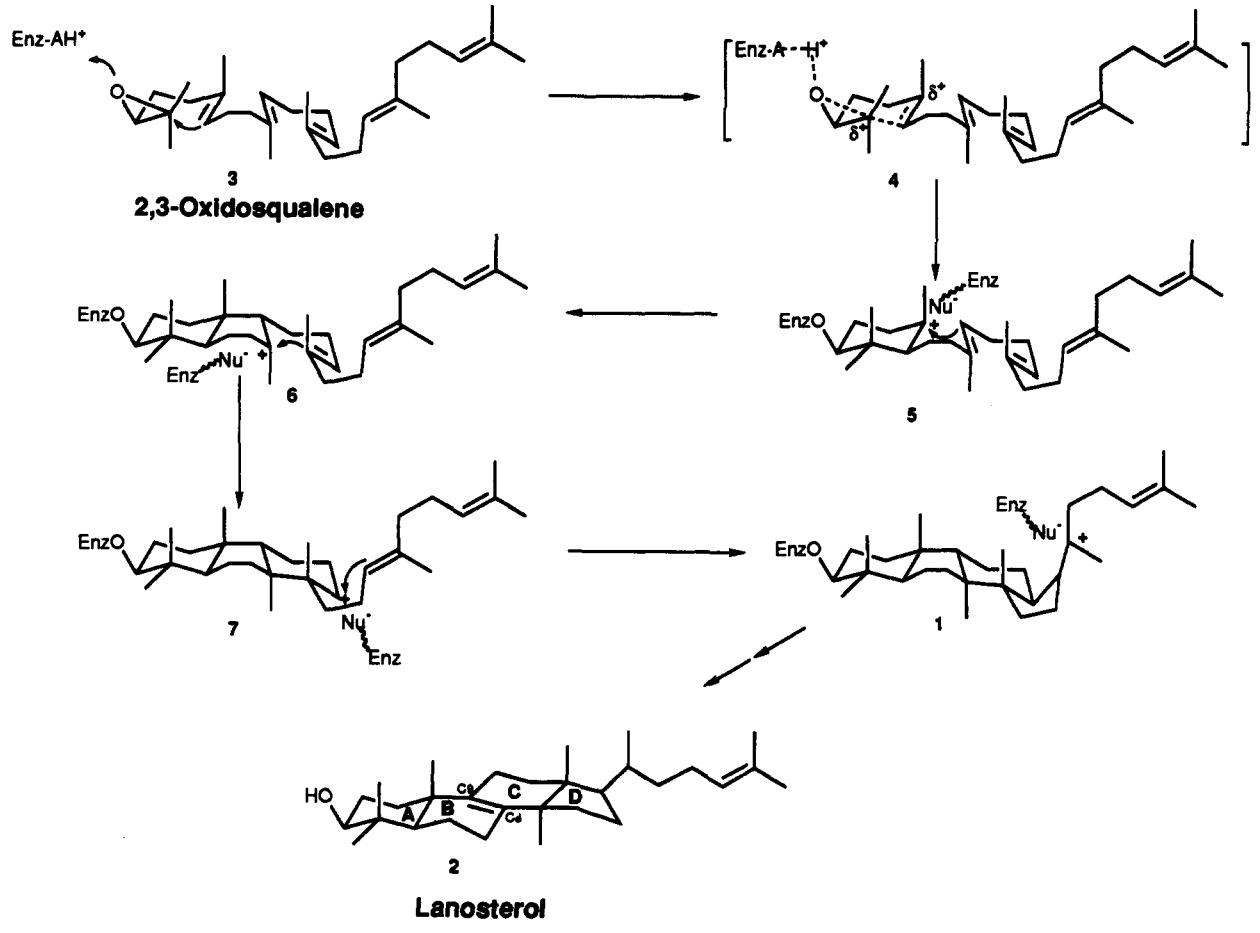
(9) (a) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522. (b) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806.

(10) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1984**, *106*, 1744.

(11) Boar, R. B.; Couchman, L. A.; Jaques, A. J.; Perkins, M. J. *J. Am. Chem. Soc.* **1984**, *106*, 2476.

0022-3263/92/1957-2794$03.00/0

Scheme I



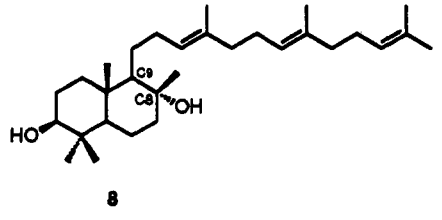


Figure 1.

a 3β-hydroxyl group are efficient inhibitors.[12-14] The results of these studies have demonstrated the importance of both the β-hydroxyl group and the branched methyls in the hydrophobic side chain on the azadecalin mimics. As well, alteration of the degree of unsaturation and/or shortening of the side chain decreases the effectiveness of the inhibitors.

Results and Discussion

We now report the syntheses of ammonium ion mimics (**21**, **22**, **45a**, **45b**) (Figure 2) of intermediate **5** presumed to be produced upon the initial formation of ring A of protosterol. We have varied the length of the side chain, the positions of the side-chain branch methyls, and substituents on the ring to examine the structural requirements for inhibition. Although these compounds are racemic mixtures, the syn relationship between the C-4 β-hydroxyl group and the C-2 side chain of the piperidinols has been maintained and it is believed that only the active enantiomer will inhibit the enzyme. The amines **20**, **44a**, and **44b** are expected to be fully protonated at physiological pH and thus should also mimic intermediate **5** to

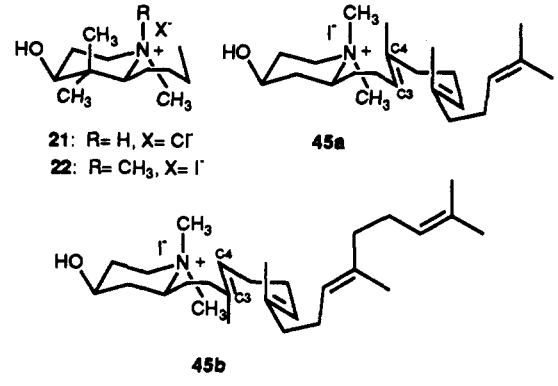
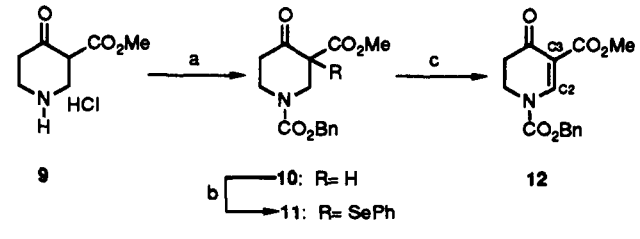


Figure 2.

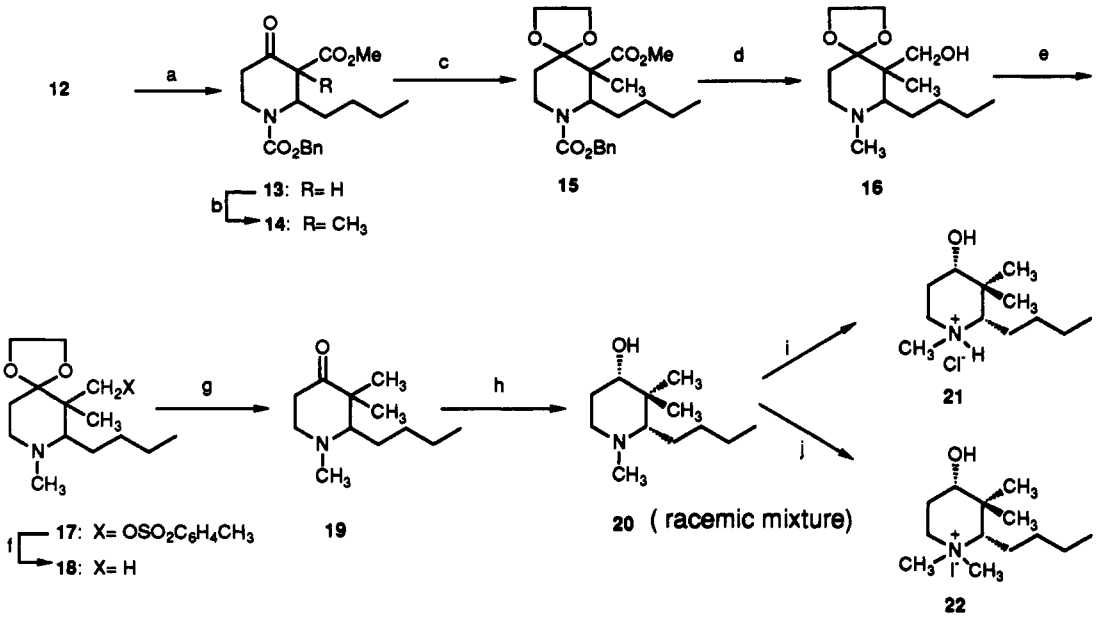
Scheme II[a]



[a] (a) $ClCO_2Bn$, Et_3N, CH_2Cl_2; (b) NaH, PhSeBr, THF; (c) 5% H_2O_2–H_2O, CH_2Cl_2.

(12) Gerst, N.; Duriatti, A.; Schuber, F.; Taton, M.; Benveniste, P.; Rahier, A. *Biochem. Pharmacol.* **1988**, *37*, 1955.
(13) Taton, M.; Benveniste, P.; Rahier, A. *Pure Appl. Chem.* **1987**, *59*, 287.
(14) Duriatti, A.; Bouvier-Navé, P.; Benveniste, P.; Schuber, F.; Delprino, I.; Balliano, G.; Cattel, L. *Biochem. Pharmacol.* **1985**, *34*, 2765.

Scheme III[a]



[a] (a) n-$Bu_2Cu(CN)Li_2$, THF, −78 °C; (b) NaH, MeI, DMF; (c) $(CH_2OH)_2$, TsOH, toluene; (d) $LiAlH_4$, THF; (e) n-BuLi, TsCl, Et_2O; (f) $LiBEt_3H$, THF; (g) 6 N HCl, acetone–H_2O; (h) $LiAlH_4$, THF, −78 °C; (i) anhydrous HCl–Et_2O; (j) MeI, Et_2O.

an extent similar to that of quaternary ammonium methiiodide salts **22**, **45a**, and **45b** and the hydrochloride salt **21**.

Retro-synthetic analysis revealed that the required compounds could be prepared from the conjugate addition of organocuprates, derived from the appropriate Grignard or lithium species, to a α,β-unsaturated 4-piperidone.[15] We found 1-(carbobenzyloxy)-3-carbomethoxy-5,6-dihydro-4-pyridone (**12**)[16] to be an excellent candidate for this strategy (Scheme II). It allowed introduction of various alkyl groups at C-2 of the 4-pyridone as well introduction of geminal methyl groups, as in compounds **20** and its ammonium salts, at C-3. Cuprates prepared from alkyllithium or Grignard reagents reacted with **12** to give high yields of conjugate addition products.

Synthesis of 5,6-Dihydro-4-pyridone (12). 5,6-Dihydro-4-pyridone (**12**) was obtained in three steps in 70–75% overall yield from commerically available methyl 4-oxopiperidine-3-carboxylate hydrochloride (**9**).[17] The latter was protected as the benzyl carbamate derivative **10** and selenylated[18] at C-3 to give **11** as a light yellow crystalline solid (70–80%). Best results were obtained in the selenylation when the sodium salt of β-keto ester **10** was generated with NaH in THF at 0 °C and then cooled to −50 °C prior to the addition of PhSeBr. The selenylated product **11** was easily purified by recrystallization from ethyl acetate–hexanes or treated as a crude isolate with 5% H_2O_2(aq) in CH_2Cl_2 at 0–5 °C to give, after chromatography, the unsaturated piperidone **12**.

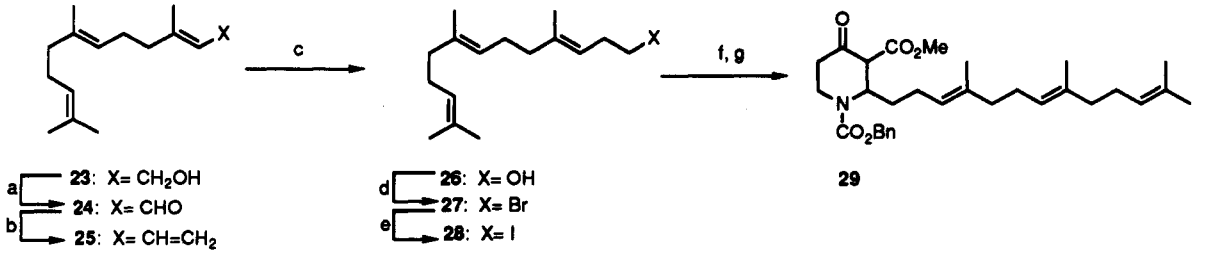
Synthesis of Inhibitors 20, 21, and 22. Amine **20** and its salts **21** and **22** were synthesized as models to test the minimal structural requirements of the side chain of analogues of **5** for inhibition of 2,3-oxidosqualene-lanosterol cyclase (Scheme III). Fabrication of this amine required the introduction of a relatively small carbon chain (C_4) at C-2 of **12** via conjugate addition of n-$Bu_2Cu(CN)Li_2$ and modification of C-3 to give geminal methyls.

The conjugate addition of n-$Bu_2Cu(CN)Li_2$ to **12** to give **13** was instantaneous and high yielding (87–91%) at −78 °C. ^{1}H NMR spectral assignments of **13** were complicated due to the restricted rotation about the nitrogen–carbon bond of the carbamate combined with enol–keto tautomerization of the β-keto ester. Methylation of **13** at room temperature was facilitated in DME to give **14** in 72% yield. Protection of the latter as the ethylene ketal **15** followed by treatment with $LiAlH_4$ in refluxing THF reduced the methyl ester and the benzyl carbamate in good yield to a hydroxymethyl and an N-methyl, respectively (**16**). The structure of the product was confirmed by the absence of the ^{1}H NMR signal due to the hydrogens (δ 3.70) of the methyl ester as well as the appearance of the signal due to the hydrogens of the N-methyl (δ 2.25). The hydroxyl group of **16** was converted to tosylate **17** (84%) by generation of the lithium alkoxide with n-BuLi in ether at 0 °C followed by addition of p-TsCl. Other methods of tosylation such as pyridine/p-TsCl and KOH/p-TsCl were unsuccessful. Tosylate **17** decomposed slowly upon storage, even at −20 °C, and was used within a day of preparation. Hydride displacement of the tosylate with $LiEt_3BH$[20] in refluxing THF gave the geminal dimethyl containing ketal **18** in 91% yield. Hydrolysis of **18** to give the 4-piperidone **19** required refluxing 6 N HCl (74% yield). The latter was reduced[19] at −78 °C with $LiAlH_4$ to give the equatorial alcohol as a racemic mixture (**20**), in an overall yield of 24% in 9 steps, with >95% diastereoselectivity as verified by gas chromatographic analysis. The equatorial stereochemistry of the hydroxyl group of **20** was confirmed by ^{1}H NMR, which revealed a doublet of doublets at δ 3.20 (J = 12.0, 5.0 Hz) for the axial methine hydrogen on the hydroxyl-bearing carbon.

Treatment of **20** with ether solutions of anhydrous HCl or MeI gave the respective ammonium salts **21** and **22** as white hygroscopic powders.

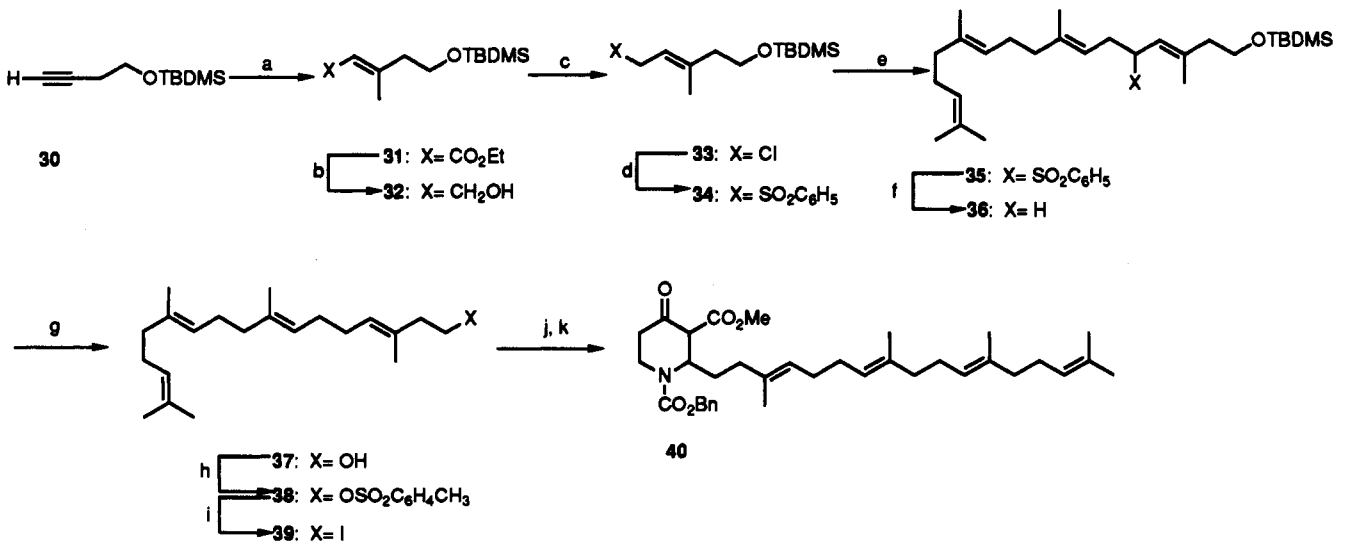
(15) (a) Lutz, A. H.; Schnider, O. *Helv. Chim. Acta* **1956**, *39*, 81. (b) Horii, Z.-I.; Morikawa, K.; Ninomiya, I. *Chem. Pharm. Bull.* **1969**, *17*, 846. (c) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445. (d) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549.
(16) Dodd, D. S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1991**, *32*, 3643.
(17) Available from Aldrich.
(18) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
(19) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064.
(20) Balasubramanian, M.; Padna, W. *Tetrahedron Lett.* **1960**, 23. Hydride reductions of N-alkyl-4-piperidones are known to give predominantly the equatorial alcohol.

Scheme IV[a]



[a] (a) Swern oxidation; (b) CH_2=PPh_3, THF; (c) Sia_2BH, THF, H_2O_2, NaOH; (d) PPh_3, Br_2, pyridine, CH_2Cl_2; (e) NaI, acetone; (f) 2.2 equiv of *t*-BuLi, Et_2O, −78 °C, then (2-Th)Cu(CN)Li in THF; (g) **12**, THF.

Scheme V[a]



[a] (a) $Zr(Cp)_2Cl_2$, $AlMe_3$, then $ClCO_2Et$, CH_2Cl_2; (b) Dibal-H, THF; (c) NCS–DMS, CH_2Cl_2; (d) $NaSO_2C_6H_5$, DMF; (e) *n*-BuLi, farnesyl bromide; (f) Li, $EtNH_2$, THF; (g) Bu_4NF, THF; (h) TsCl, Pyr; (i) NaI, acetone; (j) 2.2 equiv of *t*-BuLi (1.7 M in pentane), Et_2O, −78 °C then (2-Th)Cu(CN)Li, THF; (k) **12**, THF.

Synthesis of Inhibitors 44a and 44b and Methiiodide Salts 45a and 45b. The incorporation of a medium sized side chain in these inhibitors containing branched methyls and unsaturation was the next logical extension. The homofarnesyl side chain was choosen for this purpose and introduced to compound **44a** and its methiiodide salt **45a**. The homofarnesyl chain as well as meeting the above requirement also provided the opportunity to test if the position of the branched methyls (side-chain C-3 methyl moved to C-4, see **45a** and **45b**, Figure 2) on the chain affects the mode of inhibition.

The homofarnesyl chain was prepared from (*E*),(*E*)-farnesol in an analogous procedure to that described by Leopold[21a] for the synthesis of homogeraniol from geraniol. (*E*),(*E*)-Farnesol (**23**) was first converted to farnesal[22] (**24**) in 92% yield via Swern oxidation.[23] The latter was reacted with methylenetriphenylphosphorane, generated from methyltriphenylphosphonium iodide and PhLi in THF at −78 °C, to give the tetraene **25**[22] in 91% (Scheme IV). Hydroboration of **25** with disiamylborane[24] followed by oxidative workup gave homofarnesol (**26**)[21b,c] in 81% yield. Treatment with bromotriphenylphosphonium bromide gave bromide **27**, which was converted to homofarnesyl iodide (**28**)[21c] by reaction with NaI in acetone.

The method of choice for the introduction of homofarnesyl chain **28** (and **39**) to C-2 of enone **12** in a cuprate-mediated 1,4-conjugate addition fashion involved generation of the higher order (H.O.)[25] lithio cuprate from the homoallylic lithium species produced from **28** (and **39**) and lithium (2-thienyl)cyanocuprate, (2-Th)Cu(CN)Li.[17] A model study with a Grignard of a similiar homoallylic bromide revealed that copper-catalyzed addition or addition of the Grignard-derived cuprate to **12** on a relatively small scale was troublesome and the yields were consistently poor (45–55%). Gas chromatographic analysis of the quenched homoallylic Grignard revealed that several species accompanied the protonated products, suggesting that β-elimination and/or self-coupling had taken place upon formation of the Grignard. By comparison, the conversion of homoallylic iodide **28** to the corresponding lithium species via lithium–iodine exchange using *tert*-butyllithium at −78 °C in diethyl ether[26] was very clean. Lithium–iodine exchange presumably minimizes β-elimination as well as Wurt-type coupling that occurs during the generation of the corresponding Grignard species.

Addition of lithium (2-thienyl)cyanocuprate in THF to the homoallyllithium species generated from **28** (and **39**) at −78 °C gave the corresponding H.O. cuprate as a brown solution. Reaction of the cuprate with **12** produced **29** in

(21) Leopold, E. J. *Org. Synth.* **1986**, *64*, 164. (b) Homofarnesol synthesis also by Lucius, G. *Chem. Ber.* **1960**, *93*, 2263 and (c) Kocieński, P.; Wadman, S.; Cooper, K. *J. Org. Chem.* **1989**, *54*, 1215.

(22) Maurer, B.; Hanser, A.; Froidevaux, J.-C. *Tetrahedron Lett.* **1986**, *27*, 2111.

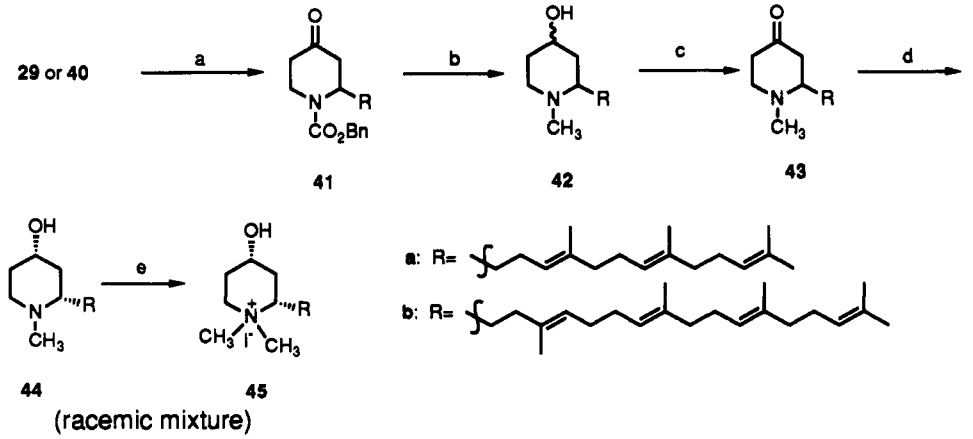
(23) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(24) Brown, H. C. *Organic Syntheses via Boranes*; Wiley; New York, 1983; Vol. 13.

(25) Lipshutz, B. H.; Koerner, M.; Parker, D. A.; *Tetrahedron Lett.* **1987**, *28*, 945.

(26) (a) Negishi, E.-I.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406. (b) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404.

Scheme VI[a]



[a] (a) NaCl, DMSO–H_2O; (b) $LiAlH_4$, THF; (c) Ac_2O–DMSO; (d) $LiAlH_4$, THF, −78 °C; (e) MeI, Et_2O.

85% yield (overall yield of 46% starting with **23**). ^1H NMR of **29** revealed the presence of an enolic proton (δ 12.2) and the absence of the vinyl hydrogen of **12**, confirming that transfer of **28** to C-2 of **12** had occurred.

The iodide **39** possessing the actual tetraene side chain found in the presumptive cationic intermediate **5** (Scheme I) was similarly coupled to C-2 of enone **12**. The synthesis of **39** required the preparation and the coupling of the valuable intermediate **34** to farnesyl bromide.

The synthesis of **31** was most conveniently carried out in yields of 45–50% (in ~95% isomeric purity) by one-pot carboalumination[27] of silyl-protected homopropargyl alcohol **30** and trapping the vinyl alane with ethyl chloroformate (Scheme V). Emulsions encountered during the usual aqueous workup were overcome by quenching the reaction with a minimum amount of water (~10 equiv) followed by addition of Celite and hexane. This provided metal salts that were easily filtered. Aqueous workup of the filtrate and evaporation of volatile impurities under high vacuum resulted in relatively pure (~85% by GC) ester **31**.[28] This was reduced without further purification by DIBAL-H to alcohol **32**,[28] which was easily purified by flash chromatography. Conversion of **32** to the allylic chloride **33**[28] was accomplished, in nearly quantitative yield, by treatment of the alcohol with the NCS–DMS complex. Reaction of **33** with the sodium salt of benzenesulfinic acid in DMF gave sulfone **34** in 84% yield in two steps. Generation of the allylic anion[29] of **34** with *n*-BuLi in THF at −78 °C followed by addition of farnesyl bromide gave the coupled product **35** in 89% yield. Removal of the sulfone group with Li in $EtNH_2$ at −78 °C yielded **36**, which was subsequently deprotected by treatment with tetrabutylammonium fluoride to give the free alcohol **37**. Tosylation of **37** with *p*-TsCl in pyridine gave **38**, which was converted to **39** by reaction with NaI in refluxing acetone. The corresponding H.O. cuprate[25] was again generated by treatment of **39** with 2.2 equiv of *tert*-butyllithium in Et_2O at −78 °C followed by addition of (2-Th)Cu(CN)Li in THF. Reaction of the cuprate with **12** at −78 °C in THF gave the C-2-coupled product **40** in 90% yield (overall yield of 14% starting with **30**).

Synthesis of the C-3-unsubstituted analogues **44a** and **44b** commenced by decarboxylation of **29** and **40**, respectively, using the Krapcho conditions[30] of heating with NaCl in wet DMSO at 100 °C for 5–8 h (Scheme VI). Reduction of the ketones **41a** and **41b** with $LiAlH_4$ was accompanied by reduction of the carbamates to *N*-methyls. This treatment gave amino alcohols **42a** and **42b** as nearly 1:1 (axial:equatorial alcohols) diastereoisomeric mixtures as deduced from integration of the ^1H NMR ($CDCl_3$) signals due to the methine hydrogen on the hydroxy-bearing carbons [$\delta_{\text{axial H}}$ 3.60 (septet due to overlapping tt, J = 11.0, 4.50 Hz); $\delta_{\text{equatorial H}}$ 4.07 (multiplet)] and the signal due to *N*-CH_3 hydrogens. The latter appeared as two signals at δ 2.32 and 2.24 due to the diastereoisomer containing the axial hydroxyl group and the equatorial hydroxyl group, respectively. The diastereoisomeric ratio was improved to >95% (equatorial alcohol), racemic alcohols **44a** (50% in 4 steps) and **44b** (44% in 4 steps), when the pair of diastereomers were first oxidized to *N*-methyl-4-piperidones **43a** and **43b** and re-reduced using $LiAlH_4$ at −78 °C.[20] The oxidation was achieved with Ac_2O in DMSO (Albright–Goldman procedure).[31] This procedure gave the ketones in fairly good yields (76–81%) with only minor amounts of O-acetylation. Treatment of racemic amino alcohols **44a** and **44b** with MeI in dry diethyl ether yielded the quaternary ammonium iodides **45a** and **45b**, respectively, as slightly yellow, hygroscopic semisolids.

Ammonium ions **45a** and **45b** as well as the free amines **44a** and **44b** are potent inhibitors of 2,3-oxidosqualene-lanosterol cyclase in in vivo studies. They inhibited growth of both *Saccharomyces cerevisiae* and cells of *Candida albicans*. Preliminary results show that these compounds are specific and seem to target only 2,3-oxidosqualene-lanosterol cyclase as verified by the increase in the ratio of oxidosqualenes vs ergosterol contents of the growing cells. Compounds **20**, **21**, and **22** failed to inhibit cell growth. These compounds are currently being evaluated in a cell-free in vitro system. The details of the inhibition studies will be reported soon.[32]

Experimental Section

General Procedures. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dimethoxyethane (DME) were all distilled from sodium benzophenone–ketyl. Diisopropylamine, triethylamine, and pyridine were distilled from CaH_2 and stored under nitrogen atmosphere; dimethyl sulfide (DMS), dichloromethane, and

(27) Rand, C. L.; van Horn, D. E.; Moore, M. W.; Negishi, E.-I. *J. Org. Chem.* **1981**, *46*, 4093.

(28) The ester **31** has also been prepared, as *E*/*Z* mixture, by the addition Me_2CuLi to ethyl 5-(*tert*-butyldimethylsiloxy)-2-pentynoate as well its conversion to **32** and **33** by the sequence in this text. Still, W. C.; Gennari, C.; Noguez, J. A.; Pearson, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 260.

(29) Grieco, P. A.; Masaki, Y. *J. Org. Chem.* **1974**, *39*, 2135.

(30) Krapcho, A. P. *Synthesis* **1982**, 805.

(31) (a) Albright, J. D.; Goldman, L. J. *J. Am. Chem. Soc.* **1965**, *87*, 4214. (b) Broka, C. A.; Gerlits, J. F. *J. Org. Chem.* **1988**, *53*, 2144.

(32) Dodd, D. S.; Oehlschlager, A. C.; Georgopapadakou, N. H. Manuscript in preparation.

pentane were freshly distilled from CaH_2 prior to use. *N*-Chlorosuccinimde (NCS) was recrystallized from glacial acetic acid, washed with ice–water, and dried under high vacuum. Unless otherwise stated, chemicals obtained from commercial sources were used without further purification. All moisture- and air-sensitive reactions were conducted under a positive pressure of argon in glassware that was flame-dried under vacuum. A nitrogen glovebag was used to weigh all the moisture- and oxygen-sensitive compounds. Syringes and cannulas were used to transfer oxygen- and water-sensitive liquid reagents. Unless specifically stated standard workup refers to the combined organic extracts being washed with ice-cold brine and dried over $MgSO_4$ (or anhydrous K_2CO_3 for amine compounds) and the solvent being removed with a rotary evaporator. Chromatography refers to flash chromatography using Merck silica gel 60, mesh 230–400.

1-(Carbobenzyloxy)-3-carbomethoxy-4-piperidone (10). To a slurry of methyl 4-piperidone-3-carboxylate hydrochloride (**9**) (5.0 g, 25.8 mmol) in 50 mL of CH_2Cl_2 and Et_3N (9.0 mL, 65.0 mmol) at 0 °C was added benzyl chloroformate (5.0 g, 28.0 mmol) over 20 min. This was stirred at 0 °C for 0.5 h and at rt for 1 h. The reaction mixture was poured into an ice-cold 2 N HCl solution (100 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The extracts were combined and washed with an ice-cold saturated $NaHCO_3$ solution. Standard workup gave **10** (6.7 g, 91%), the only product detected by ^1H NMR and TLC, as an oil. An analytical sample was prepared by chromatography with hexane/ethyl acetate (7/3) as the eluant: IR (film) 2200–3700 (b), 1740, 1600 cm^{-1}; mass spectrum, CI *m/e* (isobutane, rel intensity) 292 (M^+ + 1, 100); ^1H NMR (CD_3Cl, ppm) 12.00 (s, exchangeable/D_2O), 7.36 (m, 5 H), 5.16 (s, 2 H), 4.13 (bs, 2 H), 3.78 (s, 3 H), 3.64 (m, 2 H), 2.40 (bs, 2 H); ^{13}C NMR [218 K, $CDCl_3$, ppm (major/minor rotomers)] 163.4/163.2, 154.5/154.4, 151.7, 140.7–126.4 (m, aromatic, 6 C), 115.5/115.0, 70.4/67.4 and 63.3/64.6 (OCH_2Ph), 52.0, 41.6/41.8, 39.0/39.4, 28.4/28.7. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.90; N, 3.94. Found: C, 61.80; H, 5.84; N, 4.18.

1-(Carbobenzyloxy)-3-carbomethoxy-3-(phenylselenyl)-4-piperidone (11). To a stirred slurry of NaH (1.7 g, 42.5 mmol, 60% in oil), washed free of oil with pentane (4 × 10 mL), in THF (250 mL) at 0 °C under argon was added dropwise a solution of **10** (10.0 g, 35.0 mmol) in of THF (30 mL) over 20 min. The solution was stirred at rt for 45 min and then cooled to −50 °C. To this was added dropwise a solution of phenylselenyl bromide (9.25 g, 39.2 mmol) in 50 mL of THF over 50 min. The mixture was stirred at −50 °C for 2 h and at rt for 1 h, poured into an ice-cold saturated K_2CO_3 solution (200 mL), and extracted with Et_2O (3 × 50 mL). Standard workup gave **11** (15.2 g, crude) as a yellow oil that crystallized on standing. A small sample was recrystallized from CH_2Cl_2/hexane to give light yellow crystals, mp 108–109 °C: IR (KBr pellet) 2950 (b), 1700 (b), 1410, and 1260 cm^{-1}; mass spectrum, CI *m/e* (isobutane, rel intensity) 448 (M^+ + 1, 100); ^1H NMR ($CDCl_3$, ppm) 7.40 (m, 10 H), 5.10 (s, 2 H), 4.60 (bm, 1 H), 4.10 (bs, 1 H), 3.62 (s, 3 H), 3.38 (bs, 1 H), 3.55 (bs, 1 H), 2.66 (bs, 2 H); ^{13}C NMR [243 K, $CDCl_3$, ppm (major/minor rotomers)] 200.8, 167.8, 154.3, 138.0–123.0 (m, 12 C), 62.5/67.7, 60.6, 53.3, 51.5, 43.3, 40.2/40.0. Anal. Calcd for $C_{21}H_{20}NO_5Se$: C, 56.51; H, 4.74; N, 3.14. Found: C, 56.71; H, 4.62; N, 2.95.

1-(Carbobenzyloxy)-3-carbomethoxy-5,6-dihydro-4-pyridone (12). To a vigorously stirred solution of **11** (15.0 g, crude) in CH_2Cl_2 (150 mL) at 0 °C was added dropwise a solution of H_2O_2 (7.8 g, 30% by weight in H_2O) in distilled water (40 mL) while the disappearance of **11** was monitored by TLC. The reaction was warmed to rt over 30 min and poured into ice-cold saturated K_2CO_3 (100 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). Standard workup followed by chromatography with ethyl acetate/hexane (7/3) as the eluant yielded **12** (7.7 g, 76% in two steps) as an oil that crystallized on standing, mp 74–75 °C: IR (film) 2950, 1700, 1760, 1400, and 1250 cm^{-1}; mass spectrum, CI *m/e* (isobutane, rel intensity) 290 (M^+ + 1, 100); ^1H NMR ($CDCl_3$, ppm) 8.83 (s, 1 H), 7.40 (bs, 5 H), 5.30 (s, 2 H), 4.05 (t, J = 7.0 Hz, 2 H), 3.82 (s, 3 H), 2.63 (t, J = 7.0 Hz, 2 H); ^{13}C NMR [218 K, $CDCl_3$, ppm (major/minor rotomers)] 189.2, 164.6/164.0, 151.8/152.0, 151.4, 133.6/133.4, 129.1, 128.9, 128.7, 107.5/108.0, 69.9, 52.4/52.2, 42.1/42.5, 35.6. Anal. Calcd for $C_{15}H_{15}O_5N$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.14; H, 5.31; N, 4.76.

2-*n*-Butyl-1-(carbobenzyloxy)-3-carbomethoxy-4-piperidone (13). To a slurry of CuCN (1.07 g, 12.0 mmol) in THF (70 mL), under argon at −78 °C, was added dropwise *n*-BuLi (9.60 mL, 24.0 mmol, 2.5 M solution in hexane), and the reaction was stirred for 30 min. To the cuprate, at −78 °C, was added dropwise a solution of enone **12** (2.9 g, 10.0 mmol) in THF (25 mL) over 15 min. The resulting yellow solution was stirred for an additional 30 min, at which time saturated NH_4Cl/NH_4OH (50 mL, pH ~8) was added. The slurry was stirred while being warmed to 0 °C and then extracted with Et_2O (4 × 40 mL). Standard workup followed by chromatography using hexane/ethyl acetate (9/1) as eluant afforded **13** (3.2 g, 91%) as a an oil that crystallized on standing, mp 60–61 °C: IR (KBr) 2950 (b), 1650, 1700 (b), and 1430 cm^{-1}; mass spectrum, *m/e* (rel intensity) 347 (M^+, 20), 316 (37), 290 (46), 214 (100); ^1H NMR ($CDCl_3$, ppm) 12.50 (bs, enolic H), 7.10 (bm, 5 H), 5.10 (bm, 2 H), 4.00 (bs, 1 H), 3.31 (bs, 3 H), 2.80 (bm, 1 H), 2.26 (bs, 1 H), 1.81 (bm, 1 H), 1.61 (bs, 1 H), 1.31 (bm, 6 H), 0.81 (bm, 3 H); ^{13}C NMR [213 K, $CDCl_3$, ppm (major/minor rotomers)] 170.9, 169.6/170.3, 154.9, 135.9, 128.2–127.7 (5 C, m), 100.6/101.1, 66.9, 51.7, 48.8, 34.3/34.8, 33.1/32.8, 28.2, 27.9, 22.1, 14.0. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.67; H, 7.25; N, 4.03. Found: C, 65.36; H, 7.43; N, 4.04.

2-*n*-Butyl-1-(carbobenzyloxy)-3-carbomethoxy-3-methyl-4-piperidone (14). To a slurry of NaH (427.0 mg, 10.0 mmol, 60% in oil) washed free of oil with dry pentane, in freshly distilled 1,2-dimethoxyethane (DME) (50 mL), under argon at 0 °C, was added dropwise over 20 min a solution of **13** (3.0 g, 9.0 mmol) in DME (25 mL). The mixture warmed to rt and stirred for 45 min. MeI (1.7 mL, 27.0 mmol) was then added and the reaction mixture stirred at rt for 48–50 h. The reaction was poured into NH_4Cl solution (50 mL) and extracted with Et_2O (3 × 50 mL). Standard workup followed by chromatography using hexanes/ethyl acetate (8/2) as eluant gave the methyl product **14** (2.7 g, 72%) as an oil that crystallized on standing, mp 55–57 °C: IR (KBr) 3400, 2950, 1700 (b), 1690, 1720, 1760, and 1425 cm^{-1}; mass spectrum, CI *m/e* (isobutane, rel intensity) 362 (M^+ + 1, 100); ^1H NMR ($CDCl_3$, ppm) 7.35 (m, 5 H), 5.17 (s, 2 H), 4.47 (m, 2 H), 3.70 (s, 3 H), 3.00 (bm, 1 H), 2.70 (bs, 1 H), 2.45 (bs, 1 H), 1.60 (bs, 2 H), 1.45 (bs, 2 H), 1.20 (bm, 5 H), 0.78 (s, 3 H); ^{13}C NMR [213 K, $CDCl_3$, ppm (major/minor rotomers)] 206.2, 170.7/170.9, 155.6, 135.4, 128.3–127.7 (5C, m), 67.4, 60.0/60.2, 58.3/58.2, 52.5, 36.7/37.0, 35.9/36.0, 28.3/28.5, 27.1/27.2, 22.1, 22.0, 14.0. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.47; H, 7.53; N, 3.88. Found: C, 66.20; H, 7.59; N, 3.78.

2-*n*-Butyl-1-(carbobenzyloxy)-3-carbomethoxy-3-methyl-4-piperidone Ethylene Ketal (15). Compound **14** (2.0 g, 5.5 mmol) in 50 mL of toluene containing ethylene glycol (1.0 g, 16.7 mmol) and 50.0 mg of *p*-TsOH were refluxed for 20 h in a 100-mL flask fitted with Dean–Stark collector. The cooled reaction mixture was poured into ice-cold saturated $NaHCO_3$ (50 mL) and extracted with ether (3 × 30 mL). Standard workup followed by chromatography using hexanes/ethyl acetate (7/3) as eluant gave **15** (2.0 g, 89%) as an oil that crystallized on standing, mp 80–81 °C: IR (KBr) 2945, 1770, 1685, and 1420 cm^{-1}; mass spectrum, CI *m/e* (isobutane, rel intensity) 406 (M^+ + 1, 100); ^1H NMR ($CDCl_3$, ppm) 7.30 (m, 5 H), 5.17 (m, 2 H), 4.60/4.40 (rotomers, d, 1 H), 4.25 (bs, 1 H), 4.20 (m, 2 H), 3.96 (m, 2 H), 3.70 (s, 3 H), 3.10 (m, 1 H), 1.83 (m, 1 H), 1.35 (m, 3 H), 1.17 (br m, 6 H), 0.78 (m, 3 H); ^{13}C NMR [213 K, $CDCl_3$, ppm (major/minor rotomers)] 172.6, 155.9/155.8, 136.2/136.0, 127.7–128.2 (m, 5 C), 108.7, 66.9, 65.3, 64.0, 58.5/58.3, 52.1/52.2, 51.7/51.6, 35.9/36.1, 30.7/31.3, 28.6/28.5, 27.8, 22.2/22.4, 21.4/21.7, 14.2. Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.21; H, 7.70; N, 3.46. Found: C, 64.94; H, 7.61; N, 3.29.

2-*n*-Butyl-1-(carbobenzyloxy)-3-(hydroxymethyl)-3-methyl-4-piperidone Ethylene Ketal (16). To a slurry of $LiAlH_4$ (1.0 g, 26.0 mmol) in 30 mL of THF, under an atmosphere of argon, was added dropwise a solution of ketal **15** (2.5 g, 6.1 mmol) in 15 mL of THF. The reaction was refluxed for 3 h at which time excess $LiAlH_4$ was destroyed at 0 °C by slow addition of 1.0 g of water followed by 1.0 g of 15% NaOH followed by 3.0 g of water. The solids were filtered and rinsed thoroughly with small portions of Et_2O (5 × 25 mL). Standard workup followed by chromatography using ethyl acetate/MeOH/Et_3N (95/3/2) as eluant afforded **16** (1.5 g, 88%) as an oil: IR (neat) 3600–3100

(b), 2800–3000 (b), 1675, and 1450 cm^{-1}; mass spectrum, CI *m/e* (isobutane, rel intensity) 258 ($M^+ + 1$, 100); ^1H NMR ($CDCl_3$, ppm) 3.90 (m, 4 H), 3.77 (s, 2 H), 2.80 (m, 1 H), 2.40 (m, 2 H), 2.25 (s, 3 H), 2.17 (m, 1 H), 1.70 (m, 2 H), 1.47 (m, 2 H), 1.30 (m, 4 H), 0.88 (t, J = 7.0 Hz, 3 H), 0.70 (s, 3 H); ^{13}C NMR ($CDCl_3$, ppm) 110.3, 70.8, 66.6, 65.0, 64.6, 54.2, 45.2, 42.9, 32.8, 32.5, 28.5, 23.0, 15.2, 13.8. Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.34; H, 10.58; N, 5.45. Found: C, 65.15; H, 10.60; N, 5.63.

2-*n*-Butyl-1,3-dimethyl-3-[[(*p*-toluenesulfonyl)oxy]-methyl]-4-piperidone Ethylene Ketal (17). To a solution of **16** (1.75 g, 7.0 mmol) in dry Et_2O (25 mL), under a positive pressure of argon at 0 °C, was added *n*-BuLi (3.35 mL, 8.4 mmol, 2.5 M in hexanes), and the reaction was stirred for 10 min. A solution of *p*-toluenesulfonyl chloride (1.90 g, 10.0 mmol) in Et_2O (10 mL) was added dropwise and the mixture stirred at 0 °C for 5 h. The reaction was then diluted with a 15% NaOH solution (25 mL) and extracted with Et_2O (3 × 30 mL). Standard workup followed by chromatography using diethyl ether/ethyl acetate/triethylamine (95/3/2) as eluant gave the tosylate **17** (2.41 g, 84%) as crystalline solid (unstable to prolonged storage, no mp obtained): IR (KBr) 3400 (b), 2940, 2940, 1600, and 1350 cm^{-1}; mass spectrum, CI *m/e* (isobutane, rel intensity) 240 ($M^+ + 1$, $-C_7H_7O_2S$, 100); ^1H NMR ($CDCl_3$, ppm) 7.78 (m, 2 H), 7.33 (m, 2 H), 4.10–3.85 (bm, 6 H), 2.60 (m, 1 H), 2.43 (s, 3 H), 2.25 (s, 3 H), 1.85 (m, 2 H), 1.60 (bm, 2 H), 1.30–1.20 (bm, 6 H), 1.03 (s, 3 H), 0.87 (m, 3 H); ^{13}C NMR ($CDCl_3$, ppm) 144.4, 138.7, 128.4 (2 C), 125.8 (2 C), 110.0, 78.4, 65.7, 65.5, 58.6, 46.7, 44.5, 29.8, 27.3, 24.9, 22.8, 21.1, 13.6, 10.2. Anal. Calcd for $C_{21}H_{33}N:O_5S$ C, 61.25; H, 8.08; N, 3.40. Found: C, 61.01; H, 8.08; N, 3.48.

2-*n*-Butyl-1,3,3-trimethyl-4-piperidone Ethylene Ketal (18). To a solution of **17** (2.0 g, 5.0 mmol) in THF (30 mL) under argon was added $LiBEt_3H$ (10.0 mL, 10.0 mmol, 1.0 M in THF), and the solution was refluxed for 3 h. The reaction was cooled to rt and then poured into an ice-cold 15% NaOH solution (25 mL), stirred for 30 min, and extracted with ether (4 × 30 mL). Standard workup followed by chromatography with hexanes/ethyl acetate/triethyl amine (70/27/3) as eluant gave **18** (1.1 g, 91%) as an oil: IR (film) 2950 (b), 2870, 2790, and 1455 (b) cm^{-1}; mass spectrum, *m/e* (rel intensity) 241 (M^+, 4), 212 (13), 198 (10), 184 (100), 98 (44); ^1H NMR ($CDCl_3$, ppm) 3.90 (m, 4 H), 2.70 (ddd, J = 12.0, 4.5, 3.0 Hz, 1 H), 2.25 (td, J = 12.0, 3.0 Hz, 1 H), 2.21 (s, 3 H), 1.91 (dt, J = 13.0, 4.5 Hz, 1 H), 1.77 (m, 1 H), 1.45 (bm, 3 H), 1.24 (m, 4 H), 0.99 (s, 3 H), 0.86 (t, J = 7.0 Hz, 3 H), 0.82 (s, 3 H); ^{13}C NMR ($CDCl_3$, ppm) 110.5, 70.7, 65.0, 64.8, 54.3, 44.2, 44.1, 43.7, 33.8, 31.4, 30.3, 24.2, 20.5, 19.3, 15.2; HRMS calcd for $C_{14}H_{27}NO$ 241.2043, found 241.2017.

2-*n*-Butyl-1,3,3-trimethyl-4-piperidone (19). A solution of ketal **18** (1.0 g, 4.0 mmol) in acetone (25 mL) and 6 N HCl (10 mL) was refluxed for 6 h. The cooled reaction mixture was diluted with ice water (25 mL), neutralized with solid $NaHCO_3$, and extracted with ether (5 × 30 mL). Standard workup followed by chromatography using ethyl acetate/methanol/triethylamine (95/3/2) as eluant afforded the 4-piperidone **19** (600 mg, 73%) as an oil: IR (film) 2950, 2790, and 1710 cm^{-1}; mass spectrum *m/e* (rel intensity) 197 (M^+, 38), 168 (33), 140 (69), 126 (13), 112 (100), 98 (85), 84 (15), 70 (15), 57 (25); ^1H NMR ($CDCl_3$, ppm) 2.92 (overlapping dt, J = 13.0, 5.0 Hz, 1 H), 2.50 (m, 3 H), 2.37 (s, 3 H), 2.10 (m, 1 H), 1.42 (m, 1 H), 1.30 (m, 5 H), 1.20 (s, 3 H), 1.07 (s, 3 H), 0.90 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, ppm) 213.8, 72.2, 52.3, 50.0, 42.6, 37.7, 32.6, 26.4, 23.6, 22.9, 20.8, 13.8; HRMS calcd for $C_{12}H_{23}NO$ 197.1781, found 197.1786.

2-*n*-Butyl-1,3,3-trimethyl-4-piperidinol (20). To a slurry of $LiAlH_4$ (100 mg, 2.6 mmol) in THF (15 mL) at −78 °C, under a positive pressure of argon, was added dropwise a solution of piperidone **19** (50 mg, 2.8 mmol) in THF (10 mL). Excess $LiAlH_4$ was destroyed after 30 min by the addition of 0.1 g of H_2O followed by 0.1 g of a 15% NaOH solution followed by 0.3 g of H_2O at 0 °C. The resulting solid was filtered and rinsed thoroughly with Et_2O (5 × 25 mL). Standard workup followed by chromatography using ethyl acetate/methanol/triethylamine (90/7/3) as the eluant gave pure 4-piperidinol **20** (460 mg, 83%) in a 95:5 equatorial:axial diastereoisomeric mixture, as a clear viscous oil: IR (film) 3100–3500 (b), 2950, and 1450 cm^{-1}; mass spectrum, *m/e* (rel intensity) 199 (M^+, 45), 182 (20), 142 (100), 98 (38), 57 (33); ^1H NMR ($CDCl_3$, ppm) 3.20 (dd, J = 12.0, 5.0 Hz, 1 H), 2.83 (td, J = 12.0, 4.0 Hz, 1 H), 2.20 (s, 3 H), 2.03 (dt, J = 12.0, 4.0 Hz, 1 H), 1.75 (dq, J = 12.0, 4.0 Hz, 1 H), 1.70 (m, 1 H), 1.55 (m, 1 H), 1.30 (bm, 6 H), 0.95 (s, 3 H), 0.90 (t, J = 7.0 Hz, 3 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$, ppm) 76.9, 72.8, 55.6, 43.6, 39.9, 33.0, 30.5, 29.4, 24.1, 23.1, 13.9, 13.5; HRMS calcd for $C_{12}H_{25}NO$ 199.1936, found 199.1898. Anal. Calcd for $C_{12}H_{25}NO$: C, 72.31; H, 12.64; N, 7.03. Found: C, 71.99; H, 12.48; N, 6.83.

2-*n*-Butyl-1,3,3-trimethyl-4-hydroxypiperidinium Chloride (21). To a solution of **20** (50 mg, 0.25 mmol) in 1 mL of dry Et_2O in a tapered test tube was added 3 drops of 1 M HCl in Et_2O. The amine hydrochloride salt precipitated as white flakes. The ether was evaporated under a stream of nitrogen and the hydrochloride salt rinsed with dry Et_2O (3 × 1 mL). The residual solvent was removed under reduced pressure to give the hydrochloride salt **21** (40 mg) as white flakes, mp 150–155 °C: IR (KBr) 3600–3200 (b), 2930, 2700, and 1410 cm^{-1}; mass spectrum, FAB *m/e* (Xenon/glycerol, rel intensity) 200 ($M^+ - Cl^-$, 100); ^1H NMR (CD_3OD, ppm) 3.40 (m, 2 H), 3.10 (m, 1 H), 2.84 (s, 3 H), 2.73 (bs, 1 H), 1.87 (bm, 3 H), 1.58 (bm, 1 H), 1.47 (bs, 1 H), 1.40 (m, 4 H), 1.11 (s, 3 H), 0.96 (t, J = 7.5 Hz, 3 H), 0.96 (s, 3 H); ^{13}C NMR (218 K, CD_3OD, ppm) 73.2 (2 C), 54.9, 42.2, 41.6, 34.1, 28.8, 28.6, 24.0, 23.8, 14.5, 12.2.

2-*n*-Butyl-1,1,3,3-tetramethyl-4-hydroxypiperidinium Iodide (22). To a solution of **20** (100 mg, 0.5 mmol) in 5.0 mL of dry Et_2O in a tapered screw cap test tube was added MeI (0.2 mL). The reaction was placed in the dark at rt for 24 h. The ether was evaporated under a flow of nitrogen and the crystals were rinsed with dry Et_2O (3 × 2 mL). The residual solvent was removed under vacuum to give the salt **22** (120 mg) as a white powder, mp 161–163 °C: IR (KBr) 3400 (b), 2975 and 1470 cm^{-1}; mass spectrum, FAB *m/e* (Xenon/glycerol, rel intensity) 214 ($M^+ - I^-$, 100); ^1H NMR (CD_3OD, ppm) 3.35 (m, 2 H), 3.12 (m, 1 H), 3.10 (s, 3 H), 3.00 (s, 3 H), 2.10 (bm, 1 H), 1.93 (bm, 1 H), 1.76 (bm, 2 H), 1.60 (bm, 1 H), 1.44 (bm, 4 H), 1.09 (s, 3 H), 1.04 (s, 3 H), 0.97 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (CD_3OD, ppm) 81.5, 74.1, 65.1, 56.5, 45.2, 42.6, 35.2, 27.1, 27.0, 26.7, 23.6, 15.3, 13.9. Anal. Calcd for $C_{13}H_{28}NOI$: C, 45.75; H, 8.27; N, 4.10. Found: C, 45.67; H, 8.50; N, 3.93.

3,7,11-Trimethyl-2(*E*),6(*E*),10-dodecatrien-1-al (Farnesal) (24).[22] This was prepared by Swern oxidation[23] of farnesol (**23**) (10.0 g, 45.0 mmol) according to the procedure of Leopold et al.[21a] for the oxidation of geraniol to geranial. Chromatography using ethyl acetate/hexanes (10/90) gave **24** in 91% yield: ^1H NMR ($CDCl_3$, ppm) 9.98 (d, J = 8.1 Hz, 1 H), 5.88 (d, J = 8.1 Hz, 1 H), 5.07 (m, 3 H), 2.23 (m, 4 H), 2.15 (s, 3 H), 2.05 (m, 2 H), 1.97 (m, 2 H), 1.67 (s, 3 H), 1.60 (s, 3 H); ^{13}C NMR ($CDCl_3$, ppm) 191.0, 163.5, 136.4, 131.3, 127.3, 124.0, 122.6, 40.4, 39.5 (2 C), 25.5, 24.7 (2 C), 17.5, 17.4, 15.9.

4,8,12-Trimethyl-1,3(*E*),7(*E*),11-tridecatetraene (25).[22] This was also prepared in as analogous fashion according to the procedure of Leopold et al.[21a] in 85% yield: ^1H NMR ($CDCl_3$, ppm) 6.55 (dt, J = 17, 10 Hz, 1 H), 5.85 (d, J = 10 Hz, 1 H), 5.09 (m, 3 H), 4.97 (dd, J = 10, 1 Hz, 1 H), 2.00 (m, 8 H), 1.17 (s, 3 H), 1.67 (s, 3 H), 1.57 (s, 6 H).

4,8,12-Trimethyl-3(*E*),7(*E*),11-tridecatrien-1-ol (Homofarnesol) (26). Hydroboration of tetraene **25** (6.5 g, 30.0 mmol) with disiamylborane gave **26** in 85% yield according to the procedure of Leopold et al.[21a] **26**: ^1H NMR ($CDCl_3$, ppm) 5.08 (m, 3 H), 3.60 (t, J = 6.5 Hz, 2 H), 2.27 (q, J = 6.7 Hz, 2 H), 2.15–1.90 (m, 8 H), 1.67 (s, 3 H), 1.64 (s, 3 H), 1.59 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.8, 135.3, 131.3, 124.4, 121.0, 119.9, 63.4, 39.8, 39.7, 31.5, 26.8, 26.5, 25.6, 17.6, 16.2, 16.0; mass spectrum, *m/e* (rel intensity) 236 (M^+, 1), 193 (4), 136 (15), 123 (14), 107 (10), 93 (12), 81 (51), 69 (100). The spectra are in agreement with those reported in ref 21c.

1-Bromo-4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatriene (Homofarnesyl Bromide) (27). To a solution of PPh_3 (7.3 g, 28.0 mmol) in CH_2Cl_2 (100 mL) under argon at 0 °C was added Br_2 dropwise until a yellow color persisted. A few crystals of PPh_3 were added to consume the excess Br_2. Pyridine (2.9 mL, 35.0 mmol) was added followed by the dropwise addition of homofarnesol (**26**) (5.5 g, 23.3 mmol) in CH_2Cl_2 (20 mL). The reaction was stirred for 5 h. The solvent was evaporated in vacuo, and the precipitate was diluted with hexane (50 mL) and filtered through a pad of Celite. The precipitate was rinsed well with hexane. Standard workup followed by filtration through a small silica gel column using hexane as eluant gave bromide **27** (6.1 g,

88%) as an oil: ^{1}H NMR ($CDCl_3$, ppm) 5.10 (m, 3 H), 3.33 (t, J = 7.3 Hz, 2 H), 2.57 (dt, J = 7.3, 7.0 Hz, 2 H), 2.20–1.95 (m, 8 H), 1.67 (s, 3 H), 1.62 (s, 3 H), 1.60 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.5, 135.2, 131.2, 124.4, 123.9, 120.9, 39.7, 39.6, 32.9, 31.7, 26.8, 26.4, 25.6, 17.6, 16.2, 16.0; mass spectrum, m/e (rel intensity) 257/255 (M^+, 2), 189/187 (3), 136 (20), 121 (11), 95 (15), 93 (10), 91 (90), 81 (63), 69 (100), 67 (40), 55 (18), 53 (15).

1-Iodo-4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatriene (Homofarnesyl Iodide) (28). To a solution of **27** (6.0 g, 20.0 mmol) in acetone (50 mL) was added NaI (5.0 g, 33.3 mmol), and the mixture was stirred for 6 h at rt and then refluxed for 2 h. Most of the solvent was evaporated in vacuo; then the residue was diluted with water (50 mL) and extracted with ether (3 × 50 mL). The extracts were combined and washed with 5% aqueous sodium thiosulfate (1 × 20 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (2/98) as eluant afforded the iodide **28** (6.5 g, 94%) as an oil: ^{1}H NMR ($CDCl_3$, ppm) 5.09 (m, 3 H), 3.10 (t, J = 7.4 Hz, 2 H), 2.6 (dt, J = 7.5, 7.0 Hz, 2 H), 2.1–1.9 (m, 8 H), 1.67 (s, 3 H), 1.61 (s, 3 H), 1.60 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.1, 135.1, 131.2, 124.4, 123.9, 123.0, 39.7, 39.6, 32.4, 26.8, 26.4, 25.7, 17.7, 16.3, 16.0, 5.8; mass spectrum, m/e (rel intensity) 346 (M^+, 1), 303 (4), 137 (9), 136 (28), 123 (11), 121 (11), 109 (6), 107 (8), 95 (20), 93 (10), 91 (8), 82 (10), 81 (59), 79 (15), 77 (8), 69 (100), 67 (40), 55 (10). The spectra are in agreement with those reported in ref 21c.

1-(Carbobenzyloxy)-3-carbomethoxy-2-[4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl]-4-piperidone (29). To iodide **28** (1.73 g, 5.0 mmol), deoxygenated under high vacuum and purged with argon, was added dry Et_2O (50 mL), and the solution was cooled to −78 °C. *t*-BuLi (6.2 mL, 11.0 mmol, 1.7 M in pentane) was added dropwise over 15 min and the yellow solution was stirred for 30 min. Lithium (2-thienyl)cyanocuprate (20.2 mL, 5.05 mmol, 0.25 M in THF) was added to the alkyllithium over 10 min. The resulting brown suspension was warmed to −30 °C for 30 min to solubilize the reagent. The clear H.O. cuprate solution obtained was recooled to −78 °C and **12** (1.5 g, 5.0 mmol) in THF (25 mL) was added dropwise to this. The reaction was stirred for another 45 min and quenched with a saturated NH_4Cl/NH_4OH solution (50 mL, pH ~8). The slurry was warmed to 0 °C and extracted with Et_2O (4 × 50 mL). Standard workup followed by chromatography with ethyl acetate/hexanes (15/85) gave **29** (2.2 g, 85%) as an oil: IR (film) 2917, 2855, 1703, 1659, 1617, 1440, 1384, 1359, 1303, 1245, 1212, 1110, 1068, 1011 and 821 cm^{-1}; mass spectrum, CI m/e (isobutane, rel intensity) 510 (M^+ + 1, 8), 466 (6), 376 (11), 374 (6), 348 (5), 153 (100), 127 (33), 125 (40); ^{1}H NMR [$CDCl_3$, ppm (major/minor rotomers)] 12.2 (m, enolic proton, ~1 H), 7.4 (m, 5 H), 5.30–5.05 (m, 5 H), 5.00/4.85 (dm, J = 7.0 Hz, 1 H), 4.30/4.15 (dd, J = 10.0, 7.0 Hz, 1 H), 3.8 (s, 3 H), 3.21–3.10 (m, 1 H), 2.55–2.42 (m, 1 H), 2.2 (m, 1 H), 2.10–1.90 (m, 10 H), 1.68 (s, 3 H), 1.60 (s, 6 H), 1.57 (s, 3 H), 1.50 (m, 2 H); ^{13}C NMR [$CDCl_3$, 243 K, ppm (major/minor rotomers)] 171.3/171.2, 170.9/170.1, 155.2, 136.5, 135.5/135.4, 134.8, 131.3, 128.6–127.9 (3 C), 124.3, 124.1, 123.6/123.3, 101.3/100.9, 67.3, 51.7, 49.5, 39.7, 39.6, 35.4/35.0, 34.0/33.6, 28.7/28.3, 26.6, 26.5, 25.9, 24.9, 17.8, 16.1 (2 C). Anal. Calcd for $C_{31}H_{43}NO_5$: C, 73.06; H, 8.50; N, 2.75. Found: C, 72.81; H, 8.49; N, 2.94.

Ethyl 5-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2(*E*)-pentenoate (31). To a slurry of $ZrCp_2Cl_2$ (29.0 g, 100 mmol) in dry CH_2Cl_2 (250 mL) under argon was added dropwise $AlMe_3$ (20.0 mL, 200 mmol) over 10 min. 1-[(*tert*-Butyldimethylsilyl)oxy]-4-butyne (**30**) (19.0 g, 100 mmol) in CH_2Cl_2 (25.0 mL) was then added and the reaction stirred for 42 h. The resulting vinyl alane was cooled to 0 °C; then freshly distilled ethyl chloroformate (19.1 mL, 200 mmol) was added dropwise. After 3 h at rt, excess $AlMe_3$ was destroyed (*caution*!!) by the addition of 11 mL of distilled water under a stream of argon at 0 °C. The slurry was diluted with 200 mL of hexanes; then 10 g of Celite was added and the salts were filtered. The Celite pad was rinsed thoroughly with hexane (~200 mL). The filtrate was concentrated in vacuo, diluted with 150 mL of hexanes, and washed with distilled water. Standard workup followed by the removal of volatile impurities under high vacuum (0.05 mmHg) gave the unsaturated ester **31** (15.5 g), <95% isomerically pure, in 80–85% purity as judged by GC analysis. A small sample was chromatographed using hexane/ethyl acetate (9/1) as eluant: IR (film) 2940 (b), 1710, 1650, 1470, and 1390 cm^{-1}; mass spectrum, m/e (rel intensity) 257 (M^+ − CH_3, 3), 227 (19), 216 (14), 215 (90), 169 (20), 133 (20), 125 (13), 103 (100), 95 (33), 89 (55), 75 (75), 57 (20); ^{1}H NMR ($CDCl_3$, ppm) 5.65 (m, 1 H), 4.14 (q, J = 7.0 Hz, 2 H), 3.73 (t, J = 7.0 Hz, 2 H), 2.36 (t, J = 7.0 Hz, 2 H), 2.17 (d, J = 1.2 Hz, 3 H), 1.26 (t, J = 7.0 Hz, 2 H), 0.87 (s, 9 H), 0.032 (s, 6 H); ^{13}C NMR ($CDCl_3$, ppm) 166.6, 156.7, 117.3, 61.3, 59.4, 44.0, 25.8 (3 C), 19.1, 18.2, 14.3, −5.4 (2 C). Anal. Calcd for $C_{14}H_{27}O_3Si$: C, 61.95; H, 10.02. Found: C, 61.67; H, 10.21.

5-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2(*E*)-penten-1-ol (32). To a THF (100 mL) solution of ester **31** (15.0, ~80% pure) at −78 °C, under a positive pressure of argon, was added neat diisobutylaluminum hydride (DIBAL-H) (16.0 mL, 90 mmol). The reaction was warmed to 0 °C and stirred for 2 h. Excess reagent was destroyed by the addition of EtOAc (5 mL), and the solution was poured into a vigorously stirred ice-cold 25% aqueous solution of tartaric acid (150 mL). The mixture was extracted with Et_2O (4 × 50 mL) and the combined extracts were washed with an ice-cold saturated $NaHCO_3$ solution. Standard workup followed by chromatography using ethyl acetate/hexanes (15/85) as eluant gave the allylic alcohol **32** (9.0 g, 38% in two steps) as an oil: mass spectrum, m/e (rel intensity) 173 (M^+ − C_4H_9, 6), 155 (6), 105 (100), 89 (9), 81 (10), 75 (95), 73 (22); ^{1}H NMR ($CDCl_3$, ppm) 5.42 (t, J = 7.0 Hz, 1 H), 4.14 (d, J = 7.0 Hz, 2 H), 3.69 (t, J = 7.0 Hz, 2 H), 2.24 (t, J = 7.0 Hz, 2 H), 1.69 (s, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, ppm) 136.6, 125.3, 62.1, 59.2, 42.8, 25.9 (3 C), 18.72, 16.62, −5.34 (2 C).

5-[(*tert*-Butyldimethylsilyl)oxy]-1-chloro-3-methyl-2(*E*)-pentene (33). To a solution of *N*-chlorosuccinimide (NCS) (1.07 g, 8.0 mmol) in dry CH_2Cl_2 (45 mL) at 0 °C, under an argon atmosphere, was added dimethyl sulfide (DMS) (0.74 mL, 10.0 mmol), and the slurry was cooled to −25 °C. To the cooled NCS–DMS complex was added dropwise a solution of **32** (1.0 g, 4.4 mmol) in CH_2Cl_2 (10 mL). The mixture was warmed to 0 °C and stirred for 8 h. The reaction was poured into ice-cold distilled water (50 mL) and extracted with hexanes (4 × 30 mL). Standard workup gave **33** (1.0 g, 92%) as an oil: mass spectrum, m/e (rel intensity) 192/190 (M^+ − C_4H_9, 6, 16), 155 (10), 145 (10), 125 (65), 123 (100), 95 (61), 93 (94), 81 (90), 75 (30), 73 (45), 57 (20); ^{1}H NMR ($CDCl_3$, ppm) 5.47 (t, J = 8 Hz, 1 H), 4.09 (d, J = 8 Hz, 2 H), 3.69 (t, J = 7 Hz, 2 H), 2.26 (t, J = 7 Hz, 2 H), 1.74 (d, J = 1 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, ppm) 139.9, 122.1, 101.7, 42.6, 40.7, 25.9 (3 C), 18.2, 16.4, −5.4 (2 C).

1-(Benzenesulfonyl)-5-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-2(*E*)-pentene (34). To a solution of **33** (1.0 g, 4.0 mmol) in dry DMF (15 mL) at rt, under an argon atmosphere, was added $NaSO_2Ph$ (1.0 g, 6.0 mmol), and the mixture was stirred overnight (~10 h). The contents of the flask were poured into distilled (50 mL) water and extracted with hexane (4 × 30 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (15/85) as eluant afforded the sulfone **34** (1.2 g, 86%) as an oil: IR (film) 2925, 2856, 1472, 1447, 1318, 1253, 1132, and 1086 cm^{-1}; mass spectrum, m/e (rel intensity) 241 (M^+ − $C_6H_{15}Si$, 3), 217 (68), 199 (100), 135 (71), 89 (45), 81 (55), 73 (52); ^{1}H NMR ($CDCl_3$, ppm) 7.87 (d, J = 7.0 Hz, 2 H), 7.64 (t, J = 7.0 Hz, 1 H) 7.53 (t, J = 7.0 Hz, 2 H), 5.22 (tq, J = 7.5, 1.0 Hz, 1 H), 3.80 (d, J = 7.5 Hz, 2 H), 3.60 (t, J = 7.0 Hz, 2 H), 2.2 (t, J = 7.0 Hz, 2 H), 1.32 (d, J = 1 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, ppm) 143.6, 138.6, 133.5, 128.9 (2 C), 128.5 (2 C), 112.0, 61.7, 56.0, 42.8, 25.8 (3 C), 18.2, 16.5, −5.4 (2 C). Anal. Calcd for $C_{18}H_{30}O_3SiS$: C, 60.98; H, 8.53. Found: C, 60.90; H, 8.65.

5-(Benzenesulfonyl)-1-[(*tert*-butyldimethylsilyl)oxy]-3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraene (35). To sulfone **34** (1.0 g, 2.8 mmol), deoxygenated under high vacuum, under a positive pressure of argon in dry THF (20 mL) at −78 °C was added dropwise *n*-BuLi (1.20 mL, 3.1 mmol, 2.5 M in hexanes). The yellow solution was stirred for 1 h and a solution of farnesyl bromide (900 mg, 3.1 mmol) in THF (10 mL) was added dropwise. After stirring for 7 h at −78 °C, MeOH (3 mL) was added followed by water (50 mL). The mixture was warmed to 0 °C and extracted with Et_2O (3 × 40 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (1/9) as eluant yielded **35** (1.4 g, 89%) as an oil: IR (film) 2930, 1664, 1446, 1383, 1305, 1253, 1147, and 1086 cm^{-1}; mass spectrum, m/e (rel intensity) 559 (M^+, 15), 419 (6), 418 (17), 417 (53), 286 (18), 285 (86), 259 (15), 257 (20), 217 (14), 191 (15), 143 (100), 133

(14), 123 (26); ^{1}H NMR ($CDCl_3$, ppm) 7.85 (d, J = 8.0 Hz, 2 H), 7.60 (t, J = 8.0 Hz, 1 H), 7.50 (t, J = 8.0 Hz, 2 H), 5.00 (m, 4 H), 3.72 (td, J = 10.0, 3.5 Hz, 1 H), 3.52 (td, J = 7.5, 2.0 Hz, 2 H), 2.88 (ddd, J = 14.0, 7.0, 3.5 Hz, 1 H), 2.35 (ddd, J = 14.0, 7.0, 3.5 Hz, 1 H), 2.16 (t, J = 7.0 Hz, 2 H), 2.0 (bm, 8 H), 1.67 (s, 3 H), 1.60 (s, 3 H), 1.59 (s, 3 H), 1.56 (s, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, ppm) 142.4, 138.6, 138.3, 135.1, 133.2, 131.1, 129.1 (2 C), 128.6 (2 C), 124.2, 123.9, 118.7, 118.6, 64.8, 61.9, 43.0, 39.7 (2 C), 26.7, 26.6, 26.5, 25.9 (3 C), 25.6, 18.2, 17.6, 16.9, 16.3, 15.9, -5.4 (2 C). Anal. Calcd for $C_{33}H_{54}O_3SiS$: C, 70.91; H, 9.74. Found: C, 70.88; H, 9.76.

1-[(*tert*-Butyldimethylsilyl)oxy]-3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraene (36). To $EtNH_2$ (~25 mL) at -78 °C, under argon, was added sulfone **35** (500 mg, 1.0 mmol) in 4 mL of THF, followed by small pieces of lithium wire (~50 mg, excess). This was stirred until the solution became dark blue (35 min). Solid NH_4Cl (500 mg) was added and the excess lithium was removed with forceps. The mixture diluted with water (25 mL) and extracted with ether (4 × 40 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (5/95) as eluant gave **36** (360 mg, 86%) as an oil: IR (film) 2925, 2856, 1666, 1446, 1382, 1254, 1096, and 836 cm^{-1}; mass spectrum, CI m/e (isobutane, rel intensity) 419 (M^+ + 1, 10), 316 (13), 288 (14), 287 (63), 285 (14), 261 (25), 231 (13), 217 (12), 205 (37), 203 (20), 193 (14), 191 (26), 179 (15), 177 (31), 165 (13), 163 (45), 161 (62), 159 (96), 151 (26), 149 (38), 137 (100), 135 (20), 133 (20), 125 (13), 123 (35); ^{1}H NMR ($CDCl_3$, ppm) 5.13 (m, 4 H), 3.65 (t, J = 7.1 Hz, 2 H), 2.19 (t, J = 7.1 Hz, 2 H), 2.00 (bm, 12 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.60 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, ppm) 135.1, 134.8, 132.1, 131.1, 126.2, 124.4, 124.4, 124.3, 124.2, 62.5, 43.1, 37.6 (2 C), 28.3, 28.2, 26.8, 26.7, 25.9 (3 C), 25.6, 18.3, 17.6, 16.4, 16.0, 15.9, -5.3 (2 C). Anal. Calcd for $C_{27}H_{50}OSi$: C, 77.44; H, 12.03. Found: C, 77.41; H, 12.26.

3,8,12,16-Tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraen-1-ol (37). Silyl ether **36** (2.2 g, 5.4 mmol) was dissolved in 30 mL of a 1.0 M solution of tetrabutylammonium fluoride in THF, and the solution was stirred for 4 h at rt. The solution was diluted with water (100 mL) and extracted with ether (4 × 40 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (2/8) as the eluant yielded **37** (1.5 g, 90%) as an oil: mass spectrum, CI m/e (isobutane, rel intensity) 305 (M^+ + 1, 60), 287 (16), 219 (30), 205 (21), 193 (28), 191 (20), 179 (20), 177 (20), 163 (25), 153 (25), 151 (36), 149 (320, 137 (100), 136 (20), 135 (20), 125 (21), 123 (41); ^{1}H NMR ($CDCl_3$, ppm) 5.24 (m, 1 H), 5.10 (m, 3 H), 3.64 (t, J = 6.0 Hz, 2 H), 2.24 (t, J = 6.0 Hz, 2 H), 2.05 (m, 8 H), 1.98 (m, 4 H), 1.68 (s, 3 H), 1.62 (s, 3 H), 1.59 (s, 9 H); ^{13}C NMR ($CDCl_3$, ppm) 135.6, 135.0, 131.3, 131.2, 127.9, 124.4, 124.2, 124.0, 60.1, 42.7, 39.7 (2 C), 28.3, 28.1, 26.8, 26.7, 25.7, 17.7, 16.1, 16.0, 15.8. Anal. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.90. Found: C, 83.04; H, 12.17.

1-[(*p*-Toluenesulfonyl)oxy]-3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraene (38). To a stirred solution of **37** (1.5 g, 5.1 mmol) in pyridine (10 mL) and CH_2Cl_2 (25 mL) at 0 °C was added *p*-TsCl (1.07 g, 5.6 mmol). The reaction was stirred for 10 h at 0 °C and poured into ice–water (50 mL) and extracted with ether (3 × 50 mL). The extracts were combined and washed with an ice-cold 2 N HCl solution followed by ice-cold saturated $NaHCO_3$. Standard workup gave tosylate **38** (2.4 g) as an oil. An analytical sample was purified by chromatography using ethyl acetate/hexanes (5/95) as eluant: IR (film) 2922, 1598, 1448, 1363, 1188, 1177, 1098, and 964 cm^{-1}; mass spectrum, m/e (rel intensity) 458 (M^+, 1), 229 (4), 192 (3), 161 (3), 155 (4), 149 (10), 147 (4), 137 (10), 136 (15), 123 (9), 121 (15), 107 (15), 95 (18), 94 (15), 93 (15), 93 (20), 91 (30), 82 (23), 81 (100), 79 (20), 69 (83), 68 (22), 67 (27), 55 (10), 53 (9); ^{1}H NMR ($CDCl_3$, ppm) 7.78 (d, J = 8.3 Hz, 2 H), 7.33 (d, J = 8.3 Hz, 2 H), 5.01 (m, 4 H), 4.06 (t, J = 7.0 Hz, 2 H), 2.44 (s, 3 H), 2.30 (t, J = 7.0 Hz, 2 H), 2.05 (m, 4 H), 1.98 (m, 8 H), 1.67 (s, 3 H), 1.60 (s, 6 H), 1.58 (s, 3 H), 1.51 (s, 3 H); ^{13}C NMR ($CDCl_3$, ppm) 144.5, 135.4, 134.9, 133.4, 131.4, 131.1, 129.7 (2 C), 129.4, 128.0, 127.8 (2 C), 124.3, 124.2, 123.9, 69.0, 39.7 (2 C), 38.7, 28.2, 27.9, 26.7, 26.6, 25.6, 21.5, 17.6, 15.9 (2 C). Anal. Calcd for $C_{28}H_{42}O_3S$: C, 73.32; H, 9.23. Found: C, 73.33; H, 9.20.

1-Iodo-3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraene (39). To a solution of tosylate **38** (2.3 g, crude, 5.0 mmol) in acetone (50 mL) was added powdered NaI (1.1 g, 7.3 mmol), and the mixture was refluxed for 4 h. The cooled reaction mixture was poured into ice–water (50 mL) and extracted with diethyl ether (3 × 40 mL). The combined extracts were washed with 5% aqueous sodium thiosulfate (1 × 20 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (5/95) as eluant afforded iodide **39** (1.6 g, 77% in two steps) as an oil: IR (film) 2964, 2923, 2854, 1666, 1444, 1381, 1243, 1168 cm^{-1}; mass spectrum, CI m/e (isobutane, rel intensity) 415 (M^+ + 1, 60), 413 (29), 333 (18), 287 (20), 269 (15), 205 (20), 193 (54), 191 (27), 177 (18), 165 (15), 163 (21), 151 (30), 149 (26), 143 (22), 137 (100), 136 (23), 135 (23), 125 (30), 123 (50); ^{1}H NMR ($CDCl_3$, ppm) 5.22 (m, 1 H), 5.14 (m, 3 H), 3.21 (t, J = 7.5 Hz, 2 H), 2.52 (t, J = 7.5 Hz, 2 H), 2.02 (m, 12 H), 1.69 (s, 3 H), 1.6 (s, 12 H); ^{13}C NMR ($CDCl_3$, ppm) 135.2, 134.8, 133.6, 131.1, 127.4, 124.4, 124.2, 124.0, 43.9, 39.7 (2 C), 28.3, 27.9, 26.8, 26.7, 25.7, 17.67, 16.1, 160, 15.4, 4.71. Anal. Calcd for $C_{21}H_{35}I$: C, 60.87; H, 8.51. Found: C, 60.94; H, 8.44.

1-(Carbobenzyloxy)-3-carbomethoxy-2-[3,8,12,16-tetramethyl-3(*E*),7(*E*),8(*E*),11(*E*),15-heptadecatetraenyl]-4-piperidone (40). This compound was prepared using the same conditions as for preparation of **29**. Reaction of **39** (700 mg, 1.7 mmol) in dry Et_2O (25 mL), *t*-BuLi (2.2 mL, 3.75 mmol, 1.7 M in pentane), lithium (2-thienyl)cyanocuprate (7.2 mL, 1.8 mmol, 0.25 M in THF), and enone **12** (540 mg, 1.9 mmol) in THF (10.0 mL) gave **40** (900 mg, 90%) as an oil, after chromatography using ethyl acetate/hexanes (1/9) as eluant: IR (film) 2920, 2855, 1705, 1660, 1617, 1440, 1385, 1359, 1302, 1245, 1212, 1110, 1068, 1011, and 820 cm^{-1}; mass spectrum, CI m/e (isobutane, rel intensity) 578 (M^+ + 1, 62), 534 (33), 444 (33), 306 (35), 290 (100), 200 (40), 156 (38), 137 (37), 123 (31); ^{1}H NMR [$CDCl_3$, ppm (major/minor rotomers)] 12.20 (m, enolic proton, ~1 H), 7.3 (m, 5 H), 5.25–5.05 (bm, 6 H), 4.97/4.84 (dm, J = 10.0 Hz, 1 H), 4.27/4.14 (dd, J = 10.0, 7.0 Hz, 1 H), 3.78 (s, 3 H), 3.15 (m, 1 H), 2.52 (m, 1 H), 2.20 (m, 1 H), 2.10 (bm, 4 H), 2.00 (bm, 10 H), 1.70 (s, 3 H), 1.60 (s, 12 H), 1.55 (m, 2 H); ^{13}C NMR [$CDCl_3$, ppm (major/minor rotomers)] 171.3/171.1, 170.7/170.0, 155.2, 136.7, 135.1, 134.9, 134.4, 131.0, 129–127 (m, 4 C), 124.5, 124.4, 124.2, 101.3/100.9, 67.3, 51.6, 49.7, 39.6 (2 C), 35.9, 35.2, 34.7, 31.9/31.8, 28.5, 28.2, 28.1, 26.5, 25.8 (2 C), 17.7, 16.4, 16.0, 15.9. Anal. Calcd for $C_{36}H_{51}NO_5$: C, 74.84; H, 8.90; N, 2.42. Found: C, 75.02; H, 8.84; N, 2.30.

1-(Carbobenzyloxy)-2-[4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl]-4-piperidone (41a). A DMSO (20 mL) solution of **29** (1.0 g, 2.0 mmol), H_2O (150 mg, 8.0 mmol), and powdered NaCl (230 mg, 4.0 mmol) was heated at 100–120 °C for 6 h under an argon atmosphere. The reaction was cooled to rt, diluted with ice–water, and extracted with ether (4 × 50 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (3/7) as eluant gave **41a** (735 mg, 81%) as an oil: IR (film) 2965, 2917, 2855, 1702, 1423, 1381, 1351, 1347, 1309, 1233, 1177, 1110, and 1010 cm^{-1}; mass spectrum, CI m/e (isobutane, rel intensity) 452 (M^+ + 1, 100), 360 (73), 316 (40), 232 (60), 142 (50), 136 (30); ^{1}H NMR ($CDCl_3$, ppm) 7.40 (m, 5 H), 5.20 (s, 2 H), 5.10 (m, 3 H), 4.70 (bs, 1 H), 4.40 (bs, 1 H), 3.20 (tm, J = 12 Hz, 1 H), 2.70 (m, 1 H), 2.50 (bs, 1 H), 2.30 (m, 2 H), 2.10 (m, 4 H), 2.00 (m, 6 H), 1.70 (s, 3 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 1.56 (s, 3 H), 1.55–1.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, ppm) 207.4, 155.3, 136.4, 136.3, 135.0, 131.2, 128.6, 128.2, 128.0, 124.4, 124.1, 122.6, 67.6, 52.2, 45.4, 40.6, 39.7, 39.6, 38.5, 32.5, 26.8, 26.6, 25.7, 24.2, 17.7, 16.0 (2 C). Anal. Calcd for $C_{29}H_{41}NO_3$: C, 77.12; H, 9.15; N, 3.10. Found: C, 76.86; H, 8.99; N, 3.07.

1-(Carbobenzyloxy)-2-[3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]-4-piperidone (41b) was prepared from **40** (650 mg, 1.13 mmol), DMSO (7.0 mL) containing H_2O (82 mg, 4.0 mmol), and powdered NaCl (132 mg, 2.0 mmol) in the same manner as **41a**. Chromatography using ethyl acetate/hexanes (2/8) as eluant gave **41b** (520 mg, 85%) as an oil: IR (film) 2917, 1703 (b), 1422, 1343, 1309, 1233, and 1113 cm^{-1}; mass spectrum, CI m/e (isobutane, rel intensity) 520 (M^+ + 1, 25), 476 (15), 428 (20), 386 (100), 151 (29), 137 (55), 123 (55); ^{1}H NMR ($CDCl_3$, ppm) 7.37 (bs, 5 H), 5.18 (s, 2 H), 5.10 (bm, 4 H), 4.60 (bs, 1 H), 4.40 (bs, 1 H), 3.23 (tm, J = 12.0 Hz, 1 H), 2.67 (bm, 1 H), 2.47 (bs, 1 H), 2.35 (bs, 1 H), 2.30 (bs, 1 H), 2.06 (bm, 4 H), 1.98 (bm, 10 H), 1.68 (s, 3 H), 1.59 (s, 9 H), 1.55 (s, 3 H), 1.54 (bs, 2 H); ^{13}C NMR ($CDCl_3$, ppm) 207.4, 155.3, 136.4, 135.2, 134.9, 133.5, 131.1, 128.5 (2 C), 128.1, 128.0, 127.9 (2 C), 125.2, 124.4, 124.2, 124.1, 67.6, 52.2, 45.2, 40.6, 39.7 (2 C), 38.5, 35.6, 30.8,

28.3, 28.2, 28.1, 26.7, 26.6, 25.6, 17.64, 16.0, 15.9 (2 C). Anal. Calcd for $C_{34}H_{49}NO_3$: C, 78.57; H, 9.50; N, 2.69. Found: C, 78.41; H, 9.30; N, 2.43.

1-Methyl-2-[4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl]-4-piperidone (43a). A solution of piperidone **41a** (1.3 g, 2.8 mmol) in THF (10 mL) was added dropwise to a slurry of $LiAlH_4$ (530 mg, 14 mmol) in THF (20 mL) under an argon atmosphere. The mixture was refluxed for 2 h and cooled to 0 °C, and the excess hydride was destroyed by addition of 0.55 mL of H_2O, followed by 0.55 mL of a 15% NaOH solution followed by 1.65 mL of H_2O (1 mL). The salts were filtered and rinsed thoroughly with Et_2O (5 × 25 mL). The organic washes were combined and dried (anhydrous K_2CO_3), and the solvent was evaporated in vacuo. Chromatography using ethyl acetate/methanol/triethylamine (95/3/2) as eluant gave **42a** (800 mg, 87%) as a mixture of (axial/equatorial) alcohols (~50/50). ^1H and ^{13}C NMR spectra of the product showed two sets of signals for the diastereoisomers. The ratio was determined by the integration of the signals due to the methine hydrogen (δ_{axial} 3.37, tt, J = 11.0, 4.5 Hz, vs $\delta_{equatorial}$ 3.80, m, C_6D_6) of the hydroxy-bearing carbon (C-4) and the integration of the two signals due to the *N*-methyl ($\delta_{axial\ OH}$ 2.30, $\delta_{equatorial\ OH}$ 2.25, $CDCl_3$).

The pair of diastereoisomers was oxidized to ketone **43a** using Albright–Goldman conditions. The diastereoisomeric mixture of **42a** (400 mg, 1.2 mmol) in DMSO (4 mL) was added to DMSO–Ac_2O complex prepared from acetic anhydride (6.0 mL) and DMSO (30 mL). After being stirred overnight (~10 h) at room temperature, the reaction mixture was poured into ice-cold saturated $NaHCO_3$ (50 mL), stirred for 1 h, and extracted with Et_2O (5 × 50 mL). Standard workup followed by chromatography using CH_2Cl_2/Et_2O (1/1) as eluant gave ketone **43a** (320 mg, 81%) as slightly yellow oil as well as some of the O-acetylated product. **43a**: IR (film) 2923, 2854, 2790, 1723, 1450, 1374, 1275, 1242, 1133, and 1010 cm^{-1}; mass spectrum, m/e (rel intensity) 331 (M^+, 7), 262 (18), 194 (23), 174 (7), 138 (16), 125 (14), 119 (5), 112 (100), 96 (31), 91 (6), 81 (6), 68 (40), 69 (27); ^1H NMR ($CDCl_3$, ppm) 5.08 (m, 3 H), 3.12 (dtm, J = 12.0, 4.0 Hz, 1 H), 2.65–2.47 (m, 3 H), 2.40 (s, 3 H), 2.45–2.25 (m, 3 H), 2.45–2.27 (m, 10 H), 1.68 (s, 3 H), 1.60 (s, 9 H), 1.5 (m, 2 H); ^{13}C ($CDCl_3$, ppm) 209.2, 135.8, 135.0, 131.2, 124.3, 124.1, 123.4, 62.3, 54.1, 44.8, 40.3, 40.2, 39.7, 39.6, 32.6, 26.7, 26.5, 25.6, 23.4, 17.0, 16.0, 15.9; HRMS calcd for $C_{22}H_{37}NO$ 331.2877, found 331.2880.

1-Methyl-2-[3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]-4-piperidone (43b). This compound was prepared in the same manner as **43a**. Ketone **41b** (500 mg, 1.0 mmol) and $LiAlH_4$ (200 mg, 5.0 mmol) gave **42b** (320 mg, 82%) as a ~50/50 mixture of diastereoisomers. Oxidation of **42b** (250 mg, 0.62 mmol) with a solution of acetic anhydride (3.0 mL) and DMSO (20 mL) at rt after 16 h gave **43b** (190 mg, 76%) as a yellow oil: IR (film) 2917, 1703 (b), 1422, 1343, 1309, 1233, and 1113 cm^{-1}; mass spectrum, CI m/e (isobutane, rel intensity) 400 (M^+ + 1, 100); ^1H NMR ($CDCl_3$, ppm) 5.12 (m, 4 H), 3.12 (ddd, J = 12.0, 10.0, 4.0 Hz, 1 H), 2.60 (m, 1 H), 2.50 (m, 1 H), 2.39 (s, 3 H), 2.39–2.25 (m, 4 H), 2.05 (m, 4 H), 2.00 (m, 10 H), 1.68 (s, 3 H), 1.59 (s, 12 H), 1.50 (m, 2 H); ^{13}C NMR ($CDCl_3$, ppm) 209.1, 135.2, 134.9, 134.3, 131.2, 124.8, 124.4, 124.2, 124.1, 62.3, 54.0, 44.8, 40.3, 40.2, 39.7 (2 C), 34.8, 30.8, 28.2, 28.1, 26.8, 26.6, 25.6, 17.63, 16.0 (3 C). Anal. Calcd for $C_{27}H_{45}NO$: C, 81.15; H, 11.35; N, 3.51. Found: C, 81.10; H, 11.46; N, 3.53.

1-Methyl-2-[4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl]-4-piperidinol (44a). To a slurry of $LiAlH_4$ (50 mg, 1.5 mmol) in THF (10 mL) at −78 °C under an argon atmosphere was added dropwise piperidone **43a** (250 mg, 0.75 mmol) in THF (5.0 mL). After being stirred for 30 min, the reaction was warmed to 0 °C, a 15% NaOH solution (10 mL) was added, and the mixture was extracted with Et_2O (5 × 25 mL). Standard workup followed by chromatography using ethyl acetate/methanol/triethylamine (95/3/2) as eluant afforded **44a** (220 mg, 88%) as an oil (>95% equatorial): IR (film) 3330 (b), 2924, 2855, 2770, 1066, 1450, 1370, 1273, 1110, 1080, and 990 cm^{-1}; mass spectrum, CI m/e (isobutane, rel intensity) 334 (M^+ + 1, 100); ^1H NMR (C_6D_6, ppm) 5.30 (m, 3 H), 3.37 (tt (septet), J = 11.0, 4.5 Hz, 1 H), 2.67 (dt, J = 12.0, 3.5 Hz, 1 H), 2.25 (bm, 6 H), 2.16 (m, 4 H), 2.12 (s, 3 H), 2.05 (bm, 1 H), 1.92 (td, J = 12.0, 2.5 Hz, 1 H), 1.77 (bm, 2 H), 1.72 (s, 3 H), 1.66 (bs, 6 H), 1.61 (s, 3 H), 1.60–1.53 (m, 3 H), 1.38 (q, J = 12.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, ppm) 135.2, 134.8, 131.1, 124.3, 124.1, 124.0, 69.0, 61.6, 55.3, 41.6, 39.7, 39.6, 39.5, 33.5, 32.6, 26.7, 26.5, 25.6, 23.4, 17.6, 16.0, 15.9. Anal. Calcd for $C_{22}H_{39}NO$: C, 79.22; H, 11.99; N, 4.20. Found: C, 79.01; H, 11.78; N, 3.97.

1-Methyl-2-[3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]-4-piperidinol (44b). This was prepared in the same manner as **44a**. Reaction of $LiAlH_4$ (27 mg, 0.7 mmol) and piperidone **43b** (120 mg, 0.30 mmol) at −78 °C followed by chromatography using ethyl acetate/methanol/triethylamine (95/3/2) as eluant gave amino alcohol **44b** (100 mg, 83%, >95% equatorial): IR (film) 3330 (b), 2926, 2854, 1666, 1449, 1375, and 1081 cm^{-1}; mass spectrum, m/e (rel intensity) 401 (M^+, 2), 264 (5), 196 (6), 127 (11), 115 (7), 114 (100), 96 (10), 70 (11), 69 (13); ^1H NMR (C_6D_6, ppm) 5.30 (m, 4 H), 3.37 (tt (septet), J = 11.0, 4.5 Hz, 1 H), 2.67 (dt, J = 12.0, 3.5 Hz, 1 H), 2.25 (bm, 14 H), 2.12 (s, 3 H), 2.05 (bm, 1 H), 1.92 (td, J = 12.0, 2.5 Hz, 1 H), 1.77 (bm, 2 H), 1.72 (s, 3 H), 1.66 (bs, 9 H), 1.61 (s, 3 H), 1.60–1.53 (m, 3 H), 1.38 (q, J = 12.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, ppm) 135.0, 134.9, 134.7, 131.0, 124.3 (2 C), 124.2, 124.1, 69.0, 61.5, 55.3, 41.7, 39.7, 39.6, 34.8, 31.8, 28.2, 28.1, 26.7, 26.6, 25.6, 17.6, 16.0 (3 C). Anal. Calcd for $C_{27}H_{47}NO$: C, 80.74; H, 11.79; N, 3.49. Found: C, 80.86; H, 11.92; N, 3.31.

1,1-Dimethyl-2-[4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl]-4-hydroxypiperidinium Iodide (45a). To a solution of **44a** (25 mg, 0.072 mmol) in dry Et_2O (1 mL), in a screw-cap vial, was added MeI (0.10 mL). The mixture was placed in the dark for 15 h. Excess MeI and ether were evaporated under a gentle stream of argon and the yellow paste was washed with small portions of dry Et_2O (4 × 2 mL). The residual solvent was removed under reduced pressure (0.1 mmHg) to give the salt **45a** (25 mg, 73%) as light yellow, hygroscopic, semisolid: IR (KBr) 3386 (b), 2923, 1450, 1381, 1072 (m) cm^{-1}; mass spectrum, FAB m/e (xenon, Noba, rel intensity) 348 ($M^+ - I^-$, 100); ^1H NMR ($CDCl_3$, ppm) 5.1 (m, 3 H), 4.15 (m, 1 H), 4.08 (bm, 1 H), 3.35 (td, J = 13.0, 3.0 Hz, 1 H), 3.68 (t, J = 12 Hz, 1 H), 3.36 (s, 3 H), 3.17 (s, 3 H), 2.40–1.90 (bm, 14 H), 1.70 (s, 3 H), 1.60 (s, 3 H), 1.58 (bs, 6 H), 1.45–1.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, ppm) 138.2, 135.2, 131.3, 124.2, 123.8, 121.1, 71.2, 64.74, 64.3, 53.3, 43.4, 39.7, 39.6, 34.3, 29.8, 29.3, 26.7, 26.6, 25.6, 24.5, 17.7, 16.4, 16.0.

1,1-Dimethyl-2-[3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]-4-hydroxypiperidinium Iodide (45b). This was prepared in the same manner as **45a** (80%). **45b**: IR (KBr) exactly as reported for **45a**; mass spectrum, FAB m/e (Xenon, Noba) 416 ($M^+ - I^-$); ^1H NMR ($CDCl_3$, ppm) 5.20 (bm, 1 H), 5.10 (bs, 3 H), 4.14–4.0 (bm, 2 H), 3.83 (td, J = 13.0, 3.0 Hz, 1 H), 3.62 (t, J = 11 Hz, 1 H), 3.36 (s, 3 H), 3.17 (s, 3 H), 2.40–2.10 (m, 2 H), 2.10–1.85 (bm, 16 H), 1.66 (s, 3 H), 1.60 (s, 3 H), 1.57 (bs, 9 H), 1.56–1.45 (m, 2 H); ^{13}C NMR ($CDCl_3$, ppm) 135.5, 134.9, 132.3, 131.2, 126.9, 124.3, 124.1, 123.8, 71.4, 64.8, 64.4, 53.3, 43.5, 39.7 (2 C), 35.8, 34.3, 29.8, 28.3, 28.1, 27.5, 26.7, 26.6, 25.6, 17.6, 16.0 (3 C).

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for support of this work through operating and strategic grants to A.C.O. We also thank the British Columbia Health Care Research Foundation for a grant to A.C.O. in support of this work.