(3 H, d), 0.83 (3 H, d), 1.04 (3 H, d), 1.11 (3 H, d), 1.14–1.38 (3 H, m), 1.28 (3 H, s), 1.51 (2 H, m), 1.64 (3 H, m), 1.70 (3 H, s), 1.85 (1 H, dd), 1.93 (1 H, dd), 2.46 (1 H, br), 2.65 (1 H, d), 2.97 (1 H, dd), 3.32 (1 H, d), 3.50 (1 H, br), 3.52 (3 H, s), 3.64 (2 H, t), 3.78 (1 H, quintet), 5.48 (1 H, dd), 5.92 (1 H, d), 6.31 (1 H, dd); ^{13}C NMR (100 MHz, CD_3OD) δ 140.7, 136.4, 129.5, 126.6, 92.1, 88.5, 76.4, 69.9, 67.9, 62.6, 61.9, 60.1, 48.1, 40.0, 36.52, 36.45, 33.69, 33.69, 33.3, 22.7, 19.8, 18.2, 16.8, 12.2, 11.6; DP/EI-MS m/z 424 $(M)^+$, DP/CI-MS m/z 425 $(M + H)^+$.

6-[6-[3-[3-(Acetyloxy)-2-methoxy-1-methylbutyl]-2-methyloxiranyl]-1,5-dimethyl-1,3-hexadienyl]tetrahydro-5-methyl-2*H*-pyran-2-acetic Acid Methyl Ester (11). A solution of **9** (0.6288 g), pyridine (10 mL), and acetic anhydride (14 mL) was stirred at room temperature for 4.5 h. Solvent was removed in vacuo, and the resulting material was dissolved in ether and extracted with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give **11** as a yellow oil (0.5796 g, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (3 H, d), 0.85 (3 H, d), 1.04 (3 H, d), 1.19 (3 H, d), 1.19–1.27 (2 H, br), 1.26 (3 H, s), 1.33 (1 H, m), 1.45 (1 H, m), 1.52 (1 H, m), 1.69 (1 H, br), 1.70 (3 H, s), 1.84 (1 H, dd), 1.91 (1 H, dd), 2.05 (3 H, s, $COCH_3$), 2.35–2.45 (1 H, br), 2.40 (1 H, dd), 2.56–2.63 (1 H, br), 2.60 (1 H, dd), 3.23 (1 H, dd), 3.32 (1 H, d), 3.53 (3 H, s), 3.67 (3 H, s, CO_2CH_3), 3.77 (1 H, m), 5.00 (1 H, quintet), 5.44 (1 H, dd), 5.89 (1 H, d), 6.23 (1 H, dd); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.5, 139.3, 135.2, 128.2, 125.2, 90.7, 84.4, 73.8, 72.5, 65.9, 61.5, 60.7, 51.6, 46.9, 41.4, 35.3, 35.1, 32.3, 32.1, 31.7, 22.1, 21.4, 17.6, 16.8, 16.7, 11.9, 10.6; DP/CI-MS m/z 495 $(M + H)^+$ (major ions at m/z 435, 403, 265).

Ozonolysis of Compound 11. Ozone gas was bubbled through a solution of **11** (0.4383 g, 0.89 mmol), $CHCl_3$ (30 mL), and MeOH (0.568 g, 8.9 mmol) at −50 °C until a blue color persisted. The reaction was allowed to stir for 40 min during which time it warmed to −10 °C and became clear. A small amount of ozone was added, and the solution was stirred for an additional 5 min. Dimethyl sulfide (0.6 mL) was added at −10 °C and the solution allowed to warm to room temperature. Following extraction with $CHCl_3/H_2O$, drying of the organic layer over $MgSO_4$, and evaporation under reduced pressure, 0.473 g of a clear liquid was obtained. SiO_2 gel chromatography (chromatotron, 2 mm, hexane/EtOAc) afforded 7 fractions. Two compounds (**12** and **13**) were isolated in sufficient quantity and purity to enable further characterization.

6-Acetyltetrahydro-5-methyl-2*H*-pyran-2-acetic Acid Methyl Ester (12). Impure **12** (146.5 mg, 77% yield) was purified by SiO_2 gel chromatography (chromatotron, 2 mm, hexane/$CHCl_3/CH_3OH$ (8:2:1)) to yield **12** in 98% purity (23.5 mg) as a clear liquid: R_f = 0.67; 2:1 hexane/EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (3 H, d, H_3-20), 1.21 (1 H, m, H_a-5), 1.34 (1 H, ddd, H_a-4), 1.47 (1 H, m, H-6), 1.64 (1 H, ddd, H_b-4), 1.81 (1 H, ddd, H_b-5), 2.08 (3 H, s, H_3-21), 2.38 (1 H, dd, H_a-2), 2.51 (1 H, dd, H_b-2), 3.35 (1 H, d, H-7), 3.60 (3 H, s, CO_2CH_3), 3.72 (1 H, m, H-3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.8, 171.5, 89.0, 73.8, 51.7, 41.2, 32.2, 31.8, 31.1, 25.8, 16.9; DP/CI-MS m/z 215 $(M + H)^+$.

5-[4-(Acetyloxy)-1-hydroxy-3-methoxy-2-methylpentyl]-dihydro-3,5-dimethyl-2-(3*H*)-furanone (13). Compound **13** (108.7 mg, 40%) was a yellow solid: R_f = 0.13; 2:1 hexane/EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3 H, d, H_3-24), 1.23 (3 H, d, H_3-19), 1.29 (3 H, d, H_3-22), 1.42 (3 H, s, H_3-23), 1.93 (1 H, t, H_a-13), 1.98 (1 H, m, H-16), 2.09 (3 H, s, $COCH_3$), 2.26 (1 H, dd, H_b-13), 2.29 (1 H, m, H-12), 3.48 (1 H, br, OH), 3.53 (3 H, s, H_3-25), 3.55 (1 H, dd, H-17), 3.56 (1 H, d, H-15), 5.12 (1 H, br, H-18); ^{13}C NMR (400 MHz $CDCl_3$) δ 180.2 (C-11), 171.5 ($COCH_3$), 86.8 (C-14), 85.8 (C-17), 80.1 (C-15), 73.0 (C-18), 61.2 (C-25), 40.9 (C-13), 36.3 (C-16), 35.4 (C-12), 22.6 ($COCH_3$), 22.2 (C-23), 18.7 (C-19), 16.6 (C-22), 14.1 (C-24); DP/CI-MS m/z 303 $(M + H)^+$ (major ions at m/z 211, 243).

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Supplementary Material Available: Figures 1–6 consisting of the NOESY, HMQC, and HMBC spectra of **1** and proton NMR spectra of new compounds **1–13** (19 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of Inhibitors of 2,3-Oxidosqualene–Lanosterol Cyclase. 2. Cyclocondensation of γ,δ-Unsaturated β-Keto Esters with Imines

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Synthesis and the biological evaluation of ammonium ion analogues of the first carbocyclic cationic intermediate **4** presumed to formed during the cyclization of 2,3-oxidosqualene to protosterol, **2**, by 2,3-oxidosqualene–lanosterol cyclase (OSC) is presented. Preparation of the required 4-hydroxy-2,3-substituted-4-piperidine **12** (and its corresponding methiiodide salt **13**) involved, as a key step, cyclocondensation of imine **17** with methyl 2-methyl-3-oxo-4-pentenoate (**16**) to give C-2,C-3-substituted 4-piperidone **15** as a single diastereoisomer. Subsequent elaboration to give **13** was accomplished in six steps in an overall yield of 50%. Analogue **12** inhibited 2,3-oxidosqualene–lanosterol cyclase of *Candida albicans* with an IC_{50} of 0.23 μM.

I. Introduction

2,3-Oxidosqualene cyclases (OSC)[1] comprise a class of enzymes that catalyze the cyclization of (3*S*)-2,3-oxidosqualene (**1**) to a number of sterols. The cyclases catalyze the sequential formation of four new carbon–carbon bonds leading to the tetracyclic protosterol **2**. Backbone rearrangement of **2** by OSC's gives lanosterol **3** (Figure 1), in fungi and mammals, and cycloartenol or β-amyrin in photosynthetic plants. There is considerable circumstantial evidence to suggest the conversion of 2,3-oxido-

(1) (a) Schroepfer, G. J., Jr. *Ann. Rev. Biochem.* **1982**, *51*, 555. (b) Dean, P. D. G. *Steroidologia* **1971**, *2*, 143. (c) Mulheirn, L. J.; Ramm, P. *J. Chem. Soc. Rev.* **1972**, 259.

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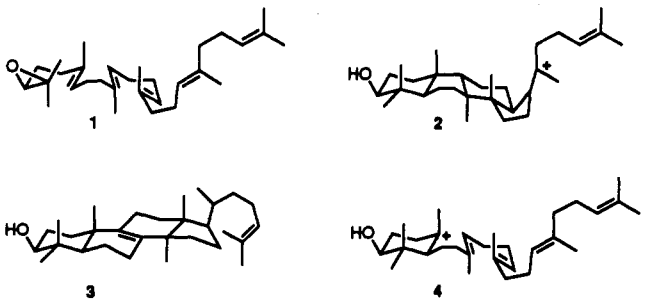
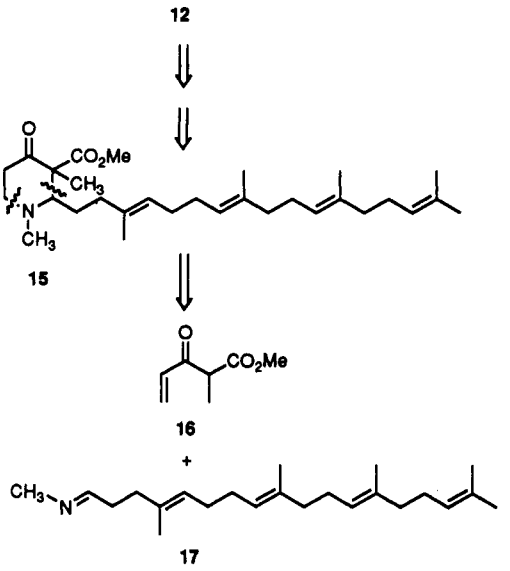


Figure 1.

squalene (1) to protosterol (2) involves conformationally rigid, enzymatically-stabilized carbocation intermediates, produced concurrent with the formation of each ring.[2-8]

One approach to test for the involvement of carbocation intermediates in enzymatically mediated processes is to inhibit the respective enzymes by the administration of heteroatom[9-11] mimics of the presumptive cationic intermediates. In previous papers[12] we reported the synthesis of ammonium analogues 5–11 (Figure 2) of presumptive intermediate 4. We also required C-3 *gem*-dimethyl-substituted aza-analogues 12 and 13 (Figure 3) that would be equivalent in every aspect to 4. The introduction of *gem*-dimethyls at C-3 of 5 (and 6 and 7) was reported,[12] but due to the delicate nature of the side chain of 12 (and 13) the strategy used for the preparation of 5 (and 6 and 7) could not be applied.[13] Although modifications to the earlier strategy would have allowed preparation of 12 (and 13),

Scheme I



we sought a different route. The new methodology we report herein utilizes cyclocondensation of Nazarov-type γ,δ-unsaturated-β-keto esters with imines to generate C-2,C-3-substituted 4-piperidones.

The new route allows facile synthesis of the C-3 *gem*-dimethyl-substituted aza analogues 12 and 13. Biological evaluation of 12 and 13 along with previously prepared compounds 5 to 11 as inhibitors of 2,3-oxidosqualene-lanosterol cyclase from the fungus *Candida albicans* is also presented.

II. Results and Discussion

While 3-oxo-4-pentenoates (Nazarov's reagent)[14,15] have been established as excellent annulating agents in the synthesis of several terpenes and alkaloids,[16-18] of particular interest to us was the use of this reagent in the preparation of functionalized 4-piperidones.[17,18]

Hohenlohe-Oehringen[17a] had reported the synthesis of 3-carbethoxy-2-benzyl-1-methyl-4-piperidone, 29% yield, from the reaction mixture of phenylacetaldehyde, methylamine, and ethyl 3-oxo-4-pentenoate (14). Presumably, the imine 2-phenylethylidenemethylamine generated in situ reacts in a Michael fashion with 14 generating an iminium intermediate that was trapped to give the cyclized product. More recently, Nakatsuka and co-workers[17b] have used the same methodology to prepare ^{14}C-labeled *N*-benzyl-4-piperidone from paraformaldehyde and benzylamine. On these precedents we developed our strategy for the synthesis of 12 (and 13).

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(3) For reviews on the proposed mechanisms of lanosterol biosynthesis from 2,3-oxidosqualene see: (a) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9. (b) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (c) Cornforth, J. W. *Angew. Chem., Intl. Ed. Engl.* **1968**, *7*, 903.

(4) For alternative hypothesis in the biosynthesis of lanosterol from squalene see: (a) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890. (b) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (c) Stadler, P. G.; Eschenmoser, A.; Shenz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191.

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(6) (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.

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

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(9) For a more comprehensive list of references on inhibitors of 2,3-oxidosqualene–lanosterol cyclase see: Oehlschlager, A. C.; Czyzewska, E. In *Emerging Targets in Antibacterial and Antifungal Chemotherapy*; Sutcliffe, J., Georgopapadakou, N. H., Eds.; Routledge, Chapman & Hall: New York, 1992; pp 437–475.

(10) For inhibition of 2,3-oxidosqualene cyclases by rationally designed ammonium ion analogues see: (a) Cattel, L.; Ceruti, M.; Viola, F.; Delprino, L.; Balliano, G.; Duriatti, A.; Bouvier-Navé *Lipids* **1986**, *21*, 31. (b) Ceruti, M.; Delprino, L.; Cattel, L.; Bouvier-Navé, P.; Duriatti, A.; Schuber, F.; Benveniste, P. *J. Chem. Soc., Chem. Commun.* **1985**, 1054. (c) Duriatti, A.; Bouvier-Navé, P.; Benveniste, P.; Schuber, F.; Delprino, l.; Balliano, G.; Cattel, L. *Biochem. Pharmacol.* **1985**, *34*, 2765. (d) Rahier, A.; Taton, M.; Benveniste, P. *Biochem. Soc. Trans.* **1990**, *18*, 48.

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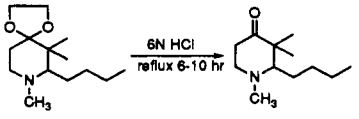
(12) (a) Dodd, D. S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1991**, *32*, 3643. (b) Dodd, D. S.; Oehlschlager, A. C. *J. Org. Chem.* **1992**, *57*, 2794.

(13) The drastic conditions (6 N HCl, reflux 4–6 h) that were required to remove a ketal protecting group of the 4-piperidone in the synthesis of 5 (ref 12) would have certainly isomerized alkene geometry of the side chains of 12 (and 13), if an analogous strategy was used. We were unable to hydrolyze the ketal using more mild methods.



(14) (a) Nazarov, I. N.; Zavyalov, S. I. *Zh. Obshch. Khim.* **1953**, 23, 1703; *Chem. Abstr.* **1954**, *48*, 13667h.

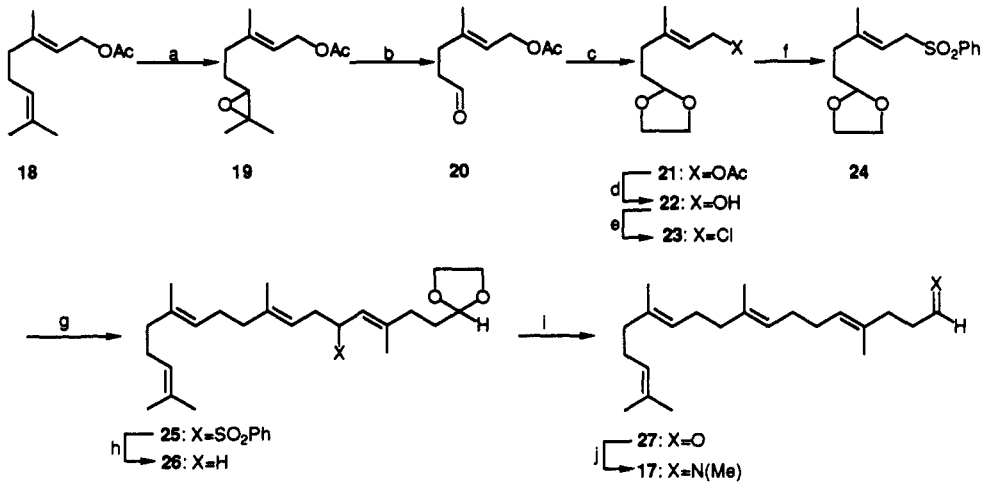
(15) (a) Zibuck, R.; Streiber, J. *J. Org. Chem.* **1989**, *54*, 4717. (b) van den Goorberg, J.; van der Gen, A. *Tetrahedron Lett.* **1980**, *21*, 3621 and references cited therein. (c) Stork, G.; Guthikonda, R. *Tetrahedron Lett.* **1972**, *13*, 2755. (d) Trost, B. M.; Kunz, R. A. *J. Org. Chem.* **1974**, *39*, 2648.

(16) (a) Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991**, *56*, 2701 and literature cited therein. (b) Pelletier, S. W.; Chappell, R. L.; Prabhakar, *J. Am. Chem. Soc.* **1968**, *90*, 2889. (c) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109. (d) Wenkert, E.; Afonso, A.; Bredenberg, J.; Kaneko, C.; Tahara, A. *J. Am. Chem. Soc.* **1964**, *86*, 2038.

(17) (a) Hohenlohe-Oehringen, K. *Monatsh. Chem.* **1962**, *93*, 576. (b) Nakatsuka, I.; Kawahara, K.; Yoshitake, A. *J. Label Compound. Radiopharm.* **1981**, *18*, 495.

(18) For synthesis of 5,6-dihydro-4-pyridone using Michael addition of cyclic imino ethers to 14 see: (a) Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152. (b) Imhof, R.; Kyburz, E.; Daly, J. J. *J. Med. Chem.* **1984**, *27*, 165. (c) For reaction of thioimidates to 14 see: Takahata, H.; Yamabe, K.; Yamazaki, T. *Heterocycles* **1986**, *24*, 37.

Scheme II[a]



[a] Key: (a) *m*-CPBA, NaOAc, CH_2Cl_2, −20 °C; (b) HIO_4–H_2O, THF/Et_2O; (c) $(CH_2OH)_2$, *p*-TsOH, toluene; (d) K_2CO_3, MeOH; (e) NCS–DMS, CH_2Cl_2; (f) $NaSO_2Ph$, DMF; (g) *n*-BuLi, THF, −78 °C then farnesyl bromide; (h) Li, $EtNH_2$, −78 °C; (i) *p*-TsOH, acetone–H_2O, reflux; (j) $MeNH_2$, 3A molecular sieves, toluene, −20 °C.

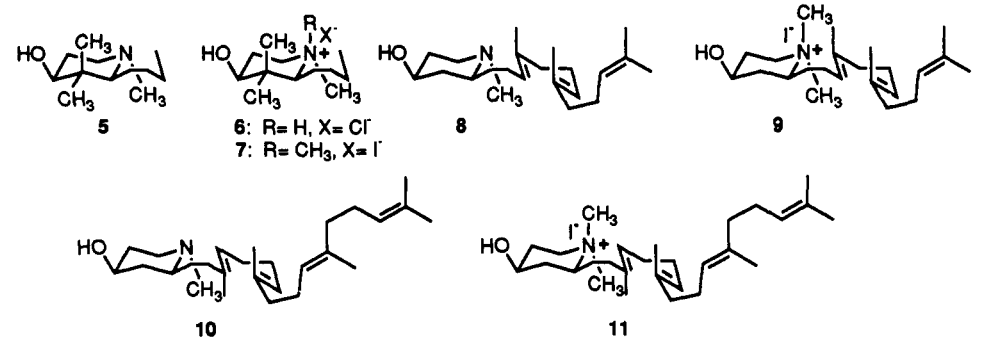


Figure 2.

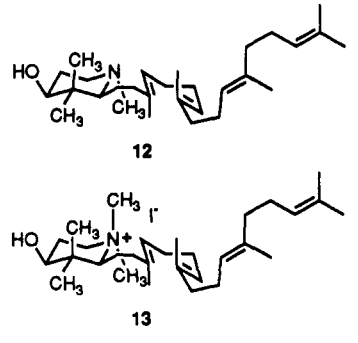
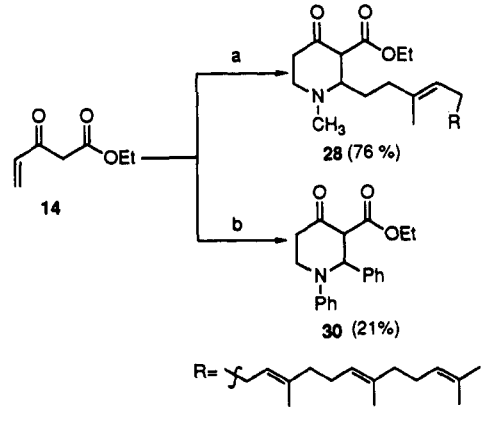


Figure 3.

Scheme III[a]



[a] Key: (a) **16**, EtOH, rt; (b) **29**, EtOH, rt.

A. Synthesis Section. We required a *N*-methyl-4-piperidone-3-carboxylate that was substituted at C-2 with the appropriate tetraene side chain and at C-3 with a methyl group (**15**) (Scheme I). We envisioned that the carbomethoxy at C-3 could then be transformed to the second C-3 methyl via by sequential reduction followed by tosylation and hydride displacement. This strategy required preparation of C-2 substituted γ,δ-unsaturated-β-keto ester **16** and reaction with tetraene methylimine, **17**.

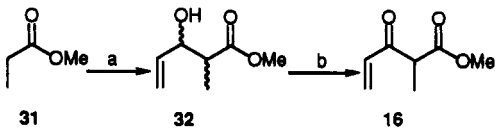
1. Synthesis of 17. We began synthesis of the tetraene imine **17** by selective epoxidation of geranyl acetate (**18**) with *m*-CPBA at −20 °C to give **19** (Scheme II). Epoxide **19** was oxidatively cleaved using HIO_4·H_2O to give aldehyde **20**. The crude mixture of **20** was treated with ethylene glycol and *p*-TsOH in toluene to give acetal **21** which, in turn, was deacetalated ($MeOH/K_2CO_3$) and purified by flash chromatography to give alcohol **22** (pure, 47% in three steps).[19] The latter was then converted to chloride **23** using NCS/DMS,[20] and this was treated with $NaSO_2Ph$ in DMF[21] to give sulfone **24** in 86% yield, over two steps. The sulfone was then treated successively with *n*-BuLi and farnesyl bromide at −78 °C in THF to give coupled product **25**, which was subsequently treated with Li/$EtNH_2$ to give

(19) For an alternative synthesis of **20** by ozonalysis of **18** and its conversion to **21** and **22** see: (a) Corey, E. J.; Cane, D. E.; Libit, L. *J. Am. Chem. Soc.* **1971**, *93*, 7016. (b) Attempted purification of aldehyde **19** by distillation under reduced pressure gave a substantial amount of polymerization.

(20) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *42*, 4339.

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

Scheme IV[a]



31 32 16

[a] Key: (a) LDA, THF, −78 °C then acrolein; (b) Jones' oxidation.

protected tetraene **26** in a combined yield of 84%. The ethylene acetal of **26** was then removed by reluxing with *p*-TsOH in aqueous acetone to give aldehyde **27** in 90% yield.

We realized that we might be able to increase the yields of the cyclization if we were to isolate the imines prior to their treatment with the γ,δ-unsaturated β-keto esters, instead of using the imines in situ as previously described.[17] Imine **17** was therefore prepared, isolated, and used immediately in the cyclization reaction. Preparation of **17** was accomplished, in nearly quantitative yield, by reaction of $MeNH_2$ (5–10 equiv) with aldehyde **27** in a sealed tube over activated powdered 3A molecular sieves in dry toluene at −20 °C for 6–8 h.

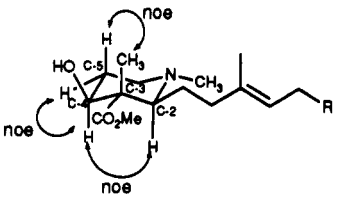
2. Cyclocondensation of Nazarov's Reagent with 17 and 29. Cyclocondensation of imine **17** was initially attempted with C-2-unsubstituted ethyl 3-oxo-4-pentenoate (**14**).[14,15] The cyclized product, **28** (Scheme III), was isolated in ~60% yield over two steps (**27** → **17** → **28**) using DMSO/THF (9/1) as solvent. We were able to increase the yield to 76% when anhydrous EtOH was used as the solvent. Aside from enhancing the solubility of the imine, reactions in EtOH required much shorter times and aqueous workup was not needed. Several additional solvents[21] including THF, CH_2Cl_2, and CH_3CN as well combinations were examined. Except for CH_3CN and DMSO, in which imine **17** was immisible, the other solvents gave reasonable yields although longer reaction times were required than when EtOH was used.

We attempted a cyclization using a more stable imine, benzylideneaniline (**29**). The best yield of cyclization product **30** was 21% (from EtOH), obtained when 2 equiv of **14** was used. The decreased yield in the latter reaction was attributed to the decreased nucleophilicity (Michael donor) of the nitrogen lone pair.[22]

3. Synthesis of 16. Having successfully accomplished the cyclization of **14** with **17**, we initiated synthesis of the required C-2-substituted methyl 2-methyl-3-oxo-4-pentenoate (**16**). This synthesis was easily accomplished using a method analogous to that described by Zibuck and Strieber[15a] for the preparation of 3-oxo-4-pentenoates. Treatment of methyl propionate (**31**) with LDA at −78 °C followed by the dropwise addition of acrolein gave hydroxy ester **32** as 1:1 mixture of diastereoisomers in nearly 80% yield. Hydroxy ester **32** was then oxidized with Jones' reagent at 0 °C to give **16** in 55–60% yield (Scheme IV).

4. Synthesis of 12 and 13. Addition of 2 equiv of **16** to freshly prepared imine **17**, in EtOH, gave the cyclized product **15** in 26–30% yield in two steps (Scheme V). We were unable to increase the yield of this cyclization. This reaction gave several other very polar uncharacterized products. It appears that the steric encumbrance generated by the CH_3 substituent at C-2 of **15** is sufficiently large to decrease reactivity of this reagent. Cyclization failed completely with *N*-benzylideneaniline (**29**).

We were surprised to find that the reaction of **16** and **17** gave only one diastereomer (**15**). A NOESY analysis



33

Figure 4.

of the reduction product **33** showed a pattern that was indicative of the stereochemistry presented in Figure 4 (and Scheme V). It appears that the CH_3 at C-3 and the side chain at C-2 have a syn relationship. NOE's were observed between the CH_3 hydrogen and the axial hydrogen at C-5 of the piperidine ring as well as between the axial hydrogen at C-4 and the axial hydrogens at C-2 and C-6. The observed stereochemistry could have arise from **16** reacting in the *Z* enolic form[23] via a chairlike transition state (Scheme VI).

Transformation of the ring substituents began with the reduction of ketone **15** to the hydroxy derivative **33** in nearly quantitative yield using $NaBH_4$. The equatorial alcohol was the only diastereoisomer detected by ^1H NMR [$CDCl_3$, $\delta_{4\text{-Haxial}}$ = 3.90 (dd, J = 12.0, 6.0 Hz)]. Alcohol **33** was protected as the THP ether **34**, which was obtained as mixture of diastereoisomers in 81% yield after chromatographic purification. Attempted purification of **33** led to much lower yields. Although the THP diastereoisomers could be separated by flash chromatography, we elected to carry the mixture forward. The ester of **34** was next reduced to **35** using $LiAlH_4$ in refluxing THF. Again silica gel chromatography was avoided at this step since there was substantial loss of the product upon chromatography. The hydroxymethyl group of **35** was transformed to the required methyl group via tosylation and hydride displacement in a one-pot procedure. Thus, to **35** was added sequentially *n*-BuLi and *p*-TsCl to generate, in situ, the tosylate, treatment of which with $LiBEt_3H$ gave the *gem*-dimethyl-substituted product **36** in 73% yield. The THP protecting group of **36** was easily removed by treatment with *p*-TsOH in MeOH to give C-2,C-3-substituted 4-hydroxypiperidine **12** in 85–90% yield. As judged by ^1H NMR [$CDCl_3$, $\delta_{H\text{-}3axial}$ = 3.16 (dd, J = 11.5, 5.0 Hz)] the hydroxyl group was equatorial. Treatment of **12** with MeI in Et_2O gave methiiodide salt **13**.

B. Biological Results. Amine analogues **8**, **10**, and **12** and their methiiodide salts **9**, **11**, and **13**, respectively, were found to be potent inhibitors of mammalian[24] and fungal OSC's. They inhibited OSC of *C. albicans*[25] both in cell-free extracts and in whole cells. Preliminary studies of the inhibition of 2,3-oxidosqualene cyclase and antifungal activity results are presented in Table I.

We have found that for all mimics of intermediate **4** studied the piperidine ring, even in the ammonium ion

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(24) These compounds have also been tested on purified pig liver 2,3-oxidosqualene cyclase in collaboration with Professor G. Prestwich at State University of New York at Stony Brook, Stony Brook, NY. The inhibition results along with the kinetic analysis will be reported elsewhere. Perez, A. L.; Oehlschlager, A. C.; Abe, I.; Prestwich, G.; Dodd, D. S. Unpublished results.

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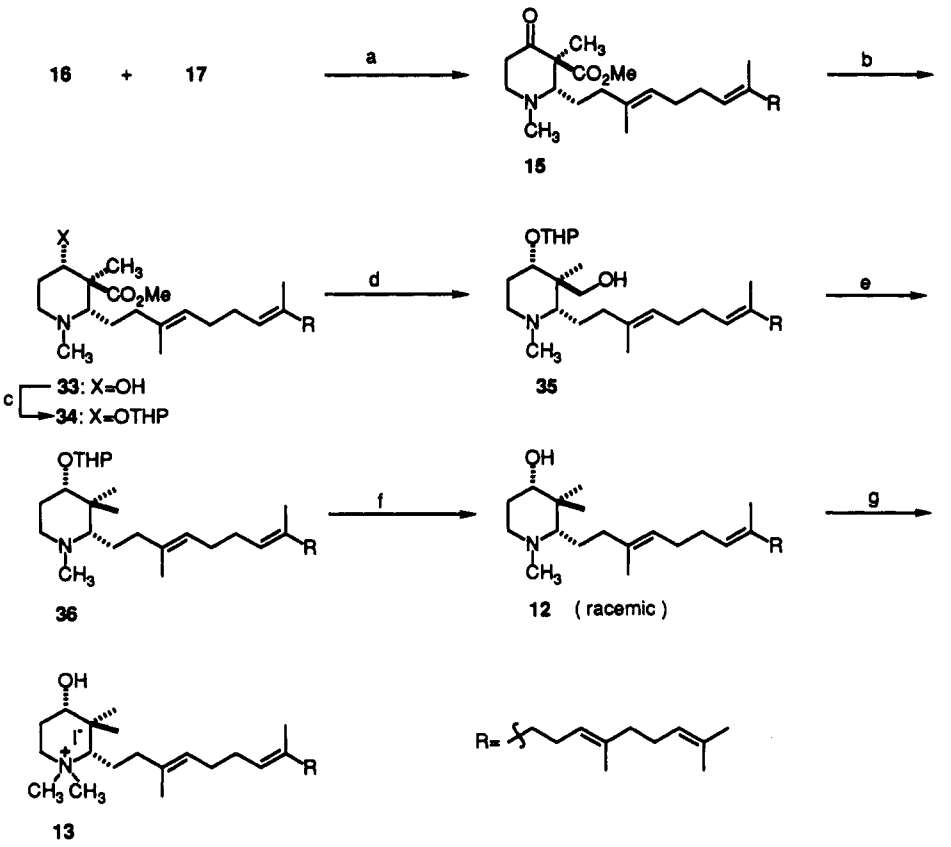
Table I

compd	C. albicans cyclase: intact-cells	C. albicans cyclase: cell-free	in vitro activity MIC[b] (μg/mL): C. albicans	S. cerevisiae	H. capsulatum	A. fumigatus	T. mentagrophytes
5	>250	ND[c]	100	ND	ND	ND	ND
6	>250	ND	100	ND	ND	ND	ND
7	>250	ND	100	ND	ND	ND	ND
8	150	9.6	200	50	100	10	10
9	10.5	4.2	200	200	100	100	100
10	12.5	0.67	200	50	10	>100	>100
11	3.7	5.53	50	50	100	>100	>100
12	23	0.23	>200	200	10	>100	>100
13	3.5	14	50	50	100	>100	>100

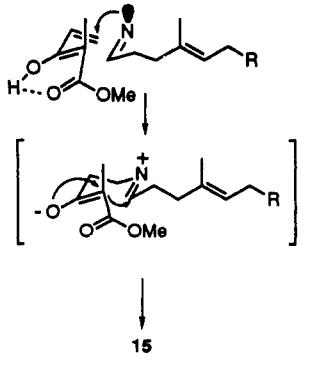
[a] IC_{50}: concentration of inhibitor required to reduce enzyme activity by 50%. [b] MIC: minimum inhibitory growth concentration. [c] ND: not determined.

Scheme V[a]



[a] Key: (a) anhydrous EtOH, rt; (b) $NaBH_4$, EtOH; (c) DHP, *p*-TsOH, CH_2Cl_2; (d) $LiAlH_4$, THF, reflux; (e) MeLi, THF 0 °C, then *p*-TsCl followed by $LiBEt_3H$, THF, reflux; (f) *p*-TsOH, MeOH; (g) MeI, Et_2O.

Scheme VI



form, is not sufficient for inhibition; the properly substituted, π-bond-containing side chain is also required. Compounds 5–7, containing the butyl side chain at C-2 of the piperidine ring, all failed to inhibit the cyclase up to 50 μg/mL (~250–200 μM) in whole cells and consequently were not evaluated in the cell-free preparations of the enzyme. These results are not unexpected. The extremely short side chain renders these ions hydrophilic. The natural substrate 2,3-oxidosqualene (1), on the other hand is very hydrophobic. One can safely surmise that the active site of OSC's contains a hydrophobic substrate-binding domain. Cattel et al.[10a] also found that ammonium ion mimics of the intermediate formed upon initial epoxide opening required "lipophilic" squalenoid chains to make them efficient inhibits of the OSC's.

Consider the IC_{50} (Table I) of free amine analogue 8 vs amines 10 and 12. On the cell-free OSC, 8 is over 14-fold less potent than 10 and nearly 42-fold less potent than 12. Amine 8 has a side chain shortened by five carbons, one olefinic bond omitted, and a methyl at C-3 of the side chain relocated to C-4 and the *gem*-dimethyls at C-3 of the piperidine ring were also absent compared with the structure of the ion (4) it is presumed to be mimicking. Structural deviations of 10 from presumptive intermediate 4 are limited to omission of the *gem*-dimethyls at C-3 on the

piperidine ring. In keeping with previous observations,[10a] the size of the side chain, the number of olefinic sites in the chain and the positioning of the methyls in the chains are important for inhibitory activity.

Analogue 12 meets all the requirements of presumptive intermediate 4 and should show the best interactions with the putative hydrophobic pocket on the enzyme. Free amine 12 was indeed found to be the best inhibitor, being nearly 3-fold more potent than amine 10. Thus, introduction of the *gem*-dimethyls at the C-3 of the piperidine (10 vs 12) clearly enhances the inhibitory activity.

At the pH of the assay medium (pH ~ 7.0) free amines are expected to be fully protonated and should mimic the cationic intermediates. In spite of this, permanently charged ammonium ions have been found to be stronger inhibitors than the corresponding free amines. Surprisingly, the methiiodide salts 11 and 13 were much less inhibitory than expected in the cell-free system. There is a strong possibility that the salts were unstable in aqueous solution, as stock solutions of the methiodide salts tended to lose inhibitory activity with time.

The amines and their methiiodide salts were also examined for their antifungal activity (MIC, minimum growth inhibitory concentration) against several pathogenic fungi (Table I). For a given compound, antifungal activity does not always correlate with inhibitory activity against OSC (IC_{50}). For instance, 12 has an IC_{50} of 23 μM against whole cells of *C. albicans* OSC, yet shows a MIC of 200 μg/mL against this organism. Compound 8 shows antifungal activity against *Aspergillus fumigatus* and *Trichophyton mentagrophytes*[25] at 10 μg/mL and a MIC of 200 μM against *C. albicans* while exhibiting an IC_{50} against whole cells of *C. albicans* of 150 μM. Several explanations can be offered for the observed antifungal activity: the permeability of the cell envelope may be different for different compounds; the cyclase of different fungi may be inhibited with different potency by the compounds; the antifungal activity could be due in part to the ability of these compounds to act as detergents and interrupt the integrity of the cell membrane (those with MIC's > 100 μg/mL). Significantly, the compounds also showed activity against the Gram-positive bacterium *Staphylococcus aureus*, an organism that does not contain sterols. Compounds 5–7 showed no significant inhibitory activity against the OSC, yet displayed MIC's of 100 μM against *C. albicans*.

The inhibition results are in agreement with the postulate that the enzymatic cyclization of 2,3-oxidosqualene to lanosterol by 2,3-oxidosqualene–lanosterol cyclase involves an intermediate such as 4.[2] Compound 12, a close structural analogue of 4, displays a IC_{50} that is comparable 2,3-iminosqualene[26] (IC_{50} of 0.15 μM for *C. albicans*),[11] one of the most powerful inhibitors of *C. albicans* 2,3-oxidosqualene cyclase.

III. Experimental Section

A. General Procedures. 1. Chemical. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dimethoxyethane (DME) were freshly distilled from sodium benzophenone–ketyl. Diisopropylamine, triethylamine, and pyridine were distilled from CaH_2 and stored under an argon atmosphere; dimethyl sulfide (DMS), dichloromethane, toluene, and pentane were freshly distilled from CaH_2 prior to use. *N*-chlorosuccinimide (NCS) was recrystallized from glacial acetic acid, washed with ice–water, and dried under high vacuum; *p*-TsCl was purified by distillation under reduced vacuum (0.5 mmHg). 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 removed using a rotary evaporator. Chromatography refers to flash chromatography[27] using Merck silica gel 60, mesh 230–400.

B. Biological. 1. In Vitro Antifungal Activity. The minimum inhibitory concentrations (MIC, concentration of inhibitor required to completely inhibit growth of the organism in vitro) of the inhibitors were measured on Rowley agar against standard strains of *C. albicans* and *A. fumigatus* after 2 days incubation and *Histoplasma capsulatum* and *T. mentagrophytes* after 7 days.

2. Sterol Biosynthesis Inhibition Assays in Whole Cells. Procedure as previously described in ref 25. *C. albicans* were grown at 37 °C in 10 mL of YECD broth (0.5% yeast extract, 0.5% Casitone, and 0.5% glucose) and supplemented with 0.01 mM [^{14}C]acetate (1 μCi) and the the appropriate concentrations of inhibitor until late-log phase (optical density a 660 nm, 1.3). Cells were harvested after 8 h by centrifugation, washed once with cold 5% trichloroacetic acid, and extracted once with 1.5 mL of methanol followed by 1 mL of a 1:1 mixture of methanol–benzene. The extracts were spotted on silica gel TLC plates and developed with heptane/acetic acid/isopropyl ether (60/4/35) as the eluant. The ergosterol/oxidosqualenes (sum of 2,3-oxido and 2,3:22,23-dioxidosqualene) was established by removal of the respective band or bands into scintillation vials. The TLC material was diluted with 5 mL of Aquasol and the radioactivity determined. The inhibition of 2,3-oxidosqualene cyclases results in the accumulation of 2,3-oxidosqualene, the production of 2,3:22,23-dioxidosqualene and a decrease in ergosterol production. Inhibition was determined for several concentrations of inhibitor and that which reduced the ratio of ergosterol/oxidosqualenes to 50% of control was reported as the IC_{50}.

3. Enzyme Inhibition Assays. As previously described in ref 11. IC_{50} values (the concentration of the inhibitor required to decrease the activity of the enzyme by 50%) were measured using a cell-free preparation of *C. albicans*. Cells were collected from an 8-h culture in TYG medium and were digested for 30 min with Zymolase 100T (Seikagaku Kogyo, Japan). For each gram of cell mass were used 1.0 mg of Zymolase, 12.5 μL of 2-mercaptoethanol, and 5.0 mL of a digestion buffer (50 mM phosphate, pH 7.4, containing 1.0 M mannitol). The resulting protoplasts were collected by centrifugation and lysed in 100 mM phosphate buffer pH 6.9. The supernatant after centrifugation at 15000*g* is the cell-free extract which retains full cyclase activity as shown by a 42% incorporation of racemic [^{14}C]-2,3-oxidosqualene in the presence of the nonionic detergent Decyl Poe (*n*-decylpentaoxyethlene, Bacem, Switzerland). This detergent inhibits the further metabolisation of lanosterol to fungal sterols by the cell-free preparation and thus allows an accurate measurement of the inhibitory activity of the test compounds. The nonsaponifiable lipids were extracted and applied to TLC plates (silica gel F-254, Merck, Germany) which were developed twice in dichloromethane. The radiolabeled spots, in this case only oxidosqualene and lanosterol, were quantified with an automatic TLC scanner (Rita 3200, Raytest, Germany). The % activity was plotted against log inhibitor concentration to determine the IC_{50}.

C. Experimental. 6,7-Epoxygeranyl Acetate (19). To a mechanically stirred solution of geranyl acetate (18) (32.0 g, 163 mmol) in CH_2Cl_2 (500 mL) at −35 to −20 °C containing NaOAc (13.5 g, 165 mmol) was added *m*-CPBA (37.0 g, 165 mmol, 80% by weight) in 3.0-g portions over 1.5 h. The mixture was warmed to 0 °C, stirred for an additional 2 h, and poured into 500 mL of saturated $NaHCO_3$ and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The extracts were combined and washed with ice-cold 1 N NaOH aqueous solution (100 mL). Standard workup gave (>95% pure)

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epoxide **19** (34.0 g, 98%) as an clear oil: mass spectrum CI *m/e* (isobutane, rel intensity) 213 ($M^+ + 1$, trace amount), 153 (100, $M^+ - OAc$), 135 (24); ^1H NMR (CDCl ppm) 5.37 (1 H, tq, J = 7.5, 1.2 Hz), 4.57 (2 H, d, J = 7.0 Hz), 2.68 (1 H, t, J = 6.0 Hz), 2.15 (2 H, m), 2.03 (3 H, s), 1.72 (3 H, s), 1.65 (2 H, m), 1.28 (3 H, s), 1.23 (3 H, s); ^{13}C NMR ($CDCl_3$, ppm) 170.6, 140.9, 118.9, 63.6, 60.9, 58.0, 36.0, 26.9, 24.6, 20.7, 18.5, 16.2.

6-Acetoxy-4-methyl-4(*E*)-hexenal (20). To a mechanically stirred solution of epoxide **19** (20.0 g, 94 mmol) in Et_2O (300 mL) at 0 °C was added dropwise $HIO_4 \cdot 2H_2O$ (23.0 g, 100 mmol) dissolved in THF (200 mL) over 2 h. The slurry was stirred for an additional 0.5 h and poured into H_2O (250 mL), the layers were partitioned, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined extracts were washed with saturated $NaHCO_3$ (2 × 50 mL). Standard workup gave **20** (15.4 g, 82% crude), which was used without purification in the next step: mass spectrum EI *m/e* (rel intensity) 126 ($M^+ - C_2H_3O$, 26), 110 ($M^+ - C_2H_3O_2$, 39), 95 (10), 84 (100), 83 (12), 82 (25), 81 (52), 79 (28), 77 (10), 68 (26), 67 (48), 55 (27), 54 (20); ^1H NMR ($CDCl_3$, ppm) 9.80 (1 H, t, J = 1.50 Hz), 5.52 (1 H, tq, J = 7.0, 1.0 Hz), 4.55 (2 H, d, J = 7.0 Hz), 2.60 (2 H, t, J = 7.5 Hz), 2.35 (2 H, t, J = 7.5 Hz), 2.00 (3 H, s), 1.70 (3 H, s); ^{13}C NMR ($CDCl_3$, ppm) 201.3, 170.6, 139.7, 118.5, 60.7, 39.2, 31.2, 20.6, 16.36.

6-(Ethylenedioxy)-1-acetoxy-3-methyl-2(*E*)-hexene (21). A solution of **20** (15.0 g, 75 mmol, crude), $(CH_2OH)_2$ (8.0 g, 132 mmol), and *p*-TsOH (300 mg) in toluene (200 mL) were refluxed for 5 h under a nitrogen atmosphere using a Dean-Stark separator to remove the water. A solution of saturated $NaHCO_3$ (100 mL) was added, the organic layer separated, and the aqueous layer extracted with Et_2O (2 × 50 mL). Standard workup gave **21** (15.5 g, 96%, crude), which was used without purification in the next step: mass spectrum CI *m/e* (isobutane, rel intensity) 215 ($M^+ + 1$, trace amount), 155 (100); ^1H NMR ($CDCl_3$, ppm) 5.37 (1 H, tq, J = 7.0, 1.0 Hz), 4.85 (1 H, t, J = 4.5 Hz), 4.55 (2 H, d, J = 7.0 Hz), 3.95 (2 H, m), 3.85 (2 H, m), 2.15 (2 H, m), 2.04 (3 H, s), 1.77 (2 H, m), 1.70 (3 H, s); ^{13}C NMR ($CDCl_3$, ppm) 170.6, 141.0, 118.3, 103.7, 64.5 (2C), 60.9, 33.3, 31.7, 20.6, 16.0.

6-(Ethylenedioxy)-3-methyl-2(*E*)-hexenol (22). To a solution of **21** (15.5 g, 72 mmol, crude) in MeOH (500 mL) was added K_2CO_3 (2.0 g). After the solution was stirred for 10 h, most of the MeOH was removed in vacuo, and the resulting slurry was diluted with H_2O (100 mL) and extracted with Et_2O (3 × 50 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (50/50) as the eluant gave **22** (7.7 g, 65%; 47% yield over three steps) as a clear oil: IR (film) 3408, 2953–2883 (m), 1669, 1445, 1410, 1140, 1032, and 897 cm^{-1}; mass spectrum CI *m/e* (isobutane, rel intensity) 171 ($M^+ + 1$, trace amount), 155 (100); ^1H NMR ($CDCl_3$, ppm) 5.43 (1 H, tq, J = 6.5, 1.3 Hz), 4.85 (1 H, t, J = 5.0 Hz), 4.13 (2 H, d, J = 7.0 Hz), 3.95 (2 H, m), 3.83 (2 H, m), 2.13 (2 H, t, J = 7.5 Hz), 1.77 (2 H, m), 1.68 (3 H, s); ^{13}C NMR ($CDCl_3$, ppm) 137.8, 123.7, 104.0, 64.6 (2 C), 58.77, 33.4, 31.84, 16.0.

6-(Ethylenedioxy)-1-chloro-3-methyl-2(*E*)-hexene (23). Alcohol **22** (2.5 g, 14.6 mmol) in CH_2Cl_2 (25 mL) was added dropwise to NCS–DMS complex in CH_2Cl_2 (50 mL) at −20 °C. The NCS–DMS complex was prepared from NCS (3.0 g, 22.5 mmol) and DMS (2.2 mL, 30 mmol) at 0 °C according to the procedure of Corey et al.[20] The cloudy mixture was stirred at 0 °C for 6 h and poured into water (50 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). Standard workup gave chloride **23** (2.70 g, 97% pure by GC) as an oil: IR (film) 2955.4, 2883.6, 1721.6, 1662.7, 1448.8, 1386.5, 1254.5, 1140.1, 1036.7, and 944 cm^{-1}; mass spectrum CI *m/e* (isobutane, rel intensity, major isotope) 191 ($M^+ + 1$, 34), 155 (93), 131 (32), 129 (100); ^1H NMR ($CDCl_3$, ppm) 5.45 (1 H, tq, J = 7.5, 1.2 Hz), 4.83 (1 H, t, J = 4.5 Hz), 4.05 (2 H, d, J = 8.0 Hz), 3.93 (2 H, m), 3.82 (2 H, m), 2.15 (2 H, t, J = 7.5 Hz), 1.75 (2 H, m), 1.70 (3 H, s); ^{13}C NMR ($CDCl_3$, ppm) 140.8, 120.4, 103.8, 64.7 (2 C), 40.8, 33.4, 31.8, 15.9.

6-(Ethylenedioxy)-1-(benzenesulfonyl)-3-methyl-2(*E*)-hexene (24). To a solution of **23** (2.5 g, 13 mmol, crude) in DMF (20 mL) at 0 °C was added $NaSO_2Ph$ (2.35 g, 14.3 mmol). After the solution was stirred for 5 hr, water (50 mL) was added and the aqueous layer extracted with Et_2O (5 × 25 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (1/1) gave the sulfone **24** (3.10 g, 86%) as an oil: IR (film) 2955, 2886, 1663, 1447, 1407, 1305, 1240, 1150, 1085, 1034, 902, 741, and 690 cm^{-1}; mass spectrum CI *m/e* (isobutane, rel intensity) 297 ($M^+ + 1$, 100), 235 (33), 157 (15), 155 (73), 143 (62); ^1H NMR ($CDCl_3$, ppm) 7.87 (2 H, d, J = 7.0 Hz), 7.64 (1 H, t, J = 7.0 Hz), 7.53 (2 H, t, J = 7.0 Hz), 5.20 (1 H, tq, J = 7.5, 1.2 Hz), 4.80 (1 H, t, J = 4.5 Hz), 3.93 (2 H, m), 3.83 (2 H, m), 3.78 (2 H, d, J = 8.0 Hz), 2.10 (2 H, t, J = 7.5 Hz), 1.65 (2 H, m), 1.30 (3 H, s); ^{13}C NMR ($CDCl_3$, ppm) 145.5, 138.5, 133.5, 128.9 (2 C), 128.4 (2 C), 110.6, 103.7, 64.8 (2 C), 55.9, 33.6, 31.8, 16.0. Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.62; H, 6.51.

1-(Ethylenedioxy)-6-(benzenesulfonyl)-4,9,13,17-tetramethyl-4(*E*),8(*E*),12(*E*),16-octadecatetraene (25). To a solution of sulfone **24** (3.0 g, 10.0 mmol) in THF (30 mL) under argon at −78 °C was added *n*-BuLi (4.4 mL, 11.0 mmol, 2.5 M in hexanes). After the solution was stirred for 1.5 h, farnesyl bromide (3.1 g, 11 mmol) in THF (10 mL) was added dropwise and this was stirred for 5 h at −78 °C. MeOH (2 mL) was added followed by H_2O (50 mL) and the slurry warmed to rt and extracted with Et_2O (4 × 50 mL). Standard workup followed by chromatography gave **25** (4.7 g, 94%) as an oil: IR (film) 2923 (m), 1665, 1585, 1446, 1383, 1304, 1146, 1085, 1036, 896, and 741 cm^{-1}; mass spectrum EI *m/e* (rel intensity) 500 (M^+, trace amount), 359 (6), 221 (10), 297 (9), 159 (10), 147 (13), 136/137 (15), 125 (12), 121 (15), 119 (15), 109 (15), 107/105 (13), 99 (31), 93 (37), 91 (13), 81 (60), 79 (15), 77 (14), 73 (43), 69 (100), 55 (12); ^1H NMR ($CDCl_3$, ppm) 7.87 (2 H, d, J = 7.0 Hz), 7.64 (1 H, t, J = 7.0 Hz), 7.53 (2 H, t, J = 7.0 Hz), 5.05 (3 H, m), 4.95 (1 H, t, J = 7.5 Hz), 4.77 (1 H, t, J = 4.5 Hz), 3.95 (2 H, m), 3.85 (2 H, m), 3.70 (1 H, td, J = 10.0, 3.0 Hz), 285 (1 H, ddd, J = 14.5, 7.5, 3.0 Hz), 2.35 (1 H, overlapping ddd, J = 14.5, 7.5, 3.0 Hz), 2.10–1.90 (10 H, m), 1.67 (3 H, s), 1.65–1.60 (2 H, m), 1.60 (3 H, s), 1.57 (3 H, s), 1.55 (3 H, s), 1.18 (3 H, d, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, ppm) 144.2, 138.5, 138.0, 135.0, 133.2, 131.0, 128.9 (2 C), 128.6 (2 C), 124.2, 123.7, 118.4, 117.3, 103.6, 64.8 (2 C), 64.6, 39.6 (2 C), 33.7, 31.8, 26.6, 26.4, 26.3, 25.5, 17.5, 16.3, 16.2, 15.8. Anal. Calcd for $C_{30}H_{44}O_4S$: C, 71.96; H, 8.86. Found: C, 71.82; H, 8.72.

1-(Ethylenedioxy)-4,9,13,17-tetramethyl-4(*E*),8(*E*),12(*E*),16-octadecatetraene (26). To $EtNH_2$ (35 mL) at −78 °C under an argon atmosphere were added small pieces of Li wire (500 mg, 70 mmol) followed by a solution of **25** (4.7 g, 9.4 mmol) in THF (10 mL). This was stirred until the solution became blue, at which time solid NH_4Cl (5 g) was added and the excess Li metal removed from forceps. Water (50 mL) was added, and this was extracted with Et_2O (4 × 40 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (5/95) as the eluant gave **26** (3.0 g, 89%) as an oil: mass spectrum CI *m/e* (isobutane, rel intensity) 361/360 ($M^+ + 1$, 60/15), 300/299 (23/100), 229 (9), 218/217 (7/37), 205 (10), 203 (15), 193 (10), 192 (10), 191 (18), 189 (20), 175 (25); ^1H NMR ($CDCl_3$, ppm) 5.20–5.05 (4 H, m), 4.84 (1 H, t, J = 4.5 Hz), 3.95 (2 H, m), 3.85 (2 H, m), 2.2–1.92 (14 H, m), 1.75 (2 H, m), 1.67 (3 H, d, J = 1.2 Hz), 1.62 (3 H, s), 1.58 (9 H, bs); ^{13}C NMR (CDCl3, ppm) 135.2, 134.8, 134.2, 131.2, 124.6, 124.5, 124.3, 124.2, 64.8 (2 C), 39.7 (2 C), 33.9, 32.5, 28.3, 28.2, 26.8, 26.7, 25.6, 17.6, 16.0 (3 C). Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.95; H, 11.18. Found: C, 79.84; H, 10.82.

4,9,13,17-Tetramethyl-4(*E*),8(*E*),12(*E*),16-octadecatetraenal (27). A solution of acetal **26** (3.0 g, 8.3 mmol) and *p*-TsOH (200 mg), in acetone/H_2O (85/15, 100 mL), was refluxed for 12 h. Most of the acetone was removed in vacuo and the concentrate diluted with H_2O (50 mL) and extracted with Et_2O (5 × 25 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (5/95) as the eluant gave **27** (2.5 g, 95%) as an oil: IR (film) 2924 (bm), 1727, 1443, 1382, and 1126 cm^{-1}; mass spectrum CI *m/e* (isobutane, rel intensity) 317 ($M^+ + 1$, 22), 299 (23), 235 (7), 217 (25), 205 (8), 203 (9), 193 (30), 191 (16), 189 (14), 179 (11), 175 (14), 165 (14), 163 (19), 161 (13), 153 (11), 151 (22), 149 (49), 147 (11), 139 (10), 138 (10), 137 (100), 136 (28), 135 (21); ^1H NMR ($CDCl_3$, ppm) 9.80 (1 H, t, J = 1.8 Hz), 5.00–5.30 (4 H, m), 2.50 (2 H, td, J = 7.5, 1.8 Hz), 2.30 (2 H, t, J = 7.5 Hz), 2.1–1.95 (12 H, bm), 1.68 (3 H, s), 1.61 (3 H, s), 1.60 (9 H, s); ^{13}C NMR ($CDCl_3$, ppm) 197.8, 130.8, 130.3, 128.5, 126.6, 120.9, 119.9, 119.7, 119.4, 37.6, 35.2 (2 C), 27.3, 23.6, 23.5, 22.2, 22.1, 21.113.1, 11.5, 11.4 (2 C). Anal. Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.46. Found: C, 83.53; H, 11.36.

3-Carbethoxy-1-methyl-2-[3,8,12,16-tetramethyl-3(*E*),7-(*E*),11(*E*),15-heptadecatetraenyl]-4-piperidone (28). To a

suspension of activated powdered 3A molecular sieves (2.5 g) in dry toluene (15 mL), in a sealed tube, was added aldehyde **27** (0.550 g, 1.6 mmol), and the mixture was cooled to −78 °C. Into the tube was then condensed a preweighed amount of $MeNH_2$ (0.51 g, 16 mmol). The system was sealed and stirred at −20 °C for 6 h. Excess $MeNH_2$ was evaporated, and the solution was filtered and transferred via canuula into a round-bottom flask. The molecular sieves were rinsed well with dry Et_2O (5 × 10 mL). The organic washes were combined and concentrated in vacuo, using a vacuum pump (0.5 mmHg), to give the imine **17** as an oil (almost quantitative conversion as judged by GC analysis).

Imine **17** was dissolved in anhydrous EtOH (10 mL) and cooled to 0 °C. To this was added dropwise ethyl 3-oxo-4-pentenoate (**14**) prepared according to the procedure of Zibuck et al.[15a] (0.50 g, 3.52 mmol) in EtOH (5 mL). After the solution was stirred for 5 h, the solvent was removed in vacuo and the oil chromatographed using ethyl acetate/hexanes (25/75) as eluant to give **28** (0.57 g, 76%) as a mixture of enol–keto tautomers: IR (film) 3406 (b), 2929 (m), 1744, 1720, 1650, 1600, 1446, 1379, 1299, 1223, 1195, 1061, and 830 cm^{-1}; mass spectrum EI *m/e* (rel intensity) 471 (M^+, trace amount), 426 (trace amount), 344 (2), 220 (7), 197 (13), 185 (13), 184 (100), 151 (7), 149 (11), 139 (9), 138 977), 136 (8), 125 (8), 112 (10), 95 (11), 93 (11), 85 (10), 84 (11), 81 (19), 71 (11), 69 (44), 67 (12), 57 (15), 55 (20); ^1H NMR ($CDCl_3$, ppm) 12.20 (enolic H, s), 5.20–5.05 (4 H, m), 4.30–4.10 (2 H, m), 3.35–3.03 (~2.5 H, contains ketonic H, m), 2.75 (1 H, m), 2.50 (1 H, m), 2.35 (3 H, s), 2.20–1.90 (15 H, m), 1.68 (3 H, s), 1.58 (14 H, bs), 1.30 (3 H, m). Anal. Calcd for $C_{30}H_{49}NO_3$: C, 76.39; H, 10.47; N, 2.97. Found: C, 76.11; H, 10.61; N, 3.03.

3-Carbethoxy-1,2-diphenyl-4-piperidone (30). To a solution of benzylideneaniline[22] (**29**) (181.0 mg, 1.0 mmol) in EtOH or THF (5 mL) was added dropwise ethyl 3-oxo-4-pentenoate (**14**) (284 mg, 2.0 mmol) in EtOH or THF (5 mL). After the solution was stirred for 24 h, the solvent was removed in vacuo and the residual oil chromatographed using ethyl acetate/hexanes (5/95) as eluant to give **26** as a solid essentially in the enol form (^1H NMR, $CDCl_3$). EtOH as the solvent gave **30**, 70 mg (22%), while use of THF gave **30**, 60 mg (19%): mass spectrum EI *m/e* (rel intensity) 323 (M^+, 5), 246 (5), 218 (7), 200 (18), 181 (87), 180 (100), 152 (5), 131 (7), 106 912), 105 (8), 104 (21), 103 (6), 89 (8), 84 (10), 78 (18), 78 (92), 51 (26); ^1H NMR ($CDCl_3$, ppm) 12.50 (enolic H, s), 7.20 (7 H, m), 7.00 (2 H, d, J = 6.3 Hz), 6.85 (1 H, t, J = 6.3 Hz), 4.15 (2 H, t, J = 7.0 Hz), 3.50 (1 H, app dd, J = 14.5, 6.5 Hz), 3.25 (1 H, ddd, J = 14.5, 11.5, 4.5 Hz), 2.65 (1 H, ddd, J = 18.0, 11.5, 6.5 Hz), 2.25 (1 H, ddd, J = 18.0, 4.5, 2.5 Hz), 1.10 (3 H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, ppm) 172.1, 171.0, 149.4, 141.6, 129.2–128.7 (5 C), 127.9, 127.8, 127.0, 119.4, 116.6, 99.4, 60.4, 57.4, 39.8, 27.0, 14.0. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 72.48; H, 6.55; N, 4.33. Found: C, 74.60; H, 6.24; N, 4.33.

Methyl 3-Hydroxy-2-methyl-4-pentenoate (32). To a solution of LDA (0.11 mmol) in THF (300 mL) at −78 °C under an argon atmosphere was added dropwise, via a syringe, neat methyl propionate (**31**) (9.63 mL, 100 mmol) over 15 min. After the solution was stirred for 0.5 h, neat acrolein (6.60 mL, 100 mmol) was added dropwise over a 5-min period and stirring continued for an additional 5 min. Saturated NH_4Cl (50 mL) was then added to produce a slurry that was poured into a separatory funnel containing Et_2O (200 mL), this was shaken vigorously, and the layers were separated. The aqueous layer was extracted again with Et_2O (100 mL), and the organic extracts were combined. Standard workup followed by bulb to bulb distillation (58–62 °C (0.5 mmHg)) gave **32** (11.43 g, 80%) as 1/1 mixture of diastereoisomers, as an oil: IR (film) 3464 (b), 2984, 2952, 2883, 1738, 1460, 1436, 1354, 1259, 1201, 1175, 1048, 929; mass spectrum EI *m/e* (rel intensity) 144 (M^+, trace amount), 113 (5), 88 (100), 57 (76), 56 (25), 55 (20); ^1H NMR ($CDCl_3$, ppm) 5.88–5.75 (1 H, m), 5.35–5.25 (1 H, dm, J = 17 Hz), 5.22–5.15 (1 H, dm, J = 11 Hz), 4.40/4.17 (1 H, diastereotopic, δ 4.40, bm; δ 4.17, t, J = 7.0 Hz), 3.70 (3 H, s), 2.70–2.55 (2 H, bm), 1.16 (3 H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, ppm, diastereoisomers) 175.7/175.4, 137.9/137.5, 116.7/115.9, 74.6/73.0, 51.6, 45.2/44.7, 13.6/11.2.

Methyl 2-Methyl-3-oxo-4-pentenoate (16). To a mechanically stirred solution of hydroxy ester **32** (7.2 g, 50 mmol) in acetone (200 mL) at 0 °C was added dropwise Jones' reagent [55 mmol, prepared from CrO_3 (5.5 g, 55 mmol) and concd H_2SO_4 (5.5 mL) diluted to 55 mL with H_2O]. After the solution was stirred for 2 h, MeOH (5 mL) was added and the stirring maintained for an additional 20 min. The contents were poured into ice-cold water (250 mL) and Et_2O (250 mL). The organic layer was partitioned and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined extracts were washed with ice–water (3 × 100 mL) and saturated NaCl solution (100 mL) and treated with anhydrous $MgSO_4$, and the solvent was removed by simple distillation. Bulb to bulb distillation (receiving bulb cooled to −78 °C with dry ice, bp ~43–46 °C (0.5 mmHg)) gave keto ester **16** (4.0 g, 56%), a mixture of enol–keto tautomers, as an oil: IR (film) 3540 (b), 2950 (m), 1745, 1702, 1655, 1614, 1578, 1440, 1402, 1353, 1246, 1074, 1040, 982, 861, and 822 cm^{-1}; mass spectrum EI *m/e* (rel intensity) 142 (M^+, trace amount), 114 (15), 55 (100); ^1H NMR ($CDCl_3$, ppm, enol/keto tautomers) 12.40 (enol H, s), 6.65–5.55 (2 H, enol/keto tautomers), 3.80 (ketonic H, q, J = 7.0 Hz), 3.78–3.70 (3 H, s), 1.83/1.35 [(CH_3); δ 1.53 (s), δ 1.35 (d, J = 7.0 Hz)]; ^{13}C NMR ($CDCl_3$, ppm, keto tautomer) 195.0, 174.0, 134.2, 129.5, 52.2, 50.0, 12.7.

3-Carbomethoxy-1,3-dimethyl-2-[3,8,12,16-tetramethyl-3-(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]-4-piperidone (15). Imine **17** was prepared as described for the synthesis of **28**. Reaction of aldehyde **27** (1.71 g, 5.4 mmol) in toluene (20 mL), containing powdered 3A molecular sieves (5.0 g) and $MeNH_2$ (1.10 g, 32 mmol) in a sealed tube at −20 °C, gave **17**, in nearly quantitative yield.

Imine **17** was dissolved in anhydrous EtOH (25 mL) and cooled to 0 °C, and β-keto ester **16** (1.9 g, 13.4 mmol) dissolved in EtOH (5 mL) was added dropwise. After the solution was stirred at rt for 12 h, the solvent was evaporated in vacuo and the oil chromatographed using ethyl acetate/hexanes (20/80) as the eluant to give cyclized product **15** (0.67 g, 26% in two steps) and substantial amounts of polymeric material. The structure of **15** was deduced by ^1H NMR to be a single diastereomer: IR (film) 2926, 2853, 1715 (b), 1448, 1377, 1255, 1207, 1116, and 1077 cm^{-1}; mass spectrum EI *m/e* (rel intensity) 471 (M^+, 3), 402 (6), 185 (8), 184 (59), 136 (12), 95 (20), 98 (23), 199 (40), 149 (12), 142 (31), 124 (14), 121 (10), 111 (12), 109 (10), 85 (10), 82 (13), 81 (50), 70 (23), 69 (100), 68 (14), 67 (20), 57 (21), 55 (32); ^1H NMR (C_6D_6, ppm) 5.30 (4 H, bm), 3.42 (1 H, t, J = 5.0 Hz), 3.40 (3 H, s), 2.90 (1 H, overlapping ddd, J = 14.5, 10.0, 7.5 Hz), 2.53 (1 H, app td, J = 14.5, 4.5 Hz), 2.40–2.35 (1 H, tm, J = 7.5 Hz), 2.20–2.00 (18 H, m), 1.72 (3 H, s), 1.68 (6 H, s), 1.60 (3 H, s), 1.58 (3 H, s), 1.50 (1 H, bm), 1.42 (3 H, s), 1.25 (1 H, bm); ^{13}C NMR ($CDCl_3$, ppm) 207.0, 173.6, 135.2, 134.8, 134.2, 131.0, 125.2, 124.3, 124.1, 124.0, 67.2, 62.6, 52.2, 48.8, 42.5, 39.6 (2 C), 38.6, 36.6, 28.2, 28.0, 26.7, 26.6, 25.5, 22.6, 17.5, 17.1, 15.6 (3 H); HRMS calcd for $C_{30}H_{49}NO_3$ 471.3712, found 471.3705. Anal. Calcd for $C_{30}H_{49}NO_3$: C, 76.39; H, 10.47; N, 2.97. Found: C, 76.22; H, 10.23; N, 2.69.

3-Carbomethoxy-1,3-dimethyl-2-[3,8,12,16-tetramethyl-3-(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]-4-piperidinol (33). To a solution of ketone **15** (315 mg, 0.67 mmol) in EtOH (5 mL) at 0 °C was added $NaBH_4$ (60 mg, 1.5 mmol). After the solution was stirred for 1 h, 15% aqueous NaOH (10 mL) was added and the resulting slurry extracted with Et_2O (5 × 25 mL). Standard workup gave the reduced product **33** (300 mg, 95%) as a single diastereoisomer. Chromatography was avoided at this step, since it substantially decreased the yield: IR (film) 3406, 2926, 2854, 1725, 1446, 1377, 1257, 1220, 1137, 1102, and 1035 cm^{-1}; mass spectrum EI *m/e* (rel intensity) 473 (M^+, 4), 404 (4), 336 (11), 288 (4), 268 (20), 186 (100), 85 (15), 69 (30); ^1H NMR ($CDCl_3$, ppm) 5.10 (4 H, m), 3.90 (1 H, dd, J = 12, 6.0 Hz), 3.70 (3 H, s), 2.80 (1 H, dt, J = 12.0, 4.0 Hz), 2.25 (3 H, s), 2.15 (1 H, m), 2.05 (6 H, bm), 2.00 (8 H, bm), 1.88 (1 H, td, J = 12.0, 6.0 Hz), 1.70 (1 H, m), 1.68 (3 H, s), 1.63 (1 H, m), 1.59 (6 H, s), 1.56 (6 H, s), 1.45 (1 H, m), 1.35 (1 H, m), 1.20 (3 H, s); ^{13}C NMR ($CDCl_3$, ppm) 176.4, 135.1, 134.8 (2C), 131.1, 124.6, 124.4, 124.2, 124.1, 73.9, 67.7, 55.1, 54.3, 51.9, 42.8, 39.7 (2 C), 30.4, 29.4, 28.2, 28.1, 26.7, 26.6, 25.6, 17.6, 16.0, 15.9, 15.8, 9.1, missing one carbon; HRMS calcd for $C_{30}H_{51}NO_3$ 473.3868, found 473.3869. Anal. Calcd for $C_{30}H_{51}NO_3$: C, 76.06; H, 10.85; N, 2.96. Found: C, 75.70; H, 10.61; N, 3.04.

3-Carbomethoxy-1,3-dimethyl-4-(tetrahydropyran-2-yloxy)-2-[3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]piperidine (34). A solution of alcohol **33** (300 mg, 0.67 mmol), 5,6-dihydropyran (DHP) (100 mg, 1.2 mmol), and *p*-TsOH (150 mg, 0.74 mmol) in CH_2Cl_2 (5 mL) was stirred for 6 h, treated with 15% aqueous NaOH (10 mL), and extracted with

CH_2Cl_2 (5 × 20 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (15/85) as the eluant gave **33** (310 mg, 81%) as a mixture of separable diastereoisomers (not separated by carried as a mixture through the synthesis): IR (film) 2946, 2851, 2782, 1739, 1442, 1379, 1281, 1260, 1220, 1136, 1078, 1029, and 978 cm^{-1}; mass spectrum EI *m/e* (rel intensity) 557 (M^+, trace amount), 456 (80), 352 (5), 270 (100), 186 (270), 170 (73), 85 (67), 69 (50); ^1H NMR ($CDCl_3$, ppm, major diastereoisomer) 5.50 (4 H, m), 4.75 (1 H, t, J = 2.6 Hz), 3.98 (1 H, dd, J = 11.5, 4.6 Hz), 3.70 (3 H, s), 3.62 (1 H, m), 3.42 (1 H, m), 2.90 (1 H, m), 2.28 (3 H, s), 2.20 (1 H, bm), 2.10 (7 H, bm), 2.00 (8 H, bm), 1.90–1.65 (3 H, m), 1.68 (2 H, s), 1.68–1.3 (20 H, overlapping multiplets), 1.25 (3 H, s); HRMS calcd for $C_{35}H_{59}NO_4$ 557.4447, found 557.4444. Anal. Calcd for $C_{35}H_{59}NO_4$: C, 75.36; H, 10.66; N, 2.51. Found: C, 75.27; H, 10.61; N, 2.74.

1,3-Dimethyl-3-(hydroxymethyl)-4-(tetrahydropyran-2-yloxy)-2-[3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]piperidine (35). To a solution of the diastereoisomers of ester **34** (230 mg, 0.41 mmol) in THF (5 mL) under argon was added LAH (100 mg, 2.6 mmol) and the mixture refluxed for 1 h. The mixture was cooled to 0 °C, diluted with Et_2O (20 mL) and treated successively with H_2O (0.10 mL), 15% NaOH solution (0.10 mL), and H_2O (0.30 mL). The solids were filtered, rinse well with Et_2O (5 × 10 mL), and dried over anhydrous K_2CO_3, and the solvent was removed in vacuo to give **35** (230 mg, crude) as a mixture of diastereoisomers. Chromatography was avoided at this step since it is accompanied by a decrease in yield: IR (film) 3456 (bs), 2937 (m), 1443, 1379, 1275, 1167, 1133, 1075, 1026, 980 cm^{-1}; mass spectrum EI *m/e* (rel intensity) 530 (M^+, 2), 428 (17), 242 (72), 158 (3), 142 (12), 124 (3), 111 (5), 110 (9), 101 (12), 97 (7), 95 (6), 87 (17), 85 (100), 84 (12), 81 (10), 70 (17), 69 (47), 67 914), 57 (15), 55 (12); ^1H NMR ($CDCl_3$, ppm, characteristic peaks) 5.15 (4 H, m), 4.70–4.45 (anomeric H, m), 4.00–3.30 (5 H, m), 2.60/2.40 (3 H, s), 2.20–1.30 (~41 H, m), 0.88/0.78 (3 H, s); HRMS calcd for $C_{34}H_{59}NO_3$, 529.4494, found 529.4506.

4-(Tetrahydropyran-2-yloxy)-2-[3,8,12,16-tetramethyl-3-(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]-1,3,3-trimethylpiperidine (36). A solution of **35** (130 mg, 0.25 mmol) in THF (5 mL) at 0 °C, under an argon atmosphere, was treated with MeLi (0.35 mL, 0.5 mmol, 1.4 M in Et_2O), followed by dropwise addition of freshly distilled *p*-TsCl (150 mg, 0.79 mmol) in THF (3 mL), and the mixture stirred for 4 h. To the cloudy mixture was then added $LiBEt_3H$ (2.5 mL, 2.5 mmol, 1 M in THF), and this was refluxed for 1 h, cooled to 0 °C, and diluted with 15% aqueous NaOH (20 mL). Standard workup using Et_2O (5 × 25 mL) followed by chromatography using Et_3N/ethyl acetate/hexanes (1/19/80) as the eluant gave **36** (95 mg, 73%) as a mixture of diastereomers: IR (film) 2938 (m), 1442, 1382, 1360, 1188, 1118, 1077, 1027, 980, and 817 cm^{-1}; mass spectrum EI *m/e* (rel intensity) 514 (M^+, 3), 413 (19), 412 (53), 227 (14), 226 (100), 142 (5), 138 (9), 126 (11), 124 (5), 98 (6), 85 (22), 83 (7), 70 (20), 69 (25), 67 (7), 55 (77); ^1H NMR ($CDCl_3$, ppm, mixture of diastereoisomers) 5.12 (4 H, bm), 4.75/4.58 (anomeric H, app t, J = 2.5/4.0 Hz), 3.90 (1 H, m), 3.45 (1 H, m), 3.20/3.00 (1 H, dd, J = 11.5, 4.5 Hz; app t, J = 12.0 Hz), 2.85 (1 H, m), 2.25 (3 H, bs), 2.20–1.30 (~41 H, m), 1.02/0.92 and 0.90/0.87 (6 H, s); HRMS calcd for $C_{34}H_{59}NO_2$ 513.4545, found 513.4551. Anal. Calcd for $C_{34}H_{59}NO_2$: C, 79.48; H, 11.57; N, 2.73. Found: C, 79.18; H, 11.55; N, 2.90.

2-[3,8,12,16-Tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]-1,3,3-trimethyl-4-piperidinol (12). A mixture of **36** (95 mg, 0.184 mmol) and *p*-TsOH (50 mg) in MeOH (5 mL) was stirred for 5 h and most of the solvent removed in vacuo. The slurry was diluted with saturated $NaHCO_3$ (10 mL), extracted with Et_2O (5 × 10 mL), and dried over anhydrous K_2CO_3 and the solvent evaporated in vacuo. Chromatography on a small column using MeOH/ethyl acetate/hexanes (5/35/60) as the eluant gave racemic amino alcohol **12** (76 mg, 96%): IR (film) 3388, 2930 (m), 1445, 1374, 1275, 1171, 1082, and 990 cm^{-1}; mass spectrum EI *m/e* (rel intensity) 429 (M^+, trace amount), 412 ($M - H_2O$, trace amount), 155 (5), 142 (100), 98 (10), 81 (5), 69 (19); ^1H NMR ($CDCl_3/D_2O$, ppm) 5.15 (4 H, m), 3.16 (1 H, dd, J = 11.5, 5.0 Hz), 2.82 (1 H, dt, J = 12.0, 3.5 Hz), 2.22 (3 H, s), 2.15–1.90 (16 H, bm), 1.75 (1 H, app dq, J = 12.0, 5.0 Hz), 1.68 (3 H, s), 1.64 (1 H, m), 1.60 (9 H, m), 1.57 (3 H, s), 1.35 (2 H, m), 0.95 (3 H, s), 0.87 (3 H, s); ^{13}C NMR ($CDCl_3$, ppm) 135.2, 135.1, 134.9, 131.2, 124.6, 124.4, 124.3, 124.2, 76.8, 72.3, 55.5, 43.6, 40.7, 40.0, 39.7 (2 C), 30.4, 28.4, 28.2 (2 C), 26.8, 26.7, 25.6, 24.0, 17.6, 16.1, 16.0, 15.9, 13.6; HRMS calcd for $C_{29}H_{51}NO$ 429.3970, found 429.3963. Anal. Calcd for $C_{29}H_{51}NO$: C, 81.06; H, 11.96; N, 3.26. Found: C, 80.98; H, 12.03; N, 3.36.

4-Hydroxy-2-[3,8,12,16-tetramethyl-3(*E*),7(*E*),11(*E*),15-heptadecatetraenyl]-1,1,3,3-tetramethylpiperidinium Iodide (13). To a solution of amino alcohol **35** (20 mg, 0.047 mmol) in dry Et_2O (1 mL) in a tapered screw-capped centrifuge tube was added MeI (0.10 mL), and the mixture was left in the dark. After 24 h, the solvent and excess MeI were evaporated under a gentle stream of argon to give a white paste. Dry pentane (1 mL) was added, the mixture was vortexed and then centrifuged, and the pentane was decanted. This cycle was repeated three times; the residual solvent was evaporated under high vacuum to give salt **36** (26 mg, 93%) as a hygroscopic solid: IR (KBr) 3385 (b), 2925, 1450, 1380, 1072 (m) cm^{-1}; mass spectrum FAB *m/e* (Xenon/noba, rel intensity) 444 ($M^+ - I^-$, 100); ^1H NMR ($CDCl_3$, ppm) 5.20 (1 H, bm), 5.10 (3 H, m), 4.15 (1 H, app td, J = 13.0, 4.0 Hz), 4.00 (2 H, bs), 3.72 (1 H, bm), 3.38 (3 H, s), 3.12 (3 H, s), 2.40–2.15 (4 H, bm), 2.10–1.91 (12 H, m), 1.9–1.80 (2 H, m), 1.67 (3 H, s), 1.58 (12 H, bs), 1.18 (3 H, s), 1.15 (3 H, s); ^{13}C NMR ($CDCl_3$, ppm) 135.4, 134.9, 133.2, 131.2, 126.3, 124.4, 124.2, 123.9, 78.5, 71.8, 63.5, 55.4, 45.6, 41.5, 41.0, 39.7 (2 C), 28.3, 28.0, 26.8, 26.7 (2 C), 26.3, 25.7, 25.4, 17.7, 16.2, 16.1, 16.0, 15.8.

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