Inhibitors of Cholesterol Biosynthesis. 2. Hypocholesterolemic and Antioxidant Activities of Benzopyran and Tetrahydronaphthalene Analogues of the Tocotrienols[1,2]

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Tocotrienols exhibit antioxidant and cholesterol-biosynthesis-inhibitory activities and may be of value as antiatherosclerotic agents. The mechanism of their hypolipidemic action involves posttranscriptional suppression of HMG-CoA reductase (HMGR) in a manner mimicking the action of putative non-sterol feedback inhibitors. The in vitro cholesterol-biosynthesis-inhibitory and HMGR-suppressive activities in HepG2 cells of an expanded series of benzopyran and tetrahydronaphthalene isosteres and the hypocholesterolemic activity of selected compounds assessed in orally dosed chickens are presented. Preliminary antioxidant data of these compounds have been obtained using cyclic voltammetry and Cu-induced LDL oxidation assays. The farnesyl side chain and the methyl/hydroxy substitution pattern of γ-tocotrienol deliver a high level of HMGR suppression, unsurpassed by synthetic analogues of the present study. In orally dosed chickens, 8-bromotocotrienol (**4o**), 2-desmethyltocotrienol (**4t**), and the tetrahydronaphthalene derivative **35** exhibit a greater degree of LDL cholesterol lowering than the natural tocotrienols.

Introduction

Hypercholesterolemia is a well-recognized risk factor for heart disease. In particular, elevated levels of low-density lipoprotein (LDL) are positively associated with coronary heart disease, whereas high-density lipoproteins (HDL) are a negative risk factor.[3] The role of LDL oxidation in the genesis of atherosclerosis is gaining much attention in the literature.[4] It is postulated that under pathological conditions, LDL becomes oxidatively stressed and is no longer recognized by the LDL receptor. The oxidized LDL is avidly taken up by macrophages within the subendothelial space, leading to the formation of fatty streaks, which form the basis for more advanced lesions. The tocotrienols possess both hypolipidemic and LDL antioxidant properties, a profile that may be particularly antiatherogenic.

The tocotrienols are structurally related to the lipid-soluble antioxidant vitamin E (tocopherols) and differ by possessing a farnesyl rather than phytyl side chain (Figure 1). Vitamin E (tocopherol) is an effective inhibitor of LDL oxidation and may have greater importance in the prevention of atherosclerosis than is generally appreciated.[5] The antioxidant properties of the tocotrienols appear to be comparable to those of the tocopherols.[6]

The mechanism of the cholesterol-biosynthesis-inhibitory activity of the tocotrienols appears to involve posttranscriptional suppression of HMG-CoA reductase (HMGR).[7] Tocotrienols retard the rate of [2-^{14}C]acetate but not [^{3}H]mevalonate incorporation into cholesterol in a dose- and time-dependent manner; this strongly supports an inhibitory role at the point of HMGR. Tocotrienols suppress HMGR-protein synthesis and enhance HMGR-degradation rates even in the presence of high levels of lovastatin (competitive inhibitor of HMGR), U-18666A (inhibitor of oxidosqualene cyclase), and ketoconazole (inhibitor of lanosterol 14-α-demethylase). These data advocate a mechanism of sterol-biosynthesis inhibition consistent with a putative non-sterol feedback suppressor[8] or the recently described oxidolanosterol feedback suppressors.[9]

The initial structure–activity relationships involving sterol regulation for the naturally occurring tocotrienols and their racemic synthetic analogues have been previously discussed.[2] The importance of side-chain unsaturation for cholesterol-suppressive activity was demonstrated. The tocopherols do not share any cholesterol-biosynthesis-inhibitory activity. It was also ascertained that γ-tocotrienol, δ-tocotrienol, and tocotrienol, which lack 5-methyl substitution (see Figure 1 for ring numbering), are significantly more potent than α-tocotrienol in suppressing HMGR. In addition, the chirality at C-2 appears to play a minor role for sterol-inhibitory activity. In this paper, an improved synthesis of prenylated benzopyrans is discussed and a more extensive examination of structure–activity relationships involving sterol regulation and antioxidant properties with this new class of sterol-biosynthesis inhibitors is presented. Benzopyran modifications of the benzenoid ring substituents, pyran ring oxidation level, prenyl side-chain length, and olefin configuration are explored. A series of substituted chromanols containing fatty-acid-type side chains have been prepared to gain further insight into the role of the prenyl-containing configuration found in the tocotrienols. Two new tetrahydronaphthalene analogues, wherein the oxygen at the 1-position is replaced with a methylene carbon, have been prepared and evaluated as suitable isosteres for the benzopyran ring.

Synthetic Chemistry

Benzopyran Analogue Synthesis (Schemes 1–4). The compounds in Table 1 were synthesized by modifi-

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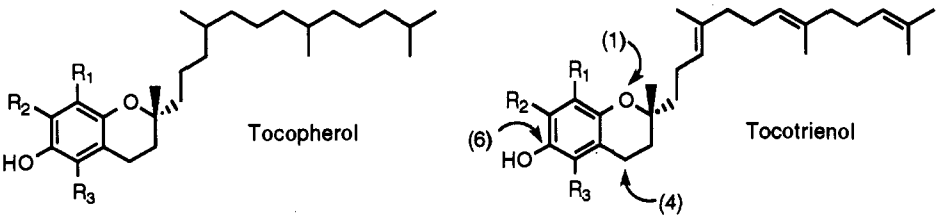


Figure 1.

cation of the chromanone synthesis reported by Kabbe and Heitzer.[10] The yields were improved for the condensation step, using ethanol as the solvent and molecular sieves as a water trap. The utility of the reaction has been expanded to include a diverse number of methyl alkyl ketones and farnesylacetaldehyde (Schemes 1 and 2). In the case of **3q**, pyrrolidine introduced during the condensation step displaced the hydroxy substituent at R_2, consistent with the results of ApSimon.[11]

Another modification of Kabbe's route involved reduction of the 4-oxo substituent to the methylene oxidation state. An aluminum chloride–lithium aluminum hydride (LAH) mixture (2:1) works well for the reduction of electron-rich benzopyranones but gives increasing amounts of 3,4-dehydrobenzopyrans upon ring deactivation.[12] The 3,4-dehydrobenzopyrans resulting from elimination rather than from reduction are difficult to separate from the desired products.[13] Significant amounts of ether-cleavage products were obtained when the C-2 and C-8 positions are hydrogen-substituted. In cases where elimination and/or ether cleavage was problematic, an alternative reduction method was employed. The benzopyranones were reduced to the benzylic alcohols with LAH followed by further reduction with lithium in ammonia/THF to provide excellent yields of the fully reduced products.[14,15]

Tocotrienol analogues possessing fatty-acid-type side chains were prepared as indicated in Scheme 1. Methyllithium addition to commercially available free fatty acids provided the precursor methyl ketones.[16] These were condensed with 2,5-dihydroxy-3,4-dimethylacetophenone to afford chromanones **3v–3z** possessing the benzopyran ring pattern of γ-tocotrienol. Reduction proceeded smoothly using the aluminum chloride/LAH reagent to give chromans **4v–4z**.

The acetylenic derivative 8 and the C-3′ *trans* and *cis* triprenylated homologues **9** and **11** were synthesized as shown in Scheme 2. These 4′-desmethyl derivatives were synthetically accessible from the known acetylene **5**.[17] Acetylenic tocotrienol **7** was prepared from ketone **6** using the Aldol condensation procedure (59%). Reduction of the acetylenic chromanone **7** with hydrogen over Pd-($BaSO_4$) gave the *cis* olefin **10**. Both **7** and **10** were reduced with the mixed aluminum chloride/LAH reagent to give **8** (67%) and **11** (86%), respectively. Reduction of acetylenic tocotrienol **8** with lithium in ethylamine produced the *trans* olefin **9**.

3,4-Dehydro-γ-tocotrienol (**14**) was prepared as shown in Scheme 3. Compound **3j** was first protected as its *tert*-butyldimethylsilyl (TBS) ether derivative, **12**, and then reduced with LAH to give alcohol **13**. The alcohol when mesylated in the presence of excess triethylamine gave the 2,3-dehydro product of elimination. Deprotection of the silyl ether gave the oxidatively unstable target compound **14**.

The 2,3-dehydro compound **20** which lacks the 2-methyl substituent was prepared by the route shown in Scheme 4. Starting with 2,5-diacetoxy-3,4-dimethylacetophenone (**15**),[18] the acetoacetate derivative **16** was prepared from a DBU-promoted intramolecular rearrangement. The β-diketone **16** underwent cyclodehydration and deacylation to give chromanone **17**. Phenol **17** was converted to its TBS ether, **18** (for greater solubility in tetrahydrofuran), metalated with LDA, and alkylated with farnesyl bromide to give the homologated compound **19**. Deprotection of **19** with fluoride provided **20**. Conjugate reduction of the 2,3-double bond in **19** followed by nitroso transfer provided oxime **22** using the procedure of Dann.[19] Hydrolysis of **22** gave the 3-hydroxy analogue **23**.

Benzopyran **36** (Table 2) is a known compound.[20] Derivatives **37, 41**, and **42** were prepared using standard methods. The synthetic route to racemic tocotrienols previously described[2] was applied to 7-fluorotocotrienol (**38**). The diol **39** was a byproduct of an aluminum hydride reduction in this sequence. The 8-cyano-substituted analogue **40** was prepared from the silyl-ether-protected derivative of **4o** by reaction with cuprous cyanide.[21,22]

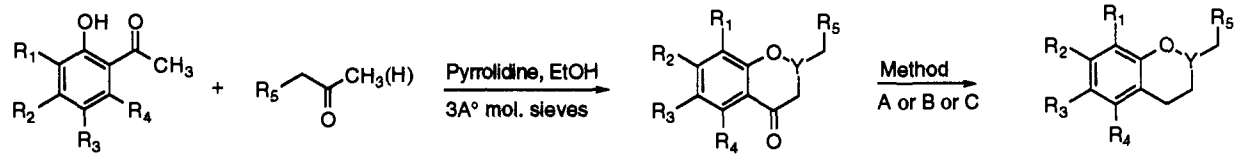
Tetrahydronaphthalene Analogue Synthesis. Synthesis of tetrahydronaphthalenols **29** and **35** is outlined in Schemes 5 and 6. 6-Methoxy-1-tetralone was converted to the hydroxymethylene derivative **24**.[23] Reduction of **24** using borane[24] gave alcohol **25**, which was converted into the trifluoromethanesulfonate ester **26**. (*E,E*)-Farnesyl *p*-tolyl sulfone[25] was metalated with *n*-butyllithium and alkylated with triflate **26** using the coupling methodology of Inomata et al.[26] Reductive cleavage of sulfone **27** occurs without olefin isomerization (Pd(II) and superhydride[26]) to give the farnesylated compound **28**. The methyl ether was dealkylated[27] to give phenol **29** (Scheme 5).

Synthesis of the 2-methyl-naphthalenol derivative **35** begins with the known tetralone **30** (Scheme 6).[23] Demethylation with pyridine hydrochloride at 220 °C gave the known phenol **31**.[28] The phenol, protected as its TBS ether, **32**, was metalated (lithium diisopropylamide) and the enolate coupled with homofarnesyl iodide to give ketone **33** in modest yield.[29] Treatment of ketone **33** with LAH gave the intermediate diastereomeric alcohols. Activation of the alcohols by acetylation followed by reduction with lithium in ammonia provided naphthalenol **34**.[30] Deprotection of the silyl ether with fluoride ion gave tetrahydronaphthalene **35**.

Methods

HepG2 Cell Culture Model. The human hepatoma HepG2 cell culture model was employed to determine cholesterol-biosynthetic-inhibitory and HMG-CoA-reductase-suppression activities of the tocotrienol derivatives (Table 2). HepG2 cells were incubated with selected compounds for 4 h at 10 μM, and cholesterol synthesis was assayed by [^{14}C]acetate incorporation during the final hour of incubation. HMG-CoA reductase suppression was

Scheme 1[a]



1 2 3a - 3z 4a - 4z

[a] Reagents: method A, $AlCl_3/LiAlH_4$ (2:1), Et_2O, −5 °C; method B, (1) TBS-Cl, imidazole, DMF; (2) $AlCl_3/LiAlH_4$ (2:1), Et_2O, −5 °C; (3) TBAF, THF; method C, (1) TBS-Cl, imidazole, DMF; (2) $LiAlH_4/Et_2O$; (3) Li/NH_3, NH_4Cl; (4) TBAF, THF.

Table 1

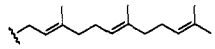
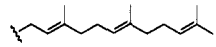
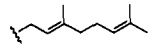
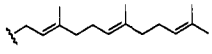
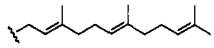
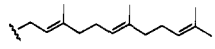
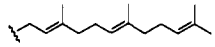
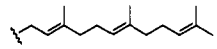
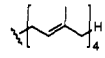
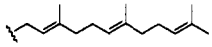
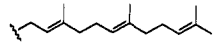
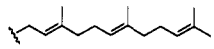
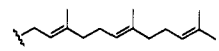
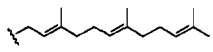
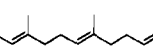
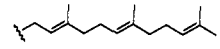
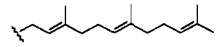
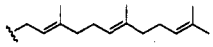
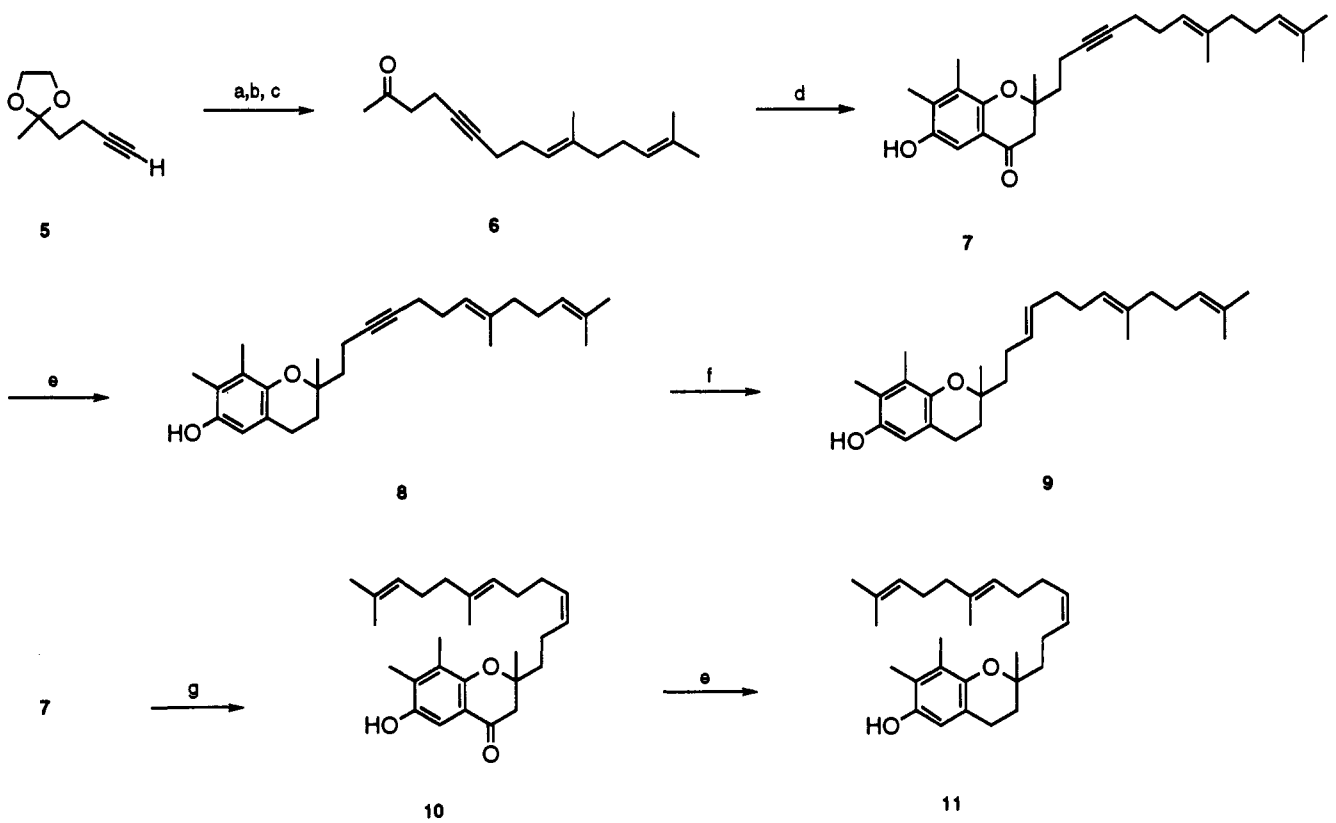
entry	R_1	R_2	R_3	R_4	R_5	Y	3, % yield	3, formula[a]	4, method/ % yield	4, formula[a]
a	H	H	H	H		CCH_3	59	$C_{28}H_{36}O_2$	A/64	$C_{28}H_{38}O_1$
b	H	H	OH	H		CCH_3	95	$C_{26}H_{36}O_3$	C/79	$C_{26}H_{38}O_2$
c	H	H	OH	H		CCH_3	62	$C_{21}H_{26}O_3 \cdot 0.1H_2O$	C/80	$C_{21}H_{30}O_2$
d	H	H	OH	H		CCH_3	60	$C_{21}H_{26}O_3$	B/38	$C_{21}H_{30}O_2$
e	H	H	OH	H		CCH_3	92	$C_{16}H_{20}O_3$	C/97	$C_{16}H_{22}O_2$
f	H	OH	H	H		CCH_3	42	$C_{28}H_{36}O_3 \cdot 0.3H_2O$	A/91	$C_{28}H_{38}O_2$
g	H	H	H	OH		CCH_3	54	$C_{26}H_{36}O_3$	A/21	*b*
h	OH	H	H	H		CCH_3	62	$C_{26}H_{36}O_3$	B/61	$C_{26}H_{38}O_2$
i	OH	OH	H	H		CCH_3	48	$C_{26}H_{36}O_4$	A/60	$C_{26}H_{38}O_3$
j	CH_3	CH_3	OH	H		CCH_3	60	$C_{26}H_{40}O_3$	A/60	$C_{28}H_{42}O_2$
k	CH_3	CH_3	OH	H		CCH_3	67	$C_{33}H_{48}O_3$[c]	A/69	$C_{33}H_{50}O_2$
l	CH_3	H	OH	CH_3		CCH_3	75	$C_{28}H_{40}O_3$[d]	A/57	$C_{28}H_{42}O_2$
m	H	CH_3	OH	CH_3		CCH_3	78	$C_{26}H_{40}O_3$	A/65	$C_{28}H_{42}O_2$
n	H	tBr	OH	H		CCH_3	69	$C_{30}H_{44}O_3$	A/79	$C_{30}H_{46}O_2 \cdot 0.4H_2O$
o	Br	H	OH	H		CCH_3	93	$C_{26}H_{35}Br_1O_3$	B/87	$C_{26}H_{37}Br_1O_2$
p			OH	H		CCH_3	38	$C_{30}H_{35}O_3$[e]	A/65	$C_{30}H_{40}O_2$
q	H		H	OH		CCH_3	24	$C_{25}H_{35}N_1O_3$	A/23	$C_{25}H_{37}N_1O_2 \cdot 0.1H_2O$[f]
r	H	H	F	H		CCH_3	46	$C_{26}H_{35}F_1O_2$	A/74	$C_{26}H_{37}F_1O_1$
s	H	CH_3	CH_3	H		CCH_3	58	$C_{28}H_{40}O_2$	A/60	$C_{28}H_{42}O_1$[g]
t	H	H	OH	H		CH	43	$C_{25}H_{34}O_3$	C/91	$C_{25}H_{36}O_2$
u	CH_3	CH_3	OH	H		CH	73	$C_{27}H_{38}O_3$[h]	C/76	$C_{27}H_{40}O_2$
v	CH_3	CH_3	OH	H	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3$-, *all-Z* configuration	CCH_3	39	$C_{29}H_{42}O_3$	A/86	$C_{29}H_{44}O_2 \cdot 0.2H_2O$
w	CH_3	CH_3	OH	H	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_6$-, *all-Z* configuration	CCH_3	34	$C_{29}H_{44}O_3$	A/69	$C_{29}H_{46}O_2$
x	CH_3	CH_3	OH	H	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_6$-, *all-E* configuration	CCH_3	35	$C_{29}H_{44}O_3$[i]	A/76	$C_{29}H_{46}O_2$

Table 1 (Continued)

entry	R_1	R_2	R_3	R_4	R_5	Y	3, % yield	3, formula[a]	4, method/ % yield	4, formula[a]
y	CH_3	CH_3	OH	H	$CH_3(CH_2)_7CH{=}CH(CH_2)_6$-, *E* configuration	CCH_3	34	$C_{29}H_{46}O_3$[j]	A/84	$C_{29}H_{48}O_2$
z	CH_3	CH_3	OH	H	*n*-$C_{12}H_{25}$	CCH_3	50	$C_{25}H_{40}O_3$	A/80	$C_{25}H_{42}O_2$

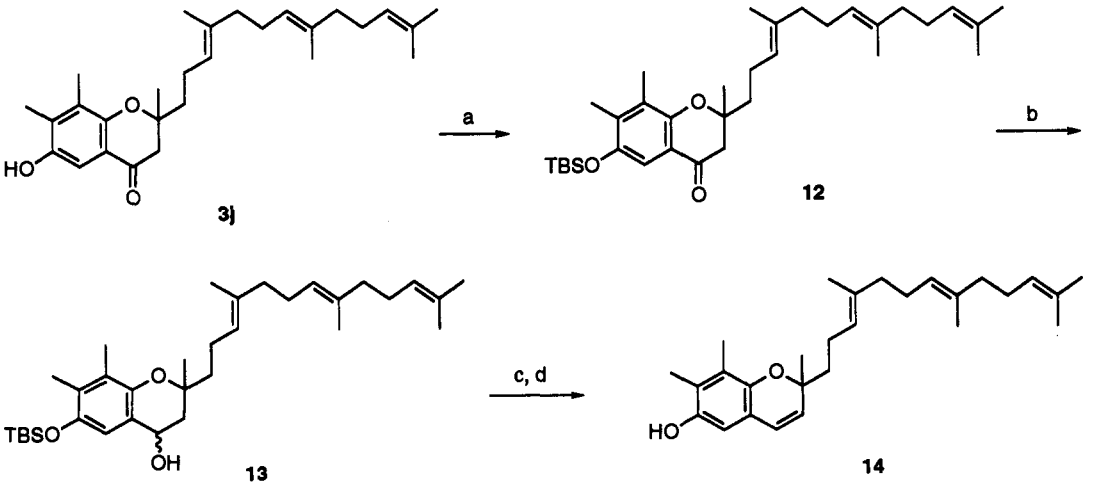
[a] The analyses are within ±0.4% of theoretical values. [b] HRMS exact mass calcd for $C_{26}H_{36}O_3$ 382.2872 (M^+), found 382.2871. [c] Calcd: C, 80.44. Found: C, 81.01. [d] Calcd: H, 9.50. Found: H, 10.10. [e] Calcd: H, 8.58. Found: H, 9.01. [f] Calcd: H, 9.73. Found: H, 9.29. [g] Calcd: H, 11.20. Found: H, 10.73. [h] Calcd: C, 78.98. Found: C, 79.40. [i] Calcd: C, 79.04. Found: C, 79.73. [j] Calcd: C, 78.69. Found: C, 79.22.

Scheme 2[a]



[a] Reagents: (a) MeMgCl, THF, Δ; (b) homogeranyl iodide, CuI, DMPU, 65 °C; (c) acetone, PPTS, Δ; (d) 2,5-dihydroxy-3,4-dimethylacetophenone, pyrrolidine, 3-Å molecular sieves, ethanol; (e) $AlCl_3/LiAlH_4$ (2:1), Et_2O, −5 °C; (f) Li, $EtNH_2$; (g) 1 atm of H_2, $Pd/BaSO_4$ (poisoned with lead), EtOAc.

Scheme 3[a]

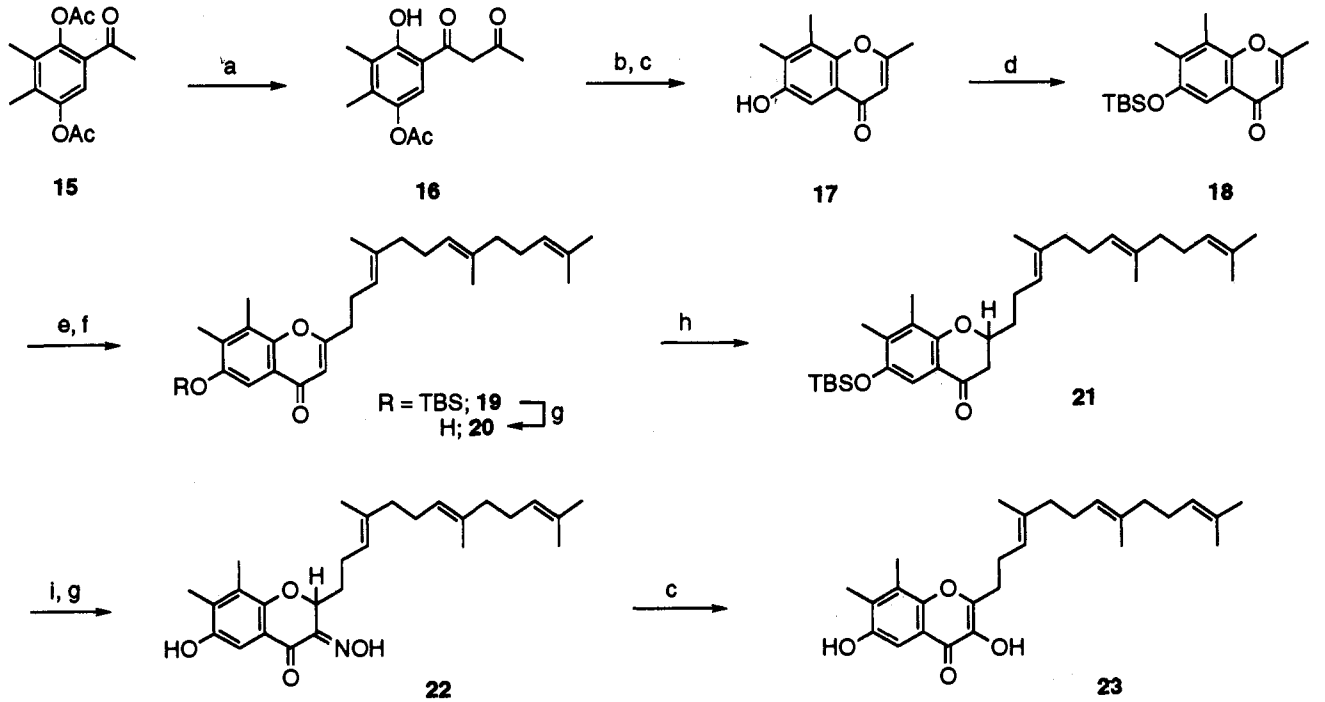


[a] Reagents: (a) TBSCl, imidazole, DMF; (b) $LiAlH_4$, ether, −78 °C; (c) MsCl, Et_3N, CH_2Cl_2; (d) $(n\text{-}Bu)_4NF$, ether.

assayed in the microsomal fraction isolated from HepG2 cultures at the end of the 4-h incubation.[2,7]

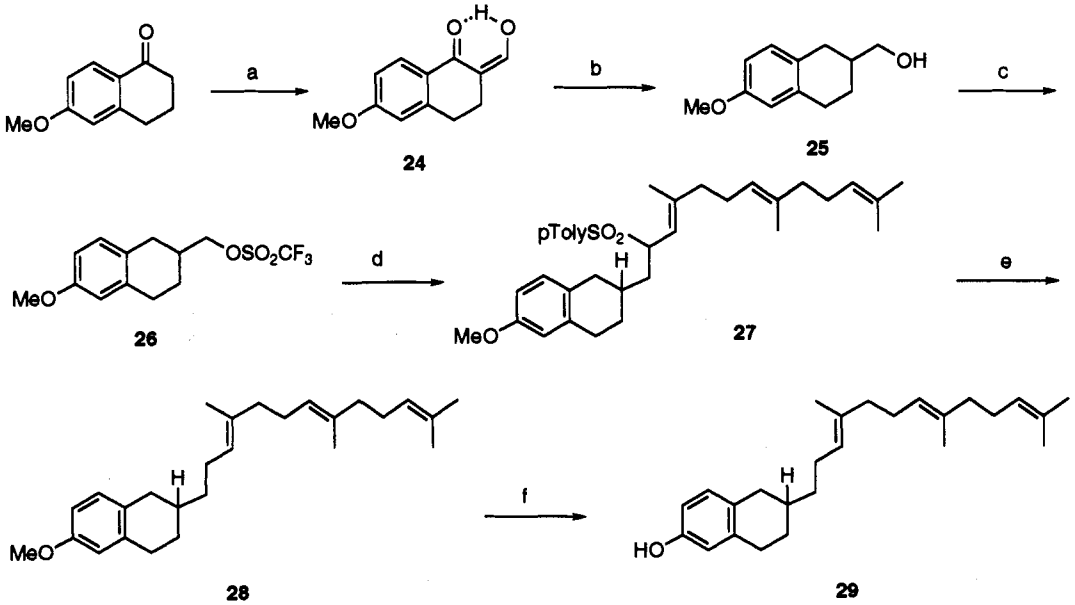
Evaluation in Vivo of Tocotrienol Derivatives in Normocholesterolemic Chickens. Hypocholesterolemic activity was evaluated for selected tocotrienol derivatives in normocholesterolemic chickens[31] in four separate experimental studies. Newborn male chicks (6–12 for each group) were raised on a standard corn–soybean-based

Scheme 4[a]



[a] Reagents: (a) DBU, 23 °C; (b) *p*-TSA, PhH, Δ; (c) 10% HCl/EtOH, Δ; (d) TBS-Cl, imidazole, DMF; (e) LDA, THF, -78 °C; (f) farnesyl bromide; (g) $(n\text{-Bu})_4NF$, THF; (h) $LiAlH_4$, THF, -78 °C; (i) $i\text{-}C_5H_{11}ONO$, *t*-BuOK, THF.

Scheme 5[a]



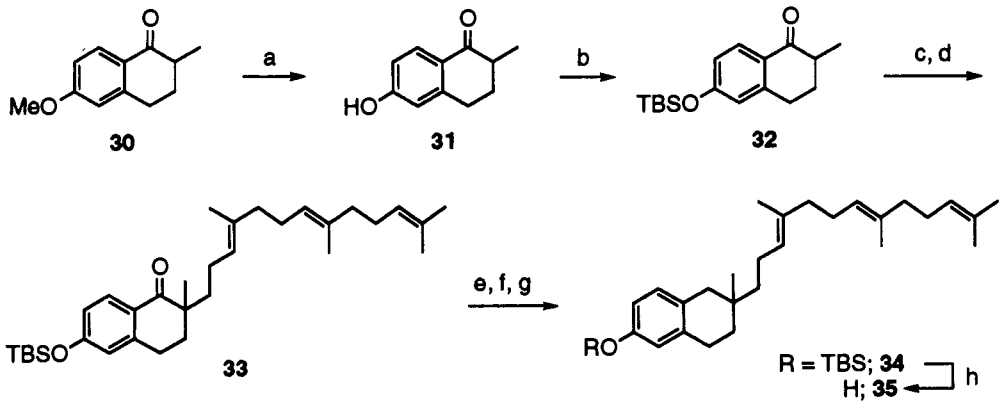
[a] Reagents: (a) tBuOK, EtO_2CH, toluene; (b) $tBuNH_2\text{-}BH_3$, $BF_3\text{-}Et_2O$, CH_2Cl_2; (c) $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2; (d) farnesyl *p*-tolyl sulfone, *n*-BuLi, THF/HMPA; then triflate **26**; (e) $PdCl_2$–dppb, $LiEt_3BH$, THF; (f) *p*-aminothiophenol, Cs_2CO_3, DMPU, Δ.

control diet for 2 weeks and then switched to either control or experimental diets for 4 weeks. Drug treatment consisted of the addition of test compound (50 ppm) to the corn–soybean-based control diet. At the end of the feeding period, all the birds were fasted (36 h) and refed (48 h) to induce cholesterolgenic enzymes prior to sacrifice. Total serum cholesterol, LDL and HDL cholesterol pools, the ratio of HDL/total cholesterol, and triglyceride levels were examined (Table 3).

Cyclic Voltammetry. The second-order rate constants for hydrogen-atom transfer (stopped-flow spectrophotometry) are linearly related to the half-peak oxidation potentials ($E_{P/2}$) (cyclic voltammetry) for a series of structurally related tocopherol derivatives.[32] As a preliminary antioxidant assay, a series of reference and test compounds were evaluated for their oxidation potentials using the protocol established by Mukai et al. (Table 2).[32] Cyclic voltammograms (Princeton Applied Research Model 264A voltametric analyzer) were obtained at ambient temperatures under nitrogen using platinum and saturated calomel reference electrodes in anhydrous acetonitrile containing 40 mM tetrabutylammonium perchlorate. The scan limits were from 0.0 to 1.5 V versus the reference electrode, and the scan rate was 50 mV/s with a variability of ±20 mV. Peak oxidation potentials (E_P) are determined; the majority of compounds displayed irreversibility in their voltammograms (data not shown).

Copper-Induced Oxidation of LDL. Commercial

Scheme 6[a]



[a] Reagents: (a) pyridine hydrochloride, 220 °C; (b) TBS-Cl, imidazole, DMF; (c) LDA, THF/HMPA, -5 °C; (d) homofarnesyl iodide; (e) $LiAlH_4$, ether, -78 °C; (f) Ac_2O, pyridine, CH_2Cl_2; (g) Li, NH_3/THF, NH_4Cl; (h) $(n\text{-}Bu)_4NF$, ether.

LDL lipoprotein[33] was incubated in the presence of copper-(II).[34] LDL oxidation is measured by spectrophotometric determination of thiobarbituric-acid-reactive substances (TBARS), and the results (IC_{50} values) are shown in Table 2. The ability of the test compounds to inhibit LDL oxidation is an indication of general antioxidant capacity. Expectedly, compounds that provide stable radicals are good antioxidants in this assay.

Results and Discussion

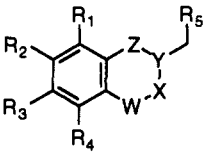
Inhibition of Sterol Biosynthesis and Suppression of HMG-CoA Reductase. Table 2. From the data presented in Table 2, it is apparent that compounds lacking aromatic hydroxy substitution (**4a**, **4r**, and **4s**) exhibit decreased cholesterol-biosynthesis-inhibitory activity compared to that of their phenol analogues (e.g., **4b**). The methyl ether of γ-tocotrienol, compound **41**, exhibits no activity. Compound **4a**, lacking a hydroxyl moiety, exhibits weak activity toward sterol-biosynthesis inhibition and is completely inactive in the HMGR-suppression assay. The origin of the low-level cholesterol-biosynthesis inhibition of compounds **4a**, **4r**, and **4s** is not clear but may indicate a multicomponent mechanism. Within the simple hydroxy-substituted tocotrienols, the 6-hydroxy (**4b**), 5-hydroxy (**4g**), and 7-hydroxy (**4f**) compounds exhibit similar potency. In contrast, the 8-hydroxy isomer (**4h**) and the 7,8-dihydroxy analogue (**4i**) are markedly less active compared to the 6-hydroxy substitution pattern found in the natural products (**4b** and **4j**), which express maximal activity. The 6-hydroxy-7,8-benzo-fused analogue **4p** exhibited nearly equivalent HMGR suppression and cholesterol-biosynthesis inhibition to that of γ-tocotrienol (**4j**). Introduction of a 8-bromo (**4o**), 8-cyano (**40**), 7-pyrrolidino (**4q**), or 7-fluoro (**38**) does not appear to significantly alter cholesterol inhibition relative to tocotrienol (**4b**); however, a marked diminution of HMGR-suppressive activity was observed for **38**. The sterically demanding *tert*-butyl substituent at C-7 (**4n**) led to a significant reduction of activity. As previously disclosed, the natural tocotrienols lacking 5-methyl substitution were the most potent suppressors of HMGR. Consistent with these observations, β-tocotrienol (**4l**) and ε-tocotrienol (**4m**), which possess 5-methyl substitution, are less active as HMGR-suppressor agents than the 5-desmethyl tocotrienols (**4b** and **4j**).

Within the homologous prenylated series (**36**, **4e**, **4c**, and **4b**), the triprenylated (farnesyl) side chain found in the natural product, tocotrienol (**4b**), exhibits optimal activity. The diprenylated (geranyl) analogue **4c** is less active than **4b** within statistical significance. The monoprenyl analogue **4e** is weakly active, and the geranylgeranyl- and methyl-side-chain-containing compounds **4k** and **36** were inactive. The side-chain-containing allylic alcohol **39** was comparatively less active than **4e** in the cholesterol assay. The data suggest a similar level of cholesterol-biosynthesis inhibition and HMGR suppression with the 2-desmethyl derivatives (**4t** and **4u**) compared to the 2-methyl series (**4b** and **4j**). Side-chain derivatives containing fatty-acid-type chains (γ-linolenic (**4v**), linoleic (**4w**), linolelaidic (**4x**), elaidic (**4y**), and myristic (**4z**)) uniformly exhibit diminished cholesterol-biosynthesis inhibition. Taken together, these results indicate that the posttranscriptional HMGR suppression mediated by these compounds requires a *farnesyl* or *geranyl* component in the chromanol derivative.

In order to further investigate the geometrical influence of the side chain on cholesterol-biosynthesis inhibition, a series of side-chain configurational isomers were prepared. The first group of compounds examined the variation of the Δ-3′ olefin by replacement with alkyne **8** and 4′-desmethyl olefins **9** and **11**. The *E* olefin (**9**) exhibited comparable sterol-biosynthesis inhibition to γ-tocotrienol, but unexpectedly, the equipotent alkyne (**8**) and the *Z* olefin (**11**) were better inhibitors of sterol biosynthesis than **9**. However, **8** and **11** possessed diminished HMGR suppression compared to γ-tocotrienol. Within the diprenylated analogues, the *E* and *Z* olefins (**4c** and **4d**) were equipotent as inhibitors of cholesterol biosynthesis. Consistent with the triprenylated compounds, the diprenyl *Z* olefin **4d** showed weaker HMGR suppression than the diprenyl *E* olefin **4c**. Biller et al.[35] have observed a similar phenomenon within a series of squalene synthase inhibitors, which suggests that a common recognition element exists for both HMGR and squalene synthase suppression.

In general, the benzopyran-4-ones exhibit significantly greater cholesterol-biosynthesis inhibition than the corresponding benzopyrans (see the supplementary material). Unfortunately, 4-oxo-γ-tocotrienol (**3j**) showed only minimal HMGR suppression. It was determined that the cholesterol-biosynthesis inhibition of **3j** and presumably other compounds in this series is mediated primarily through the inhibition of fatty-acid synthesis.[36] These observations reveal that changes such as the introduction of a 4-oxo substituent can lead to a stark divergence in biochemical mechanism. The 4-hydroxy-substituted γ-tocotrienol derivative **37** attenuated activity relative to

Table 2. In Vitro Cholesterol-Biosynthesis Inhibition, HMG-CoA-Reductase Suppression, Anodic Peak Potentials (APP), and LDL Antioxidant Profile of Tocotrienol Analogues



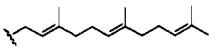
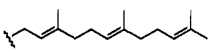
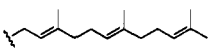
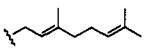
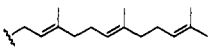
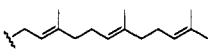
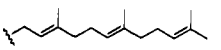
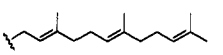
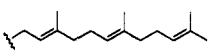
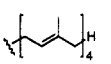
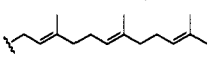
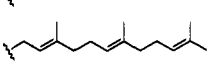
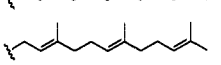
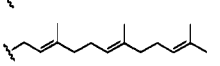
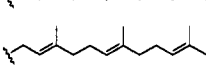
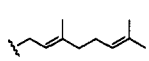
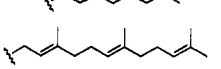
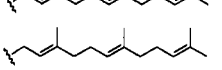
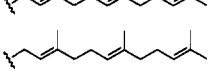
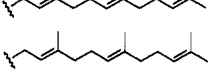
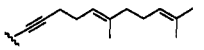
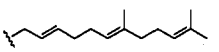
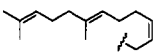
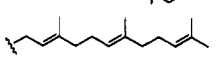
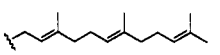
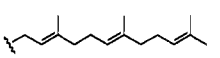
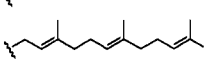
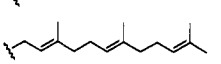
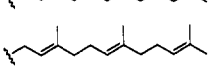
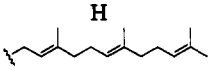
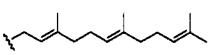
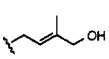
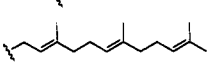
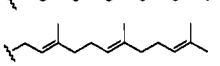
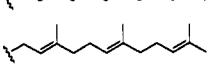
entry	R_1	R_2	R_3	R_4	R_5	W	X	Y	Z	formula[a]	% inhib [^{14}C]Ac; HMGR	APP (V); LDL ox. (IC_{50}, μM)
3j	CH_3	CH_3	OH	H		CO	CH_2	CCH_3	O	Table 1	93 ± 3;[k] 16	1.20; 2.0
4a	H	H	H	H		CH_2	CH_2	CCH_3	O	Table 1	45 ± 4;[o] 0	*b*; ND
4b[c]	H	H	OH	H		CH_2	CH_2	CCH_3	O	Table 1	62 ± 7;[i,m] 53 ± 13[k,i,m]	1.05; 0.6
4c	H	H	OH	H		CH_2	CH_2	CCH_3	O	Table 1	48 ± 9;[n,o] 52	ND; 2.0
4d	H	H	OH	H		CH_2	CH_2	CCH_3	O	Table 1	55; 39	ND; 2.0
4e	H	H	OH	H		CH_2	CH_2	CCH_3	O	Table 1	35; ND	1.20; 2.0
4f	H	OH	H	H		CH_2	CH_2	CCH_3	O	Table 1	58; ND	1.44; >10
4g	H	H	H	OH		CH_2	CH_2	CCH_3	O	Table 1	62; ND	1.27; ND
4h	OH	H	H	H		CH_2	CH_2	CCH_3	O	Table 1	46; ND	1.24; ND
4i	OH	OH	H	H		CH_2	CH_2	CCH_3	O	Table 1	27; ND	1.26; ND
4j[d]	CH_3	CH_3	OH	H		CH_2	CH_2	CCH_3	O	Table 1	69 ± 6;[i,m] 61 ± 7[j]	0.94; 1.8
4k	CH_3	CH_3	OH	H		CH_2	CH_2	CCH_3	O	Table 1	0; ND	ND; ND
4l[e]	CH_3	H	OH	CH_3		CH_2	CH_2	CCH_3	O	Table 1	43; 21	1.05; 7.0
4m[f]	H	CH_3	OH	CH_3		CH_2	CH_2	CCH_3	O	Table 1	42; 40 ± 2[m]	1.06; >10
4n	H	tBu	OH	H		CH_2	CH_2	CCH_3	O	Table 1	38; ND	ND; 10
4o	Br	H	OH	H		CH_2	CH_2	CCH_3	O	Table 1	62 ± 7;[i,m] ND	ND; ND
4p			OH	H		CH_2	CH_2	CCH_3	O	Table 1	57; 57	0.8; ND
4q	H		H	OH		CH_2	CH_2	CCH_3	O	Table 1	54; ND	ND; 4
4r	H	H	F	H		CH_2	CH_2	CCH_3	O	Table 1	35; ND	ND; ND
4s	H	CH_3	CH_3	H		CH_2	CH_2	CCH_3	O	Table 1	33; ND	ND; ND
4t	H	H	OH	H		CH_2	CH_2	CH	O	Table 1	71 ± 4;[j] ND	ND; ND
4u	CH_3	CH_3	OH	H		CH_2	CH_2	CH	O	Table 1	62 ± 7;[i,m] 67	ND; ND
4v	CH_3	CH_3	OH	H	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3$-, *all-Z* configuration	CH_2	CH_2	CCH_3	O	Table 1	22; ND	ND; ND
4w	CH_3	CH_3	OH	H	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_6$-, *all-Z* configuration	CH_2	CH_2	CCH_3	O	Table 1	18; ND	ND; ND
4x	CH_3	CH_3	OH	H	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_6$-, *all-E* configuration	CH_2	CH_2	CCH_3	O	Table 1	17; ND	ND; ND
4y	CH_3	CH_3	OH	H	$CH_3(CH_2)_7CH{=}CH(CH_2)_6$-, *E* configuration	CH_2	CH_2	CCH_3	O	Table 1	10; ND	ND; ND
4z	CH_3	CH_3	OH	H	*n*-$C_{12}H_{25}$	CH_2	CH_2	CCH_3	O	Table 1	16; ND	ND; ND

Table 2 (Continued)

entry	R_1	R_2	R_3	R_4	R_5	W	X	Y	Z	formula[a]	% inhib [^{14}C]Ac; HMGR	APP (V); LDL ox. (IC_{50}, μM)
8	CH_3	CH_3	OH	H		CH_2	CH_2	CCH_3	O	$C_{27}H_{38}O_2$	81; 46	ND; ND
9	CH_3	CH_3	OH	H		CH_2	CH_2	CCH_3	O	$C_{27}H_{40}O_2$	68; ND	ND;ND
11	CH_3	CH_3	OH	H		CH_2	CH_2	CCH_3	O	$C_{27}H_{40}O_2$	81; 45	ND; ND
14	CH_3	CH_3	OH	H		CH	CH	CCH_3	O	$C_{28}H_{40}O_2$	69; ND	0.92; ND
20	CH_3	CH_3	OH	H		CO	CH	C	O	$C_{27}H_{36}O_3$[g]	71; ND	ND; ND
22	CH_3	CH_3	OH	H		CO	CNOH	CH	O	*h*	84; ND	ND; ND
23	CH_3	CH_3	OH	H		CO	COH	C	O	*i*	61; ND	1.20; ND
29	H	H	OH	H		CH_2	CH_2	CH	CH_2	$C_{28}H_{38}O_1$	40 ± 3;[o] ND	ND; ND
35	H	H	OH	H		CH_2	CH_2	CCH_3	CH_2	$C_{27}H_{40}O_1$	58 ± 2;[m,n] ND	1.48; ND
36	H	H	OH	H	H	CH_2	CH_2	CCH_3	O	*j*	0; ND	1.1; 0.4
37	CH_3	CH_3	OH	H		CHOH	CH_2	CCH_3	O	$C_{26}H_{42}O_3 \cdot 0.20H_2O$	56; ND	0.96; ND
38	H	F	OH	H		CH_2	CH_2	CCH_3	O	$C_{26}H_{37}F_1O_2$	60 ± 2;[l,m] 33	1.21; 3.0
39	H	F	OH	H		CH_2	CH_2	CCH_3	O	$C_{16}H_{21}F_1O_3 \cdot 0.5H_2O$	15; ND	ND; >10
40	CN	H	OH	H		CH_2	CH_2	CCH_3	O	$C_{27}H_{37}N_1O_2$	63; ND	ND; ND
41	CH_3	CH_3	OCH_3	H		CH_2	CH_2	CCH_3	O	$C_{29}H_{44}O_2$	0; ND	ND; ND
42	CH_3	CH_3	OAc	H		CH_2	CH_2	CH	O	$C_{29}H_{42}O_3$	ND; ND	ND; ND

[a] The analyses are within ±0.4% of theoretical values. [b] Compound 4a was not electrochemically active within the scan range. [c] (d,l)-Tocotrienol. [d] (d,l)-γ-Tocotrienol. [e] (d,l)-β-Tocotrienol. [f] (d,l)-ε-Tocotrienol. [g] Calcd: C, 79.37. Found: C, 79.82. [h] HRMS exact mass calcd for $C_{27}H_{37}N_1O_4$ 440.2801 (MH^+), found 440.2800. [i] HRMS exact mass calcd for $C_{27}H_{36}O_4$ 425.2692 (MH^+), found 425.2706. [j] Reference 20. [k–o] Values not sharing a common superscript letter are different at $p < 0.01$. Cholesterol-synthesis inhibition and HMG-CoA-reductase suppression were assayed in HepG2 cells incubated for 4 h with the compounds indicated at 10 μM. Values represent mean percent inhibition versus controls (variability, SD ≤ ±10%, $n \geq 8$) receiving DMSO vehicle. Single values are means from experiments repeated in duplicate or triplicate, where standard deviations are indicated; interassay experiments were performed with an $n \geq 2$. All anodic oxidation potentials are expressed in volts using a platinum working electrode and measured versus a saturated calomel (SCE) reference electrode. LDL oxidation values are expressed as the concentration (μM) which inhibits 50% of TBARS production from LDL. ND = not determined.

Table 3. Effects of Tocotrienol Analogues on Lipid Metabolism in 6-Week-Old Male Chickens[a]

experiment number	test compound	total cholesterol	LDL cholesterol	HDL cholesterol	HDL/total cholesterol	triglycerides
study 1	control	159 ± 9[b] (100)	53 ± 1[b] (100)	102 ± 3[b] (100)	0.64	63 ± 2[b] (100)
	3j	133 ± 3[c] (84)	36 ± 2[c] (68)	108 ± 4[b] (106)	0.81	64 ± 2[b] (102)
	4j	121 ± 2[c] (76)	29 ± 1[d] (55)	89 ± 3[c] (87)	0.74	62 ± 2[b] (98)
study 2	control	183 ± 5[b] (100)	63 ± 3[b] (100)	100 ± 2[b] (100)	0.55	84 ± 1[b] (100)
	4b	150 ± 5[c] (82)	43 ± 2[c] (68)	92 ± 1[c] (92)	0.61	80 ± 1[c] (95)
	4t	118 ± 2[d] (65)	23 ± 2[d] (37)	86 ± 1[d] (86)	0.73	81 ± 1[c] (96)
	35	125 ± 3[e] (68)	28 ± 1[e] (44)	85 ± 1[d] (85)	0.68	86 ± 1[b] (102)
study 3	control	176 ± 3[b] (100)	67 ± 2[b] (100)	100 ± 2[b] (100)	0.57	88 ± 3[b] (100)
	4j	151 ± 3[d] (86)	51 ± 2[c] (76)	94 ± 2[c] (94)	0.62	83 ± 2[c] (94)
	4o	139 ± 3[f] (79)	45 ± 1[d] (67)	93 ± 2[c,d] (93)	0.67	87 ± 2[b] (99)
	4p	160 ± 3[c] (91)	61 ± 1[e] (91)	97 ± 2[b] (97)	0.61	81 ± 2[c] (92)
	4u	197 ± 8[e] (112)	85 ± 2[f] (127)	102 ± 1[b] (102)	0.52	86 ± 3[b] (98)
	29	152 ± 3[d] (86)	57 ± 1[g] (85)	94 ± 2[c,d] (94)	0.62	76 ± 2[d] (86)
	40	151 ± 1[d] (86)	54 ± 1[g] (81)	94 ± 1[c] (94)	0.62	83 ± 3[c] (94)
study 4	control	182 ± 2[b] (100)	73 ± 2[b] (100)	102 ± 1[b] (100)	0.56	85 ± 1[b] (100)
	4c	130 ± 2[c,e] (71)	33 ± 2[c] (45)	93 ± 1[c] (91)	0.72	73 ± 2[c] (86)
	4d	142 ± 3[d] (78)	39 ± 1[d] (53)	94 ± 2[c,d] (92)	0.66	67 ± 3[d] (79)
	4e	131 ± 4[c] (72)	32 ± 1[c] (44)	93 ± 1[c] (91)	0.71	73 ± 3[c] (86)
	4j	125 ± 3[e] (69)	33 ± 2[c] (45)	85 ± 2[c] (83)	0.68	57 ± 2[e] (67)
	4u	178 ± 4[b] (98)	76 ± 1[b] (104)	97 ± 1[d] (95)	0.54	83 ± 4[b] (98)
	42	139 ± 2[d] (76)	44 ± 2[d] (60)	87 ± 4[c] (85)	0.63	67 ± 4[d] (79)

[a] Test compound added to the corn control diet at 50 ppm; data expressed as means ± SD; n = 6–12 chickens per group; cholesterol values expressed as mg/100 mL; triglyceride values expressed as mg/100 mL; values in parentheses indicate percent of control values. [b–g] Values not sharing a common superscript within each study are different at $p < 0.01$.

γ-tocotrienol (**4j**). Further adjustment of the pyran ring oxidation level with derivatives **14**, **20**, and **23** did not lead to an increase in cholesterol-biosynthesis-inhibitory activity. Oxime **22** did show an enhancement in cholesterol-

biosynthesis-inhibitory activity relative to γ-tocotrienol. However, given the change in mechanism exhibited by compound **3j**, all of these oxygenated compounds and the pyrrolidine derivative **4q** may exhibit a similar pattern.

Antioxidant Profile.[37] **Table 2.** Placement of a hydroxyl moiety into the 6-position (**4b** vs **4f**) and increasing methyl substitution (**4j** vs **4b**) on the benzopyran ring lower the oxidation potential (APP V) as predicted on the basis of resonance/hyperconjugative stabilization of a radical or a radical cation.[38] Analogue **4a**, lacking a phenolic moiety, was not electrochemically active within this range (0–1.5 V). As expected, the tetrahydronaphthalene analogue **35** is more difficult to oxidize than the benzopyrans. This observation reflects the enhanced orbital mixing (between the ether oxygen and a radical center) in the benzopyran ring as a result of the lone-pair spatial configuration. The benzo-fused analogue **4p** was the most easily oxidized of the compounds examined. This is consistent with the observations of Battioni et al.,[38b] wherein a structurally similar benzopyran displayed enhanced antioxidant properties. Oxime **22** and enol **23** were prepared on the premise of enhanced antioxidant capacity. Both compounds could exert additional antioxidant effects through the binding of transition metals such as iron and/or through radical-scavenging activity much like the flavanoids and vitamin C. Analogue **23** exhibits an oxidation potential of 1.20 V, matching the oxidation potential of **3j**. Most of these compounds showed irreversibility in their voltammograms, indicating some instability in the electochemically generated radical species.

The copper-induced LDL oxidation results are predictive of the chemical antioxidant capacity of the compounds evaluated, wherein compounds expected to provide stable radicals demonstrated a good antioxidant profile. However, chromanol **36** exhibits maximal LDL protection in the series. On the basis of kinetic measurements,[38c] α-tocopherol is a better antioxidant than γ- or δ-tocopherol. The stepwise decrease in LDL protective properties observed in the series: chromanol **36** (IC_{50} = 0.4 μM) < tocotrienol (**4b**) (0.6 μM) < γ-tocotrienol (**4j**) (1.8 μM) < γ-tocopherol (3.9 μM) < α-tocotrienol (8.2 μM) < α-tocopherol (10 μM) appears to be related to compound lipophilicity rather than to radical-stabilizing capacity wherein α-tocopherol (0.81 V) is more easily oxidized than α-tocotrienol (0.90 V) or γ-tocopherol (0.91 V).

In Vivo Activity of Tocotrienol Analogues. The effects of selected tocotrienol analogues on lipid metabolism in 6-week-old male chickens is shown in Table 3. Due to batch variation, it is important to examine the relative lipid profile for each study. γ-Tocotrienol has been included as an internal control in each study with the exception of number 2 wherein tocotrienol was used. Total serum cholesterol, LDL and HDL cholesterol pools, the ratio of HDL/total cholesterol, and triglyceride levels were examined. Comparison of γ-tocotrienol (**4j**) to 4-oxo-γ-tocotrienol (**3j**) (study 1) reveals that while **3j** is a more potent inhibitor of cholesterol biosynthesis in vitro (Table 2), it is somewhat less effective in vivo as an LDL-cholesterol-lowering agent. It was noted that 4-oxo-γ-tocotrienol (**3j**) is a significantly weaker HMGR suppressor and that unlike γ-tocotrienol (**4j**), its mechanism of sterol suppression involves the inhibition of fatty-acid synthesis. Replacement of the 2-methyl substituent of tocotrienol with hydrogen resulted in a marked enhancement in cholesterol-lowering activity (study 2, **4b** vs **4t**). In striking contrast to **4t**, the 2H-γ-tocotrienol derivative **4u** was void of any cholesterol-lowering activity (studies 3 and 4). Ostensibly, these observations could be explained by differences in pharmacokinetics, since **4u** is an effective suppressor of HMGR in vitro (Table 2). As a means to further evaluate the lack of observed in vivo activity of **4u**, the acetate ester was prepared and examined in the chick model. A side-by-side comparison of **4u** and its acetate ester, **42**, did reveal increased activity in the prodrug form (study 4). There is a consistent correlation of the in vitro and in vivo activities of the benzo-fused analogue **4p** (study 3). 8-Cyanotocotrienol (**40**) looks very much like γ-tocotrienol, whereas 8-bromotocotrienol (**4o**) is more active in vivo. The shorter chain analogues **4c** and **4e** exhibit comparable in vivo activity to that of γ-tocotrienol in spite of their lower in vitro potency (study 4). Again, these observations could be explained by differences in pharmacokinetics. The absorption of highly lipophilic compounds such as tocotrienol and tocopherol is generally poor.[39] The less lipophilic analogues **4c** and **4e** would be expected to have enhanced absorption. The Δ-3′ *cis* olefin analogue **4d** is less active than the Δ-3′ *trans* isomer **4c**, reflecting differences in HMGR suppression (Table 2). Substitution of the benzopyran oxygen in tocotrienol with a methylene group results in orally active compounds. The 2-methyl analogue **35** exhibits greater potency in vitro and in vivo than its 2-hydrogen congener, **29**. In general, triglyceride levels were only modestly effected. The decrease in triglyceride levels with **4j** (study 4) appears to be anomalous. With the exception of **4u**, the drug-treated birds showed improvements in their HDL/total cholesterol as a measure of atherogenic index.

Conclusions

The data presented here extend our initial understanding of the structural features important for cholesterol-biosynthesis inhibition and HMGR suppression for this class of compounds. There appears to be a specific requirement for prenyl-type side chains, of either *E* or *Z* configuration. Compounds of the *E* configuration are somewhat more potent as suppressors of HMGR. The farnesyl side chain and the methyl/hydroxy substitution pattern of γ-tocotrienol deliver a high level of HMGR suppression, unsurpassed by synthetic analogues of the present study. While compounds containing monoprenyl and geranyl side chains were less active in vitro, they exhibited very good in vivo activity, possibly a reflection of enhanced absorption. Assuming 4-oxo-γ-tocotrienol (**3j**) is prototypical for the series, these compounds inhibit cholesterol biosynthesis by a mechanism consistent with the inhibition of fatty-acid synthesis and indicate that changes in ring substitution can lead to a divergence in the biochemical effect. Using the benzopyran template of γ-tocotrienol, which possesses optimal antioxidant and HMGR-suppressive activities, additional compounds have been prepared wherein the side chain has been optimized for oral absorption and are the subject of a future publication. In general, the benzopyran analogues exhibit comparable antioxidant properties to those of the tocopherols in the preliminary data shown here. More extensive antioxidant models are under evaluation and are the subject of a future publication.

Experimental Section

Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are un-

corrected. Infrared spectra were obtained on a Perkin-Elmer Model 1800 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer or a Varian Gemini 300 NMR spectrometer; nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) with tetramethylsilane as an internal standard. Mass spectra were measured on a Finnegan 4500 spectrometer (low resolution) or a kratos MS50 spectrometer (high resolution). Spectroscopic data and elemental analyses were obtained by the Analytical Department, Bristol-Myers Squibb, Wallingford, CT.

Thin-layer chromatography was performed on silica gel 60 F-254 plates purchased from E. Merck and Co. (visualization with iodine or phosphomolybdic acid); flash chromatography[40] was performed on fine silica (EM Sciences, 230–400 mesh). HPLC analyses were performed on a Spectra-Physics apparatus. Dry solvents were purchased[41] anhydrous in sealed bottles and transferred by syringe under N_2. Most commercially available starting materials did not require further purification.

General Procedure for Benzopyran-4-one Synthesis. A mixture of the appropriate acetophenone[42] (30 mmol); polyprenylacetone[43] (30 mmol), fatty-acid methyl ketone[44] (30 mmol), or farnesylacetaldehyde[45] (30 mmol); and pyrrolidine (90 mmol) was dissolved in 30 mL of absolute ethanol under N_2. Powdered 3-Å molecular sieves (5 g) were added to the mixture. The mixture was stirred at 23–60 °C for 24–96 h depending on the substrates. The reactions were monitored by TLC. The 4-oxo-tocotrienols can be recognized by TLC as blue fluorescent chromophoric (254 nm) spots slightly less polar than the acetophenones. The reaction mixtures were poured into 1 N HCl and extracted with ether. The organic extracts were dried (brine, $MgSO_4$) and concentrated in vacuo to thick oils. In general, most of the unreacted acetophenones can be removed from the crude reaction mixtures by trituration with hexanes followed by filtration of the highly crystalline acetophenones. After removal of unreacted acetophenone, the benzopyran-4-ones were purified by flash chromatography. The pale yellow benzopyran-4-ones, when crystalline, were recrystallized from hexanes or acetonitrile/hexanes.

Reduction to Benzopyrans. Method A. Aluminum chloride (20 mmol) was dissolved in 20 mL of dry ether and then cooled to −5 °C under N_2. Lithium aluminum hydride (10 mmol) was added to the ether solution portionwise. The alane slurry was stirred for 5 min at −5 °C before addition of the benzopyran-4-one (4 mmol) as an ether solution (5 mL). The reductions were monitored by TLC and were usually complete after 0.5–1 h at 0–23 °C. The mixtures were cooled to −5 °C and the reactions quenched with saturated sodium sulfate (caution). The aluminum salts could be removed by filtration and washed with methanol/ether. The combined organic washings were poured into water or 1 N HCl and extracted with fresh ether. The ether solutions were dried (brine, $MgSO_4$) and concentrated in vacuo. The crude benzopyrans were purified by flash chromatography.[46] **Method B.** The phenols (3 mmol) were silylated with *tert*-butyldimethylsilyl chloride (3.3 mmol) and imidazole (3.6 mmol) in DMF (5 mL) for 18 h at 23 °C. The mixture was poured into water and extracted into ether. The ether solutions were dried (brine, $MgSO_4$) and concentrated in vacuo. The crude silylated benzopyrans were purified by flash chromatography. The reduction process was carried out in the same manner as in method A. The silylated benzopyrans were then deprotected (n-Bu_4NF) and purified by flash chromatography. **Method C.** The ketones were silylated as described in method B and then reduced with lithium aluminum hydride (1 equiv) in ether at −78 °C. The crude alcohols (3 mmol) were added to lithium (9 mmol) dissolved in a 1:1 mixture of liquid ammonia:THF (24 mL) at −78 °C.[47] Solid powdered ammonium chloride (3 g) was added to the mixture. The reactions were usually complete within 2 h. Evaporation of the ammonia gave the crude silylated benzopyrans.

2,3-Dihydro-6-hydroxy-2-(4,8,12-trimethyltrideca-3(*E*),7-(*E*),11-trienyl)-2,7,8-trimethyl-4*H*-1-benzopyran-4-one (3j): light yellow solid (hexanes), mp 85–87 °C; IR (KBr) 3430, 2920, 1670, 1612, 1460, 1245, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.56 (s, 9 H), 1.66 (s, 3 H), 1.80 (m, 1 H), 1.90–2.15 (m, 11 H), 2.15 (s, 3 H), 2.20 (s, 3 H), 2.59 and 2.73 (AB q, J = 16.6 Hz, 2 H), 5.07 (m, 3 H), 5.21 (s, 1 H), 7.16 (s, 1 H); MS m/e 425 (MH$^+$). Anal. ($C_{28}H_{40}O_3$) C, H.

3,4-Dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltrideca-3(*E*),7(*E*),11-trienyl)-2*H*-1-benzopyran-6-ol (4j): pale yellow oil; IR (film) 3420, 2980, 2940, 2860, 1440, 1215, 1081 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.59 (s, 3 H), 1.60 (s, 6 H), 1.69 (s, 3 H), 1.77 (m, 2 H), 1.95–2.10 (m, 12 H), 2.12 (s, 3 H), 2.13 (s, 3 H), 2.68 (t, J = 6.2 Hz, 2 H), 4.22 (s, 1 H), 5.07–5.15 (m, 3 H), 6.37 (s, 1 H); MS m/e 411 (MH$^+$). Anal. ($C_{28}H_{42}O_2$) C, H.

10,14-Dimethyl-9,13-pentadecadien-5-yn-2-one (6). Ketal **5** (4.0 g, 28.57 mmol) was dissolved in 15 mL of dry THF, and methylmagnesium chloride (10.48 mL, 3.0 M) was added dropwise. The mixture was stirred at 23 °C for 2 h and then warmed to 60 °C for 1 h. Copper(I) iodide (544 mg, 2.86 mmol) was added to the metalated acetylene followed by homogeranyl iodide[48] (8.74 g, 31.4 mmol). Additional dry THF (10 mL) and dry DMPU (15 mL) were added to the mixture, and the solution was stirred in an oil bath (75 °C) for 50 h. The solution was poured into water and extracted into ether. The organic extracts were dried (brine, $MgSO_4$) and concentrated in vacuo. The crude oil was purified by flash chromatography (20:1 hexanes:ether) to give the coupled adduct (4.5 g) contaminated by trace impurities. The oil was further purified by distillation in a Kugelrohr oven, collecting the fraction (3.10 g, 10.7 mmol, 37%) boiling at 140–145 °C/0.1 mmHg which gave a purified product: ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.62 (s, 6 H), 1.68 (s, 3 H), 1.88 (m, 2 H), 1.95–2.11 (m, 4 H), 2.16 (m, 4 H), 2.2–2.3 (m, 2 H), 3.94 (m, 4 H), 5.10 (m, 1 H), 5.17 (m, 1 H).

The ketal (1.0 g, 3.45 mmol) was dissolved in 6 mL of wet THF (1 mL of H_2O), and 0.25 mL of concentrated HCl was added. The mixture was stirred at 23 °C for 3 days and then poured into 1 N HCl and extracted into ether. The organic layers were dried (brine, $MgSO_4$) and concentrated in vacuo to give crude **6** (950 mg) which was purified by distillation in a Kugelrohr oven (bath 140 °C/0.1 mmHg) to give a colorless oil: IR (film) 2966, 2916, 1720, 1436, 1364, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 6 H), 1.67 (s, 3 H), 1.93–2.08 (m, 4 H), 2.13 (m, 4 H), 2.15 (s, 3 H), 2.40 (m, 2 H), 2.62 (t, J = 9.0 Hz, 2 H), 5.08 (m, 1 H), 5.13 (m, 1 H); MS m/e 247 (MH$^+$). Anal. ($C_{17}H_{26}O_1$) C, H.

2-(8,12-Dimethyl-7(*E*),11-tridecadien-3-ynyl)-2,3-dihydro-6-hydroxy-2,7,8-trimethyl-4*H*-1-benzopyran-4-one (7): yellow–tan solid, mp 83–86 °C; IR (KBr) 3440, 2922, 1668, 1608, 1460, 1366, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.58 (s, 6 H), 1.66 (s, 3 H), 1.76–1.90 (m, 1 H), 1.90–2.09 (m, 9 H), 2.22–2.35 (m, 2 H), 2.59 and 2.74 (AB q, J = 16.7 Hz, 2 H), 4.92 (br s, 1 H), 5.07 (m, 1 H), 5.12 (m, 1 H), 7.11 (s, 1 H); MS m/e 409 (MH$^+$). Anal. ($C_{27}H_{36}O_3$) C, H.

3,4-Dihydro-2,7,8-trimethyl-2-(8,12-dimethyl-7(*E*),11-tridecadien-3-ynyl)-2*H*-1-benzopyran-6-ol (8): brown oil; IR (film) 3444, 2970, 2924, 1428, 1378, 1242, 1102, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.58 (s, 6 H), 1.66 (s, 3 H), 1.70–1.90 (m, 4 H), 1.90–2.15 (m, 8 H), 2.28 (m, 2 H), 2.67 (t, J = 6.8 Hz, 2 H), 4.23 (s, 1 H), 5.07 (m, 1 H), 5.14 (m, 1 H), 6.35 (s, 1 H); MS m/e 394 (M$^+$). Anal. ($C_{27}H_{38}O_2$) C, H.

2-(8,12-Dimethyl-3(*Z*),7(*E*),11-tridecatrienyl)-2,3-dihydro-6-hydroxy-2,7,8-trimethyl-4*H*-1-benzopyran-4-one (10). A mixture of **7** (1.1 g, 2.70 mmol) and palladium on barium sulfate (poisoned with lead) (200 mg) in ethyl acetate (5 mL) was hydrogenated under a balloon of hydrogen for 2.5 h at 23 °C. The Lindlar catalyst was removed by filtration, and the product was purified by flash chromatography (gradient 18:1–4:1 hexanes:ether) to yield **10** (1.048 g, 2.56 mmol, 95%) as a light tan oil that crystallized upon storage at −20 °C (mp 25 °C): IR (film) 3426, 2926, 1668, 1608, 1442, 1378, 1350, 1230, 1086, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.58 (s, 6 H), 1.66 (s, 3 H), 1.75–1.90 (m, 2 H), 1.90–2.13 (m, 10 H), 2.15 (s, 3 H), 2.20 (s, 3 H), 2.58 and 2.71 (AB q, J = 16.6 Hz, 2 H), 5.07 (m, 2 H), 5.31 (m, 2 H), 7.13 (s, 1 H); MS m/e 411 (MH$^+$). Anal. ($C_{29}H_{38}O_3$) C, H.

3,4-Dihydro-2,7,8-trimethyl-2-(8,12-dimethyl-3(*Z*),7(*E*),11-tridecatrienyl)-2*H*-1-benzopyran-6-ol (11): brown oil; IR (film) 3416, 2926, 1428, 1376, 1240, 1224, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3 H), 1.58 (s, 6 H), 1.60–1.85 (m, 4 H), 1.66 (s, 3 H), 1.90–2.13 (m, 10 H), 2.10 (s, 3 H), 2.11 (s, 3 H), 2.64 (t, J = 5.9 Hz, 2 H), 4.21 (s, 1 H), 5.08 (m, 2 H), 5.35 (m, 2 H), 6.35 (s, 1 H); MS m/e 396 (M$^+$). Anal. ($C_{27}H_{40}O_2$) C, H.

3,4-Dihydro-2,7,8-trimethyl-2-(8,12-dimethyltrideca-3(*E*),7-(*E*),11-trienyl)-2*H*-1-benzopyran-6-ol (9). Ethylamine gas was condensed (8 mL) into a flask fitted with a cold finger condenser.

Alkyne 8 (353 mg, 0.89 mmol) was dissolved in the ethylamine, and lithium metal (15 mg, 2.1 mmol) was added giving rise to a transient blue color. After all the lithium had reacted, the cold finger was removed and the solvent evaporated. The residue was treated with ether and poured into 1 N HCl. The organic extracts were dried (brine, $MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (gradient 18:1–4:1 hexanes:ether) to yield **22** (277 mg, 0.69 mmol, 79%) which was distilled in a Kugelrohr oven (bath 170–180 °C/0.03 mmHg) to yield a colorless oil: IR (film) 3416, 2926, 1448, 1428, 1240, 1224, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) 1.22 (s, 3 H), 1.58 (s, 6 H), 1.60–1.80 (m, 4 H), 1.66 (s, 3 H), 1.90–2.10 (m, 10 H), 2.08 (s, 3 H), 2.11 (s, 3 H), 2.65 (t, J = 6.6 Hz, 2 H), 4.22 (s, 1 H), 5.08 (m, 2 H), 5.41 (m, 2 H), 6.35 (s, 1 H); MS m/e 396 (M^+). Anal. ($C_{27}H_{40}O_2$) C, H.

2-(4,8,12-Trimethyltrideca-3(*E*),7(*E*),11-trienyl)-2,3-dihydro-6-[dimethyl(1,1-dimethylethyl)silyl]-2,7,8-trimethyl-4*H*-1-benzopyran-4-one (12). Phenol **3j** (1.0 g, 2.36 mmol), imidazole (225 mg, 3.30 mmol), and *tert*-butyldimethylsilyl chloride (391 mg, 2.59 mmol) were dissolved in 5 mL of dry DMF. The mixture was stirred at 23 °C for 18 h and then treated with ether and poured into 1 N HCl. The organic extracts were dried (brine, $MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (20:1 hexanes:ether) to yield **12** (1.28 g, 2.36 mmol): ^1H NMR ($CDCl_3$) δ 0.18 (s, 6 H), 0.98 (s, 9 H), 1.36 (s, 3 H), 1.56 (s, 6 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.76 (m, 2 H), 1.89–2.10 (m, 10 H), 2.10 (s, 3 H), 2.13 (s, 3 H), 2.56 and 2.68 (AB q, J = 16.5 Hz, 2 H), 5.08 (m, 3 H), 7.08 (s, 1 H).

2,7,8-Trimethyl-2-(4,8,12-trimethyltrideca-3(*E*),7(*E*),11-trienyl)-2*H*-1-benzopyran-6-ol (14). Silyl ketone **12** (420 mg, 0.78 mmol) was dissolved in ether (8 mL), and the solution was cooled to −78 °C under N_2. Lithium aluminum hydride (35 mg, 0.92 mmol) was added to the ether solution. TLC analysis (0.25 h) indicated a clean conversion to the more polar diastereomeric alcohols **13** (two spots). The reaction was quenched at −78 °C with saturated sodium sulfate solution, and the mixture was filtered and concentrated in vacuo to a colorless oil (450 mg).

Alcohols **13** (450 mg) were treated with excess triethylamine (0.5 mL) and methanesulfonyl chloride (107 mg, 0.94 mmol) in methylene chloride at 23 °C. After the solution was stirred for 48 h at 23 °C, the solvent was removed in vacuo and the residue was purified by flash chromatography (20:1 hexanes:ether) to give the silylated 3,4-dehydro-γ-tocotrienol (394 mg, 0.75 mmol, 97%): ^1H NMR ($CDCl_3$) δ 0.16 (s, 6 H), 1.0 (s, 9 H), 1.35 (s, 3 H), 1.58 (s, 9 H), 1.60–1.70 (2 H), 1.66 (s, 3 H), 1.90–2.10 (m, 10 H), 2.10 (s, 3 H), 2.11 (s, 3 H), 5.10 (m, 3 H), 5.52 (d, J = 9.0 Hz, 1 H), 6.23 (d, J = 9.0 Hz, 1 H), 6.38 (s, 1 H).

The silyl ether was dissolved in 5 mL of ether, and tetra-*n*-butylammonium fluoride (1.0 mL, 1 M in THF) was added. After being stirred at 23 °C for 10 min, the mixture was poured into water and extracted into ether. The organic extracts were dried (brine, $MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (10:1 hexanes:ether) to give **14** (292 mg, 0.71 mmol, 95%) as a unstable brown oil. Compound **14** exhibited noticeable decomposition (TLC) after only 2 days at −20 °C. The sample required chromatographic purification (9:1 hexanes:ether) before analysis and testing: IR (film) 3416, 2924, 1448, 1376, 1250, 1228, 1078 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.56 (s, 6 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 1.65 (m, 2 H), 1.90–2.10 (m, 10 H), 2.11 (s, 3 H), 2.12 (s, 3 H), 4.24 (s, 1 H), 5.07 (m, 3 H), 5.53 (d, J = 9.7 Hz, 1 H), 6.22 (d, J = 9.7 Hz, 1 H), 6.92 (s, 1 H); MS m/e 408 (M^+). Anal. ($C_{28}H_{40}O_2$) C, H.

1-[2,5-Bis(acetyloxy)-3,4-dimethylphenyl]ethanone (15). A mixture of 2,5-dihydroxy-3,4-dimethylacetophenone[27] (11.5 g, 0.06 mol), acetic anhydride (20 g, 0.19 mol), and sodium acetate (16 g, 0.19 mol) was heated to reflux temperature for 2.5 h. The solution solidified on cooling. The solid was triturated with ether, and the sodium acetate was removed by filtration. The title compound crystallized from ether/hexanes to give white crystals (9.23 g, 0.03 mol, 58%), mp 98–99 °C: IR (KBr) 3504, 2932, 1762, 1686, 1428, 1366, 1300, 1220, 1192, 1170, 1084 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 3 H), 2.12 (s, 3 H), 2.33 (s, 3 H), 2.35 (s, 3 H), 2.49 (s, 3 H), 7.33 (s, 1 H); MS m/e 265 (MH^+). Anal. ($C_{14}H_{16}O_5$) C, H.

1-[5-(Acetyloxy)-2-hydroxy-3,4-dimethylphenyl]-1,3-butanedione (16). The diacetoxyacetophenone **15** (9.1 g, 34.5 mmol) was dissolved in 20 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and the mixture was stirred at 23 °C for 48 h. The solution was poured into 1 N HCl and extracted into ether. The ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo to give a yellow oil (7.67 g, 0.029 mol, 84%) which crystallized on standing. Recrystallization from ether/hexanes afforded **16** as yellow crystals (mp 113–115 °C): IR (KBr) 3404, 2924, 1764, 1672, 1608, 1576, 1490, 1452, 1380, 1370, 1330, 1206, 1154, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 6 H), 2.18 (s, 3 H), 2.30 (s, 3 H), 6.04 (s, 1 H), 7.13 (s, 1 H), 12.15, 12.32 (s, 1 H); MS m/e 265 (MH^+). Anal. ($C_{14}H_{16}O_5$) C, H.

6-Hydroxy-2,7,8-trimethyl-4*H*-1-benzopyran-4-one (17). Butanedione **16** (7.6 g, 0.029 mol) and *p*-toluenesulfonic acid monohydrate (500 mg, 2.6 mmol) were dissolved in 350 mL of benzene. The mixture was heated to reflux for 4 h while the water was removed by azeotropic distillation. The solution was cooled, and the benzene was removed in vacuo. The solid material was recrystallized from ethanol/hexanes to yield 6-(acetyloxy)-2,7,8-trimethyl-4*H*-1-benzopyran-4-one as white crystals (4.25 g, 0.017 mol, 60%), mp 164–165 °C: IR (KBr) 3060, 2926, 1772, 1750, 1646, 1574, 1424, 1392, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H), 2.33 (s, 3 H), 2.38 (s, 6 H), 6.12 (s, 1 H), 7.65 (s, 1 H); MS m/e 247 (MH^+). Anal. ($C_{14}H_{14}O_4$) C, H. The acetoxy compound (4.25 g, 17.3 mmol) was dissolved in 100 mL of warm ethanol, and 25 mL of 10% HCl was added. The mixture was heated to reflux for 1 h, leaving a heavy white precipitate. The solid was recovered by filtration and washed successively with water and ether. The phenol (3.37 g, 1.65 mmol, 96%) was recovered as a white solid which was recrystallized from hot DMF to give **17** as colorless needles, mp >260 °C: IR (KBr) 3174, 1626, 1584, 1446, 1366, 1266, 1088, cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.19 (s, 3 H), 2.31 (s, 3 H), 2.37 (s, 3 H), 6.11 (s, 1 H), 7.21 (s, 1 H), 9.83 (s, 1 H); MS m/e 205 (MH^+). Anal. ($C_{12}H_{12}O_3$) C, H.

6-[Dimethyl(1,1-dimethylethyl)silyl]-2,7,8-trimethyl-4*H*-1-benzopyran-4-one (18). A mixture of phenol **17** (3.37 g, 16.5 mmol), *tert*-butyldimethylsilyl chloride (2.99 g, 19.8 mmol), and imidazole (1.41 g, 21 mmol) was heated in 15 mL of dry DMF at 60 °C for 18 h. The mixture was diluted with ether and poured into water. The aqueous solution was extracted with fresh ether, and the organic layers were washed with water and dried (brine, $MgSO_4$). Concentration of the ether gave a white precipitate which was recrystallized from hexanes to give the title compound **18** (4.69 g, 14.7 mmol, 89%) as small white needles, mp 126–127 °C: IR (KBr) 3502, 2928, 1658, 1644, 1608, 1444, 1390, 1100, 834 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.25 (s, 6 H), 1.0 (s, 9 H), 2.26 (s, 3 H), 2.37 (s, 6 H), 6.10 (s, 1 H), 7.35 (s, 1 H); MS m/e 319 (MH^+). Anal. ($C_{18}H_{26}O_3Si_1$) C, H.

6-[Dimethyl(1,1-dimethylethyl)silyl]-2-(4,8,12-trimethyltrideca-3(*E*),7(*E*),11-trienyl)-4*H*-1-benzopyran-4-one (19). Silyl ether **18** (4.026 g, 12.7 mmol) was dissolved in 70 mL of dry THF, and the mixture was cooled to −78 °C under N_2. Lithium diisopropylamide (9.28 mL, 1.5 M) was added dropwise giving rise to an orange-colored anion. The anion was stirred for 45 min before the addition of farnesyl bromide (3.97 g, 13.9 mmol) in 10 mL of dry THF. The mixture was stirred at −78 °C for 5 h and then at 0 °C for 48 h before being poured into acidified water (pH 5). The product was extracted into ether, and the ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo. The coupled product was purified by flash chromatography (4:1 hexanes:ether) to yield the title compound (4.39 g, 8.40 mmol, 66%) as a white solid, mp 42–44 °C: IR (KBr) 2926, 1646, 1604, 1446, 1382, 1208, 1100, 864 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.25 (s, 6 H), 1.01 (s, 9 H), 1.55 (s, 3 H), 1.57 (s, 3 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.90–2.10 (m, 8 H), 2.25 (s, 3 H), 2.36 (s, 3 H), 2.39 (q, J = 7.4 Hz), 2.63 (t, J = 7.0 Hz, 2 H), 5.06 (t, J = 6.8 Hz, 2 H), 5.15 (t, J = 7.1 Hz, 1 H), 6.09 (s, 1 H), (s, 1 H), 7.34 (s, 1 H); MS m/e 523 (MH^+). Anal. ($C_{33}H_{50}O_3Si_1$) C, H.

6-Hydroxy-7,8-dimethyl-2-(4,8,12-trimethyltrideca-3(*E*),7-(*E*),11-trienyl)-4*H*-1-benzopyran-4-one (20). The silyl ether was deprotected with fluoride in the usual manner (compound **14**) to give **20** as a semisolid. The material was distilled in a Kugelrohr oven (bp 240–260 °C/0.1 mmHg) giving a white solid, which was recrystallized from acetonitrile to give white plates (65%), mp 148–149 °C: IR (KBr) 3328, 2920, 1622, 1590, 1580,

1460, 1082, 844 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.57 (s, 3 H), 1.58 (s, 3 H), 1.90–2.10 (m, 8 H), 2.32 (s, 3 H), 2.38 (s, 3 H), 2.43 (q, J = 7.3 Hz, 2 H), 2.67 (t, J = 7.1 Hz, 2 H), 5.06 (t, J = 6.8 Hz, 2 H), 5.16 (t, J = 6.7 Hz, 1 H), 6.18 (s, 1 H), 7.88 (s, 1 H), 8.51 (s, 1 H); MS m/e 409 (MH^+). Anal. ($C_{27}H_{36}O_3$) H; C: 0.45.

6-Hydroxy-7,8-dimethyl-2-(4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl)-2*H*-1-benzopyran-3,4-dion-3-oxime (22). Silyl ether **19** (1.48 g, 2.83 mmol) was dissolved in 15 mL of dry THF. The solution was cooled to −78 °C under N_2, and then, a solution of lithium aluminum hydride (2.91 mL, 1.0 M THF) was added. The mixture was stirred for 7 h at −78 °C and then the reaction quenched at −78 °C with acetic acid. The solution was poured into 1 N HCl and extracted into ether. The ether layers were dried (brine, $MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (8:1 hexanes:ether) gave ketone **21** (1.35 g, 2.57 mmol, 91%): ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 6 H), 1.0 (s, 9 H), 1.58 (s, 3 H), 1.60 (m, 2 H), 1.60 (s, 3 H), 1.63 (s, 3 H), 1.68 (s, 3 H), 1.91–2.13 (m, 8 H), 2.18 (s, 6 H), 2.24 (m, 2 H), 2.60 (s, 1 H), 2.62 (d, J = 3.6 Hz, 1 H), 4.35 (br m, 1 H), 5.08 (m, 2 H), 5.17 (m, 1 H), 7.12 (s, 1 H). Ketone **21** (1.20 g, 2.29 mmol) was dissolved in 10 mL of dry THF, and the solution was cooled to −5 °C under N_2. A THF solution (4 mL) of potassium *tert*-butoxide (385 mg, 3.44 mmol) and isoamyl nitrite (0.46 mL, 3.44 mmol) was added to the ketone, giving rise to a deep red color. After 1 h at −5 °C, the mixture was poured into 1 N HCl and extracted into ether. The ether extracts were dried (brine, $MgSO_4$), concentrated in vacuo, and chromatographed on silica gel (gradient 4:1–1:1 hexanes:ether) to yield the silylated oxime (295 mg, 0.53 mmol, 23%) as a red foam. The silyl group was removed with fluoride in the usual manner (compound **14**), and the resulting phenol was purified by flash chromatography (CH_2Cl_2 and then 1% MeOH in CH_2Cl_2) to yield **22** (170 mg, 0.39 mmol, 73%) as a yellow–orange solid: IR (KBr) 3450, 3224, 2916, 1690, 1606, 1448, 1338, 1228, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 6 H), 1.59 (s, 3 H), 1.60–1.90 (m, 2 H), 1.64 (s, 3 H), 1.90–2.10 (m, 8 H), 2.18 (s, 3 H), 2.20 (m, 2 H), 2.23 (s, 3 H), 5.08 (m, 3 H), 5.80 (d, J = 6.6 Hz, 1 H), 7.38 (s, 1 H); MS m/e 440 (MH^+); HRMS exact mass calcd for $C_{27}H_{37}N_1O_4$ 440.2801 (MH^+), found 440.2800.

3,6-Dihydro-7,8-dimethyl-2-(4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl)-4*H*-1-benzopyran-4-one (23). Oxime **22** (100 mg, 0.23 mmol) was dissolved in 2:1 ethanol:10% HCl (3 mL) and the solution stirred at 23 °C for 48 h. The mixture was poured into water and extracted with ether, and the organic extracts were dried (brine, $MgSO_4$) and concentrated in vacuo. The crude compound was purified by flash chromatography (1:1 hexanes:ether) to yield a foam that crystallized from hexanes to give **23** (69 mg, 0.16 mmol, 70%) as light tan crystals, mp 100–103 °C: IR (KBr) 3364, 2922, 1594, 1564, 1472, 1382, 1250, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 6 H), 1.65 (s, 3 H), 1.69 (s, 3 H), 1.90–2.10 (m, 8 H), 2.31 (s, 3 H), 2.40 (s, 3 H), 2.46 (q, J = 7.4 Hz, 2 H), 2.89 (t, J = 7.1 Hz, 2 H), 5.06 (t, J = 7.0, 2 H), 5.21 (t, J = 7.2 Hz, 1 H), 6.05 (br s, 1 H), 7.42 (br s, 1 H), 7.66 (s, 1 H); MS m/e 425 (MH^+); HRMS exact mass calcd for $C_{27}H_{38}O_4$ 425.2692 (MH^+), found 425.2706.

2-(Hydroxymethylene)-6-methoxy-1-tetralone (24). A mixture of 6-methoxy-1-tetralone (20 g, 0.113 mol) and ethyl formate (16.82 g, 0.23 mol) was dissolved in 250 mL of toluene. The solution was cooled to −78 °C under N_2 and mechanically stirred while potassium *tert*-butoxide (25.5 g, 0.23 mol) was added in portions, giving rise to a reddish colored solution. The mixture was slowly warmed to −5 °C over a period of 1 h, at which time TLC analysis (1:1 EtOAc:hexanes) indicated complete conversion to the less polar product. The reaction was quenched with 10% HCl and the mixture extracted with ether. The ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo to yield 24.4 g of a dark brown oil. The oil was purified by distillation in a Kugelrohr oven (bath temperature 160–180 °C/0.1 mmHg) to yield the title compound as a yellow oil (22.6 g, 0.11 mol, 98% yield) that solidified on standing (mp 66–68 °C lit.[23] mp 68–69 °C).

1,2,3,4-Tetrahydro-6-methoxy-2-naphthalenemethanol (25). 2-(Hydroxymethylene)-6-methoxy-1-tetralone (**24**) (4.81 g, 0.024 mol) and a borane–*tert*-butylamine complex (10.25 g, 0.12 mol) were dissolved in 250 mL of CH_2Cl_2, and the solution was cooled to −78 °C. Boron trifluoride etherate (14.5 mL, 0.12 mol) was added dropwise, and the mixture was stirred for 1 h and then warmed to 23 °C and stirred for an additional 2 h. The reaction was quenched with 1 N HCl and the mixture extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude oil was purified by flash chromatography (gradient 3:1–1:2 hexanes:ether) to yield the title compound as a light yellow oil (3.41 g, 0.018 mol, 75% yield): IR (film) 3362, 2996, 2918, 1610, 1504, 1464, 1264, 1234, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 1 H), 1.47 (s, 1 H), 1.95 (m, 2 H), 1.39, 1.45 (dd, J = 10.6, 16.1 Hz, 1 H), 2.81 (m, 2 H), 3.62 (d, J = 6.3 Hz, 2 H), 3.77 (s, 3 H), 6.62 (d, J = 2.6 Hz, 1 H), 6.68 (dd, J = 8.4, 2.6 Hz, 1 H), 6.98 (d, J = 8.4 Hz, 1 H); MS m/e 193 (MH^+). Anal. ($C_{12}H_{16}O_2$) C, H.

1,2,3,4-Tetrahydro-6-methoxy-2-naphthalenemethanol Trifluoromethanesulfonate (26). 1,2,3,4-Tetrahydro-6-methoxy-2-naphthalenemethanol (2.0 g, 10.42 mmol) and triethylamine (2.2 mL, 15.6 mmol) were dissolved in 20 mL of CH_2Cl_2, and the solution was cooled to −78 °C under N_2. Triflic anhydride (2.27 mL, 13.54 mmol) was added dropwise to the stirred mixture at −78 °C. After the addition, the mixture was warmed to −5 °C, at which time TLC (2:1 hexanes:EtOAc) indicated complete conversion to the less polar triflate ester. The reaction was quenched with 1 N HCl and the mixture extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude oil was purified by flash chromatography (5:1 hexanes:ether) to yield the title compound (3.15 g, 9.72 mmol, 93% yield) as a light yellow oil that solidified on standing, mp 52–54 °C. The triflate ester was somewhat unstable; a small sample turned black after several hours at about 23 °C. The bulk was stored at −20 °C and used without delay in the next step: ^{1}H NMR ($CDCl_3$) δ 1.55 (m, 1 H), 2.03 (m, 1 H), 2.30 (m, 1 H), 2.49, 2.55 (dd, J = 10, 16 Hz, 1 H), 2.85 (m, 3 H), 3.77 (s, 3 H), 4.50 (d, J = 6 Hz, 2 H), 6.64 (d, J = 2 Hz, 1 H), 6.71 (dd, J = 8.2 Hz, 1 H), 7.01 (d, J = 8 Hz, 1 H).

6-Methoxy-2-[2-[(4-methylphenyl)sulfonyl]-4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl]-1,2,3,4-tetrahydronaphthalene (27). *n*-Butyllithium (7.3 mL, 1.6 M, 11.66 mmol) was added dropwise to a solution of *all-trans*-farnesyl *p*-tolyl sulfone (3.85 g, 10.69 mmol) in THF (30 mL) under N_2 at −78 °C. The orange-colored anion was stirred for 45 min at −78 °C, and then, HMPA (5 mL) was added followed by **26** (3.15 g, 9.72 mmol) as a THF solution (3 mL). The mixture was slowly warmed to 23 °C over a period of 2 h, at which time TLC (2:1 hexanes:EtOAc) indicated complete consumption of the triflate, commensurate with the formation of a spot coeluting with farnesyl *p*-tolyl sulfone. The reaction mixture was poured into water and extracted with ether. The ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo to give a light oil. Purification of the crude material by flash chromatography (gradient 6:1–5:1 hexanes: ether) yielded the title compound **27** as a clear viscous oil (5.62 g, >100%) which contained about 10% farnesyl *p*-tolyl sulfone as indicated by NMR. An analytical sample was obtained by crystallization from methanol which yielded white crystals, mp 64–66 °C: IR (film) 3444, 2964, 2916, 1610, 1504, 1450, 1298, 1146 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 1.2 Hz, 2 H), 1.20–1.34 (m, 2 H), 1.54 (s, 3 H), 1.55 (s, 3 H), 1.57 (s, 3 H), 1.66 (s, 3 H), 1.70–2.10 (m, 9 H), 2.37–2.47 (m, 1 H), 2.46 (s, 3 H), 2.60–2.80 (m, 3 H), 3.75 (s, 3 H), 3.90 (dt, J = 3.0, 10.9 Hz, 1 H), 4.92–5.0 (m, 3 H), 6.57 (d, J = 2.6 Hz, 1 H), 6.65 (dd, J = 8.4, 2.6 Hz, 1 H), 6.92 (d, J = 8.4 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.71 (d, J = 8.0 Hz, 2 H); MS m/e 379 (M − $(C_7H_7S_1O_2)^+$). Anal. ($C_{34}H_{46}O_3S_1$) C, H.

6-Methoxy-2-(4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl)-1,2,3,4-tetrahydronaphthalene (28). Sulfone **27** (2.5 g, 4.68 mmol) was dissolved in 20 mL of THF. Palladium chloride: (diphenylphosphinyl)butane (141 mg, 0.23 mmol) was added, and the heterogeneous mixture was cooled to −5 °C under N_2. Lithium triethylborohydride (9.4 mL, 1.0 M, 9.4 mmol) was added dropwise, giving rise to a brown homogeneous solution. The mixture was stirred for 12 h at −3 °C and then poured into water and extracted with ether. The ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo to give a light oil. Purification of the crude material by flash chromatography (gradient hexanes to 20:1 hexanes:ether) yielded **28** as a clear oil (1.03 g, 2.71 mmol, 58%). A sample was distilled in a Kugelrohr oven (bath 160–180 °C/0.1 mmHg) for analysis: IR (film) 2916, 2852, 1612, 1504, 1452, 1266, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (m, 2 H), 1.50–

1.70 (m, 3 H), 1.58 (s, 6 H), 1.62 (s, 3 H), 1.66 (s, 3 H), 1.88–2.10 (m, 10 H), 2.30, 2.35 (dd, J = 10.6, 16.4 Hz, 1 H), 2.77 (m, 3 H), 3.76 (s, 3 H), 5.10 (m, 3 H), 6.60 (d, J = 2.6 Hz, 1 H), 6.66 (dd, J = 8.4, 2.6 Hz, 1 H), 6.96 (d, J = 8.4 Hz, 1 H); MS m/e 381 (MH^+). Anal. ($C_{27}H_{40}O_1$) C, H.

1,2,3,4-Tetrahydro-2-(4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl)-6-naphthalenol (29). Methyl ether **28** (957 mg, 2.51 mmol), *p*-aminothiophenol (630 mg, 5.03 mmol), and cesium carbonate (410 mg, 1.26 mmol) were suspended in 3 mL of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU). The flask was purged well with N_2, and the mixture was heated to 200 °C for 3.5 h. The honey-colored mixture was poured into 1 N HCl and extracted with ether. The ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo. Purification of the crude material by flash chromatography (gradient 20:1–10:1 hexanes:ether) yielded **29** as a clear oil (800 mg, 2.19 mmol, 87%). A sample was distilled in a Kugelrohr oven (bath 180–200 °C/0.1 mmHg) for analysis: IR (film) 3346, 2916, 2852, 1612, 1502, 1450, 1230, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (m, 2 H), 1.50–1.70 (m, 3 H), 1.58 (s, 6 H), 1.62 (s, 3 H), 1.66 (s, 3 H), 1.88–2.10 (m, 10 H), 2.30, 2.35 (dd, J = 10.6, 16.4 Hz, 1 H), 2.77 (m, 3 H), 4.45 (s, 1 H), 5.10 (m, 3 H), 6.53 (d, J = 2.6 Hz, 1 H), 6.57 (dd, J = 8.4, 2.6 Hz, 1 H), 6.91 (d, J = 8.4 Hz, 1 H); MS m/e 367 (MH^+). Anal. ($C_{26}H_{38}O_1$) C, H.

6-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-2-methyl-1-tetralone (32). 2-Methyl-6-hydroxy-1-tetralone[28] **31** (14.5 g, 0.082 mol), *tert*-butyldimethylsilyl chloride (14.9 g, 0.099 mol), and imidazole (14.6 g, 0.21 mol) were dissolved in 330 mL of DMF. The mixture was allowed to stir at 23 °C for 12 h. The reaction mixture was poured into water and extracted with ether. The ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo to give a light brown oil. Purification of the crude material by flash chromatography (10:1 hexanes:EtOAc) yielded **32** as a light yellow oil (23.2 g, 0.08 mol, 97%): ^1H NMR ($CDCl_3$) δ 0.22 (s, 6 H), 0.97 (s, 9 H), 1.23 (d, J = 6.8 Hz, 3 H), 1.85 (m, 1 H), 2.15 (m, 1 H), 2.52 (m, 1 H), 2.90 (m, 2 H), 6.62 (d, J = 2.3 Hz, 1 H), 6.72 (dd, J = 2.3, 8.6 Hz, 1 H), 7.94 (d, J = 8.6 Hz, 1 H); MS m/e 291 (MH^+).

3,4-Dihydro-6-[[(1,1-dimethylethyl)silyl]oxy]-2-methyl-2-(4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl)-1(2*H*)-naphthalenone (33). Lithium diisopropylamide (24 mL, 1.5 M, 0.036 mol) was added to 25 mL of dry THF under N_2 at −78 °C. Silyl ether **32** (6.96 g, 0.024 mol) was added to the LDA solution as a THF solution (15 mL). The mixture was stirred at −78 °C for 2 h, and then, 5 mL of DMPU followed by homofarnesyl iodide[48] (8.3 g, 0.024 mol) was added. The mixture was stirred at −3 °C for 12 h and then warmed to 23 °C and stirred for an additional 24 h. The reaction was quenched with 1 N HCl and the mixture extracted with ether. The ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo to give a dark brown oil. The oil was purified by flash chromatography (50:1 ether:hexanes) to yield **33** as a light yellow oil (1.8 g, 0.004 mol, 15%): ^1H NMR ($CDCl_3$) δ 0.22 (s, 6 H), 0.97 (s, 9 H), 1.18 (s, 3 H), 1.45–1.69 (m, 4 H), 1.56 (s, 6 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.85–2.11 (m, 10 H), 2.88 (m, 2 H), 5.07 (m, 3 H), 6.60 (d, J = 2.1 Hz, 1 H), 6.72 (dd, J = 2.1, 8.6 Hz, 1 H), 7.94 (d, J = 8.6 Hz, 1 H); MS m/e 509 (MH^+).

2-[[(1,1-Dimethylethyl)silyl]oxy]-6-methyl-6-(4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl)-5,6,7,8-tetrahydronaphthalene (34). Ketone **33** (1.8 g, 3.5 mmol) was added as an ether solution (5 mL) to a suspension of lithium aluminum hydride (133 mg, 3.5 mmol) in 75 mL of ether at −78 °C. The mixture was stirred for 1 h at −78 °C and then warmed to −5 °C, at which time TLC (10:1 hexanes:ether) indicated complete conversion to the more polar alcohol. The reaction was quenched at −5 °C with saturated Na_2SO_4 solution and the mixture poured into 1 N HCl and extracted with ether. The ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo to give a light brown oil which was used directly in the next step.

A mixture of the above alcohol (1.4 g, 2.7 mmol), dimethylaminopyridine (33 mg, 0.27 mmol), triethylamine (416 mg, 4.1 mmol), and acetic anhydride (308 mg, 3.0 mmol) was dissolved in 15 mL of CH_2Cl_2 and stirred at 23 °C for 12 h. The organic fractions were washed successively with 1 N HCl and saturated $NaHCO_3$ solutions and then dried ($MgSO_4$) and concentrated in vacuo to give a light brown oil (1.5 g): ^1H NMR ($CDCl_3$) δ 0.18 (s, 6 H), 0.96 (s, 9 H), 0.87, 0.96 (s, 3 H) (diastereomeric methyl signals), 1.45–1.69 (m, 4 H), 1.58 (s, 9 H), 1.66 (s, 3 H), 1.85–2.11 (m, 10 H), 2.03, 2.05 (s, 3 H) (diastereomeric acetoxy signals), 2.67 (m, 2 H), 5.07 (m, 3 H), 5.68, 5.70 (s, 1 H) (diastereomeric benzylic methine signals), 6.56 (m, 1 H), 6.60 (m, 1 H), 7.09, 7.16 (dd, J = 8.6 Hz, 1 H) (diastereomeric aryl signals); MS m/e 493 ($M - (C_2H_3O_2)^+$).

To a 2:1 mixture of ammonia/THF (30 mL) at reflux temperature was added lithium metal (57 mg, 8.1 mmol) followed by the acetate ester (1.5 g, 2.7 mmol) as a THF solution (3 mL). Solid NH_4Cl (1.6 g, mortar ground) was added to the solution, and the cooling bath was removed. The reaction mixture was poured into water and extracted with ether. The ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo to give a light oil. Purification of the crude material by flash chromatography (20:1 hexanes:ether) yielded **34** as a light oil (1.0 g, 2.0 mmol, 57% overall yield).

5,6,7,8-Tetrahydro-6-methyl-6-(4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl)-2-naphthalenol (35). Silyl ether **34** (1.0 g, 2.0 mmol) was dissolved in 5 mL of ether. The solution was cooled to −5 °C, and tetrabutylammonium fluoride (2.2 mL, 1 M, 2.2 mmol) was added. The mixture was allowed to warm to 23 °C and stirred for an additional 10 min. The reaction mixture was poured into water and extracted with ether. The ether extracts were dried (brine, $MgSO_4$) and concentrated in vacuo to give a light oil. Purification of the crude material by flash chromatography (20:1 hexanes:ether) yielded **35** as a clear oil (700 mg, 1.84 mmol, 92%): IR (film) 3344, 2964, 2916, 1612, 1502, 1448, 1218, 1104 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 3 H), 1.20–1.34 (m, 2 H), 1.50–1.70 (m, 2 H), 1.59 (s, 9 H), 1.67 (s, 3 H), 1.88–2.10 (m, 10 H), 2.45 (AB q, J = 16.8 Hz, 2 H), 2.72 (t, J = 6.8 Hz, 2 H), 4.46 (s, 1 H), 5.10 (m, 3 H), 6.56 (s, 1 H), 6.57 (d, J = 8.0 Hz, 1 H), 6.88 (d, J = 8.0 Hz, 1 H); MS m/e 381 (MH^+). Anal. ($C_{27}H_{40}O_1$) C, H.

3,4-Dihydro-4,6-dihydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl)-2*H*-1-benzopyran (37). Ketone **3j** (500 mg, 1.18 mmol) was dissolved in 20 mL of methanol. Sodium borohydride (134 mg, 3.54 mmol) was added portionwise to the methanol solution over a 1-h period. The mixture was stirred for an additional 2 h at 23 °C and then poured into water. The alcohol was extracted into ether, and the organic extracts were dried (brine, $MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (gradient 6:1–1:1 hexanes:ether) to yield **37** (302 mg, 0.71 mmol, 60%) as an off-white waxy solid: IR (film) 3360, 2950, 1445, 1380, 1225, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22, 1.37 (s, 3 H), 1.55, 1.58, 1.60, 1.66 (s, 12 H), 1.70–1.84 (m, 2 H), 1.90–2.13 (m, 12 H), 4.56 (s, 1 H), 4.76 (p, J = 7.48 Hz, 1 H), 5.08 (m, 3 H), 6.72, 6.75 (s, 1 H); MS m/e 426 (M^+). Anal. ($C_{28}H_{42}O_3 \cdot 0.20\ H_2O$) C, H.

7-Fluoro-3,4-dihydro-2-methyl-2-(4,8,12-trimethyltrideca-3(*E*),7(*E*),11-trienyl)-2*H*-1-benzopyran-6-ol (38): colorless oil; IR (film) 3420, 2940, 1515, 1150, 1110, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 3 H), 1.50–1.85 (m, 4 H), 1.58 (s, 9 H), 1.66 (s, 3 H), 1.95–2.10 (m, 10 H), 2.65 (t, J = 6.9 Hz, 2 H), 4.60 (br s, 1 H), 5.08 (m, 3 H), 6.52 (d, J = 11.8 Hz, 1 H), 6.65 (d, J = 9.8 Hz, 1 H); MS m/e 401 (MH^+). Anal. ($C_{26}H_{37}F_1O_2$) C, H.

7-Fluoro-3,4-dihydro-2-(5-hydroxy-4-methylpent-3(*E*)-enyl)-2-methyl-2*H*-1-benzopyran-6-ol (39): light tan oil; IR (film) 3350, 2950, 1520, 1445, 1160, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.40–1.85 (m, 4 H), 1.63 (s, 3 H), 2.11 (q, J = 7.8 Hz, 2 H), 2.65 (t, J = 6.6 Hz, 2 H), 3.97 (s, 2 H), 4.77 (br s, 1 H), 5.37 (t, J = 7.1 Hz, 1 H), 6.50 (d, J = 11.8 Hz, 1 H), 9.65 (d, J = 9.8 Hz, 1 H); MS m/e 280 (M^+). Anal. ($C_{16}H_{21}F_1O_3 \cdot 0.5\ H_2O$) C, H.

3,4-Dihydro-6-hydroxy-2-methyl-2-(4,8,12-trimethyltrideca-3(*E*),7(*E*),11-trienyl)-2*H*-1-benzopyran-8-carbonitrile (40). The *tert*-butyldimethylsilyl ether of **4o** (prepared as described in the general procedure) (952 mg, 1.66 mmol) and cuprous cyanide (193 mg, 2.15 mmol) were heated under N_2 in DMF at reflux temperature for 3.5 h. The mixture was poured into water, extracted with ether, and filtered to remove insoluble copper salts. The organic layers were dried (brine, $MgSO_4$) and concentrated in vacuo to an oil. The crude oil was purified by flash chromatography (20:1 hexanes:ether) to yield the silyl ether of **40** (603 mg, 1.16 mmol, 70%). The silyl ether was treated directly with tetrabutylammonium fluoride (2.4 mL, 1.0 M in

THF) in THF (5 mL) for 20 min at 23 °C. The mixture was poured into water and extracted with ether. The organic layers were dried (brine, $MgSO_4$) and concentrated in vacuo to an oil. The crude oil was purified by flash chromatography (10:1 hexanes: ether) to yield compound **40** (435 mg, 1.07 mmol, 92%), isolated as a light brown oil: IR (film) 3372, 2926, 2232, 1454, 1380, 1262, 1246, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.58 (s, 3 H), 1.59 (s, 6 H), 1.67 (s, 3 H), 1.75 (m, 2 H), 1.95–2.05 (m, 10 H), 2.09 (m, 2 H), 2.72 (t, J = 6.8 Hz, 2 H), 4.78 (s, 1 H), 5.08 (m, 3 H), 6.77 (d, J = 3.0 Hz, 1 H), 6.83 (d, J = 3.0 Hz, 1 H); MS m/e 408 (MH^+). Anal. ($C_{27}H_{37}N_1O_2$) C, H, N.

3,4-Dihydro-6-methoxy-2,7,8-trimethyl-2-(4,8,12-trimethyl-3(*E*),7(*E*),11-tridecatrienyl)-2*H*-1-benzopyran (41). Compound **3j** (745 mg, 1.76 mmol) and methyl iodide (127 μL, 2.05 mmol) were dissolved in 3 mL of dry DMF. Powdered potassium carbonate (315 mg, 2.29 mmol) was added, and the suspension was stirred at 23 °C for 12 h. The mixture was poured into water and extracted with ether. The organic layers were dried (brine, $MgSO_4$) and concentrated in vacuo to an oil. The crude oil was purified by flash chromatography (gradient 9:1–3:1 hexanes:ether) to yield 2,3-dihydro-6-methoxy-2,7,8-trimethyl-2-(4,8,12-trimethyltrideca-3(*E*),7(*E*),11-trienyl)-4*H*-1-benzopyran-4-one (603 mg, 1.38 mmol, 78%) which was distilled in a Kugelrohr oven (bath 210–220 °C/0.1 mmHg) to give a yellow oil: IR (film) 2930, 1690, 1610, 1560, 1520, 1285, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3 H), 1.59 (s, 9 H), 1.60–1.85 (m, 2 H), 1.67 (s, 3 H), 1.90–2.15 (m, 10 H), 2.16 (s, 3 H), 2.18 (s, 3 H), 2.61 and 2.73 (AB q, J = 16.6 Hz, 2 H), 3.80 (s, 3 H), 5.08 (m, 3 H), 7.12 (s, 1 H); MS m/e 439 (MH^+). Anal. ($C_{29}H_{42}O_3$) C, H. **Reduction using method A (95%):** pale yellow oil (Kugelrohr oven (bath 210–220 °C/0.1 mmHg)); IR (film) 2930, 1465, 1230, 1128, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.58 (s, 9 H), 1.60–1.85 (m, 4 H), 1.66 (s, 3 H), 1.90–2.13 (m, 10 H), 2.10 (s, 6 H), 2.71 (t, J = 6.6 Hz, 2 H), 3.73 (s, 3 H), 5.08 (m, 3 H), 6.40 (s, 1 H); MS m/e 424 (M^+). Anal. ($C_{29}H_{44}O_2$) C, H.

3,4-Dihydro-7,8-dimethyl-2-(4,8,12-trimethyltrideca-3(*E*),7-(*E*),11-trienyl)-2*H*-1-benzopyran-6-yl Acetate (42): colorless oil; IR (film) 2924, 1760, 1478, 1440, 1368, 1204, 1074 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (s, 6 H), 1.63 (s, 3 H), 1.67 (s, 3 H), 1.73 (m, 2 H), 1.88–2.10 (m, 10 H), 2.01 (s, 3 H), 2.12 (s, 3 H), 2.22 (m, 2 H), 2.28 (s, 3 H), 2.60–2.85 (m, 2 H), 3.92 (m, 1 H), 5.09 (m, 2 H), 5.18 (t, J = 7.4 Hz, 1 H), 6.55 (s, 1 H); MS m/e 438 (M^+). Anal. ($C_{29}H_{42}O_3$) C, H.

Copper-Induced Oxidation of LDL. Low-density lipoprotein purchased from Sigma was used as the substrate in a sodium chloride (0.9%) and 4-(2-hydroxyethyl)-1-piperazinemethanesulfonic acid (HEPES) buffer (pH 7) solution. Test compounds were routinely dissolved in ethanol at 100 times the desired final concentration and added in 4-μL aliquots immediately prior to adding the oxidant (copper sulfate). The mixture was incubated at 37 °C to allow for oxidation of the LDL. The reaction was stopped with EDTA (which chelates the copper), and the extent of LDL oxidation was measured using thiobarbituric acid. Tubes were placed in a boiling water bath, at which time a pink color developed. Absorbance was read at 535 nm. Standards consisted of varying concentrations of tetramethoxypropane which generated malonodialdehyde in acid. A standard curve was used to calculate the nanomoles of malonodialdehyde equivalents formed for each compound.

A sufficient number of 12- × 75-mm disposable glass culture tubes were numbered to run compounds, controls, and reference agent(s) in duplicate. Probucol was used as the reference agent. The total volume of the reaction mixture was 0.4 mL as follows: 0.15 mL of saline, 0.1 mL of 20 mM HEPES buffer, 0.1 mL of LDL (0.5 mg/mL of protein), and 4 μL of drug (or absolute ethanol for controls) followed by 50 μL of copper sulfate (4×10^{-4} M). Tubes were mixed by shaking the rack between various additions, covered with a large piece of parafilm, and incubated in a 37-°C water bath for 5 h.

At the end of the incubation time, 0.1 mL of 1 mM EDTA was added to each tube to chelate the copper. Blanks consisting of 0.5 mL of saline were incorporated at this point as were standards consisting of 0.35 mL of saline and 0.15 mL of the various dilutions of tetramethoxypropane; 1.0 mL of trichloroacetic acid/thiobarbituric acid (TCA/TBA) reagent was added to each tube and the tube vortexed. The tubes were incubated in a boiling water bath for 30 min (cover half on), at which time a pink color developed. The tubes were spun at approximately 1500 rpm for 10–15 min.

After spinning, the tubes were decanted into new culture tubes and vortexed to eliminate bubbling. The absorbance of each sample was read at 535 nm.

Nanomoles of malonodialdehyde equivalents were calculated for each control, sample, and reference agent by plotting optical density of standards against nanomoles (3, 2, 1, and 0.5). Percent inhibitions and IC_{50}'s were then calculated using control values.

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Supplementary Material Available: Table of the cholesterol-biosynthesis-inhibition data of benzopyran-4-ones **3a–i** and **3k–z** and complete spectroscopic data (IR, NMR, MS, elementary analyses) for benzopyran-4-ones **3a–i** and **3k–z** and benzopyrans **4a–i** and **4k–z** (24 pages). Ordering information is given on any current masthead page.

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