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Total Syntheses of (+)-Chloropuupehenone and (+)-Chloropuupehenol and Their Analogues and Evaluation of Their Bioactivities

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Tetracyclic pyrans (+)-chloropuupehenone (**1**) and (+)-chloropuupehenol (**5**) and its C8-*R*-isomer (+)-**3** were synthesized via a one-pot condensation of 1-chloro-2-lithio-3,5,6-tris(*tert*-butyldimethylsilyloxy)benzene (**8**) with (4a*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde (**7**). The major condensation product, (4a*S*,6a*R*,12b*S*)-2*H*-9,10-bis(*tert*-butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene (**4**), after desilylation provided tetracyclic pyran (+)-(4a*S*,6a*R*,12b*S*)-2*H*-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene-9,10-diol (**3**). At a dosage of 42 mg/rat over 8 h, pyran diol **3** inhibited the intestinal absorption of cholesterol by 71% in rats. Tetracyclic pyran **4** was also converted to *o*-quinone **28**, which inhibited cholesteryl ester transfer protein (CETP) activity and L1210 leukemic cell viability with IC_{50} values of 31 and 2.4 μM, respectively. Diol (+)-**5** inhibited CETP activity with an IC_{50} value of 16 μM. The minor condensation product, (4a*S*,6a*S*,12b*S*)-2*H*-9,10-bis(*tert*-butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene (**6**), was transformed into (+)-**5** and (+)-**1**. A stepwise stereoselective synthesis of (+)-**1** was also developed utilizing an oxyselenylation ring-closure reaction. The synthetic sequence also produced four biologically active naturally occurring drimanic sesquiterpenes, (+)-drimane-8α,11-diol (**34**), (−)-drimenol (**38**), (+)-albicanol (**39**), and (−)-albicanal (**31**) as intermediates.

I. Introduction

As part of our studies of the syntheses of pyranopyrones[1] and their related bioactive compounds,[2] the total synthesis of pyranomethine quinone natural products was undertaken. (+)-Chloropuupehenone (**1**; Figure 1), a pyranomethine quinone, isolated from marine sponges[3] in Hawaii, strongly inhibits the effect of cholesteryl ester transfer protein (CETP; IC_{50} = 0.3 μM) and possesses other bioactivity.[4] CETP, a hydrophobic neutral glycoprotein, mediates the net transfer of cholesteryl ester from high-density lipoprotein (HDL) to low-density lipoprotein (LDL). Low levels of HDL cholesterol and high levels of LDL cholesterol are found in patients with atherosclerosis.[5] Inhibition of CETP may improve lipid parameters of HDL, LDL, and triglyceride blood levels and prevent the formation of more atherogenic lipoprotein particles in certain patient populations.[5d] The inhibi-

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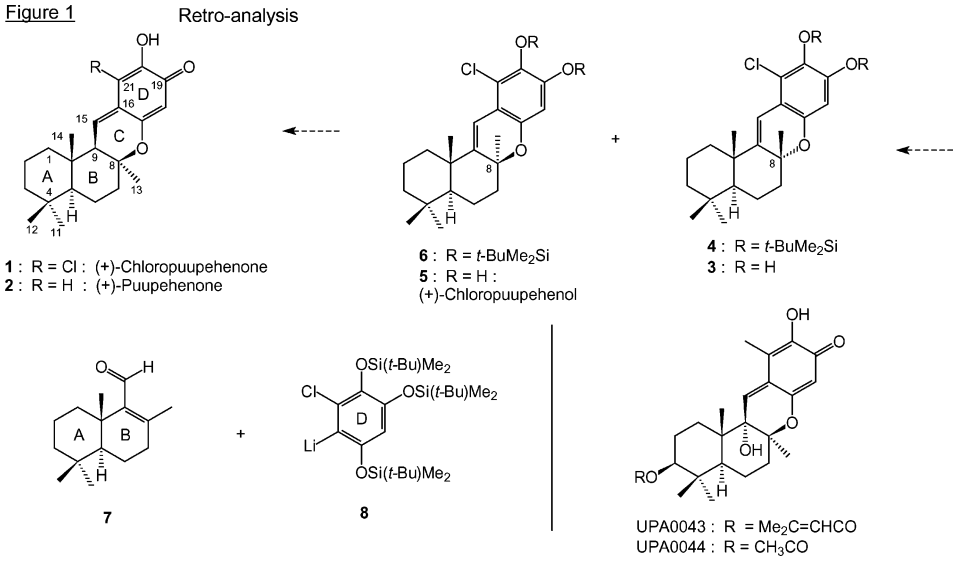

FIGURE 1. Retroanalysis.

tion of CETP should increase HDL and decrease LDL levels.[5] Although various syntheses of puupehenone (**2**),[6] a natural analogue of **1**, have been reported, the synthesis of **1** itself has not appeared. Our goals were to synthesize (+)-**1** and its analogues and to evaluate their CETP activities and the inhibition of lymphatic absorption of cholesterol.[7a] Analogues include stereoisomers at C8 (the natural product's numbering system is used). Lipid lowering by targeting CETP and other cholesterol regulators has been studied,[7b] and CETP inhibitors such as torcetrapib[7d] are reportedly lipid-lowering agents. Herein, we describe two methods leading to (+)-**1**, (+)-chloropuupehenol (**5**),[3e] its C8-*R*-isomer (+)-**3**, and the inhibition of CETP and lymphatic absorption of cholesterol. A new and facile two-bond forming reaction for the coupling of the A−B and the D ring fragments is discussed.

II. Results and Discussion

1. Synthesis. Two approaches to the synthesis of puupehenone (**2**) have been reported. The first involves a cationic cyclization of a C17 hydroxyl group with C7,8 and C8,13 double bonds,[6a−c] and the second incorporates a ring closure by the attack of C8 hydroxyl group onto the oxidatively activated 1,2-dihydroxyphenyl moiety.[6d] Beside these approaches, a ring opening of a C8,9 epoxide from a C17 hydroxyl group was utilized in the construction of two related *p*-methine quinone natural products, UPA0043 and UPA0044.[8] We envision that tetracyclic pyran **5**, a precursor of **1**, and its C8 epimer **3** could be assembled in one pot by tandem formation of C15−C16 and C8−O22 bonds from (4a*S*,8a*S*)-carboxaldehyde **7** and aryllithium **8**, as illustrated in Figure 1. The one-pot cyclization would utilize the ease of displacing the resulting benzylic allylic alcohol resulting from **7** and **8** and would not produce a stereoselective formation at C8 but would provide different stereoisomers for bioevaluation. Indeed, compound **3** is the most active compound in the inhibition of lymphatic cholesterol absorption (vide infra). In the following section, we describe a one-pot cyclization of aryllithium **8** and enal **7** via a benzylic allylic alcohol intermediate, followed by a second method involving a stereoselective ring closure reaction.

(a) Synthesis of Aldehyde 7. Compound **7** was previously prepared[9a,b] from (−)-sclareol and (+)-sclareolide (**9**).[9c] Our synthesis of **7**, starting from 3a*R*-(+)-sclareolide (**9**), which is less expensive than sclareol, was accomplished in four steps via a strategy similar to that reported in wiedendiol A synthesis,[9c] but with different reagents (Scheme 1). Hence, hydroxylation of lactone **9** with LDA in THF at −78 °C, followed by MoO_5·pyridine·HMPA[10] complex gave α-hydroxylactone **10** (65.6% yield) and *β*-isomer **11** (12.4% yield) with 20% recovery of starting material **9**. Compounds **10** and **11** were readily separated by silica gel column chromatography. The absoluate configuration at C1 of **10** and **11** were tentatively assigned on the basis of the ^{1}H *J* values of C1-H's. The *J* value of C1−H of **10** is 12 Hz (axial−axial coupling); the *J* value of C1H of **11** is 3.2 Hz (axial−

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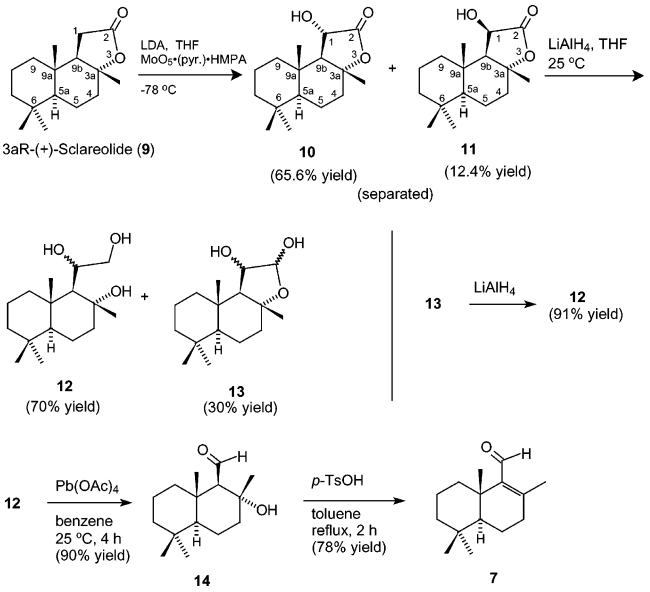
SCHEME 1



equatorial coupling). Because the stereocenter at C1 of **10** and **11** would be destroyed later in the synthesis, a mixture of **10** and **11** was used. Reduction of **10** and **11** with lithium aluminum hydride (LAH) in THF at room temperature produced triol **12** (70% yield) and lactol **13** (30% yield), the latter being further reduced to triol **12** (91% yield). Oxidative cleavage of triol **12** with lead tetraacetate in benzene at 25 °C provided *β*-hydroxyaldehyde **14** (90% yield),[9c] which on dehydration with *p*-toluenesulfonic acid in refluxing toluene for 2 h furnished enal **7** (78% yield).[9]

(b) Synthesis of Aryl Bromide 15, Precursor of Lithium 8. Scheme 2 outlines a practical synthesis of D-ring fragment **15**, a precursor of lithium **8**, in six steps from 3-chlorovanillin (**16**), readily prepared by the chlorination of vanillin with chlorine in acetic acid (85% yield).[11]Demethylation[12] of **16** with BBr_3 in CH_2Cl_2 (94% yield) followed by protection of the resulting diol, **17**, with *tert*-butyldimethylsilyl chloride, triethylamine, and 4-(dimethylamino)pyridine (DMAP) gave aldehyde **18** (93% yield). Baeyer−Villiger oxidation[13] of **18** with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride (70% yield) followed by removal of the resulting formyl ester function by treatment with potassium carbonate (90% yield) and silylation of the phenolic hydroxyl group of **20** with *tert*-butyldimethylsilyl chloride (83% yield) afforded trisilyl ether **21**. Selective bromination of **21** at C4 (less hindered site than C6) with *N*-bromosuccinimde (NBS) in *N*,*N*-dimethylformamide (DMF) at 25 °C gave **15** (67% yield) as the only product. It is important to note that although no C6 isomer **22** was detected in the bromination at 25 °C, when carried out at 50 °C, a 2:1 ratio of **22** to **15** was obtained, and these products were separated by column chromatography.

Alternatively, a higher yield of bromide **15** was obtained from the bromination of phenol **20** with NBS in DMF (70% yield) followed by silylation with *tert*-butyldimethylsilyl chloride (99% yield) (Scheme 2). The regiochemistry of aryl bromides **15** and **22** was initially based only on the ^{1}H NMR chemical shifts of the aromatic hydrogen atoms but later was confirmed through the transformation of compound **15** to (+)-chloropuupehenone (vide infra). The ^{1}H NMR resonace of the only aromatic H of **15** (H-5), *δ* 6.41 ppm, is affected by a greater electron-donating effect from two adjacent silyloxy groups than is H-5 of **22**, *δ* 6.54 ppm, which is flanked by a silyloxy group and a chlorine.

(c) One-Pot Synthesis of Tetracyclic Pyranes 4 and 6. The reaction of aryllithium **8** with aldehyde **7** turned out to be a one-pot synthesis of tetracyclic pyranes **4** and **6**. Thus, treatment of bromide **15** with 2 equiv of *t*-BuLi in diethyl ether at −78 °C followed by aldehyde **7** afforded a mixture of two stereoisomers at C6a (IUPAC numbering system), **4** (45% yield) and **6** (9.1% yield) (Scheme 3). Apparently, attack by lithiated arene **8** on the aldehyde function of **7** produced a mixture of two diastereoisomeric alcohols **24**. Both alcohols underwent an intramolecular ring closure by an elimination of the benzylic allylic hydroxyl group during aqueous workup to form a carbocation intermediate, **25A** or **25B**, followed by ring closure from the attack of C7 oxygen and the release of the *tert*-butyldimethylsilyl group with water. The C7 oxygen attacks the carbocation preferentially from the opposite side of the C12b methyl (less hindered face) to give **4** as the predominant product and isomer **6** as minor product. Removal of the silyl ether protecting groups of **4** and **6** separately gave 6a*R*-diol **3** (82% yield) and (+)-chloropuupehenol (**5**) (81.4% yield),[3e] respectively. The stereochemistry at C6a of pyrans **4** and **6** was established by 2D NOESY spectroscopy. Compound **4** exhibited NOE correlation between C6a and C12b methyls, while compound **6** exhibited no NOE correlation.

To synthesize (+)-chloropuupehenone and its analogues, reduction of the C12−12a double bond followed by oxidation of the substituted catachol functionality to the methine quinone are needed. Therefore, tetracyclic pyranes **4** and **6** were stereoselectively hydrogenated with hydrogen and palladium/carbon in ethanol to give **26** and **29**, respectively (Scheme 4). The palladium hydrogens approach the C12−C12a double bond of **4** and **6** from the less hindered α-face (opposite to the two angular methyls). Desilylation of C6a-*R*-**26** with tetra-*n*-butylammonium fluoride in THF (83% yield) followed by oxidation with pyridinium chlorochromate (PCC) provided a 77% yield of *o*-quinone **28**. No methine quinone was detected. Attempts with other oxidizing reagents, viz., pyridinium dichromate (PDC), 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ), and KOH−O_2 failed to provide methine quinone; only *o*-quinone **28** was obtained.

Contrary to the oxidation of C6a-*R*-**27**, the C6a-*S* isomer, **29**, after desilylation with tetra-*n*-butylammonium fluoride, was successfully oxidized to the methine quinone (+)-chloropuupehenone (**1**) (73% yield). The methine quinone structure of **1** was readily ascertained by ^{1}H NMR spectroscopy, in which the C12-olefinic H appears as a doublet at *δ* 7.14; *o*-quinone **28** does not possess an olefinic H. It is apparent that only the *cis*-annulate pyran (the C ring of the tetracyclic structure),

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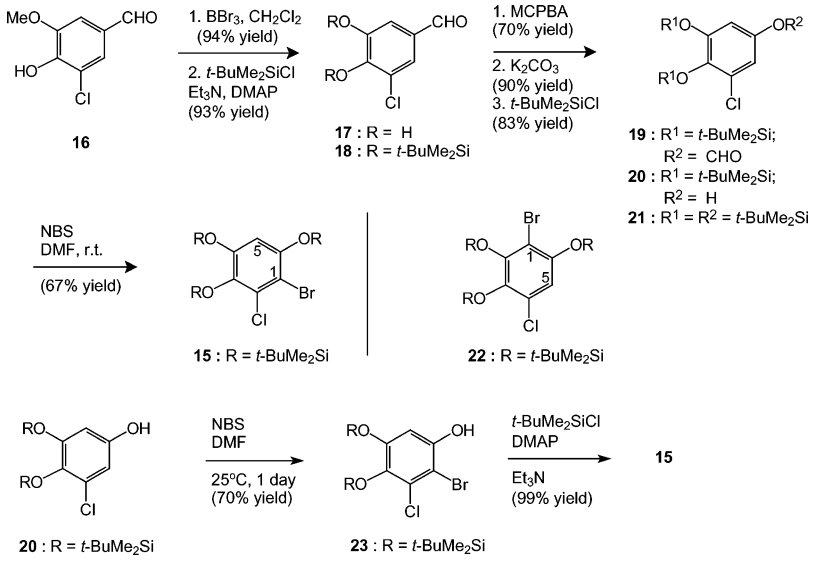
SCHEME 2



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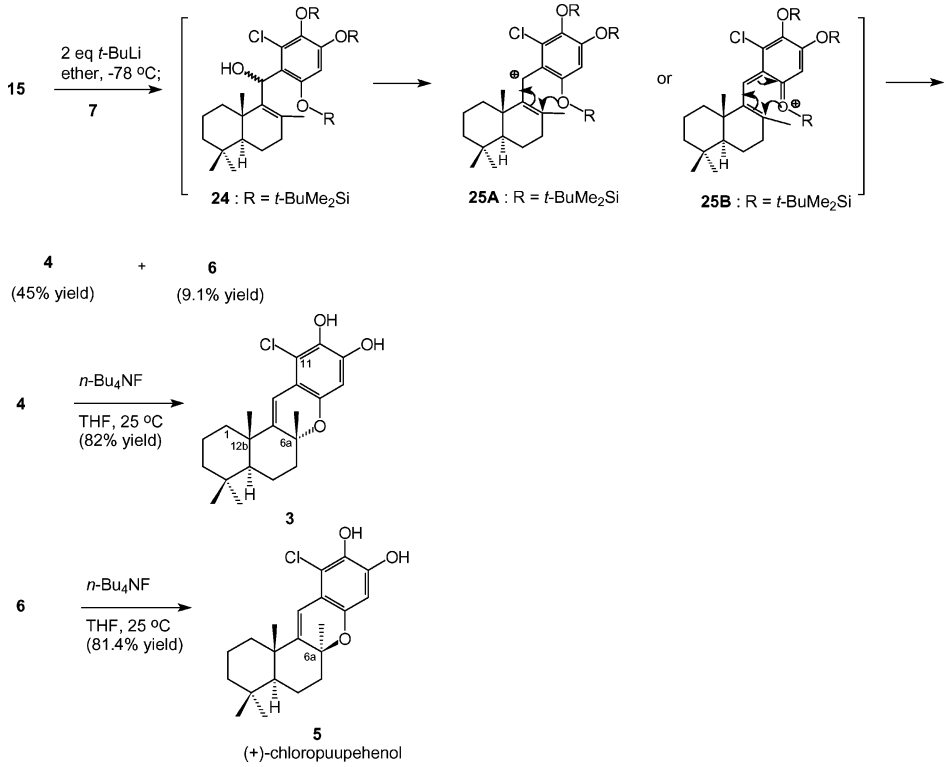

30, produced methine quinone upon oxidation; oxidation of the *trans*-annulate pyran, **27**, produced only the *o*-quinone.

It should be noted that tetracyclic pyran diol **3** effected a complete inhibition of lymphatic cholesterol absorption in mice (vide infra).

(d) Stepwise Stereoselective Synthesis of (+)-Chloropuupehenone [(+)-1]. The above synthetic route produced (+)-**1** as the minor product. To synthesize (+)-**1** stereoselectively, a stepwise synthetic route was investigated starting with nonconjugated aldehyde **31** or **32** (Scheme 5). We also found that the silyl ether protecting group of aryl halide **23** is incompatible to the reaction conditions after the coupling of **23** with aldehyde **31** or **32**, and hence a benzyl ether protecting group, i.e., aryl bromide **33**, was used in the synthesis (Scheme 6).

First, in the synthesis of aldehydes **31** and **32**, elimination of the C2-hydroxyl group of **14** is required. Hence, reduction of **14** with lithium aluminum hydride in ether at 0 °C gave drimane-8α,11-diol (**34**)[14] (97% yield), which upon selective protection of its primary hydroxyl function by reaction with *tert*-butyldimethylsilyl chloride and imidazole (98% yield), followed by elimination when

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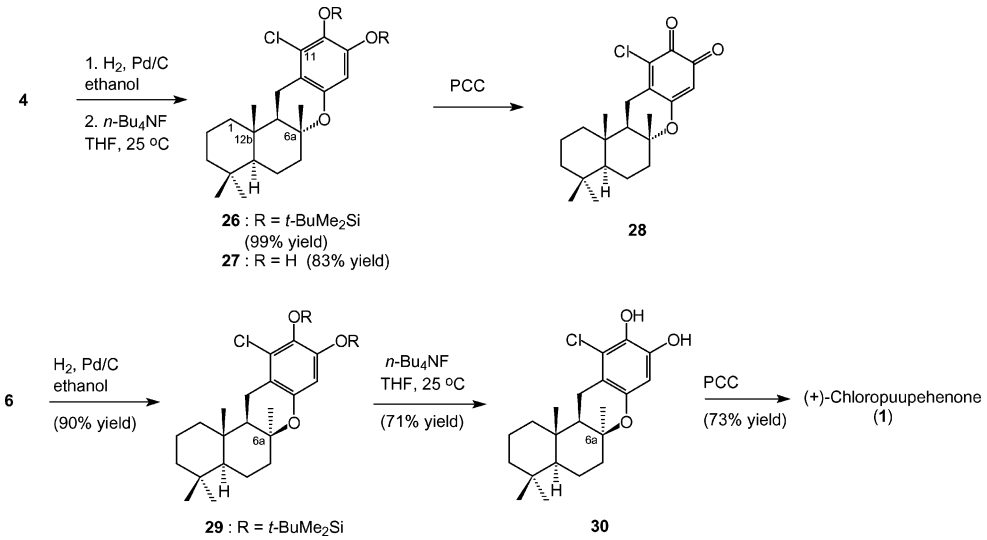
SCHEME 4



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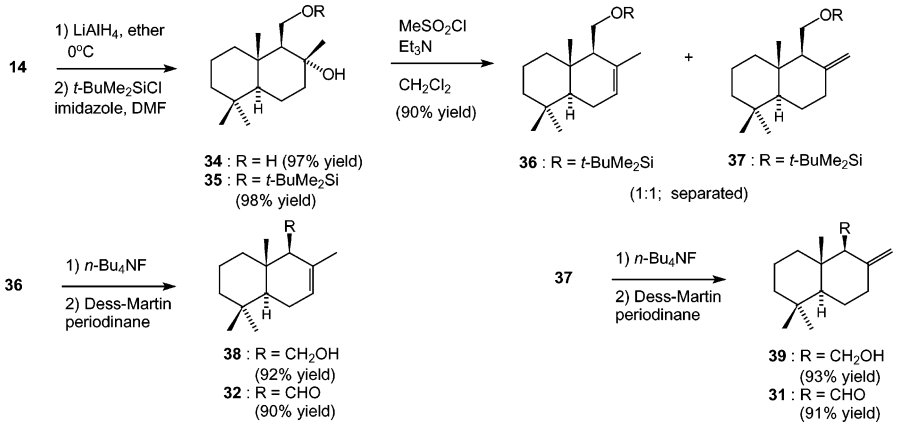

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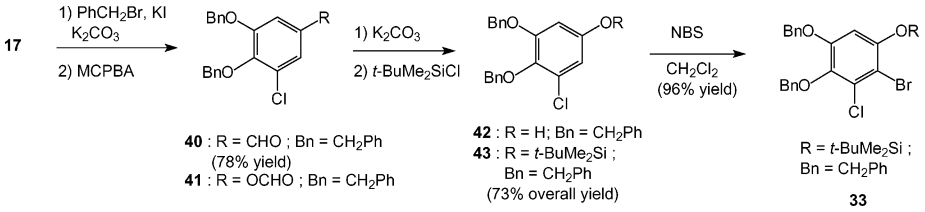

treated with methanesulfonyl chloride and triethylamine, afforded a 1:1 ratio of alkene **36** and **37** (90% yield; Scheme 5). Bicyclic alkene **36** and **37** were separated by silica gel column chromatography. Desilylation of alkene **36** with tetra-*n*-butylammonium fluoride gave (−)-drimenol[3f] (**38**) (92% yield), which was oxidized with Dess−Martin periodinane to aldehyde **32** (90% yield). Via a similar sequence of reactions, desilylation of *exo*-bicyclic alkene **37** gave (+)-albicanol (**39**)[15a] (93% yield); subsequent oxidation provided (−)-albicanal (**31**)[15b−d] (91% yield).

The benzyl-protected aryl bromide **33** was synthesized via a similar method used to prepare the silyl-protected bromide **15** (Scheme 6). Hence, benzylation of catachol **17** with benzyl bromide, potassium iodide, and potassium carbonate provided aldehyde **40** (78% yield). Baeyer−Villiger oxidation of **40** with MCPBA in dichloromethane, followed by hydrolysis with potassium carbonate in methanol, and silylation with *tert*-butyldimethylsilyl chloride and triethylamine afforded aryl chloride **43** in 73% overall yield (from **40**). Regioselective oxidation of **43** with NBS in dichloromethane provided bromide **33** (96% yield); no *p*-bromochloro isomer was detected.

Coupling of bromide **33** with aldehyde **31** was carried out like that of **15** with **7**. Treatment of bromide **33** with 1.1 equiv of *tert*-butyllithium in ether at −78 °C, followed by *exo*-cycloalkenal **31** (89% yield), and desilylation with *n*-Bu_4NF in THF (93% yield) afforded diol **45** as a mixture

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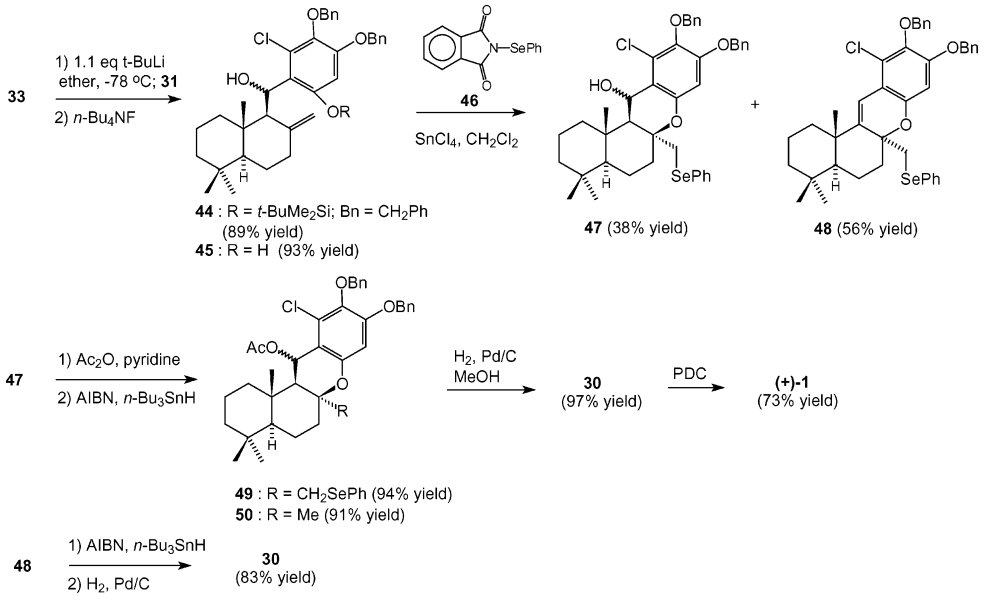
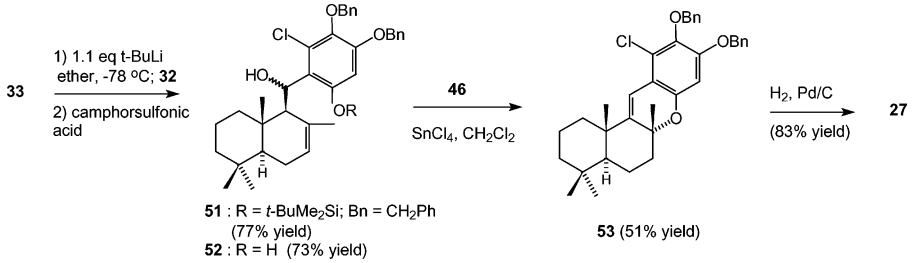
SCHEME 7



SCHEME 8



of two isomers at the newly created stereogenic center (Scheme 7). Because this stereocenter will be removed in later steps, both isomers were used in the subsequent reaction. Oxyselenylation[16] of diol **45** with 1.1 equiv of *N*-phenylselenophthalimide (N-PSP; **46**) and 0.1 equiv of tin tetrachloride in dichloromethane at 25 °C gave selenyl pyran **47** (38% yield) and unsaturated pyran **48** (56% yield), which were separated by column chromatography. Compound **48** apparently was formed from the dehydration of alcohol **47** catalyzed by either tin tetrachloride or HCl (generated from the hydroxyl moiety and tin tetrachloride). The stereochemistry at C6a of **47** and **48** were revealed after conversion of these two compounds to tetracyclic pyran **30** (vide infra). Most likely, the phenylselenyl reagent approaches the *exo* double bond of **45** from the opposite face (α face) of C12a side chain and C12b methyl, and O7-phenolic oxygen attacks C6a *anti*[16] from the phenylselenyl group providing **47**. Acetylation of **47** with acetic anhydride and pyridine (94% yield) followed by 2,2′-azobisisobutyronitrile (AIBN) and tri-*n*-butyltin hydride in refluxing toluene furnished pyran **50** (91% yield). Removal of the benzyl ether and benzylic acetate groups of **50** with 10% palladium on activated carbon in methanol afforded **30** (97% yield). Similarly to that described in Scheme 4, oxidation of **30** with PDC gave (+)-**1**.

Selenide **48**, likewise deselenylated with AIBN and tri-*n*-butyltin hydride followed hydrogenation with H_2−Pd/C in methanol produced **30** (83% overall yield).

endo-Bicyclic alkenal **32**, similarly treated with the aryllithium generated from bromide **33**, gave adduct **51** (77% yield) as a mixture of two stereoisomers at the hydroxyl carbon (Scheme 8). As described above, because this stereocenter will be destroyed in later steps, they were used in subsequent reactions without separating the isomers. Attempted cyclization of **51** with (+)-camphorsulfonic acid[6e] in dichloromethane at 25 °C gave diol **52** (73% yield) along with intractable materials. No cyclized tetracyclic pyran (such as **53**) was detected.[6e] Diol **52** was independently synthesized from the reaction of **51** and *n*-Bu_4NF in THF. Contrary to the reaction of diol **45**, reaction of **52** with N-PSP and a catalytic amount of tin tetrachloride produced tetracyclic pyran **53** (51% yield), but no selenylated products were detected. Instead of tin tetrachloride, other additives such as *p*-TsOH, (+)-camphorsulfonic acid, and BF_3·ether were tried, but again no selenylated products were observed. It is possible that hydrochloric acid was formed from the alcohol **52** and tin tetrachloride, which catalyzed a cationic cyclization whose rate was faster than that of the reaction of the bicyclic alkene with N-PSP. Hydrogenation of **53** with H_2−Pd/C in methanol afforded tetracyclic pyran **27**.

It is noteworthy that oxyselenylation of *exo*-bicyclic alkene **45** took place readily, although no oxyselenylation was observed with the *endo*-bicyclic alkene **52**. This may

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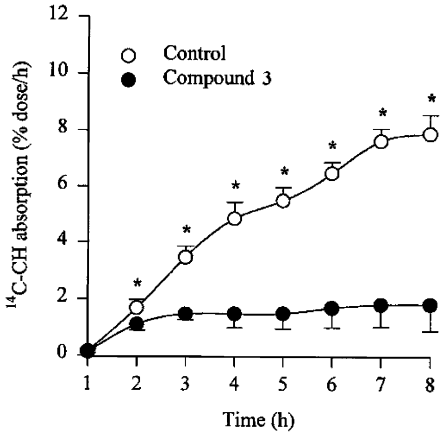

FIGURE 2. Hourly rates of lymphatic absorption of ^{14}C-labeled cholesterol (^{14}C-CH) in rats for 8 h during intraduodenal infusion of lipid emulsion containing compound **3** (5.25 mg/h), respective to lipid emulsion containing no compound **3** (control; CT). Values are expressed as means ± SD, $n = 5$. Asterisk denotes a significant difference from rats infused with compound **3** at each time, $P < 0.05$.

TABLE 1. Total Lymphatic Absorption of ^{14}C-Cholesterol (^{14}C-CH), Output of Oleic Acid, and Lymph Volume in Rats Infused with Lipid Emulsion Containing Compound 3, Respective to That Containing No Compound 3 (control)[a]

lymph lipids	control	compound **3**
^{14}C-CH (% dose/8 h)	37.7 ± 1.8	10.9 ± 3.3*
oleic acid (μmol/8 h)	596.5 ± 61.3	229.2 ± 45.7*
lymph (mL/8 h)	18.3 ± 2.4	16.6 ± 4.2

[a] Means ± SD, $n = 5$. Asterisk denotes a significant difference from control group ($P < 0.05$).

attribute to the rapid reaction of *exo*-terminal alkenes with N-PSP[16] and a slower reaction from *endo*-trisubstituted alkenes with N-PSP.

2. Bioactivities. The inhibition of CETP[17] with compounds **28**, **50**, (+)-**1**, and (+)-**5** were examined, and IC_{50} values are 31, >100, 28, and 16 μM, respectively. Under our CETP assay conditions, the IC_{50} value of (+)-**1** is much higher than that reported.[4a] The iron-containing *o*-iminoquinone ferroverdin A[18] exhibits an IC_{50} value of 20 μM under similar CETP assay conditions. This observation prompted us to examine their effect on another potential role of these compounds in cholesterol metabolism, i.e., intestinal cholesterol absorption,[19] as they are structurally related to cholesterol. Interestingly, pyran diol **3** inhibits the intestinal absorption of cholesterol by 71% in rats with a dosage of 42 mg/rat over 8 h. Interestingly, it also inhibits the absorption of fat by 62%. The hourly rates of cholesterol absorption, as affected by this compound, are shown by Figure 2, and the cumulative absorptions of cholesterol and fat over 8 h are summarized in Table 1. No apparent toxicity was observed after this treatment and all internal organs were normal, including intestine. Similar to the blood circulation system, the lymphatic system is composed of fine capillaries located adjacent to the blood vessels. The lymphatic system transports nutrients to the cells and collects waste products. Hence, diol **3** may serve as a cholesterol-lowering drug.

o-Quinone **28** inhibited the viability of L1210 leukemic cells with an IC_{50} value of 2.4 μM after 4 days in culture. The antileukemic activity agrees with the finding by Popov et al.,[4b] in that sesquiterpenequinones possess cytotoxic activity against Ehrlich ascites tumor cells. The activity probably contributes from the *o*-quinone functionality.[20]

III. Conclusions

Two synthetic routes were investigated in the total syntheses of (+)-chloropuupehenone (**1**), (+)-chloropuupehenol, and their stereoisomers. A one-pot addition followed by cyclization of aryllithium **8** and bicyclic alkenal **7** was found. The major product of this one-pot condensation reaction was desilylated to give tetracyclic pyran **3**, which possesses strong inhibitory of cholesterol absorption in rats. This facile cyclization reaction can be used in the synthesis of other pyran natural products.[21] Compound **3** and its analogues are being investigated as cholesterol-lowering drugs. An oxyselenylation reaction was utilized in a stepwise stereoselective synthesis of (+)-**1**, and only the *exo*-bicyclic alkenal, **45**, provided the expected product. Such results can be used in planning future synthesis involving oxyselenylation. Four biologically active naturally occurring drimanic sesquiterpenes, (+)-drimane-8α,11-diol (**34**), (−)-drimenol (**38**), (+)-albicanol (**39**), and (−)-albicanal (**31**), were also produced as synthetic intermediates in the total synthesis.

IV. Experimental Section

General Methods. Unless otherwise indicated, NMR spectra were obtained at 400 MHz for ^{1}H and 100 MHz for ^{13}C in $CDCl_3$ and reported in ppm. Infrared spectra are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were taken using 2,5-dihydroxybenzoic acid as a matrix. Tetrahydrofuran and diethyl ether were distilled over sodium and benzophenone before use. Methylene chloride was distilled over CaH_2, and toluene and benzene were distilled over $LiAlH_4$.

(1*S*,3a*R*,5a*S*,9a*S*,9b*R*)-1-Hydroxy-dodecahydro-3a,6,6,9a-tetramethylnaphtho-[2,1-*b*]furan-2-one (10) and (1*R*,3a*R*,5a*S*,9a*S*,9b*R*)-1-Hydroxy-dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-2-one (11). To a cold (−78 °C) solution of 1.02 mL (7.79 mmol) of diisopropylamine in 40 mL of THF under argon was added 6.36 mL (7.19 mmol) of *n*-BuLi (1.6 M in hexane). The solution was stirred at −78 °C for 1 h, and a solution of 1.50 g (5.99 mmol) of (+)-sclareolide (**9**) in 20 mL of THF was added via cannula dropwise. The solution was stirred at −78 °C for 1 h, added to 5.10 g (0.012 mol) of MoO_5·pyridine·HMPA, and stirred for 30 min. The mixture was diluted with saturated aqueous Na_2SO_3 and extracted three times with ethyl acetate, and the organic layer was washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ether (9:1) as an eluent to give 1.05 g (65.6% yield) of compound **10** and 0.20 g (12% yield) of compound **11** along with 0.296 g (20% recovery) of **9**. Compound **10**:[9c] $[\alpha]^{22}_D$ =

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(21) For a review, see: Vilella, D.; Sanchez, M.; Platas, G.; Salazar, O.; Genilloud, O.; Royo, I.; Cascales, C.; Martin, I.; Diez, T.; Silverman, K. C.; Lingham, R. B.; Singh, S. B.; Jayasuriya, H.; Pelaez, F. *J. Ind. Microbiol. Biotechnol.* **2000**, *25*, 315−327.

+97.1° (*c* 1.0, $CHCl_3$); MS (electrospray) *m*/*z* 267 (M + 1); ^{1}H NMR δ 4.48 (d, *J* = 12 Hz, 1 H, CHO, axial), 2.06 (d, *J* = 12 Hz, 1 H, C9b-axial H), 1.95−1.06 (m, 11 H), 1.38 (s, 3 H, Me), 1.03 (s, 3 H, Me), 0.88 (s, 3 H, Me), 0.84 (s, 3 H, Me); ^{13}C NMR δ 179.0 (s, C=O), 83.5, 68.7, 64.2, 56.4, 42.3, 39.4, 39.3, 36.9, 33.4, 33.2, 23.5, 21.1, 20.7, 18.1, 15.9. Compound **11**:[9c] $[\alpha]^{22}_D$ = −19.1° (*c* 1.0, $CHCl_3$); MS (electrospray) *m*/*z* 267 (M + 1); ^{1}H NMR δ 4.37 (dd, *J* = 5.6, 3.2 Hz, 1 H, CHO, equatorial), 2.32 (d, *J* = 3.2 Hz, 1 H, OH), 2.06 (d, *J* = 12 Hz, 1 H), 1.89−0.98 (m, 10 H), 1.69 (s, 3 H, Me), 1.21 (s, 3 H, Me), 0.87 (s, 3 H, Me), 0.85 (s, 3 H, Me); ^{13}C NMR δ 177.6 (s, C=O), 88.8, 70.2, 62.6, 57.8, 42.4, 39.8, 38.7, 37.3, 27.1, 25.2, 21.1, 20.8, 18.3, 17.3.

1-[(1′*S*) and (1′*R*)-1,2-Dihydroxyethyl)]-(1*R*,2*R*,4a*S*,8a*S*)-decahydro-2,5,5,8a-tetramethyl-naphthalen-2-ol (12) and (3a*R*,5a*S*,9a*S*,9b*R*)-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan-1,2-diol (13). To a solution of 0.90 g (3.4 mmol) of **10** in 20 mL of THF under argon was added 0.66 g (17.3 mmol) of $LiAlH_4$, and the mixture was stirred for 4 h at 25 °C. To it, 60 mL of water and 16 mL of 1 N HCl were added, and the solution was extracted with diethyl ether three times (50 mL each). The combined ether extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 0.65 g (71% yield) of triol **12** and 0.27 g (30% yield) of lactol **13**. Two stereoisomers (1:1) at C1′ of **12** were separated from the above column chromatography. Compound **12** (the less polar isomer): [9c] $[\alpha]^{22}_D$ = −7.2° (*c* 0.8, CH_3OH); MS (electrospray) *m*/*z* 271 (M + 1); ^{1}H NMR δ 4.53 (m, 1 H, CHO), 4.08 (dd, *J* = 10, 8 Hz, 1 H, CH_2O), 3.64 (dd, *J* = 10, 4 Hz, 1 H, CH_2O), 1.95 (d, *J* = 4 Hz, 1 H), 1.70−1.01 (m, 11 H), 1.43 (s, 3 H, Me), 1.10 (s, 3 H, Me), 0.90 (s, 3 H, Me), 0.82 (s, 3 H, Me); ^{13}C NMR δ 82.9, 75.2, 71.8, 68.8, 48.7, 42.4, 38.4, 36.3, 34.9, 33.7, 33.2, 28.3, 23.0, 21.9, 20.0, 18.5. Compound **12** (the more polar isomer): MS (electrospray) *m*/*z* 271 (M + 1); ^{1}H NMR δ 3.87 (m, 1 H, CHO), 3.68 (dd, *J* = 11, 3 Hz, 1 H, CH_2O), 3.42 (dd, *J* = 11, 8 Hz, 1 H, CH_2O), 3.15 (broad s, 3 H, OH), 1.80−0.8 (m, 12 H), 1.54 (s, 3 H, Me), 0.99 (s, 3 H, Me), 0.87 (s, 3 H, Me), 0.81 (s, 3 H, Me). Compound **13** (as a mixture of 4 diastereomers at C1 and C2): MS (electrospray) *m*/*z* 269 (M + 1); ^{1}H NMR δ 5.38, 5.32 (broad s, 1 H), 5.33, 5.22 (s, 1 H), 4.36, 4.35 (t, *J* = 5 Hz, 1 H), 2.8, 2.5 (broad s, 1 H, OH), 1.9−0.9 (m, 12 H), 1.49, 1.34 (s, 3 H, Me), 1.19, 1.16 (s, 3 H, Me), 0.97, 0.86 (s, 3 H, Me), 0.87, 0.84, 0.83 (s, 3 H, Me); ^{13}C NMR δ 94.5, 79.2, 73.1, 70.8, 64.3, 62.9, 60.6, 57.1, 56.9, 42.5, 40.8, 40.4, 39.9, 37.0, 36.8, 33.8, 33.3, 25.3, 25.2, 24.6, 21.6, 21.3, 20.8, 18.4, 16.4, 16.2.

Compound 12 from Reduction of 13. To a solution of 20 mg (75 μmol) of **13** in 2 mL of THF under argon was added 9 mg (0.23 mmol) of lithium aluminum hydride. After the mixture was stirred for 3 h, aqueous NH_4Cl was added, and the mixture was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using hexane/ethyl acetate (1:1) as an eluant to give 19 mg (91% yield) of **12**.

(1*R*,2*R*,4a*S*,8a*S*)-Decahydro-2-hydroxy-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde (14) from Triol 12. To a solution of 0.65 g (2.4 mmol) of triol **12** in 25 mL of benzene under argon was added 1.3 g (2.9 mmol) of lead tetraacetate. After stirring at 25 °C for 4 h, the mixture was diluted with diethyl ether, and the organic layer was washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 0.52 g (90% yield) of aldehyde **14**:[9c] $[\alpha]^{22}_D$ = +31.9° (*c* 0.75, $CHCl_3$); MS (electrospray) *m*/*z* 239 (M + 1); ^{1}H NMR δ 10.06 (d, *J* = 3 Hz, 1 H, CHO), 2.93 (broad s, 1 H, OH), 2.15 (d, *J* = 3 Hz, 1 H, C1-H), 1.8−0.9 (a series of m, 11 H), 1.20 (s, 3 H, Me), 1.17 (s, 3 H, Me), 0.90 (s, 3 H, Me), 0.86 (s, 3 H, Me); ^{13}C NMR δ 208.3, 72.9, 71.4, 55.3, 42.9, 41.8, 39.9, 37.5, 33.5, 30.5, 25.4, 21.5, 20.0, 18.3, 17.7.

(4a*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde (7). To a flask equipped with a Dean−Stark apparatus under argon were added 10 mg (42 μmol) of aldehyde **14**, 10 mL of toluene, and 3 mg (17 μmol) of *p*-toluenesulfonic acid. After the solution was reflux for 2 h, the solution was cooled to 25 °C, diluted with saturated aqueous sodium bicarbonate, and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 7.2 mg (78% yield) of aldehyde **7**.[9c] In a larger-scale synthesis of **7**, the product was distilled under reduced pressure to give colorless oil, bp 60 °C/3 mmHg (to eliminate trace amount of water), and the distilled product was used in next step: $[\alpha]^{22}_D$ = +52° (*c* 1, $CHCl_3$), lit.[9c] +46.2 (*c* 0.65, $CHCl_3$); MS (electrospray) *m*/*z* 221 (M + 1); ^{1}H NMR δ 10.04 (s, 1 H, CHO), 2.55 (d, *J* = 13 Hz, 1 H), 2.26 (dd, *J* = 8, 4 Hz, 1 H), 2.03 (s, 2 H, Me), 1.70−1.40 (m, 6 H), 1.18 (s, 3 H, Me), 1.17−0.91 (m, 2 H), 0.90 (s, 3 H, Me), 0.86 (s, 3 H, Me); ^{13}C NMR δ 192.8 (C=O), 153.7 (C=C), 143.9 (C=C), 51.8, 41.8, 37.8, 36.7, 36.4, 33.6, 33.5, 33.2, 21.8, 20.4, 19.1, 18.5.

3-Chloro-4-hydroxy-5-methoxybenzaldehyde (16).[11] To a solution of 2.50 g (16.4 mmol) of vanillin in 15 mL of glacial acetic acid was added chlorine gas through a glass tubing over 30 min (with a slow gas flow) at 25 °C. White solid product was collected by filtration, washed with 50 mL of hexane, and dried in vacuo to give 2.03 g of **16**. The acetic acid filtrate was again treated with chlorine gas as above for 30 min to give another 0.66 g of **16**. A total of 2.69 g (88% yield) of **16** was obtained. The white solids were used in next step without purification: ^{1}H NMR δ 10.04 (s, 1 H, OH), 9.76 (s, 1 H, CHO), 7.56 (d, *J* = 1.6 Hz, 1 H, Ar), 7.37 (d, *J* = 1.6 Hz, 1 H, Ar), 3.91 (s, 3 H, OMe); ^{13}C NMR δ 190.5 (C=O), 149.0 (s, 2 C), 128.2 (s), 125.6 (d), 120.1 (s), 109.2 (d), 56.3 (q).

5-Chloro-3,4-dihydroxybenzaldehyde (17).[12] To a solution 2.00 g (10.7 mmol) of aldehyde **16** in 20 mL of dichloromethane under argon at 0 °C was added 1.20 mL (11.8 mmol) of boron tribromide. The solution was stirred at 0 °C for 0.3 h and 25 °C for 4 h and diluted with 40 mL of methanol, and the solvents were removed on a rotary evaporator (trimethyborate was removed). To it was added 40 mL of methanol, and methanol and trimethyl borate were removed by evaporation on a rotary evaporator; this process was repeated three times. The residue was diluted with dichloromethane and filtered and washed with a small amount of dichloromethane to give 1.72 g (94% yield) of pure **17**.[12] This material was used in next step without purification: ^{1}H NMR δ 10.43 (s, 2 H, OH), 9.70 (s, 1 H, CHO), 7.42 (d, *J* = 2.0 Hz, 1 H, C6-H), 7.22 (d, *J* = 2.0 Hz, 1 H, C2-H); ^{13}C NMR (DMSO-d_6) δ 190.6 (C=O), 148.3 (s), 146.9 (s), 128.4 (d), 124.2 (d), 120.3 (s), 112.5 (s).

3,4-Bis(*tert*-butyldimethylsilyloxy)-5-chlorobenzaldehyde (18). To a solution of 1.68 g (9.70 mmol) of **17** and 0.21 g (2.80 mmol) of 4-(dimethylamino)pyridine (DMAP) in 20 mL of dichloromethane under argon at 0 °C were added 9.80 mL (68.0 mmol) of distilled triethylamine and 4.40 g (59.2 mmol) of *tert*-butyldimethylsilyl chloride. The reaction mixture was stirred at 0 °C for 1 h and 25 °C for 3 h, 100 mL of saturated aqueous NH_4Cl was added, and the mixture was extracted three times with diethyl ether (80 mL each). The combined extracts were washed with 60 mL of brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 3.64 g (93% yield) of **18**: ^{1}H NMR δ 9.77 (s, 1 H, CHO), 7.50 (d, *J* = 2.0 Hz, 1 H, C6-H), 7.27 (d, *J* = 2.0 Hz, 1 H, C2-H), 1.04 (s, 9 H, *t*-Bu), 0.98 (s, 9 H, *t*-Bu), 0.26 (s, 6 H, Me), 0.23 (s, 6 H, Me); ^{13}C NMR δ 189.3 (C=O), 149.5 (s), 149.2 (s), 130.3 (s), 127.8 (s), 125.7 (d), 118.8 (d), 26.1 (q, 3 C, *t*-Bu), 26.0 (q, 3 C, *t*-Bu), 18.7 (s, 2 C, *t*-Bu), −3.4 (q, 2 C, Me), −3.6 (q, 2

C, Me). Anal. Calcd for $C_{19}H_{33}ClO_3Si_2$: C, 56.90; H, 8.29. Found: C, 56.62; H, 8.41.

3,4-Bis(*tert*-butyldimethylsilyloxy)-5-chlorophenyl Formate (19). To a solution of 1.73 g (4.30 mmol) of **18** in 15 mL of dichloromethane under argon was added 2.03 g (6.50 mmol) of 55% *m*-chloroperbenzoic acid (MCPBA). After refluxing for 10 h, the solution was diluted with 30 mL of water and extracted three times with diethyl ether (50 mL each). The combined extracts were washed twice with saturated aqueous $NaHCO_3$ (30 mL each), 30 mL of water, and 30 mL of brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using hexane as an eluent to give 1.24 g (70% yield) of **19**: ^{1}H NMR δ 8.22 (s, 1 H, CHO), 6.79 (d, J = 3.2 Hz, 1 H), 6.58 (d, J = 3.2 Hz, 1 H), 1.03 (s, 9 H, *t*-Bu), 0.96 (s, 9 H, *t*-Bu), 0.22 (s, 6 H, Me), 0.19 (s, 6 H, Me); ^{13}C NMR δ 159.0 (s, C=O), 148.8 (s), 143.0 (s), 142.4 (s), 127.1 (s), 115.5 (d), 113.1 (d), 26.2 (q, 6 C, *t*-Bu), 18.8 (s, 2 C, *t*-Bu), −3.3 (q, 2 C, Me), −3.6 (q, 2 C, Me). Anal. Calcd for $C_{19}H_{33}ClO_4Si_2$: C, 54.71; H, 7.97. Found: C, 54.90; H, 8.13.

3,4-Bis(*tert*-butyldimethylsilyloxy)-5-chlorophenol (20). To a solution of 1.24 g (2.97 mmol) of **19** in 10 mL of methanol was added 2.05 g (15.0 mmol) of potassium carbonate at 25 °C. The solution was stirred for 30 min, diluted with 35 mL of water, and extracted three times with diethyl ether (50 mL each). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 1.03 g (90% yield) of **20**: ^{1}H NMR δ 6.45 (d, J = 2.8 Hz, 1 H), 6.31 (d, J = 2.8 Hz, 1 H), 1.00 (s, 9 H, *t*-Bu), 0.93 (s, 9 H, *t*-Bu), 0.18 (s, 6 H, Me), 0.15 (s, 6 H, Me); ^{13}C NMR δ 149.7 (s), 148.9 (s), 137.7 (s), 126.9 (s), 109.8 (d), 107.8 (d), 26.3 (q, 3 C), 26.2 (q, 3 C), −3.6 (q, 2 C, Me), −3.4 (q, 2 C, Me). Anal. Calcd for $C_{18}H_{33}ClO_3Si_2$: C, 55.57; H, 8.55. Found: C, 55.39; H, 8.87.

3-Chloro-1,2,5-tris(*tert*-butyldimethylsilyloxy)benzene (21). To a mixture of 1.03 g (2.65 mmol) of **20**, 0.60 g (4.00 mmol) of *tert*-butyldimethylsilyl chloride, and 48 mg (0.40 mmol) of 4-(dimethylamino)pyridine in 10 mL of dichloromethane under argon at 25 °C was added 1.30 mL (9.3 mmol) of triethylamine. After stirring at 25 °C for 10 h, the mixture was diluted with 30 mL of water and extracted three times with diethyl ether (50 mL each). The combined extracts were washed with 30 mL of brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 1.10 g (83% yield) of **21**: ^{1}H NMR δ 6.49 (d, J = 2.8 Hz, 1 H, Ar, C4-H), 6.30 (d, J = 2.8 Hz, 1 H, C6-H), 1.04−0.97 (broad s, 27 H, *t*-Bu), 0.18 (s, 6 H, Me), 0.175 (s, 12 H, Me); ^{13}C NMR δ 149.3 (s), 148.6 (s), 138.6 (s), 126.8 (s), 114.6 (d), 112.1 (d), 26.3 (q, *t*-Bu), 25.9 (q, *t*-Bu), 18.9 (s), 8.8 (s), −3.5 (q, 2 C, Me), −3.4 (q, 2 C, Me), −4.3 (q, 2 C, Me). Anal. Calcd for $C_{24}H_{47}ClO_3Si_3$: C, 57.27; H, 9.41. Found: C, 57.37; H, 9.55.

5-Bromo-6-chloro-1,2,4-tris(*tert*-butyldimethylsilyloxy)benzene (15). A mixture of 0.65 g (1.3 mmol) of **21** and 0.28 g (1.6 mmol) of *N*-bromosuccinimide in 10 mL of DMF under argon was stirred at 25 °C for 5 days. The reaction mixture was diluted with 30 mL of water, extracted three times with diethyl ether (50 mL each), and the combined extracts were washed with 30 mL of water, and 30 mL of brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent gave 0.51 g (67% yield) of **15**: ^{1}H NMR δ 6.41 (s, 1 H, Ar, C3-H), 1.03 (s, 9 H, *t*-Bu), 1.02 (s, 9 H, *t*-Bu), 0.97 (s, 9 H, *t*-Bu), 0.23 (s, 6 H, Me), 0.22 (s, 6 H, Me), 0.18 (s, 6 H, Me); ^{13}C NMR δ 147.3 (s), 147.2 (s), 139.4 (s), 128.3 (s), 111.1 (d), 108.4 (s), 29.9 (q, *t*-Bu), 26.3 (q, *t*-Bu), 26.2 (q), 26, 18.9 (s), 18.6 (s), −3.3 (q, Me), −3.4 (q, Me), −3.5 (q, Me), −4.0 (q). Anal. Calcd for $C_{24}H_{46}BrClO_3Si_3$: C, 49.51; H, 7.96. Found: C, 49.78; H, 8.11.

2-Bromo-3-chloro-4,5-bis(*tert*-butyldimethylsilyoxy)-phenol (23). A solution of 50 mg (0.12 mmol) of **20** and 23 mg (0.12 mmol) of NBS in 2 mL of DMF under argon was stirred at 25 °C for 1 day. The reaction mixture was diluted with 30 mL of water and extracted three times with diethyl ether (40 mL each), and the combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to give 42 mg (70% yield) of **23**. This material was used in next step without purification: ^{1}H NMR δ 6.53 (s, 1 H, Ar, C6-H), 1.03 (s, 9 H, *t*-Bu), 0.96 (s, 9 H, *t*-Bu), 0.22 (s, 6 H, Me), 0.17 (s, 6 H, Me); ^{13}C NMR δ 148.3 (s), 147.4 (s), 138.8 (s), 127.0 (s), 106.9 (d), 102.9 (s), 26.2 (q, *t*-Bu), 18.8 (s), −3.3 (q, Me), −3.5 (q, Me). HRMS calcd for $C_{18}H_{32}BrClSi_2O_3$ (M + H) 471.0791, found 471.0780.

Preparation of 15 from Silylation of 23. To a mixture of 42 mg (90 μmol) of **23**, 16 mg (0.11 mmol) of *tert*-butyldimethylsilyl chloride, and 3 mg (10 μmol) of DMAP in 2 mL of dichloromethane under argon at 25 °C was added 50 μL (0.26 mmol) of triethylamine. The reaction mixture was stirred for 3 h, diluted with 30 mL of water, and extracted three times with diethyl ether (30 mL each). The combined ether extracts were with 30 mL of brine, dried ($MgSO_4$), and concentrated to give 51 mg (99% yield) of **15**.

2-Bromo-5-chloro-1,3,4-tris(*tert*-butyldimethylsilyloxy)-benzene (22). A solution of 0.10 g (0.20 mmol) of **21** and 0.035 g (0.20 mmol) of NBS in 2 mL of DMF under argon was stirred at 50 °C for 2 day. The solution was diluted with 30 mL of water and extracted three times with diethyl ether (30 mL each), and the combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane and diethyl ether (100:1) as an eluent to give 31 mg (27% yield) of **15** and 63 mg (54% yield) of **22**. Compound **22**: ^{1}H NMR δ 6.54 (s, 1 H, Ar, C6-H), 1.03 (s, 18 H, *t*-Bu), 0.97 (s, 9 H, *t*-Bu), 0.23 (s, 12 H, Me), 0.17 (s, 6 H, Me). Anal. Calcd for $C_{24}H_{46}BrClO_3Si_3$: C, 49.51; H, 7.96. Found: C, 49.73; H, 8.07.

(4a*S*,6a*R*,12b*S*)-2*H*-9,10-Bis(*tert*-butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene (4) and (4a*S*,6a*S*,12b*S*)-2*H*-9,10-Bis(*tert*-butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene (6). In a dried flask was placed 2.60 g (4.5 mmol) of bromide **15**,which was dried by adding 1 mL of freshly distilled toluene (distilled over sodium) followed by evaporation under vacuum. This addition-evaporation of toluene process was repeated and maintained under argon. To it was added 25 mL of dried diethyl ether, cooled to −78 °C, and 2.7 mL (4.50 mmol) of *t*-BuLi (1.7 M in pentane) was added via syringe. After 0.5 h of stirring at −78 °C, a solution of 0.82 g (3.7 mmol) of aldehyde **7** in 10 mL of diethyl ether (−78 °C) was added via cannula, and the resulting solution was stirred at −78 °C for 10 min and 25 °C for 1 h (the reaction was monitored by TLC). The reaction solution was diluted with 10 mL of saturated aqueous NH_4Cl and extracted three times with diethyl ether, and the combined extracts were washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and toluene and then hexane and ether as eluents to give 0.98 g (45% yield) of **4** and 0.20 g (9.1% yield) of **6**. Compound **4**: $[\alpha]^{22}_D$ = +56° (*c* 3.3, $CHCl_3$); ^{1}H NMR δ 6.43 (s, 1 H, C8-H), 6.28 (s, 1 H, C12-H), 2.18 (d, J = 12 Hz, 1 H), 2.02 (d, J = 12 Hz, 1 H), 1.90−1.00 (a series of m, 9 H), 1.37 (s, 3 H, Me), 1.16 (s, 3 H, Me), 1.03 (s, 9 H, *t*-BuSi), 0.95 (s, 9 H, *t*-BuSi), 0.92 (s, 3 H, Me), 0.87 (s, 3 H, Me), 0.21 (s, 3 H, MeSi), 0.20 (s, 3 H, MeSi), 0.17 (s, 9 H, MeSi), 0.16 (s, 3 H, MeSi); ^{13}C NMR δ 151.3, 147.3, 146.1, 138.1, 123.6, 115.7, 111.7, 107.9, 78.0, 52.4, 41.8, 41.7, 39.5, 38.2, 33.8, 33.6, 26.4 (3 C, *t*-Bu), 26.3 (3 C, *t*-Bu), 26.1, 23.7, 21.9, 19.5, 19.1, 18.9, −3.2, −3.46, −3.49, −3.6. Anal. Calcd for $C_{33}H_{55}ClO_3Si_2$: C, 67.02; H, 9.37. Found: C, 67.15; H, 9.53. Compound **6**: white solids, mp 83−85 °C; $[\alpha]^{22}_D$ = +50° (*c* 1.8, $CHCl_3$); ^{1}H NMR δ 6.39 (s, 1 H, C8-H), 6.31 (s, 1 H, C12-H), 2.20−0.90 (m, 11 H), 1.31 (s, 3 H, Me), 1.23 (s, 3 H, Me), 1.03 (s, 9 H, *t*-Bu), 0.96 (s, 9 H, *t*-Bu), 0.95 (s, 3 H, Me), 0.86 (s, 3 H, Me), 0.21 (s, 3 H, MeSi), 0.20 (s, 3 H, Me), 0.18 (s, 3 H, Me), 0.15 (s, 3 H, Me); ^{13}C NMR δ 151.9, 147.5, 146.0, 138.0, 123.8, 116.5, 111.9, 108.0, 78.0, 52.2, 44.1, 42.3, 39.4, 39.1, 34.0, 33.0, 31.1, 26.4 (3 C, *t*-Bu),

26.3 (3 C, *t*-Bu), 26.1, 25.6, 25.1, 23.7, 21.4, 19.2, 18.9, 18.8, 17.6, −3.3, −3.4, −3.5, −3.6. Anal. Calcd for $C_{33}H_{55}ClO_3Si_2$: C, 67.02; H, 9.37. Found: C, 67.11; H, 9.16.

2D NOESY spectra were obtained, and in compound **4**, C6a methyl and C12b methyl have NOE connectivity; however, in compound **6**, C6a methyl and C12b methyl have no NOE connectivity.

(4a*S*,6a*R*,12b*S*)-2*H*-11-Chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene-9,10-diol (3). To a solution of 0.16 g (0.27 mmol) of **4** in 3 mL of THF under argon at 25 °C was added 0.58 mL (0.60 mmol) of tetra-*n*-butylammonium fluoride (1.0 M in THF). After 5 min of stirring at 25 °C, 0.30 mL of acetic acid was added, and the resulting solution was concentrated on a rotary evaporator and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 0.08 g (82% yield) of **3**: $[\alpha]^{22}_D = +0.11°$ (*c* 1.8, CH_2Cl_2); ^{1}H NMR δ 6.42−6.20 (broad s, 3 H, C8H, C12H, and OH), 5.8 (broad s, 1 H, OH), 2.18 (d, $J = 12$ Hz, 1 H), 2.01 (d, $J = 12$ Hz, 1 H), 1.86−0.90 (a series of m, 9 H), 1.42 (s, 3 H, Me), 1.15 (s, 3 H, Me), 0.92 (s, 3 H, Me), 0.87 (s, 3 H, Me); ^{13}C NMR δ 151.3, 147.3, 146.1, 138.1, 123.6, 115.7, 111.7, 107.9, 78.0, 42.3, 41.8, 38.2, 34.0, 33.9, 33.5, 33.0, 21.9, 21.4, 20.9, 19.5, 19.1. Anal. Calcd for $C_{21}H_{27}ClO_3$: C, 69.51; H, 7.50. Found: C, 69.28; H, 7.32.

(+)-Chloropuupehenol (5). To a solution of 60 mg (0.10 mmol) of **6** in 2 mL of THF under argon at 25 °C was added 0.22 mL (0.22 mmol) of tetra-*n*-butylammonium fluoride (1.0 M in THF). After 10 min of stirring at 25 °C, 0.10 mL of acetic acid was added, the solution was concentrated on a rotary evaporator, and the residue was column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 30 mg (81.4% yield) of **5**:[3e] $[\alpha]^{22}_D = +105°$ (*c* 0.3, CH_3OH), lit.[3e] +112° (*c* 0.35, MeOH); MS *m*/*z* 363 (M + 1); ^{1}H NMR δ 6.38 (s, 1 H, C8H), 6.31 (s, 1 H, C12H), 5.36 (broad s, 1 H, OH), 5.03 (broad s, 1 H, OH), 2.20−1.05 (a series of m, 11 H), 1.44 (s, 3 H, Me), 1.23 (s, 3 H, Me), 0.96 (s, 3 H, Me), 0.87 (s, 3 H, Me); ^{13}C NMR δ 151.3, 148.5, 146.1, 133.6, 123.6, 116.5, 110.6, 103.0, 78.0, 43.8, 42.0, 39.1, 33.8, 32.7, 30.8, 30.3, 25.0, 21.2, 20.5, 18.9, 17.2.

(4a*S*,6a*R*,12a*R*,12b*S*)-2*H*-9,10-Bis(*tert*-butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene (26). A mixture of 0.18 g (0.30 mmol) of compound **4** and 0.40 g of 10% palladium/carbon in 7 mL of distilled ethanol was charged with 1 atm of hydrogen gas (by the use of a hydrogen balloon), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered through a short Celite column, the column was washed with ethanol, and the combined filtrate was concentrated and column chromatographed on silica gel using a gradient mixture of hexane and toluene as an eluent to give 0.18 g (99% yield) of **26**: $[\alpha]^{22}_D = +35.6°$ (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 6.23 (s, 1 H, C8H), 2.64 (dd, $J = 17$, 5 Hz, 1 H, C12H), 2.33 (dd, $J = 17$, 12 Hz, 1 H, C12H), 2.02 (dt, $J = 12$, 3 Hz, 1 H), 1.80−1.15 (a series of m, 11 H), 1.12 (s, 3 H, Me), 1.03 (s, 9 H, *t*-Bu), 0.95 (s, 9 H, *t*-Bu), 0.90 (s, 6 H, Me), 0.85 (s, 3 H, Me), 0.194 (s, 3 H, MeSi), 0.191 (s, 3 H, MeSi), 0.17 (s, 3 H, MeSi), 0.15 (s, 3 H, MeSi); ^{13}C NMR δ 147.4, 146.5, 137.4, 126.8, 114.4, 108.2, 76.8, 56.4, 52.2, 42.1, 41.1, 39.4, 37.1, 33.7, 33.4, 26.4 (3 C, *t*-Bu), 26.3 (3 C, *t*-Bu), 25.2, 24.1, 21.8, 20.7, 20.0, 18.9, 18.7, 15.0−3.2 (MeSi), −3.4, −3.5 (2 C). Anal. Calcd for $C_{33}H_{57}ClO_3Si_2$: C, 66.79; H, 9.68. Found: C, 67.15; H, 9.45.

(4a*S*,6a*R*,12aR,12b*S*)-2*H*-11-Chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene-9,10-diol (27). To a solution of 39 mg (66 μmol) of **26** in 2 mL of THF under argon at 25 °C was added 0.20 mL (0.20 mmol) of tetra-*n*-butylammonium fluoride (1 M in THF). The solution was stirred for 30 min, 1 drop of acetic acid was added, and the resulting red solution was concentrated to dryness and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 20 mg (83% yield) of diol **27**: $[\alpha]^{22}_D = +5.6°$ (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 6.35 (s, 1 H, C8H), 5.33 (broad s, 1 H, OH), 5.06 (broad s, 1 H, OH), 2.61 (d, $J = 17$ Hz, 1 H, C12H), 2.34 (m, 1 H, C12H), 2.02 (m, 1 H), 1.80−0.90 (a series of m, 11 H), 1.14 (s, 3 H, Me), 0.91 (s, 6 H, Me), 0.85 (s, 3 H, Me); when the proton NMR spectrum was measured in benzene-d_6 solvent, all methyl groups are separated, δ 0.99 (s, 3 H, Me), 0.77 (s, 3 H, Me), 0.71 (s, 3 H, Me), 0.61 (s, 3 H, Me); ^{13}C NMR (C_6D_6) δ 149.1, 144.0, 134.5, 120.4, 111.3, 104.7, 76.6, 55.9, 51.9, 41.9, 41.0, 39.0, 36.8, 33.4, 33.1, 30.0, 21.6, 19.8, 19.1, 18.7, 14.7; HRMS calcd for $C_{21}H_{30}ClO_3$ (M + H) 365.1885, found 365.1901.

(4a*S*,6a*R*,12aR,12b*S*)-2*H*-11-Chloro-1,3,4,4a,5,6,6a,9,10,12,12a,12b-dodecahydro-4,4,6a,12b-tetramethyl-benzo[*a*]-xanthene-9,10-dione (28). To a solution of 10 mg (0.027 mmol) of diol **27** in 1 mL of dichloromethane under argon at 25 °C was added 3 mg of pyridinium dichromate (PDC). After stirring for 2 h, the mixture was diluted with a small amount of dichloromethane, filtered through Celite, concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 7.7 mg (77% yield) of **28**: $[\alpha]^{22}_D = +16°$ (*c* 0.03, $CHCl_3$); ^{1}H NMR δ 5.80 (s, 1 H, C8H), 2.84 (dd, $J = 20$, 5 Hz, 1 H, C12H), 2.50 (dd, $J = 20$, 13 Hz, 1 H, C12H), 2.11 (dt, $J = 13$, 3 Hz, 1 H), 2.22−0.90 (a series of m, 11 H), 1.33 (s, 3 H), 0.93 (s, 3 H), 0.92 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR δ 178.3, 177.2, 163.8, 155.3, 127.6, 107.2, 75.0, 56.0, 51.0, 41.8, 41.1, 40.5, 38.7, 33.5, 29.9, 21.6, 20.9, 19.8, 19.5, 18.4, 14.8; HRMS calcd for $C_{21}H_{28}ClO_3$ (M + H) 363.1728, found 363.1722.

(4a*S*,6a*S*,12aR,12b*S*)-2*H*-9,10-Bis(*tert*-butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene (29). A mixture of 60 mg (0.1 mmol) of compound **6** and 80 mg of 10% palladium/carbon in 2 mL of distilled ethanol was charged with 1 atm of hydrogen gas (by the use of a hydrogen balloon), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered through Celite and washed with dichloromethane, and the combined filtrate was concentrated and column chromatographed on silica gel using a gradient mixture of hexane and toluene as an eluent to give 54 mg (90% yield) of compound **29** as white solids: mp 67−69 °C; $[\alpha]^{22}_D = -35°$ (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 6.21 (s, 1 H, C8H), 2.75 (d, $J = 18$ Hz, 1 H, C12H), 2.64 (dd, $J = 18$, 8 Hz, 1 H, C12H), 2.10 (d, $J = 11$ Hz, 1 H), 1.85 (d, $J = 12$ Hz, 1 H), 1.62−1.10 (a series of m, 10 H), 1.11 (s, 3 H, Me), 1.03 (s, 9 H, *t*-Bu), 0.95 (s, 9 H, *t*-Bu), 0.89 (s, 3 H, Me), 0.81 (s, 3 H, Me), 0.64 (s, 3 H, Me), 0.20 (s, 3 H, MeSi), 0.18 (s, 3 H, MeSi), 0.16 (s, 3 H, MeSi), 0.157 (s, 3 H, MeSi); ^{13}C NMR δ 148.9, 146.3, 137.3, 126.0, 114.6, 108.4, 75.4, 55.5, 49.7, 42.1, 40.7, 40.3, 38.6, 33.9, 33.5, 27.1, 26.4 (3 C, *t*-Bu), 26.3 (3 C, *t*-Bu), 22.1, 21.9, 18.9, 18.7, 18.5, 14.1, −3.3 (2 C, MeSi), −3.5, −3.6. Anal. Calcd for $C_{33}H_{57}ClO_3Si_2$: C, 66.79; H, 9.68. Found: C, 66.92; H, 9.78.

(4a*S*,6a*S*,12aR,12b*S*)-2*H*-11-Chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene-9,10-diol (30). To a solution of 50 mg (84 μmol) of **29** in 2 mL of THF under argon at 25 °C was added 0.25 mL (0.25 mmol) of tetra-*n*-butylammonium fluoride (1 M in THF). The solution was stirred for 15 min, 1 drop of acetic acid was added, and the resulting red solution was concentrated to dryness and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 10 mg (50% yield) of diol **30**: $[\alpha]^{22}_D = -38.7°$ (*c* 0.45, $CHCl_3$); ^{1}H NMR δ 6.33 (s, 1 H, C8H), 5.24 (broad s, 1 H, OH), 5.01 (bs, 1 H, OH), 2.72 (d, $J = 17$ Hz, 1 H, C12H), 2.64 (dd, $J = 17$, 7 Hz, 1 H, C12H), 1.84 (d, $J = 13$ Hz, 1 H), 1.60−0.90 (a series of m, 11 H), 1.12 (s, 3 H, Me), 0.89 (s, 3 H, Me), 0.81 (s, 3 H, Me), 0.67 (s, 3 H, Me); ^{13}C NMR δ 149.1, 143.1, 133.3, 119.1, 112.4, 103.3, 75.7, 68.2, 55.4, 49.4, 42.1, 40.6, 40.3, 38.5, 33.9, 33.4, 27.1, 22.1, 18.7, 18.4, 14.3; HRMS calcd for $C_{21}H_{30}ClO_3$ (M + H) 365.1885, found 365.1890.

(+)-Chloropuupehenone (1). To a solution of 6 mg (16 μmol) of **30** in 1 mL of dichloromethane under argon at 25 °C was added 12 mg (32 μmol) of PDC. After stirring for 15 min, the solution was filtered through Celite, rinsed with diethyl ether, concentrated, and column chromatographed on silica gel

using a gradient mixture of hexane and diethyl ether as an eluent to give 3 mg (50% yield) of (+)-chloropuupehenone (**1**). The ^{1}H and ^{13}C NMR data are similar to those reported,[3a,3d] and the optical rotation has not been reported previously: $[\alpha]^{22}_D = +137.5°$ (*c* 0.04, $CHCl_3$); MS (CI) *m*/*z* 363, 362 (M + 1 and M^+), 211, 173, 84; ^{1}H NMR δ 7.14 (d, $J = 7$ Hz, 1 H, C12H), 5.84 (s, 1 H, C8H), 2.18 (d, $J = 7$ Hz, 1 H, C12aH), 1.80−0.80 (a series of m, 11 H), 1.24 (s, 3 H, Me), 0.93 (s, 3 H, Me), 0.86 (s, 3 H, Me), 0.82 (s, 3 H, Me); ^{13}C NMR δ 180.0 (C=O), 162.7, 144.4, 141.2, 127.7, 111.1, 105.2, 79.3, 54.9, 54.0, 41.8, 41.2, 40.3, 39.2, 33.9, 33.6, 28.2, 22.2, 18.6, 18.3, 15.4.

(+)- Driman-8α,11-diol [(1*S*,2*R*,4a*S*,8a*S*)-Decahydro-2-hydroxy-2,5,5,8a-tetramethylnaphthalene-1-methanol] (34). To a cold (0 °C) solution of 80 mg (2.1 mmol) of $LiAlH_4$ in 15 mL of diethyl ether under argon was added 1.0 g (4.2 mmol) of aldehyde **14**. After stirring at room temperature for 1 h, the reaction mixture was diluted with aqueous NH_4Cl and extracted three times with dichloromethane. The organic layers were washed with brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (2:1) as an eluent to give 0.98 g (97% yield) of **34**:[14] $[\alpha]^{20}_D = +2.1°$ (*c* 0.5, $CHCl_3$), lit.[14a] +1.6° (*c* 0.63, $CHCl_3$); ^{1}H NMR δ 3.93 (d, $J = 7$ Hz, 2 H, CH_2O), 1.9−0.8 (a series of m, 12 H), 1.35 (s, 3 H, Me), 0.88 (s, 3 H, Me), 0.79 (s, 6 H, 2 Me); ^{13}C NMR δ 75.2, 61.3, 60.7, 56.1, 44.7, 41.9, 40.2, 33.7, 33.5, 31.2, 24.5, 21.8, 20.4, 18.8, 16.2.

[(1*S*,2*R*,4a*S*,8a*S*)-1-(*tert*-Butyldimethylsilyloxymethyl)-decahydro-2,5,5,8a-tetramethylnaphthalen-2-ol] (35). To a cold (0 °C) solution of 0.90 g (3.8 mmol) of diol **34** and 1.0 g (15 mmol) of imidazole in 5.0 mL of DMF under argon was added a solution of 0.62 g (4.1 mmol) of *tert*-butyldimethylsilyl chloride in 6 mL of DMF. After stirring at 25 °C for 2 h, the reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined ethyl acetate layer was washed with brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (10:1) as an eluent to give 1.3 g (98% yield) of **35**: mp 64−65 °C; $[\alpha]^{20}_D = +30.1°$ (*c* 0.73, $CHCl_3$); ^{1}H NMR δ 5.06 (s, 1 H, OH), 3.99 (dd, $J = 10$, 4 Hz, 1 H, CH_2O), 3.89 (t, $J = 10$ Hz, 1 H, CH_2O), 1.84 (dt, $J = 12$, 3 Hz, 1 H), 1.7−0.96 (a series of m, 11 H), 1.30 (s, 3 H, Me), 0.90 (s, 9 H, *t*-Bu), 0.88 (s, 3 H, Me), 0.80 (s, 3 H, Me), 0.79 (s, 3 H, Me); ^{13}C NMR δ 73.2, 62.4, 59.3, 56.1, 43.1, 41.8, 40.4, 37.4, 33.8, 33.4, 26.0 (3 C), 25.1, 21.9, 20.0, 18.8, 18.2, 16.0, −5.4, −5.5; HRMS calcd for $C_{21}H_{43}O_2Si$ (M + H) 355.3034, found 355.3039.

[(1*S*,4a*S*,8a*S*)-1-(*tert*-Butyldimethylsilyloxymethyl)-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalene] (36) and [(1*S*,4a*S*,8a*S*)-1-(*tert*-Butyldimethylsilyloxymethyl)-3*H*-1,4,4a,5,6,7,8,8a-octahydro-2-methylene-5,5,8a-trimethylnaphthalene] (37). To a cold (0 °C) solution of 1.0 g (2.8 mmol) of **35** in 5 mL of THF under argon were added 1.4 g (14 mmol) of triethylamine and 0.48 g (4.2 mmol) of methanesulfonyl chloride. After stirring at 25 °C for 4 h, the reaction mixture was diluted with cold water and extracted three times with ethyl acetate. The combined extract was washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using hexane as an eluent to give 0.42 g (45% yield) of **36** and 0.42 g (45% yield) of **37**.[15] Compound **36**: ^{1}H NMR δ 5.44 (s, 1 H, =CH), 3.76 (dd, $J = 10$, 3.2 Hz, 1 H, CH_2O), 3.60 (t, $J = 10$, 6 Hz, 1 H, CH_2O), 1.95−1.00 (a series of m, 10 H), 1.73 (s, 3 H, Me), 0.88 (s, 12 H, *t*-Bu & Me), 0.85 (s, 3 H, Me), 0.80 (s, 3 H, Me), 0.04 (s, 3 H, Me), 0.03 (s, 3 H, Me); ^{13}C NMR δ 134.6, 122.7, 61.2, 57.2, 50.2, 42.4, 40.0, 36.2, 33.6, 33.2, 26.1, 23.9, 22.3, 22.2, 19.1, 18.3, 14.9, −5.2, −5.3; HRMS calcd for $C_{21}H_{41}OSi$ (M + H) 337.2928, found 337.2939. ^{1}H and ^{13}C NMR spectra of compound **37** are identical with those reported.[15]

(−)-Drimenol (38).[3f] A solution of 0.50 g (1.5 mmol) of **36** and 2.0 mL (2 mmol) of *n*-Bu_4NF (1.0 M in THF) was stirred under argon at 25 °C for 36 h, diluted with aqueous NH_4Cl, and extracted with ethyl acetate twice. The combined extract was washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (5:1) as an eluent to give 0.304 g (92% yield) of **38**:[3f] $[\alpha]^{22}_D = -15°$ (*c* 1.0, $CHCl_3$), lit.[3f] −14° (*c* 0.28, $CHCl_3$); ^{1}H NMR δ 5.54 (m, 1 H, =CH), 3.84 (ddd, 1 H, $J = 11$, 5.2, 3.4 Hz, 1H, CH_2O), 3.75 (dt, $J = 11$, 5.2 Hz, 1 H, CH_2O), 2.02−1.0 (a series of m, 10 H), 1.79 (s, 3 H, Me), 0.89 (s, 3 H, Me), 0.86 (s, 3 H, Me), 0.85 (s, 3 H, Me); ^{13}C NMR δ 133.0, 124.3, 61.2, 57.5, 50.1, 42.4, 40.2, 36.4, 33.6, 33.2, 23.9, 22.4, 22.2, 19.1, 15.3.

(1*S*,4a*S*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde (32) [(+)-Drim-7-en-11-al]. A mixture of 0.30 g (1.35 mmol) of alcohol **38** and 0.858 (2.0 mmol) of Dess−Martin periodinane in 5 mL of dichloromethane under argon was stirred at 25 °C for 2 h, diluted with aqueous $Na_2S_2O_3$, and extracted with diethyl ether three times. The combined extract was washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate/triethylamine (20:1:0.01) as an eluent to give 0.27 g (90% yield) of aldehyde **32**:[6e] $[\alpha]^{22}_D = +23.4°$ (*c* 1.89, $CHCl_3$), lit.[6e] +18.8° (*c* 0.32, $CHCl_3$); ^{1}H NMR δ 9.69 (d, $J = 5$ Hz, 1 H, CHO), 5.69 (m, 1 H, =CH), 2.59 (m, 1 H, C1-H), 2.0 (m, 2 H), 1.7−1.1 (a series of m, 7 H), 1.62 (s, 3 H, Me), 1.07 (s, 3 H, Me), 0.92 (s, 3 H, Me), 0.87 (s, 3 H, Me); ^{13}C NMR δ 206.9, 142.6, 125.7, 49.3, 42.2, 40.6, 37.2, 35.6, 33.5, 33.2, 23.9, 22.3, 21.8, 18.5, 15.9.

(1*S*,4a*S*,8a*S*)-3*H*-2-Methylene-1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethylnaphthalene-1-methanol (39) [(+)-Albicanol]. A similar reaction procedure as that described above (**29**) was followed, and a 93% yield of **39** was obtained: $[\alpha]^{22}_D = +14.0°$ (*c* 1.0, $CHCl_3$), lit.[15b] +13.4° (*c* 0.84, $CHCl_3$); ^{1}H and ^{13}C NMR spectral data are identical to those reported.[15a]

(1*S*,4a*S*,8a*S*)-3*H*-2-Methylene-1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethylnaphthalene-1-carboxaldehyde (31) [(−)-Albicanal]. A mixture of 0.30 g (1.35 mmol) of alcohol **39** and 0.858 (2.0 mmol) of Dess−Martin periodinane in 5 mL of dichloromethane under argon was stirred at 25 °C for 2 h, diluted with aqueous $Na_2S_2O_3$, and extracted with diethyl ether three times. The combined extract was washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane:ethyl acetate (20:1) as an eluent to give 0.27 g (91% yield) of aldehyde **31**:[15b,c] $[\alpha]^{22}_D = -68.3°$ (*c* 1.3, $CHCl_3$), lit.[15c] −69.8° (*c* 3.1, $CHCl_3$); ^{1}H NMR[15d] δ 9.87 (d, $J = 5$ Hz, 1 H, CHO), 4.92 (s, 1 H, =CH), 4.50 (s, 1 H, =CH), 2.45 (m, 2 H), 2.10 (m, 1 H), 1.8−1.0 (a series of m, 9 H), 1.15 (s, 3 H, Me), 0.88 (s, 3 H, Me), 0.86 (s, 3 H, Me); ^{13}C NMR[15d] δ 205.8, 145.3, 109.5, 68.1, 54.2, 42.1, 40.1, 39.2, 36.9, 33.7, 33.6, 23.3, 22.1, 18.9, 16.2.

3,4-Dibenzyloxy-5-chlorobenzaldehyde (40).[22] A mixture of 1.00 (5.8 mmol) of **17**, 2.18 g (12.7 mmol) of benzyl bromide, 0.19 g (1.2 mmol) of KI, and 2.40 g (17.4 mmol) of K_2CO_3 in 100 mL of acetone was heated under reflux for 25 h, cooled to 25 °C, filtered through Celite, concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (10:1) as an eluent to give 1.60 g (78% yield) of **40**:[22] ^{1}H NMR δ 9.83 (s, 1 H, CHO), 7.52 (d, $J = 2$ Hz, 1 H), 7.45 − 7.30 (m, 11 H), 5.18 (s, 2 H), 5.17 (s, 2 H); ^{13}C NMR δ 190.1, 153.7, 150.2, 136.6, 135.9, 132.7, 129.7, 128.9, 128.8, 128.6, 128.5 (2 C), 127.8, 126.1, 111.4, 75.4, 71.5. Anal. Calcd for $C_{21}H_{17}ClO_3$: C, 71.49; H, 4.86. Found: C, 71.24; H, 5.00.

3,4-Dibenzyloxy-5-chlorophenol (42). A mixture of 1.6 g (4.5 mmol) of aldehyde **40** and 1.2 g (6.8 mmol) of 3-chloroperoxybenzoic acid in 20 mL of dichloromethane under argon was heated under reflux for 18 h, cooled to 25 °C, diluted with ethyl acetate, and washed with aqueous $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4) and concentrated to give formate **41**, which was used in the next step without

(22) Kaiser, C.; Colella, D. F.; Pavloff, A. M.; Wardell, J. R. J. *J. Med. Chem.* **1974**, *17*, 1071−1075.

purification. It hydrolyzed on silica gel column to give phenol **42**. Formate **41**: ^{1}H NMR δ 8.24 (s, 1 H), 7.48−7.28 (m, 10 H), 6.85 (d, J = 2.5 Hz, 1 H), 6.73 (d, J = 2.5 Hz, 1 H), 5.09 (s, 2 H), 5.03 (s, 2 H); ^{13}C NMR δ 158.8, 153.6, 145.7, 140.0, 137.0, 136.0, 129.3, 128.8, 128.7, 128.6, 128.5, 128.3, 127.7, 115.1, 106.8, 75.3, 71.6. A solution of crude formate **41** and 0.50 g (3.62 mmol) of K_2CO_3 in 10 mL of methanol was stirred at 0 °C for 1 h, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated to give phenol **42**: ^{1}H NMR δ 7.43−7.30 (m, 10 H), 6.47 (d, J = 2.5 Hz, 1 H, Ar), 6.41 (d, J = 2.5 Hz, 1 H, Ar), 5.06 (s, 2 H), 5.00 (bs, 1 H, OH), 4.97 (s, 2 H); ^{13}C NMR δ 153.7, 152.3, 138.9, 137.2, 136.5, 129.1, 128.9, 128.8, 128.5, 128.3, 128.1, 127.6, 108.8, 101.5, 75.5, 71.2. This material was used in the next step without purification. A small amount of the compound was purified on silica gel column using a gradient mixture of hexane and ethyl acetate as an eluent to give an analytical sample. Anal. Calcd for $C_{20}H_{17}ClO_3$: C, 70.49; H, 5.03. Found: C, 70.13; H, 5.11.

1,2-Dibenzyloxy-3-chloro-5-(*tert*-butyldimethylsilyloxy)-benzene (43). The above crude phenol **42** was dissolved in 15 mL of dichloromethane under argon. To it were added 1.5 g (14 mmol) of triethylamine, 50 mg (0.41 mmol) of 4-(dimethylamino)pyridine, and a solution of 70 mg (4.6 mmol) of *tert*-butyldimethylsilyl chloride in 6 mL of dichloromethane. The mixture was stirred at 25 °C for 8 h, diluted with water, and extracted three times with ethyl acetate. The combined extracts were washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (20:1) as an eluent to give 1.49 g (73% overall yield from compound **40**) of **43**: ^{1}H NMR δ 7.45−7.30 (m, 10 H), 6.48 (d, J = 2.5 Hz, 1 H, Ar), 6.37 (d, J = 2.5 Hz, 1 H, Ar), 5.07 (s, 2 H), 5.00 (s, 2 H), 0.95 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR δ 153.3, 152.1, 139.7, 137.5, 136.7, 128.8, 128.6, 128.4, 128.2, 128.1, 127.5, 126.2, 113.6, 106.2, 75.2, 71.3, 26.1, 25.8 (3 C), −4.4 (2 C). Anal. Calcd for $C_{26}H_{31}ClO_3Si$: C, 68.62; H, 6.87. Found: C, 68.43; H, 7.00.

4-Bromo-3-chloro-1,2-dibenzyloxy-5-(*tert*-butyldimethylsilyoxy)benzene (33). To a solution of 1.40 g (3.08 mmol) of **43** in 20 mL of dichloromethane under argon was added 0.64 mg (3.60 mmol) NBS. The solution was stirred at 25 °C for 8 h, diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (20:1) to give 1.59 g (96% yield) of **33**: ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 2 H), 7.4−7.30 (m, 8 H), 6.42 (s, 1 H, Ar), 5.08 (s, 2 H), 5.00 (s, 2 H), 1.00 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR δ 151.9, 149.9, 141.6, 140.6, 137.2, 136.4, 130.4, 128.8, 128.7, 128.5, 128.3, 128.2, 127.3, 105.9, 75.3, 71.5, 26.1, 25.9 (3 C), −4.1 (2 C). Anal. Calcd for $C_{26}H_{30}BrClO_3Si$: C, 58.48; H, 5.66. Found: C, 58.81; H, 5.74.

(1*S*,4a*S*,8a*S*)-1-[(3,4-Dibenzyloxy-6-*tert*-butyldimethylsilyloxy-2-chlorophenyl)-hydroxymethyl]-3*H*-2-methylene-1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethylnaphthalene (44). To a cold (−78 °C) solution of 0.83 g (1.55 mmol) of bromide **33** in 5 mL of diethyl ether under argon was added 0.88 mL (1.50 mmol) of *t*-BuLi (1.7 M in *n*-pentane). After the solution was stirred for 30 min, a solution of 0.30 g (1.36 mmol) of (−)-albicanal (**31**) in 2 mL of diethyl ether was added via cannula. The solution was stirred at −78 °C for 2 h, diluted with aqueous NH_4Cl, and extracted with diethyl ether three times. The combined extracts were washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (20:1) as an eluent to give a total of 0.82 g (89% yield) of **44** as a mixture of two isomers at C15 (follows chloropuupehenone's numbering system). A partial separation was achieved from the above chromatography. The less polar isomer: $[\alpha]^{22}_D$ = −17.1° (*c* 1.6, $CHCl_3$); ^{1}H NMR δ 7.46 (m, 2 H), 7.40−7.30 (m, 8 H), 6.27 (s, 1 H, Ar), 5.35 (t, J = 8 Hz, 1 H, CHO), 5.06 (dd, J = 7, 6 Hz, 2 H), 4.96 (s, 2 H), 4.41 (s, 1 H, =CH), 3.83 (s, 1 H, =CH), 2.3−0.9 (m, 12 H), 0.98 (s, 9 H, *t*-Bu), 0.98 (s, 3 H), 0.86 (s, 3 H), 0.85 (s, 3 H), 0.17 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR δ 151.4, 150.4, 149.2, 137.3, 136.5, 129.7, 129.0, 128.7, 128.4, 128.2, 127.9, 127.6, 127.4, 126.7, 126.4, 125.4, 108.7, 107.9, 105.6, 105.4, 75.0, 71.1, 66.8, 55.2, 40.9, 38.1, 33.9, 33.6, 26.0, 25.9, 25.3, 21.7, 21.6, 19.5, 18.3, 15.8, 15.7, −4.1, −4.2. Anal. Calcd for $C_{41}H_{55}ClO_4Si$: C, 72.91; H, 8.21. Found: C, 73.15; H, 8.02. The more polar isomer: $[\alpha]^{22}_D$ = −39.8° (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 7.51 (m, 2 H), 7.38−7.31 (m, 8 H), 6.30 (s, 1 H, Ar), 5.44 (d, J = 10 Hz, 1 H, CHO), 5.10 (s, 2 H), 5.08 (s, 1 H, =CH), 4.99 (s, 2 H), 4.86 (s, 1 H, =CH), 3.11 (d, J = 10 Hz, 1 H), 2.57 (m, 1 H), 2.44 (dt, J = 11, 4 Hz, 1 H), 2.04 (m, 1 H), 1.78 (m, 1 H), 1.4−1.0 (m, 6 H), 0.99 (s, 9 H, *t*-Bu), 0.87 (s, 3 H), 0.83 (s, 3 H), 0.75 (s, 3 H), 0.18 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR δ 151.4, 150.9, 149.1, 147.9, 137.2, 136.5, 136.4, 129.6, 128.6, 128.2, 128.1, 128.0, 127.9, 127.5, 127.4, 127.0, 125.4, 108.0, 105.5, 104.9, 74.9, 71.1, 61.9, 42.5, 41.9, 40.9, 33.9, 33.7, 33.6, 26.0, 25.9, 22.0, 21.6, 19.4, 18.3, 15.7, 15.6, −4.0, −4.1. A mixture of the two diastereomers was used in the following experiment.

(1*S*,4a*S*,8a*S*)-1-[(3,4-Dibenzyloxy-2-chloro-6-hydroxyphenyl)-hydroxymethyl]-3*H*-2-methylene-1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethylnaphthalene (45). To a cold (0 °C) solution of 0.45 g (0.67 mmol) of **44** in 5 mL of THF under argon was added 0.8 mL (0.8 mmol) of *n*-Bu_4NF (1.0 M in THF). After stirring at 0 °C for 4 h, the solution was diluted with diethyl ether, washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (5:1) as an eluent to give 0.35 g (93% yield) of **45** as a mixture of two diastereomers at C15: $[\alpha]^{22}_D$ = −56.1° (*c* 3.1, $CHCl_3$); ^{1}H NMR δ 8.15 (s, 1 H, OH), 7.45−7.3 (m, 10 H), 6.51 (s, 1 H, Ar), 5.60 (d, J = 9 Hz, 1 H, CHO), 5.12 (d, J = 12 Hz, 1 H), 5.10 (s, 1 H, =CH), 5.07 (d, J = 12 Hz, 1 H), 4.93 (d, J = 10 Hz, 1 H), 4.88 (d, J = 10 Hz, 1 H), 4.87 (s, 1 H, =CH), 2.74 (d, J = 9 Hz, 1 H), 2.46 (m, 1 H), 2.08 (m, 1 H), 1.80 (m, 1 H), 1.43−0.7 (m, 8 H), 0.95 (s, 3 H), 0.83 (s, 3 H), 0.76 (s, 3 H); ^{13}C NMR δ 153.1, 151.9, 147.8, 136.9, 136.5, 128.8, 128.6, 128.5, 128.2, 128.0, 127.6, 127.5, 118.6, 110.5, 101.8, 75.0, 73.7, 70.7, 60.2, 51.3, 42.2, 42.0, 40.1, 33.6, 33.5, 33.4, 25.6, 23.0, 22.3, 19.1. Anal. Calcd for $C_{35}H_{41}ClO_4$: C, 74.91; H, 7.36. Found: C, 74.85; H, 7.41.

(4a*S*,6a*S*,12a*S*,12b*S*)-2*H*-9,10-Dibenzyloxy-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-6a-[(phenylseleno)-methyl]-4,4,12b-trimethyl-benzo[*a*]xanthen-12-ol (47) and (4a*S*,6a*S*,12b*S*)-2*H*-9,10-Dibenzyloxy-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-6a-[(phenylseleno)methyl]-4,4,12b-trimethyl-benzo[*a*]xanthene (48). To a cold (−78 °C) solution of 122 mg (0.22 mmol) of diol **45** in 1 mL of dichloromethane under agon were added 76 mg (0.25 mmol) of *N*-(phenylseleno)-phthalimide (**46**) and 0.1 mL (0.023 mmol) of a solution of $SnCl_4$ (0.23 M) in dichloromethane. After stirring for 4 h, the solution was warmed to 0 °C, diluted with aqueous $NaHCO_3$, and extracted with diethyl ether three times. The combined extracts were washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (15:1) to give 62 mg (38% yield) of **47** and 90 mg (56% yield) of **48**. Compound **47**: $[\alpha]^{22}_D$ = −42.3° (*c* 1.25, $CHCl_3$); ^{1}H NMR δ 7.42 − 7.16 (m, 15 H), 6.35 (s, 1 H, Ar), 4.99 (s, 2 H), 4.97 (s, 2 H), 4.82 (d, J = 3 Hz, 1 H), 3.48 (d, J = 13 Hz, 1 H, CHSe), 3.29 (d, J = 13 Hz, 1 H, CHSe), 2.77 (d, J = 3 Hz, 1 H), 2.29 (d, J = 15 Hz, 1 H), 2.0−1.0 (a series of m, 10 H), 0.91 (s, 3 H), 0.80 (s, 3 H), 0.58 (s, 3 H); ^{13}C NMR δ 138.0, 137.4, 136.5, 132.5, 129.1, 128.8, 128.7, 128.5, 128.3, 128.2, 127.8, 126.6, 124.1, 120.4, 117.6, 115.8, 108.3, 101.9, 75.4, 71.0, 62.3, 55.1, 54.8, 41.9, 39.9, 38.6, 37.7, 37.6, 33.9, 33.5, 29.9, 22.2, 18.6, 18.1, 14.7. Anal. Calcd for $C_{41}H_{45}ClO_4Se$: C, 68.76; H, 6.33. Found: C, 69.02; H, 6.07. Compound **48**: ^{1}H NMR δ 7.50−7.15 (m, 15 H), 6.53 (s, 1 H, =CH), 6.28 (s, 1 H, Ar), 4.98 (d, J = 11 Hz, 1 H), 4.95 (s, 2 H), 4.92 (d, J = 11 Hz, 1 H), 3.50 (d, J = 13 Hz, 1 H, CHSe), 3.26 (d, J = 13 Hz, 1 H, CHSe), 2.83 (bd, J = 12 Hz, 1 H), 2.06 (bd, J = 12 Hz, 1 H), 1.80−1.10 (a series of m, 9 H), 1.18 (s, 3 H), 0.91 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR δ 152.3, 149.2, 147.8,

139.3, 137.3, 128.9, 128.7, 128.5, 128.4, 128.1, 127.8, 127.6, 114.1, 112.8, 101.5, 101.3, 75.1, 70.8, 52.4, 41.4, 39.3, 38.1, 37.2, 33.6, 33.2, 29.6, 23.8, 22.7, 21.6, 20.6, 18.8. Anal. Calcd for $C_{41}H_{43}ClO_3Se$: C, 70.53; H, 6.21. Found: C, 70.39; H, 6.05.

(4a*S*,6a*S*,12a*S*,12b*S*)-2*H*-12-Acetoxy-9,10-dibenzyloxy-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-6a-[(phenylseleno)methyl]-4,4,12b-trimethyl-benzo[*a*]xanthene (49). A solution of 50 mg (70 μmol) of **47**, 11 mg (0.11 mmol) of acetic anhydride, 2.0 mg (20 μmol) of 4-(dimethylamino)pyridine, and 22 mg (0.28 mmol) of pyridine in 2 mL of dichloromethane was stirred under argon at 25 °C for 18 h, diluted with water, and extracted three times with ethyl acetate. The combined extracts were washed with 10% aqueous HCl, $NaHCO_3$, water, and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (10:1) as an eluent to give 50 mg (94% yield) of **49**: $[\alpha]^{22}_D = -28.2°$ (*c* 0.55, $CHCl_3$); ^{1}H NMR δ 7.48−7.20 (m, 15 H), 6.38 (s, 1 H, Ar), 6.03 (s, 1 H, CHO), 5.03 (s, 2 H), 4.96 (s, 2 H), 3.49 (d, J = 13 Hz, 1 H, CHSe), 3.10 (d, J = 13 Hz, 1 H, CHSe), 2.24 (m, 1 H), 2.06 (s, 3 H), 1.9−0.8 (a series of m, 11 H), 0.89 (s, 3 H), 0.80 (s, 3 H), 0.64 (s, 3 H); ^{13}C NMR δ 169.7, 153.8, 151.3, 139.1, 137.2, 136.2, 132.0, 131.4, 129.4, 129.1, 128.6, 128.5, 128.2, 128.1, 128.0, 127.5, 126.7, 111.5, 101.3, 78.4, 75.0, 70.8, 64.8, 54.3, 52.8, 41.6, 39.9, 38.0, 37.9, 37.1, 33.8, 33.3, 29.7, 22.0, 21.4, 18.4, 14.7. Anal. Calcd for $C_{43}H_{47}ClO_5Se$: C, 68.11; H, 6.25. Found: C, 67.96; H, 6.65.

(4a*S*,6a*S*,12a*S*,12b*S*)-2*H*-12-Acetoxy-9,10-dibenzyloxy-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene (50). A solution of 30 mg (40 μmol) of **49**, 3.3 mg (20 μmol) of AIBN, and 11 mg (40 μmol) of *n*-Bu_3SnH in 3 mL of toluene was heated under reflux for 15 h, cooled to 25 °C, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (20:1) as an eluent to give 22 mg (91% yield) of **50**: $[\alpha]^{22}_D = -68.8°$ (*c* 0.25, $CHCl_3$); ^{1}H NMR δ 7.44−7.26 (m, 10 H), 6.44 (s, 1 H, Ar), 6.02 (s, 1 H, CHO), 5.06 (s, 2 H), 4.98 (s, 2 H), 2.20 (m, 1 H), 2.12 (m, 1 H), 2.04 (s, 3 H), 1.65−1.05 (a series of m, 10 H), 1.31 (s, 3 H), 0.89 (s, 3 H), 0.81 (s, 3 H), 0.64 (s, 3 H); ^{13}C NMR δ 169.0, 153.0, 151.0, 138.4, 137.3, 136.3, 128.5, 128.2, 128.1, 128.0, 127.5, 127.2, 115.7, 101.6, 75.5, 75.1, 70.8, 62.6, 57.1, 54.8, 41.7, 40.6, 39.6, 37.2, 33.7, 33.3, 27.7, 21.9, 18.4, 18.2, 14.4. Anal. Calcd for $C_{37}H_{43}ClO_5$: C, 72.67; H, 7.19. Found: C, 72.88; H, 7.34.

Conversion of Compound 50 to Tetracyclic Pyran Diol 30. A mixture of 20 mg (33 μmol) of compound **50** and 20 mg of 10% Pd/C in methanol under 1 atm of hydrogen was stirred at 25 °C for 10 h, diluted with ethanol, filtered through Celite, concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (10:1) as an eluent to give 11.6 mg (97% yield) of diol **30**. Spectral data and optical rotation were identical with those described above.

Conversion of Compound 48 to Pyran Diol 30. A solution of 50 mg (72 μmol) of compound **48**, 5.9 mg (36 μmol) of AIBN, and 23 mg (79 μmol) of *n*-Bu_3SnH in 3 mL of toluene was heated under reflux for 15 h, cooled to 25 °C, concentrated to dryness, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (10:1) as an eluent to give 36 mg (92% yield) of (4a*S*,6a*S*,12b*S*)-2*H*-9,10-dibenzyloxy-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene (**54**): ^{1}H NMR δ 7.50−7.30 (m, 10 H), 6.44 (s, 2 H, Ar, =CH), 5.07 (d, J = 12 Hz, 1 H), 5.02 (d, J = 12 Hz, 1 H), 4.95 (s, 2 H), 2.10−0.90 (a series of m, 11 H), 1.00 (s, 3 H), 0.91 (s, 3 H), 0.85 (s, 3 H); HRMS calcd for $C_{35}H_{40}ClO_3$ (M + H) 543.2668, found 543.2701. A mixture of 25 mg (46 mmol) of **54** and 20 mg of 10% Pd/C in 1.5 mL of methanol was stirred under 1 atm of hydrogen at 25 °C for 10 h, diluted with ethanol, filtered through Celite, concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (10:1) as an eluent to give 15 mg (89.5% yield) of diol **30**.

(1*S*,4a*S*,8a*S*)-1-[(3,4-Dibenzyloxy-6-*tert*-butyldimethylsilyloxy-2-chlorophenyl)-hydroxymethyl]-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalene (51). To a cold (−78 °C) solution of 0.900 g (1.69 mmol) of bromide **33** in 8 mL of diethyl ether under argon was added 0.96 mL (1.60 mmol) of *t*-BuLi (1.7 M in *n*-pentane). After the solution was stirred for 1 h, a solution of 0.326 g (1.48 mmol) of aldehyde **32** in 2 mL of diethyl ether was added via cannula. The solution was stirred at −78 °C for 2 h and 0 °C for 30 min, diluted with aqueous NH_4Cl, and extracted with diethyl ether three times. The combined extracts were washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (20:1) as an eluent to give 0.770 g (77% yield) of **51** as a mixture two stereoisomers at C15 (follows chloropuupehenone's numbering system): $[\alpha]^{22}_D = -169°$ (*c* 0.055, $CHCl_3$); MS (electrospray) *m*/*z* 657.20 $(M - H_2O + H)^+$; ^{1}H NMR δ 7.50 (m, 4 H), 7.39−7.30 (m, 6 H), 6.27 (s, 1 H, Ar), 5.57 (m, 1 H, =CH), 5.18 (dd, J = 10, 7 Hz, 1 H, CHO), 5.10 (s, 2 H), 5.01 (d, J = 10 Hz, 1 H), 4.97 (d, J = 10 Hz, 1 H), 3.52 (d, J = 10 Hz, 1 H, OH), 2.73 (m, 1 H), 1.92 (m, 1 H), 1.90 (s, 3 H), 1.40−0.90 (a series of m, 8 H), 0.98 (s, 9 H), 0.89 (s, 3 H), 0.83 (s, 3 H), 0.82 (s, 3 H), 0.16 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR δ 151.4, 150.9, 149.1, 147.9, 137.2, 136.5, 136.4, 128.6, 128.2, 128.0, 127.9, 127.0, 125.4, 108.0, 105.5, 104.9, 74.9, 71.1, 71.0, 61.9, 60.3, 55.2, 42.5, 41.9, 40.9, 33.7, 33.6, 26.0, 25.9, 22.0, 21.6, 19.4, 15.6, −4.0, −4.1. Anal. Calcd for $C_{41}H_{55}ClO_4Si$: C, 72.91; H, 8.21. Found: C, 73.16; H, 8.37.

(1*S*,4a*S*,8a*S*)-1-[(3,4-Dibenzyloxy-2-chloro-6-hydroxyphenyl)-hydroxymethyl]-1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalene (52). A solution of 0.62 g (0.95 mmol) of **51** and 0.22 g (0.95 mmol) of (+)-10-camphorsulfonic acid in 2.5 mL of dichloromethane was stirred at 25 °C for 0.5 h, diluted with aqueous $NaHCO_3$, and extracted with ethyl acetate three times. The combined extracts were washed with brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 0.372 g (73% yield) of diol **52**: $[\alpha]^{22}_D = -110°$ (*c* 0.04, $CHCl_3$); ^{1}H NMR δ 10.30 (s, 1 H, OH; exchanged with D_2O), 7.50−7.25 (m, 10 H), 6.33 (s, 1 H, Ar), 5.64 (m, 1 H, =CH), 5.40 (bs, 1 H, CHO), 5.04 (s, 2 H), 4.91 (s, 2 H), 3.02 (bs, 1 H, OH; exchanged with D_2O), 2.72 (bs, 1 H), 2.20−1.10 (a series of m, 9 H), 1.65 (s, 3 H), 0.98 (s, 3 H), 0.88 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR δ 154.5, 151.8, 136.9, 136.6, 136.4, 132.0, 128.9, 128.5, 128.3, 128.1, 128.0, 127.6, 127.3, 126.2, 116.4, 102.2, 75.2, 73.5, 70.5, 58.2, 50.2, 42.0, 40.2, 38.7, 33.7, 33.1, 23.4, 22.6, 21.6, 18.8, 16.2. Anal. Calcd for $C_{35}H_{41}ClO_4$: C, 74.91; H, 7.36. Found: C, 74.85; H, 7.41.

Tranformation of Compound 52 to 27. To a cold (−78 °C) solution of 60 mg (0.11 mmol) diol **52** in 1 mL of dichloromethane under agon were added 41 mg (0.14 mmol) of *N*-(phenylseleno)phthalimide (**46**) and 55 μL (0.011 mmol) of a solution of $SnCl_4$ (0.20 M) in dichloromethane. After stirring for 4 h, the solution was warmed to 0 °C, diluted with aqueous $NaHCO_3$, and extracted with diethyl ether three times. The combined extracts were washed with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (15:1) to give 30 mg (51% yield) of (4a*S*,6a*R*,12b*S*)-2*H*-9,10-dibenzyloxy-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene (**53**): $[\alpha]^{22}_D = +40.6°$ (*c* 0.19, $CHCl_3$); ^{1}H NMR δ 7.47−7.31 (m, 10 H), 6.53 (s, 1 H), 6.47 (s, 1 H), 5.10 (d, J = 12 Hz, 1 H, CH_2O), 5.06 (d, J = 12 Hz, 1 H, CH_2O), 4.97 (s, 2 H), 2.02 (m, 2 H), 1.80−1.24 (a serious of m, 9 H), 1.41 (s, 3 H), 1.17 (s, 3 H), 0.94 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR δ 149.3, 147.6, 137.5, 136.0, 128.8, 128.7, 128.4, 128.3, 128.2, 127.6, 112.6, 109.9, 109.4, 101.8, 95.6, 80.7, 75.3, 73.3, 71.3, 45.5, 43.1, 41.7, 39.1, 37.8, 33.3, 33.2, 25.4, 25.2, 23.6, 21.9, 19.0. Anal. Calcd for $C_{35}H_{39}ClO_3$: C, 77.40; H, 7.24. Found: C, 77.28; H, 6.95.

A mixture of 20 mg (37 μmol) of **53** and 20 mg of 10% Pd/C in 2 mL of methanol was stirred at 25 °C under 1 atm of

hydrogen for 10 h, diluted with ethanol, filtered through Celite, concentrated, and column chromatographed on silica gel using a mixture of hexane/ethyl acetate (10:1) as an eluent to give 11 mg (83% yield) of **27**.

Biological Studies. The reported procedures for the inhibitory activities of CETP[23a] and L1210 leukemic cells[23b] were followed.

Studies of Cholesterol Absorption. Animals and Diet. Ten male Sprague−Dawley rats (Harlan Sprague Dawley, Inc., Indianapolis, IN) weighing 274.3 ± 7.8 were housed individually in plastic cages in an environmentally controlled room of illumination (12:12-h light/dark cycle with the dark period from 0330 to 1530), humidity (60−70%), and temperature (22−25 °C) throughout the study. Rats had free access to deionized water and a nutritionally adequate diet containing soybean oil as the fat source and egg white as the protein source. The diet was formulated according to the AIN-93G recommendations.[24,25] Animals were cared for in an animal care facility accredited by the American Association for the Accreditation of Laboratory Animal Care. Rats were maintained in accordance with the policies and guidelines for animal care and use procedures of the Kansas State University Institutional Animal Care and Use Committee.

Mesenteric Lymph Duct Cannulation. At 6 weeks, rats were starved overnight for 17 h but allowed water ad libitum prior to the surgical placement of a lymph cannula and duodenal infusion catheter. The mesenteric lymph duct was cannulated as described previously.[26] Briefly, while rats were under anesthesia (2.0% halothane in 2.0 L O_2/min delivered via a halothane vaporizer), a midline abdominal incision was made. The superior mesenteric lymph duct was cannulated with polyethylene tubing (SV.31 tubing, i.d. 0.50 mm, o.d. 0.80 mm; Dural Plastics, Auburn, Australia). The cannula was fixed in place with ethyl cyanoacrylate glue (Elmer's Products, Columbus, OH) and externalized through the right flank. An indwelling infusion catheter (Silastic laboratory tubing, i.d. 1.0 mm, o.d. 2.2 mm; Dow Corning, Midland, MI) was introduced via the gastric fundus into the upper duodenum and secured in place with a purse-string suture (4−0 silk, Ethicon, Somerville, NJ) around the fundic incision. The infusion catheter was exteriorized alongside the lymph cannula. After the abdominal incision was closed, the rats were placed in restraining cages and housed in a recovery chamber at 30 °C for postoperative recovery for 22−24 h. During the recovery period, rats were infused continuously with glucose in phosphate-buffered saline (PBS) (in mmol/L: 277 glucose, 6.75 Na_2HPO_4, 16.5 NaH_2PO_4, 115 NaCl, and 5 KCl; pH 6.7) via the infusion catheter at 3.0 mL/h by a syringe pump (Harvard Apparatus, model 935, South Natick, MA) to ensure adequate hydration and nutritional status of the animals.

Determination of Lymphatic ^{14}C-Cholesterol Absorption. After postoperative recovery, each rat was infused with a lipid emulsion containing compound **3** at 3 mL/h for 8 h via the duodenal catheter in subdued light. The lipid emulsion consisted of 451.8 μmol of triolein (95%, Sigma Chemical, St. Louis, MO), 33.3 kBq [4-^{14}C]-cholesterol (^{14}C-CH; specific activity, 1.85 GBq/mmol, American Radiolabeled Chemicals, St. Louis, MO), 20.7 μmol of cholesterol, 3.1 μmol of α-tocopherol (all-rac-*dl*-α-tocopherol, 97%, Aldrich Chemical, Milwaukee, WI) as an antioxidant, and 396.0 μmol of sodium taurocholate (Sigma Chemical, St. Louis, MO) in 24 mL of PBS buffer with or without 114.9 μmol of compound **3** (41.9 mg) (Table 2). Lipid emulsion was prepared under a gentle N_2 stream and subdued light for 55 min using a microprocessor-controlled untrasonicator equipped with a microtip (XL-2020 Ultrasonic Liquid Processor, Misonix, Farmingdale, NY). During the duodenal infusion of lipid infusion, the lymph samples were collected hourly in preweighed ice-chilled centrifuge tubes containing 4 mg of Na_2-EDTA and 30 μg of *n*-propyl gallate (Sigma Chemical, St. Louis, MO) as antioxidants. The hourly lymph samples (100 μL) were mixed with scintillation liquid (ScintiVerse; Fisher Scientific, Fair Lawn, NJ) and counted by scintillation spectrometry (Beckman LS-6500; Beckman Instruments, Fullerton, CA). The total ^{14}C-radioactivity appearing in hourly lymph volume (the hourly rates of ^{14}C-CH absorption) was expressed as a percentage of the total radioactivity infused (% dose). All samples were ice chilled and handled in subdued light.

TABLE 2. Composition of Lipid Emulsion in 24 mL of PBS Buffer (pH, 6.7)

ingredients	amount (μmol/rat/8 h)
cholesterol labeled with ^{14}C (^{14}C-CH)[a]	20.7
triolein (oleic acid)	451.8
α-tocopherol	3.6
sodium taurocholate	396.0
compound **3**	114.9

[a] Results of the inhibition of cholesterol absorption are summarized in Figure 2.

Fatty Acid Analysis. For oleic acid analysis, total lipids from lymph were extracted with a chloroform/methanol mixture. Then the lipid extracts were hydrolyzed with methanolic NaOH, and fatty acids were saponified and methylated simultaneously with BF_3−methanol.

The fatty acid methyl esters (FAME) were analyzed by capillary gas chromatography (Hewlett-Packard, Model 6890, Palo Alto, CA) using a HP-INNOWax cross-linked poly(ethylene glycol) phase capillary column (15 m, i.d. 0.53 mm; Resteck Corp., Bellefonte, PA).

Statistical Analysis. All statistical analyses were performed using PC SAS (SAS Institute, Cary, NC). Repeated measures ANOVA and the least significance difference were used to compare group means. The level of significance was determined at $P < 0.05$.

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