A class of novel compounds is described for use in affecting the absorption of cholesterol.

Class of novel compounds: 

Absorption compounds affecting cholesterol

Inventors: Duy H. Hua, Sung I. Koo, Sang K. Noh

Assignee: Kansas State University Research Foundation

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Abstract:

A class of novel compounds is described for use in affecting lymphatic absorption of cholesterol. Compounds of particular interest are defined by Formula I:

![Chemical Structure](image_url)

or a pharmaceutically acceptable salt thereof.

51 Claims, 4 Drawing Sheets
OTHER PUBLICATIONS


FIG. 1

$^{14}$C-CH absorption (% dose/h)

- Control
- Compound I

Time (h)

1 2 3 4 5 6 7 8
FIG. 2

Oleic acid output (μmol/h)

Control

Compound I

Time (h)

0 30 60 90 120 150

1 2 3 4 5 6 7 8

*
FIG. 3

[Graph showing inhibition (%) on the y-axis and concentration on the x-axis. Two lines labeled '1st' and '2nd' are plotted.]
FIG. 4

Concentration (µM)

Inhibition (%)

Concentration (µM)

Ferroverdin A
1

COMPOUNDS AFFECTING CHOLESTEROL ABSORPTION

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

Funding for the work described above herein was provided in part by the federal government, which may have certain rights in the invention. This application was supported by government funding from the following agencies: NASA under grant number NCC8-131, National Institute of Health under grant number CA86842, and National Science Foundation under grant number 0078921.

TECHNICAL FIELD

This invention relates to novel organic compound and methods for their synthesis. More particularly, the invention relates to novel compounds affecting lymphatic absorption of cholesterol.

BACKGROUND

Atherosclerosis is a major cause of heart attack, stroke, and gangrene of the extremities and can be attributed directly to having high levels of cholesterol in the body. Cholesterol can enter the body by absorption from foods by the intestinal mucosal cells and the lymphatic system (i.e., exogenous sources). Cholesterol also is produced in the liver by a sequence of enzymatic reactions (i.e., endogenous biosynthesis). Endogenous biosynthesis of cholesterol involves a key enzyme, HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase. HMG-CoA reductase inhibitors can be used to lower total plasma cholesterol and LDL cholesterol levels in patients with primary hypercholesterolemia. Effective inhibition of HMG-CoA reductase is realized by drugs such as Lovastatin (sold as Mevacor from Merck Co.), Mevalotin (40-hydroxyLovastatin, sold as Mevalon fromevaCo.,” Mevalotin, and Pravastatin). Exogenous sources of cholesterol, however, are not affected by these drugs. Various compounds have been reported to be useful for lowering cholesterol absorption. Sec, e.g., U.S. Pat. Nos. 5,246,960, 5,175,186, 5,215,972, 5,495,048, 5,856,503, and 5,637,771. Currently, a lipase inhibitor termed Xenical® has been approved for obesity management. Xenical® has been reported to achieve a slight reduction in cholesterol.

SUMMARY

The invention features a compound of Formula I:

R₅ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkyloxyl, aryloxyl, N-alkylsulfonyl, N,N-dialkylsulfonyl, N-arlylsulfonyl, N-alkyl-N-aryl sulfonyl, carboxy, carboxyalkyl, alkylocarbonyl, alkylocarbonylalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N,N-dialkylamido, N-monoaryl amido, N-alkyl-N-aryl amido, N-alkyl-N-hydroxy amido, N-alkyl-N-hydroxy amidoalkyl, amidoalkyl, aminoalkyl, alkanaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, aclyoxy, arlyloxyl, acylamino, amino, cyano, nitro, sulfonate, alkylosil, phenylselenenyl, thiol, aryloxyl, alkyloxyl, aryloxyl, or alkylsilyloxy.

R₆ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkyloxyl, aryloxyl, N-alkylsulfonyl, N,N-dialkylsulfonyl, N-arlylsulfonyl, N-alkyl-N-aryl sulfonyl, carboxy, carboxyalkyl, alkylocarbonyl, alkylocarbonylalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N,N-dialkylamido, N-monoaryl amido, N-alkyl-N-aryl amido, N-alkyl-N-hydroxy amido, N-alkyl-N-hydroxy amidoalkyl, amidoalkyl, aminoalkyl, alkanaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, aclyoxy, arlyloxyl, acylamino, amino, cyano, nitro, sulfonate, alkylosil, phenylselenenyl, thiol, aryloxyl, alkyloxyl, aryloxyl, or alkylsilyloxy.

R₇ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkyloxyl, aryloxyl, N-alkylsulfonyl, N,N-dialkylsulfonyl, N-arlylsulfonyl, N-alkyl-N-aryl sulfonyl, carboxy, carboxyalkyl, alkylocarbonyl, alkylocarbonylalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N,N-dialkylamido, N-monoaryl amido, N-alkyl-N-aryl amido, N-alkyl-N-hydroxy amido, N-alkyl-N-hydroxy amidoalkyl, amidoalkyl, aminoalkyl, alkanaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, aclyoxy, arlyloxyl, acylamino, amino, cyano, nitro, sulfonate, alkylosil, phenylselenenyl, thiol, aryloxyl, alkyloxyl, aryloxyl, or alkylsilyloxy.

R₈ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkyloxyl, aryloxyl, N-alkylsulfonyl, N,N-dialkylsulfonyl, N-arlylsulfonyl, N-alkyl-N-aryl sulfonyl, carboxy, carboxyalkyl, alkylocarbonyl, alkylocarbonylalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N,N-dialkylamido, N-monoaryl amido, N-alkyl-N-aryl amido, N-alkyl-N-hydroxy amido, N-alkyl-N-hydroxy amidoalkyl, amidoalkyl, aminoalkyl, alkanaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, aclyoxy, arlyloxyl, acylamino, amino, cyano, nitro, sulfonate, alkylosil, phenylselenenyl, thiol, aryloxyl, alkyloxyl, aryloxyl, or alkylsilyloxy.

In some embodiments, R₅ is halo, R₆ and R₇ are hydroxy, and R₈ and R₉ are alkyl in the compound, e.g., R₈ is chloro and R₉ and R₁₀ are methyl. In other embodiments, R₅ is halo, R₆ and R₇ are alkylsilyloxy, and R₈ and R₉ are alkyl, e.g., R₈ is chloro, R₉ and R₁₀ are Os-i-tBuMe₂, and R₆ and R₇ are methyl. In one embodiment, the compound has Formula (24):
In some embodiments, \( R_1 \) is halo, \( R_2 \) and \( R_3 \) are selected from hydroxy and alkylsilyloxy, and \( R_4 \) and \( R_5 \) are alkyl, e.g., \( R_1 \) is chloro, \( R_2 \) and \( R_3 \) are hydroxy, and \( R_4 \) and \( R_5 \) are methyl. In some embodiments, \( R_1 \) is halo, \( R_2 \) and \( R_3 \) are alkylsilyloxy, and \( R_4 \) and \( R_5 \) are methyl, e.g., \( R_1 \) is chloro, \( R_2 \) and \( R_3 \) are \( \text{OSi-t-BuMe}_2 \), and \( R_4 \) and \( R_5 \) are methyl. In some embodiments the compound has Formula (23):

\[
(23)
\]

The invention also features a compound of Formula IV:

\[
IV
\]

\[
R_1 \text{ can be independently any of the groups described above for } R_1 \text{ of Formula I. } \]

\[
R_2 \text{ can be independently any of the groups described above for } R_2 \text{ of Formula I. } \]

\[
R_3 \text{ can be independently any of the groups described above for } R_3 \text{ of Formula I. } \]

\[
R_4 \text{ and } R_5 \text{ can be independently hydrido, alkyl, or hydroxyalkyl. } \]

\[
R_6 \text{ can be independently hydrido, alkyl, or hydroxyalkyl. } \]

\[
R_7 \text{ can be independently hydrido, hydroxy, or acyloxy. } \]

\[
R_8 \text{ can be independently alkyl, or arylselenylalkyl. } \]

In some embodiments, \( R_1 \) is halo, \( R_2 \) and \( R_3 \) are selected from hydroxy and alkylsilyloxy, \( R_4 \) and \( R_5 \) are alkyl, and \( R_6 \) and \( R_7 \) are methyl. In some embodiments, \( R_1 \) is halo, \( R_2 \) and \( R_3 \) are alkylsilyloxy, and \( R_4 \) and \( R_5 \) are methyl, e.g., \( R_1 \) is chloro, \( R_2 \) and \( R_3 \) are \( \text{OSi-t-BuMe}_2 \), and \( R_4 \) and \( R_5 \) are methyl. In some embodiments the compound has Formula (23):

\[
(24)
\]

The invention also features a compound of Formula II:

\[
(II)
\]

The invention also features a compound of Formula III:

\[
(III)
\]

In these compounds, \( R_1 \) can be independently any of the groups described above for \( R_1 \) of Formula I. \( R_2 \) can be independently any of the groups described above for \( R_2 \) of Formula I. \( R_3 \) can be independently any of the groups described above for \( R_3 \) of Formula I. \( R_4 \) can be independently hydrido, alkyl, or hydroxyalkyl. \( R_5 \) can be independently hydrido, alkyl, or hydroxyalkyl. \( R_6 \) can be independently hydrido, alkyl, or hydroxyalkyl. \( R_7 \) can be independently hydrido, hydroxy, or acyloxy. \( R_8 \) can be independently alkyl, or arylselenylalkyl.
The invention also features a compound of Formula V:

\[
\begin{align*}
\text{R}_1, \text{ can be independently any of the groups described} \\
\text{above for } \text{R}_1 \text{ of Formula I. } \text{R}_2 \text{ can be independently any of} \\
\text{the groups described above for } \text{R}_2 \text{ of Formula I. } \text{R}_3 \text{ can be} \\
\text{independently any of the groups described above for } \text{R}_3 \text{ of} \\
\text{Formula I. } \text{R}_4 \text{ can be independently hydrido, alkyl, or} \\
\text{hydroxyalkyl. } \text{R}_5 \text{ is independently hydrido, alkyl, or} \\
\text{hydroxyalkyl. } \text{R}_6 \text{ can be hydrido. } \text{R}_8 \text{ can be independently} \\
\text{hydroxy, or alkylsilyloxy.} \\
\end{align*}
\]

In some embodiments, \( \text{R}_1 \) is halo; \( \text{R}_2 \) and \( \text{R}_3 \) are aryla-
lkylxy; \( \text{R}_4 \) and \( \text{R}_5 \) are alkyl; \( \text{R}_6 \) is hydroxy; and \( \text{R}_8 \) is
selected from hydroxy and alkylsilyloxy, e.g., \( \text{R}_1 \) is chloro;
\( \text{R}_2 \) and \( \text{R}_3 \) are OBn; and \( \text{R}_4 \) and \( \text{R}_5 \) are methyl; \( \text{R}_6 \) is
hydroxy; and \( \text{R}_8 \) is OSi-tBuMe_. In some embodiments, \( \text{R}_1 \)
is chloro; \( \text{R}_2 \) and \( \text{R}_3 \) are OBn; \( \text{R}_4 \) and \( \text{R}_5 \) are methyl; \( \text{R}_6 \)
is hydroxy; and \( \text{R}_8 \) is hydroxy.

The inventions also features a method of synthesizing a
compound of Formula I:

\[
\begin{align*}
\text{Desilylation of compound (25) forms compound (26).} \\
\end{align*}
\]

wherein \( \text{R}_1 \) is chloro, \( \text{R}_2 \) and \( \text{R}_3 \) are OSi-tBuMe_, The
method further comprises isolating compound (18) and
deprotecting compound (18). The result is a compound of
Formula I.

The invention also features a method of synthesizing (+)
chloropuuphenone. The method comprises hydrogenating
compound (19) to form compound (25).

\[
\begin{align*}
\text{Desilylation of compound (25) forms compound (26).} \\
\end{align*}
\]

wherein \( \text{R}_1 \) is OSi-t-BuMe_, \( \text{X}_1 \) is chloro, \( \text{X}_2 \) is bromo;
Oxidation of compound (26) forms (+)-chloropuupehzone (27).

The invention also features a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of Formula 1:

The composition can be in the form of a capsule or a liquid emulsion. The composition can in a controlled release formulation, e.g., a dispersion in hydroxypropylmethyl cellulose, or in a formulation suitable for parenteral administration, e.g., a lipid emulsion. The composition can comprise a diluent such as polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, or benzyl alcohol. The pharmaceutically-acceptable carrier material can be lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, tallow, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, polyvinylpyrrolidone, or polyvinyl alcohol.

The invention also features a method for identifying a compound that inhibits lymphatic absorption of cholesterol. The method comprises administering a known amount of cholesterol and a compound of claim 1 to a non-human mammal, and determining the amount of administered cholesterol that is absorbed by the lymph. A statistically significant decrease in lymphatic cholesterol absorption relative to the lymphatic cholesterol absorption of a corresponding control mammal indicates that the compound is effective for inhibiting lymphatic absorption of cholesterol. A statistically insignificant change or a statistically significant increase in lymphatic cholesterol absorption relative to the lymphatic cholesterol absorption of a corresponding control mammal indicates the compound does not inhibit lymphatic absorption of cholesterol. The cholesterol and the compound can be administered in a lipid emulsion.

The invention also features a method of treating a cholesterol-related condition. The method comprises administering an effective amount of a compound of Formula I to a mammal. The cholesterol-related condition can be, for example, atherosclerosis, hypercholesterolemia, heart attack, gangrene, and stroke. The compound can be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, or topically, and in an amount from about 4 mg/kg to about 4 g/kg of body weight per day. The compound can be administered in a composition as described above. The method can be part of a treatment regimen comprising a diet low in cholesterol, or as part of a treatment regimen that includes administering an HMG-CoA reductase inhibitors. The method can be used to treat humans. The method can include administering the compound for 7 days or more, e.g., for one year or more. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 is a graph showing hourly rates of lymphatic absorption of cholesterol in lymph-cannulated rats. Values are expressed as means±SD, n=5. *Indicates a significant difference between treatments at p<0.05.

FIG. 2 is a graph showing hourly rates of lymphatic absorption of oleic acid in lymph-cannulated rats. Values are expressed as means±SD, n=5. *Indicates a significant difference between treatments at p<0.05.

FIG. 3 is a graph showing percent inhibition of cholesterol ester transfer protein (CETP) activity in the presence of various concentrations of compound 24. The results from two replicates of the assay are shown.

FIG. 4 is a graph showing percent inhibition of CETP activity in the presence of various concentrations of Ferroverdin A.

DETAILED DESCRIPTION

Compounds of Formula I

A class of compounds useful for inhibiting lymphatic absorption of cholesterol is defined by Formula I:

wherein R₁ is selected from hydrido, halo, alkyl, alkenyl, alkylcyi, haloalkyl, hydroxyalkyl, hydroxy, alkoxy,
Compounds of Formula II

A second class of compounds is defined by Formula II:

\[
R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, R_{58}, R_{59}, R_{60}, R_{61}, R_{62}, R_{63}, R_{64}, R_{65}
\]

wherein \( R_1 \) is selected from moieties described above for \( R_2 \) groups of Formula I, \( R_2 \) is selected from the moieties described above for \( R_3 \) groups of Formula I, \( R_3 \) is selected from the moieties described above for \( R_4 \) groups of Formula I, \( R_4 \) is selected from hydrido, alkyl, and hydroxyalkyl, and \( R_5 \) is selected from hydrido, alkyl, and hydroxyalkyl.

The class of compounds also includes pharmaceutically-acceptable salts thereof.

An exemplary class of compounds includes those compounds of Formula II wherein \( R_1 \) is halo, \( R_2 \) is selected from hydroxy and alkylsilyloxy; \( R_3 \) is selected from hydroxy and alkylsilyloxy; \( R_4 \) is selected from hydrido, alkyl, and hydroxyalkyl; and \( R_5 \) is selected from hydrido, alkyl, and hydroxyalkyl.

A family of specific compounds of particular interest within Formula II consists of compounds and their pharmaceutically acceptable salts as follows:

\[
(4aS,6aS,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benz[a]xanthene-9,10-diol (1);
\]

Compounds of Formula III

A third class of compounds is defined by Formula III:

\[
R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, R_{58}, R_{59}, R_{60}, R_{61}, R_{62}, R_{63}, R_{64}, R_{65}
\]

wherein \( R_1 \) is selected from the moieties described above for \( R_2 \) groups of Formula I, \( R_2 \) is selected from the moieties described above for \( R_3 \) groups of Formula I, \( R_3 \) is selected from the moieties described above for \( R_4 \) groups of Formula I, \( R_4 \) is selected from hydrido, alkyl, and hydroxyalkyl, and \( R_5 \) is selected from hydrido, alkyl, and hydroxyalkyl.

A family of specific compounds of particular interest within Formula III consists of compounds and their pharmaceutically acceptable salts thereof:

An exemplary class of compounds includes those compounds of Formula III wherein \( R_1 \) is halo, \( R_2 \) is selected from hydroxy and alkylsilyloxy; \( R_3 \) is selected from hydroxy and alkylsilyloxy; \( R_4 \) is selected from hydroxy and alkylsilyloxy; and \( R_5 \) is selected from hydroxy and alkylsilyloxy.
within Formula I includes compounds and their pharmaceutically acceptable salts as follows:

(4aS,6aR,12aR,12bS)-2H-9,10-Bis-(1-butylidemethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (21); and

(4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,10-diol (22).

A family of specific compounds of particular interest
within Formula III includes compounds and their pharmaceutically acceptable salts as follows:

(4aS,6aR,12aR,12bS)-2H-9,10-Bis-(1-butylidemethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (40); (4aS,6aR,12aS,12bS)-2H-12-Acetoxy-9,10-bis-(benzoyloxy)-11-chloro-6-phenylselenylmethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,12b-trimethyl-benzol[a]anthrene (41); and (4aS,6aS,12aS,12bS)-2H-12-Acetoxy-9,10-bis-(benzoyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (42).

Compounds of Formula V

A fifth class of compounds is defined by Formula V:

wherein R4 is selected from the moieties described above for R4 groups of Formula I, R5 is selected from the moieties described above for R4 groups of Formula I, R6 is selected from hydrido, alkyl, and hydroxyalkyl, and R7 is selected from hydrido, alkyl, and hydroxyalkyl.

A family of specific compounds of particular interest within Formula V includes the following compounds and their pharmaceutically acceptable salts as follows:

(4aS,8aS)-1-[[2-chloro-3,4-dibenzoyloxy-6-(1-butylidemethylsilyloxy)phenylhydroxymethyl]-2-methylene-5,5,8a-trimethyldecahydronaphthalene (37); and (4aS,8aS)-1-[[2-chloro-3,4-dibenzoyloxy-6-hydroxyphenylhydroxymethyl]-2-methylene-5,5,8a-trimethyldecahydronaphthalene (38).

The term “alkyl” embraces linear or branched saturated aliphatic radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are “lower alkyl” radicals having one to about four carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. The term alkyl also includes cycloalkyl (cyclic) groups (cyclopropyl, cyclopropyl, cyclohexyl, cyclohexyl, cyclooctyl, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups.

A fourth class of compounds is defined by Formula IV:

wherein R1 is selected from the moieties described above for R1 groups of Formula I, R2 is selected from the moieties described above for R1 groups of Formula I, R3 is selected from hydrido, alkyl, and hydroxyalkyl, and R4 is selected from hydrido, alkyl, and hydroxyalkyl.

A family of specific compounds of particular interest within Formula IV includes the following compounds and their pharmaceutically acceptable salts as follows:

(4aS,6aR,12aR,12bS)-2H-9,10-Bis-(1-butylidemethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,10-diol (26); (4aS,6aR,12aS,12bS)-2H-9,10-Bis-(benzoyloxy)-11-chloro-6-phenylselenylmethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,12b-trimethyl-benzol[a]xanthene (40); (4aS,6aR,12aS,12bS)-2H-12-Acetoxy-9,10-bis-(benzoyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (42).
The term alkyl includes both “unsubstituted alkyls” and “substituted alkyls”, the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxyalkyloxy, arylalkyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkylcarbonyloxy, aminoalkylcarbonyl, alkyaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxycarbonyl, phosphoroxy, phosphonato, phosphinato, cyanato, amino (including alkyl amino, dialkylamino, arylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, nitrile, cyanide, seleno, sulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, e.g., with the substituents described above. An “aryalkyl” moiety is an alkyl substituted with an aryl (e.g., phenylethyl or benzyl). The term “n-alkyl” means a straight chain (i.e., unbranched) unsubstituted alkyl group. The term “alkenyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond and must contain at least two carbon atoms. For example, the term “alkeny1” includes straight-chain alkenyl groups (e.g., ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), cyclic alkenyl (cyclic) groups (cyclopropenyn, cyclopentenyn, cyclohexenyn, cycloheptenyn, cyclooctenyn), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl includes both “unsubstituted alkynyls” and “substituted alkynyls”, the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkenyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxyalkyloxy, arylalkyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkylcarbonyloxy, aminoalkylcarbonyl, alkyaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxycarbonyl, phosphoroxy, phosphonato, phosphinato, cyanato, amino (including alkyl amino, dialkylamino, arylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, nitrile, cyanide, seleno, sulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, or an aromatic or heteroaromatic moiety. The term “alkynyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond and two carbon atoms. For example, the term “alkynyl” includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, and one aryl radical. The terms “carboxy” or “carboxyl”, embrace radicals having a carboxylic acid group attached directly to a carbon atom to form a carboxylic acid (—COOH). The term “haloalkyl” includes haloalkyls having two or more halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atom or a combination of different halo radicals. The term “hydroxyalkyl” embraces linear or branched alkyl radicals having one to about ten carbon atoms having one of which may be substituted with one or more hydroxyl radicals. The terms “alkoxy” and “alkoxyalkyl” embrace linear or branched oxy-containing radicals having one alkyl portion of one about ten carbon atoms, such as methoxy radical. The term “alkoxyalkyl” also embraces alkyl radicals having two or more alkyl radicals attached to the alkyl radical, that is, to form monoalkoxy-alkyl and dialkoxyalkyl radicals. The “alkoxy” or “alkoxyalkyl” radicals may be further substituted with one or more halo radicals, such as fluoro chloro or bromo to provide haloalkoxy or haloalkoxyalkyl radicals. Examples of “alkoxy” radicals include methoxy butoxy and trifluoro- methoxy. The term “aryl” alone or in combination, means a carbocyclic aromatic system containing one ring or two rings wherein such rings may be attached together in a pendant manner or may be fused. The term “aryl” embraces aromatic radicals such as phenyl, naphthyl, tetrahydro- napthyl, indane and biphenyl. The term “hetero- cyclic” embraces saturated, partially saturated and unsaturated heterocyclic radicals such as fluorine, chlorine, bromine or iodine atoms. Examples of saturated heterocyclic radicals include pyrroldiol and morpholinyl. The term “heteroaromatic” embraces unsaturated heteroaromatic radicals. Examples of unsaturated heterocyclic radicals, also termed “heteroaryl” radicals, also embrace heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzo[1,2-f]thiophene, benzothiophene, and the like. The term “sulfonyl”, whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals —SO₂—. “Alkysulfonyl”, embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term “arylsulfonyl” embraces sulfonyl radicals substituted with an aryl radical. The terms “sulfonyl” or “sulfonamido”, whether alone or used with terms such as N-alkylsulfonyl, “N-aryl-sulfonyl”, “N,N-dialkylsulfonyl” and “N-aryl-N-alkyl-sulfonyl”, denotes a sulfonaryl radical substituted with an amine radical, forming a sulfonamide (—SO₂NH₂). The terms “N-alkylsulfonyl” and “N,N-dialkylsulfonyl” denote sulfonamide radicals, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms “N-aryl-sulfonyl” and “N-alkyl-N-aryl-sulfonyl” denote sulfonamide radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The terms “carboxyl” or “carboxyl”, whether used alone or with other terms, such as “carboxyalkyl”, denotes —CO₂H. The term “carboxyalkyl” embraces radicals having a carboxy radical as defined above, attached to an alkyl radical. The term “carboxyl”, whether used alone or with other terms, such as “alkylcarbonyl”, denotes —(C=O)—. The term “alkylcarbonyl” embraces radicals having a carboxy radical attached to an alkyl radical. An example of an “alkylcarbonyl” radical is CH₃—(C=O)—. The term “alkylcarbonylalkyl”, denotes an alkyl radical substituted with an “alkylcarbonyl” radical. The term
“alkoxy carbonyl” means a radical containing an alkoxy as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such “alkoxy carbonyl” radicals include (CH₃)₂CO—C(=O)— and —(CH₃)₂C—OCH₃. The term “alkoxy carbonylalkyl” embraces radicals having “alkoxy carbonyl”, as defined above, substituted to an alkyl radical. Examples of such “alkoxy carbonylalkyl” radicals include (CH₃)₂CO—C(=O)CH₃ — and —(CH₃)₂C—OCH₂CH₃. The term “amido” when used by itself or with other terms such as “amidesulfonyl”, “N-monoamidesulfonyl”, “N-monoamidesulfinyl”, “N,N-dialkylamidesulfonyl”, “N,N-dialkylamidesulfinyl”, “N-alkyl-N-arylamido” denote amido radicals substituted with one alkyl radical and with two alkyl radicals, respectively. The terms “N-monoamidesulfonyl” and “N,N-dialkylamidesulfonyl” denote amido radicals which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The term “amidoalkyl” embraces alkyl radicals substituted with amido radicals. The term “amidesulfonylalkyl” embraces alkyl radicals having the nitrogen atom substituted with an alkyl group.

The present invention includes a pharmaceutical composition comprising one or more compounds of Formulae I, II, III, IV, or V in association with one or more pharmaceutically acceptable carriers and/or adjuvants (collectively referred to herein as “carrier” materials) and, if desired, other active ingredients. A compound of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. A compound may, for example, be administered orally, intravenously, intraperitoneally, subcutaneously, intramuscularly or topically. For oral administration, a pharmaceutical composition may be in the form of, for example, a tablet, capsule, emulsion, suspension or solution. A pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, and the desired therapeutic effect. Suitable pharmaceutical compositions may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid. Uncharged organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arolicyclic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, glutamic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylactic, mandelic, embolic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, sulfanilic, cyanocinnamic, salicylamidinocinnamic, hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylthiethylenediamine, chloroprocaine, choline, diethylamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compounds and/or compositions of this invention.

Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aliphatic, cycloaliphatic, aromatic, arolicyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, glutamic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylactic, mandelic, embolic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, sulfanilic, cyanocinnamic, salicylamidinocinnamic, hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.
of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely.

If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, t alc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated, for convenient administration. Capsule or tablet shells can contain, e.g., gelatin, titanium dioxide, and dyes. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Methods

Compounds of Formula I and related compounds can be utilized in the treatment of cholesterol-related conditions in mammals, including humans, dogs and cats. Cholesterol-related conditions include, for example, atherosclerosis, hypertriglyceridemia, hypercholesterolemia, heart attack, stroke, and gangrene of the extremities. A method of treatment includes administering an effective amount of a compound of Formula I. The compound can be administered as a pharmaceutical composition, as described above. A compound of the present invention can be administered by any suitable route, typically in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. A compound may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

The amount of compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors and can be determined by an attending physician. These factors include the age, body weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, the particular compound employed, health status, diet, other medications, and other relevant clinical factors. The amount of compound administered can range from about 4 mg/kg body weight per day to about 4 g/kg body weight per day. For example, a compound can be administered at a daily dosage of 5 mg/kg, 10 mg/kg, 100 mg/kg, 250 mg/kg, 1000 mg/kg, 1500 mg/kg, 2000 mg/kg, or 3000 mg/kg. The daily dosage can be administered once per day, twice per day, three times per day, or four or more times per day. Variations in these dosage levels can be adjusted using standard empirical routines for optimization.

The concentration of a compound of the present invention effective to treat a cholesterol-related condition in a mammal may vary, depending on a number of factors, including the preferred dosage of the compound to be administered, the chemical characteristics of the compounds employed, the formulation of the compound excipients and the route of administration. The optimal dosage of a pharmaceutical composition to be administered may also depend on such variables as the overall health status of the particular patient and the relative biological efficacy of the compound selected. The amount and dosage regimen effective for treating a cholesterol-related condition in a mammal can be determined, for example, by measuring cholesterol levels prior to the start of treatment and at various times after treatment has commenced. Assays for the quantitation of cholesterol are known, including assays for the level of cholesterol in blood or in lymph. Administration of an effective amount results in a decrease in lympathic absorption of cholesterol that is statistically significant at a p<0.05 with an appropriate parametric or non-parametric statistic, e.g., Chi-square test, Student's t-test, Mann-Whitney test, or F-test. In some embodiments, a difference in cholesterol level is statistically significant at p<0.01, p<0.005, or p<0.001.

A compound of the present invention can be administered as a single dose or can be administered for a period of from one day to many years, e.g., for 3 days or more, for 7 days or more, for 14 days or more, for 30 days or more, for one year or more, or for 3 years or more. The duration of the administration period depends upon, e.g., the daily dosage, the type of cholesterol-related condition and the patient's response to the compound.

A compound of the present invention can be administered in conjunction with a diet low in cholesterol as part of a cholesterol lowering treatment regime. A compound of the present invention also can be administered in conjunction with drugs such as Lovastatin (sold as Mevacor from Merck Co.), Mevalotin (from Sankyo Co., Japan), and analogs thereof (e.g., compounds sold under the trade names Sivastatin, Meva, and ganoget, etc.) of the cholesterol levels and to prevent and treat cholesterol-related conditions, e.g., hypercholesterolemia. A compound of the invention also can be administered in conjunction with Xenical®, a prescription medication offered for use in weight loss regimens.


Typically, a method of measuring inhibition of cholesterol absorption in vivo involves administering a predetermined amount of cholesterol and a test compound of Formulae I-V to the intestine of a mammal. Typically, the animal is a fasted mammal. The cholesterol and test compound can be administered in a lipid emulsion into the duodenum of the mammal over a period of a few hours. Suitable non-human mammals include rats, mice, guinea pigs, and hamsters. The amount of administered cholesterol that appears in the mesenteric lymph of the mammal is typically determined at various times during and after administration, typically at hourly intervals. The amount of cholesterol present in the lymph is compared to the amount present in a control animal that has had cholesterol but no test compound administered. If the amount of cholesterol appearing in the lymph of the test animal is statistically significantly less than the amount of cholesterol in the lymph of the control animal, it is concluded that the compound can inhibit intestinal absorption of cholesterol.

General Synthetic Procedures

The compounds of the invention can be synthesized according to the procedures of Schemes 1-6, wherein the R₁-R₆ substituents are as defined for Formulae I-V, above, except where further noted.
Scheme 1 shows the synthesis of enantiopure A-B fragment 3 from commercially available 3αR-(+)-sclareolide 5 (purchased from Aldrich Chemical Company). Deprotonation of optically pure lactone 5 with LDA (lithium diisopropylamide) in THF at -78°C, followed by treatment with MoO₅(pyr.) HMPA complex gave two diastereomers, 6 (65.6% yield) and 7 (12.4% yield) (which were separated by silica gel chromatography), along with 20% recovery of starting sclareolide 5. Treatment of a mixture of 6 and 7 with lithium aluminum hydride in THF at room temperature gave triol 8 (70% yield) and lactol 9 (30% yield). Oxidative cleavage of 8 with lead tetraacetate in benzene at 25°C provided an 90% yield of 10, and oxidative cleavage of 9 under similar conditions gave an 85% yield of 11. Dehydration of alcohol 10 with p-toluenesulfonic acid in refluxing toluene for 2 h gave a 78% yield of enal 3. Basic hydrolysis of the formyl ester group of 11 with potassium carbonate in methanol at 0°C provided a 92% yield of 10, which was converted into 3, as described above. The preparation of compound 3 from (-)-sclareol using a different synthetic method has been reported previously (Reeves, P. G. (1996).

Scheme 2 shows the preparation of D-ring fragment 4 starting from 3-chlorovanillin 12, derived from the chlorination of vanillin with chlorine in acetic acid (85% yield), according to the procedure of Ham et al. (J. Am. Chem. Soc., 1927, 49, 535-7). Demethylation of 12 with BBr₃ in CH₂Cl₂ (94% yield) followed by protection of the diol with tert-butyldimethylsilyl chloride, triethylamine, 4-dimethylaminopyridine (DMAP) gave aldehyde 13 (93% yield) (Jong, T. T.; Williard, P. G.; Porwoll, J. P., J. Org. Chem., 1984, 49, 735-6). Baeyer-Villiger oxidation of 13 with m-chloroperbenzoic acid (MCPBA) in methylene chloride (70% yield) followed by basic hydrolysis with potassium carbonate (90% yield) and silylation of the resulting phenol with potassium carbonate gave aldehyde 14 as the sole product; no C6 isomer 15 was isolated. Interestingly, when the silylation was carried out at 50°C, a 2:1 ratio of 15 and 4 was obtained.

Alternatively, compound 4 was also obtained from the bromination of phenol 16 (obtained from 13 with MCPBA and potassium carbonate) with tert-butyldimethylsilyl chloride (83% yield) provided trisilyl ether 17. Silylation of 17 with tert-butyldimethylsilyl chloride afforded a 99% yield of 4.
Scheme 3 shows a procedure for preparing compounds embraced by Formulae I and II from enantiopure A-B fragment 3 and D-ring fragment 4. Treatment of 4 with 2 equiv of t-BuLi in diethyl ether at -78° C. followed by aldehyde 3 afforded a mixture of two stereoisomers at C6a, 18 (45% yield) and 19 (9.1% yield). Removal of the silyl ether protecting groups of 18 and 19 separately gave compound 1 (82% yield) and compound 2 (81.4% yield), respectively. Spectral data of compound 2 was identical with those reported (Nasu, S. S.; Yeung, B. K. S.; Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M.; Goins, K., J. Org. Chem. 1995, 60, 7290-7292).
Scheme 4 shows the preparation of compounds embraced by Formulae III, IV, and VI. Selective hydrogenation of 18 with 1 atmosphere of hydrogen in the presence of palladium/carbon in ethanol gave a 99% yield of tetracyclic pyran 21 as a single diastereomer (Scheme 4a). Removal of the silyloxy protecting group of 21 with tetra-n-butylammonium fluoride in THF afforded an 83% yield of diol 22.

Oxidation of diol 22 with pyridinium dichromate (PDC) in dichloromethane gave a mixture of quinones 23 and 24 in a ratio of 6:1. Quinone structures 23 and 24 were assigned based on $^1$H NMR spectrum.

Similarly, hydrogenation of 19 with 1 atmosphere of hydrogen and palladium/carbon (90% yield) followed by desilylation with tetra-n-butylammonium fluoride in THF (31% yield) and oxidation with pyridinium dichromate afforded (+)-chloropuupehenone (27) in 50% yield.
Schemes 5 and 6 show a procedure for preparation of C6a-S tetracyclic pyran compounds embraced by Formulae IV and V. Scheme 5 shows the preparation of (1R,4aS,6aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxaldehyde (33) and (1R,4aS,6aS)-2-Methylene-5,5,8a-trimethyl-1,2,3,4,4a,5,6,7,8,8a-decacyclonaphthalene-1-carboxaldehyde (35). Reduction of aldehyde 10 with lithium aluminum hydride in diethyl ether at 0°C produced a 97% yield of diol 28. Silylation of the less hindered primary alcohol of 28 with t-butyldimethylsilyl chloride and imidazole in DMF gave alcohol 29 (98% yield). Elimination of 29 with methanesulfonyl chloride (MsCl) and triethylamine in dichloromethane afforded a mixture of alkenes 30 and 31 (1:1; 90% yield), which were separated by silica gel column chromatography. Desilylation of 30 with tetra-n-butyrammonium fluoride in THF (88% yield) followed by oxidation with Dess-Martin Periodinane in dichloromethane provided aldehyde 33 (67% yield). Similarly, silyl ether 31 was converted to aldehyde 35 under similar reaction conditions.
Referring to synthetic Scheme 6, Bromide 36 was synthesized from the dibenzylzation of 3,4-dihydroxy-5-chlorobenzaldehyde (see Scheme 2) with NaH and benzyl chloride in THF followed by a similar reaction sequence described for the synthesis of 4 from 13. Treatment of bromide 36 with 1.1 equivalent of t-butyllithium in diethyl ether at -78°C, followed by 1 equivalent of aldehyde 35 gave alcohol 37 (62% yield), which was desilylated with n-Bu₄NF in THF to give alcohol 38 (63% yield). Ring closure of 38 with phenylselenylphthalimide and tin tetra-chloride in dichloromethane afforded tetracyclic pyran 40 (50% yield) with the C6a-S configuration. The phenylselenyl reagent approaches C6a exo double bond from the opposite face of C12a alkyl group and C7 oxygen attacks the carbocation from the opposite side of the selenium ion to give 40 as the major product. Acetylation of 40 with acetic anhydride and pyridine in dichloromethane (89% yield) followed by removal of the selenyl function with AIBN (2,2'-azobisisobutyronitrile) and tri-n-butyltin hydride in refluxing toluene gave pyran 42 (90% yield). Removal of the benzyl ether protecting group of 42 with 1 atmosphere of hydrogen and palladium-carbon in methanol provided diol 26, which has identical proton NMR spectrum as that obtained in Scheme 4.
Nuclear magnetic resonance spectra were obtained at 400 MHz for $^1$H and 100 MHz for $^{13}$C in deuteriochloroform, and reported in ppm. Infrared spectra are reported in wave-numbers (cm$^{-1}$). Elemental analysis data were obtained from Desert Analytics, Tucson, Ariz. USA, and are reported as % C and % H. Mass spectra were taken from a Hewlett Packard 5890A Series II, GC-MS. Davvisil silica gel, grade 643 (200–400 mesh), was used for the flash column chromatographic separation. Tetrahydrofuran and diethyl ether were distilled over sodium and benzophenone before use.

The following representative method describes the reduction of 6 and 7 to triol 8 and lactol 9. A solution of 0.90 g (3.4 mmol) of 6 in 20 mL of THF under argon, was added 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 layer was washed with water, and brine, dried (MgSO$_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl ether as eluents to give 0.65 g (65.6% yield) of compound 6 and 0.195 g (12% yield) of compound 7 along with 0.296 g (20% recovery) of compound 8.

5. Compound 6: $\beta$ [$^2$H$_2$, $\alpha$-$\gamma$H] = +97.1° (c 0.01, CHCl$_3$); $^1$H NMR (CDCl$_3$) $\delta$ 4.48 (d, J=12Hz, 1H, CHO, axial), 2.06 (d, J=12Hz, 1H, C$_9$-axial H), 1.95–1.06 (m, 16H), 1.38 (s, 3H, Me), 1.03 (s, 3H, Me), 0.88 (s, 3H, Me), 0.84 (s, 3H, Me); $^{13}$C NMR (CDCl$_3$) $\delta$ 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 7: $\beta$ [$^2$H$_2$, $\alpha$-$\gamma$H] = –7.2° (c 0.008, CH$_2$OH); $^1$H NMR (CDCl$_3$) $\delta$ 5.43 (m, 1H, CHO), 4.06 (dd, J=10, 4Hz, 1H, CHO$_2$), 3.64 (dd, J=10, 4Hz, 1H, CHO$_2$), 1.95 (d, J=4Hz, 1H), 1.70–1.01 (m, 11H), 1.43 (s, 3H, Me), 1.10 (s, 3H, Me), 0.90 (s, 3H, Me), 0.82 (s, 3H, Me); $^{13}$C NMR (CDCl$_3$) $\delta$ 82.9, 75.2, 71.8, 68.8, 47.8, 42.4, 38.4, 36.3, 34.9, 33.7, 33.2, 28.3, 23.0, 21.9, 20.0, 18.5. Compound 9s (as a mixture of 2 diastereomers at C2): $\beta$ [$^2$H$_2$, $\alpha$-$\gamma$H] = +3.6° (c 0.01, CH$_2$OH); $^1$H NMR (CDCl$_3$) $\delta$ 5.38 (broad s, 1H), 5.33 (s, 1H), 4.35 (s, J=5Hz, 1H), 2.5 (broad s, 1H, OH), 1.9–0.9 (m, 12H), 1.49 (s, 3H, Me), 1.09 (s, 3H, Me), 0.86 (s, 3H, Me), 0.84 (s, 3H, Me).

For the 9R isomer, (1S,3aR,5aS,9aS,9bR)–Dodecahydro-3a,6,6,9a-tetramethylnaphthalene-1-carboxaldehyde (10). A solution of 0.65 g (2.4 mmol) of a mixture of triol 8S and 8R in 25 mL of benzene under argon was added 1.3 g (6.3 mmol) of lead tetraacetate. After stirring at 25°C for 4 h, the mixture was diluted with diethyl ether, 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 eluents to give 0.42 g (65.6% yield) of compound 2 along with 0.506 g (20% recovery) of compound 3.
were added. After the solution was refluxed for 2 h, the 

\[ \text{J}=13\text{Hz}, 1\text{H}, \text{2.26 (dd, J}=8, 4\text{Hz, lH), 2.03} \]

using a gradient mixture of hexane and diethyl ether as (CDC\(_1\)) \(6\) 10.43

J=3Hz, 1H, CHO), 2.93 (broad 

37.8, 36.7, 36.4, 33.6, 33.5, 33.2, 21.8, 20.4, 19.1, 18.5. over 30 minutes (with a slow gas flow) at 25° C. White solid 

solution was cooled to 25° C., diluted with saturated aque-

37.5, 33.5, 30.5, 25.4, 21.0, 20.5, 18.3, 17.7. concentrated, and column chromatographed on silica gel 

3.4. In a larger-scale synthesis of 3, the product 

was distilled under reduced pressure to give colorless oil; bp. 60° C./3 \text{mm Hg} (to eliminate trace amount of water), and the 

distilled product was used in next step. [\text{C}]=35.7°, \text{9.25 (C}, 1, \text{CHCl}_3)], \text{1H NMR (CDCl}_3) \text{d} 10.04 (s, 1H, CHO), 2.55 (d, J=13Hz, 1H), 2.26 (dd, J=8, 4 Hz, 1H), 2.03 (s, 2H, Me), 1.70–1.40 (m, 6H), 1.18 (s, 3H, Me), 1.09–0.91 (m, 2H), 0.90 (s, 3H, Me), 0.86 (s, 3H, Me), \text{13C NMR (CDCl}_3) \text{d} 192.8 (C=O), 153.7 (C=O), 143.9 (C=O), 51.8, 41.8, 37.8, 36.7, 36.4, 33.6, 33.5, 33.2, 21.8, 20.4, 19.1, 18.5. 

Preparation of (1R,2R,4aS,8aS)-Decahydro-2-

dihydroxy-2,5,5,8a-tetramethylnaphthalene-1-

carboxaldehyde (11)

To a solution of 0.30 g (1.1 mmol) of lactols 9s and 9R were removed by evaporation on a rotary evaporator, and 

dried in vacuo to give another 0.659 g of 12. 

Example 2

Preparation of (1R,2R,4aS,8aS)-Decahydro-2-

dihydroxy-2,5,5,8a-tetramethylnaphthalene-1-

carboxaldehyde (11)

To a solution of 2.50 g (16.4 mmol) of vanillin in 15 mL of glacial 

acetic acid filtrate was again treated with chlorine gas as above for 

30 minutes to give another 0.659 g of 12. 

The acetic acid filtrate was again treated with chlorine gas as above for 

30 minutes to give another 0.659 g of 12. The white solids were used 

in next step without purification. \text{1H NMR (CDCl}_3) \text{d} 10.04 (s, 1H, CHO), 9.76 (s, 1H, CHO), 7.56 (d, J=1.6Hz, 1H, Ar), 7.37 (d, J=1.6Hz, 1H, Ar), 3.91 (s, 3H, OMe), \text{13C NMR (CDCl}_3) \text{d} 190.5 (C=O), 149.0 (s, 2C), 128.2 (s, 12C), 125.6 (d), 120.1 (s), 109.2 (d), 56.3 (q).

Step 2: Preparation of 5-Chloro-3,4-dihydroxybenzaldehyde

To a solution of 2.00 g (10.7 mmol) of benzaldehyde 12 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, diluted with 40 

mL of methanol, and the solvents were removed on a rotary 

evaporator (the trimethylborate was removed). It was 

added to 40 mL of methanol and methanol and trimethyl borate 

were removed by evaporation on a rotary evaporator, and this 

process was repeated three times. The residue was 

diluted with dichloromethane and filtered and washed with a 

small amount of dichloromethane to give 1.722 g (94% yield) of pure 5-chloro-3,4-dihydroxybenzaldehyde. This 

material was used in next step without purification. \text{1H NMR (CDCl}_3) \text{d} 10.43 (s, 2H, OCH), 9.70 (s, 1H, CHO), 7.42 (d, J=2.0Hz, 1H, C6-H), 7.22 (d, J=2.0Hz, 1H, C2-H), \text{13C NMR (DMSO-d}_6) \text{d} 190.6 (C=O), 148.3 (s), 146.9 (s), 128.4 (d), 124.2 (d), 120.3 (s), 112.5 (s).

Step 3: Preparation of 3,4-bis(t-Butyldimethylsilyloxy)-5-

chlorobenzaldehyde (13)

To a solution of 1.68 g (9.70 mmol) of 5-chloro-3,4-

dihydroxybenzaldehyde and 0.212 g (2.80 mmol) of 

4-dimethylaminopyridine (DMAP) in 20 mL of dichloro-

methane under argon at 0° C. was added 9.80 g (68.0 

mmol) of distilled triethylamine and 4.40 g (59.2 mmol) of t-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\(_4\)Cl was added, and extracted three times with 

1984, 49, 735–6). To a solution of 0.350 g (1.10 mmol) of 

formyloxy-2,5,5,8a-tetramethylnaphthalene 

192.8 (C=O), 153.7 (C=O), 143.9 (C=O), 51.8, 41.8, 37.8, 36.7, 36.4, 33.6, 33.5, 33.2, 21.8, 20.4, 19.1, 18.5.

Step 4: Preparation of (4aS,8aS)-3,4,4a,5,6,7,8,8a-

tetramethylnaphthalene-1-carboxaldehyde (10)

5-Chloro-3,4-dihydroxybenzaldehyde was prepared according to the procedure of Jong et al. (J. Org. Chem.
diethyl ether (80 mL each). The combined extracts were washed with 60 mL of brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluent to give 3.64 g (93% yield). ¹H NMR (CDCl₃) δ 6.977 (s, 1H, CHO), 7.50 (d, J=2.0 Hz, 1H, C6-H), 7.27 (d, J=2.0 Hz, 1H, C2-H), 1.04 (s, 9H, t-Bu), 0.98 (s, 9H, t-Bu), 0.26 (s, 6H, Me), 0.23 (s, 6H, Me). ¹³C NMR (CDCl₃) 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, 3C, t-Bu), 26.0 (q, 3C, t-Bu), 18.7 (s, 2C, t-Bu), -3.4 (q, 2C, Me), -3.6 (q, 2C, Me). 

Example 4

5-Bromo-6-chloro-1,2,4-tris-(t-butyldimethylsilyloxy)benzene

Step 1: Preparation of 3,4-bis-(t-Butyldimethylsilyloxy)-5-chlorophenol

To a solution of 1.236 g (2.97 mmol) of 3,4-bis-(t-butyldimethylsilyloxy)-5-chlorophenol formate 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 (MgSO₄), and concentrated to give 1.028 g (90% yield) of 3,4-bis-(t-butyldimethylsilyloxy)-5-chlorophenol formate: ¹H NMR (CDCl₃) δ 6.45 (d, J=2.8 Hz, 1H), 6.31 (d, J=2.8 Hz, 1H), 1.00 (s, 9H, t-Bu), 0.93 (s, 9H, t-Bu), 0.18 (s, 6H, Me), 0.15 (s, 6H, Me). ¹³C NMR (CDCl₃) δ 149.7 (s), 148.9 (s), 137.7 (s), 126.9 (s), 109.8 (d), 107.8 (d), 26.3 (q, 3C), 26.2 (q, 3C), -3.6 (q, 2C, Me), -3.4 (q, 2C, Me). Anal. Calcd for C₃₃H₂₇ClO₇Si₃: C, 49.51; H, 8.87. Found: C, 49.78; H, 8.11.

Step 2: Preparation of 2-Bromo-3-chloro-4,5-bis-(t-butyldimethylsilyloxy)phenol

A solution of 0.050 g (0.12 mmol) of 17 and 0.023 g (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, extracted three times with diethyl ether (40 mL each), and the combined extracts were washed with brine (30 mL), dried (MgSO₄), and concentrated to give 0.042 g (70% yield). This material was used in next step without purification. ¹H NMR (CDCl₃) δ 6.53 (s, 1H, Ar, C6-H), 1.03 (s, 9H, t-Bu), 0.96 (s, 9H, t-Bu), 0.22 (s, 6H, Me), 0.17 (s, 6H, Me). ¹³C NMR (CDCl₃) 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), -4.0 (q). Anal. Calcd for C₃₃H₂₇BrClO₇Si₃: C, 49.51; H, 8.11. Found: C, 49.78; H, 8.11.
A solution of 0.100 g (0.20 mmol) of 14 and 0.0354 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, extracted three times with diethyl ether (30 mL each), and the combined extracts were washed with brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a mixture of hexane and diethyl ether Calcd for C₃₃H₆₈C₁₀₃S₁₁: c, 67.02; H, 9.37. Found: c, 67.11; H, 9.16.

Example 6

Step 1: Preparation of (4aS,6aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-10-bromo-1,3,4-tris-(t-butyldimethylsilyloxy)benzene

In a dried flask, 2.600 g (4.50 mmol) of bromide 4 was dissolved in 10 mL of diethyl ether (-78° C.) was added via cannula, and the solution of 0.100 g (0.20 mmol) of tert-BuLi (1.7 M in pentane) was added via syringe. After stirring at -78° C. for 0.5 h, a solution of 0.820 g (3.70 mmol) of aldehyde 3 (distilled under reduced pressure) in 10 mL of diethyl ether (-78° C.) was added via cannula, and the resulting solution was stirred at -78° C. for 10 min., 25° C. for 1 h (the reaction was monitored by TLC). The reaction solution was diluted with 10 mL of saturated aqueous NH₄Cl, extracted three times with diethyl ether, and the combined extracts were washed with water, and brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a mixture of hexane and diethyl ether as eluents to give 0.980 g (45% yield) of 18 and 0.200 g (9.1% yield) of 19. Compound 18: [α]D²⁰ = +56° (c 0.033, CHCl₃); ¹H NMR (CDCl₃) δ 6.43 (s, 1H, C8-H), 6.28 (s, 1H, C12-H), 2.18 (d, J=12 Hz, 1H), 2.02 (d, J=12 Hz, 1H), 1.90–1.00 (a series of m, 9H), 1.37 (3H, Me), 1.16 (s, 3H, Me), 1.03 (s, 3H, t-BuSi), 0.95 (s, 3H, t-BuSi), 0.92 (s, 3H, Me), 0.87 (s, 3H, Me), 0.21 (s, 3H, Me), 0.20 (s, 3H, SiMe), 0.17 (s, 3H, MeSi), 0.15 (s, 3H, SiMe); ¹³C NMR (CDCl₃) δ 151.3, 147.3, 146.1, 138.1, 123.6, 115.7, 117.7, 107.9, 78.0, 52.4, 41.8, 37.9, 38.2, 33.8, 33.6, 26.4 (3C, t-Bu), 26.3 (3C, t-Bu), 26.1, 23.7, 19.5, 19.1, 18.9, 3.2, -3.46, -3.49, -3.6. Compound 19: [α]D²⁰ = +50° (c 0.018, CHCl₃); ¹H NMR (CDCl₃) δ 6.39 (s, 1H, C8-H), 6.31 (3H, 1H, C12-H), 2.20–0.90 (m, 11H), 1.31 (3H, Me), 1.23 (3H, Me), 1.03 (3H, t-Bu), 0.96 (s, 9H, t-Bu), 0.95 (s, 3H, Me), 0.86 (s, 3H, Me), 0.21 (s, 3H, Me), 0.20 (s, 3H, Me), 0.18 (s, 3H, Me), 0.15 (s, 3H, Me); ¹³C NMR (CDCl₃) δ 151.9, 147.5, 146.0, 138.0, 123.8, 116.5, 111.9, 108.0, 78.0, 52.2, 44.1, 39.4, 39.1, 34.0, 33.0, 31.1, 26.4 (3C, t-Bu), 26.3 (3C, t-Bu), 26.1, 25.1, 23.7, 21.4, 19.2, 18.9, 18.8, 17.6, -3.3, -3.4, -3.5. Anal. Calc. for C₃₃H₆₈C₁₀₃S₁₁: c, 67.11; H, 9.16.

2D NOESY spectra were obtained and in compound 18, C₆a methyl and C₁₂b methyl have NOE connectivity, however, in compound 19, C₆a methyl and C₁₂b methyl have no NOE connectivity.
tetra-n-butylammonium fluoride (1.0 M in THF). After stirring at 25°C for 10 min., 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 eluent to give 30 mg (81.4% yield) of 2, \( [\alpha]_{D}^2 \) = +1,1 ~

\[ \text{Step 2: Preparation of} \]

using a gradient mixture of hexane and ethyl acetate as

\[ \text{Step 3: Preparation of} \]

(4aS,6aR,12aR,12bS)-2H-1-Chloro-1,3,4,4a,5,6,6a,12,12a-decahydro-4,4,6a,12-tetramethyl-benz[a]xanthene-9,10-dione (22)

To a solution of 39 mg (0.066 mmol) of 21 in 2 mL of THF under argon at 25°C was added 0.20 mL (0.120 mmol) of tetra-n-butylammonium fluoride (1 M in THF). The solution was stirred for 30 min., 1 drop of acetic acid was added, the resulting red solution was concentrated to dryness, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate to give 28 mg (83% yield) of diol 22. \( [\alpha]_{D}^2 \) of NMR (CDCl3) \( \delta \) 6.35 (s, 1H, C8H), 0.31 (s, 3H, Me), 0.08 (s, 3H, Me); \( ^{13}C \) NMR (CDCl3) \( \delta \) 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.

Example 8

(4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,10,12,12a-decahydro-4,4,6a,12-tetramethyl-benz[a]xanthene-9,10-dione (23) and

(4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,9,10,12-decachloro-4,4,6a,12-tetramethyl-benz[a]xanthene-9,10-dione (24)

A mixture of 0.180 g (0.300 mmol) of compound 18 and 0.040 g of 10% palladium/carbon in 7 mL of distilled ethanol was charged with 1 atmosphere 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 Celite column, washed the column with ethanol, and the residue was column chromatographed on silica gel using a gradient mixture of hexane and toluene as eluent to give 180 g (99% yield) of 21. \( [\alpha]_{D}^2 \) = +35.6 ~

\( ^{13}C \) NMR (CDCl3) \( \delta \) 147.4, 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 (2C, t-Bu), 26.3 (3C, t-Bu), 25.2, 24.1, 21.8, 20.7, 20.0, 18.9, 18.7, 15.0 ~

(24)

Example 9

(25)

\( (\cdot)\)-Chloroamphetamine

Step 1: Preparation of (4aS,6aR,12aR,12bS)-2H-9,10-bis-(t-Butyldimethylsiloxyl)-11-chloro-1,3,4,4a,5,6,6a,12,12a-decachloro-4,4,6a,12-tetramethyl-benz[a]xanthene (25)

A mixture of 0.060 g (0.10 mmol) of compound 19 and 0.080 g of 10% palladium/carbon in 2 mL of distilled
ethanol was charged with 1 atmosphere 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, washed with dichloromethane, and the combined filtrate was concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and toluene as eluent to give 0.54 g (90% yield) of compound 25. [α]D = -35° (c 0.007, CHCl3). 1H NMR (CDCl3, δ 6.12 (s, 1H, C8H), 2.72 (d, J=7 Hz, 1H, C12H), 2.64 (dd, J=7, 2 Hz, 1H, C12H), 2.10 (d, J=11 Hz, 1H, 1H), 1.85 (s, J=12 Hz, 1H, 1H), 1.62–1.10 (a series of m, 10H), 1.11 (s, 3H, Me), 1.03 (s, 3H, t-Bu), 0.95 (s, 9H, t-Bu), 0.85 (s, 3H, Me), 0.81 (s, 3H, Me), 0.64 (s, 3H, Me), 0.20 (s, 3H, Me), 0.18 (s, 3H, Me), 0.16 (s, 3H, Me), 0.157 (s, 3H, Me). 13C NMR (CDCl3, δ 148.9, 146.3, 137.3, 126.0, 114.6, 108.4, 75.5, 55.9, 49.7, 43.7, 42.9, 40.3, 39.3, 33.9, 33.4, 32.5, 27.1, 26.4 (SC, t-Bu), 26.3 (SC, t-Bu), 22.1, 21.9, 18.9, 18.7, 18.5, 14.1, -3.3 (SC, Me), -3.5, -3.6. Anal. Caled for C30H52ClO4Si2: C, 66.79; H, 9.68. Found: C, 66.92; H, 9.78.

Step 2: Preparation of (+)-Chloropuupehenone (27)
To a solution of 50 mg (0.084 mmol) of 26 in 25 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 dryness, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate to give 10 mg (50% yield) of diol 26. [α]D = +0.220 (c 0.036, CHCl3); 1H NMR (CDCl3, δ 6.33 (s, 1H, C8H), 3.59 (t, J=7 Hz, 2H, C12H), 2.79 (d, J=7 Hz, 1H, C12H), 2.64 (dd, J=7, 2 Hz, 1H, C12H), 2.02 (s, J=11 Hz, 1H, C12H), 1.84 (d, J=13 Hz, 1H, 1H), 1.60–0.98 (a series of m, 10H), 1.14 (s, Me), 0.81 (s, Me), 0.69 (s, Me). 13C NMR (CDCl3, δ 140.0, 141.1, 134.1, 131.3, 130.9, 127.6, 75.7, 68.2, 55.4, 49.3, 42.3, 40.6, 40.3, 38.5, 38.6, 36.6, 21.3, 18.7, 18.3; 14.3. 1H and 13C NMR spectral data are similar to those reported (Hanann, M. T.; Scheuer, P. J., J. Org. Chem., 1993, 58, 6565–6569).

Example 10
Lymphtic Absorption of Cholesterol
Ten male Sprague-Dawley rats (Harlan Sprague Dawley, Inc., Indianapolis, Ind.) weighing 274.3±7.8 grams 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 (Table 1) containing soybean oil as the fat source and egg white as the protein source. The diet was formulated according to AIN-93G recommendations (In: Trace Elements in Laboratory Rodents (Watson, R. R., ed.), pp. 3–37. CRC Press, Boca Raton, Fla.). 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.

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<th>Ingredient</th>
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<tbody>
<tr>
<td>Egg white</td>
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<tr>
<td>Cornstarch</td>
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</tr>
<tr>
<td>Dextrinized cornstarch</td>
<td>132.0</td>
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<td>Dextrose</td>
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<td>Cellulose</td>
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<tr>
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<tr>
<td>Mineral mix</td>
<td>35.0</td>
</tr>
<tr>
<td>Vitamin mix</td>
<td>10.0</td>
</tr>
<tr>
<td>Biotin (1 mg/kg)</td>
<td>4.0</td>
</tr>
<tr>
<td>Choline biturate</td>
<td>2.5</td>
</tr>
</tbody>
</table>

1Formulated and supplied from Dyets, Bethlehem, PA, according to the recommendations of AIN-93G.
2Contains 0.02% tert-butylhydroquinone.

At 6 wk, 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 in Koo et al., J. Nutr. 131: 717–722 (2001). Briefly, while rats were under anesthesia (2.0% halothane in 2.0 L O2/min delivered via a halothane vaporizer), a midline abdominal incision was made. The superior mesenteric lymph duct was cannulated with polyethylene tubing (SV.3 1 tubing, i.d. 0.50 mm, o.d. 0.80 mm; Dow Plastics, Auburn, Australia). The cannula was fixed in place with ethylene glycol (Elmer’s Products, Columbus, Ohio) and externalized to the right flank. An indwelling infusion catheter (Silastic® laboratory tubing, i.d. 1.0 mm, o.d. 2.2 mm; Dow Coming, Midland, Mich.) was introduced via the gastric fundus into the upper duodenum and secured in place with a purse-string suture (4-0 Silk, Ethicon, Somerville, N.J.) 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 NaH2PO4, 16.5 Na2HPO4, 115 NaCl, and 5 KCl; pH 6.7) via infusion catheter at 3.0 mL/h by a syringe pump (Harvard Apparatus, Model 935, South Natick, Mass.) to ensure adequate hydration and nutritional status of the animals.

After postoperative recovery, each rat was infused with a lipid emulsion at 3 mL/h for 8 h via the duodenal catheter in subdued light. The lipid emulsion consisted of 451.8 μmol triolein (95%, Sigma Chemical, St. Louis, Mo.), 33.5 kBq [14C]-cholesterol (14C-CH3), specific activity, 1.85 GBq/ mmol, American Radiolabeled Chemicals, St. Louis, Mo.),
20.7 μmol cholesterol, 3.1 μmol α-tocopherol (all-rac-dl-α-tocopherol, 97%, Aldrich Chemical, Milwaukee, Wis.) as an antioxidant, and 396.0 μmol sodium taurocholate (Sigma Chemical, St. Louis, Mo.) in 24 mL of PBS buffer, pH 6.5. For half of the rats, the lipid emulsion contained 114.9 μmol compound 1 (41.9 mg). Lipid emulsion was prepared under a gentle N₂ stream and subbed light for 55 min using a microprocessor-controlled ultrasonicator equipped with a microtip (XL-20 Ultrasonic Liquid Processor, Misonix, Farmingdale, N.Y.). During the duodenal infusion of lipid emulsion, lymph samples were collected hourly in preweighed ice-chilled centrifuge tubes containing 4 mg Na₂-EDTA and 30 μg n-propyl gallate (Sigma Chemical, St. Louis, Mo.) as antioxidants. A portion of each lymph sample (100 μL) was mixed with scintillation liquid (ScuriVerse; Fisher Scientific, Fair Lawn, N.J.) and counted by scintillation spectrometry (Beckman LS-6500; Beckman Instruments, Fullerton, Calif.). The total ¹⁴C-radioactivity appearing in hourly lymph volume (the hourly rates of ¹⁴C-CH absorption) was expressed as a percentage of the total radioactivity infused (% dose). All samples were ice chilled and handled in subdued light.

### Fatty Acid Analysis

Total lipids were extracted from each lymph sample with a chloroform/methanol mixture. Lipid extracts were then hydrolyzed with methanolic NaOH, and fatty acids were saponified and methylated simultaneously with BF₃-methanol. Fatty acid methyl esters (FAME) were analyzed by capillary gas chromatography (Hewlett-Packard, Model 6890, Palo Alto, Calif.) using a HP-INNOWax cross-linked polyethylene glycol phase capillary column (15 m, i.d. 0.53 mm; Restek Corp., Bellefonte, Pa.).

### Statistical analysis

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

### Results

Table 2 shows the lymphatic absorption of ¹⁴C-cholesterol and triolein, as well as lymph flow in rats infused for eight hours with lipid emulsion only (control) or containing compound 1. The lymph volume was not significantly different between the two treatments. However, total cholesterol absorption was significantly less in rats infused with compound 1, compared to control rats. In addition, absorption of triolein was significantly less in rats infused with compound 1 compared to control rats. Table 3 and FIG. 1 show the percent dose of ¹⁴C-cholesterol absorbed at hourly intervals. FIG. 2 shows the amount of oleic acid absorbed in the lymph at hourly intervals.

### Example 11

The inhibitory effect of compound 1 on the activity of cholesterol ester transfer protein (CETP) was measured, using a crude CETP preparation derived from hamster plasma. The results suggested that when the dose of compound 1 exceeded 250 μM, there was an increase in HDL total cholesterol, HDL free cholesterol, and HDL cholesterol ester. These increased HDL levels suggest that compound 1 is an inhibitor of CETP activity in vitro.

The effect of compound 24 on inhibition of CETP was tested using a purified CETP preparation. CETP was purified and assayed according to procedures described in Tomada, H.; Tabata, N.; Shinose, M.; Takahashi Y.; Woodruff, H. B.; Omura, S. J. Antibiotics, 52: 1101-1107 (1999). As shown in FIG. 4, there was 50% inhibition (IC₅₀) of CETP activity at 31 μM of compound 24. In comparison, Ferroverdin A, a known CETP inhibitor, resulted in an IC₅₀ of about 22 μM (FIG. 4). The data for compound 24 suggest that compound 24 can inhibit CETP activity in vitro.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

### What is claimed is:

1. A compound of Formula I:

   \[
   \text{R}_1 \text{H} \quad \text{R}_2 \text{H} \quad \text{R}_3 \text{H} \quad \text{R}_4 \text{H} \quad \text{R}_5 \text{H}
   \]

wherein \( \text{R}_i \) is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy,

### TABLE 2

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<tr>
<th>Time (h)</th>
<th>Control</th>
<th>Compound 1</th>
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<tbody>
<tr>
<td>0.5</td>
<td>1.36 ± 0.34</td>
<td>1.78 ± 0.34</td>
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<tr>
<td>1</td>
<td>1.37 ± 0.35</td>
<td>1.78 ± 0.35</td>
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<td>2</td>
<td>1.37 ± 0.36</td>
<td>1.78 ± 0.36</td>
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<td>3</td>
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<td>1.78 ± 0.37</td>
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<td>4</td>
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<td>1.78 ± 0.38</td>
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<tr>
<td>8</td>
<td>1.37 ± 0.42</td>
<td>1.78 ± 0.42</td>
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</table>

Values are means ± SD and cumulative at hourly intervals, n = 5. *Significantly different from control rats (P < 0.05).

### TABLE 3

<table>
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<tr>
<th>Time (h)</th>
<th>Control</th>
<th>Compound 1</th>
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<td>0.5</td>
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<td>1</td>
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<td>1.37 ± 0.36</td>
<td>1.78 ± 0.36</td>
</tr>
<tr>
<td>3</td>
<td>1.37 ± 0.37</td>
<td>1.78 ± 0.37</td>
</tr>
<tr>
<td>4</td>
<td>1.37 ± 0.38</td>
<td>1.78 ± 0.38</td>
</tr>
<tr>
<td>5</td>
<td>1.37 ± 0.39</td>
<td>1.78 ± 0.39</td>
</tr>
<tr>
<td>6</td>
<td>1.37 ± 0.40</td>
<td>1.78 ± 0.40</td>
</tr>
<tr>
<td>7</td>
<td>1.37 ± 0.41</td>
<td>1.78 ± 0.41</td>
</tr>
<tr>
<td>8</td>
<td>1.37 ± 0.42</td>
<td>1.78 ± 0.42</td>
</tr>
</tbody>
</table>

Values are means ± SD and cumulative at hourly intervals, n = 5. *Significantly different from control rats (P < 0.05).

R₃ is independently hydrido, halo, alkyl, alkenyl, alkyloxy, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonam, N-alkyl-N-arylsulfonam, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxyalkylcarbonyl, alkoxyalkylcarbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminooalkyl, alkylaminoalkyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryl, acylamino, amino, cyano, nitro, sulfonate, alkyloxyl, phenylelenylo, thiol, arylsulfonyl, alkylsulfonyl, arylsulfonyl, or arylsilyloxy;

R₄ is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonam, N-alkyl-N-arylsulfonam, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxyalkylcarbonyl, alkoxyalkylcarbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminooalkyl, alkylaminoalkyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryl, acylamino, amino, cyano, nitro, sulfonate, alkyloxyl, phenylelenylo, thiol, arylsulfonyl, alkylsulfonyl, arylsulfonyl, or arylsilyloxy;

R₅ is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonam, N-alkyl-N-arylsulfonam, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxyalkylcarbonyl, alkoxyalkylcarbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminooalkyl, alkylaminoalkyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryl, acylamino, amino, cyano, nitro, sulfonate, alkyloxyl, phenylelenylo, thiol, arylsulfonyl, alkylsulfonyl, arylsulfonyl, or arylsilyloxy;

or a pharmaceutically-acceptable salt thereof.

2. The compound of claim 1, wherein R₅ is halo, R₄ and R₃ are hydroxy, and R₂ and R₁ are alkyl.

3. The compound of claim 2, wherein R₅ is chloro and R₄ and R₃ are methyl.

4. The compound of claim 1, wherein R₅ is halo, R₂ and R₃ are alkylsilyloxy, and R₁ and R₄ are alkyl.

5. The compound of claim 4, wherein R₅ is chloro, R₂ and R₃ are OSi-t-BuMe₃, and R₁ and R₄ are methyl.

6. The compound of claim 1, wherein said compound has Formula (24):

\[
\text{Formula (24):}
\]

7. A compound of Formula II:
The compound of claim 7, wherein R₁ is halo, R₈ and R₉ are hydroxy, and R₁₀ and R₁₁ are alkyl.

The compound of claim 8, wherein said compound has formula (23):
wherein $R_1$ is independently hydrido, halo, alky, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, $N$-alkylsulfamyl, $N,N$-di(alkyl)sulfamyl, carboxy, carboxyalkyl, alkylicarbonyl alkyl, alkylicarbononylalkyl, alkoxycarbonyl, alkoxycarbononylalkyl, amino, $N$-alkylamido, $N,N$-dialkylamido, arylsulfonyl, alkylsulfonyl, alkylsulfonylalkyl, amino, $N$-alkyl-N-arylamido, $N$-alkyl-N-hydroxyamido, $N$-alkylamide, $N,N$-di(alkyl)amide, $N$-alkyl-N-arylamido, $N$-alkyl-N-hydroxyamido, alkylamido, $N$-monoarylamido, $N$-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, amino, cyano, nitro, sulfonate, thiol, arylsulfinyl, alkylthio, alkylsulfonyl, alkylsulfenyl, alkylsulfenylalkyl, phenylselenyl, or alkylsilyloxy;

wherein $R_2$ is independently hydrido, halo, alky, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, $N$-alkylsulfamyl, $N,N$-di(alkyl)sulfamyl, carboxy, carboxyalkyl, alkylicarbonyl alkyl, alkylicarbononylalkyl, alkoxycarbonyl, alkoxycarbononylalkyl, amino, $N$-alkylamido, $N,N$-dialkylamido, arylsulfonyl, alkylsulfonyl, alkylsulfonylalkyl, amino, cyano, nitro, sulfonate, thiol, arylsulfinyl, alkylthio, alkylsulfonyl, alkylsulfenyl, alkylsulfenylalkyl, phenylselenyl, or alkylsilyloxy; and $R_3$ is independently hydrido, halo, alky, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, $N$-alkylsulfamyl, $N,N$-di(alkyl)sulfamyl, carboxy, carboxyalkyl, alkylicarbonyl alkyl, alkylicarbononylalkyl, alkoxycarbonyl, alkoxycarbononylalkyl, amino, $N$-alkylamido, $N,N$-dialkylamido, arylsulfonyl, alkylsulfonyl, alkylsulfonylalkyl, amino, cyano, nitro, sulfonate, thiol, arylsulfinyl, alkylthio, alkylsulfonyl, alkylsulfenyl, alkylsulfenylalkyl, phenylselenyl, or alkylsilyloxy;

$R_4$ is independently hydrido, alkyl, or hydroxyalkyl; $R_5$ is independently hydrido, alkyl, or hydroxyalkyl; $R_6$ is independently hydrido, hydroxy, or acyloxy; and $R_7$ is independently alkyl or arylselenylalkyl; or a pharmaceutically-acceptable salt thereof.

18. The compound of claim 17, wherein $R_1$ is halo; $R_2$ and $R_3$ are selected from hydroxy, alkylsilyloxy, or aralkyloxy; $R_4$ and $R_5$ are alkyl; $R_6$ is selected from hydroxy, hydroxy, or acyloxy; and $R_7$ is selected from alkyl or arylselenylalkyl.

19. The compound of claim 18, wherein $R_1$ is chloro; $R_2$ and $R_3$ are OSi-t-BuMe$_2$; $R_4$ and $R_5$ are methyl; $R_6$ is hydrido; and $R_7$ is methyl.

20. The compound of claim 18, wherein $R_1$ is chloro; $R_2$ and $R_3$ are hydroxy; $R_4$ and $R_5$ are methyl; $R_6$ is hydrido; and $R_7$ is methyl.

21. The compound of claim 18, wherein $R_1$ is chloro; $R_2$ and $R_3$ are aryalkyloxy; $R_4$ and $R_5$ are methyl; $R_6$ is hydroxy; and $R_7$ is arylselenylalkyl.

22. The compound of claim 18, wherein $R_1$ is chloro; $R_2$ and $R_3$ are aryalkyloxy; and $R_4$ and $R_5$ are methyl; $R_6$ is acyloxy; and $R_7$ is arylselenylalkyl.

23. The compound of claim 18, wherein $R_1$ is chloro; $R_2$ and $R_3$ are aryalkyloxy; $R_4$ and $R_5$ are methyl; $R_6$ is acyloxy; and $R_7$ is methyl.

24. A compound of Formula V:
amidoalkyl, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfinyl, alkylsilyl, phenylethynyl, or alkylsilyloxy;

R₃ is independently hydrido, halo, alkyl, alkenyl, alkylaryl, haloalkyl, hydroxalkyl, hydroyk, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, aryloxy, N-alkylsulfamyl, N,N-dialkylsulfamoyl, N-arylsulfonyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxyacarbonyl, alkoxyacarbonylalkyl, amidino, N-alkylamido, N,N-dialkylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxymidoalkyl, amidoalkyl, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfinyl, alkylsilyl, phenylethynyl, or alkylsilyloxy;

R₄ is independently hydrido, halo, or hydroxalkyl; R₅ is independently hydrido, alkyl, or hydroxalkyl; R₆ is hydroxy; and R₇ is independently hydroxy, or alkylsilyloxy;

or a pharmaceutically-acceptable salt thereof.

25. The compound of claim 24, wherein R₁ is halo; R₂ and R₃ are alkylalkoxy; R₂ and R₄ are alkyl; R₅ is hydroxy; and R₆ is selected from hydroxy and alkylsilyloxy.

26. The compound of claim 25, wherein R₁ is chloro; R₂ and R₃ are OBn; and R₄ and R₅ are methyl; R₆ is hydroxy; and R₇ is OSi-t-BuMe₂.

27. The compound of claim 25, wherein R₁ is chloro; R₂ and R₃ are OBn; R₄ and R₅ are methyl; R₆ is hydroxy; and R₇ is hydroxy.

28. A method of synthesizing a compound of Formula I:

29. A method of synthesizing (+)-chloropupehenone comprising:

a) hydrogenating compound (19) to form compound (25);

b) disilylating compound (25) to form compound (26); and

c) deprotecting said intermediate compound.
c) oxidizing compound (26) to form (+) chloropuupehenone (27).
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [75], Inventors, please delete “Wrillimantic” and insert -- Willimantic -- therefor; and please delete “US” and insert -- Korea -- therefor;
Item [56], References Cited, OTHER PUBLICATIONS, “Hamann and Scheuer” reference, please delete “Sesquitepene” and insert -- Sesquiterpene -- therefor.

Signed and Sealed this
Fourth Day of January, 2005

JON W. DUDAS
Director of the United States Patent and Trademark Office