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)

or a pharmaceutically acceptable salt thereof.

51 Claims, 4 Drawing Sheets
OTHER PUBLICATIONS


FIG. 1

- Control
- Compound I

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

Time (h)

1 2 3 4 5 6 7 8
FIG. 3

Graph showing the inhibition percentage versus a logarithmic scale.

- 1st
- 2nd
FIG. 4

Concentration (µM)

Inhibition (%)
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 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 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 (from Sankyo Co., Japan), and analogs thereof (e.g., compounds sold under the trade names Sivastatin, Mevastatin, 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. See, 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 offered for obesity management. Xenical® has been reported to achieve a slight reduction in cholesterol.

SUMMARY

The invention features a compound of Formula I:

R₁ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfonylamyl, N,N-dialkylsulfonylamyl, N-arylsulfonyl, N-aryl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcyanocarbonylalkyl, alkoxycarbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylamido, N,N-dialkylamido, N-monoarylamido, N-alkyl-N-arylamido, N-aryl-N-arylamido, N-alkyl-N-arylhydroxamidomethyl, N-alkyl-N-arylhydroxyamidomethyl, amidoalkyl, aminoaalkyl, alkyaminoalkyl, amido, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkyloxysulfanyl, N-alkylamino, N,N-dialkylaminomethyl, acyl, acylamino, acyloxy, arylamino, amide, cyano, nitro, sulfonate, alkylsilyl, phenylselenenyl, thiocarbonyl, arylsulfonyl, arylsulfonylalkyl, or alkylsilyloxy,

R₂ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfonylamyl, N,N-dialkylsulfonylamyl, N-arylsulfonyl, N-aryl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcyanocarbonylalkyl, alkoxycarbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylamido, N,N-dialkylamido, N-monoarylamido, N-alkyl-N-arylamido, N-aryl-N-arylamido, N-alkyl-N-arylhydroxamidomethyl, N-alkyl-N-arylhydroxyamidomethyl, amidoalkyl, aminoaalkyl, alkyaminoalkyl, amido, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkyloxysulfanyl, N-alkylamino, N,N-dialkylaminomethyl, acyl, acylamino, acyloxy, arylamino, amide, cyano, nitro, sulfonate, alkylsilyl, phenylselenenyl, thiocarbonyl, arylsulfonyl, arylsulfonylalkyl, or alkylsilyloxy,

R₃ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfonylamyl, N,N-dialkylsulfonylamyl, N-arylsulfonyl, N-aryl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcyanocarbonylalkyl, alkoxycarbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylamido, N,N-dialkylamido, N-monoarylamido, N-alkyl-N-arylamido, N-aryl-N-arylamido, N-alkyl-N-arylhydroxamidomethyl, N-alkyl-N-arylhydroxyamidomethyl, amidoalkyl, aminoaalkyl, alkyaminoalkyl, amido, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkyloxysulfanyl, N-alkylamino, N,N-dialkylaminomethyl, acyl, acylamino, acyloxy, arylamino, amide, cyano, nitro, sulfonate, alkylsilyl, phenylselenenyl, thiocarbonyl, arylsulfonyl, arylsulfonylalkyl, or alkylsilyloxy,

R₄ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfonylamyl, N,N-dialkylsulfonylamyl, N-arylsulfonyl, N-aryl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcyanocarbonylalkyl, alkoxycarbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylamido, N,N-dialkylamido, N-monoarylamido, N-alkyl-N-arylamido, N-aryl-N-arylamido, N-alkyl-N-arylhydroxamidomethyl, N-alkyl-N-arylhydroxyamidomethyl, amidoalkyl, aminoaalkyl, alkyaminoalkyl, amido, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkyloxysulfanyl, N-alkylamino, N,N-dialkylaminomethyl, acyl, acylamino, acyloxy, arylamino, amide, cyano, nitro, sulfonate, alkylsilyl, phenylselenenyl, thiocarbonyl, arylsulfonyl, arylsulfonylalkyl, or alkylsilyloxy,

R₅ can be independently hydrido, halo, alkyl, or hydroxyalkyl.

In some embodiments, R₅ is halo, R₇ and R₈ are hydroxy, and R₆ and R₉ are alkyl in the compound, e.g., R₁ is chloro and R₃ and R₄ are methyl. In other embodiments, R₅ is halo, R₆ and R₇ are alkylsilyloxy, and R₈ and R₉ are alkyl, e.g., R₁ is chloro, R₃ and R₄ are OSi-t-BuMe2, and R₅ and R₆ are methyl. In one embodiment, the compound has Formula (24):

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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):

\[
\text{(23)}
\]

The invention also features a compound of Formula IV:

\[
\text{(IV)}
\]

$R_1$ can be independently any of the groups described above for $R_1$ of Formula I. $R_2$ and $R_3$ can be independently any of the groups described above for $R_2$ of Formula I. $R_4$ 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. However, when $R_1$ is chloro, $R_2$ and $R_3$ are not hydroxy and $R_4$ and $R_5$ are methyl.

In some embodiments, $R_1$ is halo, $R_2$ and $R_3$ are hydroxy, and $R_4$ and $R_5$ are alkyl. In some embodiments, $R_1$ is halo, $R_2$ and $R_3$ are alkylsilyloxy; and $R_4$ and $R_5$ are alkyl, 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.

The invention also features a compound of Formula III:

\[
\text{(III)}
\]

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 hydrido, alkyl, or hydroxyalkyl. $R_4$ can be independently hydrido, alkyl, or hydroxyalkyl.

R_1$ can be independently any of the groups described above for $R_1$ of Formula I. $R_2$ and $R_3$ are selected from hydroxy, alkylsilyloxy, or aralkyloxy, $R_4$ and $R_5$ are alkyl, $R_6$ is selected from hydrido, hydroxy, or acyloxy, and $R_7$ is selected from alkyl or arylselenylalkyl, e.g., $R_1$ is chloro; $R_2$ and $R_3$ are $\text{OSi-t-BuMe}_2$, $R_4$ and $R_5$ are methyl, $R_6$ is hydrido, and $R_7$ is methyl. In other embodiments, $R_1$ 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. In some embodiments, $R_1$ 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. In some embodiments, $R_1$ 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. In some embodiments, $R_1$ 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.
The invention also features a compound of Formula V:

\[
\begin{align*}
R_1 & \text{ can be independently any of the groups described above for } R_1 \text{ of Formula I. } \\
R_2 & \text{ can be independently any of the groups described above for } R_2 \text{ of Formula I. } \\
R_3 & \text{ can be independently any of the groups described above for } R_3 \text{ of Formula I. } \\
R_4 & \text{ can be independently hydrido, alkyl, or hydroxyalkyl. } \\
R_5 & \text{ can be independently hydrido, alkyl, or hydroxyalkyl. } \\
R_6 & \text{ can be hydrido, alkyl, or hydroxyalkyl. } \\
R_7 & \text{ can be hydroxy. } \\
R_8 & \text{ can be independently hydroxy, or alkylsilyloxy. }
\end{align*}
\]

In some embodiments, \( R_1 \) is halo; \( R_2 \) and \( R_3 \) are arylalkyloxy; \( R_4 \) and \( R_5 \) are alkyl; \( R_6 \) is hydroxy; and \( R_7 \) is selected from hydroxy and alkylsilyloxy, e.g., \( R_1 \) is chloro; \( R_2 \) and \( R_3 \) are OBn; and \( R_4 \) and \( R_5 \) are methyl; \( R_6 \) is hydroxy; and \( R_7 \) is OSi-t-BuMe₂. In some embodiments, \( R_1 \) is chloro; \( R_2 \) and \( R_3 \) are OBn; \( R_4 \) and \( R_5 \) are methyl; \( R_6 \) is hydroxy; and \( R_7 \) is hydroxy.

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

\[
\begin{align*}
\text{wherein } R_1 \text{ is chloro, } R_2 \text{ and } R_3 \text{ are OSi-t-BuMe}_2. \text{ The method further comprises isolating compound (18) and deprotecting compound (18). The result is a compound of Formula I. }
\end{align*}
\]

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

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

\[
\begin{align*}
\text{wherein } R_1 \text{ is chloro, } R_2 \text{ and } R_3 \text{ are OSi-t-BuMe}_2, X_1 \text{ is chloro, } X_2 \text{ is bromo; }
\end{align*}
\]
Oxidation of compound (26) forms (+) chloropuupe-henone (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 alkanoic 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 1 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 Feroverdin 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, alklyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy,

R<sub>1</sub> is selected from hydrido, halo, alkyl, alkenyl, alkylthio, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonfyl, arylsulfonfyl, N-alkylsulfonfyl, N,N-dialkylsulfonfyl, N-arylsulfonfyl, N-alkyl-N-arylsulfonfyl, carboxy, carboxylalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylamido, alkylcarbonylalkylamino, amido, N-alkylamido, N,N-dialkylamido, N-arylamido, N-alkyl-N-arylamido, N-alkyl-N-arylsulfamyl, N-arylsulfomyl, N-alkyl-N-arylsulfamyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, aminoalkyl, amidino, cyanoamino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxyl, acylamino, amino, cyano, nitro, sulfonate, alkylsilyl, phenylethynyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfinyl, and alkylsilyloxy.

R<sub>2</sub> is selected from hydrido, halo, alkyl, alkenyl, alkylthio, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonfyl, arylsulfonfyl, N-alkylsulfonfyl, N,N-dialkylsulfonfyl, N-arylsulfonfyl, N-alkyl-N-arylsulfonfyl, carboxy, carboxylalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylamido, alkylcarbonylalkylamino, amido, N-alkylamido, N,N-dialkylamido, N-arylamido, N-alkyl-N-arylamido, N-alkyl-N-arylsulfamyl, N-arylsulfomyl, N-alkyl-N-arylsulfamyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, aminoalkyl, amidino, cyanoamino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxyl, acylamino, amino, cyano, nitro, sulfonate, alkylsilyl, phenylethynyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfinyl, and alkylsilyloxy.

R<sub>3</sub> is selected from hydrido, alkyl, and hydroxyalkyl, and R<sub>4</sub> is selected from hydrido, alkyl, and hydroxyalkyl. The class of compounds also includes pharmaceutically-acceptable salts thereof.

An exemplary class of compounds includes compounds of Formula I, wherein R<sub>1</sub> is halo, R<sub>2</sub> is selected from hydroxy and alkylsilyloxy, R<sub>3</sub> is selected from hydroxy and alkylsilyloxy, R<sub>4</sub> is selected from hydrido, alkyl, hydroxyalkyl, and R<sub>5</sub> is selected from hydrido, alkyl, and hydroxyalkyl.

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

\[(4aS,6aR,12bS)-2H-9,10-Bis-(t-butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-
4,4a,5,6,6a,12b-tetramethyl-benzo[a]xanthene-9,10-diol (1);\]

\[(4aS,6aS,12bS)-2H-9,10-Bis-(t-butyldimethylsilyloxy)-11-cloro-1,3,4,4a,5,6,6a,12b-octahydro-
4,4a,5,6,6a,12b-tetramethyl-benzo[a]xanthene (18).\]
Compounds of Formula IV

A fourth class of compounds is defined by Formula IV:

wherein $R_1$ is selected from the moieties described above for $R_1$ groups of Formula I; $R_2$ is selected from the moieties described above for $R_2$ groups of Formula I; $R_3$ is selected from the moieties described above for $R_3$ groups of Formula I; $R_4$ is selected from hydrido, alkyl, and hydroxyalkyl; $R_5$ is selected from hydrido, alkyl, and hydroxyalkyl; $R_6$ is selected from hydrido, alkyl, and hydroxyalkyl; and $R_7$ is selected from alkyl and arylselenylalkyl.

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

(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 (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).

Compounds of Formula V

A fifth class of compounds is defined by Formula V:

wherein $R_1$ is selected from the moieties described above for $R_1$ groups of Formula I; $R_2$ is selected from the moieties described above for $R_2$ groups of Formula I; $R_3$ is selected from the moieties described above for $R_3$ groups of Formula I; $R_4$ is selected from hydrido, alkyl, and hydroxyalkyl; $R_5$ is selected from hydrido, alkyl, and hydroxyalkyl; $R_6$ is hydroxy, and $R_7$ is selected from hydroxy and alkylsilyloxy.

The class of compounds also includes pharmaceutically acceptable salts thereof.

An exemplary class of compounds includes those compounds of Formula V wherein $R_3$ is halo; $R_2$ is selected from hydroxy, alkylsilyloxy and aralkyloxy; $R_1$ is selected from hydroxy, alkylsilyloxy, and aralkyloxy; $R_3$ is selected from hydrido, alkyl, and hydroxyalkyl; $R_4$ is selected from hydrido, alkyl, and hydroxyalkyl; $R_5$ is selected from hydrido, alkyl, and hydroxyalkyl; and $R_6$ is selected from alkyl and arylselenylalkyl.

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

(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 (25); (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 (26); (4aS,6aR,12aS,12bS)-2H-9,10-Bis-benzyloxy)-11-chloro-6a-(phenylselenylmethyl)-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,12b-trimethyl-benzo[a]xanthene (40); (4aS,6aR,12aS,12bS)-2H-12-Acetoxy-9,10-bis-(benzylxoy)-11-chloro-6a-(phenylselenylmethyl)-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,12b-trimethyl-benzo[a]xanthene (41); and (4aS,6aR,12aS,12bS)-2H-12-Acetoxy-9,10-bis-(benzylxoy)-11-chloro-6a-(phenylselenylmethyl)-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 $R_1$ is selected from the moieties described above for $R_1$ groups of Formula I, $R_2$ is selected from the moieties described above for $R_2$ groups of Formula I, $R_3$ is selected from the moieties described above for $R_3$ groups of Formula I, $R_4$ is selected from hydrido, alkyl, and hydroxyalkyl, $R_5$ is selected from hydrido, alkyl, and hydroxyalkyl, $R_6$ is hydroxy, and $R_7$ is selected from hydroxy and alkylsilyloxy.

The class of compounds also includes pharmaceutically acceptable salts thereof.

An exemplary class of compounds includes those compounds of Formula V wherein $R_3$ is halo; $R_2$ is selected from hydroxy, alkylsilyloxy and aralkyloxy; $R_1$ is selected from hydroxy, alkylsilyloxy, and aralkyloxy; $R_3$ is selected from hydrido, alkyl, and hydroxyalkyl; $R_4$ is selected from hydrido, alkyl, and hydroxyalkyl; $R_5$ is hydroxy, and $R_6$ is selected from hydroxy and alkylsilyloxy.

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-dibenzoylxy)-6-(1-butyltrimethylsilyloxy)pheny]hydroxymethyl}2-methylene-5,5,8a-trimethyldecahydronaphthalene (37); and

(4aS,8aS)-1-{[(2-chloro-3,4-dibenzoylxy-6-hydroxy)pheny]hydroxymethyl}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 ten carbon atoms. Most preferred are lower alkyl radicals having one to about four carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, ocyl and the like. The term alkyl also includes cycloalkyl (cyclic) groups (cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), and aralkyl sub-stituted cycloalkyl groups, and cycloalkyl substituted alkyl groups.

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

(4aS,6aR,12aS,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (21); and
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, alkenyl, halogen, hydroxy, alkylcarbonyl, aryldiacyl, alkoxycarbonyl, aryloxycarbonyl, carbonatoate, alkylcarbonyl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, aryl, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, aminocarbonylamino, carbamoylamino, carbamoyl and ureido), amidino, imino, sulfonyl, cyclithio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclic, alicyclic, 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 aryI (e.g., phenylmethyl (benzyl)). The term “n-alkyl” means a straight chain (i.e., unbranched) unsubstituted alkyl group. The term “alkynyl” 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 “alkynyl” includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, cycloalkenyl (acyclic) groups (cyclopropenyl, cyclopropyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkenyl or alkynyl substituted alkynyl groups.

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 groups, alkenyl groups, halogens, hydroxy, alkylcarbonyl, aryldiacyl, alkoxycarbonyl, aryloxycarbonyl, carbonatoate, alkylcarbonyl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, aryl, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, aminocarbonylamino, carbamoylamino, carbamoyl and ureido), amidino, imino, sulfonyl, cyclithio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclic, alicyclic, 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, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkynyl or cycloalkenyl substituted alkynyl groups.

The term “hydrido” denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (—CH2—) radical. The term “halo” means halogens such as chlorine, bromine or iodine atoms. The term “haloalkyl” embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. The term “hydroxyalkyl” embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. The terms “alkoxy” and “alkoxyalkyl” embrace linear or branched oxy-containing radicals. Examples of unsaturated oxy-containing radicals include each having alkyl portions of one to about ten carbon atoms, such as methoxy radicals. 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 terms “alkoxy” or “alkoxyalkyl” radicals may be further substituted with one or more halo atoms, such as fluoro chloride or bromo to provide “haloalkoxy” or “haloalkoxyalkyl” radicals. Examples of “alkoxy” radicals include methoxy butoxy and trifluoromethoxy. The term “aryl”, alone or in combination, means a carbocyclic aromatic or heteroaromatic moiety. A sulfonamide (SO2:NH2) denotes respectively divalent radicals —SO2—NH2. “Alkylsulfonate” embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term “arylsulfonate” embraces sulfonate radicals substituted with an aryl radical. The term “sulfamyl” or “sulfonamidyl”, whether used alone or linked to other terms such as alkysulfonamidyl, or alkylsulfonamidyl, denotes “N-alkyl-N-arylsulfamyl” denote sulfamyl radicals attached to the aryl radical. The terms “N-alkylsulfamyl” and “N-aryl-N-arylsulfamyl” denote sulfamyl radicals substituted, respectively, with one aryl radical, a cycloalkyl ring, or two alkyl radicals. The terms “N-arylsulfonyl” and “N-alkyl-N-arylsulfonyl” denote sulfamyl radicals substituted, respectively, with one alkyl radical, and one alkyl and one aryl radical. The terms “carbony” 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 “carbonyl”, whether used alone or with other terms, such as “alkylcarbonyl”, denotes —C(=O)—. The term “alkylcarbonyl” embraces radicals having a carbonyl radical substituted on one, two or three carbon atoms. An example of an “alkylicarbonyl” radical is CH3—(C=O)—. The term “alkylcarbonylalkyl” denotes an alkyl radical substituted with an “alkylicarbonyl” radical. The term...
“alkoxycarbonyl” means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such “alkoxy carbonyl” radicals include \((\text{CH}_3)_2\text{CO} = \text{C}(=\text{O})-\) and \(-\text{O}=\text{C}-\text{OCH}_3\). The term “alkoxy carbonylalkyl” embraces radicals having “alkoxy carbonyl”, as defined above, substituted to an alkyl radical. Examples of such “alkoxy carbonylalkyl” radicals include \((\text{CH}_3)_2\text{CO}(\text{C}(=\text{O})(\text{CH}_3)-\) and \(-\text{O}=\text{C}-\text{OCH}(_2)(\text{C}(=\text{O})(\text{CH}_3)-\). The term “amido” when used by itself or with other terms such as “amidoalkyl”, “N-monoalkylamido”, “N-monoarylamido”, “N,N-dialkylamido”, “N-alkyl-N-arylamido”, “N-alkyl-N-hydroxyamido” and “N-alkyl-N-hydroxyamidomido” embraces a carbonyl radical substituted with an amino radical. The terms “N-alkylamido” and “N,N-dialkylamido” denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The terms “N-monoarylamido” and “N-alkyl-N-arylamido” denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term “N-alkyl-N-hydroxyamidomido” embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term “N-alkyl-N-hydroxyamido” embraces amido radicals substituted with an hydroxyl radical and with an alkyl radical. The term “amido” embraces amidoalkyl radicals substituted containing an “amidoalkyl” radical, as defined above, attached via an oxygen atom to a group.

The term “amidoalkyl” embraces amidoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term “amidino” denotes an \(-\text{C}(==\text{NH})-\text{NH}\) radical. The term “cyanamidino” denotes an \(-\text{C}==(\text{CN})-\text{NH}\) radical. The term “hetcrcycloalkyl” embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The term “heterocycloalkyl” embraces heterocyclic substituted alkyl radicals containing an “heterocycloalkyl” radical, as defined above, attached via an oxygen atom to a group.

The present invention includes a pharmaceutical composition comprising or consisting of or containing one or more of the compounds of Formula I, II, III, IV, or V in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent. The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the condition, the desired results, and the severity of the condition.

Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metal salts made from aluminum, calcium, magnesium, sodium, potassium, and phosphoric acid. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids include hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Suitable organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactone, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesyl, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamonic), methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluene-sulfonic, sulfanilic, fumaric, sodium salicylate, hydroxybutyric, salicylic, galactaric and galacturonic acid.

A pharmaceutical composition comprises one or more compounds of Formulae I-V in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents 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.
utilized in the treatment of cholesterol-related conditions in
polyvinylpyrrolidone, and/or polyvinyl alcohol, and then
particular compound employed, health status, diet, other
preferred dosage of the compound to be administered, the
compounds may be prepared from sterile powders or granules
propylene glycol, ethanol, corn oil, cottonseed oil, peanut
pounds may be dissolved in water, polyethylene glycol,
physician. These factors include the age, body weight, sex
body weight per day to about 4 g/kg of body weight per day.
intramuscularly or topically.
oral, intravascularly, intraperitoneally, subcutaneously,
intended. A compound may, for example, be administered
such a route, and in a dose effective for the treatment
composition, as described above. A compound of the present
invention therefore (e.g., compounds sold under the trade names
administration. The optimal dosage of a pharmaceutical
compounds and/or compositions of this invention depends
variables as the overall health status of the particular patient
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 by, e.g., 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
in lymph. Administration of an effective amount results in a
decrease in lymphatic 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, Mevas, and galgurid 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 may be administered by any suitable route, typi-
cally 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 of 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
Scheme 1 shows the synthesis of enantiopure A-B fragment 3 from commercially available 3aR-(+)-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 MoO$_5$(pyridine).HMPA$^{13}$ complex gave two diasteromers, 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-toluenesulfonylic 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 BBr$_3$ in CH$_2$Cl$_2$ (94% yield) followed by protection of the diol with t-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 t-butyldimethylsilyl chloride (83% yield) provided trisilyl ether 14. Selective C4 (less hindered site compared with C6) bromination of 14 with N-bromosuccinimide (NBS) in N,N-dimethylformamide (DMF) at 25°C gave an 67% yield of 4 as the sole product; no C6 isomer 15 was isolated. Interestingly, when the bromination 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 N-bromosuccinimide (NBS) in DMF to give a 70% yield of bromide 17. Silylation of 17 with t-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 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 C₆₆-S tetracyclic pyran compounds embraced by Formulae IV and V. Scheme 5 shows the preparation of (1R,4aS,6aS)-2,5,5,8₄-tetramethyl-1,4,4a,5,6,7,8,8₄-octahydronaphthalene-1-carboxaldehyde (33) and (1R,4aS,6aS)-2-Methylene-5,5,8₄-trimethyl-1,2,3,4,4a,5,6,7,8,8₄-decahydronaphthalene-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-butylammonium 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 dibenzylation 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 $-78^\circ$ C. followed by 1 equivalent of aldehyde 35 gave alcohol 37 (62% yield), which was desilylated with n-Bu$_4$NF in THF to give alcohol 38 (63% yield). Ring closure of 38 with phenylselenylyphthalimide and tin tetrachloride 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. Davisil silica gel, grade 643 (200-425 mesh), was used for the flash column chromatographic separation. 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$_4$. Chemicals and reagents were purchased either from Aldrich Chemical Company or Fisher Chemical Company, and were used without further purification.

Example 1

(4aS,8aS)-3,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde

Step 1: Preparation of (1S,3aR,5aS,9aS,9bR)-1-Hydroxydodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan-2-one (6) and (1R,3aR,5aS,9aS,9bR)-1-Hydroxydodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan-2-one (7)

To a cold (278°C) solution of 1.02 ml (7.79 mmol) of disopropylamine 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 278°C for 1 h, and a solution of 1.50 g (5.99 mmol) of (4a)-sclareolide 5 in 20 ml of THF was added via cannula dropwise. After the solution was stirred at 278°C for 1 h, the solution was added to 20 ml of 2 MeOH. The mixture was diluted with saturated aqueous Na$_2$SO$_4$, extracted three times with ethyl acetate, and the organic layer was washed with water and brine, dried (Na$_2$SO$_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane/ether (9:1) as an eluent to give 1.045 g (65.6% yield) of compound 6 and 0.195 g (12% yield) of compound 9 along with 0.296 g (20% recovery) of 5. Compound 6: [α]$_{D}^{20}$ = +97.1° (c 0.01, CHCl$_3$); $^1$H NMR (CDCl$_3$) δ 4.48 (d, J=12Hz, 1H, CHO, axial), 2.06 (d, J=12Hz, 1H, C9b-axial H), 1.95~1.06 (m, 1H), 1.38 (s, 3H, Me), 1.03 (s, 3H, Me), 0.88 (s, 3H, Me), 0.84 (s, 3H, Me); $^{13}$C NMR (CDCl$_3$) δ 179.0 (δ = C=O), 83.5, 68.7, 64.2, 56.4, 42.3, 39.4, 39.3, 36.9, 33.4, 32.3, 23.5, 21.1, 20.7, 18.1, 15.9.

Step 2: Preparation of 1-(1S,1,2-Dihydroxyethyl)-(1R,2R,4aS,8aS)-decahydro-2,5,5,8a-tetramethylnaphthalen-2-ol (8S) and (1S,3aR,5aS,9aS,9bR)-Decahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan-1,2-diol (9S)

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 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 was 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 8S and 0.273 g (30% yield) of lactol 9S. Compound 8S: [α]$_{D}^{20}$ = -7.2° (c 0.008, CH$_2$OH); $^1$H NMR (CDCl$_3$) δ 4.53 (m, 1H, CHO), 4.06 (dd, J=10, 8Hz, 1H, CHO), 3.64 (dd, J=10, 8Hz, 1H, CH$_2$O), 1.95 (d, J=4Hz, 1H), 1.70~1.01 (m, 11H), 1.43 (s, 3H, Me), 1.10 (s, 3H, Me), 0.82 (s, 3H, Me); $^{13}$C NMR (CDCl$_3$) δ 82.9, 75.2, 71.8, 68.8, 47.2, 42.4, 38.4, 34.3, 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; $^1$H NMR (CDCl$_3$) δ 5.38 (broad s, 1H), 5.33 (s, 1H), 4.35 (t, J=5Hz, 1H), 2.5 (broad s, 1H, OH), 1.9~0.9 (m, 12H), 1.49 (s, 3H, Me), 1.08 (s, 3H, Me), 0.84 (s, 3H, Me). For the 9R isomer, (1R,1,2-Dihydroxyethyl)-(1R,2R,4aS,8aS)-decachydro-2,5,5,8a-tetramethylnaphthalen-2-ol (8R); $^1$H NMR (CDCl$_3$) δ 3.87 (m, 1H, CHO), 3.68 (dd, J=10, 8Hz, 1H, CH$_2$O), 1.95 (d, J=4Hz, 1H), 1.70~1.01 (m, 11H), 1.43 (s, 3H, Me), 1.10 (s, 3H, Me), 0.82 (s, 3H, Me); $^{13}$C NMR (CDCl$_3$) δ 94.5, 26.7, 25.2, 24.9, 23.5, 20.8, 14.4. Compound 9R: (as a mixture of 2 diastereomers at C2); $^1$H NMR (CDCl$_3$) δ 5.32 (broad s, 1H), 5.32 (s, 1H), 4.35 (t, J=5Hz, 1H), 2.5 (broad s, 1H, OH), 1.9~0.9 (m, 12H), 1.49 (s, 3H, Me), 1.08 (s, 3H, Me), 0.84 (s, 3H, Me). For the 9S isomer, (1R,3aR,5aS,9aS,9bR)-Decahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan-1,2-diol (9S): (as a mixture of 2 diastereomers at C2); $^1$H NMR (CDCl$_3$) δ 5.32 (broad s, 1H, CHO, 1H, CHO of 1 diastereomer), 5.22 (d, J=6Hz, 1H, CHO of 1 diastereomer), 1.90~0.9 (m, 24H for 2 diastereomers), 1.34 (s, 3H, Me), 1.16 (s, 3H, Me), 0.97 (s, 3H, Me), 0.95 (s, 3H, Me), 0.87 (s, 6H, 2Me), 0.83 (s, 6H, 2Me); $^{13}$C NMR (CDCl$_3$) 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. Step 3: Preparation of (1R,2R,4aS,8aS)-Decahydro-2-hydroxy-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde (10)

To 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 (2.9 mmol) of lead tetaacetate. 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
were added. After the solution was reflux for 2 h, the 1H NMR (CDCl3) δ 10.06 (d, J=13Hz, 1H), 2.26 (dd, J=8, 4 Hz, 1H), 2.03 (s, 3H, Me), 1.71 (s, 3H, Me), 0.90 (s, 3H, Me), 0.86 (s, 3H, Me); 13C NMR (CDCl3) 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. Step 4: Preparation of (4aS,8aS)-3,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde (3)

To a flask equipped with a Dean-Stark apparatus under argon, 10 mg (0.042 mmol) of toluene, and 3 mg (0.017 mmol) of p-toluenesulfonic acid was added. 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 (MgSO4), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluent to give 0.25 g (85% yield) of aldehyde 10. [α]20D=+520 (c 1, CHCl3); 'H NMR (CDCl3) δ 208.3, 72.9, 71.4, 55.3, 42.9, 41.8, 39.9, 37.5, 33.4, 22.3, 21.6, 21.8, 20.0, 18.1, 17.2. Step 2: Preparation of (1R,2R,4aS,8aS)-Decahydro-2-hydroxy-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 the 30 product was collected by filtration, washed with 50 mL of Example 2 hexane, and dried in vacuo to give 2.033 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. A total of 2.691 g (88% yield) of 12 was obtained. The white solids were used in next step without purification. 1H NMR (CDCl3) δ 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); 13C NMR (CDCl3) δ 190.5 (C=O), 149.0 (s, 2C), 128.2 (s), 125.6 (d), 121.0 (s), 109.2 (d), 56.3 (q). Step 2: Preparation of 5-Chloro-3,4-dihydroxybenzaldehyde (12) To a solution 0.200 g (10.7 mmol) of benzaldehyde 12 in 20 mL of dichloromethane under argon at 0°C, it was diluted with dichloromethane and filtered and washed with 40 mL of methanol, and the solvents were removed on a rotary evaporator (the trimethylborate was removed). It was added 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. 1H NMR (CDCl3) δ 10.43 (s, 2H), 9.70 (s, 1H, CHO), 7.42 (d, J=2.0Hz, 1H, C6-H), 7.32 (d, J=2.0Hz, 1H, C2-H); 13C NMR (CDCl3) δ 198.4, 149.7 (C=O), 146.9 (s), 146.6 (d), 124.8 (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-dimethyaminopyridine (DMAP) in 20 mL of dichloromethane under argon at 0°C, it was added 9.80 mL (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 NH4Cl was added, and extracted three times with
Example 4

\[
\text{Me}_3\text{Bu-Si-Cl}_2 \quad \text{Br}
\]

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

Step 1: Preparation of 3,4-bis-(t-Butyldimethylsilyloxy)-5-chlorophenol (16)

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. H 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). Analy. Calc for C₂₈H₂₆Cl₂O₂Si₃: C, 55.57; H, 8.55. Found: C, 55.39; H, 8.87.

Step 2: Preparation of 2-Bromo-3-chloro-4,5-bis-(t-butyldimethylsilyloxy)phenol (17)

A solution of 0.050 g (0.12 mmol) of 16 and 0.023 g (0.12 mmol) of NBS in 2 mL of DMF under argon 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. H 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), -3.4 (q, Me), -3.5 (q, Me), -4.0 (q). Anal. Calc for C₂₈H₂₆Br₂Cl₂O₂Si₃: C, 49.51; H, 7.96. Found: C, 49.78; H, 8.11.

Step 3: Preparation of 5-Bromo-6-chloro-1,2,4-tris-(t-butyldimethylsilyloxy)benzene

To a mixture of 0.050 g (0.12 mmol) of 16 and 0.023 g (0.12 mmol) of NBS in 2 mL of DMF under argon 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. H 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), -3.4 (q, Me), -3.5 (q, Me), -4.0 (q). Analy. Calc for C₂₈H₂₆Br₂Cl₂O₂Si₃: C, 49.51; H, 7.96. 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 25°C for 2 days. The solution was diluted with 30 mL of toluene and then hexane and ether as eluents to give 0.980 g (45% yield).

Step 1: Preparation of (4aS,6aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4a,6a,12b-tetramethyl-benzo[a]xanthene (18) and (4aS,6aS,12bS)-2H-9,10-bis-(t-Butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4a,6a,12b-tetramethyl-benzo[a]xanthene (19)

In a dried flask, 2.600 g (4.50 mmol) of bromide 4 was placed, it 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, 25 mL of diethyl ether (freshly distilled over sodium-benzophenone) was added, cooled to ~78°C, and 2.7 mL (4.50 mmol) of t-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 gradient mixture of hexane and toluene and then hexane and ether as eluents to give 0.980 g (45% yield)

Example 5

Example 6

Example 7

Example 8

Example 9

Example 10

Example 11
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, \( \Delta^2, \Delta^7 = \pm 1,1^\beta \). Step 2: Preparation of 60 \( \Delta^2, \Delta^7 = \pm 35.6^\circ \) (c 0.008, CHCl,).  

**Example 8**

Step 1: Preparation of 6:1 (obtained from NMR spectrum). 'H NMR (CDCl,): \( \delta \) 6.38 (s, 1H, C8H), 6.31 (s, 1H, C12H), 5.36 (broad s, 1H, OH), 5.03 (broad s, 1H, OH), 2.20–1.05 (a series of m, 11H), 1.44 (s, 3H, Me), 0.96 (s, 3H, Me), 0.194 (s, 3H, MeSi); \( ^{13} \)C NMR (CDCl,): \( \delta \) 147.4, 139.6, 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, 15.0–3.2 (MeSi), –3.4, –3.5 (2C). Anal. Calcd for C23H27ClO2Si2: C, 66.79; H, 6.98. Found: C, 67.15; H, 9.45.  

**Example 9**

Step 1: Preparation of (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-dione (22)  

To a solution of 10 mg (0.027 mmol) of diol 22 in 1 mL of dichloromethane 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. A 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 20 mg (83% yield) of diol 22. 'H NMR (CDCl,): \( \delta \) 6.35 (s, 1H, C8H), 5.06 (broad s, 1H, OH), 2.61 (d, J=17 Hz, 1H, C12H), 2.34 (m, 1H, C12H), 2.02 (m, 1H), 1.80–0.90 (a series of m, 11H), 1.14 (s, 3H, Me), 0.91 (s, 6H, Me), 0.85 (s, 3H, Me). When the proton NMR spectrum was measured in benzene-d6 solvent, all methyl groups are separated, \( \delta \) 0.99 (s, 3H, Me), 0.77 (s, 3H, Me), 0.71 (s, 3H, Me), 0.61 (s, 3H, Me). \( ^{13} \)C NMR (CDCl,): \( \delta \) (the aromatic carbons are not well defined and are not described here) 76.6, 55.9, 51.9, 41.9, 41.0, 39.0, 36.8, 34.3, 33.1, 30.0.  

Step 2: Preparation of (4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6a,9,10,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,10-dione (24)  

To a solution of 10 mg (0.027 mmol) of diol 22 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, and concentrated to dryness to give 9.0 mg of a mixture of 23 and 24 in a ratio of 8:1 (obtained from NMR spectrum). 'H NMR (CDCl,): \( \delta \) 6.74 (s, 1H, C8H), 5.80 (s, 1H, C8H of 23), 2.84 (dd, J=20, 5 Hz, 1H, C12H of 23), 2.50 (dd, J=20, 13 Hz, C12H of 23), 2.11 (dt, J=13, 3 Hz, H, C12H, 2.22–0.90 (a series of m, 11H of 23 and 11H of 24), 1.33 (s, 3H, Me of 23), 0.93 (s, 3H, Me of 23), 0.92 (s, 3H, Me of 23), 0.85 (s, 3H, Me of 23).
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 25 = 35° (c 0.007, CHCl3). 1H NMR (CDCl3) δ 6.21 (s, 1H, C8H), 5.84 (d, J=7 Hz, 1H, C12H2), 2.64 (dd, J=18 Hz, 1H, 1H), 1.84 (s, J=16 Hz, 1H), 1.62-1.10 (a series of m, 10H), 1.11 (s, 3H, Me), 1.03 (s, 9H, t-Bu), 0.95 (s, 9H, t-Bu), 0.89 (s, 3H, Me), 0.81 (s, 3H, Me), 0.64 (s, 3H, Me), 0.20 (s, 3H, MeSi), 0.18 (s, 3H, MeSi), 0.16 (s, 3H, MeSi), 0.157 (s, 3H, MeSi). 13C NMR (CDCl3) δ 148.9, 146.3, 137.3, 126.0, 114.6, 108.4, 75.5, 55.9, 49.7, 42.1, 40.7, 40.3, 38.6, 33.9, 33.5, 35.5, 27.1, 26.4 (3C, t-Bu), 26.3 (3C, t-Bu), 22.1, 21.9, 18.9, 18.7, 18.5, 14.1, -3.3 (2C, MeSi), -5.3. -5.6. Analyt. Calc'd for C39H57ClO3Si3: C, 71.02; H, 4.69. Found: C, 71.24; H, 5.00.

Lymphatic 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.

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; Dural Plastics, Auburn, Australia) and exteriorized through 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, 67.5 Na2HPO4, 16.5 NaH2PO4, 115 NaCl, and 5 KCl; ϕH 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 subcutaneous fat. The lipid emulsion consisted of 451.8 μmol tritolein (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.),
Thus, compound 1 is a more potent inhibitor than green tea catechins, since an inhibitory effect was observed with only 41.9 mg of compound 1. Rats exhibited no gross motor or behavioral abnormalities.

Rats were sacrificed at the day end of the infusion, and the intestine and other organs were dissected and visually examined. No abnormalities were found in any of the organs of either control or treated rats.

### Table 3

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<th>Compound 1 % dose</th>
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<td>0.12 ± 0.04</td>
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<tr>
<td>2</td>
<td>1.84 ± 0.37</td>
<td>1.22 ± 0.25*</td>
</tr>
<tr>
<td>3</td>
<td>5.31 ± 0.74</td>
<td>2.70 ± 0.42*</td>
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<td>4</td>
<td>10.16 ± 1.31</td>
<td>4.18 ± 0.92*</td>
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<td>5</td>
<td>15.66 ± 1.75</td>
<td>5.68 ± 1.37*</td>
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<td>7</td>
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<td>9.13 ± 2.41*</td>
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<tr>
<td>8</td>
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</tbody>
</table>

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

#### 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. 3, 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 1:

   ![Chemical Structure](image)

   where R₁ is independently hydroxyl, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy,
alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, alkoxyalcohol, alkoxyalcoholalkyl, halo, amido, aminooxy, acyl, aminooxy, acyl, amino, cyano, nitro, sulfonate, alkylsilyl, phenylesseny1, thiol, arylsulfonyl, arylsulfonyl, arylsulfonyl, or alkylsilyloxy; R, is independently hydrido, halo, alkyl, alkexyl, alkylyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, amidooxy, acyl, acylx0, arylx0, amidoalkyl, aminoalkyl, aminoalkyl, aminoalkyl, amidooxy, acyl, acylx0, arylx0, acyl, acylx0, acyl, amino, cyano, nitro, sulfonate, alkylsilyl, or phenylesseny1, thiol, arylsulfonyl, alkylsulfonyl, arylsulfonyl, arylsulfonyl, or alkylsilyloxy; R, is independently hydrido, halo, alkyl, alkexyl, alkylyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, amido, N-N-dialkylamido, N-N-dialkylamido, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, amidooxy, acyl, acylx0, arylx0, amidoalkyl, aminoalkyl, aminoalkyl, amidooxy, acyl, acylx0, arylx0, acyl, acylx0, acyl, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfonyl, arylsulfonyl, or alkylsilyloxy; R, is independently hydrido, halo, alkyl, alkexyl, alkylyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, amido, N-N-dialkylamido, N-N-dialkylamido, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, amidooxy, acyl, acylx0, arylx0, amidoalkyl, aminoalkyl, aminoalkyl, amidooxy, acyl, acylx0, arylx0, acyl, acylx0, acyl, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfonyl, arylsulfonyl, or alkylsilyloxy; R, is independently hydrido, halo, alkyl, alkexyl, alkylyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, amido, N-N-dialkylamido, N-N-dialkylamido, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, amidooxy, acyl, acylx0, arylx0, amidoalkyl, aminoalkyl, aminoalkyl, amidooxy, acyl, acylx0, arylx0, acyl, acylx0, acyl, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfonyl, arylsulfonyl, or alkylsilyloxy; R, is independently hydrido, halo, alkyl, alkexyl, alkylyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, amido, N-N-dialkylamido, N-N-dialkylamido, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxy carbonyl, alkoxycarbonylalkyl, amidooxy, acyl, acylx0, arylx0, amidoalkyl, aminoalkyl, aminoalkyl, amidooxy, acyl, acylx0, arylx0, acyl, acylx0, acyl, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfonyl, arylsulfonyl, or alkylsilyloxy; or a pharmaceutically-acceptable salt thereof.

2. The compound of claim 1, R, is halo, R, and R, are hydroxy, and R, and R, are alkyl.

3. The compound of claim 2, wherein R, is chloro and R, and R, are methyl.

4. The compound of claim 1, wherein R, is halo, R, and R, are alkylsilyloxy, and R, and R, are alkyl.

5. The compound of claim 4, wherein R, is chloro, R, and R, are OSi-t-BuMe,, and R, and R, are methyl.
45  arylsulfenyl, alkylsulfenyl, arylsulfanyl, alkylsilyl, phenylselenyl, or alkylsilyloxy.

R₃ is independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkyloxysulfanyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-aryl- N-arylsulfamyl, N-aryl-N-arylsulfamyl, carboxy, carboxyalkyl, alkyloxyalkyl, alkloxyalkylalkyl, alkloxyaralkylalkyl, alkloxyaralkyalkyl, amido, N-alkylamido, N,N-dialkylamido, N-aryl-N-arylamido, N-aryl-N-arylamido, N-aryl-N-arylamido, N-aryl-N-arylamido, N,N-dialkylamino, acyl, aclyoxy, aryloxy, alkyloxy, aminoo, amino, cyano, nitro, sulfonate, thiol, arylsulfenyl, alkylsulfenyl, aryloxyl, alkylsilyloxy.

The compound of claim 7, wherein R₁ is halo, R₂ and R₃ are hydroxy, and R₄ and R₅ are alkyl.

9. The compound of claim 7, wherein R₁ is halo, R₂ and R₃ are alkysilyloxy, and R₄ and R₅ are alkyl.

10. The compound of claim 9, wherein Rᵢ is chloro, R₂ and R₃ are OSᵢ-t-BuMe₃, and R₄ and R₅ are methyl.

11. A compound of Formula III:

\[
\begin{align*}
& \text{ where } R₁ \text{ is independently hydrido, halo, alkyl, alkenyl, } \\
& \text{ alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, } \\
& \text{ alkoxyalkyl, haloalkoxy, haloalkoxygenalkyl, aryl, } \\
& \text{ heterocyclic, heteroaryl, alkyloxysulfanyl, arylsulfonyl, } \\
& \text{ N-alkylsulfamyl, N,N-dialkylsulfamyl, N-aryl-N- } \\
& \text{ arylsulfamyl, N-aryl-N-arylsulfamyl, carboxy, } \\
& \text{ carboxyalkyl, alkyloxyalkyl, alkloxyalkylalkyl, } \\
& \text{ alkloxyaralkylalkyl, alkloxyaralkyalkyl, amido, } \\
& \text{ N-alkylamido, N,N-dialkylamido, N-aryl-N- } \\
& \text{ arylamido, N-aryl-N-arylamido, N-aryl-N- } \\
& \text{ arylamido, N,N-dialkylamino, acyl, aclyoxy, aryloxy, } \\
& \text{ alkyloxy, aminoo, amino, cyano, nitro, sulfonate, thiol, } \\
& \text{ arylsulfenyl, alkylsulfenyl, aryloxyl, alkylsilyloxy. }
\end{align*}
\]

R₃ is independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkyloxysulfanyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-aryl-N-arylsulfamyl, N-arylsulfonyl, N-aryl-N-arylsulfamyl, carboxy, carboxyalkyl, alkyloxyalkyl, alkloxyalkylalkyl, alkloxyaralkylalkyl, alkloxyaralkyalkyl, amido, N-alkylamido, N,N-dialkylamido, N-aryl-N-arylamido, N-aryl-N-arylamido, N-aryl-N-arylamido, N,N-dialkylamino, acyl, aclyoxy, aryloxy, alkyloxy, aminoo, amino, cyano, nitro, sulfonate, thiol, arylsulfenyl, alkylsulfenyl, aryloxyl, alkylsilyloxy.
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, arylsulfenyl, alkylsulfenyl, arylsulfinyl, alkylsilyl, phenylelsenyl, or alkysilyloxy;

R, is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-aryl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxyhydroxyloxyalkyl, amido, N,N-dialkylamido, N,N-dialkylamido, N,N-arylamido, N,N-dialkylacetamido, amidals, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfenyl, alkylsulfenyl, arylsulfinyl, alkylsilyl, phenylelsenyl, or alkysilyloxy;

R, is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-aryl-N-arylsulfamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxyhydroxyloxyalkyl, amido, N,N-dialkylamido, N,N-dialkylamido, N,N-arylamido, N,N-dialkylacetamido, amidals, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfenyl, alkylsulfenyl, arylsulfinyl, alkylsilyl, phenylelsenyl, or alkysilyloxy;

R, is independently hydrido, halo, alkyl, or hydroxyalkyl;

R, is independently hydrido, alkyl, or hydroxyalkyl;

R, is hydroxy; and

R, is independently hydroxy, or alkysilyloxy;

or a pharmaceutically-acceptable salt thereof.

25. The compound of claim 24, wherein R, is halo; R, and R, are arylalkyloxy; R, and R, are alkyl; R, is hydroxy; and R, is selected from hydroxy and alkysilyloxy.

26. The compound of claim 25, wherein R, is chloro; R, and R, are OBn; and R, and R, are methyl; R, is hydroxy; and R, is OSi-t-BuMe,.

27. The compound of claim 25, wherein R, is chloro; R, and R, are OBn; R, and R, are methyl; R, is hydroxy; and R, is hydroxy.

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

\[
\text{R, is chloro, R, and R, are OSi-t-BuMe,;}
\]

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

c) deprotecting said intermediate compound (18);

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

e) reacting compound (4),

wherein R, is chloro, X, is chloro, X, is halo, and X, is hydroxy;

wherein R, is chloro, R, and R, are OSi-t-BuMe,;

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

c) deprotecting said intermediate compound.

29. A method of synthesizing (+)-chloropuphenone 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).

30. A method for identifying a compound that inhibits lymphatic absorption of cholesterol, comprising:
   a) administering a known amount of cholesterol and a compound of claim 1 to a non-human mammal; and
   b) measuring lymphatic absorption of said known amount of cholesterol, wherein a statistically significant decrease in said cholesterol absorption relative to the lymphatic cholesterol absorption of a corresponding control non-human mammal indicates said compound inhibits lymphatic absorption of cholesterol, and wherein a statistically insignificant change or a statistically significant increase in said cholesterol absorption relative to the lymphatic cholesterol absorption of a corresponding control non-human mammal indicates said compound does not inhibit lymphatic absorption of cholesterol.

31. The method of claim 30, wherein said known amount of cholesterol and said compound are administered in a liposome emulsion.

32. The method of claim 30, wherein said non-human mammal is a rat.

33. The method of claim 32, wherein said non-human mammal is fasted prior to said administering step.

34. A composition comprising a compound of Formula 1:

\[
\text{(1)}
\]

at least one pharmaceutically-acceptable carrier material.
UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,727,277 B1
DATED : April 27, 2004
INVENTOR(S) : Duy H. Hua, Sung I. Koo and Sang K. Noh

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