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

14C-CH absorption (% dose/h)

Control

Compound I

Time (h)

0 1 2 3 4 5 6 7 8
FIG. 2

Oleic acid output (μmol/h)

- Control
- Compound I

Time (h)

1 2 3 4 5 6 7 8

0 30 60 90 120 150

* indicates significant difference compared to Control.
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COMPOUNDS AFFECTING CHOLESTEROL ABSORPTION

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

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TECHNICAL FIELD

This invention relates to novel organic compounds 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. 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 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, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylicarbonyl, alkylicarbonylalkyl, alkoxyalkyl, alkoxyalkylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkyldiaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycolalkyl, cycloalkenyl, alkythio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, arylxoy, acylaminoc, amino, cyano, nitro, sulfinate, alkylsilyl, phenylselenenyl, thioly, arylsulfenyl, arylsulfinyl, or arylsilyloxy.

R₂ can be independently hydrido, 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, alkylicarbonyl, alkylicarbonylalkyl, alkoxyalkyl, alkoxyalkylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkyldiaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycolalkyl, cycloalkenyl, alkythio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, arylxoy, acylaminoc, amino, cyano, nitro, sulfinate, alkylsilyl, phenylselenenyl, thioly, arylsulfenyl, arylsulfinyl, or arylsilyloxy.

R₃ can be independently hydrido, alkyl, or hydroxyalkyl.

R₄ can be independently hydrido, alkyl, or hydroxyalkyl.

R₅ can be independently hydrido, alkyl, or hydroxyalkyl.

In some embodiments, R₅ is halo, R₇, and R₈ are hydroxy, and R₉ and R₁₀ are alkyl in the compound, e.g., R₅ is chloro and R₇ and R₈ are methyl. In other embodiments, R₅ is halo, R₇, and R₈ are alkylsilyloxy, and R₉ and R₁₀ are alkyl, e.g., R₅ is chloro, R₇ and R₈ are OSi-t-BuMe₂, and R₉ and R₁₀ are methyl. In one embodiment, the compound has Formula (24):
In some embodiments, R₁ is halo, R₂ and R₃ are selected from hydroxy and alkylsilyloxy, and R₄ and R₅ are alkyl, e.g., R₁ is chloro, R₂ and R₃ are hydroxy, and R₄ and R₅ are methyl. In some embodiments, R₁ is halo, R₂ and R₃ are alkylsilyloxy, and R₄ and R₅ are methyl, e.g., R₁ is chloro, R₂ and R₃ are OSi-t-BuMe₃, and R₄ and R₅ are methyl. In some embodiments the compound has Formula (23):

\[
\text{(23)}
\]

\[
\begin{align*}
R₁ & \text{ is halo, } R₂ \text{ and } R₃ \text{ are selected from hydroxy and alkylsilyloxy, and } R₄ \text{ and } R₅ \text{ are alkyl, e.g., } R₁ \text{ is chloro, } R₂ \text{ and } R₃ \text{ are hydroxy, and } R₄ \text{ and } R₅ \text{ are methyl. In some embodiments, } R₁ \text{ is halo, } R₂ \text{ and } R₃ \text{ are alkylsilyloxy, and } R₄ \text{ and } R₅ \text{ are methyl, e.g., } R₁ \text{ is chloro, } R₂ \text{ and } R₃ \text{ are OSi-t-BuMe₃, and } R₄ \text{ and } R₅ \text{ are methyl. In some embodiments the compound has Formula (23):} \\
\end{align*}
\]

The invention also features a compound of Formula II:

\[
\text{(II)}
\]

R₁ can be independently any of the groups described above for R₁ of Formula I. R₂ can be independently any of the groups described above for R₂ of Formula I. R₃ can be independently any of the groups described above for R₃ of Formula I. R₄ can be independently hydrido, alkyl, or hydroxyalkyl. R₅ can be independently hydrido, alkyl, or hydroxyalkyl. However, when R₁ is chloro, R₂ and R₃ are not hydroxy and R₄ and R₅ are methyl.

In some embodiments, R₁ is halo, R₂ and R₃ are hydroxy, and R₄ and R₅ are alkyl. In some embodiments, R₁ is halo, R₂ and R₃ are alkylsilyloxy, and R₄ and R₅ are alkyl, e.g., R₁ is chloro, R₂ and R₃ are OSi-t-BuMe₃, and R₄ and R₅ are methyl.

The invention also features a compound of Formula III:

\[
\text{(III)}
\]

In these compounds, R₁ can be independently any of the groups described above for R₁ of Formula I. R₂ can be independently any of the groups described above for R₂ of Formula I. R₃ can be independently any of the groups described above for R₃ of Formula I. R₄ can be independently hydrido, alkyl, or hydroxyalkyl. R₅ can be independently hydrido, alkyl, or hydroxyalkyl.

In some embodiments, R₁ is halo, R₂ and R₃ are selected from hydroxy, alkylsilyloxy, or aralkyloxy, R₄ and R₅ are alkyl, R₆ is selected from hydrido, hydroxy, or acyloxy, and R₇ is selected from alkyl or arylselenylalkyl, e.g., R₁ is chloro, R₂ and R₃ are OSi-t-BuMe₃, and R₄ and R₅ are methyl, R₆ is hydrido, and R₇ is methyl. In other embodiments, R₁ is chloro, R₂ and R₃ are hydroxy, R₄ and R₅ are methyl, R₆ is hydrido, and R₇ is methyl. In some embodiments, R₁ is chloro, R₂ and R₃ are aralkyloxy; R₄ and R₅ are methyl, R₆ is hydrido, and R₇ is methyl. In some embodiments, R₁ is chloro, R₂ and R₃ are aralkyloxy, R₄ and R₅ are methyl, R₆ is acyloxy, and R₇ is arylselenylalkyl. In some embodiments, R₁ is chloro, R₂ and R₃ are aralkyloxy, and R₄ and R₅ are methyl, R₆ is acyloxy, and R₇ is arylselenylalkyl. In some embodiments, R₁ is chloro, R₂ and R₃ are aralkyloxy; R₄ and R₅ are methyl, R₆ is acyloxy, and R₇ is methyl.
The invention also features a compound of Formula V:

\[
\text{(V)}
\]

\[
\begin{align*}
\text{R}_1, & \text{ can be independently any of the groups described above for } \text{R}_1 \text{ of Formula I. } \\
\text{R}_2, & \text{ can be independently any of the groups described above for } \text{R}_2 \text{ of Formula I. } \\
\text{R}_3, & \text{ can be independently any of the groups described above for } \text{R}_3 \text{ of Formula I. } \\
\text{R}_4, & \text{ can be independently hydrido, alkyl, or hydroxyalkyl. } \\
\text{R}_5, & \text{ can be independently hydrido, alkyl, or hydroxyalkyl. } \\
\text{R}_6, & \text{ can be hydrido, alkyl, or hydroxyalkyl. } \\
\text{R}_7, & \text{ can be hydroxy. } \\
\text{R}_8, & \text{ can be independently hydroxy, or alkylsilyloxy. }
\end{align*}
\]

In some embodiments, \( \text{R}_1 \) is halo; \( \text{R}_2 \) and \( \text{R}_3 \) are arylaalkyloxy; \( \text{R}_4 \) and \( \text{R}_5 \) are alkyl; \( \text{R}_6 \) is hydroxy; and \( \text{R}_7 \) is selected from hydroxy and alkylsilyloxy, e.g., \( \text{R}_7 \) 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 feature a method of synthesizing a compound of Formula I:

\[
\text{(I)}
\]

\[
\begin{align*}
\text{R}_1, & \text{ is chloro; } \\
\text{R}_2 \text{ and } \text{R}_3, & \text{ are OSi-tBuMe. The method further comprises isolating compound (18) and deprotecting compound (18). The result is a compound of Formula I. }
\end{align*}
\]

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

\[
\text{(25)}
\]

Desilylation of compound (25) forms compound (26).

\[
\text{(26)}
\]

wherein \( \text{R}_1 \) is chloro, \( \text{R}_2 \) and \( \text{R}_3 \) are OSi-tBuMe, \( \text{X}_1 \) is chloro, \( \text{X}_2 \) is bromo; 

\[
\begin{align*}
\text{R}_4 \text{ and } \text{R}_5, & \text{ are methyl. The method comprises reacting compound (4) with compound (3) to form intermediate compound (18). }
\end{align*}
\]

\[
\text{(4)}
\]

wherein \( \text{R}_6 \) is OSi-tBuMe, \( \text{X}_1 \) is chloro, \( \text{X}_2 \) is bromo;
Oxidation of compound (26) forms (+) chloropuupeheneone (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 be 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 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, intravenously, 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.

The composition can be in the form of a capsule or a liquid emulsion. The composition can be 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 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, intravenously, 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.
Compounds of Formula II

A second class of compounds is defined by Formula II:

\[
\begin{align*}
&\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5 \text{ is selected from hydrido, halo, alkyl, and hydroxyalkyl. The class of compounds also includes pharmaceutically-acceptable salts thereof.}
\end{align*}
\]

wherein \( \text{R}_1 \) is selected from moieties described above for \( \text{R}_1 \) groups of Formula I, \( \text{R}_2 \) is selected from the moieties described above for \( \text{R}_2 \) groups of Formula I, \( \text{R}_3 \) is selected from the moieties described above for \( \text{R}_3 \) groups of Formula I, \( \text{R}_4 \) is selected from hydrido, alkyl, and hydroxyalkyl, and \( \text{R}_5 \) 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 \( \text{R}_1 \) is halo, \( \text{R}_2 \) is selected from hydroxy and alkylsilyloxy; \( \text{R}_3 \) is selected from hydroxy, and alkylsilyloxy; \( \text{R}_4 \) is selected from hydrido, alkyl, and hydroxyalkyl; and \( \text{R}_5 \) 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:

\[
\text{Compounds of Formula III}
\]

A third class of compounds is defined by Formula III:

\[
\begin{align*}
&\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5 \text{ is selected from hydrido, halo, alkyl, and hydroxyalkyl.}
\end{align*}
\]

wherein \( \text{R}_1 \) is selected from the moieties described above for \( \text{R}_1 \) groups of Formula I, \( \text{R}_2 \) is selected from the moieties described above for \( \text{R}_2 \) groups of Formula I, \( \text{R}_3 \) is selected from the moieties described above for \( \text{R}_3 \) groups of Formula I, \( \text{R}_4 \) is selected from hydrido, alkyl, and hydroxyalkyl, and \( \text{R}_5 \) 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 III wherein \( \text{R}_1 \) is halo, \( \text{R}_2 \) is selected from hydroxy and alkylsilyloxy; \( \text{R}_3 \) is selected from hydroxy, and alkylsilyloxy; \( \text{R}_4 \) is selected from hydrido, alkyl, and hydroxyalkyl; and \( \text{R}_5 \) is selected from hydrido, alkyl, and hydroxyalkyl.
A family of specific compounds of particular interest within Formula III includes compounds and their pharmaceutically acceptable salts as follows:

\[ (4aS,6aR,12aR,12bS)-2H-9,10-Bis-(1-butyldimethylsilyloxy)-11-chloro-3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,6,4a,12b-tetramethyl-benz[a]xanthene (21); \]

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

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

\[ (4aS,6aR,12aR,12bS)-2H-11-Chloro-3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,6,12b-tetramethyl-benz[a]xanthene-9,10-diol (23); \]

\[ (4aS,6aR,12aS,12bS)-2H-11-Chloro-3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,6,12b-tetramethyl-benz[a]xanthene-9,10-diol (24). \]

A fourth class of compounds is defined by Formula IV:

\[ \text{(IV)} \]

Compounds of Formula IV

A fifth class of compounds is defined by Formula V:

\[ \text{(V)} \]

Compounds of Formula V

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

\[ (4aS,6aR,12aS,12bS)-2H-11-Chloro-3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,6a,12b-tetramethyl-benz[a]xanthene-9,10-diol (26); \]

\[ (4aS,6aR,12aS,12bS)-2H-9,10-Bis-(benzoxyl)-11-chloro-3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,12b-trimethyl-benz[a]xanthene (27); \]

\[ (4aS,6aR,12aS,12bS)-2H-12-Acetoxy-9,10-Bis-(benzoxyl)-11-chloro-3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,6a,12b-tetramethyl-benz[a]xanthene (42). \]
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, alkenyl, alkynyl, halogen, hydroxy, alkylcarboxylatoxy, arylicarboxylatoxy, aroyloxycarboxylatoxy, carboxylate, alkylcarboxyl, arylcarboxyl, alkoxycarboxyl, aminoarboxyl, alkylaminocarboxyl, dialkylaminocarboxyl, alklythiocarboxyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, and alkylarylamino), aerylamin (including alkylcarboxylamin, arylicarboxylamin, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthlio, thiocarboxylate, sulfates, alksulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluromethyl, cyano, azido, heterocyclic, alkylnyl, 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., phenylmethyl (benzyl)). The term “n-alkyl” means a straight chain (i.e., unbranched) unsubstituted alkyl group. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxy, alkylcarboxylatoxy, arylicarboxylatoxy, aroyloxycarboxylatoxy, carboxylate, alkylcarboxyl, arylcarboxyl, alkoxycarboxyl, aminoarboxyl, alkylaminocarboxyl, dialkylaminocarboxyl, alklythiocarboxyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamin, and alkylarylamino), acylamin (including alkylcarboxylamin, arylicarboxylamin, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthlio, thiocarboxylate, sulfates, alksulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluromethyl, cyano, azido, heterocyclic, alkylnyl, 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 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 (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycolyc or cycloalkenyl substituted alkenyl groups.

The term alkyl includes both “unsubstituted alkylens” and “substituted alkylens”, 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, alkynyl groups, halogens, hydroxy, alkylcarboxylatoxy, arylicarboxylatoxy, aroyloxycarboxylatoxy, carboxylate, alkylcarboxyl, arylcarboxyl, alkoxycarboxyl, aminoarboxyl, alkylaminocarboxyl, dialkylaminocarboxyl, alklythiocarboxyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamin, and alkylarylamino), acylamin (including alkylcarboxylamin, arylicarboxylamin, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthlio, thiocarboxylate, sulfates, alksulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluromethyl, cyano, azido, heterocyclic, alkylnyl, 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 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, and cycloalkyl of 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 hydroxy radicals may be attached to a carbon atom to form a methylenedioxy radicals (—CH(OH)O—) radical. The term “halo” means halogens such as fluorine, chlorine, bromine or iodine atoms. The term “halomethyl” expresses 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 “hydroxylalkyl” embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more halo radicals. The term “alkoxy” and “alkoxyalkyl” embrace linear or branched oxy-containing radicals. Examples of unsaturated alkyl radicals having one or more alkyl portions of one to 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 monoalkoxyalkyl and dialkoxalkyl radicals. The term “alkoxycarboxyalkyl” embraces radicals having a carboxy radical as defined above, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms “N-arylsulfoxamyl” and “N-aryl-N-arylsulfoxamyl” denote sulfonamido radicals substituted, respectively, with one aryl radical and one alkyl and one aryl radical. The terms “carboxy” or “carboxyl”, whether used alone or with other terms, such as “carboxymethyl”, denotes —CO₂H. The term “carboxyalkyl” embraces radicals having a carboxyl radical substituted with an alkyl radical. An example of an “alkylcarboxyl” radical is CH₃—(C=O)—. The term “alkylcarboxylalkyl” denotes an alkyl radical substituted with an “alkylcarboxyl radical”. The term
“alkoxyalkyl” means a radical containing an alkoxy group, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such “alkoxyalkyl” radicals include \((\text{CH}_3)_2\text{CO} - \text{C}(-\text{O}) - \text{C} - \text{OCH}_3\). The term “alkoxyalkyl” embraces radicals having “alkoxyalkyl”, as defined above, attached to an alkyl radical. Examples of such “alkoxyalkyl” radicals include \((\text{CH}_3)_2\text{CO} - \text{C}(-\text{O}) - \text{C} - \text{OCH}_3\) and \((\text{CH}_2)_2\text{CO} - \text{C}(-\text{O}) - \text{C} - \text{OCH}_3\). The term “amido” when used by itself or with other terms such as “amidoalkyl”, “N-monoalkylamido”, “N-alkyl-N-arylaminido”, “N,N-dialkylamido”, “N-alkyl-N-hydroxyamido” and “N-alkyl-N-hydroxyamidoalkyl” embraces a carbonyl radical substituted with an amino radical. The terms “N-alkylamido” and “N,N-dialkylamido” denote amido radicals which have been substituted with one alkyl and with two alkyl radicals, respectively. The terms “N-alkoxyamido” and “N-alkyl-N-hydroxyamidoalkyl” denote amido radicals substituted, with one alkyl radical, and with one alkyl and one aryl radical. The term “N-alkyl-N-hydroxyamido” embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term “N-alkyl-N-hydroxyamidoalkyl” embraces amido radicals substituted with an aryl radical and with one alkyl radical. The “amidoalkyl” embraces amido radicals substituted with an alkyl radical and with an aryl radical. The terms “N-alkylaminoalkyl” embraces amido radicals substituted with a hydroxyl radical and with one alkyl radical. The term “N-alkyl-N-acylamino” embraces amido radicals substituted with a hydroxyl radical and with one alkyl radical. The term “N-alkyl-N-acylaminoalkyl” embraces amido radicals substituted with an alkyl radical and with one alkyl radical. The term “N-alkyl-N-acylaminoalkyl” embraces amido radicals substituted with an alkyl radical and with one alkyl radical. 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utilized in the treatment of cholesterol-related conditions in polyvinylpyrrolidone, and/or polyvinyl alcohol, and then various buffers. Other adjuvants and modes of administration are dependent on 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 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 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 or in lymph. Administration of an effective amount results in a decrease in lymphatic absorption of cholesterol that is statistically significant at a p-value of 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 gangurol 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, 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, intravenously, intraperitoneally, subcutaneously, intramuscularly or topically.

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, hypercholesterolemia, heart attack, stroke, and gangrene of the extremities. 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, intravenously, 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.

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 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 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 MoO₃pyridine-HMPA 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-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 t-butyldimethylsiloxyl chloride, triethylamine, 4-dimethylaminopyridine (DMAP) gave aldehyde 13 (93% yield). 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 (90% yield) followed by protection of the diol with t-butyldimethylsiloxyl chloride (83% yield) provided trisilylether 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-butyldimethylsiloxyl 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.

Scheme 4
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-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-butyldimethylsilane chloride and imidazole in DMF gave alcohol 29 (98% yield). Elimination of 29 with methane-sulfonfyl 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 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 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 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 \(^1\text{H}\) and 100 MHz for \(^{13}\text{C}\) 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 60 (200–425 mesh), was used for the flash column chromatographic separation. Tetrahydropyran 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**

\[(\text{4S,8aS})-3,4,4a,5,6,7,8,8a-\text{Octahydro-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde}\]

Step 1: Preparation of \((\text{1S,3aR,5aS,9aS,9bR})-1-\text{Hydroxy-dodecahydro-3a,6,6,9a-tetramethylnaphthalene-2,1-diol}\)

To a cold (\(-78^\circ\text{C}\)) 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 \(\text{n-BuLi}\) (1.6 M in hexane). The solution was stirred at \(-78^\circ\text{C}\) for 1 h, and a solution of 1.50 g (5.99 mmol) of (+)-sclareolide 5 in 20 mL of THF was added via cannula dropwise. After the solution was stirred at \(-78^\circ\text{C}\) for 1 h, the mixture was diluted with diethyl ether, the organic layer was washed with water, and brine, dried (\(\text{Na}_2\text{SO}_4\)), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 0.67 g (65.6% yield) of compound 6 and 0.195 g (12% yield) of compound 9 along with 0.296 g (20% recovery) of compounds 7 and 8.

Step 2: Preparation of \((-\text{1S,1,2-Dihydroxymethyl})-(\text{1R,2R,4aS,8aS})-\text{Decahydro-2,5,5,8a-tetramethylnaphthalene-2,1-diol}\)

The following representative method describes the reduction of 6 to 7 to triol 8 and lactol 9. A solution of 0.90 g (3.4 mmol) of compound 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 were added, and the solution was extracted with diethyl ether three times (50 mL each). The combined ether extracts were washed with brine, dried (\(\text{MgSO}_4\)), 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 8 and 0.273 g (30% yield) of lactol 9.

Step 3: Preparation of \((-\text{1S,1,2-Dihydroxymethyl})-(\text{1R,2R,4aS,8aS})-\text{Decahydro-2,5,5,8a-tetramethylnaphthalene-2,1-diol}\)

The mixture was diluted with saturated aqueous \(\text{Na}_2\text{SO}_4\), extracted three times with ethyl acetate, and the organic layer was washed with water, and brine, dried (\(\text{Na}_2\text{SO}_4\)), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluent to give 0.50 g (74% yield) of compound 10.
eluent to give 0.516 g (90% yield) of aldehyde 10. [α]D 20.9° (c 0.0075, CHCl3); 1H NMR (CDCl3) δ 10.06 (d, J=3Hz, 1H, CHO), 2.93 (broad s, 1H, OH), 2.15 (d, J=3Hz, 1H, C1-H), 1.8-0.9 (a series of m, 11H), 1.20 (s, 3H, Me), 1.17 (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, 41.9, 38.9, 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-tetramethyl napthalene-1-carboxaldehyde (10)

To a flask equipped with a Dean-Stark apparatus under argon, 10 mg (0.042 mmol) of aldehyde 10, 10 mL of toluene, and 3 mg (0.017 mmol) of p-toluenesulfonic acid (PTS) 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 0.241 g (92% yield) of aldehyde 10.

Preparation of 5-Chloro-6-chloro-1,2,4-tris-(t-butyldimethylsilyloxy)benzene (12)

Compound 12 was prepared according to the procedure of Hann et al. (J. Am. Chem. Soc. 1927, 49, 535-7). To a solution of 2.50 g (16.4 mmol) of vanillin in 15 mL of glacial acetic acid was added chlorine gas through a glass tubing over 30 minutes (with a slow gas flow) at 25° C. White solid product was collected by filtration, washed with 50 mL of hexane, and dried in vacuo to give 2.033 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 of 12 was obtained. The white solids were collected in next step without purification. 1H NMR (CDCl3) δ 10.04 (s, 1H, OH), 9.76 (s, 1H, CHO), 7.56 (d, J=1.6 Hz, 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 (11)

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 1 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). To 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, OH), 9.70 (s, 1H, CHO), 7.42 (d, J=2.0Hz, 1H, C6-H), 7.22 (d, J=2.0Hz, 1H, C2-H); 13C NMR (CDCl3) δ 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 dichloromethane under argon at 0° C. were added 9.80 mL (68.0 mmol) of distilled triethylamine and 4.40 g (59.2 mmol) of 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 1H NMR (DMSO-d6) 6 190.6 (C=O), 148.3 (s), 146.9 (s), 128.4 (d), 124.2 (d), 120.3 (s), 112.5 (s).
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-chlorophenyl 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). Anal. Calcd for C₂₆H₂₇BrClO₃Si₆: C, 53.12; H, 7.21; Br, 19.10; Cl, 10.32. Found: C, 53.19; H, 7.23; Br, 19.25; Cl, 10.35.

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 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 the next step without purification. H NMR (CDCl₃) δ 6.53 (s, 1H, Ar), 6.13 (s, 1H, Ar), 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). Anal. Calcd for C₁₄H₁₀BrClO₃Si₃: C, 49.51; H, 9.76. Found: C, 49.78; H, 8.11.

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

A mixture of 0.650 g (1.30 mmol) of 14 and 0.276 g (1.60 mmol) of N-bromosuccinimide (NBS) in 10 mL of DMF under argon was stirred at 25°C for 5 days. The reaction mixture was diluted with 30 mL of water, extracted three times with diethyl ether (50 mL each), and the combined extracts were washed with 30 mL of brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluent to give 0.045 g (99% yield) of 4.

Example 4

\[
\begin{align*}
\text{Me}-\text{Bu-SiO} & \quad \text{OSi-tBu-Br-Me} \\
\text{Me}-\text{Bu-SiO} & \quad \text{Br}
\end{align*}
\]
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 gradient mixture of hexane and diethyl ether (90:10) as eluent to give 31.4 mg (27% yield) of 4 and 62.9 mg (11% yield) of 6.54 (s, 1H, Ar, C6-H), 1.03 (s, 18H, t-Bu), 0.97 (s, 9H, t-Bu), 0.23 (s, 12H, Me), 0.17 (s, 6H, Me).

Step 1: Preparation of (4aS,6aR,12bS)-2H-9,10-bis-(t-Butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,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-4,4,6a,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 water, 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) of 18 and 0.200 g (9.1% yield) of 19. Compound 18: [α]D<sub>22</sub><sup>2</sup> = +50° (c 0.018, CHCl₃); 1H NMR (CDCl₃) δ 6.43 (s, 1H, Cl-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, 9H, t-BuSi), 0.95 (s, 9H, t-BuSi), 0.92 (s, 3H, Me), 0.87 (s, 3H, Me), 0.21 (s, 3H, MeSi), 0.20 (s, 3H, MeSi), 0.17 (s, 3H, MeSi). 13C NMR (CDCl₃) δ 151.3, 147.3, 146.1, 138.1, 123.6, 115.7, 111.7, 107.9, 78.0, 52.3, 41.8, 38.2, 33.8, 33.6, 26.4 (3C, t-Bu), 26.3 (3C, t-Bu), 26.1, 25.1, 23.7, 19.5, 19.1, 18.9, –3.2, –3.46, –3.49, –3.6. Compound 19: [α]D<sub>22</sub><sup>2</sup> = +50° (c 0.018, CHCl₃); 1H NMR (CDCl₃) δ 6.39 (s, 1H, Cl-H), 6.31 (s, 1H, Cl2-H), 2.20–0.90 (m, 11H), 1.31 (3H, Me), 1.23 (s, 3H, Me), 1.03 (s, 9H, 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, 52.4, 41.2, 39.4, 39.1, 34.0, 33.2, 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. Calcd for C₃₃H₄₃ClO₃Siz: c, 67.02; H, 9.37. Found: 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.

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

To a solution of 0.160 g (0.270 mmol) of 18 in 3 mL of THF under argon at 25°C was added 0.58 mL (0.600 mmol) of tetra-n-butylammonium fluoride (1.0 M in THF). After stirring at 25°C for 5 min., 0.30 mL of acetic acid was added, the resulting solution was concentrated on a rotary evaporator, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluent to give 0.080 g (82% yield) of 1. [α]<sub>D</sub> = +50° (c 0.018, CHCl₃); 1H NMR (CDCl₃) δ 6.42–6.20 (broad s, 3H, OH), 6.28 (broad s, 1H, OH), 6.21 (d, J=12 Hz, 1H), 2.01 (d, J=12 Hz, 1H), 1.86–0.90 (a series of m, 9H), 1.42 (3H, Me), 1.15 (s, 3H, Me), 0.92 (s, 3H, Me), 0.87 (s, 3H, Me). 13C NMR (CDCl₃) δ 151.3, 147.3, 146.1, 138.1, 123.6, 115.7, 111.7, 107.9, 78.0, 52.3, 41.8, 38.2, 33.9, 33.5, 33.0, 21.9, 21.4, 20.9, 19.5, 19.1.
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, [α]_D^22=+1,1~ (. Step 2: Preparation of 

0.194 MeSi), 0.15 (s, 3H, Me); 13C NMR (CDCl, ) δ 151.3, 148.5, 146.1, 133.6, 123.6, 116.5, 110.6, 103.0, 78.0, 43.8, 42.0, 39.1, 33.8, 32.7, 30.8, 30.3, 25.0. 6a, 9, 10, 12, 12a, 12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,10-dione (22) was added to 0.20 mL (0.20 mmol) of tetra-n-butylammonium fluoride (1 M in THF). The solution was stirred for 30 min., 1 drop of acetic acid was added, 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. [H NMR (CDCl, ) δ 6.35 (s, 1H, C8H), 2.61 (d, J=17 Hz, 1H, C12H), 2.34 (m, 1H, C12H), 2.02 (dt, J=12, 3 Hz, lH), 1.80–0.90 (a series of m, 11H), 1.14 (s, 3H, Me). 0.85 (s, 3H, Me). When the proton NMR spectrum was measured in benzene-d6 solvent, all methyl groups are separated, 8 0.99 (s, 3H, Me), 0.71 (s, 3H, Me), 0.61 (s, 3H, Me). 13C NMR (CDCl, ) δ (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, 21.6, 19.8, 19.1, 18.7, 14.7. Step 3: Preparation of 

(4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,9,10,12b-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 6:1 (obtained from NMR spectrum). [H NMR (CDCl, ) δ 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, 1H, 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). Example 9

(4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,9,10,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (21) A mixture of 0.180 g (0.300 mmol) of compound 18 and 0.400 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 short Celite column, washed the column with ethanol, and the combined filtrate was concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and toluene as eluent to give 0.180 g (99% yield) of 60. 

Example 8

Step 1: Preparation of 

(4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,9,10,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (21) A mixture of 0.180 g (0.300 mmol) of compound 18 and 0.400 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 short Celite column, washed the column with ethanol, and the combined filtrate was concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and toluene as eluent to give 0.180 g (99% yield) of 60. 

Example 9

Step 1: Preparation of 

(4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,9,10,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (21) A mixture of 0.180 g (0.300 mmol) of compound 18 and 0.400 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 short Celite column, washed the column with ethanol, and the combined filtrate was concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and toluene as eluent to give 0.180 g (99% yield) of 60.
was filtered through Celite, rinsed with diethyl ether, 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 6.21 (s, 1H, C8H), 7.75 (d, J = 18 Hz, 1H, C12H), 2.64 (dd, J = 18, 8 Hz, 1H, C1H), 2.10 (d, J = 11 Hz, 1H, C1H), 1.85 (d, J = 12 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, 27.1, 26.4 (2C, t-Bu), 26.3 (3C, t-Bu), 22.1, 21.9, 18.9, 18.7, 18.5, 14.1, –3.3 (2C, MeSi), –3.5, –3.6. Anal. Calcd for C20H17ClO3Si: C, 71.49; H, 4.86. Found: C, 71.24; H, 5.00.

To a solution of 50 mg (0.084 mmol) of 25 in 2 mL of THF under argon at 25° C. was added 0.25 mL (0.25 mmol) of 4-Br-3-CH2Cl-4-OH. The solution was stirred for 15 min., 1 drop of acetic acid was added, the resulting red solution was concentrated to provide 0.54 g (90% yield) of compound 26. [α]D = +0.220 (c 0.032 mmol, CHCl3); 1H and 13C NMR spectral data are similar to those reported (M attorney, P. J., J. Org. Chem., 1993, 58, 6565–6569).

Example 10

### Lympmatic 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.

### TABLE 1

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (g/kg)</th>
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<tbody>
<tr>
<td>Egg white</td>
<td>200.0</td>
</tr>
<tr>
<td>Corn starch</td>
<td>39.5</td>
</tr>
<tr>
<td>Dextinsized corn starch</td>
<td>132.0</td>
</tr>
<tr>
<td>Dextrose</td>
<td>100.0</td>
</tr>
<tr>
<td>Cellulose</td>
<td>50.0</td>
</tr>
<tr>
<td>Soybean oil2</td>
<td>70.0</td>
</tr>
<tr>
<td>Mineral mix</td>
<td>35.0</td>
</tr>
<tr>
<td>Vitamin mix</td>
<td>10.0</td>
</tr>
<tr>
<td>Biotin (1 mgg biotin sucrose mix)</td>
<td>4.0</td>
</tr>
<tr>
<td>Choline bitriate</td>
<td>2.5</td>
</tr>
</tbody>
</table>

1Formulated and supplied from Dyets, Bethlehem, PA, according to the recommendations of the AIN-93.
2Contained 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. 1.00 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 NaHPO4, 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 lip 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.), 33.3 kBq [3-L-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 subdued light for 55 min using a microprocessor-controlled ultrasonicator equipped with a microtip (XI-2020 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 (ScintiVerse; Fisher Scientific, Fair Lawn, N.J.) and counted by scintillation spectrometry (Beckman LS-6500; Beckman Instruments, Fuller-ton, Calif.). The total 14C-radioactivity appearing in hourly lymph volume (the hourly rates of 14C-CH₃ 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 methylethered 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.

### Table 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Control 14C-CH₃ %</th>
<th>Compound 1 14C-CH₃ %</th>
</tr>
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<tbody>
<tr>
<td>1 h</td>
<td>0.16 ± 0.07</td>
<td>0.12 ± 0.04</td>
</tr>
<tr>
<td>3 h</td>
<td>1.84 ± 0.37</td>
<td>1.22 ± 0.25*</td>
</tr>
<tr>
<td>5 h</td>
<td>3.51 ± 0.74</td>
<td>2.70 ± 0.42*</td>
</tr>
<tr>
<td>7 h</td>
<td>10.16 ± 1.31</td>
<td>4.18 ± 0.92*</td>
</tr>
<tr>
<td>9 h</td>
<td>15.96 ± 1.75</td>
<td>5.68 ± 1.37*</td>
</tr>
<tr>
<td>11 h</td>
<td>22.14 ± 1.81</td>
<td>7.32 ± 1.78*</td>
</tr>
<tr>
<td>13 h</td>
<td>29.79 ± 1.65</td>
<td>9.13 ± 2.41*</td>
</tr>
<tr>
<td>15 h</td>
<td>37.69 ± 1.76</td>
<td>10.95 ± 3.20*</td>
</tr>
</tbody>
</table>

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

After 8 hours of treatment, the control rats (without drug) had a percent cholesterol absorption of 37.69%, while the treated rats (treated with compound 1) had a percent cholesterol absorption of 10.95%. Under similar test conditions, rats infused with 120.5 mg of green tea catechins per rat per 8 hours had a percent cholesterol absorption of about 10%.

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

<table>
<thead>
<tr>
<th>Table 3</th>
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<tbody>
<tr>
<td>Time</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1 h</td>
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<tr>
<td>3 h</td>
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<td>13 h</td>
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<tr>
<td>15 h</td>
</tr>
</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 I:

   ![](I)

   wherein Rᵢ is independently hydroxido, halo, alkyl, alkenyl, alkyloxy, haloalkyl, hydroxalkyl, hydroxy, alkoxy,
alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alky carboxynalkyl, alky carbonylandalkyl, alkoxy carbonyl, alkoxy carbonylandalkyl, N,N-dialkylsulfamyl, N,alkylsulfonyl, alky lamido, amidino, amino, aminoalkyl, alklylaminoalkyl, amidino, cyano, cyanamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, hydroxy, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, alkylsilyloxy; R₂ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcarbonyl, alkyl carbonylandalkyl, alkoxy carbonyl, alkoxy carbonylandalkyl, N,N-dialkylsulfamyl, N,alkylsulfonyl, alky lamido, amidino, amino, aminoalkyl, alklylaminoalkyl, amidino, cyano, cyanamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, hydroxy, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, alkylsilyloxy; R₃ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcarbonyl, alkyl carbonylandalkyl, alkoxy carbonyl, alkoxy carbonylandalkyl, N,N-dialkylsulfamyl, N,alkylsulfonyl, alky lamido, amidino, amino, aminoalkyl, alklylaminoalkyl, amidino, cyano, cyanamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, hydroxy, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, alkylsilyloxy; R₂ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcarbonyl, alkyl carbonylandalkyl, alkoxy carbonyl, alkoxy carbonylandalkyl, N,N-dialkylsulfamyl, N,alkylsulfonyl, alky lamido, amidino, amino, aminoalkyl, alklylaminoalkyl, amidino, cyano, cyanamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, hydroxy, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, alkylsilyloxy; or a pharmaceutically-acceptable salt thereof.

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

3. The compound of claim 2, wherein R₂ is chloro and R₄ and R₅ are methyl.

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

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

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

7. A compound of Formula II:

wherein R₂ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcarbonyl, alkyl carbonylandalkyl, alkoxy carbonyl, alkoxy carbonylandalkyl, N,N-dialkylsulfamyl, N,alkylsulfonyl, alky lamido, amidino, amino, aminoalkyl, alklylaminoalkyl, amidino, cyano, cyanamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, hydroxy, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, alkylsilyloxy; R₂ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcarbonyl, alkyl carbonylandalkyl, alkoxy carbonyl, alkoxy carbonylandalkyl, N,N-dialkylsulfamyl, N,alkylsulfonyl, alky lamido, amidino, amino, aminoalkyl, alklylaminoalkyl, amidino, cyano, cyanamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, hydroxy, sulfonate, thiol, arylsulfenyl, alkylsilyl, phenylselenyl, or alkylsilyloxy; R₃ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcarbonyl, alkyl carbonylandalkyl, alkoxy carbonyl, alkoxy carbonylandalkyl, N,N-dialkylsulfamyl, N,alkylsulfonyl, alky lamido, amidino, amino, aminoalkyl, alklylaminoalkyl, amidino, cyano, cyanamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, hydroxy, sulfonate, thiol, arylsulfenyl, alkylsilyl, phenylselenyl, or alkylsilyloxy; R₄ is independently hydrido, alkyl, or hydroxalkyl; or a pharmaceutically-acceptable salt thereof.

2. The compound of claim 1, wherein R₂ is halo, R₃ and R₄ are hydroxy, and R₅ and R₆ are alkyl.

3. The compound of claim 2, wherein R₂ is chloro and R₆ and R₇ are methyl.

4. The compound of claim 1, wherein R₂ is halo, R₃ and R₆ are alkylsilyloxy, and R₇ and R₈ are alkyl.

5. The compound of claim 4, wherein R₂ is chloro, R₃ and R₇ are O,Si-t-BuMe₃, and R₆ and R₇ are methyl.
wherein R₂ is independently hydrido, halo, alkyl, alkenyl, alkylalkyl, haloalkoxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N-arylsulfonyl, carboxy, carboxyalkyl, alkylenecarbonyl, alkylcarbonylalkyl, alkoxyalcohol, alkoxyalkylcarbonyl, alkylcarbonylalkyl, alkoxyalkylcarbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monooamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxymido, N-aryl-N-hydroxymido, N,N-dialkylamido, a pharmaceutically-acceptable salt thereof.

10. A compound of claim 11, wherein R₁ is chloro, R₂ and R₃ are not hydroxy and R₄ is methyl.

11. A compound of Formula III:

\[
\begin{align*}
R₁ & = \text{independently hydrido, halo, alkyl, alkenyl, alkylalkyl, haloalkoxy, haloalkoxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N-arylsulfonyl, carboxy, carboxyalkyl, alkylenecarbonyl, alkylcarbonylalkyl, alkoxyalcohol, alkoxyalkylcarbonyl, alkylcarbonylalkyl, alkoxyalkylcarbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monooamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxymido, N-aryl-N-hydroxymido, N,N-dialkylamido, a pharmaceutically-acceptable salt thereof.}
\end{align*}
\]

12. The compound of claim 11, wherein R₁ is halo, R₂ and R₃ are selected from hydroxy and alkylsilyloxy, and R₄ is alkyl.

13. The compound of claim 11, wherein R₁ is chloro, R₂ and R₃ are hydroxy, and R₄ and R₅ are methyl.

14. The compound of claim 11, wherein R₁ is halo, R₂ and R₃ are alkylsilyloxy, and R₄ and R₅ are methyl.

15. The compound of claim 14, wherein R₁ is chloro, R₂ and R₃ are OsI₅BuMe₂, and R₄ and R₅ are methyl.

16. The compound of claim 11, wherein said compound has Formula (23):
17. A compound of Formula IV:

amidoalkyl, aminooalkyl, alkylamidoalkyl, amidino,
cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl,
cycloalkenyl, alkythio, alky sulfanyl, N-alkylamido,
N,N-dialky lamino, acyl, acyloxy, aryloxy, acylamino,
aminoo, cyano, nitro, sulfonate, thiol, aryl sulfenyl, alky sulfanyl, aryl sulfinyl, alkylsilyl,
phenylselenyl, or alkylsilyloxy;
R₃ is independently hydrido, halo, alkyl, alkenyl,
alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy,
alkoxyalkyl, haloalcoxyalkyl, aryl, heterocyclic, heteroaryl, alky sulfonyl, aryl sulfonyl,
N-alkylsulfamyl, N,N-dialkylsulfamyl,
N-aryl sulfonfonyl, N-alkyl-N-aryl sulfamyl, carboxy,
carboxyalkyl, alky carbonyl, alkyl carbonylalkyl,
alkoxycarbonyl, alkoxycarbonylalkyl, amidino,
N-alkylamido, N,N-dialkylamido,
N-monooxazolamido, N-alkyl-N-aryl amido, N-alkyl-
N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl,
amidoalkyl, aminooalkyl, alkylamidoalkyl, amidino,
cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl,
cycloalkenyl, alkythio, alky sulfanyl, N-alkylamido,
N,N-dialky lamino, acyl, acyloxy, aryloxy, acylamino,
aminoo, cyano, nitro, sulfonate, thiol, aryl sulfenyl, alky sulfanyl, aryl sulfinyl, alkylsilyl,
phenylselenyl, or alkylsilyloxy;
R₄ is independently hydrido, alkyl, or hydroxyalkyl;
R₅ is independently hydrido, alkyl, or hydroxyalkyl;
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 arylalkyloxy; R₄ and R₅ are alkyl; R₆ is hydroxy; and
R₇ is selected from hydroxy and alkoxyalkyloxy.

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:

wherein, R₈ is OSi-t-BuMe₂, X₁ is chloro, X₂ is bromo,
with compound (3);

50.

50. The compound of claim 24, wherein, R₁ is chloro,
R₂ and R₃ are OSi-t-BuMe₂,
b) isolating said intermediate compound (18); and
c) deprotecting said intermediate compound.

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

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

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

wherein, R₁ is chloro, R₂ and R₃ are OSi-t-BuMe₂,
R₄ is OSi-t-BuMe₂, and
R₅ is hydrido.
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 lipid 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:

   \[
   \begin{array}{c}
   \text{OH} \\
   \text{Cl} \\
   \text{H}
   \end{array}
   \]

   at least one pharmaceutically-acceptable carrier material.

35. The composition of claim 34, wherein said at least one pharmaceutically-acceptable carrier material is selected from the group consisting of lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, 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 polyvinyl alcohol.

36. The composition of claim 34, wherein said composition is in the form of a capsule or a liquid emulsion.

37. The composition of claim 34, wherein said composition is provided in a controlled release formulation.

38. The composition of claim 37, wherein said composition is provided as a dispersion in hydroxypropylmethyl cellulose.

39. The composition of claim 34, wherein said composition is in a formulation suitable for parenteral administration.

40. The composition of claim 39, wherein said formulation is a lipid emulsion.

41. The composition of claim 34, wherein said composition comprises a diluent selected from the group consisting of polyethylene glycol, propylene glycol, 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.

42. A method of treating a cholesterol-related condition, comprising administering an effective amount of a compound of Formula 1 to a mammal.

43. The method of claim 42, wherein said cholesterol-related condition is selected from the group consisting of atherosclerosis, hypercholesterolemia, heart attack, gangrene, and stroke.

44. The method of claim 42, wherein said cholesterol-related condition is selected from the group consisting of atherosclerosis, hypercholesterolemia, heart attack, gangrene, and stroke.

45. The method of claim 42, wherein said compound is administered orally, intravenously, intraperitoneally, subcutaneously, intramuscularly, or topically.

46. The method of claim 42, wherein said compound is administered in an amount from about 4 mg/kg to about 4 g/kg of body weight per day.

47. The method of claim 42, wherein said compound is administered as part of a treatment regimen comprising a diet low in cholesterol.

48. The method of claim 42, wherein said compound is administered as part of a treatment regimen comprising one or more HMG-CoA reductase inhibitors.

49. The method of claim 42, wherein said mammal is a human.

50. The method of claim 49, wherein said compound is administered for 7 days or more.

51. The method of claim 48, wherein said compound is administered in an amount from about 4 mg/kg body weight to about 4 g/kg body weight per day.

* * * * *
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