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

![Diagram](https://ntrs.nasa.gov/search.jsp?R=20080005998)

or a pharmaceutically acceptable salt thereof.

51 Claims, 4 Drawing Sheets
OTHER PUBLICATIONS


FIG. 1

![Graph showing 
\[
\text{\^{14}C-CH absorption (\% dose/h)}
\]
vs.
\[
\text{Time (h)}
\]
for Control (○) and Compound I (●). The graph indicates a time-dependent increase in 
\[
\text{\^{14}C-CH absorption}
\]
with significant differences marked by asterisks (*).}
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
FIG. 3
FIG. 4

Concentration (μM)

Inhibition (%)

Concentration (μM)

Ferroverdin A
1

COMPONDS AFFECTING CHOLESTEROL ABSORPTION

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

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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 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® (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® (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, alkoxycarbonyl, haloalkoxycarbonyl, alkoxycarbonyl, haloalkoxycarbonylalkyl, amido, N-alkylamidoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkylsulfenyl, N-alkylamino, N,N-dialkylamino, acyl, aceloxy, arloxy, acylamino, amino, cyano, nitro, sulfonate, alkyisilyl, phenyliselenenyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfenyl, or arylsilylsoxy.

R₂ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxycarbonyl, haloalkoxycarbonyl, alkoxycarbonyl, haloalkoxycarbonylalkyl, amido, N-alkylamidoalkyl, amidino, cyanoamidino, heterocyclusocalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkylsulfenyl, N-alkylamino, N,N-dialkylamino, acyl, aceloxy, arloxy, acylamino, amino, cyano, nitro, sulfonate, alkyisilyl, phenyliselenenyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfenyl, or arylsilylsoxy.

R₃ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxycarbonyl, haloalkoxycarbonyl, alkoxycarbonyl, haloalkoxycarbonylalkyl, amido, N-alkylamidoalkyl, amidino, cyanoamidino, heterocyclusocalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkylsulfenyl, N-alkylamino, N,N-dialkylamino, acyl, aceloxy, arloxy, acylamino, amino, cyano, nitro, sulfonate, alkyisilyl, phenyliselenenyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfenyl, or arylsilylsoxy.

R₄ can be independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxycarbonyl, haloalkoxycarbonyl, alkoxycarbonyl, haloalkoxycarbonylalkyl, amido, N-alkylamidoalkyl, amidino, cyanoamidino, heterocyclusocalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkylsulfenyl, N-alkylamino, N,N-dialkylamino, acyl, aceloxy, arloxy, acylamino, amino, cyano, nitro, sulfonate, alkyisilyl, phenyliselenenyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfenyl, or arylsilylsoxy.

R₅ can be independently hydrido, alkyl, or hydroxyalkyl.

R₆ can be independently hydrido, alkyl, or hydroxyalkyl.

R₇ can be independently hydrido, alkyl, or hydroxyalkyl.

In some embodiments, R₁ is halo, R₂ and R₃ are hydroxy, and R₄ and R₅ are alkyl in the compound, e.g., R₁ is chloro and R₂ and R₃ are methyl. In other 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-BuMe₂, and R₄ and R₅ are methyl. In one embodiment, the compound has Formula (24):
In some embodiments, $R_1$ is halo, $R_2$ and $R_3$ are selected from hydroxy and alkylsilyloxy, and $R_4$ and $R_5$ are alkyl, e.g., $R_1$ is chloro, $R_2$ and $R_3$ are hydroxy, and $R_4$ and $R_5$ are methyl. In some embodiments, $R_1$ is halo, $R_2$ and $R_3$ are alkylsilyloxy, and $R_4$ and $R_5$ are methyl, e.g., $R_1$ is chloro, $R_2$ and $R_3$ are OSi-t-BuMe$_2$, and $R_4$ and $R_5$ are methyl. In some embodiments the compound has Formula (23):

\[
\text{Formula (23)}
\]

The invention also features a compound of Formula IV:

\[
\text{Formula (IV)}
\]

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

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

In some embodiments, \( R_1 \) is halo; \( R_2 \) and \( R_3 \) are arylaalkyloxy; \( R_4 \) and \( R_5 \) are alkyl; \( R_6 \) is hydroxy; and \( R_7 \) is selected from hydroxy and alkylsilyloxy, e.g., \( R_7 \) is chloro; \( R_2 \) and \( R_3 \) are OBn; and \( R_4 \) and \( R_5 \) are methyl; \( R_6 \) is hydroxy; and \( R_8 \) is OSi-t-BuMe,. 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 \( R_8 \) is hydroxy.

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

\[
\begin{align*}
\text{Desilylation of compound (25) forms compound (26).}
\end{align*}
\]
Oxidation of compound (26) forms (+) chloropaupehenone (27).

\[
\begin{align*}
\text{Cl} & \quad \text{OH} \\
\text{Cl} & \quad \text{OH} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{Cl} & \quad \text{OH} \\
\text{Cl} & \quad \text{OH} \\
\end{align*}
\]

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 can be lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, tallow, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, polyvinylpyrrolidone, or polyvinyl alcohol.

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

The invention also features a method of treating a cholesterol-related condition. The method comprises administering an effective amount of a compound of Formula I to a mammal. The cholesterol-related condition can be, for example, atherosclerosis, hypercholesterolemia, heart attack, gangrene, and stroke. The compound can be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, or topically, and in an amount from about 4 mg/kg to about 4 g/kg of body weight per day. The compound can be administered in a composition as described above. The method can be part of a treatment regimen comprising a diet low in cholesterol, or as part of a treatment regimen that includes administering an HMG-CoA reductase inhibitors. The method can be used to treat humans. The method can include administering the compound for 7 days or more, e.g., for one year or more.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

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

**DESCRIPTION OF DRAWINGS**

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

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

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

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

**DETAILED DESCRIPTION**

Compounds of Formula I

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

\[
\begin{align*}
R_1 & \quad R_2 & \quad R_3 & \quad R_4 & \quad R_5 \\
\end{align*}
\]

wherein R₁ is selected from hydrido, halo, alkyl, alkenyl, alkylyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy,
Compressed text of the image can be expanded as follows:

Within Formula I, wherein R₁ is selected from moieties described above for R₁ groups of Formula I, R₂ is selected from the moieties described above for R₂ groups of Formula I, R₃ is selected from the moieties described above for R₃ groups of Formula I, R₄ is selected from hydrido, alkyl, and hydroxyalkyl, and R₅ 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 R₁ is halo, R₂ is selected from hydroxy and alkylsilyloxy; R₃ is selected from hydroxy, and alkylsiloxyl; R₄ is selected from hydrido, alkyl, and hydroxyalkyl; and R₅ 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:

Compounds of Formula III consists of compounds and their pharmaceutically acceptable salts thereof as follows:

(4aS,6aR,12bS)-2H-9,10-Diol (1); and

(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 (19).

Compounds of Formula III consists of compounds and their pharmaceutically acceptable salts thereof as follows:

(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 (19).
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-butylidemethylbenzoyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decachydro-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-decachydro-4,4,6a,12b-tetramethyl-benzo[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-1,3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,10-dione (23); and

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

Compounds of Formula IV

A fourth class of compounds is defined by Formula IV:

wherein R₂ is selected from the moieties described above for R₂ groups of Formula I, R₃ is selected from the moieties described above for R₃ groups of Formula I, R₄ is selected from hydrido, alkyl, and hydroxyalkyl, R₅ is selected from hydrido, alkyl, and hydroxyalkyl, R₆ is selected from hydrido, hydroxy, and acyloxy, and R₇ is selected from alkyl and arylselenylalkyl. The class of compounds also includes pharmaceutically acceptable salts thereof.

An exemplary class of compounds includes those compounds of Formula IV wherein R₂ is halo, R₃ is selected from hydroxy, alkyloxyl and aralkyloxyl, R₄ is selected from hydroxy, alkylxoyl and aralkyloxyl, R₅ is selected from hydrido, alkyl, and hydroxyalkyl, R₆ is selected from hydrido, hydroxy, and acyloxy and R₇ is selected from alkyl and arylselenylalkyl.

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

(4aS,6aR,12aR,12bS)-2H-9,10-Bis-(1-butylidemethylbenzoyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (25); (4aS,6aS,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,10-diol (26); (4aS,6aR,12aS,12bS)-2H-9,10-Bis-(benzoyloxy)-11-chloro-hydroxy-6a-(phenylselenylmethyl)-1,3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,12b-trimethyl-benzo[a]xanthene (40); (4aS,6aR,12aS,12bS)-2H-12-Acetoxy-9,10-bis-(benzoyloxy)-11-chloro-hydroxy-6a-(phenylselenylmethyl)-1,3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,12b-trimethyl-benzo[a]xanthene (41); and (4aS,6aS,12aS,12bS)-2H-12-Acetoxy-9,10-bis-(benzoyloxy)-11-chloro-hydroxy-6a-(phenylselenylmethyl)-1,3,4,4a,5,6,6a,12,12a,12b-decachydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (42).

Compounds of Formula V

A fifth class of compounds is defined by Formula V:
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, alklenyl, alkenyll, halogen, hydroxyl, alkylcarbonyloxy, aryalkoxyalkyloxoy, alkoxycarbonyloxy, aryloxyalkyloxoy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkylox, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino), aryalkylamino, carbonamyl and ureido), imino, amino, sulfhydryl, alklythio, thioxyalcohol, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocycl, alkylaryl or alkylaryl substituted cycloalkyl or cycloalkenyl groups, and whether used alone or with other terms, such as acetamido, amidino, imino, 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. The term “alkenyl” includes both “unsubstituted alkenyls” and “substituted alkenyls”, the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkenyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, aryalkoxyalkyloxoy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkylox, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino), aryalkylamino, carbonamyl and ureido), imino, amino, sulfhydryl, alklythio, thioxyalcohol, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl or alkylaryl substituted cycloalkyl or cycloalkenyl groups, and whether used alone or with other terms, such as acetamido, amidino, imino, or an aromatic or heteroaromatic moiety. The term “alkenyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkenyl groups described above, but which contain at least one triple bond and must contain at least two carbon atoms. For example, the term “alkenyl” includes straight-chain alkenyl groups (e.g., ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene, nonylene, decylene, etc.), branched-chain alkenyl groups, cycloalkenyl (cyclic) groups (cyclopropenyl, cyclopropenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl 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, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, aryalkoxyalkyloxoy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkylox, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino), aryalkylamino, carbonamyl and ureido), imino, amino, sulfhydryl, alklythio, thioxyalcohol, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl or alkylaryl substituted cycloalkyl or cycloalkenyl groups, and whether used alone or with other terms, such as acetamido, amidino, imino, or an aromatic or heteroaromatic moiety. The term “alkenyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkenyl groups described above, but which contain at least one triple bond and two carbon atoms. For example, the term “alkenyl” includes straight-chain alkenyl groups (e.g., ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene, nonylene, decylene, etc.), branched-chain alkenyl groups, cycloalkenyl (cyclic) groups (cyclopropenyl, cyclopropenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl 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 to two hydroxyl radicals may be attached to a carbon atom to form a methylenone (—CH2—) radical. The term “halo” means halogens such as fluoride, 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. Dichloro 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 hydroxyl radicals. The terms “alkoxy” and “alkoxyalkyl” embrace linear or branched oxy-containing radicals, each having alkylenone portions of one to about ten carbon atoms, such as methoxy radical. The term “alkoxyalkyl” also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The “alkoxy” or “alkoxyalkyl” radicals may be further substituted with one or more halo atoms, such as fluoro chloro 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 carbohydrate aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused. The term “aryl” embraces aromatic radicals such as phenyl, naphthyl, tetrahydroanaphtyl, indane and biphenyl. The term “heterocyclic” embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heternatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include pyrroldiol and morpholinyl. The term “heteroaryl” embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals also termed “heteroaryl” radicals, also included thienyl, pyrrolyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyryl and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The term “sulfonyl”, whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals —SO2—. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The terms "sulfonyl" or "sulfonylamidyl", whether alone or used with terms such as "N-alkylsulfonyl" or "N-arylalkylsulfonyl" is used with such prefixes as "N-alkylsulfonylamidyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide (−SO2NH2). The terms "N-alkylsulfonyl" and "N-arylalkylsulfonyl" denote sulfonyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or alkyl radicals. The terms "N-arylsulfonylamidyl" and "N-arylsulfonylamidyl" denote sulfonyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The terms “carbonyloxy” or “carbonyl”, whether used alone or with other terms, such as “carboxylic”, aromatic system containing one, two or three rings. An example of an “alkylenone” radical is CH2— (C==0)—. The term “alkylenonealkyl” denotes an alkyl radical substituted with an “alkylenone” radical. The term
“alkoxy carbonyl” means a radical containing an alkoxy carbonyl, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such “alkoxy carbonyl” radicals include \((CH_3)CO\) and \(-O\) radicals. The term “alkoxy carbonylalkyl” embraces radicals having “alkoxy carbonyl”, as defined above, substituted to an alkyl radical. Examples of such “alkoxy carbonylalkyl” radicals include \((CH_3)COCH(C(O)(CH_3))\) and \(-O\) radicals. The term “amido” when used by itself or with other terms such as “amidino”, “N-monoamido”, “N, N-dialkylamido”, “N-alkyl-N-aryl amido”, “N-alkyl-N-hydroxyamido” and “N-alkyl-Nhydroxyamidoalkyl”, embraces a carbonyl radical substituted with an amino radical. The terms “N-alkylamido” and “NN-dialkylamido” denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The terms “N-monamido” and “N-alkyl-N-aryl amido” denote amido radicals substituted, respectively, with one aryl radical, and 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 alkyl radical. The term “amidoalkyl” embraces alkyl radicals substituted with amido radicals. The term “aminoalkyl” embraces alkyl radicals having the nitrogen atom substituted with an alkyl radical. The term “amidino” denotes an \(-C(=NH)-\) radical. The term “cyanoamidino” denotes an \(-C(=CN)-\) radical. The term “het erocycloalkyl” embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The term “alkylthioalkyl” embraces alkyl radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. The term “arylsulfonyl” embraces aryl radicals attached to a divalent sulfur atom (\(-S=OAr\)). An example of “alkylthio” is methylthio, \((CH_3)S-\). The term “alkylsulfanyl” embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent \(-S(O)-\) atom. The term “arylsulfonyl” embraces aryl radicals attached to a divalent \(-S(O)-\) atom (e.g., \(-S(O)=Ar\)). The terms “N-alkylamino” and “N,N-alkylamino” denote amine groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The term “acyl”, whether used alone, or within a term such as “acylamino”, denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term “acylamino” embraces an amine radical substituted with an acyl group. An example of an “acyl” radical is acetylamine, \((CH_3)COH\) or \(-COH-\). A pharmaceutical composition comprises one or more compounds of Formula I-V in association with one or more pharmaceuticallyacceptable base addition salts. Suitable pharmaceuticallyacceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N-dibenzylethylene diamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound or Formula I, II, III, IV or V by reacting, for example, the appropriate acid or base with the compound of Formula I, II, III, IV or V. Suitable pharmaceuticallyacceptable base addition salts of compounds of Formula I include metallic salts made from calcium, magnesium, potassium, sodium, and zinc or organic salts made from N,N-dibenzylethylene diamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound or Formula I, II, III, IV or V by reacting, for example, the appropriate acid or base with the compound of Formula I, II, III, IV or V. The present invention includes a pharmaceutical composition for inhibiting lymphatic absorption of cholesterol, comprising a therapeutically-effective amount of a compound of Formula I in association with at least one pharmaceuticallyacceptable carrier, adjuvant or diluent. A pharmaceutical composition comprises one or more compounds of Formula I-V in association with one or more pharmaceuticallyacceptable carriers and/or adjuvants (collectively referred to herein as “carrier” materials) and, if desired, other active ingredients. A compound of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. A compound may, for example, be administered orally, intravenously, intraperitoneally, subcutaneously, intramuscularly or topically. For oral administration, a pharmaceutical composition may be in the form of, for example, a tablet, capsule, emulsion, suspension or solution. A pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. The amount of therapeuticallyactive compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the sever-
ity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely.

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

Methods

Compounds of Formula I and related compounds can be utilized in the treatment of cholesterol-related conditions in mammals, including humans, dogs and cats. Cholesterol-related conditions include, for example, atherosclerosis, hypercholesterolemia, heart attack, stroke, and gangrene of the extremities. A method of treatment includes administering a compound, or a composition, as described above. A compound of the present invention can be administered by any suitable route, typically in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. A compound may, for example, be administered orally, 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 mg/kg body weight per day. For example, a compound can be administered at a daily dosage of 5 mg/kg, 10 mg/kg, 100 mg/kg, 250 mg/kg, 1000 mg/kg, 1500 mg/kg, 2000 mg/kg, or 3000 mg/kg. The daily dosage can be administered once per day, twice per day, three times per day, or four or more times per day. Variations in these dosage levels can be adjusted using standard empirical routines for optimization.

The concentration of a compound of the present invention effective to treat a cholesterol-related condition in a mammal may vary, depending on a number of factors, including the preferred dosage of the compound to be administered, the chemical characteristics of the compounds employed, the formulation of the compound excipients and the route of administration. The optimal dosage of a pharmaceutical composition to be administered may also depend on such variables as the overall health status of the particular patient and the relative biological efficacy of the compound selected. The amount and dosage regimen effective for treating a cholesterol-related condition in a mammal can be determined 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<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 guggulsterone) for treating cholesterol-related conditions, e.g., hypercholesterolemia. A compound of the invention also can be administered in conjunction with Xenical®, a prescription medication offered for use in weight loss regimens.


Typically, a method of measuring inhibition of cholesterol absorption in vivo involves administering a predetermined amount of cholesterol and a test compound of Formulae I-V to the intestine of a mammal. Typically, the animal is a fasted mammal. The cholesterol and test compound can be administered in a lipid emulsion into the duodenum of the mammal over a period of a few hours. Suitable non-human mammals include rats, mice, guinea pigs, and hamsters. The amount of administered cholesterol that appears in the mesenteric lymph 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-R₈ 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 MoO₅(pyr.)HMPA complex gave two diastereomers, 6 (65.6% yield) and 7 (12.4% yield) (which were separated by silica gel chromatography), along with 20% recovery of starting sclareolide 5. Treatment of a mixture of 6 and 7 with lithium aluminum hydride in THF at room temperature gave triol 8 (70% yield) and lactol 9 (30% yield). Oxidative cleavage of 8 with lead tetraacetate in benzene at 25°C provided an 90% yield of 10, and oxidative cleavage of 9 under similar conditions gave an 85% yield of 11. Dehydration of alcohol 10 with p-toluenesulfonic acid in refluxing toluene for 2 h gave a 78% yield of enal 3. Basic hydrolysis of the formyl ester group of 11 with potassium carbonate in methanol at 0°C provided a 92% yield of 10, which was converted into 3 as described above. The preparation of compound 3 from (-)-sclareol using a different synthetic method has been reported previously (Reeves, P. G. (1996).

Scheme 2 shows the preparation of D-ring fragment 4 starting from 3-chlorovanillin 12, derived from the chlorination of vanillin with chlorine in acetic acid (85% yield), according to the procedure of Ham et al. (J. Am. Chem. Soc., 1927, 49, 535-7). Demethylation of 12 with BB₃ in CH₂Cl₂ (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 Formulæ 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 teträ-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 teträ-n-butylammonium fluoride in THF (31% yield) and oxidation with pyridinium dichromate afforded (+)-chloropuupehenone (27) in 50% yield.
Schemes 5 and 6 show a procedure for preparation of C6a-S tetracyclic pyran compounds embraced by Formulae IV and V. Scheme 5 shows the preparation of (1R,4aS,6aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxaldehyde (33) and (1R,4aS,6aS)-2-Methylene-5,5,8a-trimethyl-1,2,3,4,4a,5,6,7,8,8a-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.

Scheme 5

- Reduction with LiAlH₄ ether at 0°C (97% yield)
- Silylation with t-BuMe₂SiCl and imidazole in DMF (98% yield)
- Oxidation with Dess-Martin Periodinane in CH₂Cl₂ (90% yield)

Scheme 6

- Reduction with n-Bu₄NF THF, 25°C (31% yield)
- Desilylation with n-Bu₄NF THF, 25°C (50% yield)
- Oxidation with pyridinium dichromate in CH₂Cl₂ (50% yield)

Chloropuupehenone (1:1; separated)
Referring to synthetic Scheme 6, Bromide 36 was synthesized from the dibenzylolation 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 tert-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 attacks 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. 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 used as eluents to give purification.

**EXAMPLES**

**Example 1**

\[(4s,8aS)-3,4a,5,6,7,8a-Octahydro-2,5,5a,8atetramethylnaphthalene-1-carboxaldehyde\]

**Step 1:** Preparation of \((1S,3aR,5aS,9aS,9bR)-1-Hydroxydodecahydro-3a,6,6,9a-tetramethylnaphthalen-2-ol (8)\) and \((1R,3aR,5aS,9aS,9bR)-1-Hydroxydodecahydro-3a,6,6,9a-tetramethylnaphthalen-2-ol (9)\)

To a cold (-78°C) solution of 1.02 mL (7.79 mmol) of diisopropylamine in 40 mL of THF under argon, was added 6.36 mL (7.19 mmol) of n-BuLi (1.6 M in hexane). The solution was stirred at -78°C for 1 h, and a solution of 2.32 mL (2.06 mmol) of LiAlH$_4$ was added, and the solution was extracted with diethyl ether three times (50 mL each). The combined ether extracts were washed with brine, dried (Na$_2$SO$_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as an eluent to give 0.65 g (71% yield) of triol 8 and 0.296 g (20% recovery) of lactol 9.

**Step 2:** Preparation of \((1S,1-2,3-Hydroxyethyl)-1-(1R,2R,4aS,8aS)-Decahydro-2,5,5a,8atetramethylnaphthalen-1-carboxaldehyde\)

A solution of 0.90 g (3.4 mmol) of 6 in 20 mL of THF was added to a solution of 0.65 g (2.4 mmol) of a mixture of triol 8 and lactol 9. 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 (Na$_2$SO$_4$), 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.

**Step 3:** Preparation of \((1R,2R,4aS,8aS)-Decahydro-2,5,5a,8atetramethylnaphthalene-1-carboxaldehyde\)

A solution of 0.90 g (3.4 mmol) of 8S was added to a solution of 0.65 g (2.4 mmol) of a mixture of triol 8 and lactol 9. 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 (Na$_2$SO$_4$), 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.

**Note:** 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 to a solution of 0.65 g (2.4 mmol) of a mixture of triol 8 and lactol 9. 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 (Na$_2$SO$_4$), 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.

**Step 4:** Preparation of \((1R,2R,4aS,8aS)-Decahydro-2,5,5a,8atetramethylnaphthalene-1-carboxaldehyde\)

A solution of 0.90 g (3.4 mmol) of 8S was added to a solution of 0.65 g (2.4 mmol) of a mixture of triol 8 and lactol 9. 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 (Na$_2$SO$_4$), 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.
were added. After the solution was reflux for 2 h, the J=13Hz, lH), 2.26 (dd, J=8, 4 Hz, lH), 2.03 using a gradient mixture of hexane and diethyl ether as (CDCl3) 6 10.43
37.8, 36.7, 36.4, 33.6, 33.5, 33.2, 21.8, 20.4, 19.1, 18.5. over 30 minutes (with a slow gas flow) at 25°C. White solid solution was cooled to 25°C, diluted with saturated aque-
ous sodium bicarbonate, and extracted three times with ethyl ether. 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 7.2 mg (78% yield) of aldehyde 3,14. In a larger-scale preparation of 3, the product was distilled under reduced pressure to give colorless oil; bp. 60°C/3 mm Hg (to eliminate trace amount of water), and the distilled product was used in next step. \[ \text{C}=O \], 85.9, 68.9, 55.1, 41.7, 40.0, 39.9, 39.1, 33.4, 22.3, 21.6, 21.5, 20.0, 18.1, 17.2.

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

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-toluenesulphonic acid were 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 7.2 mg (78% yield) of aldehyde 3,14. In a larger-scale preparation of 3, the product was distilled under reduced pressure to give colorless oil; bp. 60°C/3 mm Hg (to eliminate trace amount of water), and the distilled product was used in next step. \[ \text{C}=O \], 85.9, 68.9, 55.1, 41.7, 40.0, 39.9, 39.1, 33.4, 22.3, 21.6, 21.5, 20.0, 18.1, 17.2.

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

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-toluenesulphonic acid were 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 7.2 mg (78% yield) of aldehyde 3,14. In a larger-scale preparation of 3, the product was distilled under reduced pressure to give colorless oil; bp. 60°C/3 mm Hg (to eliminate trace amount of water), and the distilled product was used in next step. \[ \text{C}=O \], 85.9, 68.9, 55.1, 41.7, 40.0, 39.9, 39.1, 33.4, 22.3, 21.6, 21.5, 20.0, 18.1, 17.2.

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

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-toluenesulphonic acid were 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 7.2 mg (78% yield) of aldehyde 3,14. In a larger-scale preparation of 3, the product was distilled under reduced pressure to give colorless oil; bp. 60°C/3 mm Hg (to eliminate trace amount of water), and the distilled product was used in next step. \[ \text{C}=O \], 85.9, 68.9, 55.1, 41.7, 40.0, 39.9, 39.1, 33.4, 22.3, 21.6, 21.5, 20.0, 18.1, 17.2.

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

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-toluenesulphonic acid were 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 7.2 mg (78% yield) of aldehyde 3,14. In a larger-scale preparation of 3, the product was distilled under reduced pressure to give colorless oil; bp. 60°C/3 mm Hg (to eliminate trace amount of water), and the distilled product was used in next step. \[ \text{C}=O \], 85.9, 68.9, 55.1, 41.7, 40.0, 39.9, 39.1, 33.4, 22.3, 21.6, 21.5, 20.0, 18.1, 17.2.

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

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-toluenesulphonic acid were 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 7.2 mg (78% yield) of aldehyde 3,14. In a larger-scale preparation of 3, the product was distilled under reduced pressure to give colorless oil; bp. 60°C/3 mm Hg (to eliminate trace amount of water), and the distilled product was used in next step. \[ \text{C}=O \], 85.9, 68.9, 55.1, 41.7, 40.0, 39.9, 39.1, 33.4, 22.3, 21.6, 21.5, 20.0, 18.1, 17.2.

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

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-toluenesulphonic acid were 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 7.2 mg (78% yield) of aldehyde 3,14. In a larger-scale preparation of 3, the product was distilled under reduced pressure to give colorless oil; bp. 60°C/3 mm Hg (to eliminate trace amount of water), and the distilled product was used in next step. \[ \text{C}=O \], 85.9, 68.9, 55.1, 41.7, 40.0, 39.9, 39.1, 33.4, 22.3, 21.6, 21.5, 20.0, 18.1, 17.2.
diethyl ether (80 mL each). The combined extracts were washed with 60 mL of brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluent to give 3.64 g (93% yield).¹ H NMR (CDCl₃) δ 6.97 (s, 1H, CHO), 7.50 (d, J=2.0 Hz, 1H, C6-H), 7.27 (d, J=2.0 Hz, 1H, C2-H), 1.04 (s, 9H, t-Bu), 0.98 (s, 9H, t-Bu), 0.26 (s, 6H, Me), 0.23 (s, 6H, Me); ¹³C NMR (CDCl₃) δ 189.3 (C=O), 149.5 (s), 149.2 (s), 127.8 (s), 125.7 (d), 118.8 (d), 26.1 (q, 3C, t-Bu), 26.0 (q, 3C, t-Bu), 18.7 (s, 2C, t-Bu), -3.4 (q, 2C, Me), -3.6 (q, 2C, Me). Anal. Calc for C₁₉H₂₆ClO₅Si: C, 55.57; H, 8.55. Found: C, 55.39; H, 8.87.

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

To a solution of 1.73 g (4.30 mmol) of 13 in 15 mL of dichloromethane under argon was added 2.03 g (6.50 mmol) of 55% m-chloroperbenzoic acid (MCPBA). After reflexing for 10 h, the solution was diluted with 30 mL of water and extracted three times with diethyl ether (50 mL each). The combined extracts were washed twice with saturated aqueous NaHCO₃ (30 mL each), 30 mL of water, and 30 mL of brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using hexane as eluent to give 1.24 g (70% yield) of 3,4-bis-(t-butyldimethylsilyloxy)-5-chlorophenol. ¹ H NMR (CDCl₃) δ 8.22 (s), 6.58 (d, J=3.2 Hz, 1H), 1.03 (s, 9H, t-Bu), 0.96 (s, 9H, t-Bu), 0.22 (s, 6H, Me), 0.19 (s, 6H, Me); ¹³C NMR (CDCl₃) δ 159.0 (s, C=O), 148.8 (s), 143.0 (s), 142.4 (s), 127.1 (s), 115.5 (d), 113.1 (d), 26.2 (q, 6C, t-Bu), 18.8 (s, 2C, t-Bu), -3.3 (q, 2C, Me), -3.6 (q, 2C, Me). Anal. Calc for C₁₉H₂₆ClO₅Si: C, 55.57; H, 8.55. Found: C, 55.39; H, 8.87.

Step 5: Preparation of 1,2,5-tris-(t-Butyldimethylsilyloxy)-3-chlorobenzene (14)

To a mixture of 1.028 g (2.65 mmol) of 13 and 0.276 g (1.60 mmol) of t-butyldimethylsilyl chloride, and 0.003 g (0.010 mmol) of N-bromosuccinimide (NBS) in 2 mL of DMF under argon was stirred 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. ¹ H NMR (CDCl₃) δ 6.49 (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. Calc for C₁₉H₂₆ClO₅Si: C, 55.57; H, 8.55. Found: C, 55.39; H, 8.87.

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 1.082 g (90% yield) of 3,4-bis-(t-butyldimethylsilyloxy)-5-chlorophenol. ¹ 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. Calc for C₁₉H₂₆ClO₅Si: 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 was stirred at 25°C for 1 day. The reaction mixture was diluted with 30 mL of water, extracted three times with diethyl ether (40 mL each), and the combined extracts were washed with brine (30 mL), dried (MgSO₄), and concentrated to give 0.042 g (70% yield). This material was used in next step without purification.¹ 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), -3.5 (q, Me). Anal. Calc for C₁₉H₂₆BrClO₅Si: 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 0.650 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 water, and 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 0.506 g (67% yield) of bromide 4.¹ H NMR (CDCl₃) δ 6.81 (s, 1H, Ar, C3-H), 1.03 (s, 9H, t-Bu), 1.02 (s, 9H, t-Bu), 0.97 (s, 9H, t-Bu), 0.23 (s, 6H, Me), 0.22 (s, 6H, Me), 0.18 (s, 6H, Me); ¹³C NMR (CDCl₃) δ 147.3 (s), 147.2 (s), 139.4 (s), 128.3 (s), 111.1 (d), 108.4 (s), 29.9 (q, t-Bu), 26.3 (q, t-Bu), 26.2 (q), 26, 18.9 (s), 18.6 (s), -3.3 (q, Me), -3.4 (q, Me), -3.5 (q, Me), -4.0 (q). Anal. Calc for C₂₃H₂₄BrClO₅Si: C, 49.51; H, 7.96. Found: C, 49.78; H, 8.11.

Example 4

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

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, 31.1, 26.4 (3C, t-Bu), 26.3 (3C, t-Bu), 26.1, 25.6, 25.1, 23.7, 21.9, 21.4, 19.2, 18.9, -3.3, -3.4, -3.49, -3.34, -3.6. Anal. Calcd for C33H58SiCl03: c, 67.02; H, 9.37. Found: c, 67.11; H, 9.16.

Example 6

Step 1: Preparation of (4aS,6aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-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 diethyl ether (-78°C.) was added via cannula, and the resulting solution was stirred at -78°C. for 0.5 h, a solution of 0.820 g (3.70 mmol) of allyl chloride (distilled under reduced pressure) in 10 mL of diethyl ether (-78°C) was added via syringe, 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) of 18 and 0.200 g (9.1% yield) of 19. Compound 18: [α]D25°=+56° (c 0.033, CHCl3); 1H NMR (CDCl3) δ 6.43 (s, 1H, C8-H), 6.28 (s, 1H, C12-H), 2.18 (d, J=12 Hz, 1H), 2.02 (d, J=12 Hz, 1H), 1.90–1.00 (a series of m, 9H), 1.37 (3H, Me), 1.16 (s, 3H, Me), 1.03 (s, 9H, t-BuSi), 0.95 (s, 9H, t-BuSi), 0.92 (s, 3H, Me), 0.87 (s, 3H, Me), 0.21 (s, 3H, Me), 0.20 (s, 3H, Me), 0.17 (s, 3H, Me), 0.16 (s, 3H, Me), 0.15 (s, 3H, Me); 13C NMR (CDCl3) δ 151.9, 147.5, 146.0, 138.0, 123.6, 115.7, 110.7, 78.0, 52.4, 41.8, 37.5, 38.2, 33.8, 33.6, 26.4 (3C, t-Bu), 26.5 (3C, t-Bu), 26.1, 23.7, 21.9, 19.5, 19.1, 18.9, -3.2, -3.4, -3.49, -3.34, -3.6. Compound 19: [α]D25°=+50° (c 0.018, CHCl3); 1H NMR (CDCl3) δ 6.39 (s, 1H, C8-H), 6.31 (s, 1H, C12-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, 119.9, 108.0, 78.0, 52.2, 41.4, 23.2, 39.4, 39.1, 34.0, 33.0, 31.1, 26.4 (3C, t-Bu), 26.3 (3C, t-Bu), 26.1, 25.1, 23.7, 21.4, 19.2, 18.9, 18.8, 17.6, -3.3, -3.4, -3.5. Anal. Calcd for C33H58SiClO3: 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-octahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,10-diol (1) 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-9,10-diol (2)

To a solution of 0.160 g (0.270 mmol) of 18 in 3 mL of THF under argon at 25°C. C was added 0.058 mL (0.600 mmol) of tetra-n-butylammonium fluoride (1.0 M in THF). After stirring at 25°C. C for 5 min., 0.50 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 a gradient mixture of hexane and ethyl acetate as eluent to give 0.080 g (82% yield) of 1. [α]D25°=+41° (c 0.018, CHCl3); 1H NMR (CDCl3) δ 6.42–6.20 (broad s, 3H, C8H, and OH), 5.8 (broad s, 1H, OH), 2.18 (d, J=12 Hz, 1H), 2.01 (d, J=12 Hz, 1H), 1.86–0.90 (a series of m, 9H), 1.42 (s, 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, 42.3, 41.8, 38.2, 34.0, 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]22D = +1,1~ (. Step 2: Preparation of 10% palladiumicarbon in 7 mL of distilled water was charged with 1 atmosphere of hydrogen gas (by 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 toluene as eluent to give 0.180 g (99% yield) of 60 (obtained from NMR spectrum). 'H NMR (CDCl3) δ 6.38 (s, 1H, C8H), 2.64 (dd, J=17, 5 Hz, lH, C12H), 2.34 (m, lH, C12H), 2.02 (dt, J=12, 3 Hz, lH), 1.80–1.15 (a series of m, 11H), 1.12 (s, 3H, Me), 0.85 (s, 3H, Me). When the proton NMR spectrum was measured in benzene-d6 solvent, all methyl groups are separated, δ 0.99 (s, 3H, Me), 0.77 (s, 3H, Me), 0.61 (s, 3H, Me). 13C NMR (CDCl3) 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, 33.4, 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,9,10,12,12a,12b-dodecahydro-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 (CDCl3) δ 6.74 (s, 1H, C8H), 5.95 (s, 1H, C8H of 24), 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, 23), 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

(24)

Step 1: Preparation of [4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,9,10,12,12a,12b-dodecahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,10-dione (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 (CDCl3) δ 6.74 (s, 1H, C8H), 5.95 (s, 1H, C8H of 24), 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, 23), 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 = -35° (c 0.007, CHCl₃). ¹H NMR (CDCl₃) δ 6.21 (s, 1H, C₁₁H), 1.75 (s, 1H, C₁₂H₂), 2.64 (dd, J = 18 Hz, 1H, C₁₁H), 1.00 (t, J = 7 Hz, 3H, Me), 0.64 (s, 3H, Me). ¹³C NMR (CDCl₃) δ 151.2, 149.1, 147.2, 137.2, 126.6, 114.6, 108.4, 75.4, 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 C₅₅H₅₇ClO₅Si₂: C, 76.79; H, 6.98. Found: C, 76.77; H, 6.78.

**Step 2: Preparation of (3C, t-Bu)-2H-11-Chloro-1,3,4,4a,5,6,6a,7,12,12a-decahydro-4,4,6a,12b-tetramethyl-benz[a]xanthene-9,10-diol (26)**

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 tetra-n-butylammonium fluoride (1 M in THF). The solution was stirred for 15 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 10 mg (50% yield) of diol 26. [α]D = +0.22° (c 0.036, CHCl₃). ¹H NMR (CDCl₃) δ 6.63 (s, 1H, C₁₁H), 5.20 (broad s, 2H, OH), 2.72 (d, J = 17 Hz, 1H, C₁₂H), 2.64 (dd, J = 17 Hz, 7 Hz, 1H, C₁₂H), 2.18 (d, J = 13 Hz, 1H, C₁₁H), 1.60-0.90 (a series of m, 11H), 1.33-0.85 (s, 1H, Me). ¹³C NMR (CDCl₃) δ 149.1, 141.1, 133.3, 139.1, 112.4, 103.3, 75.7, 68.2, 55.4, 49.4, 42.1, 40.6, 40.3, 38.5, 33.9, 33.4, 27.1, 21.1, 18.7, 18.4, 14.3.

**Step 3: Preparation of (+)-Chloropuupehenone (27)**

To a solution of 6.0 mg (0.016 mmol) of 26 in 1 mL of dichloromethane under argon at 25°C was added 12 mg (0.032 mmol) of PDC. After stirring for 15 min., the solution was filtered through Celite, washed with dichloromethane, and the combined filtrate was concentrated to dryness, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate to give 0.54 g (90% yield) of compound 27. [α]D = -188° (c 18, CHCl₃); ¹H NMR (CDCl₃) δ 7.44 (d, J = 7 Hz, 1H, C₁₁H), 5.24 (s, 1H, C₁₁H), 2.48 (d, J = 7 Hz, 1H, C₁₂H₂), 1.24 (s, 3H, Me), 0.93 (s, 3H, Me), 0.86 (s, 3H, Me), 0.82 (3H, Me). ¹³C NMR (CDCl₃) δ 160.0 (C=O), 162.7, 144.4, 141.2, 127.7, 125.7, 105.2, 79.3, 54.9, 54.0, 41.8, 41.2, 40.3, 39.2, 33.9, 33.6, 28.2, 22.2, 18.6, 18.3, 15.4. ¹H and ¹³C NMR spectral data are similar to those reported (Hanann, M. T.; Scheuer, P. J., J. Org. Chem., 1993, 58, 6565–6569).

**Example 10**

**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.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg white</td>
<td>200.0</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>396.5</td>
</tr>
<tr>
<td>Dextrinized cornstarch</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 mg per biotin sucrose mix)</td>
<td>4.0</td>
</tr>
<tr>
<td>Choline bitartrate</td>
<td>2.5</td>
</tr>
</tbody>
</table>

1Formulated and supplied from Dyets, Bethlehem, PA, according to the recommendations of the AIN-91.
2Contains 0.2% test-butylibehydroquinone.

At 6 wk, rats were starved overnight for 17 h but allowed water ad libitum prior to the surgical placement of a lymph cannula and duodenal infusion catheter. The mesenteric lymph duct was cannulated as described in Koo et al., J. Nutr. 131: 717–722 (2001). Briefly, while rats were under anesthesia (2.0% halothane in 2.0 L O₂/min delivered via a halothane vaporizer), a midline abdominal incision was made. The superior mesenteric lymph duct was cannulated with polyethylene tubing (SV.3 1 tubing, i.d. 0.50 mm, o.d. 0.80 mm; Dow Plastics, Auburn, Australia). The cannula was fixed in place with ethyl cyanoacrylate glue (Elmer’s Products, Columbus, Ohio) and externalized 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, 6.75 Na₂HPO₄, 16.5 NaH₂PO₄, 115 NaCl, and 5 KCl; pH 6.7) via infusion catheter at 3.0 mL/h by a syringe pump (Harvard Apparatus, Model 935, South Natick, Mass.) to ensure adequate hydration and nutritional status of the animals.

After postoperative recovery, each rat was infused with a lipid emulsion at 3 mL/h for 8 h via the duodenal catheter in subdued light. The lipid emulsion consisted of 451.8 μmol triolein (95%, Sigma Chemical, St. Louis, Mo.), 33.5 kBq [¹⁴C]-cholesterol (6°C-CH; specific activity, 1.85 GBq/mmol, American Radiolabeled Chemicals, St. Louis, Mo.), 451.8 μmol triolein (95%, Sigma Chemical, St. Louis, Mo.), 33.5 kBq [¹⁴C]-cholesterol (6°C-CH; specific activity, 1.85 GBq/mmol, American Radiolabeled Chemicals, St. Louis, Mo.), and 6,727,277 Bq 45 triolein (95%, Sigma Chemical, St. Louis, Mo.), and 6,727,277 Bq 45 triolein (95%, Sigma Chemical, 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 ultrasonic processor equipped with a microtip (XL-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, Fullerton, 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 methylated simultaneously with BF₃-methanol. Fatty acid methyl esters (FAME) were analyzed by capillary gas chromatography (Hewlett-Packard, Model 6890, Palo Alto, Calif.) using a HP-INNOWax cross-linked polyethylene glycol phase capillary column (15 m, i.d. 0.53 mm; Restek Corp., Bellefonte, Pa.).

Statistical analysis

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

Results

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

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>
<thead>
<tr>
<th>Time</th>
<th>Control % dose</th>
<th>Compound 1 % dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 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>4 h</td>
<td>5.31 ± 0.74</td>
<td>2.70 ± 0.42*</td>
</tr>
<tr>
<td>5 h</td>
<td>10.16 ± 1.31</td>
<td>4.18 ± 0.92*</td>
</tr>
<tr>
<td>6 h</td>
<td>15.66 ± 1.75</td>
<td>5.68 ± 1.37*</td>
</tr>
<tr>
<td>7 h</td>
<td>22.14 ± 1.81</td>
<td>7.32 ± 1.78*</td>
</tr>
<tr>
<td>8 h</td>
<td>29.79 ± 1.65</td>
<td>9.13 ± 2.41*</td>
</tr>
<tr>
<td>9 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).

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:

wherein R₁ is independently hydrido, halo, alkyld, alkenyl, alkylyl, haloalkyl, hydroxalkyl, hydroxy, alkoy,
alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcobonyl, alkylicarbonylalkyl, alkoxyalkyl, alkoxyalkylalkyl, arylsulfonyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxyalkyl, alkoxyalkylalkyl, amido, N-alkylamido, N,N-dialkylamido, amido, N-alkyl-N-arylamido, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyloxy, phenylselenyl, thiol, alkylsulfenyl, alkylsilyloxy, or alkylsilyloxy; R, is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, aryloxalkyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcobonyl, alkylicarbonylalkyl, alkoxyalkyl, alkoxyalkylalkyl, amido, N-alkylamido, N,N-dialkylamido, amido, N-alkyl-N-arylamido, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyloxy, or phenylselenyl, thiol, alkylsulfenyl, alkylsilyloxy, arylsilox, or alkylsilyloxy; R, is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, aryloxalkyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcobonyl, alkylicarbonylalkyl, alkoxyalkyl, alkoxyalkylalkyl, amido, N-alkylamido, N,N-dialkylamido, amido, N-alkyl-N-arylamido, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyloxy, or phenylselenyl, thiol, alkylsulfenyl, alkylsilyloxy, arylsilox, or alkylsilyloxy; R, is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, aryloxalkyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcobonyl, alkylicarbonylalkyl, alkoxyalkyl, alkoxyalkylalkyl, amido, N-alkylamido, N,N-dialkylamido, amido, N-alkyl-N-arylamido, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyloxy, or phenylselenyl, thiol, alkylsulfenyl, alkylsilyloxy, arylsilox, or alkylsilyloxy; R, is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, aryloxalkyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfonyl, carboxy, carboxyalkyl, alkylcobonyl, alkylicarbonylalkyl, alkoxyalkyl, alkoxyalkylalkyl, amido, N-alkylamido, N,N-dialkylamido, amido, N-alkyl-N-arylamido, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyloxy, or phenylselenyl, thiol, alkylsulfenyl, alkylsilyloxy, arylsilox, or alkylsilyloxy; or a pharmaceutically-acceptable salt thereof.

2. The compound of claim 1, wherein 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.

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

7. A compound of Formula II:
R₃ is independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylalkylsulfonamidyl, N-arylalkylsulfonylamidyl, carboxy, carboxyalkyl, alkyloxyalkyl, alkoxyalkyl, alkoxyalkylcarboxyl, alkoxyalkylcarboxylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylalkylamido, N-alkyl-N-arylalkylamido, N-alkyl-N-arylalkylamidyl, amino, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfenyl, alkylsulfenyl, arylsulfinyl, alkylsulfenyl, arylsulfinyl, alkylsilyloxy, phenylselenyl, or alkylsilyloxy.

R₅ is independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylalkylsulfonamidyl, N-arylalkylsulfonylamidyl, carboxy, carboxyalkyl, alkyloxyalkyl, alkoxyalkyl, alkoxyalkylcarboxyl, alkoxyalkylcarboxylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylalkylamido, N-alkyl-N-arylalkylamido, N-alkyl-N-arylalkylamidyl, amino, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfenyl, alkylsulfenyl, arylsulfinyl, alkylsulfenyl, arylsulfenyl, alkylsilyloxy, phenylselenyl, or alkylsilyloxy.

R₆ is independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylalkylsulfonamidyl, N-arylalkylsulfonylamidyl, carboxy, carboxyalkyl, alkyloxyalkyl, alkoxyalkyl, alkoxyalkylcarboxyl, alkoxyalkylcarboxylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylalkylamido, N-alkyl-N-arylalkylamido, N-alkyl-N-arylalkylamidyl, amino, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfenyl, alkylsulfenyl, arylsulfenyl, alkylsilyloxy, phenylselenyl, or alkylsilyloxy.

R₇ is independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylalkylsulfonamidyl, N-arylalkylsulfonylamidyl, carboxy, carboxyalkyl, alkyloxyalkyl, alkoxyalkyl, alkoxyalkylcarboxyl, alkoxyalkylcarboxylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylalkylamido, N-alkyl-N-arylalkylamido, N-alkyl-N-arylalkylamidyl, amino, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfenyl, alkylsulfenyl, arylsulfenyl, alkylsilyloxy, phenylselenyl, or alkylsilyloxy.

R₈ is independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylalkylsulfonamidyl, N-arylalkylsulfonylamidyl, carboxy, carboxyalkyl, alkyloxyalkyl, alkoxyalkyl, alkoxyalkylcarboxyl, alkoxyalkylcarboxylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylalkylamido, N-alkyl-N-arylalkylamido, N-alkyl-N-arylalkylamidyl, amino, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfenyl, alkylsulfenyl, arylsulfenyl, alkylsilyloxy, phenylselenyl, or alkylsilyloxy.

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

The compound of claim 9, wherein R₁ is chloro, R₂ and R₃ are OS-i-BuMe₂, and R₄ and R₅ are methyl.

A compound of Formula III:

wherein R₁ is independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylalkylsulfonamidyl, N-arylalkylsulfonylamidyl, carboxy, carboxyalkyl, alkyloxyalkyl, alkoxyalkyl, alkoxyalkylcarboxyl, alkoxyalkylcarboxylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-arylalkylamido, N-alkyl-N-arylalkylamido, N-alkyl-N-arylalkylamidyl, amino, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryloxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfonyl, alkylsulfonyl, arylsulfenyl, alkylsulfenyl, arylsulfenyl, alkylsilyloxy, phenylselenyl, or alkylsilyloxy.
17. A compound of Formula IV:

![Chemical Structure](image)

wherein R₁ is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonfyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-aryl sulfamyl, N-alkyl-N-aryl sulfamyl, carboxy, carboxyalkyl, alkylicarbonyl, alkylicarbononylalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-monoarylamido, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, N-alkyl-N-arylsulfamyl, N-N-dialkylsulfamyl, N,N-dialkylsulfamyl, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amido alkyl, aminolalkyl, alkylaminolalkyl, amidino, cyano amidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylaminono, N,N-dialkylaminono, acyl, acyloxy, arlyoxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfinyl, alkyl sulfenyl, aryl sulfinyl, phenylselenyl, or alkylsilyloxy;

wherein R₂ is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonfyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, carboxy, carboxyalkyl, alkylicarbonyl, alkylicarbononylalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-monoarylamido, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, N-alkyl-N-arylsulfamyl, N-N-dialkylsulfamyl, N,N-dialkylsulfamyl, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amido alkyl, aminolalkyl, alkylaminolalkyl, amidino, cyano amidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylaminono, N,N-dialkylaminono, acyl, acyloxy, arlyoxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfinyl, alkyl sulfenyl, aryl sulfinyl, phenylselenyl, or alkylsilyloxy;

R₃ is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonfyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, carboxy, carboxyalkyl, alkylicarbonyl, alkylicarbononylalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, amido, N-alkylamido, N,N-dialkylamido, N-monoarylamido, N-arylsulfamyl, N-alkyl-N-arylsulfamyl, carboxy, N-alkyl-N-arylsulfamyl, N-N-dialkylsulfamyl, N,N-dialkylsulfamyl, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amido alkyl, aminolalkyl, alkylaminolalkyl, amidino, cyano amidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylaminono, N,N-dialkylaminono, acyl, acyloxy, arlyoxy, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfinyl, alkyl sulfenyl, aryl sulfinyl, phenylselenyl, or alkylsilyloxy;

R₄ is independently hydrido, alkyl, or hydroxyalkyl;

R₅ is independently hydrido, alkyl, or hydroxyalkyl;

R₆ is independently hydrido, hydroxy, or acyloxy; and R₇ is independently alkyl, or arylenylalkyl;

or a pharmaceutically-acceptable salt thereof.

18. The compound of claim 17, wherein R₁ is halo; R₂ and R₃ are selected from hydroxy, alkylsilyloxy, or aralkyloxy; R₄ and R₅ are alkyl; R₆ is selected from hydroxy, hydroxy, or acyloxy; and R₇ is selected from alkyl or arylenylalkyl.

19. The compound of claim 18, wherein R₁ is chloro; R₂ and R₃ are OSi-t-BuMe₃; R₄ and R₅ are methyl; R₆ is hydrido; and R₇ is methyl.

20. The compound of claim 18, wherein R₁ is chloro; R₂ and R₅ are hydroxy; R₆ and R₇ are methyl; R₆ is hydrido; and R₇ is methyl.

21. The compound of claim 18, wherein R₁ is chloro; R₂ and R₅ are aryalkyloxy; R₆ and R₇ are methyl; R₆ is hydrido; and R₇ is arylenylalkyl.

22. The compound of claim 18, wherein R₁ is chloro; R₂ and R₅ are aryalkyloxy; and R₆ and R₇ are methyl; R₆ is acyloxy; and R₇ is arylenylalkyl.

23. The compound of claim 18, wherein R₁ is chloro; R₂ and R₅ are aryalkyloxy; R₆ and R₇ are methyl; R₆ is acyloxy; and R₇ is methyl.

24. A compound of Formula V:

![Chemical Structure](image)
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, phenylethynyl, or alkylsilyloxy;

R, is independently hydrido, halo, alkyl, alkenyl, alkylidene, haloalkyl, hydroxyalkyl, hydroxyalkyl, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamidyl, N,N-dialkylsulfamidyl, N-arylsulfonyl, N-alkyl-N-arylsulfamidyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxyalkyl, alkoxyalkylalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, amidino, cyanoamidino, heteroaryl, alkylsulfonyl, arylsulfonyl, SH, S, to form an intermediate compound (18):

wherein, R, is OSi-t-BuMe,, X, is chloro, X, is bromo, with compound (3);

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

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, R, is chloro, R, and R, are OSi-tBuMe2; and R, is hydroxy.
A composition comprising a compound of Formula 1:

\[
\text{(1)}
\]

at least one pharmaceutically-acceptable carrier material.

c) oxidizing compound (26) to form (+) chloropupehenone (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 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:

\[
\text{(1)}
\]

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 powders, cellulose esters of alkanolic 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 claim 1 to a non-human 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 compound is administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly, or topically.

45. The method of claim 42, wherein said compound is administered in an amount from about 4 mg/kg to about 40 mg/kg of body weight per day.

46. The method of claim 42, wherein said compound is administered as part of a treatment regimen comprising dietary modifications to lower cholesterol.

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

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

49. The method of claim 48, wherein said compound is administered for 7 days or more.

50. The method of claim 49, wherein said compound is administered for one year 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 40 mg/kg body weight per day.
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