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(54) COMPOUNDS AFFECTING CHOLESTEROL ABSORPTION

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(57) ABSTRACT

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

![Chemical Structure](https://example.com/structure.png)

or a pharmaceutically acceptable salt thereof.

51 Claims, 4 Drawing Sheets
OTHER PUBLICATIONS


FIG. 1

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

- Control
- Compound I

Time (h)

1 2 3 4 5 6 7 8

*
FIG. 2

Oleic acid output (μmol/h)

- Control
- Compound I

Time (h)

1 2 3 4 5 6 7 8

* indicates significant difference
FIG. 3

![Graph showing inhibition percentages for 1st and 2nd samples with linear regression lines.]
FIG. 4

Concentration (µM)

Inhibition (%)

Concentration (µM)

Ferroverdin A
COMPONENTS AFFECTING CHOLESTEROL ABSORPTION

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

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

TECHNICAL FIELD

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

BACKGROUND

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

SUMMARY

The invention features a compound of Formula I:

\[
\text{R}_1 \text{ can be independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfonylamyl, N,N-dialkylsulfonylamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoalkylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamidol, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkanilamino, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkylsulfanyl, N-alkylamino, N-N-dialkylamino, acyl, aclyoxy, arlyoxy, acylaminono, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenenyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;}
\]

\[
\text{R}_2 \text{ can be independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfonylamyl, N,N-dialkylsulfonylamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoalkylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamidol, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkanilamino, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkylsulfanyl, N-alkylamino, N-N-dialkylamino, acyl, aclyoxy, arlyoxy, acylaminono, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenenyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;}
\]

\[
\text{R}_3 \text{ can be independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfonylamyl, N,N-dialkylsulfonylamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoalkylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamidol, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkanilamino, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkylsulfanyl, N-alkylamino, N-N-dialkylamino, acyl, aclyoxy, arlyoxy, acylaminono, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenenyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;}
\]

\[
\text{R}_4 \text{ can be independently hydrido, halo, alkyl, alkenyl, alkylid, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfonylamyl, N,N-dialkylsulfonylamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoalkylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamidol, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkanilamino, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkylsulfanyl, N-alkylamino, N-N-dialkylamino, acyl, aclyoxy, arlyoxy, acylaminono, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenenyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;}
\]

\[
\text{R}_5 \text{ can be independently hydrido, halo, or hydroxyalkyl.}
\]

In some embodiments, R5 is halo, R6 and R7 are hydroxy, and R2 and R3 are alkyl in the compound, e.g., R5 is chloro and R6 and R7 are methyl. In other embodiments, R5 is halo, R2 and R3 are alkylsilyloxy, and R2 and R3 are alkyl, e.g., R5 is chloro, R6 and R7 are Oسي-عBعMe2, and R6 and R7 are methyl. In one embodiment, the compound has Formula (24):

\[
\text{R}_1 \text{ can be independently hydrido, halo, alkylyl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfonylamyl, N,N-dialkylsulfonylamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoalkylamido, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamidol, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkanilamino, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkythio, alkylsulfanyl, N-alkylamino, N-N-dialkylamino, acyl, aclyoxy, arlyoxy, acylaminono, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenenyl, thiol, arylsulfenyl, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;}
\]
In some embodiments, R1, is halo, R2 and R3 are selected from hydroxy and alkylsilyloxy, and R4 and R5 are alkyl, e.g., R1 is chloro, R2 and R3 are hydroxy, and R4 and R5 are methyl. In some embodiments, R1 is halo, R2 and R3 are alkylsilyloxy, and R4 and R5 are methyl, e.g., R1 is chloro, R2 and R3 are OSi-t-BuMe3, and R4 and R5 are methyl. In some embodiments the compound has Formula (23): (24)

\[
\text{Formula IV}
\]

The invention also features a compound of Formula IV:

\[
\text{Formula II}
\]

The invention also features a compound of Formula III:

\[
\text{Formula III}
\]

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

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

The invention also features a compound of Formula III:

\[
\text{Formula III}
\]

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

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

\[ \text{Formula V} \]

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

In some embodiments, \text{R}_1 \text{ is halo; } \text{R}_2 \text{ and } \text{R}_3 \text{ are aryalkyloxy; } \text{R}_4 \text{ and } \text{R}_5 \text{ are alkyl; } \text{R}_6 \text{ is hydroxy; and } \text{R}_7 \text{ is OSi-tBuMe}_2. \text{ The method further comprises isolating compound (18) and deprotecting compound (18). The result is a compound of Formula I.}

The invention also features a method of synthesizing (+) chloropuupehenone. The method comprises hydrogenating compound (19) to form compound (25). Desilylation of compound (25) forms compound (26).

\[ \begin{array}{c}
\text{Formula I:} \\
\text{wherein } \text{R}_1, \text{ is chloro, } \text{R}_2 \text{ and } \text{R}_3 \text{ are OSi-tBuMe}_2. \text{ The method comprises reacting compound (4) with compound (3) to form intermediate compound (18).} \\
\text{wherein } \text{R}_1, \text{ is chloro, } \text{R}_2 \text{ and } \text{R}_3 \text{ are hydroxy, and } \text{R}_4 \text{ and } \text{R}_5 \text{ are methyl. The method comprises deprotecting compound (18).} \\
\end{array} \]
Oxidation of compound (26) forms (+) chloropuupe-
henone (27).

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

The composition can be in the form of a capsule or a liquid
emulsion. The composition can in a controlled release
formulation, e.g., a dispersion in hydroxypropylmethyl
cellulose, or in a formulation suitable for parenteral
administration, e.g., a lipid emulsion. The composition can
comprise a diluent such as polyethylene glycol, propylene
glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame
oil, or benzyl alcohol. The pharmaceutically-acceptable car-
rier material can be lactose, sucrose, starch powder, cellu-
lose esters of alkanolic acids, cellulose alkyl esters, tallow,
stea acid, magnesium stearate, magnesium oxide, sodium
and calcium salts of phosphoric and sulfuric acids, gelatin,
acacia gum, sodium alginate, microcrystalline cellulose,
sodium stear glycolate, sodium lauryl sulfate, povidone,
polyvinylpyrroldione, 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 cho-
lesterol that is absorbed by the lymph. A statistically sig-
nificant decrease in lymphatic cholesterol absorption rela-
tive to the lymphatic cholesterol absorption of a
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 cholest-
erol absorption of a corresponding control mammal
indicates the compound does not inhibit lymphatic absorption of
cholesterol. The cholesterol and the compound can be admin-
istered in a lipid emulsion.

The invention also features a method of treating a
cholesterol-related condition. The method comprises admin-
istering an effective amount of a compound of Formula 1 to
a mammal. The cholesterol-related condition can be, for
example, atherosclerosis, hypercholesterolemia, heart
attack, gangrene, and stroke. The compound can be admin-
istered orally, intravenously, intraperitoneally, subcutaneously,
imtramuscularly, 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 composi-
tion as described above. The method can be part of a
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 incorpo-
rated by reference in their entirety. In case of conflict, the
present specification, including definitions, will control. In
addition, the materials, methods, and examples are illustra-
tive 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 descrip-
tion 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 dif-
ference 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 Fer-
roverdin A.

DETAILED DESCRIPTION

Compounds of Formula I

A class of compounds useful for inhibiting lymphatic
absorption of cholesterol is defined by Formula 1:

wherein R₁ is selected from hydrido, halo, alkyl, alkenyl,
alkeyl, haloalkyl, hydroxalkyl, hydroxy, alkoxy,
A second class of compounds is defined by Formula II:

\[
A
\]

wherein \( R_1 \) is selected from moieties described above for \( R_1 \) groups of Formula I, \( R_2 \) is selected from the moieties described above for \( R_2 \) groups of Formula I, \( R_3 \) is selected from the moieties described above for \( R_3 \) groups of Formula I, \( R_4 \) is selected from hydrido, alkyl, and hydroxyalkyl, and \( R_5 \) is selected from hydrido, alkyl, and hydroxyalkyl. The class of compounds also includes pharmaceutically-acceptable salts thereof.

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

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

(4aS,6aS,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (19).

A third class of compounds is defined by Formula III:

\[
B
\]

wherein \( R_1 \) is selected from the moieties described above for \( R_1 \) groups of Formula I, \( R_2 \) is selected from the moieties described above for \( R_2 \) groups of Formula I, \( R_3 \) is selected from the moieties described above for \( R_3 \) groups of Formula I, \( R_4 \) is selected from hydrido, alkyl, and hydroxyalkyl, and \( R_5 \) is selected from hydrido, alkyl, and hydroxyalkyl. The class of compounds also includes pharmaceutically-acceptable salts thereof.

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

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

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

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

(4aS,6aR,12aS,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,lO-diol (26); and

(4aS,6aR,12aS,12bS)-2H-9,10-Bis-(benzoxyl)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,12b-trimethyl-benzo[a]xanthene (40); and

(4aS,6aR,12aS,12bS)-2H-12-Acetoxy-9,10-bis-(benzoxyl)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (42).

**Compounds of Formula IV**

A fourth class of compounds is defined by Formula IV:

wherein \( R_4 \) is selected from the moieties described above for \( R_4 \) groups of Formula I, \( R_5 \) is selected from the moieties described above for \( R_5 \) groups of Formula I, \( R_6 \) is selected from hydrido, alkyl, and hydroxyalkyl; \( R_7 \) is selected from hydrido, alkyl, and hydroxyalkyl; \( R_8 \) is selected from hydrido, hydroxy, and acyloxy, and \( R_9 \) is selected from hydrido, hydroxy, and alkylsilyloxy.

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

(4aS,6aR,12aR,12bS)-2H-9,10-Bis-(1-butylidimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-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-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (37); and (4aS,6aS,12aR,12bS)-2H-12-Acetoxy-9,10-bis-(benzoxyl)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene (38).

A fifth class of compounds is defined by Formula V:

wherein \( R_4 \) is selected from the moieties described above for \( R_4 \) groups of Formula I, \( R_5 \) is selected from the moieties described above for \( R_5 \) groups of Formula I, \( R_6 \) is selected from hydrido, alkyl, and hydroxyalkyl; \( R_7 \) is selected from hydrido, alkyl, and hydroxyalkyl; \( R_8 \) is selected from hydrido, alkyl, and hydroxyalkyl; \( R_9 \) is selected from hydrido, hydroxy, and alkylsilyloxy.

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

(4aS,8aS)-1-[[2-chloro-3,4-dibenzyloxy-6-(1-butylidimethylsilyloxy)-2-methylene-5,5,8a-trimethyldecahydronaphthalene (37); and

(4aS,8aS)-1-[[2-chloro-3,4-dibenzyloxy-6-hydroxy]phenylhydroxymethyl]-2-methylene-5,5,8a-trimethyldecahydronaphthalene (38).

The term “alkyl” embraces linear or branched saturated aliphatic radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are “lower alkyl” radicals having from one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about four carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. The term alkyl also includes cycloalkyl (cyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl 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, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxyalkyloxy, arylalkoxyalkyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, or arylamino), and alkylarylamino, acylaminio (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido radicals. The terms “carbonyl” or “carboxyl” embraces linear or branched carbonic acid radicals having a carboxyl radical substituted with an alkyl or aryl group as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. The term “hydroxyalkyl” embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. The terms “alkoxy” and “alkoxycarbonyl” embrace linear or branched oxo-containing radicals wherein each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term “alkoxyalkyl” also embraces alkyl radicals having two or more alkoxyl radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The “alkoxy” or “alkoxycarbonyl” radicals may be further substituted with one or more halo atoms, such as fluoro chloro or bromo to provide “haloalkoxy” or “haloalkoxycarbonyl” radicals. Examples of “alkoxy” radicals include methoxy butoxy and trifluoromethoxy. The term “aryl” embraces substituent radicals, the latter of which refers to aromatic radicals such as phenyl, naphthyl, tetrahydroindenyl, indane and biphenyl. The term “heteroaromatic” embraces saturated, partially saturated and unsaturated heterocyclic radicals containing rings wherein such rings may be attached together in a pendant manner or may be fused. The term “arylm” embraces aromatic radicals such as phenyl, napthyl, tetrahydroindenyl, indane and biphenyl. The term “heteroaromatic” embraces saturated, partially saturated and unsaturated heterocyclic radicals containing rings wherein such rings may be attached together in a pendant manner or may be fused. 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“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 (CH₃)₂C=O—=C(==O)— and —C(==O)—C—OH₂. The term “alkoxy carbonylalkyl” embraces radicals having “alkoxy carbonyl”, as defined above substituted to an alkyl radical. Examples of such “alkoxy carbonylalkyl” radicals include (CH₃)₂CO—C(==O)— and —(CH₂)₂(==O)COCH₂. The term “amido” when used by itself or with other terms such as “amidoalkyl”, “N-alkylamidoalkyl”, “N,N-dialkylamido”, “N,N-dialkylamido”, “N-alkyl-N-arylamido”, “N-alkyl-N-hydroxyamidoalkyl”, “N-alkyl-N-hydroxyamidoalkyl”, embraces a carbonyl radical substituted with an amino radical. The terms “N-alkylamido” and “N,N-dialkylamido” denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The terms “N,N-monoarylamido” and “N-alkyl-N-arylamido” denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term “N-alkyl-N-hydroxyamidoalkyl” embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term “N-alkyl-N-hydroxyamidoalkyl” embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term “N,N-alkylthioalkyl” embraces radicals having “alkylsilyloxy”, as defined above, attached via an oxygen atom to a group. The term “N,N-dialkylthioalkyl” embraces radicals having “alkylsilyloxy”, as defined above, attached via an oxygen atom to a group. The term “alkylsilyloxy” denotes a silyloxy radical (—OSi—) substituted with an alkyl group. The term “alkylsilyloxyalkyl” denotes an alkyl radical substituted with a silyloxy group. An example of an “arylselenylalkyl” radical is —CH₃SePh.

Also included in the family of compounds of Formulae I-V are pharmaceutically-acceptable salts thereof. The term “pharmaceutically-acceptable salts” embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula 1 may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arolicyclic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactie, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, sulfanilic, cysteinoyl, cysteinyl, iodoacetamidomethyl, hydroxybutyric, salicylic, galactaric and galacturonic acid.

Suitable pharmaceutically-acceptable 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'-dibenzylthelylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compounds of Formulae 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.

Pharmaceutical Compositions

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 pharmaceutically-acceptable carrier, adjuvant or diluent.

A pharmaceutical composition comprises one or more compounds of Formulae I-V in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as “carrier” materials) and, if desired, other active ingredients. A compound of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. A compound may, for example, be administered orally, intravenously, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, a pharmaceutical composition may be in the form of, for example, a tablet, capsule, emulsion, suspension or solution. A pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity
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 acids, cellulose alkyl esters, t alc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated, or for convenient administration. Capsule or tablet shells can contain, e.g., gelatin, titanium dioxide, and dyes. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dispersed 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, gout, and gouty arthritis of the extremities. A method of treatment includes administering an effective amount of a compound of Formula I. The compound can be administered as a pharmaceutical composition, as described above. A compound of the present invention may be administered by any suitable route, typically in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. A compound may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

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

The concentration of a compound of the present invention effective to treat a cholesterol-related condition in a mammal may vary, depending on a number of factors, including the preferred dosage of the compound to be administered, the chemical characteristics of the compounds employed, the formulation of the compound excipients and the route of administration. The optimal dosage of a pharmaceutical composition to be administered may also depend on such variables as the overall health status of the particular patient and the relative biological efficacy of the compound selected. The amount and dosage regimen effective for treating a cholesterol-related condition in a mammal can be determined 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 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 days, 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.), Mevalatin (from Sankyo Co., Japan), and analogs thereof (e.g., compounds sold under the trade names Sivastatin, Med, and gauugue), or the like. The amount of cholesterol and a test compound of Formulae I-V can be determined by administering the compound to a mammal for a predetermined period of time, e.g., for one, two, or three days, 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 levels decreased by treatment, e.g., by dietary means. A compound that is effective is one that causes a decrease in lymphatic absorption of cholesterol that is statistically significant at p≤0.01, p≤0.005, or p≤0.001.

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

General Synthetic Procedures

The compounds of the invention can be synthesized according to the procedures of Schemes 1–6, wherein the R₁-R₆ substituents are as defined for Formulae I-V, above, except where further noted.
Scheme 1 shows the synthesis of enantiopure A-B fragment 3 from commercially available 3αR-(+)-sclareolide 5 (purchased from Aldrich Chemical Company). Deprotonation of optically pure lactone 5 with LDA (lithium diisopropylamide) in THF at -78°C, followed by treatment with Mo\(_2\)O\(_5\)(pyr.) and HMPA\(^{13}\) 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 tritol 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).

\[ \text{Scheme 1} \]

\[ \text{LDA, THF} \quad \text{Mo}_2\text{O}_5\text{(pyr.) HMPA} \]

\[ -78^\circ\text{C}. \]

\[ 3\alpha\text{R}(+)-\text{Sclareolide (5)} \]

\[ \begin{align*}
6 & \quad (65.6\% \text{ yield}) \\
7 & \quad (12.4\% \text{ yield})
\end{align*} \]

\[ \text{(separated)} \]

\[ \begin{align*}
8 & \quad (70\% \text{ yield}) \\
9 & \quad (30\% \text{ yield})
\end{align*} \]

\[ \begin{align*}
\text{Pb(OAc)}_4 & \quad \text{benzene} \\
25^\circ\text{C}, 4 \text{ h} & \quad (90\% \text{ yield})
\end{align*} \]

\[ \begin{align*}
\text{p-TsOH} & \quad \text{toluene} \\
\text{reflux, 2 h} & \quad (78\% \text{ yield})
\end{align*} \]

\[ \text{Scheme 2 shows the preparation of D-ring fragment 4 starting from 3-chlorovanillin 12, derived from the chlorination of vanillin with chlorine in acetic acid (85% yield), according to the procedure of Ham et al. (J. Am. Chem. Soc., 1927, 49, 535-7). Demethylation of 12 with BBr\(_3\) in CH\(_2\)Cl\(_2\) (94% yield) followed by protection of the diol with t-butyldimethylsilyl chloride, triethylamine, 4-dimethylaminopyridine (DMAP) gave aldehyde 13 (93% yield) (Jong, T. T.; Williard, P. G.; Porwoll, J. P., J. Org. Chem., 1984, 49, 735-6). Baeyer-Villiger oxidation of 13 with m-chloroperbenzoic acid (MCPBA) in methylene chloride (70% yield) followed by basic hydrolysis with potassium carbonate (90% yield) and silylation of the resulting phenol with t-butyldimethylsilyl chloride (83% yield) provided trisilyl ether 14. Selective C4 (less hindered site compared with C6) bromination of 14 with N-bromosuccinimide (NBS) in N,N-dimethylformamide (DMF) at 25°C gave an 67% yield of 4 as the sole product; no C6 isomer 15 was isolated. Interestingly, when the bromination was carried out at 50°C, a 2:1 ratio of 15 and 4 was obtained.

Alternatively, compound 4 was also obtained from the bromination of phenol 16 (obtained from 13 with MCPBA and potassium carbonate) with N-bromosuccinimide (NBS) in DMF to give a 70% yield of bromide 17. Silylation of 17 with t-butyldimethylsilyl chloride afforded a 99% yield of 4.

\[ \text{Scheme 2} \]

\[ \text{1. BCl}_3, \text{CH}_2\text{Cl}_2 \quad (94\% \text{ yield}) \]

\[ \text{2. t-BoMe}_2\text{SCL} \quad \text{Et}_3\text{N, DMAP} \quad (93\% \text{ yield}) \]

\[ \text{1. MCPBA} \quad (70\% \text{ yield}) \]

\[ \text{2. K}_2\text{CO}_3 \quad (90\% \text{ yield}) \]

\[ \text{3. t-BoMe}_2\text{SCL} \quad (83\% \text{ yield}) \]
Scheme 3 shows a procedure for preparing compounds embraced by Formulae I and II from enantiopure A-B fragment 3 and D-ring fragment 4. Treatment of 4 with 2 equiv of t-BuLi in diethyl ether at -78°C followed by aldehyde 3 afforded a mixture of two stereoisomers at C6a, 18 (45% yield) and 19 (9.1% yield). Removal of the silyl ether protecting groups of 18 and 19 separately gave compound 1 (82% yield) and compound 2 (81.4% yield), respectively. Spectral data of compound 2 was identical with those reported (Nasu, S. S.; Yeung, B. K. S.; Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M.; Goins, K., J. Org. Chem. 1995, 60, 7290-7292).

Scheme 3
Scheme 4 shows the preparation of compounds embraced by Formulae III, IV, and VI. Selective hydrogenation of 18 with 1 atmosphere of hydrogen in the presence of palladium/carbon in ethanol gave a 99% yield of tetracyclic pyran 21 as a single diastereomer (Scheme 4a). Removal of the silyloxy protecting group of 21 with tetra-n-butylammonium fluoride in THF afforded an 83% yield of diol 22.

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

Similarly, hydrogenation of 19 with 1 atmosphere of hydrogen and palladium/carbon (90% yield) followed by desilylation with tetra-n-butylammonium fluoride in THF (31% yield) and oxidation with pyridinium dichromate afforded (+)-chloropuupehenone (27) in 50% yield.
Schemes 5 and 6 show a procedure for preparation of C₆a-S tetracyclic pyran compounds embraced by Formulae IV and V. Scheme 5 shows the preparation of (1R,4aS,6aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxaldehyde (33) and (1R,4aS,6aS)-2-Methylene-5,5,8a-trimethyl-1,2,3,4,4a,5,6,7,8,8a-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 methane-sulfonfyl chloride (MsCl) and triethylamine in dichloromethane afforded a mixture of alkenes 30 and 31 (1:1; 90% yield), which were separated by silica gel column chromatography. Desilylation of 30 with tetra-n-butyrammonium fluoride in THF (88% yield) followed by oxidation with Dess-Martin Periodinane in dichloromethane provided aldehyde 33 (67% yield). Similarly, silyl ether 31 was converted to aldehyde 35 under similar reaction conditions.
Referring to synthetic Scheme 6, Bromide 36 was synthesized from the dibenzylzation of 3,4-dihydroxy-5-chlorobenzaldehyde (see Scheme 2) with NaH and benzyl chloride in THF followed by a similar reaction sequence described for the synthesis of 4 from 13. Treatment of bromide 36 with 1.1 equivalent of t-butyllithium in diethyl ether at -78°C, followed by 1 equivalent of aldehyde 35 gave alcohol 37 (62% yield), which was disilylated with n-Bu₄NF in THF to give alcohol 38 (63% yield). Ring closure of 38 with phenylselenylphthalimide and tin tetrachloride in dichloromethane afforded tetracyclic pyran 40 (50% yield) with the C6a-S configuration. The phenylselenyl reagent approaches C6a exo double bond from the opposite face of C12a alkyl group and C7 oxygen attacks the carbocation from the opposite side of the selenium ion to give 40 as the major product. Acetylation of 40 with acetic anhydride and pyridine in dichloromethane (89% yield) followed by removal of the selenyl function with AIBN (2,2'-azobisisobutyronitrile) and tri-n-butyltin hydride in refluxing toluene gave pyran 42 (90% yield). Removal of the hydrogen and palladium-carbon in methanol provided diol 26, which has identical proton NMR spectrum as that obtained in Scheme 4.
 EXAMPLES

Nuclear magnetic resonance spectra were obtained at 400 MHz for $^1$H and 100 MHz for $^{13}$C in deuteriochloroform, and reported in ppm. Infrared spectra are reported in wave numbers (cm$^{-1}$). Elemental analysis data were obtained from Desert Analytics, Tucson, Ariz. USA, and are reported as % C and % H. Mass spectra were taken from a Hewlett Packard 5890A Series II, GC-MS. Davisil silica gel, grade 64-325, was used for the flash column chromatographic separation. Tetrahydrofuran and diethyl ether were distilled over sodium and benzophenone before use. Methylene chloride was distilled over CaH$_2$, and toluene and tetrahydrofuran were distilled over LiAlH$_4$. Chemicals and reagents were purchased either from Aldrich Chemical Company or Fisher Chemical Company, and were used without further purification.

**Example 1**

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

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

To a cold (~78°C) solution of 1.02 mL (7.79 mmol) of disopropylamine in 40 mL of THF under argon, was added 6.36 mL (7.19 mmol) of n-BuLi (1.6 M in hexane). The solution was stirred at ~78°C for 1 h, and a solution of 1.50 g (5.99 mmol) of (4S)-sclareolide 5 in 20 mL of THF was added via cannula dropwise. After the solution was stirred at ~78°C for 4 h, the mixture was diluted with diethyl ether, the organic layer was washed with water, and brine, dried (MgSO$_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluent to give 0.65 g (71% yield) of triol 6 and 0.195 g (12% yield) of compound 9 along with 0.296 g (20% recovery) of compound 7.

**Example 2**

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

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

The following representative method describes the reduction of 6 and 7 to triol 8 and lactol 9. A solution of 0.90 g (3.4 mmol) of 6 in 20 mL of THF under argon, was added 0.66 g (17.3 mmol) of LiAlH$_4$, and the mixture was stirred for 4 h at 25°C. To it, 60 mL of water and 16 mL of 1 N HCl was added, and the solution was extracted with diethyl ether three times (50 mL each). The combined ether extracts were washed with brine, dried (MgSO$_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 0.56 g (76% yield) of triol 8 and 0.241 g (17% yield) of lactol 9.

**Compound 6:** $^1$H NMR ( CDC$_3$ ) $\delta$ 5.38 (m, 1H, CHO); $^{13}$C NMR ( CDC$_3$ ) $\delta$ 179.0, 159.5, 138.0, 123.9, 118.4, 91.6, 75.1, 61.5, 57.7, 41.4, 39.7, 38.4, 37.0, 36.7, 29.7, 25.4, 24.8, 23.1, 20.6, 18.3, 17.3.

**Compound 7:** $^1$H NMR ( CDC$_3$ ) $\delta$ 4.53 (m, 1H, CHO); $^{13}$C NMR ( CDC$_3$ ) $\delta$ 178.9, 158.5, 137.9, 123.9, 118.4, 91.6, 75.1, 61.5, 57.7, 41.4, 39.7, 38.4, 37.0, 36.7, 29.7, 25.4, 24.8, 23.1, 20.6, 18.3, 17.3.

**Compound 8:** $^1$H NMR ( CDC$_3$ ) $\delta$ 4.53 (m, 1H, CHO); $^{13}$C NMR ( CDC$_3$ ) $\delta$ 179.0, 159.5, 138.0, 123.9, 118.4, 91.6, 75.1, 61.5, 57.7, 41.4, 39.7, 38.4, 37.0, 36.7, 29.7, 25.4, 24.8, 23.1, 20.6, 18.3, 17.3.

**Compound 9:** $^1$H NMR ( CDC$_3$ ) $\delta$ 4.37 (dd, J=5.6, 3.2 Hz, 1H, CHO), 2.32 (d, J=2.8 Hz, 1H, OH), 2.06 (d, J=1.2 Hz, 1H, OH), 1.89-0.98 (m, 10H), 1.69 (s, 3H, Me), 1.21 (s, 3H, Me), 0.87 (s, 3H, Me), 0.85 (s, 3H, Me); $^{13}$C NMR ( CDC$_3$ ) $\delta$ 177.6, 157.0, 136.9, 123.7, 118.4, 91.6, 75.1, 61.2, 57.7, 41.4, 39.7, 38.4, 37.0, 36.7, 29.7, 25.4, 24.8, 23.1, 20.6, 18.3, 17.3.

**Compound 10:** $^1$H NMR ( CDC$_3$ ) $\delta$ 4.53 (m, 1H, CHO); $^{13}$C NMR ( CDC$_3$ ) $\delta$ 179.0, 159.5, 138.0, 123.9, 118.4, 91.6, 75.1, 61.5, 57.7, 41.4, 39.7, 38.4, 37.0, 36.7, 29.7, 25.4, 24.8, 23.1, 20.6, 18.3, 17.3.

**Compound 11:** $^1$H NMR ( CDC$_3$ ) $\delta$ 4.37 (dd, J=5.6, 3.2 Hz, 1H, CHO), 2.32 (d, J=2.8 Hz, 1H, OH), 2.06 (d, J=1.2 Hz, 1H, OH), 1.89-0.98 (m, 10H), 1.69 (s, 3H, Me), 1.21 (s, 3H, Me), 0.87 (s, 3H, Me), 0.85 (s, 3H, Me); $^{13}$C NMR ( CDC$_3$ ) $\delta$ 177.6, 157.0, 136.9, 123.7, 118.4, 91.6, 75.1, 61.2, 57.7, 41.4, 39.7, 38.4, 37.0, 36.7, 29.7, 25.4, 24.8, 23.1, 20.6, 18.3, 17.3.
were added. After the solution was reflux for 2 h, the
using a gradient mixture of hexane and diethyl ether as (CDC\textsubscript{1})\textsubscript{3} 10.43
J=3Hz, 1H, CHO), 2.93 (broad
37.8, 36.7, 36.4, 33.6, 33.5, 33.2, 21.8, 20.4, 19.1, 18.5. over 30 minutes (with a slow gas flow) at 25\textdegree C. White solid
solution was cooled to 25\textdegree C., diluted with saturated aque-
Step 4: Preparation of (4aS,8aS)-3,4,4a,5,6,7,8,8a-
tetramethylnaphthalene-1-carboxaldehyde
To a flask equipped with a Dean-Stark apparatus under argon, 10 mg (0.042 mmol) of aldehyde 10, 10 mL of toluene, and 3 mg (0.017 mmol) of p-toluenesulfonic acid were added. After the solution was reflux for 2 h, the solution was cooled to 25\textdegree C. and 6
diluted with saturated aqueous sodium bicarbonate, and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried (MgSO\textsubscript{4}), 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 synthesis of 3, the product was distilled under reduced pressure to give colorless oil; bp. 60\textdegree C. for 4 h, it was diluted with diethyl ether, the organic layer was washed with 50 mL of 4\% aqueous NH\textsubscript{4}Cl was added, and extracted three times with diethyl ether. The combined ether
extract was washed with brine, dried (MgSO\textsubscript{4}), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluent to give 0.241 (92\% yield) of aldehyde 10.

Preparation of (1R,2R,4aS,8aS)-Decahydro-2-hydroxy-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde

Step 1: Preparation of (1R,2R,4aS,8aS)-Decahydro-2-formyloxy-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde (11)
To a solution of 0.30 g (1.1 mmol) of lactols 9s and 9R were removed by evaporation on a rotary evaporator, and 3 mg (0.017 mmol) of p-toluenesulfonic acid were added. The solution was stirred at 0\textdegree C. for 1 h and 25\textdegree C. for 3 h, 100 mL of saturated aqueous NH\textsubscript{4}Cl was added, and extracted three times with diethyl ether. The combined ether
extract was washed with brine, dried (MgSO\textsubscript{4}), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluent to give 0.241 (92\% yield) of aldehyde 10.

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

Step 1: Preparation of 5-Chloro-4-hydroxy-5-methoxybenzaldehyde (12)

Compound 12 was prepared according to the procedure of Hann et al. (J. Am. Chem. Soc. 1927, 49, 535-7). To a solution of 2.50 g (16.4 mmol) of vanillin in 15 mL of glacial acetic acid was added chlorine gas through a glass tubing over 30 minutes (with a slow gas flow) at 25\textdegree C. White solid product was collected by filtration, washed with 50 mL of hexane, and dried in vacuo to give 2.033 g of 12. The acetic acid filtrate was again treated with chlorine gas as above for 30 minutes to give another 0.659 g of 12.

To a solution of 2.00 g (10.7 mmol) of benzaldehyde 12 in 20 mL of dichloromethane under argon at 0\textdegree C. were added 9.80 mL (68.0 mmol) of distilled triethylamine and 4.40 g (59.2 mmol) of distilled triethylamine at 0\textdegree C. was added 5.01 g (35.3 mmol) of t-butyldimethylsilyl chloride. The reaction mixture was

Step 2: Preparation of 5-Chloro-3,4-dihydroxybenzaldehyde
To a solution of 0.200 g (10.7 mmol) of benzaldehyde 12 in 20 mL of dichloromethane under argon at 0\textdegree C. was added 12.20 mL (11.8 mmol) of boron tribromide. The solution was stirred at 0\textdegree C. for 30 minutes to give another 0.659 g of 12. The acetic acid filtrate was again treated with chlorine gas as above for 30 minutes to give another 0.659 g of 12. A total of 2.691 g (88\% yield) of 12 was obtained. The white solids were used in next step without purification.

To a solution of 1.68 g (9.70 mmol) of 5-chloro-3,4-dihydroxybenzaldehyde was added 5.01 g (35.3 mmol) of t-butyldimethylsilyl chloride. The reaction mixture was

Step 3: Preparation of 3,4-bis-(t-butyldimethylsilyloxy)-5-chlorobenzaldehyde (13)
To a solution of 1.68 g (9.70 mmol) of 5-chloro-3,4-dihydroxybenzaldehyde was added 5.01 g (35.3 mmol) of t-butyldimethylsilyl chloride. The reaction mixture was

To a solution of 0.350 g (1.10 mmol) of formyloxy-2,5,5,8a-tetramethylnaphthalene in 20 mL of methanol was added 0.181 g (1.32 mmol) of potassium carbonate. After the solution was stirred at 0\textdegree C. for 2 h, the solution was diluted with water and extracted three times with diethyl ether. The combined ether
extract was washed with brine, dried (MgSO\textsubscript{4}), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluent to give 0.241 (92\% yield) of aldehyde 10.
diethyl ether (80 mL each). The combined extracts were washed with 60 mL of brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluent to give 3.64 g (93% yield). ¹H NMR (CDCl₃) δ 6.977 (s, 1H, CHO), 7.50 (d, J=2.0 Hz, 1H, C6-H), 7.27 (d, J=2.0 Hz, 1H, C2-H), 1.04 (s, 9H, t-Bu), 0.98 (s, 9H, t-Bu), 0.26 (s, 6H, Me), 0.23 (s, 6H, Me); ¹³C NMR (CDCl₃) δ 189.3 (C=O), 149.5 (s), 149.2 (s), 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 C₂₃H₃₈BrClO₃Si₅: C, 49.51; H, 7.96. Found: C, 49.78; H, 8.11.

Example 4

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

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

To a solution of 1.236 g (2.97 mmol) of 3,4-bis-(t-butyldimethylsilyloxy)-5-chlorophenol 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 1.026 g (90% yield) of 3,4-bis-(t-butyldimethylsilyloxy)-5-chlorophenol. ¹H NMR (CDCl₃) δ 6.45 (d, J=2.8 Hz, 1H), 6.31 (d, J=2.8 Hz, 1H), 1.00 (s, 9H, t-Bu), 0.93 (s, 9H, t-Bu), 0.18 (s, 6H, Me), 0.15 (s, 6H, Me); ¹³C NMR (CDCl₃) δ 149.7 (s), 148.9 (s), 137.7 (s), 126.9 (s), 109.8 (d), 107.8 (d), 26.3 (q, 3C), 26.2 (q, 3C), -3.6 (q, 2C, Me), -3.4 (q, 2C, Me). Anal. Calc. for C₂₃H₃₈ClO₃Si₅: 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. ¹H NMR (CDCl₃) δ 6.53 (s, 1H, Ar), 6.50 (s, 1H, Ar), 1.03 (s, 9H, t-Bu), 0.96 (s, 9H, t-Bu), 0.22 (s, 6H, Me), 0.17 (s, 6H, Me); ¹³C NMR (CDCl₃) δ 148.3 (s), 147.4 (s), 138.8 (s), 127.0 (s), 106.9 (s), 102.9 (s), 26.2 (q, t-Bu), 18.8 (s), -3.3 (q, Me), -3.5 (q, Me). Anal. Calc. for C₂₃H₃₈BrClO₃Si₅: 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

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 1.100 g (83% yield) of 14. ¹H NMR (CDCl₃) δ 6.949 (d, J=2.8 Hz, 1H, Ar), 6.30 (d, J=2.8 Hz, 1H, C6-H), 1.04–0.97 (broad s, 27H, t-Bu), 0.18 (s, 6H, Me), 0.175 (s, 12H, Me); ¹³C NMR (CDCl₃) δ 149.3 (s), 148.6 (s), 138.6 (s), 128.6 (s), 114.6 (d), 112.1 (d), 26.3 (q, t-Bu), 25.9 (q, t-Bu), 18.9 (s), 8.8 (s), -3.5 (q, 2C, Me), -3.4 (q, 2C, Me), -4.3 (q, 2C, Me). Anal. Calc. for C₂₃H₃₈ClO₃Si₅: C, 57.27; H, 9.41. Found: C, 57.37; H, 9.55.

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

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. ¹H 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 C₂₃H₃₈BrClO₃Si₅: C, 49.51; H, 7.96. Found: C, 49.78; H, 8.11.
of 18 and 0.200 g (9.1% yield) of 19. Compound 18: \[\alpha\]_D^2 = +68° (c = 0.033, CHCl_3); \_1^H NMR (CDCl_3) 6 8.43 (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 (6H, Me), 1.03 (9H, t-BuSi), 0.95 (9H, t-BuSi), 0.87 (3H, Me), 0.92 (3H, Me), 0.21 (3H, Me), 0.20 (3H, MeSi), 0.17 (3H, MeSi), 0.16 (3H, MeSi); \_1^3C NMR (CDCl_3) 6 151.3, 147.5, 146.1, 138.1, 123.6, 115.7, 117.7, 107.9, 78.0, 52.4, 41.8, 37.3, 38.2, 33.8, 33.6, 26.4 (3C, t-Bu), 26.3 (3C, t-Bu), 26.1, 23.7, 19.5, 19.1, 18.9, -3.2, -3.4, -3.4, -3.4, -3.6. Compound 19: \[\alpha\]_D^2 = +50° (c = 0.018, CHCl_3); \_1^H NMR (CDCl_3) 6 8.43 (s, 1H, C8-H), 6.21 (s, 1H, C12-H), 2.20-0.90 (m, 11H), 1.31 (3H, Me), 1.23 (3H, Me), 1.03 (9H, t-Bu), 0.96 (6H, 9H, t-Bu), 0.95 (6H, Me), 0.86 (6H, 3H, MeSi), 0.21 (3H, MeSi), 0.20 (3H, Me), 0.18 (3H, Me), 0.15 (3H, Me), \_1^3C NMR (CDCl_3) 6 151.9, 147.5, 146.0, 138.0, 123.8, 116.5, 111.9, 108.0, 78.0, 52.2, 44.1, 39.4, 39.3, 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, -3.6. Anal. Calc. for C_{33}H_{53}C_3I_3: 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-1,3,4,5,6,6a,12b-octahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,10-diol (1)

To a solution of 0.160 g (0.270 mmol) of 18 in 3 mL of THF under argon at 25°C was added 0.58 mL (0.600 mmol) of tetra-n-butylammonium fluoride (1.0 M in THF). After stirring at 25°C for 5 min., 0.30 mL of acetic acid was added, the resulting solution was concentrated on a rotary evaporator, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluent to give a mixture of hexane and ethyl acetate at 0.080 g (82% yield) of 1. [\alpha\]_D^2 = +11° (c = 0.018, CHCl_3); \_1^H NMR (CDCl_3) 6 8.43-6.52 (broad s, 9H, C8-H), 6.31 (s, 1H), 2.18 (d, J=12 Hz, 1H), 2.02 (d, J=12 Hz, 1H), 1.86–0.90 (a series of m, 9H), 1.31 (3H, Me), 1.23 (3H, Me), 1.03 (9H, t-Bu), 0.96 (9H, t-Bu), 0.95 (6H, Me), 1.03 (9H, Me), 0.18 (3H, Me), 0.15 (3H, Me), \_1^3C NMR (CDCl_3) 6 151.3, 147.5, 146.1, 138.1, 123.6, 115.7, 111.7, 107.9, 78.0, 52.3, 44.1, 39.4, 39.3, 33.8, 33.6, 26.9, 26.4 (3C, t-Bu), 26.3 (3C, t-Bu), 26.1, 23.7, 21.4, 19.2, 18.9, 18.8, 17.6, -3.3, -3.4, -3.5, -3.6. Anal. Calc. for C_{33}H_{53}C_3I_3: c, 67.02; H, 9.16.

Example 6

2-Bromo-5-chloro-1,3,4-tris-(t-butylimethylsilyloxy)benzene

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 days. The solution was diluted with 30 mL of water, extracted three times with diethyl ether (30 mL each), and the combined extracts were washed with brine, dried (MgSO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane and diethyl ether (100:1) as eluent to give 0.980 g (45% yield) of 1. Example 7 of 18 and 0.200 g (9.1% yield) of 19. Compound 18: \[\alpha\]_D^2 = +50° (c = 0.018, CHCl_3); \_1^H NMR (CDCl_3) 6 8.43 (s, 1H, C8-H), 6.21 (s, 1H, C12-H), 2.20-0.90 (m, 11H), 1.31 (3H, Me), 1.23 (3H, Me), 1.03 (9H, t-Bu), 0.96 (9H, t-Bu), 0.95 (6H, Me), 0.86 (6H, 3H, MeSi), 0.21 (3H, MeSi), 0.20 (3H, Me), 0.18 (3H, Me), 0.15 (3H, Me), \_1^3C NMR (CDCl_3) 6 151.9, 147.5, 146.0, 138.0, 123.8, 116.5, 111.9, 108.0, 78.0, 52.2, 44.1, 39.4, 39.3, 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, -3.6. Anal. Calc. for C_{33}H_{53}C_3I_3: c, 67.02; H, 9.16.
tetrabutylammonium fluoride (1.0 M in THF). After stirring at 25°C for 10 min., 0.10 mL of acetic acid was added, the solution was concentrated on a rotary evaporator, and the residue was column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluent to give 30 mg (81.4% yield) of 2, \( \Delta^2D = +1.1 \) (Step 2: Preparation of 21 using a gradient mixture of hexane and ethyl acetate as solvent to give 0.180 g (99% yield) of 60.

\[ \text{Butyldimethylsilyloxy-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4,6a,12b-tetramethyl-benzo[a]xanthene-9,10-dione (22)} \]

To a solution of 10 mg (0.027 mmol) of diol 22 in 1 mL of dichloromethane under argon at 25°C was added 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, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate to give 20 mg (83% yield) of diol 22. \( \text{H NMR (CDCl}_3 \delta 6.35 \text{ (s, CH$_3$), 5.33 \text{ (broad } s, \text{ OH), 2.61 (dd, J=17 Hz, CH$_2$, 2.34 (m, CH$_2$, 2.02 (m, CH$_3$), 1.80-0.90 (a series of m, 11H), 1.14 (s, 3H, Me), 0.91 (s, 6H, Me), 0.85 (s, 3H, Me). When the proton NMR spectrum was measured in benzene-d$_6$ solvent, all methyl groups are separated, 0.99 (s, 3H, Me), 0.77 (s, 3H, Me), 0.71 (s, 3H, Me), 0.61 (s, 3H, Me).} \]

Example 8

\[
\begin{align*}
&\text{(4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,9,10,12a,12b-dodecacydro-4,4a,6a,12b-tetramethyl-benzo[a]xanthene-9,10-dione (23)} \\
&\text{(4aS,6aR,12aR,12bS)-2H-11-Chloro-1,3,4,4a,5,6,6a,9,10,12b-decahydro-4,4a,6a,12b-tetramethyl-benzo[a]xanthene-9,10-dione (24)}
\end{align*}
\]

Step 1: Preparation of (4aS,6aR,12aR,12bS)-2H-9,10-bis-(t-Butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4a,6a,12b-tetramethyl-benzo[a]xanthene (21)

A mixture of 0.180 g (0.300 mmol) of compound 18 and 0.400 g of 10% palladium/carbon in 7 mL of distilled ethanol was charged with 1 atmosphere of hydrogen gas (by the use of a hydrogen balloon), and the mixture was stirred at 25°C for 2 h. The reaction mixture was filtered through a short Celite column, washed the column with ethanol, and the combined filtrate was concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and toluene to give 0.180 g (99% yield) of 9,10,12a,12b-decahydro-4,4a,6a,12b-tetramethyl-benzo[a]xanthene-9,10-dione (23).

Example 9

\[
\begin{align*}
&(\text{+)-Chloropupehenone})
\end{align*}
\]

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

A mixture of 0.060 g (0.10 mmol) of compound 19 and 0.080 g of 10% palladium/carbon in 2 mL of distilled dichloromethane under argon at 25°C was added 0.10 mL of acetic acid was stirred for 30 min., 1 drop of acetic acid was added, the resulting red solution was concentrated to dryness, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate to give 20 mg (83% yield) of diol 22. \( \text{H NMR (CDCl}_3 \delta 6.35 \text{ (s, CH$_3$), 5.33 \text{ (broad } s, \text{ OH), 2.61 (dd, J=17 Hz, CH$_2$, 2.34 (m, CH$_2$, 2.02 (m, CH$_3$), 1.80-0.90 (a series of m, 11H), 1.14 (s, 3H, Me), 0.91 (s, 6H, Me), 0.85 (s, 3H, Me). When the proton NMR spectrum was measured in benzene-d$_6$ solvent, all methyl groups are separated, 0.99 (s, 3H, Me), 0.77 (s, 3H, Me), 0.71 (s, 3H, Me), 0.61 (s, 3H, Me).} \]

Example 10

\[
\begin{align*}
&(\text{+)-Chloropupehenone})
\end{align*}
\]

Step 2: Preparation of (4aS,6aR,12aR,12bS)-2H-9,10-bis-(t-Butyldimethylsilyloxy)-11-chloro-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4,4a,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, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate to give 20 mg (83% yield) of diol 22. \( \text{H NMR (CDCl}_3 \delta 6.35 \text{ (s, CH$_3$), 5.33 \text{ (broad } s, \text{ OH), 2.61 (dd, J=17 Hz, CH$_2$, 2.34 (m, CH$_2$, 2.02 (m, CH$_3$), 1.80-0.90 (a series of m, 11H), 1.14 (s, 3H, Me), 0.91 (s, 6H, Me), 0.85 (s, 3H, Me). When the proton NMR spectrum was measured in benzene-d$_6$ solvent, all methyl groups are separated, 0.99 (s, 3H, Me), 0.77 (s, 3H, Me), 0.71 (s, 3H, Me), 0.61 (s, 3H, Me).} \]

Example 11

\[
\begin{align*}
&(\text{+)-Chloropupehenone})
\end{align*}
\]
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]22D = 52.7° (c 1, CHCl3). 1H NMR (CDCl3) δ 7.21 (s, 1H, C11H), 7.12 (s, 1H, C12H), 6.91 (s, 1H, C8H), 5.20 (broad s, 1H, C2H), 2.72 (d, J=17 Hz, 1H, C12H), 2.64 (dd, J=17, 7 Hz, 1H, C12H), 1.84 (d, J=13 Hz, 1H, C12H), 1.60–0.90 (a series of m, 11H), 1.11 (s, 3H, Me). Anal. Calcd. For C20H17ClO3Si: C, 70.34; H, 4.98. Found: C, 70.19; H, 5.06.

To a solution of 6.0 mg (0.016 mmol) of 26 in 1 mL of CHCl3 was added 12 mg (0.032 mmol) of PDC. After stirring 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 as eluent to give 0.54 g (90% yield) of compound 25. [α]22D = -52.7° (c 0.036, CHCl3). 1H NMR (CDCl3) δ 7.14 (d, J=7 Hz, 1H, C12H), 5.84 (s, 1H, C8H), 2.75 (d, J=18 Hz, 1H, C12H), 2.64 (dd, J=18, 7 Hz, 1H, C12H), 2.18 (d, J=7 Hz, 1H, C12aH), 1.80–0.80 (a series of m, 11H), 1.12 (s, 3H, Me), 0.89 (s, 3H, Me), 0.81 (s, 3H, Me), 0.67 (s, 3H, Me). 13C NMR (CDCl3) δ 149.1, 143.3, 133.3, 119.1, 112.4, 103.3, 75.7, 68.2, 55.4, 49.4, 42.1, 40.6, 40.3, 38.5, 33.9, 33.4, 27.1, 18.7, 14.3, 14.3. 

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 Coming, Midland, Mich.) was introduced via the gastric fundus into the upper duodenum and secured in place with a purse-string suture (4-0 Silk, Ethicon, Somerville, N.J.) around the fundic incision. The infusion catheter was exteriorized alongside the lymph cannula. After the abdominal incision was closed, the rats were placed in restraining cages and housed in a recovery chamber at 30°C for postoperative recovery for 22–24 h. During the recovery period, rats were infused continuously with glucose in phosphate buffered saline (PBS) (in mmol/L: 277 glucose, 6.75 NaH2PO4, 16.5 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.), 33.3 kBq [1-14C]-cholesterol (14C-CH3; specific activity, 1.85 GBq/ mmol, American Radiolabeled Chemicals, St. Louis, Mo.), housed individually in plastic cages in an environmentally controlled room of illumination (12:12-h light/dark cycle with the dark period from 0330 to 1530), humidity (60–70%), and temperature (22–25°C) throughout the study. Rats had free access to deionized water and a nutritionally adequate diet (Table 1) containing soybean oil as the fat source and egg white as the protein source. The diet was formulated according to AIN-93G recommendations (In: Trace Elements in Laboratory Rodents (Watson, R. R., ed.)), pp. 3–37. CRC Press, Boca Raton, Fla.). Animals were cared for in an animal care facility accredited by the American Association for the Accreditation of Laboratory Animal Care. Rats were maintained in accordance with the policies and guidelines for animal care and use procedures of the Kansas State University Institutional Animal Care and Use Committee.

### Table 1

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg white</td>
<td>200.0</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>300.5</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 oil1</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/g biotin succose mix)</td>
<td>4.0</td>
</tr>
<tr>
<td>Choline bisistrate</td>
<td>2.5</td>
</tr>
</tbody>
</table>

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

Example 10

Lymphatic Absorption of Cholesterol

Ten male Sprague-Dawley rats (Harlan Sprague Dawley, Inc., Indianapolis, Ind.) weighing 274.3±7.8 grams were

**TABLE 1**
20.7 μmol cholesterol, 3.1 μmol α-tocopherol (all-rac-dl-α-tocopherol, 97%, Aldrich Chemical, Milwaukee, Wis.) as an antioxidant, and 396.0 μmol sodium taurocholate (Sigma Chemical, St. Louis, Mo.) in 24 mL of PBS buffer, pH 6.5. For half of the rats, the lipid emulsion contained 114.9 μmol compound 1 (41.9 mg). Lipid emulsion was prepared under a gentle N2 stream and subdued light for 55 min using a microprocessor-controlled ultrasonicator equipped with a microtip (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-CH2 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 capillary column (15 m, i.d. 0.53 mm; Resteck Corp., Bellefonte, Pa.).

Statistical analysis

All statistical analyses were performed using PC SAS (SAS Institute, Cary, N.C.). Repeated measures ANOVA and handled in subdued light.

**Results**

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

**TABLE 2**

<table>
<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>Compound 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% dose</td>
<td>% dose</td>
</tr>
<tr>
<td>1 h</td>
<td>0.16 ± 0.07</td>
<td>0.12 ± 0.04</td>
</tr>
<tr>
<td>2 h</td>
<td>1.84 ± 0.37</td>
<td>1.22 ± 0.25*</td>
</tr>
<tr>
<td>3 h</td>
<td>5.31 ± 0.74</td>
<td>2.70 ± 0.42*</td>
</tr>
<tr>
<td>4 h</td>
<td>10.16 ± 1.31</td>
<td>4.18 ± 0.92*</td>
</tr>
<tr>
<td>5 h</td>
<td>15.66 ± 1.75</td>
<td>5.68 ± 1.37*</td>
</tr>
<tr>
<td>6 h</td>
<td>22.14 ± 1.81</td>
<td>7.32 ± 1.78*</td>
</tr>
<tr>
<td>7 h</td>
<td>29.79 ± 1.65</td>
<td>9.13 ± 2.41*</td>
</tr>
<tr>
<td>8 h</td>
<td>37.69 ± 1.76</td>
<td>10.95 ± 3.20*</td>
</tr>
</tbody>
</table>

*Significantly different from control rats (P < 0.05).

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

Thus, compound 1 is a more potent inhibitor than green tea catechins, since an inhibitory effect was observed with only 41.9 mg of compound 1. Rats exhibited no gross motor or behavioral abnormalities.

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

**TABLE 3**

<table>
<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>Compound 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% dose</td>
<td>% dose</td>
</tr>
<tr>
<td>1 h</td>
<td>0.16 ± 0.07</td>
<td>0.12 ± 0.04</td>
</tr>
<tr>
<td>2 h</td>
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<td>1.22 ± 0.25*</td>
</tr>
<tr>
<td>3 h</td>
<td>5.31 ± 0.74</td>
<td>2.70 ± 0.42*</td>
</tr>
<tr>
<td>4 h</td>
<td>10.16 ± 1.31</td>
<td>4.18 ± 0.92*</td>
</tr>
<tr>
<td>5 h</td>
<td>15.66 ± 1.75</td>
<td>5.68 ± 1.37*</td>
</tr>
<tr>
<td>6 h</td>
<td>22.14 ± 1.81</td>
<td>7.32 ± 1.78*</td>
</tr>
<tr>
<td>7 h</td>
<td>29.79 ± 1.65</td>
<td>9.13 ± 2.41*</td>
</tr>
<tr>
<td>8 h</td>
<td>37.69 ± 1.76</td>
<td>10.95 ± 3.20*</td>
</tr>
</tbody>
</table>

*Significantly different from control rats (P < 0.05).

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.

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

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

What is claimed is:

I. A compound of Formula 1:
alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylicarbonyl, alkylicarbonylalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, amido, carboxyalkyl, alkylicarbonyl, alkylicarbonylalkyl, amidoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, arloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;

R₁ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylicarbonyl, alkylicarbonylalkyl, alkoxycarbonyl, alkoxy carbonylalkyl, alkoxycarbonylalkyl, amidoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, arloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;

R₂ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylicarbonyl, alkylicarbonylalkyl, alkoxycarbonyl, alkoxy carbonylalkyl, alkoxycarbonylalkyl, amidoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, arloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;

R₃ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylicarbonyl, alkylicarbonylalkyl, alkoxycarbonyl, alkoxy carbonylalkyl, alkoxycarbonylalkyl, amidoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, arloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;

or a pharmaceutically-acceptable salt thereof.

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

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

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

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

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

7. A compound of Formula II:

wherein R₁ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylicarbonyl, alkylicarbonylalkyl, alkoxycarbonyl, alkoxy carbonylalkyl, alkoxycarbonylalkyl, amidoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, arloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;

R₂ is independently hydrido, halo, alkyl, alkenyl, alkylyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonylamyl, N-alkyl-N-arylsulfonylamyl, carboxy, carboxyalkyl, alkylicarbonyl, alkylicarbonylalkyl, alkoxycarbonyl, alkoxy carbonylalkyl, alkoxycarbonylalkyl, amidoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, arloxy, acylamino, amino, cyano, nitro, sulfonate, alkylsilyl, phenylselenyl, thiol, arylsulfenyl, arylsulfinyl, or alkylsilyloxy;
45  
aryl-sulfenyl, alkylsulfenyl, arylsulfonfyl, alkylsilyl, 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, N-aryl-sulfonfyl, N-alkyl-N-aryl-sulfonfyl, carboxy, carboxyalkyl, alkylocarbonyl, alkylocarbonylalkyl, alkoxy-carbonyl, alkoxy-carbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoaryl-amido, N-alkyl-N-aryl-amido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkeny1, alkylthio, alkylsulfenyl, alkylsulfenyl, arylsulfonyl, alkylsulfonyl, phenylselenyl, or alkylsilyloxy; 
R₄ is independently hydrido, halo, alkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonfyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-aryl-sulfonfyl, N-alkyl-N-aryl-sulfonfyl, carboxy, carboxyalkyl, alkylocarbonyl, alkylocarbonylalkyl, alkoxy-carbonyl, alkoxy-carbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoaryl-amido, N-alkyl-N-aryl-amido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkeny1, alkylthio, alkylsulfenyl, alkylsulfenyl, arylsulfonyl, alkylsulfonyl, phenylselenyl, or alkylsilyloxy; 

46  
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-sulfonfyl, N-alkyl-N-aryl-sulfonfyl, carboxy, carboxyalkyl, alkylocarbonyl, alkylocarbonylalkyl, alkoxy-carbonyl, alkoxy-carbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoaryl-amido, N-alkyl-N-aryl-amido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkeny1, alkylthio, alkylsulfenyl, alkylsulfenyl, arylsulfonyl, alkylsulfonyl, 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, N-aryl-sulfonfyl, N-alkyl-N-aryl-sulfonfyl, carboxy, carboxyalkyl, alkylocarbonyl, alkylocarbonylalkyl, alkoxy-carbonyl, alkoxy-carbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoaryl-amido, N-alkyl-N-aryl-amido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkeny1, alkylthio, alkylsulfenyl, alkylsulfenyl, arylsulfonyl, alkylsulfonyl, phenylselenyl, or alkylsilyloxy; 

8. The compound of claim 7, wherein R₁ is halo, R₂ and R₃ are hydroxy, and R₄ is alkyl. 
9. The compound of claim 7, wherein R₁ is halo, R₂ and R₃ are alkylsilyloxy; and R₄ and R₅ are alkyl. 
10. The compound of claim 9, wherein R₂ is chloro, R₃ and R₄ are OSi(t-Bu)₃, and R₅ and R₆ are methyl. 
11. A compound of Formula III: 

(III) 

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-sulfonfyl, N-alkyl-N-aryl-sulfonfyl, carboxy, carboxyalkyl, alkylocarbonyl, alkylocarbonylalkyl, alkoxy-carbonyl, alkoxy-carbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoaryl-amido, N-alkyl-N-aryl-amido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkeny1, alkylthio, alkylsulfenyl, alkylsulfenyl, arylsulfonyl, alkylsulfonyl, 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, N-aryl-sulfonfyl, N-alkyl-N-aryl-sulfonfyl, carboxy, carboxyalkyl, alkylocarbonyl, alkylocarbonylalkyl, alkoxy-carbonyl, alkoxy-carbonylalkyl, amido, N-alkylamido, N-N-dialkylamido, N-monoaryl-amido, N-alkyl-N-aryl-amido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidoalkyl, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkeny1, alkylthio, alkylsulfenyl, alkylsulfenyl, arylsulfonyl, alkylsulfonyl, phenylselenyl, or alkylsilyloxy; 

12. The compound of claim 11, wherein R₁ is halo, R₂ and R₃ are selected from hydroxy and alkylsilyloxy; and R₄ and R₅ are alkyl. 
13. The compound of claim 11, wherein R₁ is chloro, R₂ and R₃ are hydroxy, and R₄ and R₅ are methyl. 
14. The compound of claim 11, wherein R₁ is halo, R₂ and R₃ are alkylsilyloxy; and R₄ and R₅ are methyl. 
15. The compound of claim 14, wherein R₁ is chloro, R₂ and R₃ are OSi(t-Bu)₃, and R₄ and R₅ are methyl. 
16. The compound of claim 11, wherein said compound has Formula (23): 

(23)
wherein $R_1$ is independently hydrido, halo, alkyl, alkenyl, alkylaryl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonfyl, arylsulfonyl, N-alkylsulfamoyl, N,N-dialkylsulfamoyl, N-arylsulfamoyl, N-alkyl-N-arylsulfamoyl, carboxy, carboxyalkyl, alkylicarboxonyl, alkylicarbononylalkyl, alkoxyalkylaminoalkyl, alkylcarbonyl, amido, N-alkylamido, N-N-dialkylamido, N-arylsulfomyl, N-alkyl-N-arylsulfamoyl, carboxy, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidooalkyl, aminoalkyl, alkylicarboxamidoalkyl, amidino, cyanoamido, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, N-arylsulfamoyl, N-alkyl-N-arylsulfamoyl, carboxy, N-alkylsulfamoyl, N,N-dialkylsulfamoyl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, alkylsilyloxy; and $R_2$ is independently hydrido, halo, alkyl, or hydroxyalkyl; $R_3$ is independently hydrido, halo, alkyl, or hydroxyalkyl; and $R_4$ is independently hydrido, halo, alkyl, or hydroxyalkyl; or a pharmaceutically-acceptable salt thereof.

18. The compound of claim 17, wherein $R_1$ is halo; $R_2$ and $R_3$ are selected from hydroxy, alkylsulfonyl, or aralkylsulfonyl; and $R_4$ is halo.

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

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

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

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

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

24. A compound of Formula V:

wherein $R_1$ is independently hydrido, halo, alkyl, alkenyl, alkylaryl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonfyl, arylsulfonyl, N-alkylsulfamoyl, N,N-dialkylsulfamoyl, N-arylsulfamoyl, N-alkyl-N-arylsulfamoyl, carboxy, carboxyalkyl, alkylicarboxonyl, alkylicarbononylalkyl, alkoxyalkylaminoalkyl, alkylcarbonyl, amido, N-alkylamido, N-N-dialkylamido, N-arylsulfomyl, N-alkyl-N-arylsulfamoyl, carboxy, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidooalkyl, aminoalkyl, alkylicarboxamidoalkyl, amidino, cyanoamido, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, N-arylsulfamoyl, N-alkyl-N-arylsulfamoyl, carboxy, N-alkylsulfamoyl, N,N-dialkylsulfamoyl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, alkylsilyloxy; and $R_2$ is independently hydrido, halo, alkyl, alkenyl, alkylaryl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonfyl, arylsulfonyl, N-alkylsulfamoyl, N,N-dialkylsulfamoyl, N-arylsulfamoyl, N-alkyl-N-arylsulfamoyl, carboxy, carboxyalkyl, alkylicarboxonyl, alkylicarbononylalkyl, alkoxyalkylaminoalkyl, alkylcarbonyl, amido, N-alkylamido, N-N-dialkylamido, N-arylsulfomyl, N-alkyl-N-arylsulfamoyl, carboxy, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidooalkyl, aminoalkyl, alkylicarboxamidoalkyl, amidino, cyanoamido, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, N-arylsulfamoyl, N-alkyl-N-arylsulfamoyl, carboxy, N-alkylsulfamoyl, N,N-dialkylsulfamoyl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, alkylsilyloxy; and $R_3$ is independently hydrido, halo, alkyl, alkenyl, alkylaryl, haloalkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonfyl, arylsulfonyl, N-alkylsulfamoyl, N,N-dialkylsulfamoyl, N-arylsulfamoyl, N-alkyl-N-arylsulfamoyl, carboxy, carboxyalkyl, alkylicarboxonyl, alkylicarbononylalkyl, alkoxyalkylaminoalkyl, alkylcarbonyl, amido, N-alkylamido, N-N-dialkylamido, N-arylsulfomyl, N-alkyl-N-arylsulfamoyl, carboxy, N-alkyl-N-arylamido, N-alkyl-N-hydroxyamido, N-alkyl-N-hydroxyamidoalkyl, amidooalkyl, aminoalkyl, alkylicarboxamidoalkyl, amidino, cyanoamido, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, carboxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, N-arylsulfamoyl, N-alkyl-N-arylsulfamoyl, carboxy, N-alkylsulfamoyl, N,N-dialkylsulfamoyl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, alkylsilyloxy; and $R_4$ is independently hydrido, alkyl, or hydroxyalkyl; $R_5$ is independently hydrido, alkyl, or hydroxyalkyl; $R_6$ is independently hydrido, hydroxy, or acyloxy; and $R_7$ is independently alkyl, or arylamidyl; or a pharmaceutically-acceptable salt thereof.
amidoalkyl, aminoalkyl, alkylaminoalkyl, amidino, cyanoamidino, heterocycloalkyl, aralkyl, cycloalkyl, cycloalkenyl, alkylthio, alkylsulfinyl, N-alkylamino, N,N-dialkylamino, acyl, acyloxy, aryl, acylamino, amino, cyano, nitro, sulfonate, thiol, arylsulfenyl, alkylsulfenyl, arylsulfinyl, alkylsilyl, phenylethynyl, or alkysilyloxy; 

$R_3$ is independently hydrido, halo, alkyl, alkenyl, alkyl, haloalkyl, hydroxalkyl, hydroxy, alkoxy, alkoxyalkyl, haloalkoxyalkyl, aryl, heterocyclic, heteroaryl, alkylsulfonyl, arylsulfonyl, N-alkylsulfamyl, N,N-dialkylsulfamyl, N-arylsulfonyl, N-alkyl-N-arylsulfamyl, carboxy, carboxyalkyl, alkyloxyalkyl, alkoxyalkyl alkylsulfonyl, arylsulfonyl, alkylsilyl, phenylethynyl, or alkysilyloxy; 

$R_5$ is hydroxy; and or alkylsilyloxy;  

$R_1$ and $R_2$ are independently hydrido, alkyl, or hydroxyalkyl; 

$R_3$ is independently hydrido, alkyl, or hydroxyalkyl; 

$R_4$ is hydrido; and 

$R_5$ is independently hydrido, or alkysilyloxy; or a pharmaceutically-acceptable salt thereof.

25. The compound of claim 24, wherein $R_1$ is halo, $R_2$ and $R_3$ are arylalkyloxy; $R_4$ and $R_5$ are alkyl; $R_6$ is hydroxy; and $R_7$ is selected from hydroxy and alkysilyloxy.

26. The compound of claim 25, wherein $R_1$ is chloro; $R_2$ and $R_3$ are OBn; and $R_4$ and $R_5$ are methyl; $R_6$ is hydroxy; and $R_7$ is OSi-t-BuMe$_2$.

27. The compound of claim 25, wherein $R_1$ is chloro; $R_2$ and $R_3$ are OBn; $R_4$ and $R_5$ are methyl; $R_6$ is hydroxy; and $R_7$ is hydroxy.

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

\[
\begin{align*}
(1) & \\
(2) & \\
(3) & \\
(4) & \\
(5) & \\
(6) & \\
\end{align*}
\]

wherein $R_1$, $R_2$, and $R_3$ are hydroxy; and $R_4$ and $R_5$ are methyl, comprising:

a) reacting compound (4),

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

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

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

b) isolating said intermediate compound (18); and 

c) deprotecting said intermediate compound.

30. A compound of Formula I:

\[
\begin{align*}
\text{Formula I} & \\
(1) & \\
(2) & \\
(3) & \\
(4) & \\
(5) & \\
\end{align*}
\]

wherein $R_1$, $R_2$, and $R_3$ are OSi-t-BuMe$_2$; $X_1$ is chloro, $X_2$ is bromo, with compound (3);

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

\[
\begin{align*}
(1) & \\
(2) & \\
(3) & \\
(4) & \\
(5) & \\
\end{align*}
\]

wherein $R_1$ is chloro, $R_2$ and $R_3$ are OSi-t-BuMe$_2$; 

b) isolating said intermediate compound (18); and 

c) deprotecting said intermediate compound.
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:

```
  OH
H
  H

(1)
```

at least one pharmaceutically-acceptable carrier material.

35. The composition of claim 34, wherein said compound is selected from the group consisting of lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, polyvinylpyrrolidone, and polyvinyl alcohol.

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

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

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

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

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

41. The composition of claim 34, wherein said composition comprises a diluent selected from the group consisting of polyethylene glycol, propylene glycol, cottonseed oil, peanut oil, sesame oil, and benzyl alcohol.

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

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

44. The method of claim 42, wherein said compound is administered orally, intravenously, 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 4 g/kg of body weight per day.

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

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

48. The method of claim 42, wherein said compound is administered in 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 4 g/kg body weight per day.
UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

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

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

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

Signed and Sealed this
Fourth Day of January, 2005

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