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[54] **ANTIHYPERCHOLESTEROLEMIC COMPOUNDS**

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[21] Appl. No.: **217,640**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 175,460, Aug. 5, 1980, abandoned, which is a continuation-in-part of Ser. No. 118,051, Feb. 4, 1980, abandoned.

[51] **Int. Cl.**^{3} **A61K 31/335;** C07D 309/30; C07C 67/02

[52] **U.S. Cl.** **424/279;** 549/292; 560/107; 560/185; 560/256; 560/119; 562/501

[58] **Field of Search** 260/343.5; 560/185, 560/119, 256, 107; 549/292; 562/501; 424/279

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[57] **ABSTRACT**

6(R)-[2-(8′-acyloxy-2′-methyl-6′-methyl (or hydrogen)-polyhydronaphthyl-1′)-ethyl]-4 (R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-ones are prepared by acylation of the corresponding 8′-hydroxy compounds. The products are strong inhibitors of the biosynthesis of cholesterol.

18 Claims, No Drawings

ANTIHYPERCHOLESTEROLEMIC COMPOUNDS

SUMMARY OF THE INVENTION

This is a continuation-in-part of copending application Ser. No. 175,460, filed August 5, 1980 (now abandoned), which in turn is a continuation-in-part of copending application Ser. No. 118,051, filed Feb. 4, 1980, (now abandoned).

This invention relates to a group of 6(R)-[2-(8'-acyloxy-2'-methyl-6'-methyl(or hydrogen)-polyhydronaphthyl-1')-ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-ones and to the hydroxy acid form of said pyranones, the pharmaceutically acceptable salts of said hydroxy acids and to the lower alkyl and phenyl, dimethylamino or acetylamino substituted lower alkyl esters of said hydroxy acid.

More specifically, this invention relates to a compound of the structure I in Table I, in which the dotted lines X, Y and Z represent possible double bonds, said double bonds being, when any are present, either X and Z together in combination or X, Y or Z alone; R represents C_{1-10} straight or branched chain alkyl (except (S)-2-butyl), C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} CF_3-substituted alkyl, phenyl, halophenyl, phenyl-C_{1-3} alkyl or substituted phenyl-C_{1-3} alkyl, in which the substituent is halo, C_{1-3} alkyl or C_{1-3} alkoxy; and the free hydroxy acids of formula II formed by opening the lactone ring of formula I in Table I.

BACKGROUND OF THE INVENTION

It is known that certain mevalonate derivatives inhibit the biosynthesis of cholesterol, cf. F. M. Singer et al, *Proc. Soc. Exper. Biol. Med.*, 102, 370 (1959) and F. H. Hulcher,*Arch. Biochem. Biophys.*, 146, 422 (1971). Nevertheless, the activity of these known compounds has not always been found to be satisfactory, i.e. to have practical application.

Recently, Endo et al, reported (U.S. Letters Pat. No. 4,049,495, U.S. Pat. No. 4,137,322 and U.S. Pat. No. 3,983,140) the production of fermentation products which were quite active in the inhibition of cholesterol biosynthesis. The most active member of this group of natural products, now called compactin, IIIa(R'=H) was reported by Brown et al [*J. Chem. Soc. Perkin I* 1165 (1976)] to have a complex mevalonolactone structure.

More recently, Monaghan et al in U.S. Pat. No. 4,231,938, which is incorporated herein by reference, reported an inhibitor, designated MK-803 and having the structure IIIa (R'=CH_3) in Table I, which was isolated from an entirely different fermentation. Albers-Schonberg et al (U.S. Ser. No. 154,157, filed May 28, 1980) described a dihydro MK-803, designated III_d (R'=CH_3) in Table I, of equal potency to MK-803 isolated from the same fermentation as was MK-803. Patchett et al (U.S. Ser. No. 118,050, filed Feb. 4, 1980) describe dihydro and tetrahydro derivatives of MK-803 of different structures ($III_{b,c\ and\ e}$ (R'=CH_3) in Table I), prepared by the catalytic hydrogenation of MK-803. Willard (U.S. Ser. No. 118,049, filed Feb. 4, 1980), described the preparation of the 8-hydroxy derivatives (IV_{a-e} (R'=CH_3) in Table I) which are the starting materials for the preparation of some of the novel compounds of this invention.

A tetrahydro analog III_e(R'=H), of compactin was reported in published Japanese Application (Kokai) 55009-024.

Very recently a dihydro-analog of compactin of structure III_d (R=H) was isolated from compactin fermentation broths as reported by Gullo et al, (U.S. Application Ser. No. 207,508, filed Nov. 17, 1980).

The preparation of the starting material, III_d, (R'=CH_3) as mentioned previously, is described by Albers-Schonberg et al in U.S. application Ser. No. 154,157, filed May 28, 1980, and is the product of the following fermentation with a strain of *Aspergillus terreus,* ATCC No. 20542, designated MF-4845 in the culture collection of MERCK & CO., Inc., Rahway, N.J.

Preparation of Compound III_d (R'=CH_3)

A. Fermentation

A tube of lyophilized culture MF-4845 was opened aseptically and the contents suspended in an unbaffled 250 ml Erlenmeyer flask (seed flask) containing approximately 10 ml of the Medium which has the following composition:

Medium		
Corn steep liquor	5	g
Tomato paste	40	g
Oatmeal	10	g
Glucose	10	g
Trace Element Solution	10	g
Distilled water	1000	ml
pH 6.8 with NaOH		
Trace Element Solution:		
$FeSO_4.7H_2O$	1000	mg
$MnSO_4.4H_2O$	1000	mg
$CuCl_2.2H_2O$	25	mg
$CaCl_2.2H_2O$	100	mg
H_3BO_3	56	mg
$(NH_4)_6MO_7O_{24}.4H_2O$	19	mg
$ZnSO_4.7H_2O$	200	mg
Distilled Deionized Water	1000	ml

The inoculated flask was incubated for 24 hours at 28° C. on a 220 rpm shaker (2 inch throw). An unbaffled 2 liter Erlenmeyer flask containing 500 ml of the medium was then inoculated with 10 ml of the first stage fermentation growth from the seed mixture. This too was shaken 24 hours at 28° C.

A 200 gallon stainless steel fermentation vat was then charged with 485 liters of a medium comprising:

Cerelose	4.5%	wt/vol
Peptonized Milk	2.5%	wt/vol
Autolyzed yeast	0.25%	wt/vol
Polyglycol P2000	0.25%	vol/vol

whose pH was adjusted to 7.0. This was sterilized 15 minutes at 121° C. One liter of the second stage above was then charged and the mixture was incubated at 85 rpm for 12 hours then at 130 rpm for 84 hours at 28° C. with an air flow of 5 cfm for 12 hours then 10 cfm for 84 hours.

B. Isolation

1. Extraction

Two batches of one hundred gallons of whole broth were combined, acidified with stirring to pH 4.1 by careful addition of 800 ml of concentrated hydrochloric acid, and extracted by addition of 75 gal of ethyl acetate and further stirring for two hours.

About 25 lbs of a silicaceous filter aid was then added and the total slurry was pumped through a 24-inch filter press. An additional 75 gal of ethyl acetate was used to wash the press cake and continue the extraction, by reversing the direction of pumping through the press four times. Then all of the wash solvent was discharged from the press and combined with the first filtrate. The two-phase filtrate was allowed to settle, and the water layer removed. The ethyl acetate layer was washed with 10 gal of deionized water, the phases were allowed to separate and the ethyl acetate extracts were concentrated under vacuum to a residue of about 10 gal.

2. Lactonization

Ethyl acetate extracts from an additional three hundred gal of broth were added to the above extract and the volume was reduced to about thirty gal by vacuum distillation. About fifty gal of toluene was added, and the batch was concentrated under vacuum to 32 gal; this step was repeated; then sufficient new toluene was added to bring the volume to 75 gal. Without vacuum, the batch was brought to reflux and maintained there for two hours, with a temperature over 106° C.

This solution was then concentrated under vacuum to a small volume, which was further concentrated to an oily residue in a large rotary evaporator under vacuum.

3. Chromatography on Silica Gel

The extract obtained above was flushed free of other solvents by addition of 2 gal of methylene chloride and reconcentration to an oil.

The oily residue was dissolved in about 5 gal of ethyl acetate-methylene chloride (30/70; v/v) mixture, and a slurry was made by addition of 2.8 kg of silica gel.

The slurry was loaded as a level layer on the top of a 12 in.×50 in. silica gel column packed in the same solvent mixture.

Elution was with ethyl acetate-methylene chloride (40/60; v/v) at 800 ml/min. A forerun of 10 gal, then further fractions of 4 gal each were collected.

Fractions 6–10 inclusive were concentrated under vacuum to an oily residue which was dissolved in hot ethyl acetate, treated with decolorizing carbon, filtered hot, and cooled. Crystals of Compound III_a (R'=CH_3) were filtered off and the mother liquors were concentrated to an oil for further chromatography.

4. Rechromatography on Silica Gel

Mother liquor residues from similar broth extract work-ups equivalent to an additional 600 gal of fermentation production were combined with the above in methylene chloride solution. One-half of this solution was taken for further silica gel chromatography. A small aliquot showed a total solids content of 325 g. The solution was treated with 40 g of decolorizing carbon, filtered, and the cake rinsed with methylene chloride. The combined filtrate and washings were concentrated under vacuum to an oily residue. This was redissolved in 800 ml of ethyl acetate/methylene chloride (30/70; v/v) and slurried with 225 g of silica gel. The slurry was loaded on top of a 14×36 cm column bed of silica gel packed in the same solvent mixture. Development was with ethyl acetate/methylene chloride (40/60; v/v). A forecut of three liters was set aside; then fractions of 800 ml each were collected.

5. Chromatography on Reverse-phase Packing

Forty ml from fraction 12 of the above chromatography were concentrated to an oil weighing 500 mg and the oil redissolved in 5 ml acetonitrile. This acetonitrile solution was charged to a ⅝" OD by 6 ft long stainless steel chromatography column packed with preparative reverse-phase liquid chromatography column packing material "Bondapak C18/PorasilB" (Waters Associates, Inc., Milford, Mass. 01757). The column was eluted with a mixture consisting of (v/v) 55% acetonitrile and 45% 0.05 M ammonium phosphate pH3. The elution volume between 1360 ml and 1700 ml was combined on the basis of refractive index detection. The organic solvent was removed in vacuo and the residual aqueous solution extracted with ethyl acetate. In vacuo removal of the ethyl acetate left 120 mg of compound which crystallized from a concentrated acetonitrile solution yielding crystals of Compound III_d (R'=CH_3), m.p. 129°–131° C.

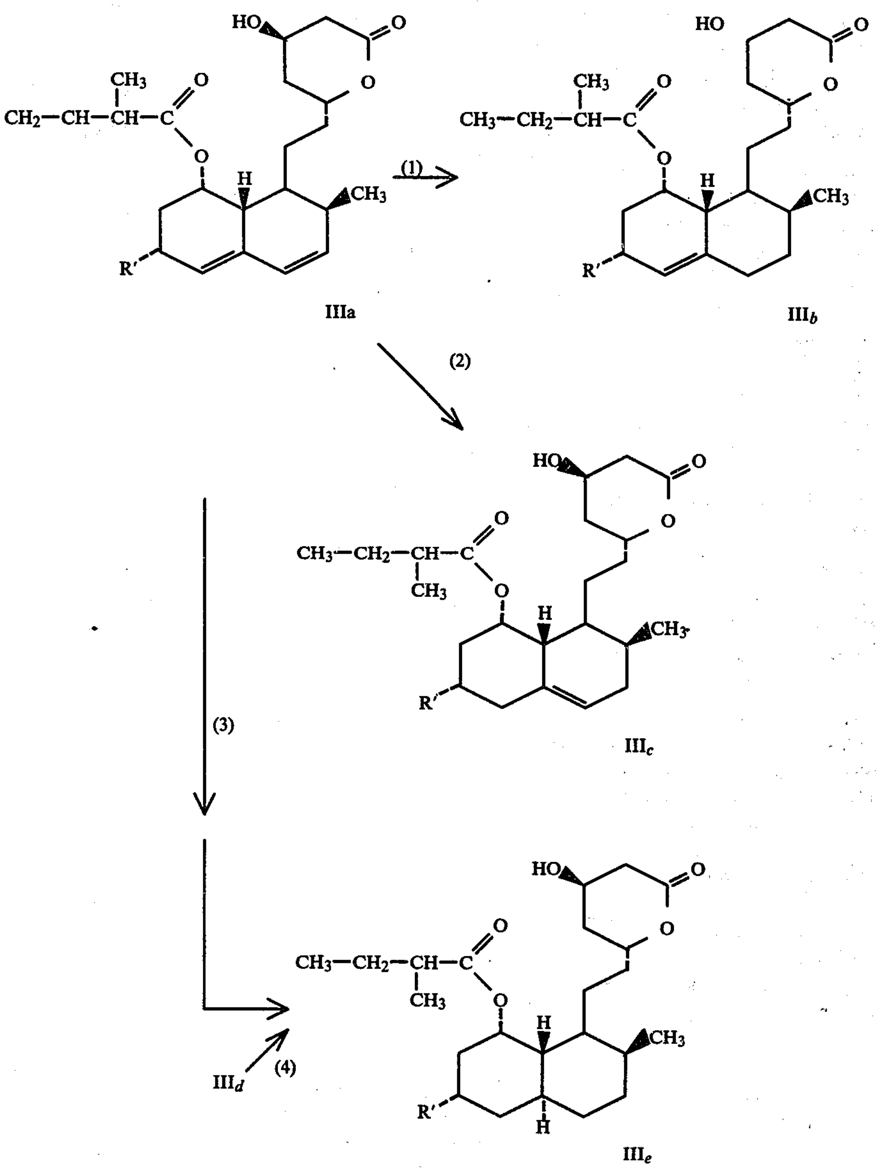
Preparation of Compounds $III_{b, c, e}$

Starting materials III_b, III_c and III_e (R'=CH_3) as mentioned above are described in U.S. application, Ser. No. 118,050, filed Feb. 4, 1980 by Patchett et al., in accordance with the following Flow Sheet and preparative methods extracted therefrom.

The desmethyl analogs, III_b, III_c and III_e (R'=H) are obtained substantially as described by Patchett et al. but starting with III_a (R'=H) in each case.

For the preparation of III_e it is advantageous to reduce III_d inasmuch as the desired trans fusion of the perhydronaphthalene ring, present in the starting materials, is retained in the final product, and the need to separate isomers is avoided.

FLOW SHEET



Reactions and Reagents

1. Hydrogenation at about 20°-75° C. and about atmospheric pressure to about 4 atmospheres over tris(triphenylphosphine)chlororhodium in an aromatic solvent such as benzene, toluene or xylene, preferably toluene. Preferred conditions are about 40° C. and about 2-7 atmospheres in toluene.

2. Hydrogenation at about 20°-25° C. and about atmospheric pressure over 5% palladium on calcium carbonate in a lower alkanol such as a C_{1-3} alkanol, especially ethanol.

3. Hydrogenation at about 20°-25° C. and atmospheric pressure over platinum oxide in ethyl acetate.

4. Hydrogenation at 20°-25° C. and atmospheric pressure over 10% Palladium on charcoal in ethyl acetate.

Preparation of 6α[2-(8'β-2-(S)-methylbutyryloxy-2'β,6'α-dimethyl-1',2',3',4',6',7',8',8'a-octahydronaphthyl-1)ethyl]-4β-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, III_b (R'=CH_3)

A mixture of 50 mg (0.1236 mmol) of Compound III_a (R'=CH_3) and an equal molar amount (114.35 mg, 0.1236 mmol) of tris(triphenylphosphine)chlororhodium in 10 ml of dry toluene was hydrogenated at room temperature for 6 days, with a total uptake of 14.6 ml of hydrogen. The mixture was evaporated in vacuo to dryness. The red residue was subjected to preparative thin-layer chromatography on silver nitrate impregnated silica plates and was developed twice in the 10% ethyl acetateether system. The yield of Compound III_b (R'=CH_3) was 22.3 mg.

Mass spectrum (M/e) 406 (m+) 304 (m-102) 286 (m-102-18) nmr ($CDCl_3$, 300 MHz) δ4.37 (m,1H) 4.60 (m,1H) 5.34 (d of t, J=2.5 Hz, 1H) 5.41 (m,1H)

Preparation of 6α[2-(8′β-2-(S)-methylbutyryloxy-2′β,6′α-dimethyl-1′,2′,3′,5′,6′,7′,8′,8′a-octahydronaphthyl-1) ethyl]-4β-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, III_c (R′=CH_3)

A solution of 80.91 mg (0.2 mmol) of Compound III_a (R′=CH_3) in 10 ml of absolute ethanol, in the presence of an equal weight of 5% Pd on $CaCO_3$ was hydrogenated at 1 atmosphere until an uptake of one mole equivalent of hydrogen was observed. The catalyst was then removed by filtration and the filtrate was evaporated to dryness (81 mg). After a purification by preparative thin-layer chromatography to remove a small amount of by-product tetrahydro compound, 72 mg of the 1,4 reduction product III_c (R′=CH_3) was isolated.

Mass spectrum (M/e) 406 (m+) 304 (m-102) 286 (304-H_2O)

nmr ($CDCl_3$, 300 MHz) δ 4.38 (m,1H) 4.64 (m,1H) 5.28 (d of t, J=3.5 Hz, 1H) 5.48 (m,1H)

Preparation of 6α-[2-(8′β-2(S)-methylbutyryloxy-2′α,6′β-dimethyl-1′,2′,3′,4′,4′aα,5′,6′,7′,8′,8′a-decahydronaphthyl-1)-ethyl]-4β-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, III_e (R′=CH_3)

A solution of 80.91 mg (0.2 mmol) of Compound III_a (R′=CH_3) in 10 ml of ethyl acetate was hydrogenated in the presence of an equal weight of platinum oxide at one atmosphere. An exact 2 mole equivalent of hydrogen was consumed within 1 hour. The catalyst was removed by filtration and the filtrate was concentrated to dryness to give an oil. The cis and trans isomers were separated by preparative thin-layer chromatography on silica gel plates (10% ethyl acetate—ether system, bands detected by water spray). The trans isomer III_e (R′=CH_3) appears as the more polar spot, compared to the cis isomer, and 60 mg was isolated.

Mass spectrum (M/e) 408 (m+) 323 (m-85) 306 (m-102)

nmr ($CDCl_3$, 300 MHz) δ 4.36 (broad singlet, 1H) 4.59 (m,1H) 5.19 (d of t, J=2.5 Hz, 1H)

Fermentative Production of Compound III_d (R′=H) A. Fermentation:

A natural isolate of *Penicillium citrinum,* NRRL 8082 was used to prepare a yeast-malt extract (YME) slant which was incubated for 2 weeks at 28° C.

A portion (1/5) of the slant (MF-4870a) was used to inoculate each of 5 unbaffled seed flasks (250 ml) containing 44 ml of KF seed medium with $CaCl_2$. They were incubated for 3 days at 28° C., and 220 rpm. A portion of the seed growth (about 1.5 ml) was used to inoculate each of 100 production medium flasks (250 ml unbaffled) containing 40 ml of LM Production Medium Without Malt Extract. The production flasks were incubated for 4 days at 25° C.

Another group of production medium flasks (140), each containing 40 ml of LM Production Medium Without Modification were inoculated and incubated under the same conditions as previously described. The broths from both fermentations were combined.

The various media employed in the foregoing fermentations are:

YME Slant	
Dextrose	4 g./l.
Malt Extract	10 g./l.
Yeast Extract	4 g./l.
Agar	20 g./l.
Dist. Water	to 1 liter
pH	7.0
KF Seed Medium with $CaCl_2$	
$CaCl_2$	10 g.
Corn steep liquor	5 g.
Tomatoe Paste	40 g.
Oatmeal	10 g.
Cerelose	10 g.
Trace Element Mix	10 ml.
Distilled Water	1000 ml.
pH	6.8
Trace Element Mix	
$FeSO_4.7H_2O$	1 g.
$MnSO_4.4H_2O$	1 g.
$CuCl_2.2H_2O$	25 mg.
$CaCl_2$	100 mg.
H_3BO_3	56 mg.
$(NH_4)_6Mo_7O_{24}.4H_2O$	19 mg.
$ZnSO_4.7H_2O$	200 mg.
Distilled Water	1000 ml.
LM Production Medium Without Malt Extract	
Dextrose	20 g.
Glycerol	20 ml.
Ardamine pH	10 g.
$CoCl_2.6H_2O$	8 mg.
Polyglycol p 2000	0.25%
Distilled Water	1000 ml.
pH	7.0
LM Production Medium Without Modification	
Dextrose	20 g.
Glycerol	20 ml.
Ardamine pH	10 g.
Malt Extract	20 g.
$CoCl_2.6H_2O$	8 mg.
Polyglycol p 2000	0.25%
Distilled Water	1000 ml.
pH	7.0

B. Isolation

The combined whole broth (10.3 liters) was filtered and the mycelia cake was washed with 2.5 liters of deionized water. The combined filtrate and wash was adjusted to pH 4.0 with 1 N hydrochloric acid. The aqueous solution was extracted with 7 liters of ethyl acetate and the extract was back-extracted with 3×2 liters of aqueous sodium hydroxide solution. The combined sodium hydroxide extract was adjusted to pH 3.8 with 1 N hydrochloric acid and extracted with 2 liters and 1 liter of ethyl acetate. The combined ethyl acetate solution was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The oily residue was dissolved in toluene and refluxed for 1 hour. The toluene solution was concentrated to dryness and the residue was dissolved in 18 ml of a mixture of n-hexane/toluene/methanol (4/1/1 by volume). This solution was loaded onto a 30 mm (ID)×40 cm. Sephadex LH-20 column equilibrated in the same solvent system. After eluting with 300 ml of solvent, a 10 ml fraction was obtained which was concentrated to an oil. High performance liquid chromatograhy (HPLC) on an ES Industries Chromega ® column (9 mm×50 cm) using a mixture of acetonitrile/water (60/40 by volume) as the eluting solvent yielded 45 mg of dihydrocompactin (Compound III_d, R′=H), m.w. 392.2560 by mass spectrum (calculated for $C_{23}H_{36}O_5$, 392.2558).

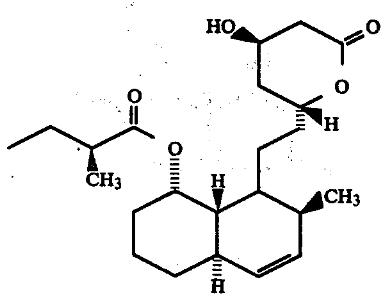
In KBr, the major IR peaks obtained from a Fourier Transform-IR (FTIR, Nicolet, Model 7199) are at 1724, 1704, 1258, 1078 and 1070 cm^{-1}. Of significance is a peak at 3005 cm^{-1} and the absence of a peak at 3030 cm^{-1}.

A nuclear magnetic resonance spectrum was obtained in $CDCl_3$, (~1 mg/0.5 ml) on a Varian SC-300 superconducting nmr spectrometer. The following are the peak positions given in ppm (δ) relative to internal tetramethylsilane (TMS).

δ	Assignment
5.62 d,d,d (2.17, 4.5, 10.0)	$H_{3'}$(d?)
5.43 d (10)	$H_{4'}$(c?)
5.20 m	$H_{8'}$
4.63 m	H_6
4.39 m	H_4
2.75 d,d (17.5, 5.5)	
2.63 d,d,d (17.5, 4.0, 1.5)	3-CH_2
2.39 m	$CH_3HCC{=}O$
2.29 m	$H_{4a'} + H_{5'}$
1.14 d	$CH_3CHC{=}O$
0.90 t	CH_3CH_2
0.84 d	$CH_3H_{2'}$

d* doublet; m: multiplet; t: triplet

The evidence indicates the structure to be:



Preparation of Compounds IV_{a-e}

The starting materials, the 8'α-hydroxy compounds IV_{a-e} (R'=CH_3) described by Willard Ser. No. 118,049) are prepared from the various 8'-esters described by Monaghan et al (III_a, R'=CH_3), Albers-Schonberg et al (III_d, R'=CH_3) and Patchett et al ($III_{b,c,e}$, R'=CH_3) by heating them with lithium hydroxide solution for extended periods. The pyranone ring readily opens but the removal of the side chain acyl group is not easily effected. The heating must be prolonged and/or pressure must be used. An inert atmosphere is also helpful.

In the case of the Compounds III_{a-e} (R'=H) the saponification of the 8'-esters is much more facile proceeding to completion in about 20 hours.

The 8'-hydroxy products are isolated by acidification and extraction with organic solvents which provides the trihydroxy acid form, in which the pyranone ring is still opened. These trihydroxy acids are relactonized by heating a solution of the acid in an appropriate organic solvent such as benzene or toluene in an apparatus permitting continuous separation of the water formed.

The Compound IV_a (R'=H) is known as ML-236A as reported by Endo et al in U.S. Pat. No. 3,983,140.

In their lactone form, these alcohols are the compounds of Formula IV_{a-e} in Table I and are prepared as described in the following preparations.

Preparation of 6(R)-[2-(8'(S)-hydroxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8'a(R)-hexahydronaphthyl-1'(S))-ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, IV_a (R'=CH_3)

A mixture of 8.0 g. (19.78 mmole) of MK-803 (III_a, R'=CH_3) and 8.31 g (197.8 mmole) of $LiOH.H_2O$ in 600 ml of water was stirred at reflux under a nitrogen atmosphere for 56 hours. The reaction mixture was cooled to 0° and treated, with stirring, with 20 ml of concentrated hydrochloric acid. The mixture was then extracted with three 250-ml portions of ether and the combined extracts were washed successively with three 200-ml portions of water and then 200 ml of saturated brine. After drying over $MgSO_4$, this organic solution was filtered and the solvent evaporated in vacuo to give an oily residue. This residue was dissolved in 200 ml of toluene and heated at reflux under a nitrogen atmosphere for 2 hours with continuous separation of water to effect relactonization. Evaporation of the toluene and trituration of the residue with hexane gave 5.15 g (81%) of the title compound IV_a (R'=CH_3) as a white solid which did not require further purification.

An analytical sample was prepared by recrystallization of a portion of this material from butyl chloride to give white clusters: m.p. 128°-131° (vacuum); NMR($CDCl_3$) δ 0.87 (d,3,J=7 Hz, CH_3), 1.16 (d,3,J=7 Hz, CH_3), 2.64 (m,2,pyran C_3H's), 4.27 (brm,1, naphthalene C_8H), 4.37 (m,1,pyran C_4H), 4.71 (m,1,pyran C_6H), 5.56 (m,1, naphthalene C_5H), 5.79 (dd,1, J=6,10 Hz, naphthalene C_3H), 6.03 (d,1,J=10 Hz, naphthalene C_4H); IR ($CHCl_3$) 3400 (OH), 1725 (C=O), 1240, 1120, 1080 cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O_4.0.1C_4H_9Cl$ C, 70.67; H, 8.84. Found: C, 70.77; H, 8.75.

Alternative preparation of 6(R)-[2-[8'(S)-hydroxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8'a(R)-hexahydronaphthyl-1'(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, IV_a (R'=CH_3)

A suspension of 188 mg (0.463 mmol) of MK-803 (III_a, R'=CH_3) in 5 ml (5 mmol) of aqueous 1 N LiOH solution is shaken for 12 hours at 135° in a 30 ml stainless steel pressure vessel. The cooled reaction mixture is acidified with 1 M H_3PO_4 and extracted with ethyl acetate. The ethyl acetate solution is dried ($MgSO_4$) and filtered and the solvent is evaporated. The residue is dissolved in 20 ml of toluene which is heated to reflux for 4 hours in a Dean-Stark apparatus to effect relactonization. Evaporation of the toluene gives the title compound.

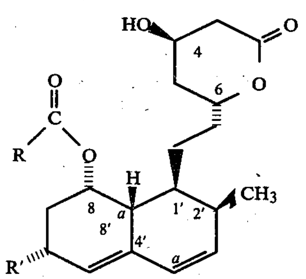
Preparation of alcohols IV_a (R'=H) and IV_b, IV_c, IV_d, and IV_e (R'=H or CH_3)

Following essentially either procedure described above but substituting an equivalent amount of esters III_a(R'=H) or III_b, III_c, III_d, or III_e (R'=H or CH_3), for III_a (R'=CH_3) used therein the corresponding alcohols IV_a(R'=H), IV_b, IV_c, IV_d and IV_e(R'=H or CH_3) are respectively obtained.

DESCRIPTION OF THE INVENTION

We have found that the 8′-hydroxy compounds of Structure IV can be acylated to give a new class of 8-acyloxy compounds of the structure defined by Formulas I and II and the definitions thereunder. These new compounds are not formed in the fermentations described by Endo, Monaghan, Albers-Schonberg or Gullo. They are inhibitors of cholesterol synthesis in vivo.

The absolute configuration of these compounds is known from X-ray diffraction. Table I provides a convenient tabulation of these structures and their stereochemical relationship. The reference numerals to the various compounds, including those of the various series of polyhydronaphthyl structures, remain the same throughout these specifications and are so used. Each of the esters I_{a-e} (R′=CH_3), of this invention contains seven or eight chiral centers. The relative and absolute configuration of these asymmetric centers is as depicted in Table I. More specifically, for ester I_a(R′=CH_3), the Cahn, Ingold, Prelog designations for the absolute configurations are 4(R), 6(R), 1′(S), 2′(S), 6′(R), 8′(S) and 8a′(R) [R. S. Cahn, C. Ingold and V. Prelog, Angew.-Chem.Int.Ed.,5, 385 (1966)].

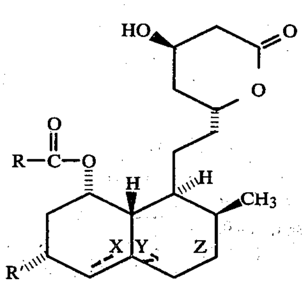


I_a(R′ = CH_3)

As is indicated in the formulas I_{a-e}, all of these compounds have the same spatial orientation of groups at each chiral carbon atom and therefore belong to the same stereochemical series. The R-S designation for each center may not be identical to that found for the ester I_a (R′=CH_3) because of the details of the sequence rules used for determining that designation. In the two esters I_d and I_e which have an additional chiral carbon atom not present in ester I_a, the hydrogen atom at 4a′ is in the down (or α) orientation as depicted in Table I, giving a trans ring junction.

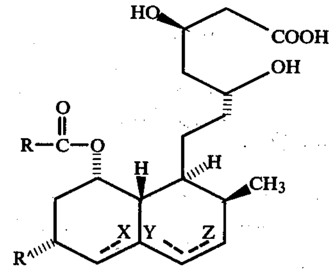
TABLE I

THE COMPOUNDS OF THIS INVENTION AND THEIR STEREO-RELATIONSHIP

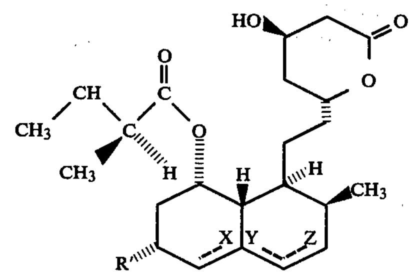


I_{a-e}

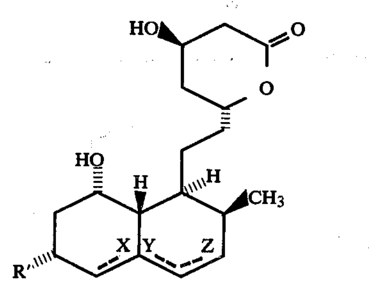
TABLE I-continued



II_{a-e}



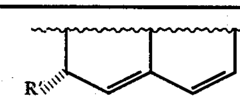
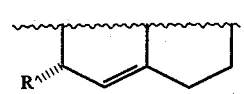
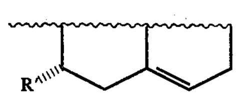
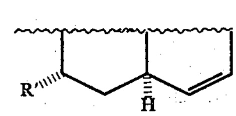
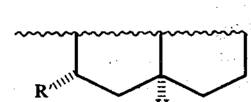
III_{a-e}



IV_{a-e}

R′ = H or CH_3

STEREOCHEMISTRY OF THE HYDRONAPHTHYL SERIES

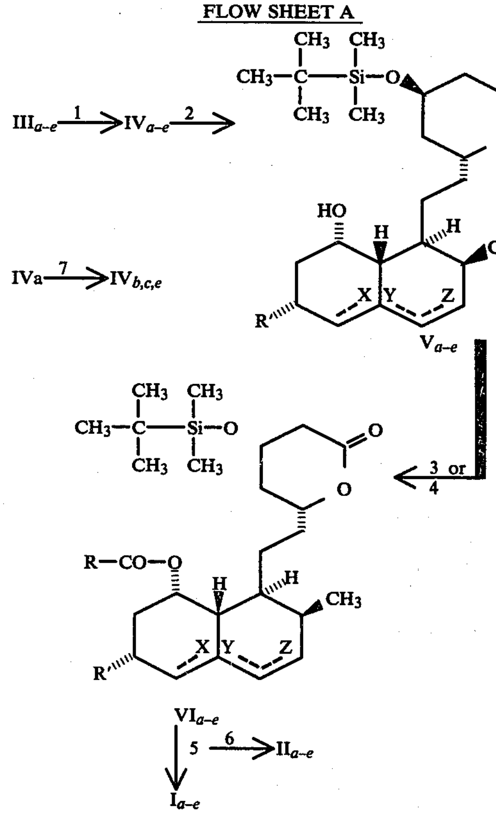
Series	Double Bonds Present	Structure
a	X and Z	
b	X	
c	Y	
d	Z	
e	None	

The compounds of this invention are useful as antihypercholesterolemic agents for the treatment of atherosclerosis, hyperlipemia and like diseases in humans. They may be administered orally or parenterally in the form of a capsule, a tablet, an injectable preparation or the like. It is usually desirable to use the oral route. Doses may be varied, depending on the age, severity, body weight and other conditions of human patients but daily dosage for adults is within a range of from about 2 mg to 2000 mg (preferably 10 to 100 mg) given in three or four divided doses. Higher doses may be favorably applied as required.

The compounds of this invention also have useful anti-fungal activities. For example, they may be used to control strains of Penicillium sp., *Aspergillus niger*, Cladosporium sp., *Cochliobolus miyabeanus* and *Helminthosporium cynodnotis*. For those utilities they are admixed with suitable formulating agents, powders, emulsifying agents or solvents such as aqueous ethanol and sprayed or dusted on the plants to be protected.

The preparation of the compounds of this invention is described in Flow Sheet A.

FLOW SHEET A



Definitions—X,Y,Z,R and R' as defined in specification and series a-e as defined in Table I.

Reactions

(1) Lithium hydroxide, heat, acidify, and lactonize

(2) t-Butyldimethylchlorsilane and imidazole in DMF at ambient temperatures in an inert atmosphere.

(3) Treatment with RCOCl and 4-dimethylaminopyridine in pyridine solution preferably under inert atmosphere.

(4) Treatment with RCOOH and N,N'-dicyclohexylcarbodiimide and 4-pyrrolidinopyridine in dichloromethane, preferably under an inert atmosphere.

(5) Three equivalents of tetrabutylammonium fluoride and four equivalents of acetic acid per equivalent of ester in THF, preferably in an inert atmosphere.

(6) Aqueous alkali followed by careful acidification with dilute acid.

(7) See Reactions and Reagents and Flow Sheet for synthesis of $III_{b,\ c,\ e}$.

In the novel process of this invention the 4-hydroxyl on the pyranone ring, of alcohols IV_{a-e} is first protected with a t-butyldimethylsilyl group by reaction with t-butyldimethylchlorosilane in an inert atmosphere at ambient temperatures in the presence of an acid acceptor such as imidazole to provide the protected alcohols V_{a-e}. The 8-hydroxyl on the polyhydronaphthyl ring is then acylated in one of two ways. The first comprises treatment with the acid chloride of the desired acyl group in pyridine in the presence of 4-dimethylaminopyridine as a catalyst. The second comprises treatment of the 8'-polyhydronaphthol with the free acid of the desired acyl group and a carbodiimide such as N,N'-dicyclohexylcarbodiimide with 4-pyrrolidinopyridine as a catalyst in dichloromethane. These procedures give the protected esters VI_{a-e}. The removal of the silyl protecting group from the 4-hydroxyl of the pyranone ring is then carried out, using three equivalents of tetrabutylammonium fluoride and four equivalents of acetic acid per equivalent of esters VI_{a-e}, to give the desired compounds I_{a-e}. The ratio of reagents in this last reaction is critical to the yield of the process and the purity of the products.

The acyl groups thus put on the 8'-hydroxyl are those in which R in I_{a-e} is:

(1) C_{1-10} straight, or branched chain alkyl except (S)-2-butyl,

(2) C_{3-10} cycloalkyl,

(3) C_{2-10} alkenyl,

(4) C_{1-10} CF_3-substituted alkyl,

(5) phenyl,

(6) halophenyl, wherein halo is chloro, fluoro, bromo or iodo,

(7) phenyl-C_{1-3} alkyl,

(8) substituted phenyl-C_{1-3} alkyl in which the substituent is halo, such as fluoro, chloro, bromo, or iodo, C_{1-3} alkyl or C_{1-3} alkoxy.

It is preferred that R' be CH_3.

Preferred definitions of R, are:

C_{2-5} straight chain alkyl,

C_{3-10} branched chain alkyl except (S)-2-butyl,

C_{3-10} cycloalkyl,

C_{3-10} alkenyl in which the unsaturation is not in conjugation with the carbonyl, especially

C_{3-10} branched chain alkyl except (S)-2-butyl.

Preferred species are those wherein R is 1,1-diethylpropyl or 1-ethyl-1-methylpropyl. And it is especially preferred that none of X, Y or Z is a double bond.

Compounds I_{a-e} can be hydrolyzed with bases such as NaOH to yield the salts such as the sodium salt of Compounds II_{a-e}. The use of bases with other pharmaceutically acceptable cations affords salts of those cations. Careful acidification of the salts affords the hydroxy acids II_{a-e} which revert to Compounds I_{a-e} at acidic pH. Treating Compound I_{a-e} under acidic or basic catalysis with methanol, ethanol, propanol, or butanol or with phenyl-, dimethylamino-, or acetylamino-alkanols yields the corresponding esters of Compounds II_{a-e} which also form a part of this invention.

The pharmaceutically acceptable salts of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, and tris(hydroxymethyl-)aminomethane.

EXAMPLE 1

6(R)-[2-(8'(S)-2",2"-dimethylpropanoyloxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8'a(R)-hexahydronaphthyl-1'(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

Step A: Preparation of 6(R)-[2-(8'(S)-hydroxy-2'(S)-6'(R)-dimethyl-1',2',6',7',8',8'a(R)-hexahydronaphthyl-1'(S))ethyl]-4(R)-(dimethyl-tert-butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one, V_a (R'=CH3)

A mixture of the alcohol IV_a (R'=CH3) (18.3 g, 57.1 mmol), 21.5 g (142.8 mmol) of tert-butyldimethylchlorosilane and 19.4 g (285.6 mmol) of imidazole in 200 ml of N,N-dimethylformamide was stirred at 20° under a nitrogen atmosphere for 18 hours. The reaction mixture was then diluted with 1500 ml of ether and washed successively with water, 2% aqueous hydrochloric acid, water and saturated sodium bicarbonate. The ether solution was dried over $MgSO_4$, filtered and reduced to a volume of 1 L. After addition of 600 ml of hexane, the volume was reduced to 600 ml on a steam bath. The product crystallized at room temperature; after isolation and air drying this provided 13.7 g of a white cottony solid. The mother liquors were reduced to 250 ml and a second crop of crystals was isolated after this solution stood at 0° overnight. The combined yield was 17.13 g (69%) of the title compound as a white cottony solid: mp 142°-144° (vac); NMR ($CDCl_3$) δ 0.10 (s,6,$(CH_3)_2Si$), 0.90 (s,9,$(CH_3)_3CSi$), 1.19 (d,3,J=7 Hz, CH_3), 2.58 (d,2,J=4 Hz, pyran C_3H's), 4.3 (m,2,pyran C_4H and naphthalene C_8H) 4.70 (m,1, pyran C_6H), 5.57 (m,1,naphthalene C_5H), 5.58 (dd,1, J=6,10 Hz, naphthalene C_3H), 6.03 (d,1, J=10 Hz, naphthalene C_4H).

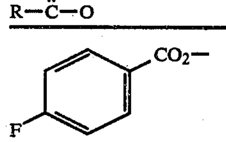
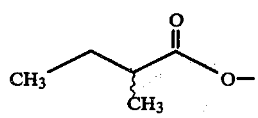
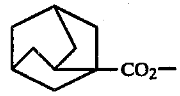
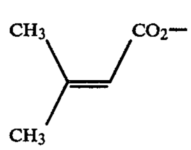
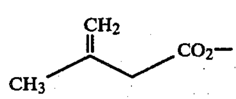
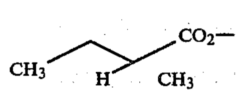
Anal. Calcd. for $C_{25}H_{42}O_4Si$: C, 69.08, H, 9.74. Found: C, 69.46; H, 9.83.

Step B: Preparation of 6(R)-[2-(8'(S)-2",2"-dimethylpropanoyloxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8'a(R)-hexahydronaphthyl-1'(S))ethyl]-4(R)-(dimethyl-tert-butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one, VI_a (R'=CH3)

A solution of 6.0 g (13.8 mmol) of the alcohol V_a (R'=CH3) from Step A and 200 mg of 4-dimethylaminopyridine in 50 ml of pyridine was cooled to 0° under a nitrogen atmosphere. To this stirred solution was added 6.8 ml (6.65 g, 55.2 mmol) of pivaloyl chloride over 15 minutes. The reaction mixture was stirred at 0° for 1 hour and then at 20° for 4 days. The reaction mixture was diluted with 750 ml of ether and washed with 2% aqueous hydrochloric acid until the wash was acidic and then with saturated $NaHCO_3$ solution. After drying over $MgSO_4$ the solution was filtered and evaporated to give 7.81 g of the title compound as a light orange oil: NMR ($CDCl_3$) δ 0.09 (s,6($CH_3)_2Si$), 0.88 (s,9,$(CH_3)_3CSi$), 1.28 (s,9, $(CH_3)_3CCO_2$—), 2.57 (d,2,J=4 Hz, pyran C_3H's), 4.32 (m,1, pyran C_4H), 4.63 (m,1, pyran C_6H), 5.34 (m,1, naphthalene C_8H), 5.54 (m,1, naphthalene C_5H), 5.78 (dd,1, J=6, 10 Hz, naphthalene C_3H), 6.03 (d,1,J=10 Hz, naphthalene C_4H).

Employing the procedure substantially as described in Example 1, Step B, but substituting for the pivaloyl chloride used therein, an equimolecular amount of the acid chloride of structure R—COCl described in Table II, there are prepared the esters of structure VI_a (R'=CH3) also described in Table II.

TABLE II

R—C(=O)—O	NMR($CDCl_3$,δ)
	7.10(t,2,J=8Hz,p-FPh—) 8.03(dd,2,J=5,8Hz,p-FPh—)
CH_3CO_2—	2.02(s,3,CH_3CO_2—)
	1.19(d,J=7Hz,α-CH_3 ester) 1.21(d,J=7Hz,α-CH_3 ester) Total 3H
$(CH_3)_2CHCH_2CO_2$—	0.83(d,6J=6Hz,$(CH_3)_2CH$—)
$(CH_3)_2CHCO_2$—	1.13(d,6,J=6Hz($CH_3)_2CH$)
$CH_3(CH_2)_3CO_2$—	0.95(t,3,J=7Hz,CH_3—$(CH_2)_3$—
	1.60-2.08(m,15,Adamantyl)
$CH_3(CH_2)_6CO_2$—	
$C_6H_{11}CO_2$—	
CH_2=CH—CO_2—	
$CF_3(CH_2)_2CO_2$—	
$C_6H_5CO_2$—	
4-$ClC_6H_4CO_2$—	
2,4-$F_2C_6H_3CO_2$—	
$C_6H_5(CH_2)_3CO_2$—	
4-$FC_6H_4CH_2CO_2$—	
2,4-$F_2C_6H_3CH_2CO_2$—	
4-$ClC_6H_4CH_2CO_2$—	
4-$FC_6H_4(CH_2)_3CO_2$—	
$CH_3CH(CF_3)$—CH_2CO_2—	
	
	
$CH_3(CH_2)_8CO_2$—	
	

Step C: Preparation of 6(R)-[2-(8'(S)-2",2"-dimethyl-propanoyloxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8'a(R)-hexahydronaphthyl-1'(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, I_a (R'=CH_3)

To a solution of 10.0 g (31.7 mmol) of $Bu_4N^+F^-.3H_2O$ and 2.4 ml (2.5 g, 42.3 mmol) of acetic acid in 50 ml of tetrahydrofuran was added 7.81 g (13.8 mmol) of the silyl ether VI_a (R'=CH_3) from Step B in 50 ml tetrahydrofuran. This mixture was stirred at 20° under a nitrogen atmosphere for 18 hours. The reaction mixture was diluted with 700 ml of ether and washed successively with 2% aqueous hydrochloric acid, water and saturated aqueous $NaHCO_3$. The organic solution was dried ($MgSO_4$) and filtered. Evaporation of the solvent left 6.45 g of an off-white solid. This material was crystallized from 100 ml of butyl chloride and the isolated crystals were dried at 35°/0.01 mm for four hours to give 4.0 g (72%) of the title compound as nearly white needles: mp 167.5°-170.5° (vac); NMR ($CDCl_3$) δ 0.88 (d,3,J=7 Hz, CH_3), 1.08 (d,3,J=7 Hz, CH_3), 1.19 (s,9,$(CH_3)_3C$), 2.67 (d,2,J=4 Hz, pyran C_3H's), 4.39 (m,1,pyran C_4H), 4.65 (m,1,pyran C_6H), 5.36 (m,1, naphthalene C_8H) 5.55 (m,1,naphthalene C_5H), 5.80 (dd,1,J=6, 10 Hz, naphthalene C_3H), 6.04 (d,1,J=10 Hz, naphthalene C_4H); HPLC (4.6 mm.×25 cm Partisil 10 PAC, 10% isopropanol/hexane, 4 ml/min) retention time 4.4 min.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.40; H, 8.93.

Employing the procedure of Example 1, Step C, but substituting for the 2,2-dimethylpropanoyloxy-silyl ether Compound VI_a (R'=CH_3) used therein, an equimolecular amount of the other esters of structure VI_a (R'=CH_3) described in Table II, there are prepared the esters of structure I_a (R'=CH_3), described in Table III.

TABLE III

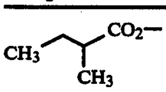
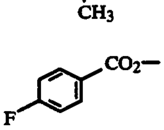
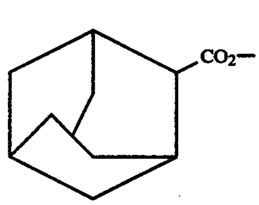
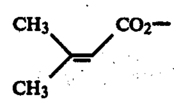
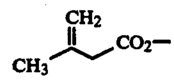
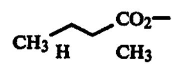
RCO_2—	Formula	MP(°C.)
	$C_{24}H_{36}O_5$	139-148
	$C_{26}H_{31}FO_5$	119.5-120.5 (vac)
$(CH_3)_2CHCH_2CO_2$—	$C_{24}H_{36}O_5$	126-128
$(CH_3)_2CHCO_2$—	$C_{23}H_{34}O_5$	144-147
$CH_3(CH_2)_3CO_2$—	$C_{24}H_{36}O_5$	
CH_3CO_2—	$C_{21}H_{30}O_5.0.1C_4H_9$	153-156 (vac)
	$C_{30}H_{42}D_5.0.05C_6H_{12}$	155-158
$CH_3(CH_2)_6CO_2$—		
$C_6H_{11}CO_2$—		
CH_2=CH—CO_2—		
$CF_3(CH_2)_2CO_2$—		
$C_6H_5CO_2$—		
4-$ClC_6H_4CO_2$—		
2,4-$F_2C_6H_3CO_2$—		
$C_6H_5(CH_2)_3CO_2$—		

TABLE III-continued

RCO_2—	Formula	MP(°C.)
4-$FC_6H_4CH_2CO_2$—		
2,4-$F_2C_6H_3CH_2CO_2$—		
4-$ClC_6H_4CH_2CO_2$—		
4-$FC_6H_4(CH_2)_3CO_2$—		
$CH_3CH(CF_3)$—CH_2CO_2—		
		
		
$CH_3(CH_2)_8CO_2$—		
		

EXAMPLE 2

6(R)-[2-(8'(S)-phenylacetoxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8'a(R)-hexahydronaphthyl-1'(S))ethyl]-4-(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

Step A: Preparation of 6(R)-[2-(8'(S)-phenylacetoxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8'a(R)-hexahydronaphthyl-1'(S))ethyl]-4(R)-dimethyl-tert-butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one, VI_a (R'=CH_3)

A solution of 434 mg (1.0 mmol) of the alcohol V_a (R'=CH_3) from Example 1, Step A, 204 mg (1.5 mmol) of phenylacetic acid, and 309 mg (1.5 mmol) of N,N'-dicyclohexylcarbodiimide in 10 ml of dichloromethane was treated with 22 mg (0.15 mmol) of 4-pyrrolidinopyridine and stirred at 20° under a nitrogen atmosphere. After 3 days the solvent was removed in vacuo and the residue was suspended in 25 ml of ether and filtered. Evaporation of the filtrate gave a viscous oil which was chromatographed on a 3×15 cm. column of silica gel (230-400 mesh). Elution (under air pressure) with ether-hexane (1:1, v:v) gave 460 mg (83%) of the title compound as a viscous oil: NMR ($CDCl_3$) δ 0.10 (s,6,$(CH_3)_2Si$), 0.90 (s, 9,$(CH_3)_3CSi$), 3.58 (s,2,$PhCH_2$—) 5.34 (m,1,naphthalene C_8H), 7.30 (s,5,Ph).

Employing the procedure of Example 2, Step A, but substituting for the phenylacetic acid used therein, an equimolecular amount of the organic acids of structure R—COOH described in Table IV there are produced the esters of structure VI_a (R'=CH_3) also described in Table IV.

TABLE IV

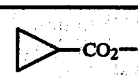
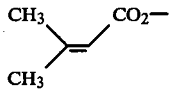
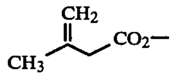
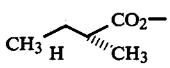
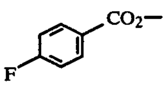
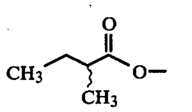
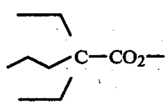
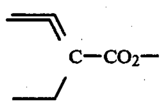
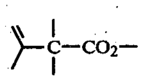
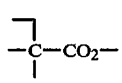
R—C(=O)—O—	NMR($CDCl_3$,δ)
	0.78-1.02 (m,4,cyclopropane)
$CH_3CH(CF_3)$—CH_2CO_2—	1.04(d,3,J = 7Hz,CH_3CHCF_3)

TABLE IV-continued

R—C(=O)—O—	NMR($CDCl_3$,δ)
	1.88(s,3,CH_3C=C) 2.17(d,3,J = 2Hz,CH_3C=C) 5.68 (brs,1,C=CH—)
	1.80 (s,3,CH_3C=C) 4.86,4.92(s,2,CH_2=C)
$CH_3(CH_2)_8CO_2$—	0.87(m,3,$CH_3(CH_2)_8CO_2$—) 1.25(m,14,$CH_3(CH_2)_7CH_2CO_2$—)
	
	
CH_3CO_2—	
	
$(CH_3)_2CHCH_2CO_2$—	
$(CH_3)_2CHCO_2$—	
$CH_3(CH_2)_3CO_2$—	
	
	
	
	
$CH_3(CH_2)_6CO_2$—	
$C_6H_{11}CO_2$—	
CH_2=CH—CO_2—	
$CF_3(CH_2)_2CO_2$—	
$C_6H_5CO_2$—	
4-$ClC_6H_4CO_2$—	
2,4-$F_2C_6H_3CO_2$—	
$C_6H_5(CH_2)_3CO_2$—	
4-$FC_6H_4CH_2CO_2$—	
2,4-$F_2C_6H_3CH_2CO_2$—	
4-$ClC_6H_4CH_2CO_2$—	
4-$FC_6H_4(CH_2)_3CO_2$—	

Step B: Preparation of 6(R)-[2-(8'(S)-phenylacetoxy-2'(S),6'(R)-dimethyl-1',2',6',7',8',8'a(R)-hexahydronaphthyl-1'(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, I_a (R'=CH_3)

Employing the procedure substantially as described in Example 1, Step C, but substituting for the propanoyloxy compound used therein an equimolar amount of the phenylacetoxy compound from Example 2, Step A, there is produced the title compound, m.p. 109°-112° C.

Employing the other esters, VI_a (R'=CH_3) described in Example 2, Step A, (Table IV) and following the procedure of Example 2, Step B, there are produced the esters of structure I_a (R'=CH_3) described in Table V.

TABLE V

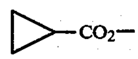
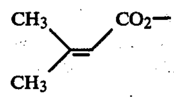
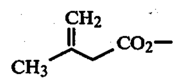
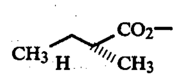
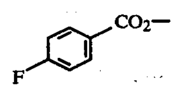
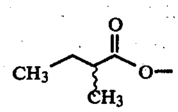
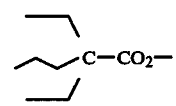
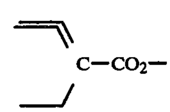
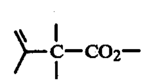
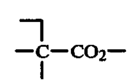
RCO_2	Formula	m.p. (°C.)
	$C_{23}H_{32}O_5$	116-119
$CH_3CH(CF_3)CH_2CO_2$—	$C_{24}H_{33}F_3O_5$	110-113
	$C_{24}H_{34}O_5$	113-118
	$C_{24}H_{34}O_5$	116-119
$CH_3(CH_2)_8CO_2$—	$C_{29}H_{46}O_5$	(wax)
	$C_{24}H_{36}O_5$	126-129
		
CH_3CO_2—		
		
$(CH_3)_2CHCH_2CO_2$—		
$(CH_3)_2CHCO_2$—		
$CH_3(CH_2)_3CO_2$—		
		
		
		
		
$CH_3(CH_2)_6CO_2$—		
$C_6H_{11}CO_2$—		
CH_2=CH—CO_2—		
$CF_3(CH_2)_2CO_2$—		
$C_6H_5CO_2$—		
4-$ClC_6H_4CO_2$—		
2,4-$F_2C_6H_3CO_2$—		
$C_6H_5(CH_2)_3CO_2$—		

TABLE V-continued

RCO_2	Formula	m.p. (°C.)
$4\text{-}FC_6H_4CH_2CO_2$—		
$2,4\text{-}F_2C_6H_3CH_2CO_2$—		
$4\text{-}ClC_6H_4CH_2CO_2$—		
$4\text{-}FC_6H_4(CH_2)_3CO_2$—		

EXAMPLE 3

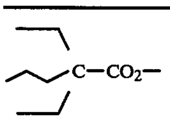
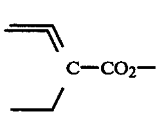
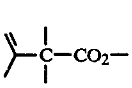
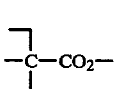
6(R)-[2-(8′(S)-2″-ethyl-2″-methylbutyryloxy-2′(S)-6′(R)-dimethyl-1′,2′,6′,7′,8′,8′a(R)-hexahydronaphthyl-1′(S))-ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

Step A: Preparation of 6(R)-[2-(8′(S)-2″-ethyl-2″-methylbutyryloxy-2′(S)-6′(R)-dimethyl-1′,2′,6′,7′,8′,8′a(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-(dimethyl-tert-butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one VI_a (R′=CH_3)

3.0 g of 2-ethyl-2-methylbutyryl chloride (20 mmol) was added to a magnetically stirred solution of 2.17 g (5 mmol) of alcohol V_a (R′=CH_3) and 74 mg of 4-pyrrolidino pyridine in 20 ml of pyridine. This reaction mixture was stirred at 100° C. under an atmosphere of N_2 for nine hours. The reaction mixture was diluted with 500 ml ether and washed with 1 N HCl until the wash was acidic and then with brine (3×50 ml). After drying over $MgSO_4$, the solution was filtered and evaporated to give 4.2 g of a brown oil. This oil was chromatographed on a 6×15 cm column of silica gel (230–400 mesh). Elution (under air pressure) with ether-hexane (1:1, v:v) gave 2.6 g (95%) of the title compound as a viscous yellow oil: NMR ($CDCl_3$) δ 0.08(s,6,$(CH_3)_2Si$), 0.9(s,9,$(CH_3)_3$ CSi), 2.57(d,2,J=4 Hz, pyran C_3H's), 4.30(m,1,pyran C_4H), 4.63(m,1,pyran C_6H), 5.42(m,1,naphththalene C_8H), 5.53(m,1,naphthalene C_5H), 5.78(dd,1,J=6,Hz,10 Hz, naphthalene C_3H), 6.03(d,1,J=10 Hz, naphthalene C_4H).

Employing the procedure substantially as described in Example 3, Step A, but substituting for the 2-ethyl-2-methylbutyryl chloride used therein, an equimolecular amount of the acid chlorides of structure R-COCl, described in Table VI, there are produced the esters of structure VI_a (R′=CH_3) also described in Table VI.

TABLE VI

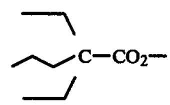
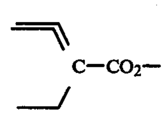
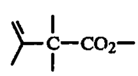
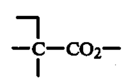
$R-\overset{\overset{O}{\parallel}}{C}O$	NMR($CDCl_3$,δ)
	0.87(m,9,$CH_3CH_2CH_2(CH_3CH_2)_2CCO_2$)
	0.78(t,9,J = Hz,$(CH_3CH_2)_3CCO_2$) 1.48(q,6,J = 7Hz,$(CH_3CH_2)_3CCO_2$)
	1.28(s,6,$(CH_3)_2CCO_2$) 2.20(s,3,CH_3—C=CH_2) 3.86(m,2,CH_2=C)
	1.12(s,6,$(CH_3)_2CCO_2$) 0.83(t,3,$(CH_3CH_2CCO_2$)

Step B: Preparation of 6(R)-[2-(8′(S)-2″-ethyl-2″-methylbutyryloxy-2′(S)-6′(R)-dimethyl-1′,2′,6′,7′,8′,8′a-(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

Employing the procedure substantially as described in Example 1, Step C, or Example 2, Step B, but employing as starting material the silyl ether compound from Example 3, Step A, there is produced the title compound, m.p. 111°–113° C. ($C_{26}H_{40}O_5$).

Similarly prepared are the esters of structure I_a described in Table VII, employing as starting materials the other esters VI_a (R′=CH_3) described in Table VI.

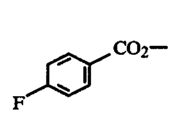
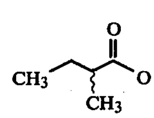
TABLE VII

ROC_2—	Formula	m.p.(°C.)
	$C_{28}H_{44}O_5$	81–83
	$C_{27}H_{42}O_5$	129–132
	$C_{26}H_{38}O_5$	75–78
	$C_{25}H_{38}O_5$	135–138

Employing the procedures of Example 1, Step A, followed by Example 1, Steps B and C, or Example 2 or 3, Steps A and B, but substituting for the diol of structure IV_a (R′=CH_3) in Example 1, Step A, the corresponding diols of structure IV_a (R′=H) or $IV_{b,c,d}$, or $_e$ (R′=H, or CH_3), there are produced in sequence the silyl ethers of structures V_a (R′=H) or $V_{b,c,d}$, and $_e$ (R′=H, or CH_3), the esters of structure VI_a (R′=H) or $VI_{b,c,d}$, and $_e$ (R′=H, or CH_3), and the novel esters of structures I_a (R′=H) or $I_{b,c,d}$ and $_e$ (R′=H or CH_3) in accordance with Flow Sheet A, wherein

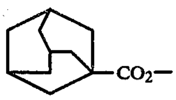
$$R-\overset{\overset{O}{\parallel}}{C}O$$

of the 8′-alkanoyl group is:

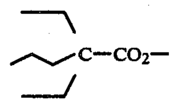
	$4\text{-}ClC_6H_4CO_2$—
CH_3CO_2—	$2,4\text{-}F_2C_6H_3CO_2$—
	$C_6H_5(CH_2)_3CO_2$—
$(CH_3)_2CHCH_2CO_2$—	$4\text{-}FC_6H_4CH_2CO_2$—
$(CH_3)_2CHCO_2$—	$2,4\text{-}F_2C_6H_3CH_2CO_2$—
$CH_3(CH_2)_3CO_2$—	$4\text{-}ClC_6H_4CH_2CO_2$—

-continued

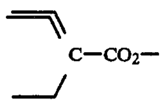
$4\text{-}FC_6H_4(CH_2)_3CO_2$—



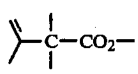
$CH_3(CH_2)_6CO_2$—



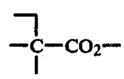
$C_6H_{11}CO_2$—



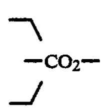
$CH_2{=}CH{-}CO_2$—



$CF_3(CH_2)_2CO_2$—

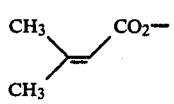


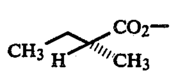
$C_6H_5CO_2$—

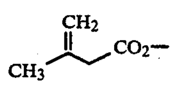


$CH_3CH(CF_3){-}CH_2CO_2$—

$CH_3(CH_2)_8CO_2$—







EXAMPLE 4

Preparation of 6(R)-{2-[8(S)(2″-ethyl-2″-methylbutyryloxy)-2′(S),6′(S)-dimethyl-1′,2′,3′,4′,4′a(S),5′,6′,7′,8′,8′a(S)-decahydronaphthyl-1′(S)]ethyl}-4(R)hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, I_e (R′=CH_3)

Step A. Preparation of 6(R)-[2-(8′(S)hydroxy-2′(S),6′(S)dimethyl-1′,2′,3′,4′,4′a(S),5′,6′,7′,8′,8′a(S)-decahydronaphthyl-1′(S))ethyl]-4(R)hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one IV_e (R′=CH_3)

A solution of 2.0 g (6.2 mmol) of the alcohol IV_a (R′=CH_3) in 100 ml of ethyl acetate was hydrogenated in the presence of platinum oxide (1 g) at 40 lbs. pressure until an uptake of two mole equivalents of hydrogen was observed. The catalyst was removed by filtration and the filtrate was evaporated to dryness to provide a white solid (1.9 g) which was chromatographed on a 6×20 cm column of silica gel (230–400 mesh). Elution (under air pressure) with acetone-methylene chloride (3:7, v:v) gave 1.0 g (50%) of the title compound as a colorless solid.

An analytical sample was prepared by recrystallization of a portion of the material from chloroform to give a white cottony solid: m.p. 166°–8°.

Step B: Preparation of 6(R)-[2-(8′(S)-hydroxy-2′(S),6′(S)-dimethyl-1′,2′,3′,4′,4′a(S),5′,6′,7′,8′,8′a(S)-decahydronaphthyl-1′(S)-ethyl]-4(R)-(dimethyl-tert-butylsilyloxy)3,4,5,6-tetrahydro-2H-pyran-2-one, V_e (R′=CH_3)

A solution of the alcohol IV_e (R′=CH_3) (1.0 g, 3.1 mmol), imidazole (1.05 g, 15.4 mmol) and tert-butyldimethylchlorosilane (1.16 g, 7.7 mmol) in 20 ml of N,N-dimethyl formamide was stirred at 20° under a nitrogen atmosphere for 18 hours. The reaction solution was diluted with 200 ml of ether and washed successively with water, 2% aqueous hydrochloric acid and brine. The ether solution was dried over $MgSO_4$ and evaporated to provide a white solid (1.8 g) which was chromatographed on a 6×20 cm column of silica (230–400 mesh). Elution under air pressure with acetone:methylene chloride (1:19, v:v) gave 1.0 g (74%) of the title compound as a white solid: m.p. 136°–138° C.

Step C: Preparation of 6(R)-{2[8′(S)(2″-ethyl-2″-methylbutyryloxy)-2′(S),6′(S)-dimethyl-1′,2′,3′,4′,4′a(S),5′,6′,7′,8′,8′a(S)-decahydronaphthyl-1′(S)]ethyl}-4(R)(dimethyl-tert-butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one VI_e (R′=CH_3)

By substituting an equimolar amount of alcohol V_e (R′=CH_3) for alcohol V_a (R′=CH_3) in Step A of Example 3 and following the procedure for Step A there was obtained a corresponding amount of the title compound, VI_e (R′=CH_3) as a yellow oil. NMR($CDCl_3$) δ 0.08(S,6,$(CH_3)_2$Si), 0.90(S,9,$(CH_3)_3$)CSi), 1.13(S,6,$(CH_3)_2CO_2$), 2.63(m,2,pyran C_3H's), 4.33(m,1,pyran C_4H), 4.60(m,1,pyran C_6H), 5.23(m,1,naphthalene C_8H).

Step D: Preparation of 6(R)-{2-[8′(S)(2″-ethyl-2″-methylbutyryloxy)-2′(S),6(S)-dimethyl-1′,2′,3′,4′,4′a(S),5′,6′,7′,8′,8′a(S)-decahydronaphthyl-1′(S)]ethyl}-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, I_e (R′=CH_3)

By substituting an equimolar amount of the silyl ether VI_e (R′=CH_3) from Example 4, Step C for the silyl ether in Step C of Example 1 and following the procedure for Step C of Example 1 there was obtained a corresponding amount of the title compound as a solid.

An analytical sample was prepared by recrystallization of the material from hexane to obtain white needles: m.p. 146°–147° C.

Employing the procedure substantially as described in Example 4 Steps A through D, but substituting for the diol of structure IV_a (R′=CH_3) in Step A, an equimolecular amount of the diol of structure IV_a (R′=H) there are produced in sequence the compounds: IV_e (R′=H) in Step A; V_e (R′=H) in Step B; VI_e (R′=H) in Step C; and I_e (R′=H) in Step D.

EXAMPLE 5

6(R)-{2-[8'(S)-(2"-ethyl-2"-methylbutyryloxy)-2'(S),6'(R)-dimethyl-1',2',3',4',6',7',8'a(S)-octahydronaphthyl-1'(S)]ethyl}-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, I_b (R'=CH_3)

Step A: Preparation of 6(R)-[2-(8'(S)-hydroxy-2'(S),6'(R)-dimethyl-1'2',3',4',6',7',8'a(S)-octahydronaphthyl-1'(S)-ethyl]-4(R)hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, IV_b (R'=CH_3)

Employing the procedure substantially as described for the preparation of the starting material IV_a (R'=CH_3) by hydrolysis of MK-803 with refluxing aqueous LiOH.H_2O for 56 hours but substituting for the MK-803 an equimolecular amount of compound III_b (R'=CH_3) there is produced, in comparable yield, the title compound IV_b (R'=CH_3), m.p. 136°-139° C.

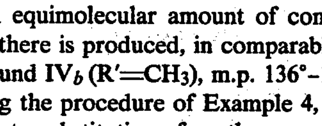
Following the procedure of Example 4, Steps B, C, and D, but substituting for the compound IV_e (R'=CH_3) used in Step B thereof, an equimolecular amount of compound IV_b (R'=CH_3) from Step A of this example, there is produced in comparable yields to those experienced in Example 4, the following compounds:

Step B:

6(R)-[2-(8'(S)-hydroxy-2'(S),6'(R)-dimethyl-1',2',3',4',6',7',8'a(S)-octahydronaphthyl-1'(S)-ethyl]-4(R)-(dimethyl-tert-butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one, V_b (R'=CH_3), m.p. 140°-142° C.

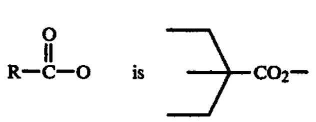
Step C:

6(R)-{2-[(8'(S)-(2"-ethyl-2"-methylbutyryloxy)-2'(S),6'(R)-dimethyl-1',2',3',4',6',7',8'a(S)-octahydronaphthyl-1'(S)]ethyl}-4(R)-(dimethyl-tert-butylsilyoxy)-3,4,5,6-tetrahydro-2H-pyran-2-one, $VI_{(b)}$ (R'=CH_3) wherein

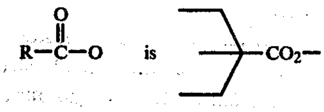


Step D:

6(R)-{2-[8'(S)(2"-ethyl-2"-methylbutyryloxy)-2'(S),6'(R)-dimethyl-1',2',3',4',6',7',8'a(S)-octahydronaphthyl-1'(S)]ethyl}-4(R)hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, I_b (R'=CH_3) m.p. 129°-131° C. wherein



Following the procedure substantially as described in Example 5, but using III_b (R'=H) or III_c, III_d, or III_e (R'=H or CH_3) as starting material in place of III_b (R'=CH_3) there are produced in turn compounds IV_b (R'=H) or $IV_{c,d,e}$ (R'=H or CH_3), V_b (R'=H) or $V_{c,d,e}$ (R'=H or CH_3), VI_b (R'=H) or $VI_{c,d,e}$ (R'=H or CH_3), and I_b (R'=H) or $I_{c,d,e}$ (R'=H or CH_3) wherein

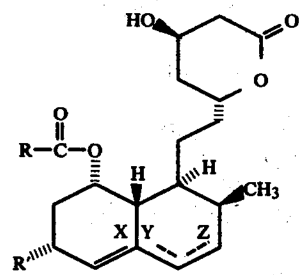


EXAMPLE 6

Typical formulations for filling a size 0 hard gelatin capsule comprise 3.125, 6.25, 12.5, 25 or 50 mg of one of the novel compounds of this invention such as the products of Example 3, Step B, Example 1, Step C, or Example 2, Step B and sufficient finely divided lactose to provide a total capsule content of about 580-590 mg.

What is claimed is:

1. A compound of the formula:



wherein R' is H or CH_3;

R is

(1) 1,1-dimethylpropyl,

(2) C_{3-10}cycloalkyl,

(3) C_{2-10}alkenyl,

(4) $C_{1-10}CF_3$-substituted alkyl,

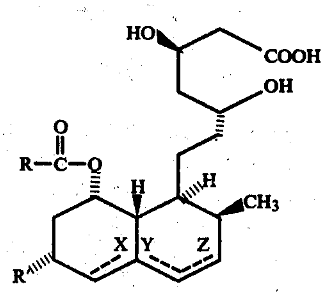
(5) phenyl,

(6) halophenyl,

(7) phenyl-C_{1-3}alkyl,

(8) substituted phenyl-C_{1-3}alkyl in which the substituent is halo, C_{1-3}alkyl or C_{1-3}alkoxy;

the dotted lines at X, Y and Z represent possible double bonds, said double bonds, when any are present, being either X and Z in combination or X, Y or Z alone; or the corresponding dihydroxy acid of the formula:



or a pharmaceutically acceptable salt of said acid, a C_{1-4}alkyl ester of said acid or a phenyl-, dimethylamino-, or acetylamino-substituted-C_{1-4}alkyl ester of said acid.

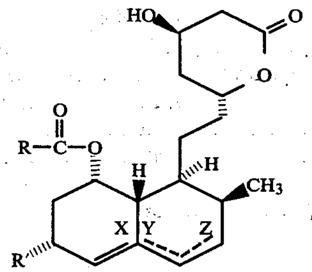
2. The compound of claim 1 wherein R' is CH_3.

3. The compound of claim 1 wherein R is 1,1-dimethylpropyl.

4. The compound of claim 2 wherein R is 1,1-dimethylpropyl.

5. The compound of claim 1 wherein none of X, Y or Z is a double bond.

6. A pharmaceutical antihypercholesterolemic composition comprising a pharmaceutical carrier and an antihypercholesterolemic effective amount of a compound of structural formula:



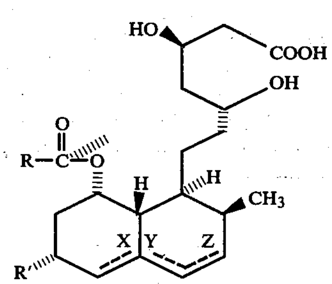
in which R' is H or CH_3;

R is

(1) 1,1-dimethylpropyl,
(2) C_{3-10}cycloalkyl,
(3) C_{2-10}alkenyl,
(4) $C_{1-10}CF_3$-substituted alkyl,
(5) phenyl,
(6) halophenyl,
(7) phenyl-C_{1-3}alkyl,
(8) substituted phenyl-C_{1-3}alkyl in which the substituent is halo, C_{1-3}alkyl or C_{1-3}alkoxy;

the dotted lines at X, Y and Z represent possible double bonds, said double bonds, when any are present, being either X and Z in combination or X, Y or Z alone; or

the corresponding dihydroxy acid of the formula:



or a pharmaceutically acceptable salt of said acid, a C_{1-4}alkyl ester of said acid or a phenyl-, dimethylamino-, or acetylamino-substituted-C_{1-4}alkyl ester of said acid.

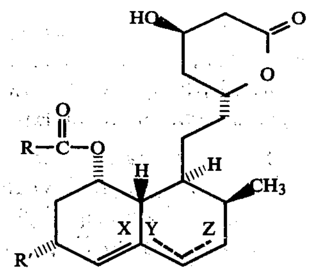
7. The composition of claim 6 wherein R' is CH_3.

8. The composition of claim 6 wherein R is 1,1-dimethylpropyl.

9. The composition of claim 7 wherein R is 1,1-dimethylpropyl.

10. The composition of claim 6 wherein none of X, Y or Z is a double bond.

11. A method of treating hypercholesterolemia in a patient in need of such treatment which comprises administration of an antihypercholesterolemic effective amount of a compound of structural formula:



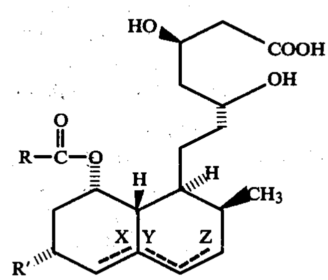
in which R' is H or CH_3;

R is

(1) 1,1-dimethylpropyl,
(2) C_{3-10}cycloalkyl,
(3) C_{2-10}alkenyl,
(4) $C_{1-10}CF_3$-substituted alkyl,
(5) phenyl,
(6) halophenyl,
(7) phenyl-C_{1-3}alkyl,
(8) substituted phenyl-C_{1-3}alkyl in which the substituent is halo, C_{1-3}alkyl or C_{1-3}alkoxy;

the dotted lines at X, Y and Z represent possible double bonds, said double bonds, when any are present, being either X and Z in combination or X, Y or Z alone; or

the corresponding dihydroxy acid of the formula:



or a pharmaceutically acceptable salt of said acid, a C_{1-4}alkyl ester of said acid or a phenyl-, dimethylamino-, or acetylamino-substituted-C_{1-4}alkyl ester of said acid.

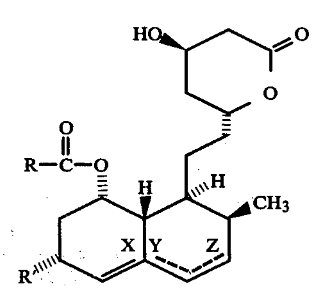
12. The method of claim 11 wherein R' is CH_3.

13. The method of claim 11 wherein R is 1,1-dimethylpropyl.

14. The method of claim 12 wherein R is 1,1-dimethylpropyl.

15. The method of claim 11 wherein none of X, Y or Z is a double bond.

16. A compound of the formula:

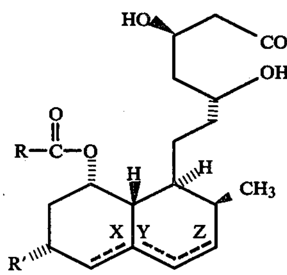


wherein R' is H or CH_3;

R is

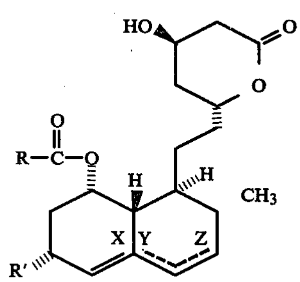
(1) C_{3-10}cycloalkyl,
(2) C_{2-10}alkenyl,
(3) $C_{1-10}CF_3$-substituted alkyl,
(4) phenyl,
(5) halophenyl,
(6) phenyl-C_{1-3}alkyl
(7) substituted phenyl-C_{1-3}alkyl in which the substituent is halo, C_{1-3}alkyl or C_{1-3}alkoxy;

the dotted lines at X, Y and Z represent possible double bonds, said double bonds, when any are present, being either X and Z in combination or X, Y or Z alone or the corresponding dihydroxy acid of the formula:



or a pharmaceutically acceptable salt of said acid, a C_{1-4}alkyl ester of said acid or a phenyl-, dimethylamino-, or acetylamino-substituted-C_{1-4}alkyl ester of said acid.

17. A pharmaceutical antihypercholesterolemic composition comprising a pharmaceutical carrier and an antihypercholesterolemic effective amount of a compound of structural formula:



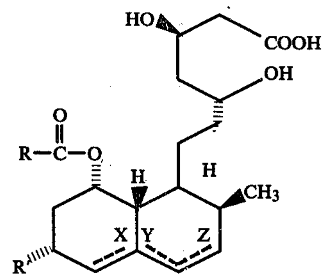
in which R' is H or CH_3;

R is

(1) C_{3-10}cycloalkyl,
(2) C_{2-10}alkenyl,
(3) $C_{1-10}CF_3$-substituted alkyl,
(4) phenyl,
(5) halophenyl,
(6) phenyl-C_{1-3}alkyl,
(7) substituted phenyl-C_{1-3}alkyl in which the substituent is halo, C_{1-3}alkyl or C_{1-3}alkoxy;

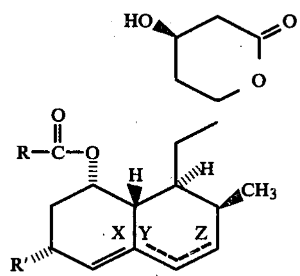
the dotted lines at X, Y and Z represent possible double bonds, said double bonds, when any are present, being either X and Z in combination or X, Y or Z alone; or

the corresponding dihydroxy acid of the formula:



or a pharmaceutically acceptable salt of said acid, a C_{1-4}alkyl ester of said acid or a phenyl-, dimethylamino-, or acetylamino-substituted-C_{1-4}alkyl ester of said acid.

18. A method of treating hypercholesterolemia in a patient in need of such treatment which comprises administration of an antihypercholesterolemic effective amount of a compound of structural formula:



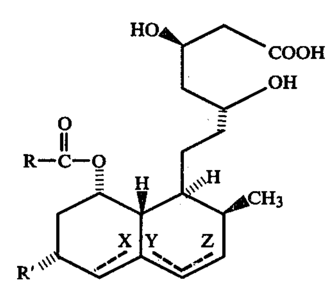
in which R' is H or CH_3;

R is

(1) C_{3-10}cycloalkyl,
(2) C_{2-10}alkenyl,
(3) $C_{1-10}CF_3$-substituted alkyl,
(4) phenyl,
(5) halophenyl,
(6) phenyl-C_{1-3}alkyl,
(7) substituted phenyl-C_{1-3}alkyl in which the substituent is halo, C_{1-3}alkyl or C_{1-3}alkoxy;

the dotted lines at X, Y and Z represent possible double bonds, said double bonds, when any are present, being either X and Z in combination or X, Y or Z alone; or

the corresponding dihydroxy acid of the formula:



or a pharmaceutically acceptable salt of said acid, a C_{1-4}alkyl ester of said acid or a phenyl-, dimethylamino-, or acetylamino-substituted C_{1-4}alkyl ester of said acid.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

PATENT NO.:	4,444,784
DATED:	April 24, 1984
INVENTORS:	William F. Hoffman et al.
PATENT OWNER:	Merck & Co., Inc.

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

1,704 DAYS

with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 20th day of May 1993.

Michael K. Kirk
Acting Commissioner of Patents and Trademarks