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Willard et al.

[11] **4,375,475**

[45] **Mar. 1, 1983**

[54] **SUBSTITUTED PYRANONE INHIBITORS OF CHOLESTEROL SYNTHESIS**

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[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **233,521**

[22] Filed: **Feb. 11, 1981**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 140,323, Apr. 14, 1980, abandoned, which is a continuation-in-part of Ser. No. 67,574, Aug. 1, 1979, abandoned.

[51] **Int. Cl.**[3] **A61K 31/365**; C07D 309/30

[52] **U.S. Cl.** **424/279**; 542/441; 549/292

[58] **Field of Search** 542/441; 260/343.5; 424/279

[56] **References Cited**

U.S. PATENT DOCUMENTS

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OTHER PUBLICATIONS

Brown et al., J. Chem. Soc., Perkin I (1976), 1165–1169.

Hulcher, Arch. Biochem & Biophys, 146, 422–427 (1971).

Singer et al., Proc. Soc. Exper. Biol. Med. 102, 370–373 (1959).

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Primary Examiner—Arthur P. Demers

Attorney, Agent, or Firm—William H. Nicholson; Mario A. Monaco

[57] **ABSTRACT**

6-Phenyl-, phenylalkyl- and phenylethenyl-4-hydroxytetrahydropyran-2-ones in the 4(R)-trans stereoisomeric forms are potent inhibitors of cholesterol synthesis by virtue of their ability to inhibit the enzyme, 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

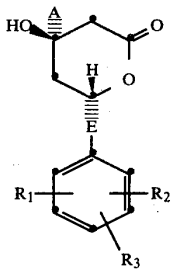
18 Claims, No Drawings

SUBSTITUTED PYRANONE INHIBITORS OF CHOLESTEROL SYNTHESIS

SUMMARY OF THE INVENTION

This is a continuation-in-part of copending application, Ser. No. 140,323 filed Apr. 14, 1980, (abandoned) which in turn is a continuation-in-part of copending application, Ser. No. 067,574, filed Aug. 1, 1979 (now abandoned).

This invention relates to new hypocholesterolemic and hypolipemic compounds having the structure (I)



I

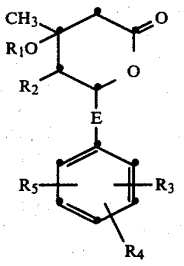
and the corresponding dihydroxy acids resulting from the hydrolytic opening of the lactone ring, and the pharmaceutically acceptable salts of said acids, and the lower alkyl and phenyl, dimethylamino or acetylamino-substituted lower alkyl esters of said dihydroxy acids; all of the compounds being the enantiomers having a 4(R) configuration in the tetrahydropyran moiety of the trans racemate shown in formula 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, 270 (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. Pat. Nos. 4,049,495, 4,137,322 and 3,983,140) the production of a fermentation product which was quite active in the inhibition of cholesterol biosynthesis. This natural product, now called compactin, was reported by Brown et al., (*J. Chem. Soc. Perkin I,* 1165 (1976)) to have a complex mevalonolactone structure.

A recent Belgian Pat. No. 867,421 disclosed a group of synthetic compounds of the generic formula II



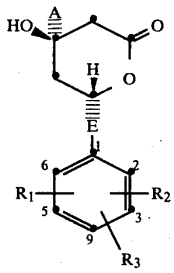
II

in which E represents a direct bond, a C_{1-3} alkylene bridge or a vinylene bridge and the various R's represent a variety of substituents.

The activity reported in the Belgian patent is less than 1% that of compactin.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to new hypocholesterolemic and hypolipemic compounds having the structure (I)



I

wherein

A is H or methyl;

E is a direct bond, $—CH_2—$, $—CH_2—CH_2—$, $—CH_2—CH_2—CH_2—$ or $—CH=CH—$;

R_1, R_2 and R_3 are each selected from

- H,
- halogen,
- C_{1-4} alkyl,
- C_{1-4} haloalkyl,
- phenyl,
- phenyl substituted by halogen,
- C_{1-4} alkoxy
- C_{2-8} alkanoyloxy
- C_{1-4} alkyl, or
- C_{1-4} haloalkyl, and

OR_4 in which R_4 is

- H,
- C_{2-8} alkanoyl,
- benzoyl,
- phenyl,
- halophenyl,
- phenyl C_{1-3} alkyl,
- C_{1-9} alkyl,
- cinnamyl,
- C_{1-4} haloalkyl,
- allyl,
- cycloalkyl-C_{1-3}-alkyl,
- adamantyl-C_{1-3}-alkyl, or
- substituted phenyl C_{1-3}-alkyl
  - in each of which the substituents are selected from
    - halogen,
    - C_{1-4} alkoxy
    - C_{1-4} alkyl, or
    - C_{1-4} haloalkyl;

and the corresponding dihydroxy acids resulting from the hydrolytic opening of the lactone ring, and the pharmaceutically acceptable salts of said acids, and the C_{1-3} alkyl and phenyl, dimethylamino or acetylamino-substituted-C_{1-3}-alkyl esters of the dihydroxy acids; all of the compounds being the enantiomers having a 4 R configuration in the tetrahydropyran moiety of the trans racemate shown in formula I.

A preferred embodiment of this invention relates to those structures of general formula I wherein

A is H or methyl;

E is —CH=CH—, or —CH_2CH_2—;

R_1, R_2 and R_3 are each selected from

halogen,

C_{1-4} alkyl,

C_{1-4} haloalkyl,

substituted phenyl in which the substituent is

halo,

C_{1-4} alkyl,

C_{1-4} alkoxy, and

R_4O in which R_4 is

phenyl,

halophenyl,

or

substituted phenyl-C_{1-3}-alkyl

wherein the substituents are selected from

halogen and

C_{1-4} haloalkyl;

and the corresponding dihydroxy acids resulting from the hydrolytic opening of the lactone ring and the pharmaceutically acceptable salts of the dihydroxy acids, and the C_{1-3} alkyl and phenyl, dimethylamino or acetylamino-substituted-C_{1-3} alkyl esters of the dihydroxy acids; all of the compounds being the enantiomer having a 4 R configuration in the tetrahydropyran moiety of the trans racemate shown in general formula I.

A more preferred embodiment of the present invention comprises those structures of general formula I wherein

A is H or methyl;

E is —CH_2CH_2— or —CH=CH—;

R_1 is situated in the 6-position and is a substituted phenyl wherein there are 1 or 2 substituents and they are independently selected from chloro, fluoro, methyl and methoxy; and

R_2 and R_3 are halo, especially chloro, or C_{1-3} alkyl, especially methyl, in the 2 and 4 positions;

and the corresponding dihydroxy acids resulting from the hydrolytic opening of the lactone ring, and the pharmaceutically acceptable salts of the dihydroxy acids, and the C_{1-3} alkyl and phenyl, dimethylamino or acetylamino-substituted-C_{1-3} alkyl esters of the dihydroxy acids; all of the compounds being the enantiomer having a 4 R configuration in the tetrahydropyran moiety of the trans racemate shown in general formula I.

The compounds in which A is hydrogen, are especially to be preferred. It is also especially preferred that E is —CH=CH—.

The designation 4 R with respect to these compounds indicates that the absolute configuration in space at the 4 -carbon of the pyranone ring is believed to be the Rectus (R) series. All the compounds synthesized in the (R) series have been found to be dextrorotatory.

It also has been found that the enantiomers of the trans compounds of Formula I having a 4 R configuration in the tetrahydropyran moiety, especially those in which A is hydrogen, E is —CH=CH— and R_1 and R_2 are Cl or —CH_3 in the 2 and 4 position and R_3 is substituted-phenyl in the 6 position, as described, are unexpectedly potent inhibitors of cholesterol biosynthesis, approaching and, in many instances, surpassing the order of magnitude of compactin.

While the compounds of Formula I in which A is methyl are 4-R enantiomers of the trans racemates of the compounds of the cited Belgian patent, the latter prior art shows no recognition of the stereochemistry of these compounds, let alone the fact that an unexpectedly large improvement in the activity would result from the separation of the cis and trans racemates and the latter's resolution, especially when the preferred 2,4,6-trisubstitution occurs in the phenyl ring. However, it has been found that the 4 R enantiomers of the trans racemates corresponding to formula I specifically inhibit with high potency the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which is known to be the enzyme involved in the rate limiting step in the process of cholesterol biosynthesis.

The inhibitory activity of these compounds for the biosynthesis of cholesterol has been measured by two methods. The experimental method A was the in vitro method of H. J. Knauss, et al., *J. Biol. Chem.*, 234, 2835 (1959) and the activity was expressed as the molar concentration IC_{50}(M) necessary for the inhibition of 50% of the enzymatic activity. The experimental method B was the method of A. A. Kandutsch, et al., *J. Biol. Chem.*, 248, 8403 (1973) for measuring the quantity of ^{14}C-cholesterol biosynthesis from acetic acid-^{14}C in mouse L cells. The activity is expressed for inhibition of 50% of the biosynthesis of cholesterol.

The results obtained in these two assays, as reported in the cited Belgian patent, show IC_{50} values of 10^{-4} to 10^{-6} in both tests. The smallest 50% effective dose cited is about 4×10^{-6}, whereas the value for compactin, in the same tests, is about 0.8×10^{-8}. We have found that the inhibitory potency is greatly increased by separation of isomers especially when this is combined with optimal selection of a 2,4,6-arrangement of R_1, R_2 and R_3 in the phenyl ring and especially when A is hydrogen and E is —CH=CH—. Thus the (+) trans enantiomer of 6-[2-(2,4-dichloro-6-(phenylmethoxy)phenyl)ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-pyran-2-one (Example 14) (a preferred compound of this invention) gives an IC_{50} of 6.8×10^{-8} in the test by method A. An even more potent and preferred compound of this invention, the (+) trans enantiomer of (E)-6-[2-(3,5-dichloro-4'-fluoro[1,1'-biphenyl]-2-yl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-pyran-2-one (Example 43) gives an IC_{50} of about 1.3×10^{-8}.

Other preferred compouds are: 6-[2-(4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-pyran-2-one ($IC_{50}=7\times10^{-9}$); 6-[2-(5-chloro-4'-fluoro-3,3'-dimethyl[1,1'-bisphenyl]-2-yl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-pyran-2-one ($IC_{50}=6\times10^{-9}$); and 6-[2-(3,3',5,5'-tetramethyl-[1,1'-biphenyl]-2-yl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-pyran-2-one ($IC_{50}=1.5\times10^{-8}$). The compounds were tested as the sodium salts of their corresponding hydroxy acid forms.

The preparation of the compounds of this invention is illustrated in the Flow Sheets.

Flow Sheet I shows the general scheme for synthesizing compounds with a vinylene bridge between the lactone and benzene rings. A starting benzaldehyde is converted to the corresponding cinnamaldehyde (this forms the bridging group) and this is subjected to an aldol reaction to elaborate a hydroxy keto ester from the terminal aldehydic moiety. Reduction of the hydroxy keto ester affords the dihydroxy ester which, upon saponification and subsequent lactonization, gives the lactone. The lactone is then separated chromatographically into its cis and trans racemates and the latter racemate is resolved to give the desired 4 R trans enantiomer.

Flow Sheet II shows the further conversion of the 4 R trans lactones into the corresponding dihydroxy acids and their salts and esters. Although this sequence is shown with the —CH=CH— bridged compounds, the same sequence can be used to give the corresponding acids, salts and esters of any of the other bridged compounds.

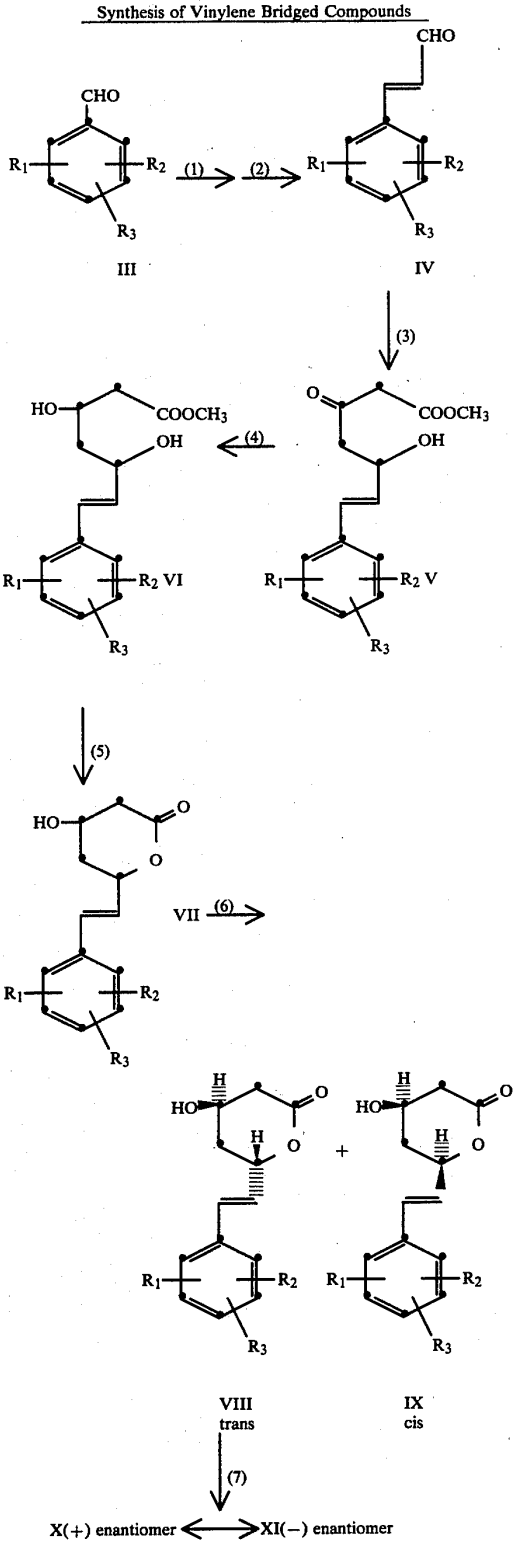
Flow Sheet III shows the synthetic routes for the preparation of the alternative bridging groups, represented by E in formula I. Compounds with a direct bond between the lactone and phenyl rings are made by the process of Flow Sheet I with omission of step 2. In this instance, the starting benzaldehyde is used directly in the Aldol reaction. Compounds with a methylene ($—CH_2—$) bridge are prepared by starting with the appropriate phenylacetaldehyde in place of the cinnamaldehyde. Compounds with an ethylene ($—CH_2—CH_2—$) bridge between the rings are prepared by reduction of the vinylene bridged compounds prepared in Flow Sheet I. Compounds with a trimethylene bridge ($—CH_2—CH_2—CH_2—$) are prepared by starting with the appropriate 1-bromo-3-phenylpropane. Compounds of formula I wherein A is a methyl group are prepared as indicated in Flow Sheet IV. Starting with the appropriate aldehyde, condensation with 1-(tri-n-butylstannyl)propan-2-one affords a β-hydroxy ketone which can be converted to the target lactones either by (a) acylation with 2-bromoacetyl bromide followed by intramolecular Reformatsky cyclization or (b) acylation with acetyl chloride followed by intermolecular Reformatsky reaction with ethyl 2-bromoacetate followed by saponification and subsequent lactonization of the resulting dihydroxy acid. Separation of the cis and trans racemic lactones and the subsequent resolution of the trans racemate to obtain the 4 R enantiomer are carried out as described in Flow Sheet I.

Flow Sheet V shows the details of the synthesis of benzaldehydes having an ortho phenyl group, followed by their use in the general scheme of Flow Sheet I to form compounds of this invention. This Flow Sheet summarizes the use of the benzaldehydes so made in the synthesis of vinylene bridged compounds as in Flow Sheet I, but they obviously can also be used as described in Flow Sheet III to produce compounds with other bridging groups. Because of the extremely high potency of the tetrahydropyranones having a 6-(6-phenyl)phenyl group, these compounds, prepared as in Flow Sheet V, are especially to be preferred.

Flow Sheet VI shows an alternate preparation of the 6-phenyl substituted benzaldehydes IIIa. The imines formed between aniline and substituted benzaldehydes are treated with palladium (II) acetate to give stable complexes. These complexes are reacted with substituted phenyl Grignard reagents in the presence of triphenylphosphine to give, after acidic hydrolysis, the 6-phenyl substituted benzaldehydes IIIa.

FLOW SHEET I

Synthesis of Vinylene Bridged Compounds

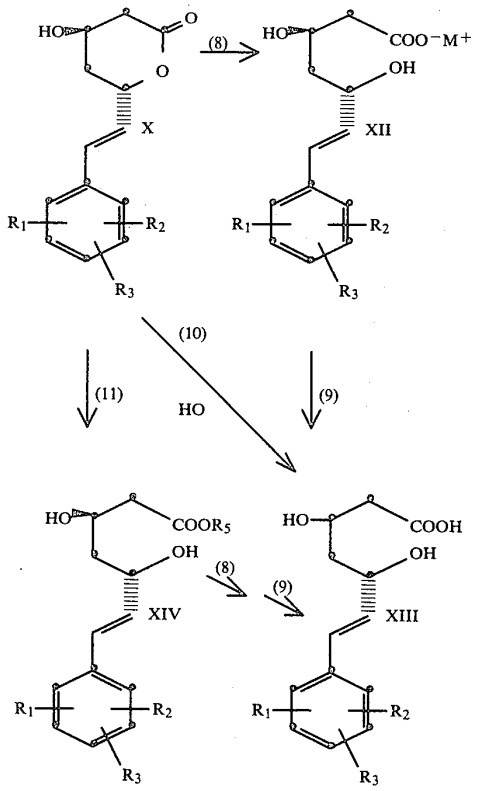


DEFINITIONS:

R_1, R_2 and R_3 are as defined in specifications for Formula I.

FLOW SHEET II

Preparation of Salts, Esters, Free Dihydroxy Acids



DEFINITIONS:

R_1, R_2 and R_3 are as defined in the specifications for Formula I

R_5=C_{1-5} lower alkyl or C_{1-5} lower alkyl substituted by a phenyl, dimethylamino or acetamido group

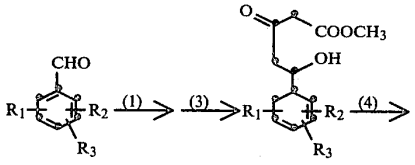
M^+=a pharmaceutically acceptable cation.

FLOW SHEET III

COMPOUNDS WITH OTHER BRIDGING GROUPS

A. Direct Bond from Phenyl Ring to Lactone Ring

[Procedure of Flow Sheet I omitting step (2)].



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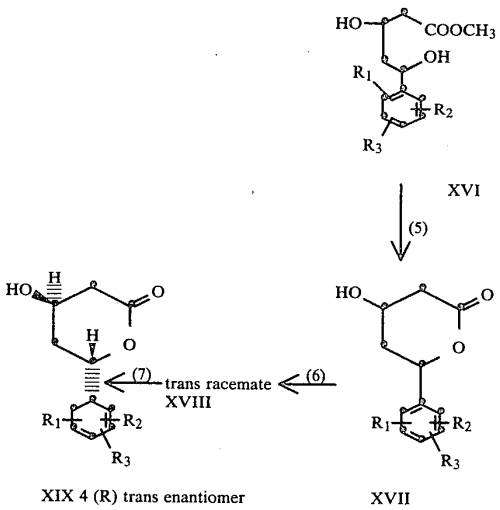
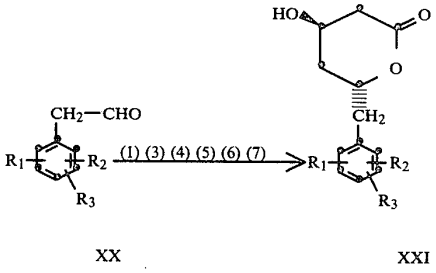
FLOW SHEET III

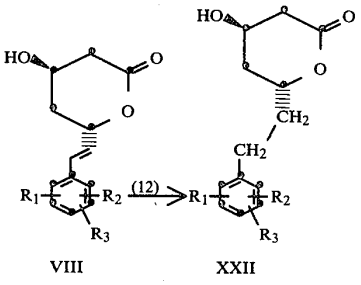
COMPOUNDS WITH OTHER BRIDGING GROUPS



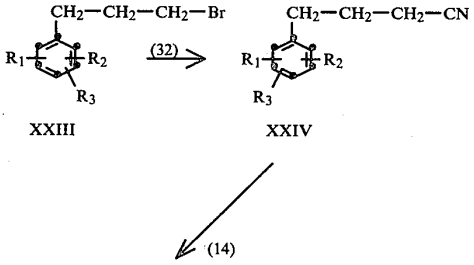
B. Methylene Bridge



C. Ethylene Bridge



D. Trimethylene Bridge



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