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[54] **3-DEMETHYLMEVALONIC ACID DERIVATIVES, AND PHARMACEUTICAL PRODUCTS BASED ON THESE COMPOUNDS**

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[30] **Foreign Application Priority Data**

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[52] **U.S. Cl.** **514/333**; 514/277; 514/334; 514/336; 514/357; 514/269; 544/333; 544/335; 546/256; 546/257; 546/258; 546/283; 546/284; 546/335; 546/341; 546/342; 546/268

[58] **Field of Search** 546/256, 268, 283, 284, 546/257, 258, 335, 341, 342, 268; 514/277, 333, 334, 336, 357

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

0306929	3/1989	European Pat. Off.	546/256
0308736	3/1989	European Pat. Off.	546/256
0325130	7/1989	European Pat. Off.	546/256
0330057	8/1989	European Pat. Off.	546/256

OTHER PUBLICATIONS

Stokker et al., "Journal of Medicinal Chemistry", vol. 28, No. 3, 1985, pp. 347–358.

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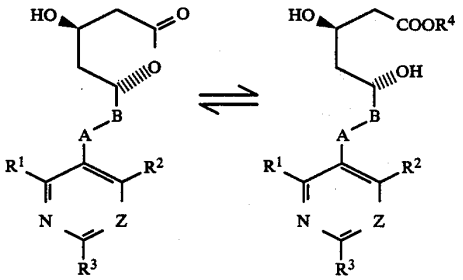
[57] **ABSTRACT**

3-Demethylmevalonic acid derivatives of the formula I (δ-lactone) and II (corresponding dihydroxy carboxylic acid derivative)



I II

in which A—B, Z, R^1, R^2, R^3 and R^4 have the indicated meanings, a process for the preparation of these compounds, their use as medicaments, and pharmaceutical products, are described. In addition, new intermediates for the preparation of the compounds of the formula I and formula II are described.

9 Claims, No Drawings

3-DEMETHYLMEVALONIC ACID DERIVATIVES, AND PHARMACEUTICAL PRODUCTS BASED ON THESE COMPOUNDS

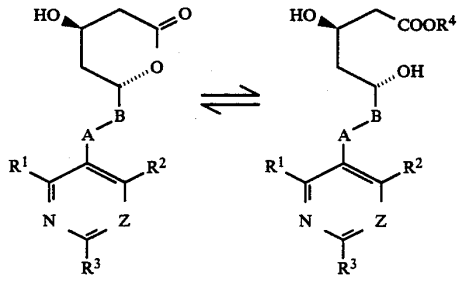
Derivatives of 3-hydroxy-3-methylglutaric acid (HMG) and of mevalonic acid have been described as inhibitors of cholesterol biosynthesis (M. T. Boots et al., J. Pharm. Sci. 69, 306 (1980), F. M. Singer et al., Proc. Soc. Exper. Biol. Med. 102, 270 (1959), H. Feres, Tetrahedron Lett. 24, 3769 (1983)). 3-Hydroxy-3-methylglutaric acid itself shows a significant cholesterol-lowering action in the rat and in human experiments (Z. Beg, Experimentia 23, 380 (1967), ibid 24, 15 (1968), P. J. Lupien et al., Lancet 1978, 1, 283).

Endo et al. (FEBS Letters 72, 323 (1976), J. Biol. Chem. 253, 1121 (1978)) reported the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the rate-determining enzyme of cholesterol biosynthesis, by the fermentation product "compactin".

Brown et al. (J. Chem. Soc. 1165 (1976) determined the chemical structure and the absolute configuration of "compactin" by a combination of chemical, spectroscopic and X-ray crystallographic methods and were able to show that "compactin" is a derivative of the lactone of 3-demethylmevalonic acid.

Compactin derivatives which inhibit the activity of HMG-CoA reductase have already been described (G. E. Stokker et al., J. Med. Chem. 28, 347–358 (1985)).

The present invention relates to new synthetic analogs of "compactin" in the form of the δ-lactone of the formula I or in the form of the dihydroxy acid derivative II



I II

In the formulae

A—B denotes a radical of the formula —CH=CH— or —CH_2—CH_2—,

Z denotes a radical of the formula —CH or a nitrogen atom,

R^1, R^2 and R^3, independently of one another, denote hydrogen, a saturated or unsaturated, straight-chain or branched hydrocarbon radical which has up to 6 carbon atoms and can optionally be substituted on the terminal carbon by a saturated or unsaturated, cyclic hydrocarbon radical having 3–6 carbon atoms, a cyclic hydrocarbon radical which has 3–7 carbon atoms and is saturated or is unsaturated once or twice, an aromatic radical selected from the group comprising phenyl, furyl, thienyl or pyridinyl, which can optionally carry in the nucleus 1–3 identical or different substituents from the following groups: halogen, trifluoromethyl, alkyl or alkenyl, each having up to 6 carbon atoms, hydroxyl, alkoxy having 1–6 carbon atoms, carboxyl, or carbalkoxy having 1–6 carbon atoms in the alkoxy moiety,

R^4 denotes hydrogen, a straight-chain or branched, saturated or unsaturated hydrocarbon radical having up to 5 carbon atoms, a benzyl radical whose nucleus can be substituted 1–2 times by halogen or an alkyl radical having 1–4 carbon atoms, an alkali metal or an ammonium ion $NR^5R^6R^7R^8$, where R^{R5}, R^6, R^7 and R^8 are identical or different and denote hydrogen, alkyl having 1–4 carbon atoms or hydroxyalkyl having 1–4 carbon atoms.

The invention relates to the pure enantiomers having the absolute configuration 4R,6S indicated in the general formula I or the absolute configuration 3R,5S depicted in formula II.

Preferred substituents R^1 and R^2 are a straight-chain or branched alkyl radical having 1–4 carbon atoms, a cycloalkyl radical having 3–6 carbon atoms, a cycloalkylmethyl or cycloalkenylmethyl radical having a ring size of 5–6 carbon atoms, a phenyl radical which can optionally carry 1–3 identical or different substituents from the following groups halogen, trifluoromethyl, alkyl having 1–4 carbon atoms, hydroxyl, alkoxy having 1–4 carbon atoms or carbalkoxy having 1–4 carbon atoms in the alkoxy moiety.

The preferred meanings for R^3 are hydrogen, a straight-chain or branched alkyl or alkenyl radical having up to 6 carbon atoms, a cycloalkyl or cycloalkenyl radical, each having 3–6 carbon atoms, a phenyl or pyridinyl radical, it being possible for the aromatic radicals optionally to carry 1–3 identical or different substituents from the following groups: halogen, alkyl having 1–4 carbon atoms, hydroxyl, alkoxy having 1–4 carbon atoms or carbalkoxy having 1–4 carbon atoms in the alkoxy moiety.

The preferred radicals R^4 are hydrogen, methyl, ethyl, isopropyl, isobutyl, benzyl, sodium, potassium, ammonium (NH_4) or methyltris(hydroxymethyl)ammonium.

Particularly preferred substituents R^1 are: methyl, ethyl, isopropyl, sec.-butyl, tert.-butyl, cyclopropyl, cyclohexyl, phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-fluoro-3-methylphenyl, 3,5-dimethylphenyl, cyclohexylmethyl and 4-trifluoromethylphenyl.

Particularly preferred substituents R^2 are methyl, ethyl, isopropyl, sec.-butyl, tert.-butyl, cyclopropyl, cyclohexyl, phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-fluoro-3-methylphenyl, 3,5-dimethylphenyl, cyclohexylmethyl and 4-trifluoromethylphenyl.

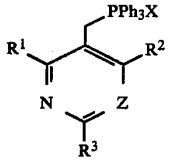
Particularly preferred substituents R^3 are hydrogen, methyl, isopropyl, tert.-butyl, cyclohexyl, phenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2,5-dimethylphenyl, 3,5-dimethylphenyl and 4-trifluoromethylphenyl.

Particularly preferred substituents R^4 are hydrogen, methyl, ethyl, sodium and potassium.

Very particular preference is given to compounds of the formula I in which Z denotes a radical of the formula —CH or N, R^1 denotes ethyl, isopropyl, cyclopropyl, R^2 denotes 4-fluorophenyl, 4-hydroxyphenyl and R^3 denotes isopropyl, tert.-butyl, cyclohexyl, phenyl, 4-hydroxyphenyl or 4-fluorophenyl, and to the sodium and potassium salts of the corresponding dihydroxy carboxylic acids of the formula II.

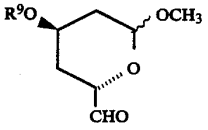
The invention also relates to a process for the preparation of compounds of the formulae I and II, which comprises

(a) reaction of the phosphonium salts of the formula III



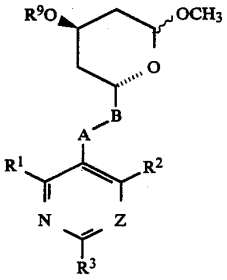
III

in which R^1, R^2, R^3 and Z have the meaning indicated for formula I, and X is Cl, Br or I, with the chiral aldehyde of the formula IV



IV

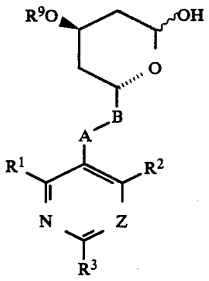
in which R^9 is a protective group which is stable to bases and weak acids, for example the t-$C_4H_9(C_6H_5)_2Si$ group, to give a compound of the formula V



V

in which R^1, R^2, R^3 and Z have the meaning given for formula I, R^9 has the meaning given for formula IV, and A-B represents the (—CH=CH—) group,

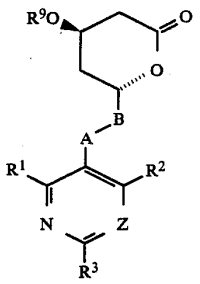
(b) acid hydrolysis of the methyl acetal group in a compound of the general formula V to give a lactol of the formula VI



VI

in which R^1, R^2, R^3 and Z have the meaning given for formula I, R^9 has the meaning given for formula IV, and A-B represents the (—CH=CH—) group,

(c) oxidation of the compound of the formula VI to give a lactone of the general formula VII



VII

in which R^1, R^2, R^3 and Z have the meaning given for formula I, R^9 has the meaning given for formula IV, and A-B represents the (—CH=CH—) group,

(d) elimination of the protective group R^9 in a compound of the general formula VII to give a compound of the formula I in which R^1, R^2, R^3 and Z have the meaning indicated for formula I, and A-B represents the (—CH=CH—) group,

(e) where appropriate hydrogenation of a resulting compound of the general formula I in which A-B represents a (—CH=CH—) group to give a compound of the general formula I in which A-B represents a (—CH_2—CH_2—) group, it also being possible for the hydrogenation to be carried out on the compounds of the formula V, VI or VII to give compounds in which A-B represents the (—CH_2—CH_2—) group,

(f) where appropriate conversion of a hydroxylactone of the general formula I into the corresponding dihydroxy acid of the formula II, or its salts, or, where appropriate, preparation from the hydroxylactone I or the free hydroxy acid II of the corresponding esters.

The phosphonium salts which are used as starting material in the process according to the invention and have the general formula III, in which R^1, R^2 and R^3 have the meaning given for the general formula I, are obtained as depicted in scheme 1.

Ketones of the general formula VIII, where R^2 and R^3 have the indicated meaning, are known from the literature or can be prepared by processes known from the literature (cf., for example, D. Vorländer and F. Kalkow, Berichte d. Dtsch. Chem. Ges. 30, 2268 (1897) or H. Stetter in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry) Vol. VII/26, 1449–1507, Thieme, Stuttgart 1976). Likewise known from the literature or amenable to preparation by processes known from the literature (for example in analogy to M. Jackman, M. Klenk, B. Fishburn, B. F. Tullar and S. Archer, J. Am. Chem. Soc. 70, 2884 (1948)) are the β-keto esters of the general formula IX, where R^1 has the abovementioned meaning, and R^{10} denotes a straight-chain or branched alkyl radical having up to 6 carbon atoms, preferably a methyl or ethyl radical.

Compounds of the formula X in which R^1, R^2, R^3 and R^{10} have the indicated meaning are prepared in analogy to literature processes, for example according to R. Connor, D. B. Andrews, J. Am. Chem. Soc. 56 2713 (1943) and literature cited therein. An example of a process used to convert compounds of the type X into pyridines of the general formula XV (in this, R^1, R^2 and R^3 have the abovementioned meaning, and Z denotes a CH group) is that described by F. Rehberg and F. Kröhnke, Liebigs Ann. Chem. 717, 91 (1968).

Dihydropyrimidines of the general formula XIV can be prepared, for example, in analogy to a literature process (E. F. Silversmith, J. Org. Chem. 27, 4090 (1962)) or, for example, also by a synthesis shown in scheme 1, route A, by reacting a β-keto ester of the general formula IX with an aldehyde of the type XI to give a compound of the general formula XII, and reacting the latter, without further purification, with an amidinium compound of the type XIII to give a dihydropyrimidinecarboxylic ester of the general formula XIV. The preparation of compounds of the type XIV from components of the general formulae IX, XI and XIII can likewise be carried out as a one-pot reaction (scheme 1, route B).

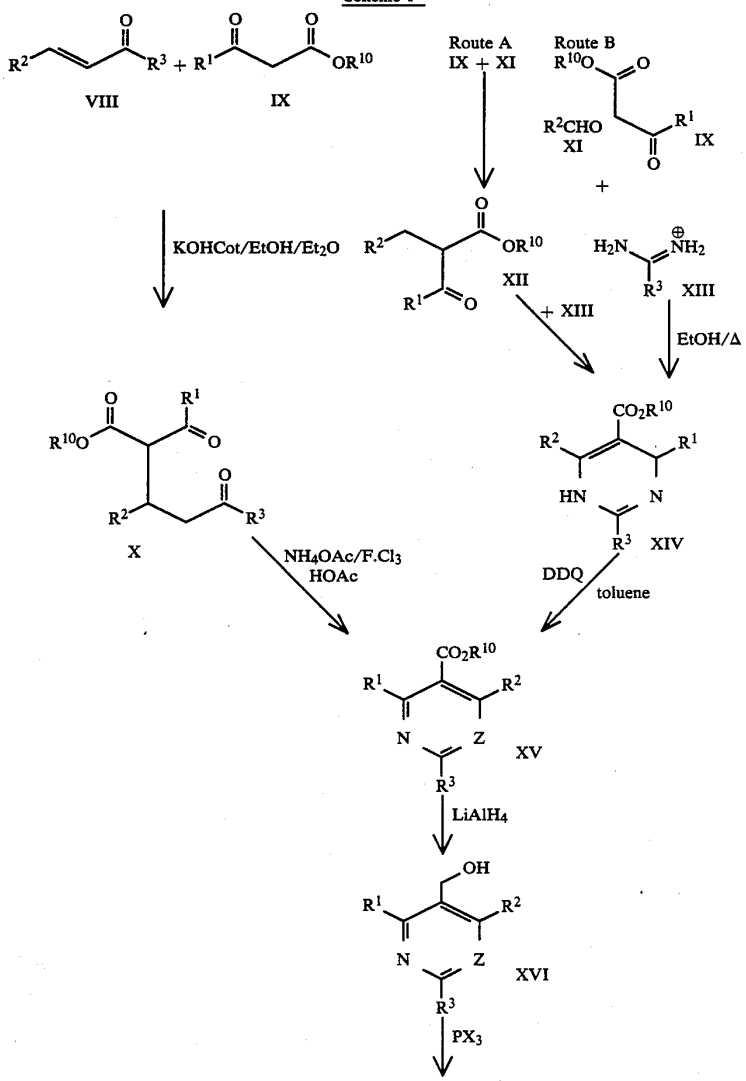
The oxidation of compounds of the formula XIV to give pyrimidinecarboxylic esters of the general formula XV in which R^1, R^2, R^3 and R^{10} have the abovementioned meaning, and Z denotes a nitrogen atom, is carried out in analogy to processes known from the literature, for example by dehydrogenation using chloroanil or 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) as described by E. A. Braude, J. Hannah, R. Linstead, J. Chem. Soc. 1960, 3257.

Compounds of the general formula XV are reduced by reaction with complex metal hydrides such as, for example, lithium aluminum hydride or diisobutylaluminum hydride, in aprotic solvents, for example diethyl ether or tetrahydrofuran, at temperatures between −30° C. and +50° C.

Alkyl halides of the general formula XVII, where R^1, R^2, R^3 and X have the abovementioned meaning, can be prepared from alcohols of the type XVI, for example by reaction with phosphorus halides in inert solvents such as, for example, dichloromethane or toluene, at temperatures between 0° and 100° C., or by reaction with hydrohalic acids.

Phosphonium salts of the general formula III are obtained by, for example, reaction of the alkyl halides XVII with triphenylphosphine in inert solvents such as toluene, at temperatures between 20° C. and 120° C. (cf. scheme 1).

Scheme 1



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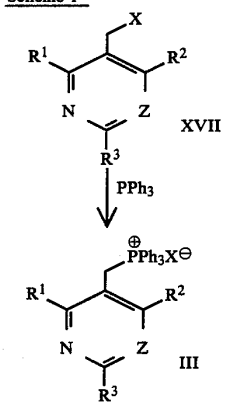
Scheme 1



The chiral aldehyde of the formula IV which is used as starting material in the process according to the invention is obtained by a process known from the literature (Yuh Lin, J. R. Falck, Tetrahedron Letters 23, 4305–4308 (1982)) from the corresponding alcohol by oxidation with, for example, CrO_3 or oxalyl chloride/-dimethyl sulfoxide in the presence of triethylamine.

Reaction of the chiral aldehyde of the formula IV with a phosphonium salt of the formula III by the Wittig method (for example Wittig, Haag, Chem. Ber. 88, 1654 (1955)) results in compounds of the formula V, a preferred embodiment comprising dissolution or suspension of phosphonium salts of the formula III in a solvent such as tetrahydrofuran, dimethyl sulfoxide or DME, liberation of the corresponding phosphoranes using a suitable strong base such as, for example, sodium hydride, potassium tert.-butylate, Li ethylate or butyllithium, and then addition of the aldehyde of the formula IV and allowing reaction to take place at −10° C. to +50° C. for 1–6 h.

In this, the compounds of the formula V are mainly obtained in the form of mixtures of the E/Z olefins. Mixtures of E/Z olefins can, where appropriate, be fractionated by chromatography. The pure Z-olefins can also be obtained, as described by G. Drefahl Chem. Ber. 94, 907 (1961), by irradiation of the E/Z mixture in solutions, such as, for example, toluene or nitrobenzene.

The corresponding pure E-olefins can be obtained, as described by De Tar et al. in J. Amer. Chem. Soc. 78, 474 (1955), by heating the E/Z mixtures in solution in the presence of iodine.

The methyl acetal protective group in the compounds of the formula V can be selectively eliminated by acid hydrolysis in the generally customary manner, preferably using a mixture of glacial acetic acid, tetrahydrofuran and water in the ratio 3:2:2, at +20° to +90° C., within 6–24 hours.

Oxidation of the compounds of the formula VI to give a lactone of the formula VII can be carried out by oxidizing agents such $CrO_3 \times 2Pyr$, or pyridinium chlorochromate in inert solvents such as, for example, methylene chloride or chloroform. Further possibilities for the oxidation comprise reaction with thioanisole/Cl_2-/NEt_3 in carbon tetrachloride, reaction with DMSO-/oxalyl chloride/NEt_3 at −20° C., or reaction with N-iodosuccinimide/tetrabutylammonium iodide in dichloromethane.

To prepare the compounds of the formula I, the protective group R^9 in the compounds of the formula VII is eliminated. This can take place with strong acids, such as 5-normal hydrochloric acid or sulfuric acid, at −10° C. to +30° C., or with fluoride ions, preferably by dissolving the compounds of the formula VII in tetrahydrofuran or diethyl ether, and adding a mixture of tetrabutylammonium fluoride and glacial acetic acid, followed by stirring at 0° C. to 40° C. for between 1 and 12 hours.

Compounds of the formula I in which A-B represents a (CH=CH) group are hydrogenated by a generally customary method, expediently at a temperature between 20° C. and 40° C. using hydrogen in the presence of a metal catalyst, preferably palladium, platinum, PtO_2 or PdO_2, to give compounds of the formula I, in which A-B denotes a $—CH_2—CH_2—$ group. This hydrogenation can be carried out under atmospheric pressure in customary solvents such as tetrahydrofuran, ethyl acetate, methanol, low molecular weight alcohols, glacial acetic acid or chloroform, or in autoclaves under elevated pressure (2–50 atm). The hydrogenation of the —CH=CH— group can also be carried out on the compounds of the formulae V, VI or VII.

The resulting compounds of the formula I can be isolated in a straightforward manner by evaporation of the solvent, where appropriate after purification by chromatography.

The compounds of the formula I are obtained in optically pure form. Concerning the configuration of the double bond (A-B=—CH=CH—), E/Z mixtures are obtained, and these can, at all stages of the synthesis, be fractionated by chromatography or isomerized to give the E form (cf. in this context, De Tar et al., J. Amer. Chem. Soc. 78 475 (1955)).

Compounds of the formula I in the form of the δ-lactone can be hydrolyzed in alkaline medium to give the corresponding salts of the dihydroxy acids, for example using NaOH or KOH in a low molecular weight alcohol such as methanol, or in ethers such as dimethoxyethane or THF, where appropriate in the presence of water. The alkali metal cation in the resulting salts of the dihydroxy acids can, after acidification, be exchanged by any desired cations in ion exchangers in the customary manner. For this purpose, for example, the dihydroxy acids are allowed to run through a column packed with a cation exchanger, such as, for example, based on polystyrene/divinylbenzene (®AMBERLITE CG-150 or ®DOWEX CCR-2). The cation

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