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Rosenblum et al.

[45] **Date of Patent:** Jun. 16, 1998[54] **HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS**[75] Inventors: **Stuart B. Rosenblum**, West Orange; **Sundeep Dugar**, Bridgewater; **Duane A. Burnett**, Fanwood; **John W. Clader**, Cranford; **Brian A. McKittrick**, Bloomfield, all of N.J.[73] Assignee: **Schering-Plough Corporation**, Kenilworth, N.J.

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[63] Continuation-in-part of PCT/US94/10099, Sep. 14, 1994, continuation-in-part of Ser. No. 257,593, Jun. 9, 1994, Pat. No. 5,631,365, which is a continuation-in-part of Ser. No. 102,440, Sep. 21, 1993, abandoned.

[51] **Int. Cl.**⁶ C07D 205/08; A61K 31/395[52] **U.S. Cl.** 514/210; 540/200[58] **Field of Search** 540/200; 514/210[56] **References Cited****U.S. PATENT DOCUMENTS**

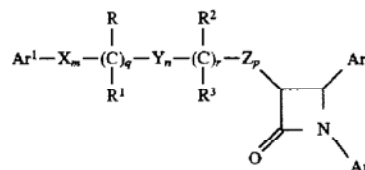
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Attorney, Agent, or Firm-Anita W. Magatti[57] **ABSTRACT**

Hydroxy-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ and Ar² are aryl or R⁴-substituted aryl;Ar³ is aryl or R⁵-substituted aryl;X, Y and Z are —CH₂—, —CH(lower alkyl)— or —C(dilower alkyl)—;R and R² are —OR⁶, —O(CO)R⁶, —O(CO)OR⁹ or —O(CO)NR⁶R⁷;R¹ and R³ are H or lower alkyl;

q is 0 or 1; r is 0 or 1; m, n and p are 0-4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1-6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1-5;

R⁴ is selected from lower alkyl, R⁵, —CF₃, —CN, —NO₂ and halogen R⁵ is selected from —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₀₋₂R⁹, —O(CH₂)₁₋₁₀—COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;R⁶, R⁷ and R⁸ are H, lower alkyl, aryl or aryl-substituted I_cR⁹ is lower alkyl, aryl or aryl-substituted lower alkyl;

are disclosed, as well as a method of lowering serum cholesterol by administering said compounds, alone or in combination with a cholesterol biosynthesis inhibitor, pharmaceutical compositions containing them; and a process for preparing them.

9 Claims, No Drawings

**HYDROXY-SUBSTITUTED AZETIDINONE
COMPOUNDS USEFUL AS
HYPOCHOLESTEROLEMIC AGENTS**

The present application is the United States national application corresponding to International Application No. PCT/US94/10099, filed Sep. 14, 1994 and designating the United States, which PCT application is in turn a continuation-in-part of U.S. application Ser. No. 08/257593, filed Jun. 9, 1994, U.S. Pat. No. 5,631,365, which is a continuation-in-part of U.S. application Ser. No. 08/102,440, filed Sep. 21, 1993, abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to hydroxy-substituted azetidinones useful as hypocholesterolemic agents in the treatment prevention of atherosclerosis, and to the combination of a hydroxy-substituted azetidinone of this invention and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis. The invention also relates to a process for preparing hydroxy-substituted azetidinones.

Atherosclerotic coronary heart disease (CHD) represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male gender, cigar smoke and serum cholesterol. A total cholesterol level in excess of 225–250 mg/dl is associated with significant elevation of risk of CHD.

Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a key step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester formation and reduction of serum cholesterol is likely to inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesteryl esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

A few azetidinones have been reported as being useful lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. Pat. No. 4,983,597 discloses N-sulfonyl-2-azetidinones as anticholesterolemic agents and Ram, et al., in *Indian J. Chem.*, Sect. B, 29B, 12 (1990), p. 1134–7, disclose ethyl 4-(2-oxoazetidin-4-yl)phenoxy-alkanoates as hypolipidemic agents. European Patent Publication 264,231 discloses 1-substituted-4-phenyl-3-(2-oxo-alkylidene)-2-azetidinones as blood platelet aggregation inhibitors. European Patent 199,630 and European Patent Application 337,549 disclose elastase inhibitory substituted azetidinones said to be useful treating inflammatory conditions resulting in tissue destruction which are associated with various disease states, e.g. atherosclerosis.

WO93/102048, published Feb. 4, 1993, discloses substituted β -lactams useful as hypocholesterolemic agents.

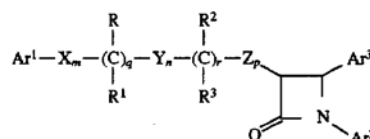
The regulation of whole-body cholesterol homeostasis in humans and animals involves the regulation of dietary cholesterol and modulation of cholesterol biosynthesis, bile acid biosynthesis and the catabolism of the cholesterol-containing plasma lipoproteins. The liver is the major organ responsible for cholesterol biosynthesis and catabolism and for this reason, it is a prime determinant of plasma cholesterol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently metabolized to low density lipoproteins (LDL) in the circulation. LDL are the predominant cholesterol-carrying lipoproteins in the plasma and an increase in their concentration is correlated with increased atherosclerosis.

When intestinal cholesterol absorption is reduced, by whatever means, less cholesterol is delivered to the liver. The consequence of this action is decreased hepatic lipoprotein (VLDL), production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Thus, the net effect of inhibiting intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

The inhibition of cholesterol biosynthesis by 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (EC1.1.1.34) inhibitors has been shown to be an effective way to reduce plasma cholesterol (Witzum, *Circulation*, 80, 5 (1989), p. 1101–1114) and reduce atherosclerosis. Combination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patients than either agent in monotherapy (Illingworth, *Drugs*, 36 (Suppl. 3) (1988), p. 63–71).

SUMMARY OF THE INVENTION

Novel hypocholesterolemic compounds of the present invention are represented by the formula I



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ and Ar² are independently selected from the group consisting of aryl and R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X, Y and Z are independently selected from the group consisting of —CH₂—, —CH(lower alkyl)— and —C(dilower alkyl)—;

R and R² are independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁹ and —O(CO)NR⁶R⁷;

R¹ and R³ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R⁴ is 1–5 substituents independently selected from the group consisting of lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)_{1–5}OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)_{0–2}R⁹, —O(CH₂)_{1–10}COOR⁶, —O(CH₂)_{1–10}CONR⁶R⁷, —(lower alkylene)COOR⁶, —CH=CH—COOR⁶, —CF₃, —CN, —NO₂ and halogen;

R⁵ is 1–5 substituents independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)_{1–5}OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)_{0–2}R⁹, —O(CH₂)_{1–10}COOR⁶, —O(CH₂)_{1–10}CONR⁶R⁷, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl.

R⁴ is preferably 1–3 independently selected substituents, and R⁵ is preferably 1–3 independently selected substituents. Preferred are compounds of formula I wherein Ar¹ is phenyl or R⁴-substituted phenyl, especially (4-R⁴)-

3

substituted phenyl. Ar² is preferably phenyl or R⁴-substituted phenyl, especially (4-R⁴)-substituted phenyl. Ar³ is preferably R⁵-substituted phenyl, especially (4-R⁵)-substituted phenyl. When Ar¹ is (4-R⁴)-substituted phenyl, R⁴ is preferably a halogen. When Ar² and Ar³ are R⁴- and R⁵-substituted phenyl, respectively, R⁴ is preferably halogen or —OR⁶ and R⁵ is preferably —OR⁶, wherein R₆ is lower alkyl or hydrogen. Especially preferred are compounds wherein each of Ar¹ and Ar² is 4-fluorophenyl and Ar³ is 4-hydroxyphenyl or 4-methoxyphenyl.

X, Y and Z are each preferably —CH₂—, R¹ and R³ are each preferably hydrogen. R and R² are preferably —OR⁶ wherein R⁶ is hydrogen, or a group readily metabolizable to a hydroxyl (such as —O(CO)R⁶, —O(CO)OR⁹ and —O(CO)NR⁶R⁷, defined above).

The sum of m, n, p, q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m, n and r are each zero, q is 1 and p is 2. Also preferred are compounds wherein p, q and n are each zero, r is 1 and m is 2 or 3. More preferred are compounds wherein m, n and r are each zero, q is 1, p is 2, Z is —CH₂ and R is —OR⁶, especially when R⁶ is hydrogen. Also more preferred are compounds wherein p, q and n are each zero, r is 1, m is 2, X is —CH₂— and R² is —OR⁶, especially when R⁶ is hydrogen.

Another group of preferred compounds is that wherein Ar¹ is phenyl or R⁴-substituted phenyl, Ar² is phenyl or R⁴-substituted phenyl and Ar³ is R⁵-substituted phenyl. Also preferred are compounds wherein Ar¹ is phenyl or R⁴-substituted phenyl, Ar² is phenyl or R⁴-substituted phenyl, Ar³ is R⁵-substituted phenyl, and the sum of m, n, p, q and r is 2, 3 or 4, more especially 3. More preferred are compounds wherein Ar¹ is phenyl or R⁴-substituted phenyl, Ar² is phenyl or R⁴-substituted phenyl, Ar³ is R⁵-substituted phenyl, and wherein m, n and r are each zero, q is 1 and p is 2, or wherein p, q and n are each zero, r is 1 and m is 2 or 3.

This invention also relates to a method of lowering the serum cholesterol level in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I. That is, the use of a compound of the present invention as an hypocholesterolemic agent is also claimed.

In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for combined use with a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels.

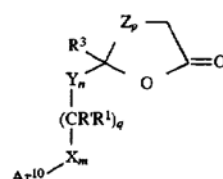
In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a hydroxy-substituted azetidinone cho-

4

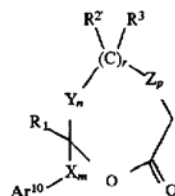
lesterol absorption inhibitor of formula I in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

In yet another aspect, the invention relates to a process for preparing certain compounds of formula I comprising the steps:

(a) treating with a strong base a lactone of the formula



or



wherein R¹ and R² are R and R², respectively, or are suitably protected hydroxy groups; Ar¹⁰ is Ar¹, a suitably protected hydroxy substituted aryl or a suitably protected amino-substituted aryl; and the remaining variables are as defined above, provided that in lactone of formula B when n and r are each zero, p is 1–4;

(b) reacting the product of step (a) with an imine of the formula



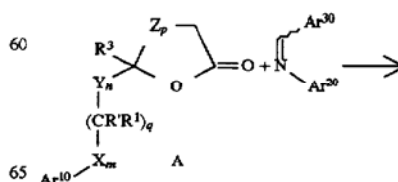
wherein Ar²⁰ is Ar², a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and Ar³⁰ is Ar³, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl;

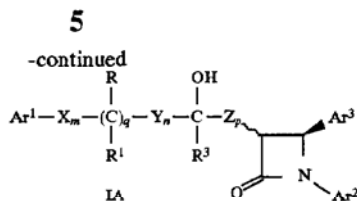
c) quenching the reaction with an acid;

d) optionally removing the protecting groups from R¹, R², Ar¹⁰, Ar²⁰ and Ar³⁰, when present; and

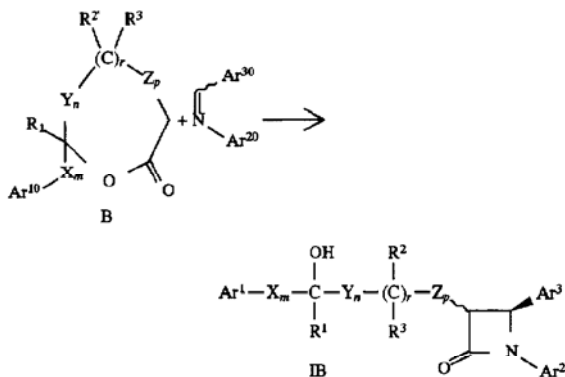
e) optionally functionalizing hydroxy or amino substituents at R, R², Ar¹, Ar² and Ar³.

Using the lactones shown above, compounds of formula IA and IB are obtained as follows:





wherein the variables are as defined above; and



wherein the variables are as defined above.

DETAILED DESCRIPTION

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl.

"Halogeno" refers to fluorine, chlorine, bromine or iodine atoms.

The above statement, wherein R⁶, R⁷ and R⁸ are said to be independently selected from a group of substituents, means that R⁶, R⁷ and R⁸ are independently selected, but also that where an R⁶, R⁷ or R⁸ variable occurs more than once in a molecule, those occurrences are independently selected (e.g., if R is —OR⁶ wherein R⁶ is hydrogen, R⁴ can be —OR⁶ wherein R⁶ is lower alkyl).

Compounds of the invention have at least one asymmetric carbon atom and therefore all isomers, including enantiomers and diastereomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture including racemic mixtures. Isomers can be prepared using conventional

6

techniques, either by reacting chiral starting materials or by separating isomers of a compound of formula I. Isomers may also include geometric isomers, e.g. when a double bond is present. All such geometric isomers are contemplated for this invention.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than another isomer.

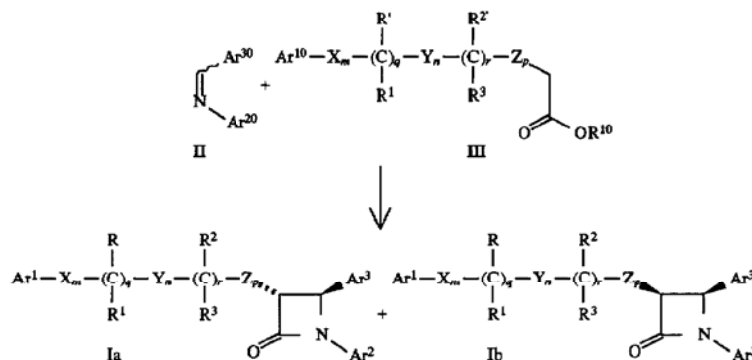
Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base form for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and CI-981; HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3R-(hydroxy-methyl)-4'-oxo-2'-R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalenyl 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other cholesterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin.

Compounds of formula I can be prepared by known methods, for example those described below and in WO93/02048.

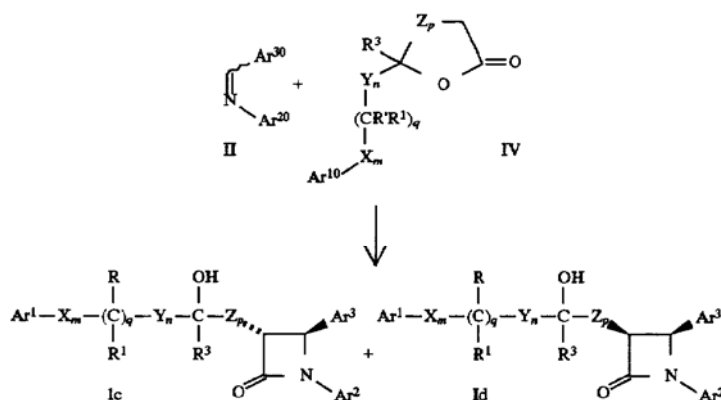
Method A:



Compounds of formula Ia and Ib, wherein Ar¹, Ar², Ar³, X, Y, Z, R¹, R², R³, m, n, p, q and r are as defined above, can be prepared by treatment of an ester of formula III, wherein R¹⁰ is lower alkyl such as ethyl or a chiral moiety such as menthyl or 10-(diisopropylsulfonamido)isobornyl, and the remaining variables are as defined above, with a strong base such as lithium diisopropylamide (LDA) in a suitable solvent such as tetrahydrofuran (THF) at -78° C. A solubilizing agent such as hexamethylphosphoric triamide (HMPA) may optionally be added as a cosolvent. An imine of formula II, wherein Ar²⁰ and Ar³⁰ are as defined above, is added, the reaction mixture is either warmed to room temperature or maintained at a suitable low temperature such as -78° C. for the appropriate time, followed by quenching with a suitable acid such as 1N HCl. The product is isolated using conventional purification techniques. When a protecting group as defined in Table I (below) is present on one or more of the optionally protected groups, an additional step comprising removal of the protecting group by conventional techniques is needed. However, for compounds of formula Ia, Ib, or any compound of formula I wherein a protected hydroxy group Ar¹⁰, Ar²⁰, Ar³⁰, R¹ or R² is an alkoxy or benzyloxy group, such a protecting group need not be removed to obtain a compound of formula I. When a chiral ester of formula III is used, the resulting compound of formula Ia or Ib is not racemic.

Imines of formula II (Ar³⁰-CH=N-Ar²⁰) can be prepared from aldehydes of the formula Ar³⁰-CHO and amines of the formula Ar²⁰-NH₂ and by procedures well known in the art. Aldehydes of formula Ar³⁰-CHO and amines of formula Ar²⁰-NH₂ are commercially available or can be prepared via known procedures.

Method A':



Compounds of formula Ic and Id, wherein the variables are as defined above, can be prepared by a process comprising the following steps:

(a) Treat a lactone of formula IV, wherein the variables are as defined above, with a strong base such as an alkyl lithium (e.g., n-butyl-lithium), a metal hydride (e.g., sodium hydride), a metal alkoxide (e.g., sodium methoxide), a metal halide (e.g., TiCl₄), metal exchange of the lithium enolate with a metal halide (e.g., zinc chloride), metal exchange of the lithium enolate with a metal alkyl (e.g., 9-borabicyclononyl triflate), or, preferably, a metalamide (e.g., LDA), in a suitable anhydrous organic solvent such as dry THF, ether or benzene, in a dry, inert atmosphere, e.g., under nitrogen. The reaction is carried out at about 0° C. to about -85° C., preferably about -78° C., over a period of

about 5 to about 60 minutes, preferably about 30 minutes. 1-50% of solubilizing cosolvents may optionally be added, preferably about 10% HMPA.

(b) Add an imine of formula II, wherein Ar²⁰ and Ar³⁰ are as defined above, to the product of step (a) over a period of 5 to 60 minutes, preferably 30 minutes, maintaining the reaction mixture at about 0° C. to about -85° C., preferably about -78° C., for 1 to 12 hours, preferably about 3 hours, or warming the reaction mixture over that time period at a rate of about 10° C. per hour to about 70° C. per hour, preferably about 30° C. per hour, to a temperature of about 20° C.

(c) Quench the reaction with a suitable acid such as HCl (1N).

(d) The protecting groups on R¹, R², Ar¹⁰, Ar²⁰ and Ar³⁰, when present, are removed, if desired, by methods well known in the art, for example silyl protecting groups are removed by treatment with fluoride.

(e) Compounds of formula I wherein any of R and R², when present, are OR⁶ wherein R⁶ is hydrogen, can be converted by well known methods to other compounds of formula I wherein R and R² are functionalized, i.e., are independently selected from the group consisting of OR^{6a}, -O(CO)R⁶, -O(CO)OR⁹ and -O(CO)NR⁶R⁷, wherein R⁶, R⁷ and R⁹ are as defined above and R^{6a} is lower alkyl, aryl, or aryl-lower alkyl. For example, treatment of the alcohol with an alkyl halide in the presence of a suitable base such as NaH will afford alkoxy-substituted compounds (i.e., R or R² is OR⁶, wherein R⁶ is lower alkyl); treatment of the alcohol with an acylating agent such as acetylchloride will result in compounds wherein R or R² is -OC(O)R⁶; treatment of the alcohol with phosgene followed alcohol of the formula HOR⁹ affords compounds substituted with a -OC

(O)OR⁹ group; and treatment of the alcohol with phosgene followed by an amine of the formula HNR⁶R⁷ affords compounds wherein R or R² is -OC(O)NR⁶R⁷. Compounds of formula I wherein any Ar¹, Ar² or Ar³ has a hydroxy or amino group can be similarly functionalized to obtain other compounds of formula I, i.e., wherein R⁴ and R⁵ are independently -OR^{6a}, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁶R⁷ or -NR⁶SO₂R⁹.

The product of step c, d or e is isolated using conventional purification techniques such as extraction, crystallization or, preferably, silica gel 60 chromatography. When a chiral lactone is used, the resulting compound of formula Ic or Id is not racemic.

Using the procedure described in steps (a)-(e), lactones of formula IVa can be used to prepare compounds of formula

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