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AUSTRALIA
Patents Act 1990

NOTICE OF ENTITLEMENT

We SCHERING CORPORATION

of 2000 Galloping Hill Road KENILWORTH NEW JERSEY 07033 USA

being the Applicant and Nominated Person, in respect of Application No. 23980/92

state the following:

Duane A BURNETT; John W CLADER; Tiruvettipuram K THIRUVENGADAM; Chou-Hong TANN; Junning LEE; Timothy MC ALLISTER; Cesar COLON; Derek H R BARTON; Ronald BRESLOW; Sundeep DUGAR; and Wayne VACCARO are the actual inventors of the invention the subject of the Application.

The applicant and nominated person is the assignee of the invention from the actual inventors.

The applicant and nominated person is entitled to rely on the applications listed in the declaration under Article 8 of the PCT.

Convention priority is claimed from the following basic applications referred to in the declaration under Article 8 of the PCT:

Basic Applicants	Application Number	Application Date	Country	Country Code
Duane A BURNETT; John W CLADER;	734,426	23 July 1991	U.S.A.	US
Tiruvettipuram K THIRUVENGADAM; Chou-Hong TANN; Junning LEE; Timothy MC ALLISTER; Cesar COLON; Derek H R BARTON;	734,652	23 July 1991	U.S.A.	US

The basic applications referred to in the declaration under Article 8 of the PCT were the first applications made in a Convention country in respect of the invention the subject of the Application.

DATED THIS 13th day of January 1994

SCHERING CORPORATION
By their Patent Attorneys
John Terry
GRIFFITH HACK & CO

2OUR REF: P16104-FO\VNV:MR

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-23980/92
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 658441

(54) Title
SUBSTITUTED BETA-LACTAM COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS AND PROCESSES FOR THE PREPARATION THEREOF

International Patent Classification(s)

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	C07D 205/085			

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(43) Publication Date : 23.02.93

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(71) Applicant(s)
SCHERING CORPORATION

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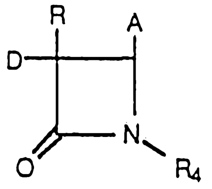
(56) Prior Art Documents
EP 199630
EP 337549

(57) Claim

1. A compound having the structural formula



wherein

A is -CH=CH-B;

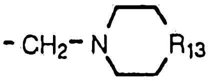
-C≡C-B;

-(CH$_2$)$_p$-X-B, wherein p is 0, 1 or 2 and X is a bond, -NH- or -S(O)$_{0-2}$-;

heteroaryl, benzofused heteroaryl, W-substituted heteroaryl or W-substituted benzofused heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, and wherein W is 1-3 substituents on the ring carbon atoms selected

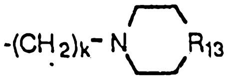
.../2

from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, $-NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, halogeno, $-NHC(O)OR_5$, $-NHC(O)R_5$, R_6O_2SNH-, $(R_6O_2S)_2N-$, $-S(O)_2NH_2$, $-S(O)_{0-2}R_{10}$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$ and



, and wherein the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, $-C(O)OR_5$, $-C(O)R_5$, OH, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, $-S(O)_2NH_2$ and 2-(trimethylsilyl)ethoxymethyl;

-C(O)-B; or



, wherein k is 1 or 2;

D is $B'-(CH_2)_mC(O)-$, wherein m is 1, 2, 3, 4 or 5;

$B'-(CH_2)_q-$, wherein q is 2, 3, 4, 5 or 6;

$B'-(CH_2)_e-Z-(CH_2)_r-$, wherein Z is -O-, -C(O)-, phenylene, $-NR_8-$ or $-S(O)_{0-2}-$, e is 0, 1, 2, 3, 4 or 5 and r is 1, 2, 3, 4 or 5, provided that the sum of e and r is 1, 2, 3, 4, 5 or 6;

$B'-(C_2-C_6$ alkenylene)-; $B'-(C_4-C_6$ alkadienylene)-;

$B'-(CH_2)_t-Z-(C_2-C_6$ alkenylene)-, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

$B'-(CH_2)_f-V-(CH_2)_g-$, wherein V is C_3-C_6 cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

$B'-(CH_2)_t-V-(C_2-C_6$ alkenylene)- or $B'-(C_2-C_6$ alkenylene)-$V-(CH_2)_t-$, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

$B'-(CH_2)_a-Z-(CH_2)_b-V-(CH_2)_d-$, wherein Z and V are as defined above and a ,b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6;

$T-(CH_2)_s-$, wherein T is cycloalkyl of 3-6 carbon atoms and s is 1, 2, 3, 4, 5 or 6; or

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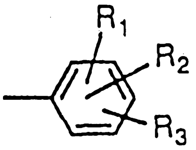
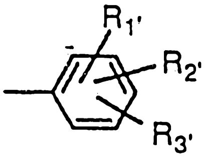
naphthylmethyl, heteroarylmethyl, or W-substituted heteroarylmethyl, wherein heteroaryl and W are as defined above;

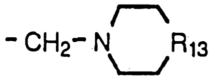
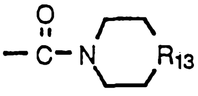
B is

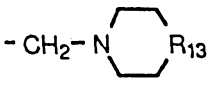
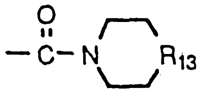


B' is naphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is as defined above, or



R is hydrogen, fluoro, C_1-C_{15} alkyl, C_1-C_{15} alkenyl, C_1-C_{15} alkynyl, or B-$(CH_2)_h$ -, wherein h is 0, 1, 2, or 3;

R_1, R_2 and R_3 are independently selected from the group consisting of H, lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, $-NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, o-halogeno, m-halogeno, $-NHC(O)OR_5$, $-NHC(O)R_5$, R_6O_2SNH-, $(R_6O_2S)_2N$-, $-S(O)_2NH_2$, $-S(O)_{0\text{-}2}R_{10}$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$,  and  , or R_1 is hydrogen and R_2 and R_3, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

$R_{1'}$, $R_{2'}$ and $R_{3'}$ are independently selected from the group consisting of H, lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, $-NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, halogeno, $-NHC(O)OR_5$, $-NHC(O)R_5$, R_6O_2SNH-, $(R_6O_2S)_2N$-, $-S(O)_2NH_2$, $-S(O)_{0\text{-}2}R_{10}$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$,  and  , or $R_{1'}$ is hydrogen and $R_{2'}$ and $R_{3'}$, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

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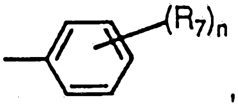
R$_4$ is , wherein n is 0, 1, 2 or 3, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl or quinolyl;

R$_5$ is lower alkyl, phenyl, R$_{14}$-phenyl, benzyl or R$_{14}$-benzyl;

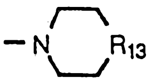
R$_6$ is OH, lower alkyl, phenyl, benzyl, R$_{14}$-phenyl or R$_{14}$-benzyl;

R$_7$ is lower alkyl, lower alkoxy, OH, halogeno, -NR$_{10}$R$_{11}$, -NHC(O)OR$_5$, -NHC(O)R$_5$, NO$_2$, -CN, -N$_3$, -SH, -S(O)$_{0-2}$-(lower alkyl), -COOR$_9$, -CONR$_{10}$R$_{11}$, -COR$_{12}$, phenoxy, benzyloxy, -OCF$_3$, or tert-butyldimethylsilyloxy, and where n is 2 or 3, the R$_7$ groups can be the same or different;

R$_8$ is H, lower alkyl, phenyl lower alkyl, or -C(O)R$_9$;

R$_9$ is H, lower alkyl, phenyl or phenyl lower alkyl;

R$_{10}$ and R$_{11}$ are independently selected from H and lower alkyl;

R$_{12}$ is H, OH, alkoxy, phenoxy, benzyloxy, , -NR$_{10}$R$_{11}$, lower alkyl, phenyl or R$_{14}$-phenyl;

R$_{13}$ is -O-, -CH$_2$-, -NH- or -N(lower alkyl)-; and

R$_{14}$ is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO$_2$, -NR$_{10}$R$_{11}$, OH or halogeno;

or a pharmaceutically acceptable salt thereof.

19. A method of inhibiting the enzyme acyl CoA:cholesterol acyl transferase by administering an effective amount of a composition of claim 10 to a mammal in need of such treatment.

OPI DATE 23/02/93 APPLN. ID 23980/92
AOJP DATE 29/04/93 PCT NUMBER PCT/US92/05972

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A1

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(63) Related by Continuation

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US	734,426 (CIP)
Filed on	23 July 1991 (23.07.91)

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(74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, One Giralda Farms, Madison, NJ 07940-1000 (US).

(81) Designated States: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

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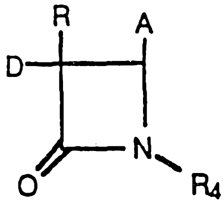
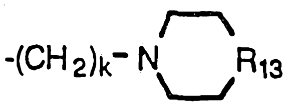


(I)



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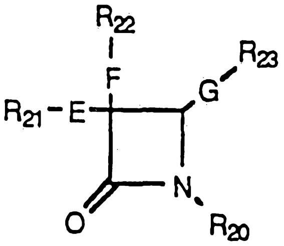


(II)

(57) Abstract

Novel compounds of formula (I) wherein A is -CH=CH-B; -C≡C-B; -$(CH_2)_p$-X-B, wherein p is 0-2 and X is a bond, -NH- or -$S(O)_{0-2}$-; optionally substituted heteroaryl or benzofused heteroaryl; -C(O)-B; or (Ia), wherein k is 1-2; D is B'-$(CH_2)_m$C(O)-, wherein m is 1-5; B'-$(CH_2)_q$-, wherein q is 2-6; B'-$(CH_2)_e$-Z-$(CH_2)_r$-, wherein Z is -O-, -C(O)-, phenylene, -NR_8- or -$S(O)_{0-2}$-, e is 0-5 and r is 1-5, provided that the sum of e and r is 1-6; B'-(alkenylene)-; B'-(alkadienylene)-; B'-$(CH_2)_t$-Z-(alkenylene), wherein t is 0-3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2-6; B'-$(CH_2)_f$-V-$(CH_2)_g$-, wherein V is cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; B'-$(CH_2)_t$-V-(alkenylene) or B'-(alkenylene)-V-$(CH_2)_t$-, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2-6; B'-$(CH_2)_a$-Z-$(CH_2)_b$-V-$(CH_2)_d$-, wherein a, b and d are 0-6, provided that the sum of a, b and d is 0-6; T-$(CH_2)_s$-, wherein T is cycloalkyl and s is 1-6; naphthylmethyl or optionally substituted heteroarylmethyl; B is optionally substituted phenyl; B' is naphthyl, optionally substituted heteroaryl or optionally substituted phenyl; R is hydrogen, fluoro, alkyl, alkenyl, alkynyl, or B-$(CH_2)_h$-, wherein h is 0-3; R_4 is optionally substituted phenyl, indanyl, benzofuranyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl or quinolyl; are disclosed, as well as their use as hypocholesterolemic agents; the method of using compounds of formula (II), wherein R_{20} is optionally substituted phenyl, optionally substituted naphthyl, optionally substituted heteroaryl, or optionally substituted benzofused heteroaryl, R_{21}, R_{22} and R_{23} are independently selected from H or R_{20}; E, F and G are independently a bond; cycloalkylene; alkylene; alkenylene; alkynylene; a substituted alkylene, alkenylene or alkynylene chain; an interrupted alkylene, alkenylene or alkynylene chain; or an interrupted alkylene, alkenylene or alkynylene chain substituted by one or more substituents; or one of R_{21}-E and R_{22}-F is selected from the group consisting of halogeno, OH, alkoxy, -OC(O)R_5, -$NR_{10}R_{11}$, -SH or -S(alkyl); R_5 is alkyl, phenyl, R_{14}-phenyl, benzyl or R_{14}-benzyl; R_{10} and R_{11} are independently selected from H and lower alkyl, or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier as hypocholesterolemic agents is also disclosed.

SUBSTITUTED BETA-LACTAM COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS AND PROCESSES FOR THE PREPARATION THEREOF

BACKGROUND OF THE INVENTION

The present invention relates to substituted β-lactams useful as hypocholesterolemic agents in the treatment and prevention of atherosclerosis and to processses for preparing β-lactams.

Atherosclerotic coronary heart disease 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 sex, cigarette smoking and serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk.

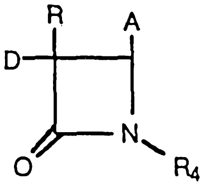
Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a key step in the intestinal absorption of dietary cholesterol. The intracellular esterification of cholesterol is catalyzed by the enzyme acyl CoA:cholesterol acyl transferase (ACAT, EC 2.3.1.26). Thus, inhibition of ACAT 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 β-lactam compounds have been reported as being useful in lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. 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-oxoalkylidene)-2-azetidinones as blood platelet aggregation inhibitors.

SUMMARY OF THE INVENTION

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



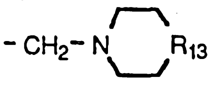
I

wherein

A is -CH=CH-B;

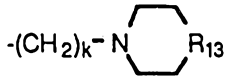
-C≡C-B;

$-(CH_2)_p$-X-B, wherein p is 0, 1 or 2 and X is a bond, -NH- or $-S(O)_{0-2}-$;

heteroaryl, benzofused heteroaryl, W-substituted heteroaryl or W-substituted benzofused heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, and wherein W is 1-3 substituents on the ring carbon atoms selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxy-imino)lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, $-NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, halogeno, $-NHC(O)OR_5$, $-NHC(O)R_5$, R_6O_2SNH-, $(R_6O_2S)_2N-$, $-S(O)_2NH_2$, $-S(O)_{0-2}R_{10}$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$ and , and wherein the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, $-C(O)OR_5$, -

$C(O)R_5$, OH, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, $-S(O)_2NH_2$ and 2-(trimethylsilyl)ethoxymethyl;

-C(O)-B; or



, wherein k is 1 or 2;

D is $B'-(CH_2)_mC(O)-$, wherein m is 1, 2, 3, 4 or 5;

$B'-(CH_2)_q-$, wherein q is 2, 3, 4, 5 or 6;

$B'-(CH_2)_e-Z-(CH_2)_r-$, wherein Z is -O-, -C(O)-, phenylene, $-NR_8-$ or $-S(O)_{0-2}-$, e is 0, 1, 2, 3, 4 or 5 and r is 1, 2, 3, 4 or 5, provided that the sum of e and r is 1, 2, 3, 4, 5 or 6;

$B'-(C_2-C_6$ alkenylene)-; $B'-(C_4-C_6$ alkadienylene)-;

$B'-(CH_2)_t-Z-(C_2-C_6$ alkenylene)-, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

$B'-(CH_2)_f-V-(CH_2)_g-$, wherein V is C_3-C_6 cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

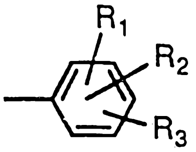
$B'-(CH_2)_t-V-(C_2-C_6$ alkenylene)- or $B'-(C_2-C_6$ alkenylene)-$V-(CH_2)_t-$, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

$B'-(CH_2)_a-Z-(CH_2)_b-V-(CH_2)_d-$, wherein Z and V are as defined above and a ,b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6;

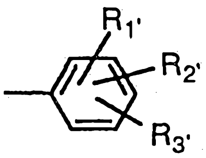
$T-(CH_2)_s-$, wherein T is cycloalkyl of 3-6 carbon atoms and s is 1, 2, 3, 4, 5 or 6; or

naphthylmethyl, heteroarylmethyl, or W-substituted heteroarylmethyl, wherein heteroaryl and W are as defined above;

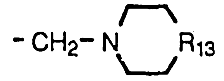
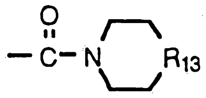
B is

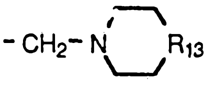
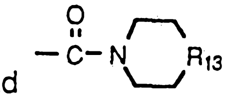


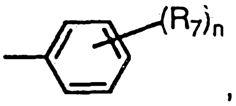
B' is naphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is as defined above, or



R is hydrogen, fluoro, C_1-C_{15} alkyl, C_1-C_{15} alkenyl, C_1-C_{15} alkynyl, or B-$(CH_2)_h$ -, wherein h is 0, 1, 2, or 3;

R_1, R_2 and R_3 are independently selected from the group consisting of H, lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, -CF_3, -OCF_3, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, -$NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, o-halogeno, m-halogeno, -NHC(O)OR_5, -NHC(O)R_5, R_6O_2SNH-, $(R_6O_2S)_2N$-, -$S(O)_2NH_2$, -$S(O)_{0\text{-}2}R_{10}$, tert-butyldimethylsilyloxymethyl, -C(O)R_{12},  and , or R_1 is hydrogen and R_2 and R_3, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

$R_{1'}$, $R_{2'}$ and $R_{3'}$ are independently selected from the group consisting of H, lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl alkanedioyl, allyloxy, -CF_3, -OCF_3, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, -$NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, halogeno, -NHC(O)OR_5, -NHC(O)R_5, R_6O_2SNH-, $(R_6O_2S)_2N$-, -$S(O)_2NH_2$, -$S(O)_{0\text{-}2}R_{10}$, tert-butyldimethyl-silyloxymethyl, -C(O)R_{12},  and , or $R_{1'}$ is hydrogen and $R_{2'}$ and $R_{3'}$, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R_4 is , wherein n is 0, 1, 2 or 3, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl or quinolyl;

R_5 is lower alkyl, phenyl, R_{14}-phenyl, benzyl or R_{14}-benzyl;

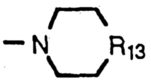
R_6 is OH, lower alkyl, phenyl, benzyl, R_{14}-phenyl or R_{14}-benzyl;

R_7 is lower alkyl, lower alkoxy, OH, halogeno, $-NR_{10}R_{11}$, $-NHC(O)OR_5$, $-NHC(O)R_5$, NO_2, -CN, $-N_3$, -SH, $-S(O)_{0-2}$-(lower alkyl), $-COOR_9$, $-CONR_{10}R_{11}$, $-COR_{12}$, phenoxy, benzyloxy, $-OCF_3$, or tert-butyldimethylsilyloxy, and where n is 2 or 3, the R_7 groups can be the same or different;

R_8 is H, lower alkyl, phenyl lower alkyl, or $-C(O)R_9$;

R_9 is H, lower alkyl, phenyl or phenyl lower alkyl;

R_{10} and R_{11} are independently selected from H and lower alkyl;

R_{12} is H, OH, alkoxy, phenoxy, benzyloxy, , $-NR_{10}R_{11}$, lower alkyl, phenyl or R_{14}-phenyl;

R_{13} is -O-, $-CH_2-$, -NH- or -N(lower alkyl)-; and

R_{14} is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO_2, $-NR_{10}R_{11}$, OH or halogeno;

or a pharmaceutically acceptable salt thereof.

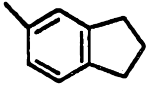
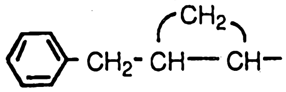
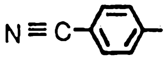
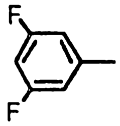
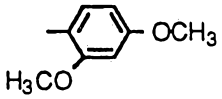
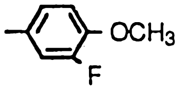
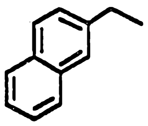
Preferred are compounds of formula I wherein R is H. Another group of preferred compounds of formula I is that wherein D is $B'-(CH_2)_q-$, $B'-(CH_2)_e-Z-(CH_2)_r-$, B'-(C_2-C_6 alkenylene)-, or $B'-(CH_2)_f-V-(CH_2)_g-$, wherein B', Z, V, q, e, r, f, and g are as defined above. A third group of preferred compounds of formula I is that wherein R_4 is phenyl, R_7-substituted phenyl or indanyl. Still another group of preferred compounds of formula I is that wherein A is $-(CH_2)_p-X-B$, wherein X, B and p are as defined above.

Especially preferred are compounds of formula I wherein D is: $B'-(CH_2)_q-$, wherein B' is phenyl and q is 3 or 4; $B'-(CH_2)_e-Z-(CH_2)_r-$, wherein B' is p-fluorophenyl or p-methoxyphenyl, e is zero, Z is -O-, and r is 2; B'-(C_2-C_6 alkenylene)- is 3-phenyl-1-propenyl; or B'-(CH_2)$_f$-V-(CH_2)$_g$-, wherein B' is phenyl, f is 1, V is cyclopropylene, and g is zero. Also especially preferred are compounds of formula I wherein A is -(CH_2)$_p$-X-B wherein p is zero and X is a bond. Preferably R_1, R_2 and R_3 are selected from H, OH, -NO_2, lower alkoxy, alkoxyalkoxy, lower alkyl lower alkandioyl, m-halogeno, $NR_{10}R_{11}$(lower alkoxy)-, allyloxy, phenoxy, alkoxycarbonylalkoxy and -C(O)R_{12}. Compounds wherein R_1 and R_3 are each H and R_2 is in the para-position are more preferred.

R_7 is preferably selected from lower alkyl, lower alkoxy, halogeno, -OCF_3, lower alkylthio, -$NR_{10}R_{11}$, -CN, OH, and -COR_{12}. More preferred are compounds wherein n is 1 and R_7 is in the para-position.

Especially preferred compounds of formula I, wherein R is hydrogen, are shown in the following Table 1:

D	A	R_4
C_6H_5-(CH_2)$_3$-	p-CH_3O-C_6H_4-	p-CH_3O-C_6H_4-
C_6H_5-(CH_2)$_4$-	p-CH_3O-C_6H_4-	p-CH_3O-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-CH_3O-C_6H_4-	C_6H_5-
C_6H_5-(CH_2)$_3$-	p-OH-C_6H_4-	p-CH_3O-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-CH_3O-C_6H_4-	p-Cl-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-CH_3CH_2-O-C_6H_4-	p-CH_3O-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-CH_3O-C_6H_4-	p-CH_3CH_2O-C_6H_4-
p-F-C_6H_4-O-(CH_2)$_2$-	p-CH_3O-C_6H_4-	p-CH_3O-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-CH_3O-C_6H_4-	p-F-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-CH_3O-C_6H_4-	m-CH_3O-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-CH_3O-C_6H_4-	p-CF_3O-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-CH_3O-C_6H_4-	p-CH_3-C_6H_4-
C_6H_5-CH_2-CH=CH-	p-CH_3O-C_6H_4-	p-CH_3O-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-(CH_3(CH_2)$_3$)-O-C_6H_4-	p-CH_3O-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-CH_3O-C_6H_4-	p-CH_3S-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-(CH_2=CH-CH_2-O)-C_6H_4-	p-CH_3O-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-(C_6H_5-O)-C_6H_4-	p-CH_3O-C_6H_4-
C_6H_5-(CH_2)$_3$-	p-($CH_3CH_2O_2C$)-C_6H_4-	p-CH_3O-C_6H_4-

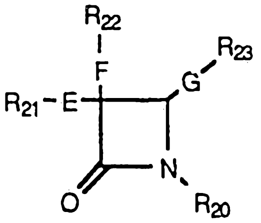
D	A	R_4
$C_6H_5-(CH_2)_3-$	$p-CH_3O-C_6H_4-$	
$C_6H_5-(CH_2)_3-$	$p-(CH_3CH_2CH_2-O)-C_6H_4-$	$p-CH_3O-C_6H_4-$
$C_6H_5-(CH_2)_5-$	$p-CH_3O-C_6H_4-$	$p-CH_3O-C_6H_4-$
$C_6H_5-(CH_2)_3-$	$p-CH_3O-C_6H_4-$	$p-((CH_3CH_2)_2N)-C_6H_4-$
$C_6H_5-(CH_2)_3-$	$p-(CH_3CH_2O)-C_6H_4-$	C_6H_5-
	$p-CH_3O-C_6H_4-$	$p-CH_3O-C_6H_4-$
$C_6H_5-(CH_2)_3-$	$p-((CH_3)_2CH-O)-C_6H_4-$	$p-CH_3O-C_6H_4-$
$p-F-C_6H_4-O-(CH_2)_2-$	$p-CH_3O-C_6H_4-$	C_6H_5-
$C_6H_5-(CH_2)_3-$	$p-CH_3O-C_6H_4-$	
$C_6H_5-(CH_2)_3-$	$p-(CH_3O_2C)-C_6H_4-$	C_6H_5-
$C_6H_5-(CH_2)_3-$	$p-CH_3O-C_6H_4-$	
$C_6H_5-(CH_2)_3-$		$p-CH_3O-C_6H_4-$
$C_6H_5-(CH_2)_3-$	$p-CH_3O-C_6H_4-$	$p-(H_3CC(O))-C_6H_4-$
$C_6H_5-(CH_2)_3-$		$p-CH_3O-C_6H_4-$
$C_6H_5-(CH_2)_3-$	$p-(CH_3OCH_2O)-C_6H_4-$	C_6H_5-
$p-CH_3O-C_6H_4-O-(CH_2)_2-$	$p-CH_3O-C_6H_4-$	C_6H_5-
$C_6H_5-(CH_2)_3-$	$p-(CH_3CH_2OC(O)CH_2O)-C_6H_4-$	$p-CH_3O-C_6H_4-$
$C_6H_5-(CH_2)_3-$	$p-(CH_3OC(O)-(CH_2)_2-C(O)-O)-C_6H_4-$	$p-CH_3O-C_6H_4-$
$C_6H_5-(CH_2)_3-$	$p-((CH_3)_2N-(CH_2)_3-O)-C_6H_4-$	$p-CH_3O-C_6H_4-$
$C_6H_5-(CH_2)_3-$	$p-HO-C_6H_4-$	$p-HO-C_6H_4-$
	$p-CH_3O-C_6H_4-$	C_6H_5-

The first-listed compound in the above table having the (3R,4S) absolute stereochemistry is more preferred.

This invention also relates to the use of a novel compound of formula I of the present invention as a hypocholesterolemic agent in a mammal in need of such treatment.

In another aspect, the invention relates to a pharmaceutical composition comprising a novel β-lactam of formula I of the present invention in a pharmaceutically acceptable carrier.

In still another aspect, the present invention relates to a pharmaceutical composition comprising a cholesterol-lowering effective amount of a compound having the structural formula II



II

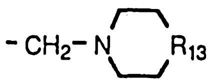
wherein

R_{20} is phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl and W-substituted benzofused heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof;

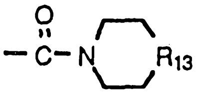
R_{21}, R_{22} and R_{23} are independently selected from H or R_{20};

W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl. lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, $-NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, halogeno, $-NHC(O)OR_5$, $-NHC(O)R_5$,

R_6O_2SNH-, $(R_6O_2S)_2N$-, $-S(O)_2NH_2$, $-S(O)_{0-2}R_{10}$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$,



and



;

E, F and G are independently a bond; C_3-C_6 cycloalkylene; C_1-C_{10} alkylene; C_1-C_{10} alkenylene; C_1-C_{10} alkynylene; an alkylene, alkenylene or alkynylene chain as defined substituted by one or more substituents independently selected from the group consisting of phenyl, W-substituted phenyl, heteroaryl and W-substituted heteroaryl, wherein heteroaryl is as defined above; an alkylene, alkenylene or alkynylene chain as defined interrupted by one or more groups independently selected from the group consisting of -O-, -S-, -SO-, $-SO_2$-, $-NR_8$, -C(O)-, C_3-C_6 cycloalkylene, phenylene, W-substituted phenylene, heteroarylene and W-substituted heteroarylene; or an interrupted alkylene, alkenylene or alkynylene chain as defined substituted by one or more substituents independently selected from the group consisting of phenyl, W-substituted phenyl, heteroaryl and W-substituted heteroaryl; or one of R_{21}-E and R_{22}-F is selected from the group consisting of halogeno, OH, lower alkoxy, $-OC(O)R_5$, $-NR_{10}R_{11}$, -SH or -S(lower alkyl);

R_5 is lower alkyl, phenyl, R_{14}-phenyl, benzyl or R_{14}-benzyl;

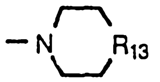
R_6 is OH, lower alkyl, phenyl, benzyl, R_{14}-phenyl or R_{14}-benzyl;

R_8 is H, lower alkyl, phenyl lower alkyl or $-C(O)R_9$;

R_9 is H, lower alkyl, phenyl or phenyl lower alkyl;

R_{10} and R_{11} are independently selected from H and lower alkyl;

R_{12} is H, OH, alkoxy, phenoxy, benzyloxy,



, $-NR_{10}R_{11}$, lower alkyl, phenyl or R_{14}-phenyl;

R_{13} is -O-, $-CH_2$-, -NH- or -N(lower alkyl)-;

R_{14} is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO_2, $-NR_{10}R_{11}$, OH or halogeno;

provided that when G is a bond, R_{23} is not H, and provided that when R_{23} is W-substituted phenyl, W is not p-halogeno;

or a pharmaceutically acceptable salt thereof;

in a pharmaceutically acceptable carrier.

It is noted that novel compounds of formula I are included within the scope of formula II.

Preferred compounds of formula II are those wherein R_{21} is H and E is a bond or lower alkylene, and those wherein R_{21} is phenyl and E is lower alkylene. Also preferred are compounds of formula II wherein R_{22} is H and F is a bond. Another group of preferred compounds of formula II is that wherein G is a bond and R_{23} is phenyl substituted by OH, $-NO_2$, lower alkoxy, alkoxyalkoxy, m-halogeno, lower alkyl lower alkandioyl, $NR_{10}R_{11}$(lower alkoxy)-, allyloxy, phenoxy, alkoxycarbonylalkoxy, and $-C(O)R_{12}$. Still another group of preferred compounds of formula II is that wherein R_{20} is phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogeno, $-OCF_3$, lower alkylthio, $-NR_{10}R_{11}$, -CN, OH or acetyl.

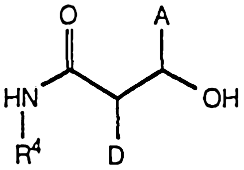
Certain compounds not within the scope of formula I but within the scope of formula II are novel compounds. Examples of such compounds are represented in the following Table 2

R_{21}-E-	R_{22}-F-	R_{23}-G-	R_{20}-
$C_{10}H_{21}$-	H	C_6H_5-	4-CH_3O-C_6H_4-
$C_{10}H_{21}$-	H	C_6H_5-	2,4,6-tri-CH_3O-C_6H_2-
$C_{10}H_{21}$-	CH_3CH_2-	C_6H_5-	4-CH_3O-C_6H_4-
$C_{10}H_{21}$-	C_6H_5-$(CH_2)_3$-	C_6H_5-	4-CH_3O-C_6H_4-
$C_{10}H_{21}$-	CH_3CH_2-	C_6H_5-	2,4,6-tri-CH_3O-C_6H_2-
$C_{10}H_{21}$-	CH_3CH_2-	C_6H_5-CH=CH-	4-CH_3O-C_6H_4-
$C_{10}H_{21}$-	CH_3-	C_6H_5-	4-CH_3O-C_6H_4-

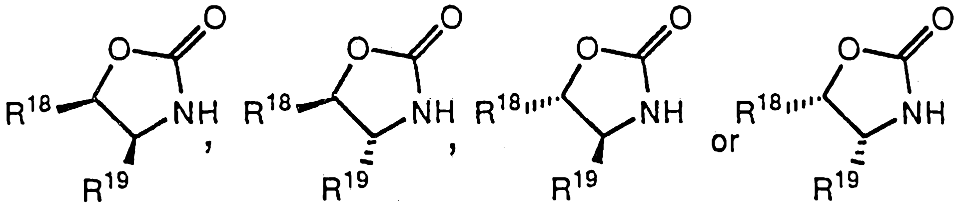
The present invention also relates to the method of lowering serum cholesterol in a mammal in need of such treatment comprising administering a pharmaceutical composition comprising a compound of formula II in a pharmaceutically acceptable carrier.

The present invention also relates to the use of a compound of formula I or II as an ACAT inhibitor.

The present invention also relates to a stereoselective process for producing β-lactams of formula I, wherein R is hydrogen ,and D and A have trans relative stereochemistry, from a hydroxyamide of the formula



wherein D, A and R^4 are as defined above, by cyclizing the hydroxyamide, and wherein the hydroxyamide is prepared from a carboxylic acid DCH_2COOH, an aldehyde A-CHO and an amine R^4NH_2, wherein D, A and R^4 are as defined above, in a process utilizing as a chiral auxiliary an oxazolidinone of the formula



wherein R^{18} and R^{19} are independently selected from the group consisting of: hydrogen, C_1-C_6 alkyl, phenyl, naphthyl, substituted phenyl, substituted naphthyl, and benzyl, wherein said chiral auxiliary is preferably R-(+)-4-benzyl-oxazolidinone.

This process, designated Method D, for producing compounds of formula I, wherein R is hydrogen, and D and A have trans relative stereochemistry, comprises the steps:

(a) reacting a carboxylic acid of the formula D-CH_2COOH, wherein D is as defined above, with a chlorinating agent;

(b) deprotonating a chiral oxazolidinone, as described above, preferably R-(+)-4-benzyloxazolidinone, with a strong base or a tertiary amine base and treating the resulting anion with the product of step (a);

(c) enolizing the product of step (b) with either:

(i) a dialkylboron triflate and a tertiary amine base; or

(ii) $TiCl_4$ and tetramethylethylenediamine (TMEDA) or a mixture of TMEDA and triethylamine;

then condensing with an aldehyde of the formula A-CHO, wherein A is as defined above;

(d) hydrolyzing the product of step (c) with a base and hydrogen peroxide;

(e) condensing the product of step (d) with an amine of the formula R^4NH_2, wherein R^4 is as defined above, by treating with a dehydrative coupling agent, optionally adding an activating agent;

(f) cyclizing the product of step (e) by reacting the product of step (e) with:

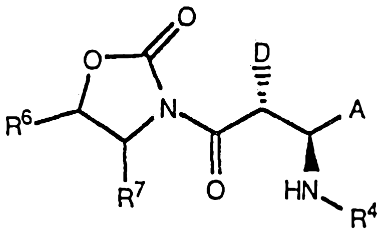
(i) a dialkylazodicarboxylate and a trialkylphosphine; or

(ii) a di- or tri-chlorobenzoyl chloride, an aqueous solution of a base and a phase transfer catalyst, then treating the resulting di- or tri-chlorobenzoate with an aqueous solution of a base and a phase transfer catalyst; or

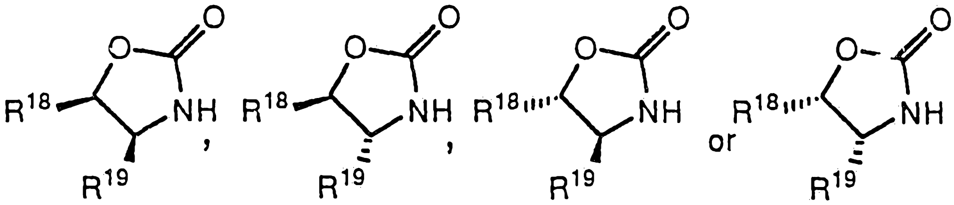
(iii) a dialkylchlorophosphate, an aqueous solution of a base and a phase transfer catalyst; or

(iv) a di- or tri-chlorobenzoyl chloride and a metal hydride.

In another embodiment, the process of this invention provides the steps of producing a β-lactam of formula I, wherein R is hydrogen, and D and A have trans relative stereochemistry, from a β-aminoamide derivative of the formula



by cyclizing the β-aminoamide, wherein the β-aminoamide is prepared from a carboxylic acid DCH_2COOH, and an imine $ACH{=}N\text{-}R^4$, wherein D, A and R^4 are as defined above, in a process utilizing as a chiral auxiliary an oxazolidinone of the formula



wherein R^{18} and R^{19} are as defined above, and wherein said chiral auxiliary is preferably R-(+)-4-benzyl-oxazolidinone.

This process, designated Method F, for producing compounds of formula I, wherein R is hydrogen, and D and A have trans relative stereochemistry, comprises the steps:

(a) enolizing the product of Method D, step (b) with $TiCl_4$ and tetramethylethylenediamine (TMEDA), then condensing with an imine of the formula $A\text{-}CH{=}N\text{-}R^4$, wherein A and R^4 are as defined above;

(b) cyclizing the product of step (a) by treating with a strong non-nucleophilic base, preferably sodium bistrimethylsilylamide.

DETAILED DESCRIPTION:

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms and "lower alkyoxy" similarly refers to alkoxy groups having 1 to 6 carbon atoms.

"Alkenyl" means straight or branched carbon chains having one or more double bonds in the chain, conjugated or unconjugated, and alkadienyl refers to chains having two double bonds in the chain. Similarly, "alkynyl" means straight or branched carbon chains having one or more triple bonds in the chain.

Where an alkyl, alkenyl or alkynyl chain joins two other variables and is therefore bivalent, the terms alkylene, alkenylene and alkynylene are used.

"Cycloalkyl" means a saturated carbon ring of 3 to 6 carbon atoms, while "cycloalkylene" refers to a corresponding bivalent ring, wherein the points of attachment to other groups include all positional isomers.

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

"Heteroaryl" includes all positional isomers for a given heteroaryl group as defined above, for example 2-pyridyl, 3-pyridyl and 4-pyridyl. Benzofused heteroaryl refers to radicals formed by the bonding of a benzene radical to adjacent carbon atoms on a heteroaryl ring; examples are indolyl, quinolyl, quinazolinyl, quinoxalinyl, benzotriazolyl, indazolyl, benzoxazolyl, benzothienyl and benzofuranyl.

"Phenylene" means a bivalent phenyl group, including ortho, meta and para-substitution and "heteroarylene" similarly means a bivalent heteroaryl group, ioncluding all positional isomers.

"(Lower alkoxyimino)lower alkyl" refers to the group (C_1-C_6 lower alkoxy)-N=CH-(C_1-C_5 lower alkyl). "Lower alkanedioyl" means radicals of the formula $-OC(O)(CH_2)_{1-4}C(O)OH$, while "lower alkyl lower alkanedioyl" means radicals of the formula $-OC(O)(CH_2)_{1-4}C(O)O$-(lower alkyl).

R_{14}-benzyl and R_{14}-benzyloxy refer to benzyl and benzyloxy radicals which are substituted on the phenyl ring.

"Tertiary amine base" means a trialkylamine, such as triethylamine or diisopropylethylamine, or a nitrogen containing heterocycle, such as pyridine.

"Base" means a metal hydroxide base such as lithium, sodium or potassium hydroxide

"Strong base" means a non-aqueous base such as a metal hydride or an alkyllithium.

"Metal hydride" means a commercially available metal hydride such as lithium, sodium or potassium hydride

"Alkyllithium" means a alkyllithium reagent such as n-butyllithium, s-butyllithium, t-butyllithium or methyllithium.

""Dehydrative coupling agent" means a carbodiimide such as 1-(3'-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DEC) or dicyclohexylcarbodiimide (DCC).

"Activating agent" means an agent used to facilitate the formation of amide bonds such as 1-hydroxybenzotriazole (HOBT) or N-hydroxysuccinimide.

"Halide salt" means a metal salt of a halogen such as sodium, lithium or potassium bromide.

The carbon chains as defined in E, F, and G, when substituted by optionally substituted phenyl or heteroaryl groups, may include independent substitution on different carbon atoms, di-substitution on one carbon atom, or both. One skilled in the art will recognize that the number of double or triple bonds present, the replacement of carbon atoms in the chain and the presence of substitutents on the carbon atoms in the chain are all dependent on the length of the chain: shorter carbon chains cannot accommodate as many double or triple bonds, carbon replacements or substituents as longer carbon chains can. In general, unsaturated carbon chains contain 1 to 4 double or triple bonds, conjugated or non-conjugated. Where carbon atoms are replaced, 1 to 4 replacement groups can be present. Similarly, when carbon atoms in the chain are substituted, 1 to 4 substituents can be present.

Examples of alkyl chains are methyl, ethyl, propyl, butyl and decyl.

Examples of unsaturated E, F and G groups are ethylene and acetylene.

Examples of E, F and G groups wherein the carbon atoms in the chain are replaced are $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2O-$,

$-CH_2CH_2CH_2O-$, $-CH_2-O-CH_2-$, $-CH_2CH_2-O-CH_2$, $-CH_2CH_2-NH-$, $-CH_2CH_2-N(CH_3)-$ and $-O-CH_2C(O)-NH-$.

Compounds of the invention have at least one asymmetrical carbon atom and therefore all isomers, including diastereomers and rotational isomers 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 techniques, either by reacting enantiomeric starting materials or by separating isomers of a compound of formula I or II.

Isomers may include geometric isomers, e.g. when E, F or G contains a double bond. All such isomers are contemplated for this invention.

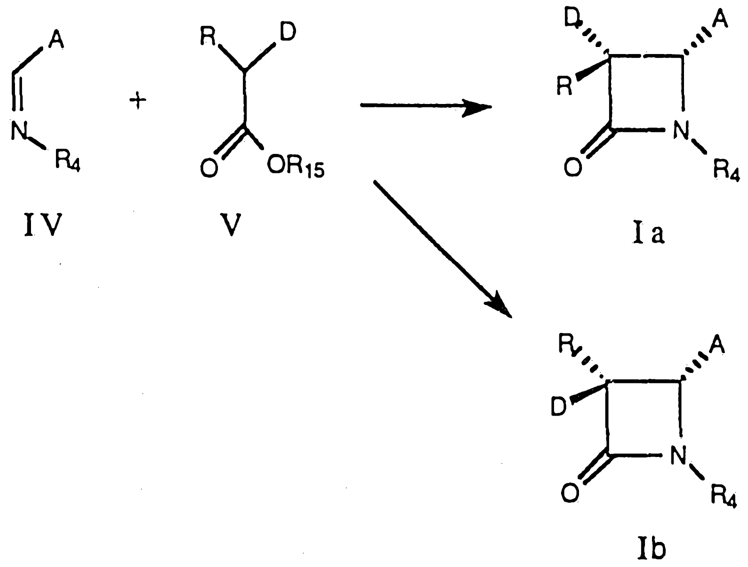
Those skilled in the art will appreciate that for some compounds of formulae I and II, one isomer will show greater pharmacological activity than another isomer.

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 forms 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.

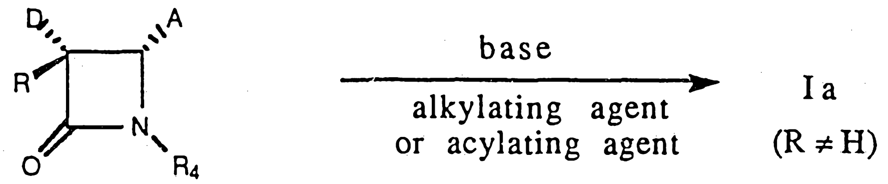
Compounds of formulae I and II can be prepared by several known methods, and in particular compounds having trans stereochemistry can be prepared by a novel method D, as disclosed in U.S. Serial No. 07/734,426, filed July 23, 1991, or novel method F.

Method A:

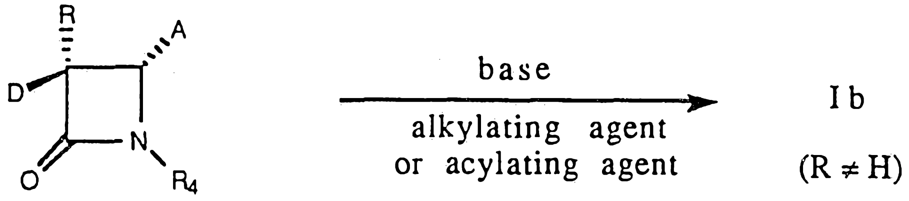


Compounds of formula Ia and Ib, wherein A, D, R and R_4 are as defined above, can be prepared by treatment of an ester of formula V, wherein R_{15} is lower alkyl such as ethyl or a chiral moiety such as menthyl or 10-(diisopropylsulfonamido)-isobornyl, with a strong base such as lithium diisopropylamide in a suitable solvent such as tetrahydrofuran (THF) at -78°C. Hexamethylphosphoric triamide (HMPA) may optionally be added as a cosolvent. An imine of formula IV is added and the reaction mixture is warmed to room temperature and the product isolated using conventional purification techniques. When a chiral ester of formula V is used, the resulting compound of formula Ia or Ib is not racemic.

Method B:



Ic (R=H)



Id (R=H)

Compounds of formula Ic or Id can be converted to compounds of formula Ia or Ib by treatment with a strong base such as lithium diisopropylamide in a suitable solvent such as THF in the presence or absence of HMPA at -78°C, followed by the addition of an alkylating agent R-R_{17}, or an acylating agent such as R-C(O)O-alkyl or R-C(O)Cl, wherein R is as defined above, except that R is not hydrogen, and R_{17} is a leaving group such as bromo or iodo.

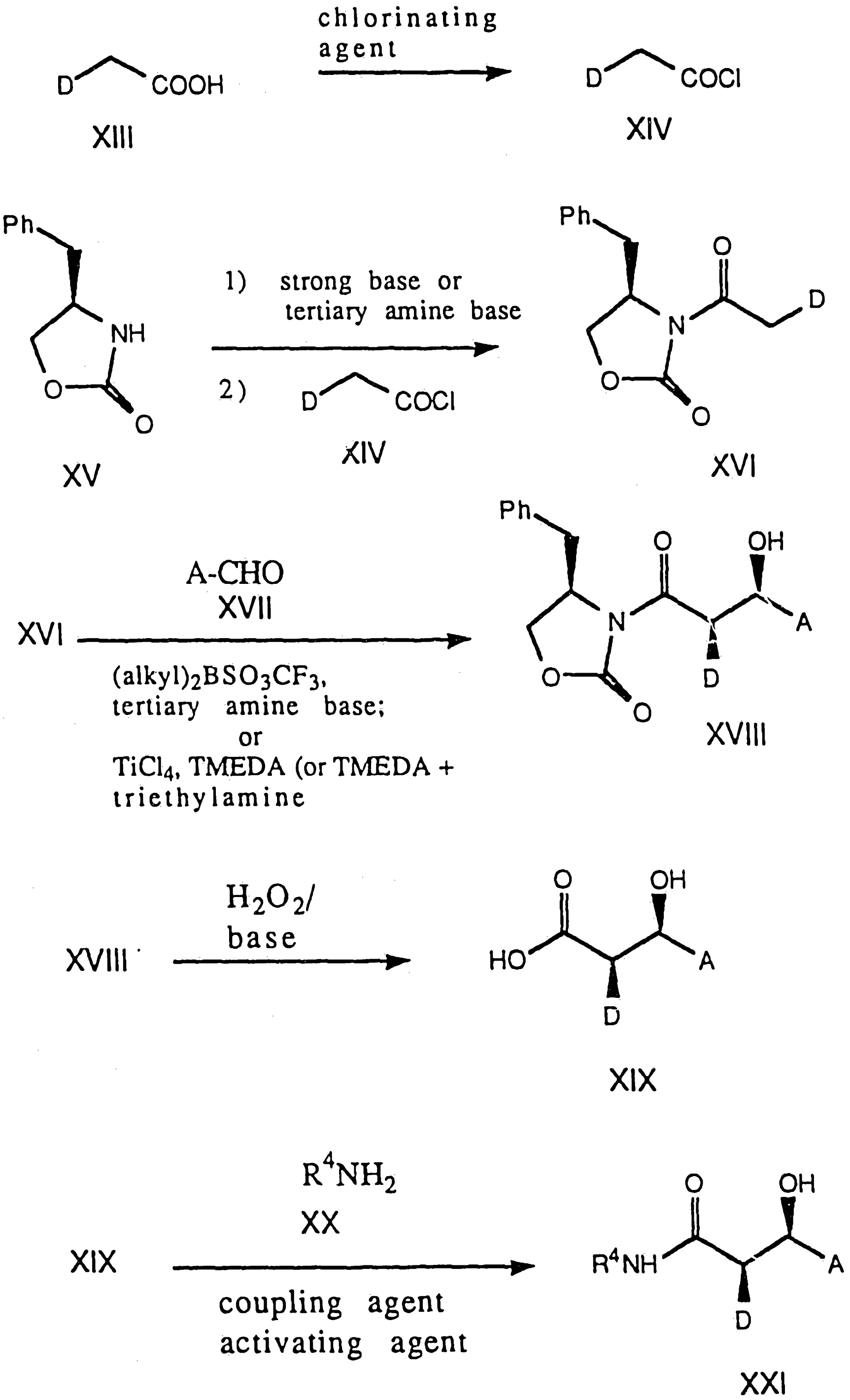
Method B':

Trans compounds of formula Id can be converted to the corresponding cis compounds of formula Ic by using Method B, above, but using a proton source such as acetic acid in place of the alkylating agent.

Method C:

Trans compounds of formula Id, wherein R is hydrogen and A, D and R_4 are as defined above can be prepared by treating cis compounds of formula Ic with a strong base such as lithium diisopropylamide or potassium t-butoxide in a suitable solvent such as THF. Those skilled in the art will appreciate that since the reaction conditions of Method C can be similar to those of Method A, the conversion of cis to trans sometimes occurs in situ under the conditions of Method A.

Method D



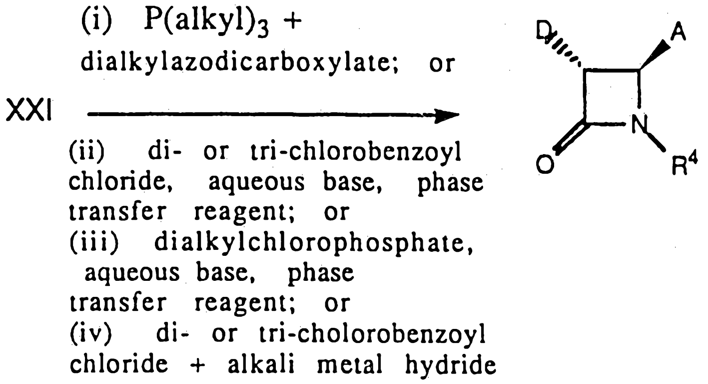
Step D1 XIII XIV

Step D2 XV XIV XVI

Step D3 XVI XVIII

Step D4 XVIII XIX

Step D5 XIX XXI



Step D6

In step D1 of Method D, the carboxylic acid XIII is treated with a chlorinating agent, e.g., thionyl chloride or oxalyl chloride, under a dry atmosphere, neat or in a suitable inert organic solvent, e.g., toluene, at 70°C to produce compound XIV.

In step D2, compound XV is converted to compound XVI in a two step reaction, first by deprotonating with a strong base, such as an alkyllithium, e.g., n-butyllithium, or metal hydride, e.g., sodium hydride, or a tertiary amine base, such triethylamine, in a suitable anhydrous organic solvent, e.g., dry THF, under a dry, inert atmosphere, e.g., nitrogen, at about 0°C to about -85°C, preferably about -78°C, over a period of about 30 to about 90 minutes, preferably about 60 minutes, and second by reacting the resulting anion, without isolation, with compound XIV in a suitable anhydrous organic solvent, e.g., dry THF, under a dry, inert atmosphere, e.g., nitrogen, at about -50°C to about -85°C, preferably about -78°C, over a period of about 30 to about 60 minutes, preferably about 45 minutes, followed by continued reaction at about -10°C to about 10°C, preferably about 0°C, for a period of about 30 to about 90 minutes, preferably about 60 minutes, then isolating the product, compound XVI, by extraction.

In step D3, compound XVI is treated with a dialkylboron triflate, e.g., di-n-butylborontriflate ($Bu_2BSO_3CF_3$), in a suitable inert organic solvent, e.g. CH_2Cl_2, under a dry, inert atmosphere, e.g., nitrogen, at about -60°C to about 10°C, preferably about -10°C to about 0°C, for a period of about 10 minutes. A tertiary amine base, e.g., diisopropylethylamine, is added at about -10°C to about 0°C, preferably about -6°C to about-3°C, for about 20 to about 40 minutes, preferably about 30 minutes. The mixture is stirred at about -50°C to about -85°C, preferably about -78°C, for about 20 to about 40 minutes, preferably about 30 minutes, then treated with compound XVII, at about -50°C to about -85°C, preferably about -78°C, for about 20 to about 40 minutes, preferably about 30 minutes. The mixture is stirred at about -10°C to about 5°C, preferably about 0°C for about 30 to about 90 minutes, preferably about 60 minutes, then quenched with an aqueous pH 7 buffer solution, e.g., an aqueous solution of KH_2PO_4 and NaOH, and treated with methanol, and hydrogen peroxide, preferably 30% hydrogen peroxide, at about -5°C to about 5°C, preferably about 0°C, for about 1 hour. The product is isolated by extraction and crystallized from a suitable solvent, e.g., hexane/ethyl acetate, to obtain compound XVIII.

Alternatively, step D3 comprises treating compound XVI with titanium tetrachloride ($TiCl_4$), in a suitable inert organic solvent, e.g. CH_2Cl_2, at about -60°C to about 0°C, preferably about -25°C to about -15°C, and most preferably at about -20°C, for a period of about 10 minutes. Tetramethylethylenediamine (TMEDA) or a combination of TMEDA and triethylamine is added slowly over a period of about 10 minutes, while maintaining the temperature at about about -25°C to about -10°C. The mixture is stirred at about -25°C to about -10°C, preferably about -15°C to about -10°C, for a period of 30 to 90 minutes, preferably about 60 minutes, then treated with a compound of the formula XVII. The mixture is stirred at about -25°C to about -10°C, preferably about -15°C to about -10°C, for a period of 30 to 90 minutes, preferably about 60 minutes, then stirred for 30 to 60 minutes, preferably about 40 minutes, while warming to about 0°C to about 10°C, preferably about 10°C. The mixture is quenched with an aqueous solution of tartaric acid, preferably a solution of about 10% tartaric acid in water. The product is then isolated by extraction with a suitable solvent, e.g. ethyl acetate, and recrystallized from a suitable solvent, such as ethyl actetate/hexane, to obtain compound XVIII.

In step D4, compound XVIII is treated with hydrogen peroxide, preferably 30% hydrogen peroxide, in a inert organic solvent, e.g., THF/ water, at about -5°C to about 5°C, preferably about 0°C, for about 10 to about 20 minutes, preferably about 15 minutes, then treated with a base, e.g., lithium hydroxide, at about -5°C to about 5°C, preferably about 0°C, until no starting material remains, as determined by thin layer chromatography (TLC), in about 2 hours to about 4 hours, preferably about 3 hours. The excess peracid is reduced by slowly adding a solution of sodium sulfite in water to the mixture over a period of about 30 to about 90 minutes, preferably about 70 minutes. The bulk of the solvent is removed under vacuum and the residue diluted with water. Compound IV is recovered from the mixture by extraction with a suitable inert organic solvent, e.g., toluene. The remaining aqueous solution is acidified to a pH of about 2.0 to about 3.0, preferably pH of about 2.4, using hydrochloric acid. The product is isolated by extraction using a suitable inert organic solvent, e.g., ethyl acetate, to provide compound XIX.

In step D5, compound XIX is reacted with compound XX, a dehydrative coupling agent, e.g., dicyclohexylcarbodiimide (DCC), and an activating agent, e.g., 1-hydroxybenzotriazole (HOBT), in a suitable inert organic solvent, e.g., dimethylformamide or acetonitrile, at about 25°C to about 50°C, preferably about 40°C. The reaction is continued until the starting material is consumed, as determined by TLC, in about 4 hours. The product is isolated by extraction to obtain compound XXI.

In step D6, compound XXI is cyclized by treating with triphenylphosphine or preferably a trialkylphosphine, e.g., tri-n-butylphosphine, and a dialkylazodicarboxylate, e.g., diethylazodicarboxylate (DEAD), in a suitable anhydrous organic solvent, e.g., dry THF, under a dry, inert atmosphere, e.g. nitrogen, at about -50°C to about -85°C, preferably about -70°C, for about 1 to about 3 hours, preferably about 2 hours. The reaction is then continued at about room temperature for about 12 to about 24 hours. The product is purified by preparative high performance liquid chromatography (HPLC) to obtain a compound of formula I, having trans relative stereochemistry. The use of tributylphosphine in this step gives reaction yields significantly higher than the yields obtained using triphenylphosphine.

Alternatively, step D6 comprises combining compound XXI and a suitable phase transfer catalyst, e.g. tetra-n-butylammonium hydrogen sulfate, in a suitable solvent, such as methylene chloride. The mixture is stirred while cooling to about 0°C to 20°C, preferably about 10°C to about 20°C, then treated with an aqueous base, such as an alkali metal hydroxide, preferably 50% aqueous sodium hydroxide. A di- or tri-chlorobenzoyl chloride, preferably 2,6-dichlorobenzoyl chloride or 2,4,6-trichlorobenzoyl chloride, is slowly added over a period of 20 to 60 minutes, preferably about 30 minutes. The mixture is stirred at about 0°C to about 25°C, preferably about 15°C to about 20°C, for a period of 2 to 4 hours, preferably about 3 hours, then poured into cold water. The organic layer is separated and washed with water to neutral pH. The di- or tri-chlorobenzoate product is isolated by crystallization from methylene chloride/heptane. The di- or tri-chlorobenzoate product is combined with a suitable phase transfer catalyst, e.g benzyltriethylammonium chloride, in a suitable solvent, such as a mixture methylene chloride and methyl t-butyl ether. The mixture is stirred at about 0°C to about 25°C, preferably about 15°C to about 20°C, and treated with an aqueous base, e.g. an alkali metal hydroxide, preferably 50% aqueous sodium hydroxide. After stirring for a period of 2 to 6 hours, preferably about 4 hours, the mixture is poured into ice water. The organic layer is washed with water to neutral pH. The product is isolated by removing the solvent, then purified by chromatography and recrystallization from a suitable solvent to give a compound of formula I, having trans relative stereochemistry.

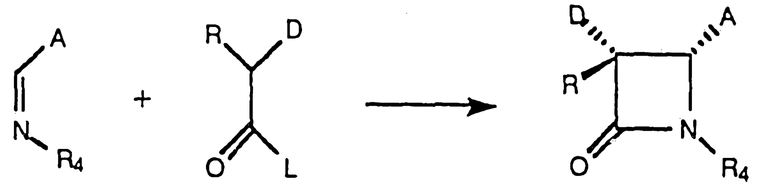
A third alternative for step D6 comprises treating compound XXI in a suitable solvent, such as CH_2Cl_2, with a dialkylchlorophosphate, preferably diethylchlorophosphate, and an aqueous base, such as an alkali metal hydroxide, preferably 50% aqueous sodium hydroxide, in the presence of phase transfer catalyst, such as tetra-n-butylammonium hydrogen sulfate or benzyltriethylammonium chloride.

Another alternative for step D6 comprises treating compound XXI with a di- or tri-chlorobenzoyl chloride, preferably 2,6-

dichlorobenzoyl chloride or 2,4,6-trichlorobenzoyl chloride, and a suitable base, such as sodium hydride in a suitable solvent, such as CH_2Cl_2, dimethylformamide, or a combination thereof. The product is isolated and purified by chromatography followed by crystallization from a suitable solvent, e.g. ether/hexane.

Starting compounds XIII, XV, XVII, and XX are all either commercially available or well known in the art and can be prepared via known methods.

Method E:



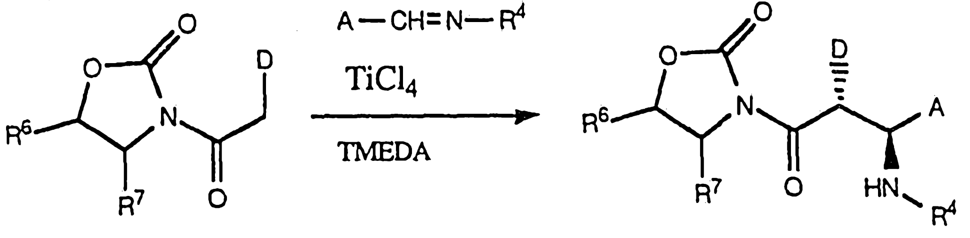
IV XII Ia

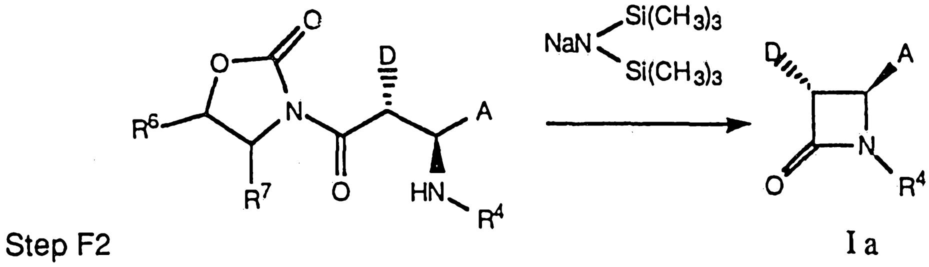
Compounds of formula Ia can also be prepared by treatment of an imine of formula IV with an activated carboxylic acid derivative of formula XII in the presence of a base such as triethylamine, tributylamine or diethylisopropylamine in an inert solvent such as CH_2Cl_2, heptane or toluene. Examples of activated carboxylic acid derivatives of formula XII include acid chlorides (L=Cl), mixed anhydrides formed with phenyl phosphorodichloridate (L=OP(O)(Cl)OPh), and N-methylpyridinium esters formed from the reaction of an acid with N-methyl-2-chloropyridinium iodide (L=2-oxy-N-methylpyridinium iodide).

Starting materials of formulae IV and V are known or can be prepared by methods well known in the art.

Method F:

Step F1





Step F2

I a

In step F1, compound XVI (from Method D, step 2) is dissolved in a suitable solvent, e.g. methylene chloride, then treated with titanium tetrachloride at about -60°C to about 0°C, preferably about -25°C to about -15°C, under a dry, inert atmosphere, preferably nitrogen, for a period of about 5 min. TMEDA is added and the mixture stirred at about -60°C to about -10°C, preferably about -25°C to about -20°C, for a period of about 1 hour. The imine (A-CH=N-R^4) is slowly over a period of 20 to 40 min., preferably about 30 min., and the mixture is stirred at about -60°C to about 0°C, preferably about -25°C to about -15°C, for 20 to 40 min., preferably about 30 min. The mixture is then warmed to about 0°C and the reaction monitored by high pressure liquid chromatography (HPLC) until complete. The mixture is then poured into a solution of tartaric acid in water, preferably 10% tartaric acid. The product is isolated by extraction with a suitable solvent, e.g. ethyl acetate, then purified by crystallization.

In step F2, the product of step F1 is treated with a strong non-nucleophilic base, such as sodium or lithium bistrimethylsilylamide, in a suitable inert organic solvent, e.g. CH_2Cl_2, at about -20°C to about 10°C, preferably about 0°C. The mixture is stirred while gradually warming to about 20° to about 25°C, then monitored by HPLC until the starting material is gone, typically after a period of 1 to 2 hours. The reaction mixture is poured into aqueous tartaric acid, preferably 10% tartaric acid, and the product isolated from the organic layer.

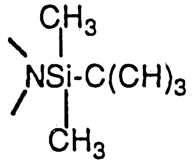
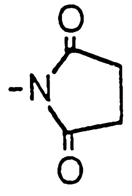
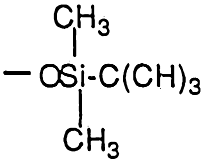
Imines of the formula A-CH=N-R^4 can be prepared from aldehydes of the formula A-CHO and amines of the formula R^4-NH_2 by procedures well known in the art. Aldehydes of formula A-CHO and amines of formula R^4-NH_2 are commercially available or can be prepared via known procedures.

Compounds of formula II can be prepared by methods similar to those described for compounds of formula I.

It will also be apparent to those skilled in the art, and by reference to the examples which follow, that compounds of formulae I and II can be converted into different compounds of formula I or II by well known methods. For example, a compound of formula I wherein A comprises a double or triple bond, or a compound of formula II wherein G comprises a double or triple bond can be converted to the corresponding saturated compound by treatment with hydrogen gas in the presence of a catalyst such as palladium or platinum on carbon.

Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following Table 3 shows some typical protecting groups:

Table 3

Group to be Protected	Group to be Protected and Protecting Group
$-COOH$	$-COO$alkyl, $-COO$benzyl, $-COO$phenyl
$>NH$	$>NCO$alkyl, $>NCO$benzyl, $>NCO$phenyl, $>NCH_2OCH_2CH_2Si(CH_3)_3$, $>NC(O)OC(CH_3)_3$, $>N$-benzyl, $>NSi(CH_3)_3$,  $>NSi(CH_3)_2$-$C(CH)_3$
$-NH_2$	
$-OH$	$-OCH_3$, $-OSi(CH_3)_3$,  $-OSi(CH_3)_2$-$C(CH)_3$

We have found that the compounds of this invention lower serum lipid levels, in particular serum cholesterol levels. Compounds of this invention have been found to inhibit the intestinal absorbtion of cholesterol and to significantly reduce the formation of liver cholesteryl esters in animal models. Some compounds also inhibit ACAT in vitro. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the esterification and/or intestinal absorption of cholesterol; they are therefore useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

In addition to the compound aspect, the present invention therefore also relates to a method of lowering serum cholesterol levels, which method comprises administering to a mammal in need of such treatment a hypocholesterolemic effective amount of a compound of formula I or II of this invention. The compound is preferably administered in a pharmaceutically acceptable carrier suitable for oral administration.

The in vitro and in vivo activity of the compounds of formulae I or II can be determined by the following procedures.

ACAT Assay (in vitro)

This assay measures the activity of ACAT by measuring the ACAT-mediated transfer of tritiated oleic acid from acyl-CoA to cholesterol to give labelled cholesteryl oleate. Rat liver microsomes are used as the source of ACAT. Assays are performed in round bottom microtiterplates using a total incubation volume of 50 µL. Each incubation well receives 10 µL assay buffer (0.5M $KHPO_4$, 10 µM dithiothreitol, pH 7.4), 7.5 µL of 40 mg/mL BSA (Bovine Serum Albumin) and 12.5 µg of microsomal protein. The test compound (in sufficient amount to bring the final concentration to from 0.1 to 25 µM), reference compound, or vehicle control is added and the final volume brought to 47 µL. The microtiterplate is then floated on the surface of a 37°C water bath for fifteen minutes. Incubations are started by the addition of 3 µL ^{3}H-acyl CoA (1µCi/well, final concentration of 10 µM acyl CoA). The plate is then returned to the water bath for 15 minutes. The incubations are then terminated by application of 15 µL from each incubation to individual lanes on a thin layer plate (Silica Gel GF 20 x 20 cm). Standards are applied to several lanes so that the cholesteryl ester band can be identified. After drying, the plates are eluted with 90:10:1 petroleum ether:diethyl ether:acetic acid. The standards are visualized via iodine vapor, and the regions corresponding to cholesteryl ester are scraped into 7 mL scintillation vials. 4 mL of scintillant are added to each vial, and the radioactivity quantified. Background count is determined by the boiled controls. Full activity is determined by activity in the presence of vehicle. The percent inhibition is calculated by subtracting the background from both control and test samples, and the test value is calculated as a percentage of the control. For IC_{50} determinations, the inhibition is plotted against drug does on a log scale and the concentration at which 50% inhibition is obtained is determined.

In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster

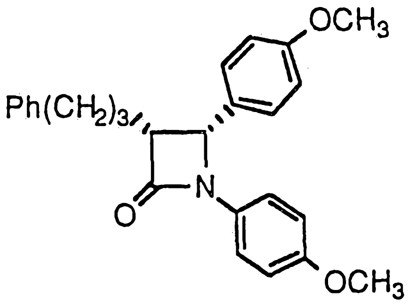
Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by IM injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I or II of this invention and a pharmaceutically acceptable carrier. The compounds of formula I or II can be administered in any conventional oral dosage form such as capsules, tablets, powders, cachets, suspensions or solutions. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesteremic dose of a compound of formula I or II is about 7 to about 30 mg/kg of body weight per day. For an average body weight of 70kg, the dosage level is therefore from about 500 to about 2000 mg of drug per day, given in a single dose or 2-4 divided doses . The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

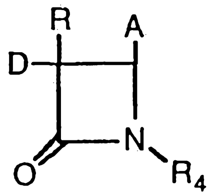
Following are examples of preparing compounds of formulae I and II. The stereochemistry listed is relative stereochemistry unless otherwise noted. The terms cis/trans refer to the relative orientations at the beta-lactam 3- and 4- positions when each is mono-substituted (i.e.. R=H).

EXAMPLE 1



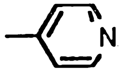
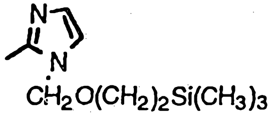
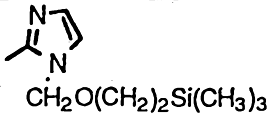
Freshly prepare lithium diisopropyl amide (LDA) by dissolving 23.96mL (17.39g, 172mmol) diisopropylamine in 230mL dry THF at -78°C under nitrogen. Add 103.9mL (166 mmol @ 1.6M in hexanes) of *n*-butyl lithium and stir at -78°C for 1h. To this cold solution add 32.58g (158mmol) of 5-phenyl valeric acid ethyl ester in 195mL dry THF over ~1h, keeping the reaction temperature below -65°C. Stir for 1h at -78°C, then add 38.13g (158mmol) of 4-methoxybenzylidine anisidine in 350mL dry CH_2Cl_2. Allow the reaction to slowly come to room temperature and the precipitate that forms will begin to go into solution. Stir the reaction mixture for 16h at room temperature. Partition the mixture between 1.2liter of 1N aqueous hydrochloric acid (HCl) and 1liter of ether. Wash the ether layer with 300 mL 1N HCl. Combine the acid layers and extract with 1 liter of ether. Combine the ether extracts, dry over $MgSO_4$ and concentrate in vacuo. Crystallize the residue (35.08g, 55%) from ~200mL ethyl acetate-hexane (1:1) to give 32.05g of the title racemic compound as an off-white crystal, mp = 90-93°C.

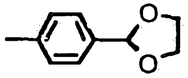
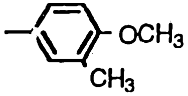
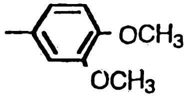
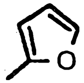
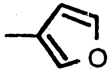
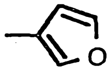
Using a similar procedure, the following compounds shown in Tables 4 and 4A can also be prepared:

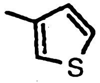


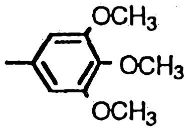
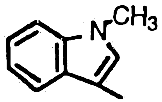
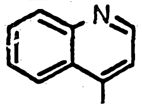
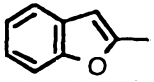
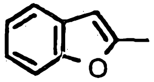
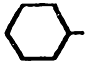
Ex.	D	R	A	Relative Stereo-chemistry	R_4	Data
1A	C_6H_5-$CH_2C(O)$-	C_6H_5-	C_6H_5-	3R,4S	p-MeO-C_6H_4-	mp=120.5-122.0°C
1B	C_6H_5-$(CH_2)_3$-	H	C_6H_5-	3R,4R	p-MeO-C_6H_4-	mp=120.5-121.5°C
1C	C_6H_5-$(CH_2)_3$-	H	C_6H_5-	3S,4R	p-MeO-C_6H_4-	mp=92.0-92.5°C
1D	C_6H_5-$(CH_2)_2$-	H	C_6H_5-	3S,4S	p-MeO-C_6H_4-	mp=151-152°C
1E	C_6H_5-$(CH_2)_2$-	H	C_6H_5-	3S,4R	p-MeO-C_6H_4-	mp=156-158°C
1F	C_6H_5-$(CH_2)_3$-	H	C_6H_5-	4:1 cis to trans	2,4,6-tri-MeO-C_6H_4-	CI MS: (M+1)432
1G	C_6H_5-$(CH_2)_3$-	H	p-NO_2-C_6H_4-	3S,4R	p-MeO-C_6H_4-	mp=116-117°C
1H	C_6H_5-$(CH_2)_3$-	H	p-NO_2-C_6H_4-	3R,4R	p-MeO-C_6H_4-	mp=120.5-122.0°C
1I	C_6H_5-$(CH_2)_3$-	CH_3CH_2-	-C_6H_5CH=CH-	3S,4S	2,4,6-tri-MeO-C_6H_4-	FAB MS: (M+1)486.2
1J	C_6H_5-$(CH_2)_3$-	CH_3CH_2-	C_6H_5-CH=CH-	3R,4S	2,4,6-tri-MeO-C_6H_4-	FAB MS: (M+1)486.2

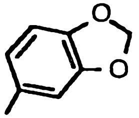
1K	$C_6H_5-(CH_2)_3-$	H	$C_6H_5-CH=CH-$	3S,4S	p-MeO-C_6H_4-	mp=119.5-120.5°C
1L	$C_6H_5-(CH_2)_3-$	H	p-OH-C_6H_4-	3S,4S	p-MeO-C_6H_4-	mp=152.5-155.0°C
1M	$C_6H_5-(CH_2)_3-$	H	p-MeO-C_6H_4- CH=CH-	3S,4S	p-MeO-C_6H_4-	mp=86-88°C
1P	$C_6H_5-(CH_2)_3-$	H	3-MeO-C_6H_4-	3S,4S	p-MeO-C_6H_4-	mp=90.5-91.0°C
1AM	$C_6H_5-(CH_2)_3-$	H	p-MeO-C_6H_4-	trans	3-pyridyl-	1H NMR (CDC13) δ 8.41 (s,1H), 8.28(s, 1H), 7.79(d, 1H), 7.20(m, 8H), 6.90(d, 2H), 4.63(s, 1H), 3.80(s, 3H), 3.20(t, 1H), 1.85(m, 4H)
1AN	$C_6H_5-(CH_2)_3-$	H	p-MeO-C_6H_4-	trans	p-CF_3O-C_6H_4-	elemental analysis: calc'd C=68.56, H=5.31, N=3.08; found C=68.32, H=5.12, N=2.97
1AO	$C_6H_5-(CH_2)_3-$	H	4-MeO-C_6H_4-	cis	p-Cl-C_6H_4-	elemental analysis: calc'd C=73.97, H=5.96, N=3.45, Cl=8.73; found C=73.63, H=5.92, N=3.52, Cl=9.12

1AP	C_6H_5-$(CH_2)_3$-	H	4-MeO-C_6H_4-	cis	p-CH_3-C_6H_4-	elemental analysis: calc'd C=81.01, H=7.06, N=3.63; found C=80.97, H=7.06, N=3.74
1AQ	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	cis	p-C_6H_5O-C_6H_4-	elemental analysis: calc'd C=80.32, H=6.31, N=3.02; found C=80.26, H=6.27, N=3.18
1AR	C_6H_5-$(CH_2)_3$-	H		trans	p-CH_3O-C_6H_4-	mp=101.5-102.5°C
1AS	C_6H_5-$(CH_2)_3$-	H	$(CH_3)_3CSi(CH_3)_2$-OCH_2-C_6H_4-	trans	p-CH_3O-C_6H_4-	EIMS (M+1)=516
1AT	C_6H_5-$(CH_2)_3$-	H	$(CH_3)_3CSi(CH_3)_2$-OCH_2-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=84-85°C
1AU	C_6H_5-$(CH_2)_3$-	H	4-CH_3S-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=103-104°C
1AV	C_6H_5-$(CH_2)_3$-	H		trans	p-CH_3O-C_6H_4-	FABMS (M+1)=492
1AW	C_6H_5-$(CH_2)_3$-	H		cis	p-CH_3O-C_6H_4-	mp=108.5-110°C

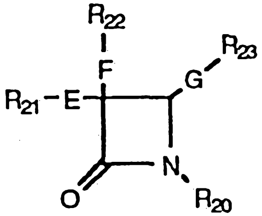
1AX	C_6H_5-$(CH_2)_3$-	H			p-CH_3O-C_6H_4-	EIMS (M)=443
1AY	C_6H_5-$(CH_2)_3$-	H	4-(($(CH_3)_2CH$-O)-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=96-97°C
1AZ	C_6H_5-$(CH_2)_3$-	H	4-($CH_3(CH)_2$-O)-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=96-97°C
1BA	C_6H_5-$(CH_2)_3$-	H		cis	p-CH_3O-C_6H_4-	mp=91.5-92.5°C
1BB	C_6H_5-$(CH_2)_3$-	H		cis	p-CH_3O-C_6H_4-	mp=86.0-87.0°C
1BC	C_6H_5-$(CH_2)_3$-	H		cis	p-CH_3O-C_6H_4-	mp=130.0-131.0°C
1BD	C_6H_5-$(CH_2)_3$-	H		trans	p-CH_3O-C_6H_4-	mp=111.0-112.5°C
1BE	C_6H_5-$(CH_2)_3$-	H		cis	p-CH_3O-C_6H_4-	mp=74.5-75°C
1BF	C_6H_5-$(CH_2)_3$-	H		trans	p-CH_3O-C_6H_4-	mp=79.5-80.5°C
1BG	C_6H_5-$(CH_2)_3$-	H	4-CF_3-C_6H_4-	trans	p-CH_3O-C_6H_4-	mp=94.5-96.0°C
1BH	C_6H_5-$(CH_2)_3$-	H	4-CF_3-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=114.0-115.5°C

1BI	C_6H_5-$(CH_2)_3$-	H		cis	p-CH_3O-C_6H_4-	mp=117-120°C
1BJ	C_6H_5-$(CH_2)_3$-	H		cis	p-CH_3O-C_6H_4-	mp=88.5-90.5°C
1BK	C_6H_5-$(CH_2)_3$-	H	3-CF_3O-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=66.0-68.0°C
1BL	C_6H_5-$(CH_2)_3$-	H	3-CF_3O-C_6H_4-	trans	p-CH_3O-C_6H_4-	CI MS (M+1)=456.2
1BM	C_6H_5-$(CH_2)_3$-	H	4-CH_3-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=124-125°C
1BN	C_6H_5-$(CH_2)_3$-	H	4-(C_6H_5-CH_2-O)-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=131-132°C
1BO	C_6H_5-$(CH_2)_3$-	H	CH_3CH_2-O-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=84-85°C
1BP	C_6H_5-$(CH_2)_3$-	H		trans	p-CH_3O-C_6H_4-	mp=68-70°C
1BQ	C_6H_5-$(CH_2)_3$-	H		trans	p-CH_3O-C_6H_4-	mp=50-52°C
1BR	C_6H_5-$(CH_2)_3$-	H	$CH_3(CH_2)_3$-O-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=71.0-72.5°C
1BS	C_6H_5-$(CH_2)_3$-	H	4-(C_6H_5-O)-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=108-109°C
1BT	C_6H_5-$(CH_2)_3$-	H	4-(C_6H_5)-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=127.5-128.5°C
1BU	C_6H_5-$(CH_2)_3$-	H	4-(CH_2=CH-CH_2-O)-C_6H_4-	cis	p-CH_3O-C_6H_4-	mp=77.0-77.5°C

1BV	$C_6H_5-(CH_2)_3-$	H		cis	p-$CH_3O-C_6H_4-$	mp=116-117°C
1BW	$C_6H_5-(CH_2)_3-$	H		cis	p-$CH_3O-C_6H_4-$	mp=129.5-130.5°C
1BX	$C_6H_5-(CH_2)_3-$	H		cis	p-$CH_3O-C_6H_4-$	mp=170.0-170.5°C
1BY	$C_6H_5-(CH_2)_3-$	H	4-$(CH_3CH_2-O)-C_6H_4-$	cis	C_6H_5-	mp=89.5-90.0°C
1BZ	$C_6H_5-(CH_2)_3-$	H		cis	p-$CH_3O-C_6H_4-$	mp=100-104°C
1CA	$C_6H_5-(CH_2)_3-$	H		trans	4-$CH_3O-C_6H_4-$	mp=91-92°C
1CB	$C_6H_5-(CH_2)_3-$	H	4-$CH_3O-C_6H_4-$	cis	$(CH_3)_3CSi(CH_3)_2-$ $O-C_6H_4-$	mp=93-94°C
1CC	$C_6H_5-(CH_2)_2-$	H	4-$CH_3O-C_6H_4-$	cis	4-$CH_3O-C_6H_4-$	mp=128-129°C
1CD	$C_6H_5-O-(CH_2)_2-$	H	4-$CH_3O-C_6H_4-$	cis	4-$CH_3O-C_6H_4-$	mp=120-121°C
1CE	$C_6H_5-(CH_2)_6-$	H	4-$CH_3O-C_6H_4-$	cis	4-$CH_3O-C_6H_4-$	mp=80-81°C
1CF	 $-(CH_2)_3-$	H	4-$CH_3O-C_6H_4-$	cis	4-$CH_3O-C_6H_4-$	mp=101-102°C

1CG	4-F-C_6H_4-O-$(CH_2)_2$-	H	4-CH_3O-C_6H_4-	cis	4-CH_3O-C_6H_4-	elemental analysis: calc'd C=71.25, H=5.74, N=3.32; found C=71.34, H=5.73, N=3.43
1CH	4-F-C_6H_4-O-$(CH_2)_2$-	H	4-CH_3O-C_6H_4-	cis	C_6H_5-	elemental analysis: calc'd C=73.64, H=5.67, N=3. ; found C=73.39, H=5.51, N=3.54
1CI	C_6H_5-$(CH_2)_4$-	H	4-CH_3O-C_6H_4-	cis	4-CH_3O-C_6H_4-	elemental analysis: calc'd C=78.04, H=7.03, N=3.37; found C=77.69, H=6.98, N=3.60
1CM	C_6H_5-$(CH_2)_3$-	H	4-CH_3S-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=104-105.5°C
1CN	C_6H_5-$(CH_2)_3$-	H		cis	4-CH_3O-C_6H_4-	mp=144.0-144.5°C
1CO	C_6H_5-$(CH_2)_3$-	H	4-($(CH_3)_2N$-$(CH_2)_3$-O)-C_6H_4-	cis	4-CH_3O-C_6H_4-	mp=92-94°C

1CP	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	cis	C_6H_5-	elemental analysis: calc'd C=80.83, H=6.78, N=3.77; found C=80.69, H=6.78, N=3.90

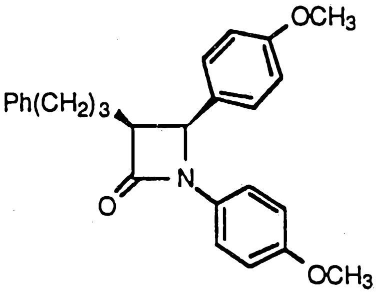


Ex.	R_{21}-E-	R_{22}-F-	R_{23}-G-	R_{20}	Rel. Stereo-chemistry	Data
1S	$C_{10}H_{21}$-	H	C_6H_5-	p-MeO-C_6H_4-	3R,4R	mp=176.0-177.0°C
1T	$C_{10}H_{21}$-	H	C_6H_5-	p-MeO-C_6H_4-	3S,4R	mp=83.5-84.0°C
1U	$C_{10}H_{21}$-	H	C_6H_5-	2,4,6-tri-MeO-C_6H_4-	3R,4R 3.6:1 cis/trans	
1V	H	C_6H_5-	C_6H_5-	p-MeO-C_6H_4-	3R,4S	mp=158.5-159.0°C
1W	H	i-Pr	C_6H_5-	p-MeO-C_6H_4-	3R,4R	mp=162-164°C
1X	C_6H_5-CH_2-	C_6H_5-	C_6H_5-	p-MeO-C_6H_4-	3S,4S	mp=185.0-186.0°C
1Y	C_6H_5-CH_2-	C_6H_5-	C_6H_5-	p-MeO-C_6H_4-	3R,4S	mp=123.0-124.5°C

1Z	CH_3CH_2-	C_6H_5-	C_6H_5-	p-MeO-C_6H_4-	3S,4S	mp=101.0-102.5°C
1AA	CH_3CH_2-	C_6H_5-	C_6H_5-	p-MeO-C_6H_4-	3R,4S	mp=73.5-75.0°C
1AB	H	CH_3CH_2-	C_6H_5-	p-MeO-C_6H_4-	3R,4R	mp=134.0-135.5°C
1AC	cyc-C_5H_{11}	C_6H_5-	C_6H_5-	p-MeO-C_6H_4-	8:5 mix cis/trans phenyl	mp=57.5-62.5°C
1AD	H	CH_3CH_2-	C_6H_5-	p-MeO-C_6H_4-	3R,4S	mp=107-109°C
1AE	H	CH_3CH_2-	C_6H_5-	2,4,6-tri-MeO-C_6H_4-	3R,4R	CI MS: (M+1)342
1AF	H	CH_3CH_2-	C_6H_5-CH=CH-	p-MeO-C_6H_4-	3R,4S	FAB MS:(M+1)307.9
1AG	H	CH_3CH_2-	C_6H_5-CH=CH-	p-MeO-C_6H_4-	3S,4S	mp=84-86°C
1AH	H	CH_3-	C_6H_5-	p-MeO-C_6H_4-	3S,4S	mp=122-123°C
1AI	H	CH_3-	C_6H_5-	p-MeO-C_6H_4-	3S,4R	mp=93-94°C
1AJ	H	CH_3CH_2-	p-NO_2-C_6H_4-	p-MeO-C_6H_4-	3S,4R	mp=115-116°C
1AK	H	CH_3CH_2-	4-NO_2-C_6H_4-	4-MeO-C_6H_4-	3R,4R	mp=101-102°C
1AL	H	CH_3CH_2-	4-MeO-C_6H_4-	4-MeO-C_6H_4-	3S,4S	mp=96-103°C

1CJ	$(CH_3)_2$-N-	H	4-MeO-C_6H_4-	C_6H_5-	cis	mp=115-117°C
1CK	C_6H_5-	CH_3CH_2-	4-MeO-C_6H_4-	4-MeO-C_6H_4-	trans	mp=56-58°C
1CL	$C_{10}H_{21}$-	H	4-MeO-C_6H_4-	4-MeO-C_6H_4-	cis	elem. anal.: calc'd C=76.56, H=8.80, N=3.31; found C=76.60, H=8.77, N=3.48

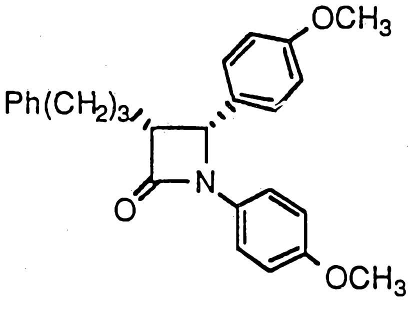
EXAMPLE 2



STEP 1: Add 39.1mL (117.2 mmol) of ethyl magnesium bromide to a 0°C solution of 31.00g (97.6 mmol) of (-)-10-(diisopropylsulfonamido)-isoborneol (See Oppolzer, et al, Tet. Lett., 25 (1984), p. 5885) in 370mL dry THF. Stir the mixture for 0.5h at 0°C, then at room temperature for 0.5h. Add 37.74mL (39.67g, 117.2mmol) of 5-phenylvaleric acid anhydride to this mixture at 0°C and stir overnight at room temperature. Pour the mixture into 1liter of half-saturated $NaHCO_3$ and extract with two-800mL portions of hexane. Dry the combined hexane layers with Na_2SO_4 and concentrate in vacuo. Chromatograph the residue (57.35g) in three portions over ~800g SiO_2 eluting with 2% ethyl acetate-CH_2Cl_2 to obtain the desired ester (42.07g, 90.2%), FAB MS : (M+1) 479.

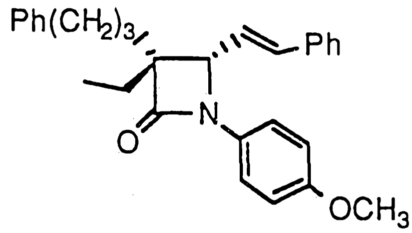
STEP 2: Using a procedure similar to Example 1, treat the ester of Step 1, washing the ether layer with 200mL 1N aqueous HCl, drying with $MgSO_4$ and concentrating in vacuo. Chromatograph the residue over 1kg SiO_2, eluting with 20% ethyl acetate-hexane to give 24.19g (79%) of the recovered alcohol and 25.66 (66%) of the title enantiomerically enriched β-lactam. This lactam can be further enriched by chromatography over a Chiralcel™ OD column (Daicel Chemical Industries, Ltd., Fort Lee, NJ), eluting with 10% isopropanol-hexanes. Crystallize the resulting enantiomerically pure (3S,4S) compound from ether-hexane to obtain a white solid, mp = 84 - 85°C, $[\alpha]_D^{25} = -98.0^\circ$ (MeOH).

Using a similar procedure, the following enantiomerically pure (3R,4R) compound (EXAMPLE 2A) can also be prepared:



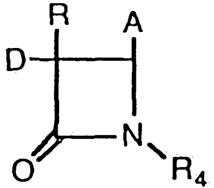
(m.p. = 84-85°C; FAB MS: (M+1) 402.2; $[\alpha]_D^{25} = +98.0°$ (MeOH)).

EXAMPLE 3



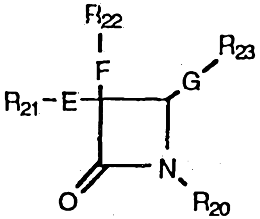
Freshly prepare a solution of lithium isopropylcyclohexyl amide (LICA) by dissolving 0.68mL (0.58g, 4.11mmol) isopropylcyclohexyl amine in 20mL THF at -78°C under nitrogen. Add 2.58mL (4.03mmol) *n*-butyl lithium (1.6M, from Aldrich, Milwaukee, WI) and stir at -78°C for 1h. Add 1.04g (2.61mmol) of the compound of Example 1K in 5mL dry THF to the solution. After 2h at -78°C, add 2.8mL (2.89g, 16mmol) of hexamethylphosphoric triamide followed by 0.33mL (641mg, 4.11mmol) of ethyl iodide at -78°C. Stir the mixture overnight at room temperature. Quench the reaction with 40mL 1N aqueous HCl and extract with two-50mL portions of CH_2Cl_2. Combine the CH_2Cl_2 layers and wash sequentially with 50mL 1N aqueous HCl and 50mL Na_2SO_3. Dry over $MgSO_4$ and concentrate in vacuo. Chromatograph the residue over 40g SiO_2, eluting with 20% ethyl acetate-hexane to give 0.95g (83%) of the title compound as a colorless oil, FAB MS : (M+1) 426.4

Using a similar procedure, the following compounds shown in Tables 5 and 5Acan also be prepared:



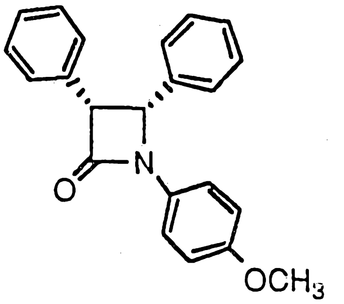
Ex.	D	R	A	Relative Stereo-chemistry	R_4	Data
3A	C_6H_5-$(CH_2)_3$-	CH_3CH_2-	C_6H_5-	3S,4S	p-MeO-C_6H_4-	mp=103.0-103.5°C
3B	C_6H_5-$(CH_2)_3$-	C_6H_5-	C_6H_5-	3R,4S	p-MeO-C_6H_4-	FAB MS: (M+1) 448
3C	C_6H_5-$(CH_2)_3$-	$C_{10}H_{21}$-	C_6H_5-	3S,4R	p-MeO-C_6H_4-	CI MS: (M+1) 512
3D	C_6H_5-$(CH_2)_3$-	CH_3CH_2-	C_6H_5-	3S,4S	2,4,6-tri-MeO-C_6H_4-	mp=145.5-147.0°C
3E	C_6H_5-$(CH_2)_3$-	CH_3CH_2-	C_6H_5-	3R,4S	p-MeO-C_6H_4-	mp=82.5-83.5°C
3F	C_6H_5-$(CH_2)_3$-	CH_3CH_2-	C_6H_5-	3R,4S	2,4,6-tri-MeO-C_6H_4-	mp=132-134°C
3G	C_6H_5-$(CH_2)_3$-	CH_3CH_2-	C_6H_5-CH=CH-	3S,4S	p-MeO-C_6H_4-	mp=98-99°C
3H	C_6H_5-$(CH_2)_2$-	CH_3CH_2-	C_6H_5-	3R,4S	p-MeO-C_6H_4-	mp=100.0-100.5°C
3I	C_6H_5-$(CH_2)_2$-	CH_3-	C_6H_5-	3R,4S	p-MeO-C_6H_4-	mp=130-131°C

Ex.	D	R	A	Relative Stereo-chemistry	R_4	Data
3J	C_6H_5-$(CH_2)_3$-	CH_3-	C_6H_5-	3S,4S	p-MeO-C_6H_4-	mp=88-89°C
3K	C_6H_5-$(CH_2)_4$-	CH_3-	C_6H_5-	3S,4S	p-MeO-C_6H_4-	mp=109-110°C
3L	C_6H_5-$(CH_2)_4$-	CH_3CH_2-	C_6H_5-	3S,4S	p-MeO-C_6H_4-	mp=95-96°C
3M	C_6H_5-$(CH_2)_3$-	CH_3CH_2-	p-MeO-C_6H_4-	3R,4S	p-MeO-C_6H_4-	FAB MS: (M+1) 430.4
3N	C_6H_5-$(CH_2)_3$-	C_6H_4-$(CH_2)_3$-	C_6H_5-CH=CH-	racemic	p-MeO-C_6H_4-	FAB MS: (M+1) 516.4
3O	C_6H_5-$(CH_2)_3$-	CH_3CH_2-	p-MeO-C_6H_4-	3S,4S	p-MeO-C_6H_4-	FAB MS: (M+1) 430.4



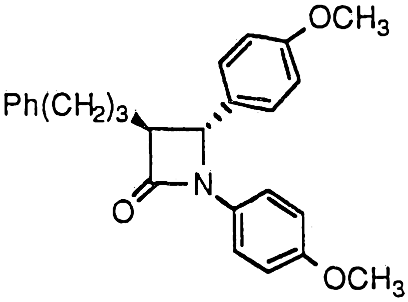
Ex.	R_{21}-E-	R_{22}-F-	R_{23}-G-	Rel. Stereo-chemistry	R_{20}	Data
3Q	$C_{10}H_{21}$-	CH_3CH_2-	C_6H_5-	3S,4S	p-MeO-C_6H_4-	mp=47.5-48.5°C
3R	$C_{10}H_{21}$-	C_6H_5-	C_6H_5-	3R,4S	p-MeO-C_6H_4-	mp=103.0-103.5°C
3T	$C_{10}H_{21}$-	CH_3CH_2-	C_6H_5-	3R,4R	p-MeO-C_6H_4-	mp=48.0-49.5°C
3U	$C_{10}H_{21}$-	C_6H_5-$(CH_2)_3$-	C_6H_5-	3R,4R	p-MeO-C_6H_4-	CI MS: (M+1) 512.6
3V	$C_{10}H_{21}$-	CH_3CH_2-	C_6H_5-	3S,4R	2,4,6-tri-MeO-C_6H_4-	CI MS: (M+1) 482
3W	$C_{10}H_{21}$-	CH_3CH_2-	C_6H_5-	3R.4R	2,4,6-tri-MeO-C_6H_4-	mp=96-98°C
3X	$C_{10}H_{21}$-	CH_3CH_2-	C_6H_5-CH=CH-	3S,4S	p-MeO-C_6H_4-	EI MS: (M^+) 425
3Y	$C_{10}H_{21}$-	CH_3-	C_6H_5-	3S,4S	p-MeO-C_6H_4-	mp=96-97°C

EXAMPLE 4



Add 100mg (0.30mmol) of the trans β-lactam of Example 1V in 2mL dry THF to a solution of 1.22mL (0.32mmol) LDA (1.5M, from Aldrich, Milwaukee, WI) in 0.5mL dry THF at -78°C under nitrogen. Stir for 5min at -78°C, then quench at low temperature with ~0.3mL acetic acid. Partition the mixture between 30mL ethyl acetate and 20mL water. Wash the organic layer with 20 mL 10% aqueous $NaHCO_3$ solution, dry over $MgSO_4$ and concentrate in vacuo to give 98mg of an oily white solid. Chromatograph the residue over SiO_2, eluting with 20% ethyl acetate-hexane to obtain 26 mg of the title cis β-lactam as a white solid, mp = 141.3 - 142.3°C.

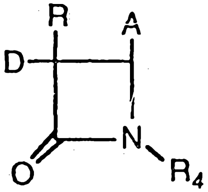
EXAMPLE 5



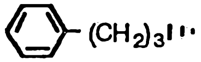
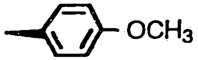
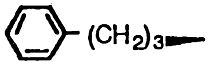
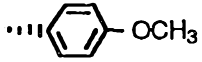
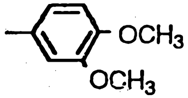
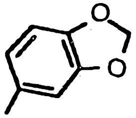
Dissolve 32.05g (79.8mmol) of the racemic cis β-lactam of Example 1 in 500mL of THF. Add 1.79g (16.0mmol) of potassium *t*-butoxide and stir at 0°C for 1.5h. Partition the reaction mixture between 600mL 1N aqueous HCl and 1.2liters of ether. Extract the aqueous layer with 400mL of ether. Combine the ether layers, dry over $MgSO_4$ and concentrate in vacuo to give 32.0g of a mixture of cis and trans β-lactams (2.7:1). Isolate the pure trans β-lactam via silica gel HPLC

chromatography, eluting with 10% ethyl acetate-hexane. Crystallize from ethyl acetate-hexane to give white crystals, mp = 96.0 - 97.5°.

Using a procedure similar to that of Example 5, the following compounds shown in Tables 6 and 6A can be prepared:

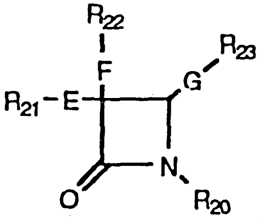


Ex.	D	R	A	Relative Stereo-chemistry	R_4	Data
5B	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	3S,4R single enantiomer	4-CH_3O-C_6H_4-	FAB MS (M+1)=402.2
5C	C_6H_5-$(CH_2)_3$-	H	3-CH_3O-C_6H_4-	3R,4S	4-CH_3O-C_6H_4-	mp=109.5-110.0°C
5D	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans	4-F-C_6H_4-	CIMS (M+1)=390
5E	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans	3-CH_3O-C_6H_4-	elemental analysis: calc'd C=77.78, H=6.78, N=3.49; found C=77.75, H=6.70, N=3.60
5G	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans	4-Cl-C_6H_4-	CIMS (M+1)=406
5H	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans	4-$(CH_3CH_2$-O)-C_6H_4-	elemental analysis: calc'd C=78.04, H=7.04, N=3.37; found C=78.01, H=7.03, N=3.47

5I	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans	4-CH_3S-C_6H_4-	elemental analysis: calc'd C=74.79, H=6.52, N=3.35; found C=74.74, H=6.44, N=3.48
5J	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans	4-CH_3-C_6H_4-	elemental analysis: calc'd C=81.01, H=7.06, N=3.63; found C=81.25, H=7.09, N=3.75
5K	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans	4-(C_6H_5-O)- C_6H_4-	elemental analysis: calc'd C=80.32, H=6.31, N=3.02; found C=80.36, H=6.29, N=3.16
5L		H		trans optically pure	C_6H_5-	mp=74-75°C $[\alpha]_D^{25}$ = -7.6°
5M		H		trans optically pure	C_6H_5-	mp=74-75°C $[\alpha]_D^{25}$ = -7.5°
5P	C_6H_5-$(CH_2)_3$-	H		trans	4-CH_3O-C_6H_4-	mp=70.5-71.5°C
5Q	C_6H_5-$(CH_2)_3$-	H		trans	4-CH_3O-C_6H_4-	mp=79.5-81.0°C

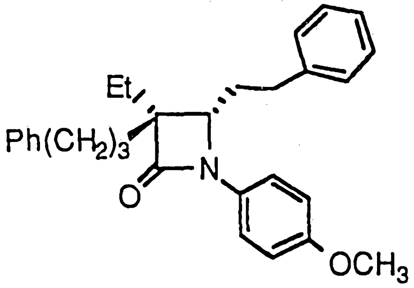
5R	C_6H_5-$(CH_2)_3$-	H	4-CH_3-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=74.5-77.0°C
5S	C_6H_5-$(CH_2)_3$-	H	4-(CH_3CH_2-O)-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=85-87°C
5T	C_6H_5-$(CH_2)_3$-	H	4-(C_6H_5-CH_2-O)-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=111-112°C
5U	C_6H_5-$(CH_2)_3$-	H	4-(CH_2=CH-CH_2-O)-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=75.5-77.0°C
5V	C_6H_5-$(CH_2)_3$-	H	4-(C_6H_5-O)-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=103.5-105.5°C
5W	C_6H_5-$(CH_2)_2$-	H	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=75-77°C
5X	C_6H_5-O-$(CH_2)_2$-	H	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=122-123°C
5Y	C_6H_5-$(CH_2)_6$-	H	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	elemental analysis: calc'd C=78.52, H=7.50, N=3.16; found C=78.32, H=7.37, N=3.25
5Z	C_6H_5-$(CH_2)_2$-O-	H	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	elemental analysis: calc'd C=74.42, H=6.25, N=3.47; found C=74.57, H=6.29, N=3.51
5AA	4-F-C_6H_4-O-$(CH_2)_2$-	H	4-CH_3O-C_6H_4-	trans	4-MeO-C_6H_4-	elemental analysis: calc'd C=71.25, H=5.74, N=3.32; found C=71.34, H=5.73, N=3.43

5AB	C_6H_5-$(CH_2)_4$-	H	4-CH_3O-C_6H_4-	trans	4-MeO-C_6H_4-	elemental analysis: calc'd C=78.04, H=7.03, N=3.37; found C=77.90, H=6.94, N=3.51



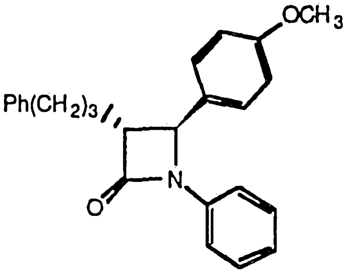
Ex.	R_{21}-E-	R_{22}-F-	R_{23}-G-	Rel. Stereo-chemistry	R_{20}	Data
5A	$(CH_3)_2CH$-	H	C_6H_5-	3S,4R	4-MeO-C_6H_4-	mp=113-115°C
5N	C_6H_5-$(CH_2)_2$-$N(CH_3)$-	H	4-CH_3O-C_6H_4-	trans	C_6H_5-	mp=122-123°C

EXAMPLE 6



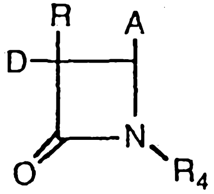
Dissolve 200mg (0.47mmol) of the β-lactam of Example 3G in 4mL EtOAc and add ~10mg 10% Pd/C. Hydrogenate at 1atm for 4h. Filter the mixture through Celite and concentrate. Chromatograph the residue over 40g SiO_2, eluting with 20% EtOAc-hexane to obtain 188mg (94%) of the title β-lactam as a colorless oil, CI MS : (M+1) 428.1.

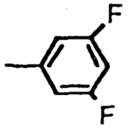
EXAMPLE 7

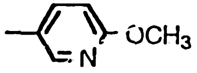
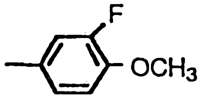
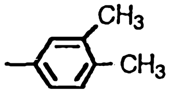
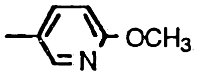
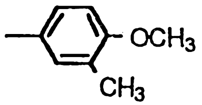


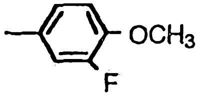
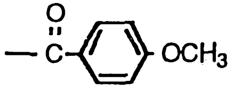
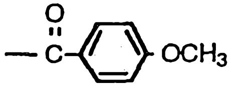
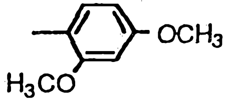
To a refluxing solution of 4.33 grams (.0205 moles) N-(4-methoxybenzylidine)-aniline and 7.6 grams (0.0410 moles) tributyl-amine in 40 mL heptane add,in portions, a solution of 4.03 grams (0.0205 moles) 5-phenylvaleroyl chloride in 15 mL heptane over about 2 hours, then reflux the solution for an additional 4 hours. Evaporate the solvent and take up the residue in 150 mL EtOAc. Wash with 1N HCl (2 x 30 mL), saturated $NaHCO_3$ (1 x 30 mL) and brine (1 x 30 mL), then dry over $MgSO_4$ and evaporate to give 7.69 grams of a semisolid. Recrystallization from 15% EtOAc in hexane to obtain 3.08 grams of the title compound, mp 75-76°C. An additional 2.31 g is obtained from the mother liquors by chromatography (silica gel, 5% ethyl acetate in hexane) and recrystallization.

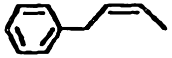
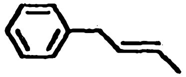
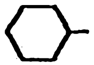
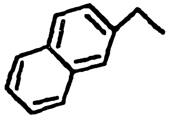
Using a procedure similar to that of Example 7, the following compounds shown in Tables 7 and 7Acan be prepared:

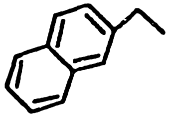
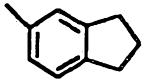
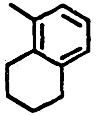
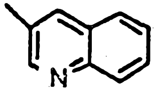


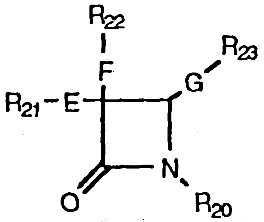
Ex.	D	R	A	Relative Stereo-chemistry	R_4	Data
7A	$C_6H_5\text{-}(CH_2)_3\text{-}$	H	$4\text{-}CH_3O\text{-}C_6H_4\text{-}$	trans	$4\text{-}(CH_3CH_2OC(O))\text{-}C_6H_4\text{-}$	mp=75-77°C
7B	$C_6H_5\text{-}(CH_2)_3\text{-}$	H	$4\text{-}CH_3O\text{-}C_6H_4\text{-}$	trans	$3\text{-}NO_2\text{-}C_6H_4\text{-}$	elemental analysis: calc'd C=72.10, H=5.81, N=6.73; found C=72.46, H=5.91, N=6.54
7C	$C_6H_5\text{-}(CH_2)_3\text{-}$	H	$4\text{-}CH_3O\text{-}C_6H_4\text{-}$	trans	$4\text{-}((CH_3CH_2)_2\text{-}N)\text{-}C_6H_4\text{-}$	mp=91-93°C
7D	$C_6H_5\text{-}(CH_2)_3\text{-}$	H	$4\text{-}CH_3O\text{-}C_6H_4\text{-}$	trans	$4\text{-}NC\text{-}C_6H_4\text{-}$	mp=79-81°C
7E	$C_6H_5\text{-}(CH_2)_3\text{-}$	H	$4\text{-}CH_3O\text{-}C_6H_4\text{-}$	trans		elemental analysis: calc'd C=73.69, H=5.69, N=3.44; found C=73.36, H=5.77, N=3.48

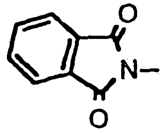
7F	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans		mp=103-104°C
7G	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans	4-($CH_3C(O)$)- C_6H_4-	elemental analysis: calc'd C=78.42, H=6.58, N=3.39; found C=78.08, H=6.51, N=3.40
7H	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans		mp=90-92°C
7I	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans		mp=129-130°C
7M	C_6H_5-$(CH_2)_3$-	H	4-($(CH_3)_2CH$-O)- C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=96.5-97.5°C
7O	C_6H_5-$(CH_2)_3$-	H		trans	C_6H_5-	mp=89-91°C
7P	C_6H_5-$(CH_2)_3$-	H	4-($CH_3(CH_2)_2$-O)- C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=92.5-93.5°C
7Q	C_6H_5-$(CH_2)_3$-	H		trans	4-CH_3O-C_6H_4-	EIMS (M)=415
7R	C_6H_5-$(CH_2)_3$-	H	4-($CH_3OC(O)$)-C_6H_4-	trans	C_6H_5-	mp=84-85°C

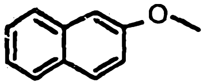
7S	$C_6H_5-(CH_2)_3-$	H		trans	$4-CH_3O-C_6H_4-$	EIMS (M)=420
7T	$C_6H_5-(CH_2)_3-$	H	$4-(CH_3OCH_2O)-C_6H_4-$	trans	C_6H_5-	CIMS (M+1)=402
7U	$C_6H_5-(CH_2)_3-$	H	$4-((CH_3)_2N)-C_6H_4-$	trans	$4-CH_3O-C_6H_4-$	mp=96.5-97.5°C
7V	$C_6H_5-(CH_2)_3-$	H		trans	$4-CH_3O-C_6H_4-$	EIMS (M)=429
7W	$C_6H_5-(CH_2)_3-$	H		cis	$4-CH_3O-C_6H_4-$	EIMS (M)=429
7X	$C_6H_5-(CH_2)_3-$	H		trans	$4-CH_3O-C_6H_4-$	EIMS (M)=431
7Y	$C_6H_5-(CH_2)_3-$	H	$4-(CH_3CH_2-O)-C_6H_4-$	trans	C_6H_5-	mp=95.0-95.5°C
7Z	$4-O_2N-C_6H_4-(CH_2)_3-$	H	$4-CH_3O-C_6H_4-$	trans	$4-CH_3O-C_6H_4-$	mp=136.5-137.0°C
7AA	$C_6H_5-(CH_2)_3-$	H	$4-CH_3O-C_6H_4-$	trans	$4-I-C_6H_4-$	mp=96.5-97.5°C
7AB	$C_6H_5-(CH_2)_3-$	H	$4-(CH_3(CH_2)_3-O)-$ C_6H_4-	trans	$4-CH_3O-C_6H_4-$	mp=79-82°C
7AE	$C_6H_5-(CH_2)_2-O-$	H	$4-CH_3O-C_6H_4-$	cis	$4-CH_3O-C_6H_4-$	mp=149-150°C

7AI		H	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	elemental analysis: calc'd C=78.17, H=6.31, N=3.51; found C=78.22, H=6.36, N=3.59
7AJ		H	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	FAB mass spec 400(100)
7AK	 $(CH_2)_3$–	H	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=105-106°C
7AM	C_6H_5-$(CH_2)_5$-	H	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	elemental analysis: calc'd C=78.29, H=7.27, N=3.26; found C=78.37, H=7.26, N=3.41
7AN	4-O_2N-C_6H_4-O-$(CH_2)_2$-	H	4-CH_3O-C_6H_4-	trans	C_6H_5-	mp=54-56°C
7AO		H	4-CH_3O-C_6H_4-	trans	C_6H_5-	mp=55-57°C
7AP	4-(CH_3O)-C_6H_4-O-$(CH_2)_2$-	H	4-CH_3O-C_6H_4-	trans	C_6H_5-	elemental analysis: calc'd C=74.42, H=6.25, N=3.47; found C=74.13, H=6.03, N=3.26

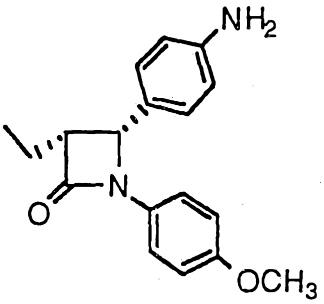
7AQ		H	4-CH_3O-C_6H_4-	cis	C_6H_5-	^1H NMR ($CDCl_3$) 7.97-7.78 (m,2H); 7.69 (d, J=8Hz,1H); 7.45-7.69 (m,10H); 6.90 (d, J=8Hz,2H); 6.63 (d,J= 8Hz, 1H); 5.17(d,J=6Hz,1H); 4.15-4.0 (m,1H); 3.82 (s,2H); 3.5 (dd,J=6,14Hz,1H); 2.96(dd, J=9,14Hz,1H)
7AR	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans		mp=111-112°C
7AS	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans		MS CI+ (M+1)=426
7AT	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans		mp=122-124°C
7AU	C_6H_5-$(CH_2)_3$-	H	4-(C_6H_5-CH_2O)-C_6H_4-	trans	4-(C_6H_5-CH_2O)-C_6H_4-	mp=105-106°C



Ex.	R_{21}-E-	R_{22}-F-	R_{23}-G-	Rel. Stereo-chemistry	R_{20}	Data
7J	CH_3O-C(O)-CH=C(CH_3)-NH-	H	4-CH_3O-C_6H_4-	cis	C_6H_5-	mp=186-187°C
7K	C_6H_5-$(CH_2)_2$-N(CH_3)-	H	4-CH_3O-C_6H_4-	cis	C_6H_5-	mp=120-123°C
7L		H	4-CH_3O-C_6H_4-	cis	C_6H_5-	mp=243-245.5°C
7N	C_6H_5-$(CH_2)_3$-	H	-C(O)OCH_2CH_3	cis	4-CH_3O-C_6H_4-	mp=97-98.5°C
7AC	C_6H_5-	C_6H_5-	4-CH_3O-C_6H_4-	---	4-CH_3O-C_6H_4-	mp=78-81°C
7AD	cyclo-C_5H_9-	C_6H_5-	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=60-63°C
7AF	C_6H_5-	C_6H_5-CH_2-	4-CH_3O-C_6H_4-	cis	4-CH_3O-C_6H_4-	mp=108-110°C

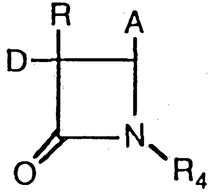
7AG	$C_{10}H_{21}$-	H	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	elemental analysis: calc'd C=76.56, H=8.80, N=3.31; found C=76.37, H=8.90, N=3.46
7AH	C_6H_5-CH_2-	C_6H_5-	4-CH_3O-C_6H_4-	cis	4-CH_3O-C_6H_4-	mp=114-117°C
7AL		H	4-CH_3O-C_6H_4-	cis	4-CH_3O-C_6H_4-	elemental analysis: calc'd C=76.22, H=5.45, N=3.29; found C=76.00, H=5.46, N=3.39

EXAMPLE 8

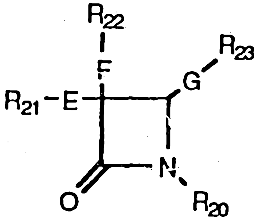


Stir a mixture of 981mg (3.01mmol) of the cis β-lactam of Example 1AK, above, and 20mg 10% palladium on carbon in 10 mL ethyl acetate under 1atm hydrogen gas at room temperature for 24h. Filter the mixture through Celite and concentrate in vacuo. Chromatograph the residue over 50g SiO_2, eluting with 40% ethyl acetate-hexane to obtain 818mg (92%) of the title compound as a yellowish solid, mp = 142.0 - 142.5°C.

Using a similar procedure, the following compounds shown in Tables 8 and 8A can be prepared, and using conventional procedures, the amino group of compound 8A and the amino group of compound 8B can be protected with a t-butoxycarbonyl (BOC) group to obtain compounds 8G and 8H, respectively:

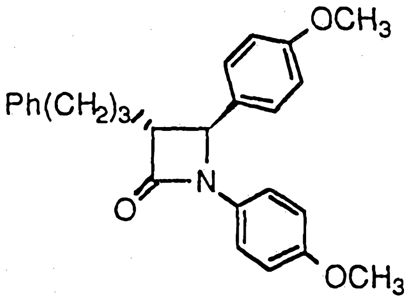


Ex.	D	R	A	Relative Stereo-chemistry	R_4	Data
8B	C_6H_5-$(CH_2)_3$-	H	4-NH_2-C_6H_4-	cis	4-CH_3O-C_6H_4-	mp=138.5-139.5°C
8C	C_6H_5-$(CH_2)_3$-	H	4-NH_2-C_6H_4-	trans	4-CH_3O-C_6H_4-	FAB MS (M+1)=387.1
8D	C_6H_5-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans	3-NH_2-C_6H_4-	mp=46-48°C
8E	4-NH_2-C_6H_4-$(CH_2)_3$-	H	4-CH_3O-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=129.0-131.0° C
8F	C_6H_5-$(CH_2)_3$-	H	4-OH-C_6H_4-	trans	4-CH_3O-C_6H_4-	mp=171.0-171.5°C
8H	C_6H_5-$(CH_2)_3$-	H	4($(CH_3)_3$C-O-C(O)-NH)-C_6H_4-	cis	4-CH_3O-C_6H_4-	CI MS:(M+1)=487



Ex.	R_{21}-E-	R_{22}-F-	R_{23}-G-	Rel. Stereo-chemistry	R_{20}	Data
8A	CH_3CH_2-	H	4-NH_2-C_6H_4-	3S,4R	4-CH_3O-C_6H_4-	mp=136-137°C
8G	CH_3CH_2-	H	4((CH$_3$)$_3$C-O-C(O)-NH)-C_6H_4-	3S,4R	4-CH_3O-C_6H_4-	CI MS:(M+1)=397

EXAMPLE 9



STEP 1: Combine 5-phenylvaleric acid (89.9 g, 0.504 mol) and thionyl chloride (89.3 mL, 1.225 mol), heat to 70°C and reflux for 1h. Vacuum distill (50 - 100 mm Hg) the excess thionyl chloride and add 200 mL of dry toluene to the resultant residue. Vacuum distill again, then add 188 mL of dry THF to the crude 5-phenylvaleroyl chloride and use the resulting solution directly in the next step.

STEP 2: Combine 76 g (0.4289 mol) of R-(+)-4-benzyl-oxazolidinone and 1.3 L of dry THF under dry nitrogen atmosphere. Cool the resulting solution to -78°C and add 278 mL of a 1.6 M solution of n-butyllithium in hexane over 30-40 minutes. Stir for an additional 30 minutes, then add the solution of Step 1 over a period of 45 min. Allow the mixture to warm to 0°C and stir for 1 h. Quench the reaction mixture by adding 673.6 mL of K_2CO_3 (1 M aqueous solution) and stir for 1 h. Distill off the THF under vacuum at 30-35°C. Dilute the residue with 1 L of water and extract with 3x800 mL of CH_2Cl_2. Combine the organic extracts and wash with 800 mL of water, then with 800 mL of brine. Dry the organic extracts over $MgSO_4$, filter, then concentrate *in vacuo* to an oil. Dissolve the oil in 200 mL of hexane, then distill off the hexane under vacuum. Repeat the hexane treatment two more times, then dissolve the oil in 1.7 mL of CH_2Cl_2. The resulting solution is used directly in the next step.

STEP 3: Cool the solution of Step 2 to -5°C to 0°C under dry nitrogen atmosphere. Add 129.8 mL of di-n-butylboron triflate, maintaining the temperature of the reaction mixture at -6°C to -3°C. Following the addition, stir the mixture for 10 min., then add 97.12 mL of diisopropylethylamine, again maintaining the temperature at -6°C to

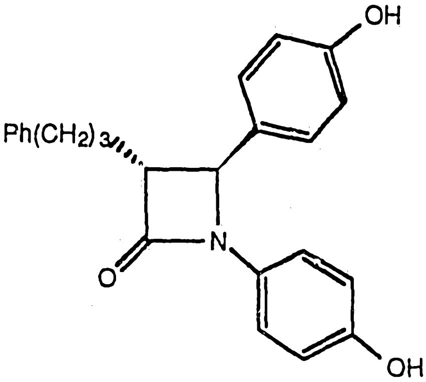
-3°C. Following the addition, stir the mixture at 0°C for 30 min., then cool the mixture to -78°C and stir for 30 min.. Add 57.4 mL of p-anisaldehyde and stir the mixture at -78°C for 30 min., then at 0°C for 1 h. While maintaining the temperature at 0°C to 5°C, quench the mixture by adding 688.2 mL of a pH 7 buffer solution (68 g KH_2PO_4, 12 g NaOH and 800 mL of water), then add 473 mL of 30% H_2O_2 and stir the resulting mixture at 0°C for 1 h. Extract the mixture with 3x600 mL hexane:ethyl actetate (1:1), combine the organic extracts and wash with 800 mL of saturated $NaHCO_3$ (aqueous), then with 800 mL of brine. Dry the organic extracts over $NaSO_4$, filter, and evaporate to an oil. Crystallize the oil from hexane/ethyl acetate (1:1) to give 176 g of the product as a white solid.

STEP 4: Combine the product of Step 3 (170 g, 0.36 Mol), 1595 mL of THF and 400 mL of water, stir the mixture and cool to about 3°C. Add 226 mL (2.156 Mol) of 30% H_2O_2 to the mixture over 15 min., then add a solution of LiOH (36.2 g, 0.862 Mol) in 400 mL of water over a period of 30 min. Stir the reaction mixture at 0°C to 5°C for 3 h. Add a solution of 272 g of sodium sulfite in 850 mL of water over 70 min., keeping the temperature under 27°C. Concentrate the solvent under vacuum and add 7 L of water. Extract with 4x1.7 L of toluene. Acidify the aqueous layers to pH 2.4 with 3 N HCl. Extract with one 2.6 L portion and two 1.7 L portions of ethyl acetate. Combine the ethyl acetate extracts, wash with brine, dry over $NaSO_4$, filter, then evaporate to give the product as a white solid, 112 g.

STEP 5: Combine the product of Step 4 (19.47 g, 62 mmol), 400 mL of acetonitrile, 9.49 g (62 mmol) of 1-hydroxybenzotriazole (HOBT), 22.91 g (186 mmol) of p-anisidine and 14.05 g (68.2 mmol) of dicyclohexylcarbodiimide (DCC). Stir the reaction mixture at 40°C for 4 h and confirm the consumption of starting material by TLC (6:4 hexane/ ethyl acetate). Concentrate the mixture to 1/3 its volume and partition between 300 mL of water and 300 mL of ethyl acetate. Filter the organic layer, then wash with 200 mL of 1 N HCl, then with two 100 mL portions of saturated $NaHCO_3$, and two 100 mL portions of brine. Dry the organic layer over $NaSO_4$ and concentrate to give the product as a brown solid, 24 g.

STEP 6: Combine the product of Step 5 (115 g, 0.2745 Mol) and 2.3 L of THF under dry nitrogen atmosphere and cool to -70°C. Stir the mixture while adding a solution of 137 mL (0.551 Mol) of tri-n-butylphosphine in 113 mL THF, and 163 mL (1.03 Mol) of diethylazodicarboxylate (DEAD) over 2 h. Allow the mixture to warm to room temperature and stir overnight. Remove the solvent under vacuum. Filter the residue through a plug of silica gel using CH_2Cl_2/ hexane/ ethyl acetate (70:24:6) as the eluant. Evaporate the solvent and purify the residue by preparative HPLC (silica gel, 15% ethyl actetate/ hexane) to give 88 g of the (3R,4S) enantiomerically pure title compound, $[\alpha]_D^{25} = -19.3^o$ (MeOH).

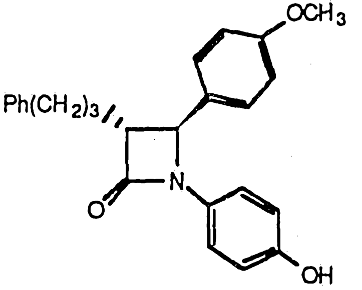
Example 10



The compound of Example 7AU (0.686 g, 0.0012 moles) dissolved in 1:1 ethanol:ethyl acetate is hydrogenated over 0.70 grams 10% Pd on carbon at 50 psi for 16 hours. The resulting product is chromatographed (silica gel, 80:20 hexane:ethyl acetate) to give 0.432 grams of the title compound, mp 160-161°C.

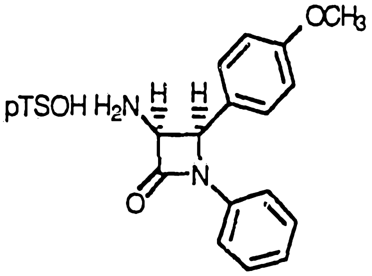
Using substantially the same procedure the following compound can be prepared:

Example 10A



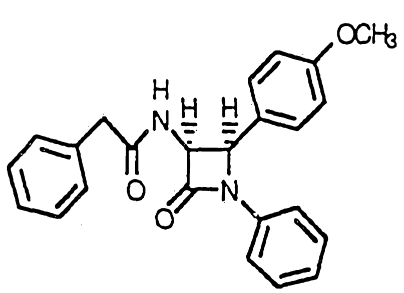
Elemental Analysis
Calculated for $C_{25}H_{25}NO_3$
C, 77.49; H, 6.50; N, 3.61
Found: C, 77.47; H, 6.46; N, 3.74

Example 11



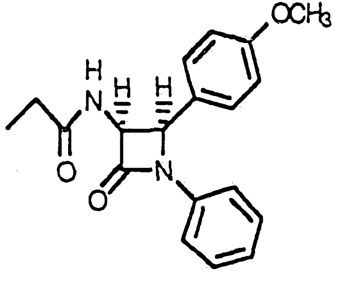
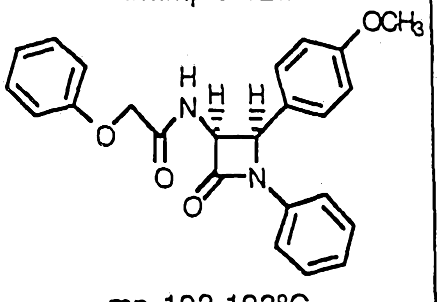
A flask is charged with the compound of Example 7J (27 g, 73.6 mmole), acetone (0.6 l), water (1.3 ml, 73 mmole), and p-toluenesulfonic acid-monohydrate (15.4 g, 81.1 mmole). The solution is stirred at 22°C for 5.5 h and the product collected by filtration (34.1 g). Recrystallization from methanol affords the title compound,26.0 g (79% yield), mp 200-202°C.

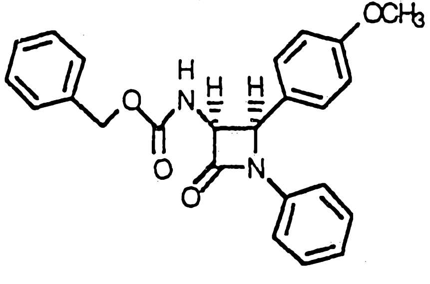
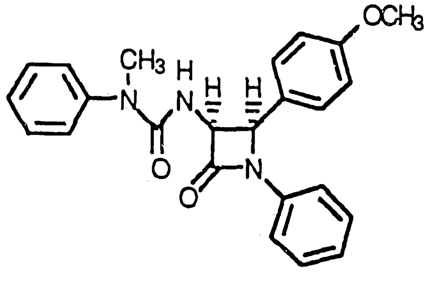
Example 12



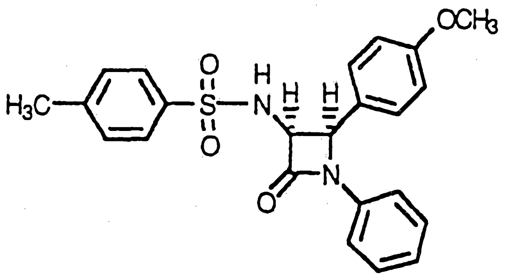
To a solution of the product of Example 11 (0.60 g, 1.36 mmole), triethylamine (0.14 g, 1.4 mmole) in CH_2Cl_2 (2 ml) was added phenylacetylchloride (0.310 g, 2.0 mmole) dropwise over 0.5 h. After 5 h the reaction mixture was concentrated to dryness, and the residue purified by chromatography (silica, 2:1 hexane: ethyl acetate) to afford 0.27 g (51% yield) of the title compound, mp 217-218°C.

Using substantially the same procedure, the following compounds can be prepared:

Example 12A	Example 12B
	
mp 167-168°C	mp 192-193°C

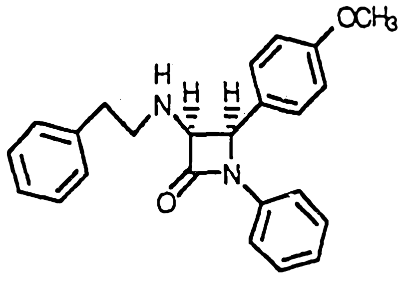
Example 12C	Example 12D
	
194-195°C	mp 161.5-163°C

Example 13



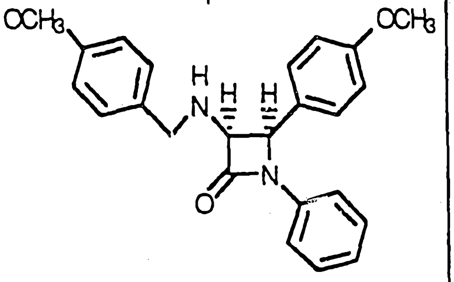
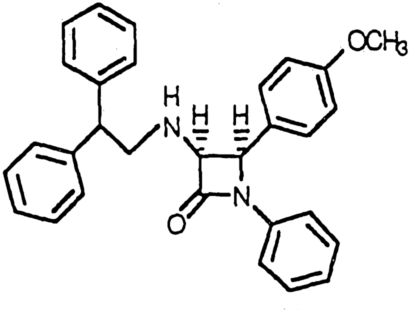
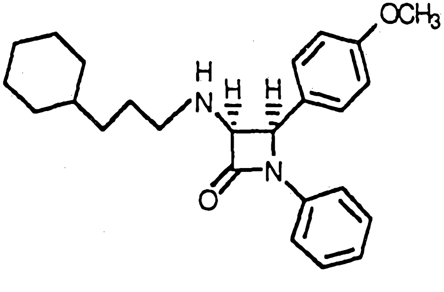
To a biphasic mixture of the product of Example 11 (0.80 g, 1.8 mmole), CH_2Cl_2 (15 ml) and 30% aqueous tetrabutylammonium hydroxide (2.36 ml, 3.64 mmole) was added p-toluenesulfonylchloride (0.515 g, 2.7 mmole). After 2 h the reaction mixture was washed with 1X 1 N HCl, 2X H_2O and the organic layer dried over $MgSO_4$. Concentration followed by recrystillaztion from ethyl acetate afforded 0.38 g (50% yield) of the title compound, mp 204-205°C.

Example 14

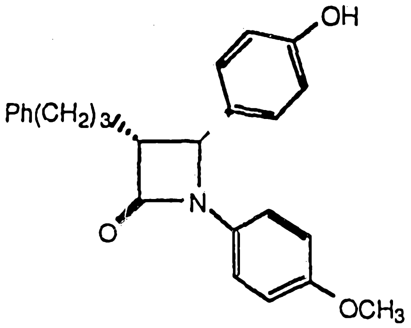


To a solution of the product of Example 11 (0.8 g, 1.8 mmole), methanol (20 ml) and triethylamine (0.19 g, 1.8 mmole) was added phenylacetaldehyde (0.44 g, 3.6 mmole). After 0.25 h , $NaBH_3CN$ (0.172 g, 2.7 mmole) and $ZnCl_2$ (0.174 g, 1.3 mmole) were added to the reaction. After 3.5 h, the reaction was quenched with ammonium chloride, concentrated partially in vacuo, and dissolved in CH_2Cl_2. The organic layer was washed 2X with water, dried and concentrated to afford crude product. Recrystallization from CH_2Cl_2 afforded 0.44 g (65% yield) of the title compound, mp 138-139.5°C.

Using substantially the same procedure, the following compounds can be prepared:

Example 14A  mp 148-149°C	Example 14B  mp 179-180°C
Example 14C  mp 100-101°C	

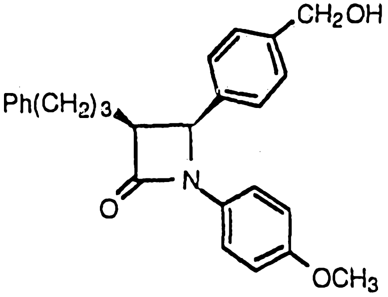
Example 15



Add 49 mL (49 mmol) of 1M tetrabutylammonium fluoride 49 mL, 49 mmol, 1M in THF)to a room temperature solution of the compound of Example 1AS (5.1g, 9.8 mmol) in THF (25 mL). Allow the mixture to stir overnight. TLC (50% EtOAc/hexanes) indicates consumption of starting material. Transfer the reaction mixture to a separatory funnel, partion between saturated ammonium chloride and ether, extract with ether. Combine the etheral extracts, wash with water and brine, dry over anhydrous Na_2SO_4, filter and concentrate to a residue. Chromatograph (SiO_2, 30-40% EtOAc/hexane) affords 3.31g (84%) of the title compound, mp 91-92°C.

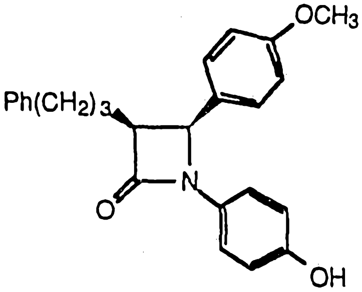
The following compounds can be prepared via substantialy the same procedure:

Example 15A



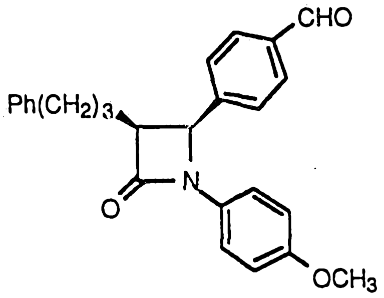
mp 112-113°C

Example 15B



mp 170-171°C

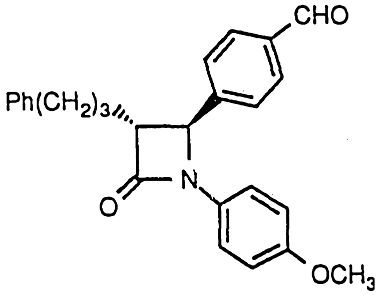
Example 16



Add MnO_2 (0.64g, 7.4 mmol) to a solution of the product of Example 15A (0.20g, 0.5 mmol) in CH_2Cl_2 (50 mL) at room temperature. Allow the mixture to stir overnight. TLC (20% EtOAc/hexanes) indicates consumption of starting material. Filter the mixture through celite washing the filtercake well with CH_2Cl_2. Concentrate the filtrate to obtain 0.19g (95%) of the title compound, mp 129-130 °C.

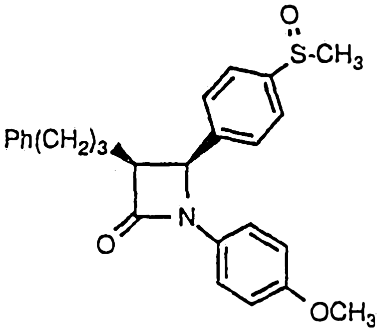
Using substantially the same procedure, the following compound can be prepared:

Example 16A

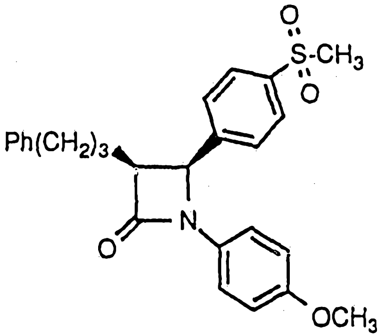


mp 100-101°C

Example 17



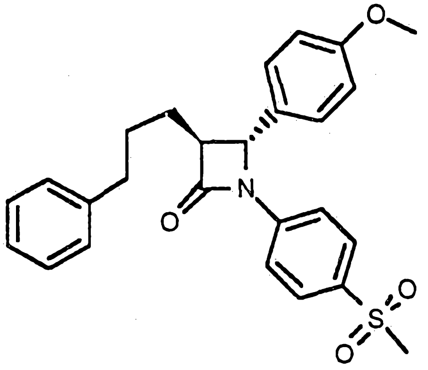
Add m-chloroperbenzoic acid (.16g, .092 mmol) to a solution of the compound of Example 1AU (0.31 g, 0.74 mmol) in CH_2Cl_2 (4 mL) at room temperature. Monitor the reaction by TLC (50% EtOAc/hexanes). Upon consumption of starting material (~1h), add $Ca(OH)_2$ (0.1g, 1.3 mmol) Stir the mixture for an additional 15 min.. Filter the mixture through celite washing the filtercake well with CH_2Cl_2. Concentrate the filtrate onto silica gel, using enough silica gel until a free flowing powder is obtained. Load the resulting powder onto a chromatography column loaded with silica gel and 5% $MeOH/CH_2Cl_2$. Elute with 5% $MeOH/CH_2Cl_2$ to obtain 0.26 g of the title sulfoxide (Example 17), mp 134-135°C and 0.50 g of the analogous sulfone: Example 17A



mp 116-117°C

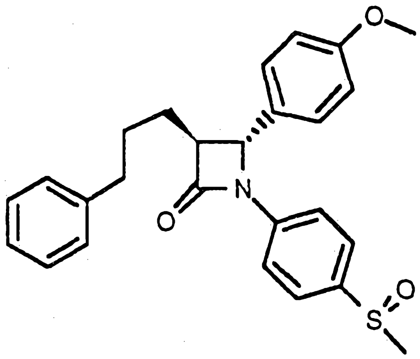
The following compounds can be prepared via substantially the same procedure:

Example 17B



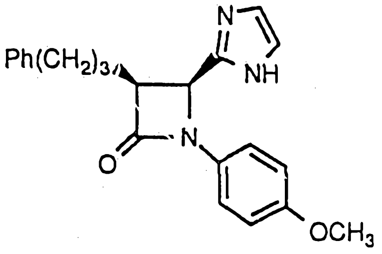
mp 56-58°C

Example 17C



mp 52-53°C

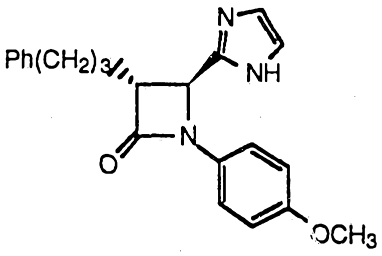
Example 18



Reflux a mixture of the compound of Example 1AW (1.72 g, 3.49 mmol), 20 mL of THF and 3N HCl (20 mL) overnight. Monitor the reaction by TLC (50% EtOAc/hexanes). Upon consumption of starting material cool the mixture to room temperature, neutralize with saturated $NaHCO_3$ and extract with ethyl acetate. Combine the extracts, wash with water and brine, dry over anhydrous Na_2SO_4, filter and concentrate to a solid. Recrystallize from CH_2Cl_2/MeOH to obtain 0.322g of the title compound, mp 190.5-191.5 °C.

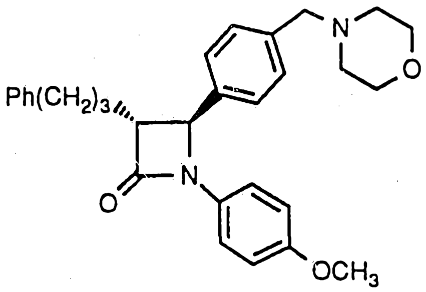
Using substantially the same procedure the following compound can be prepared:

Example 18A



mp 189-191°C

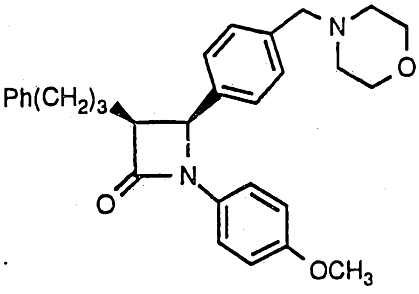
Example 19



Add a solution of $NaBH_3CN$ (0.19g, 3.0 mmol) and $ZnCl_2$ (0.21g, 1.5 mmol) in methanol to a room temperature solution of the product of Example 16A (1.0g, 2.5 mmol) and morpholine (0.44 mL, 5.0 mmol) in THF. Monitor the reaction by TLC (50% EtOAc/hexanes). Upon consumption of starting material the mixture was diluted with 0.1 N NaOH (120 mL) and remove the organic solvents on a rotary evaporator. Extract the resulting solution with ethyl acetate. Combine the extracts, wash with water and brine, dry over anhydrous Na_2SO_4, filter and concentrate to a solid. Recrystallize from Et_2O/hexanes to obtain 0.81g (69%) of the title compound, mp 100-101 °C.

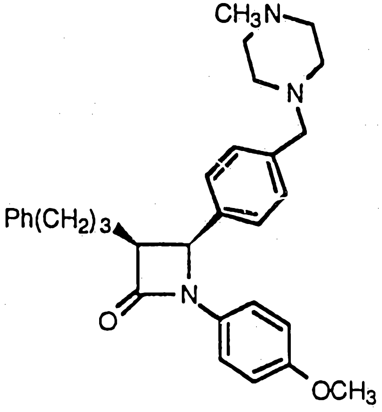
The following compounds can be prepared by substantially the same method:

Example 19A



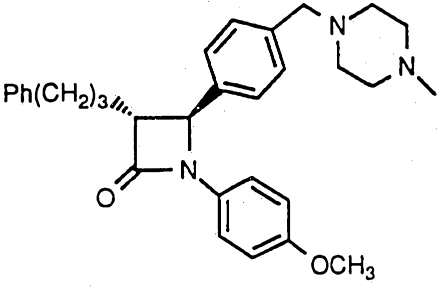
mp 97-98°C

Example 19B



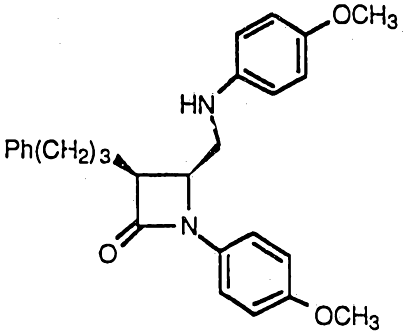
mp 141-142°C

Example 19C



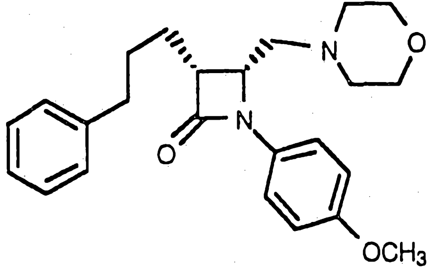
mp 103.5-104.5°C

Example 19D



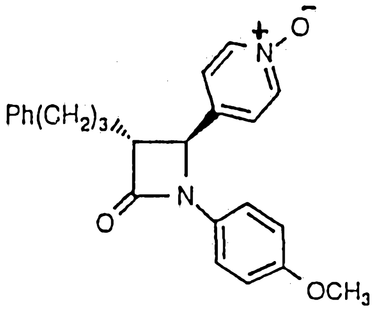
mp 94-95°C

Example 19E



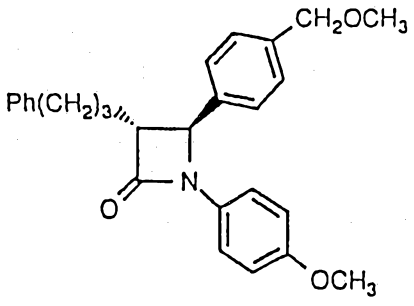
EI MS (M) = 394

Example 20



Heat a solution of the compound of Example 1AR (1.10g, 2.95 mmol), 15% H_2O_2 (0.45 mL) in acetic acid (3 mL) to a 100 °C for 3.5h with TLC monitoring (5% MeOH/CH_2Cl_2). Upon consumption of the starting compound, cool to room temperature, neutralize with sat. Na_2CO_3 and dilute with ethyl acetate. Filter the mixture and wash the filtrate with water and brine, dry over anhydrous Na_2SO_4, filter and concentrate to a residue. Chromatograph the residue (silica gel, 10% MeOH/CH_2Cl_2) to give the title compound, FAB MS (M+1) = 389.

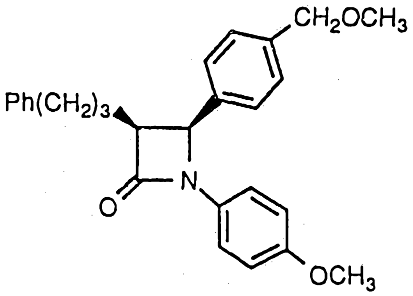
Example 21



Add freshly prepared AgO (0.40 g, 1.73 mmol) to a solution of the product of Example 15A (0.46g, 1.15 mmol) and methyl iodide (0.21 mL, 3.45 mmol)in dry DMF (5 mL). Heat the mixture to 40-45 °C.with TLC monitoring (50% EtOAc/hexanes). Add proportional amounts of AgO and methyl iodide until TLC indicates consumption of starting compound. Cool to room temperature, partion between water and ethyl acetate, extract with ethyl acetate. Combine ethyl acetate extracts, wash with water and brine, dry over anhydrous Na_2SO_4, filter and concentrate to a residue. Chromatograph the residue (silica gel, 30% EtOAc/hexanes) to give the title compound, FAB MS (M+1) = 416.

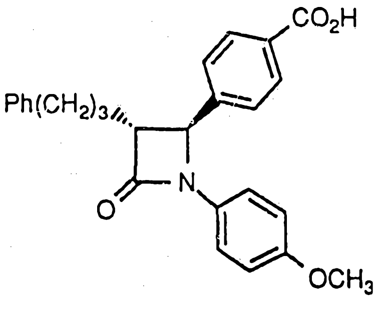
The following compound can be prepared by substantially the same procedure:

Example 21A



mp 84-85°C

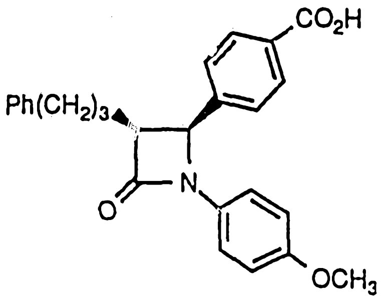
Example 22



Add freshly prepared Jone's reagent (8 mL) dropwise to a solution of the product of Example 16 (2.76, 6.94 mmol) in acetone (80 mL) maintaining the temperature of the reaction mixture between 15-20 °C. Monitor by TLC (5% MeOH/CH_2Cl_2). Upon consumption of starting compound, quench the reaction with methanol. Concentrate to a residue and partion the residue between CH_2Cl_2 and water. Extract with CH_2Cl_2, combine the extracts, wash with water, 10% Na_2SO_3 (aq) and brine, then dry over anhydrous Na_2SO_4. Filter and concentrate to afford 2.90g of the title compound, mp 64-65 °C.

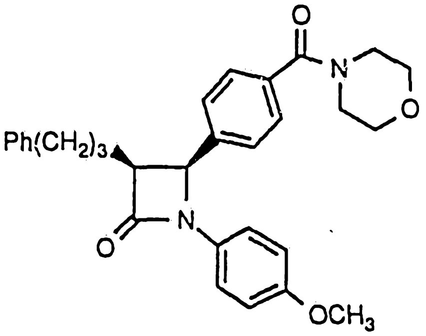
The following compound can be prepared by substantially the same procedure.

Example 22A



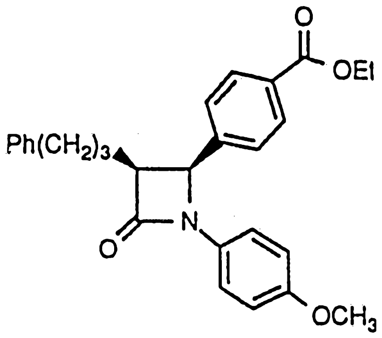
mp 158-159°C

Example 23



Add EDCI (0.2g, 1.03 mmoL) to a room temperature solution of the product of Example 22A (0.30, 0.72 mmol), N-methylmorpholine (0.11 mL, 0.94 mmol), morpholine (0.13 mL, 0.42mmol) and HOBT (0.12g, 0.87 mmol) in CH_2Cl_2 (8 mL). Stir the mixture overnight. Monitor by TLC (5% MeOH/CH_2Cl_2). Upon consumption of the starting compound, dilute with CH_2Cl_2, wash with 1M HCl, water, dry over anhydrous Na_2SO_4, filter and concentrate to a residue. Chromatogaph the residue (SiO_2, 3% MeOH/CH_2Cl_2) to afford 0.3g (86% yield) of the title compound, mp 61-62 °C.

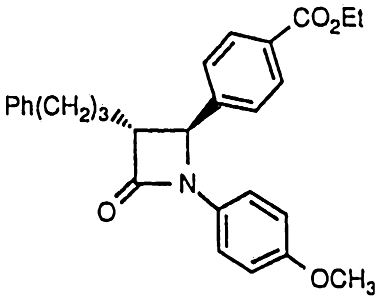
Example 24



Add EDCI (0.2g, 1.03 mmoL) to a room temperature solution of the product of Example 22A (0.30, 0.72 mmol), N-methylmorpholine (0.11 mL, 0.94 mmol), ethanol (0.1 mL, 1.44 mmol) and HOBT (0.12g, 0.87 mmol) in CH_2Cl_2 (8 mL). Stir the mixture overnight. Monitor by TLC (5% MeOH/CH_2Cl_2). Upon consumption of starting compound, dilute with CH_2Cl_2, wash with 1M HCl, water, dry over anhydrous Na_2SO_4, filter and concentrate to a residue. Chromatogaph the residue (SiO_2, 3% MeOH/CH_2Cl_2) to afford 0.33g (100% yield) of the title compound, mp 76-77 °C.

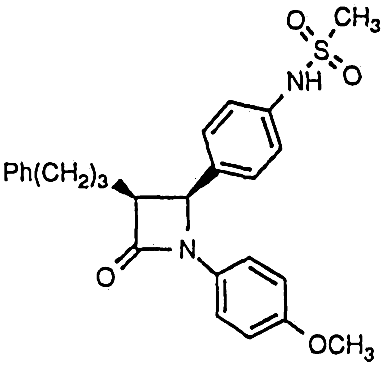
The following compound can be prepared by substantially the same procedure:

Example 24A



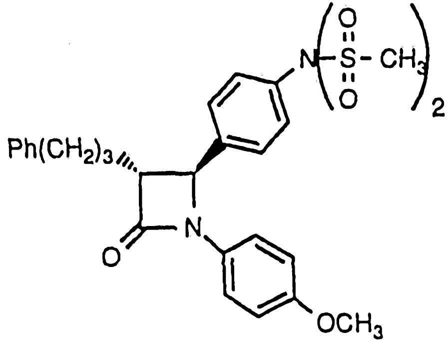
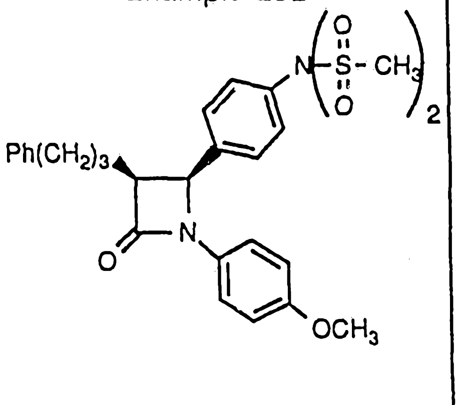
mp 74-75°C

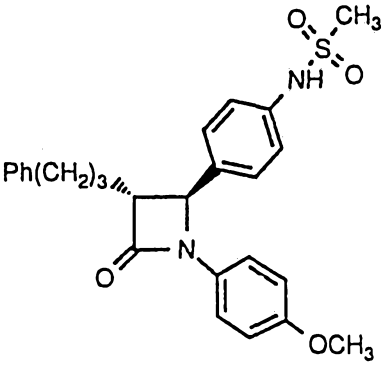
Example 25



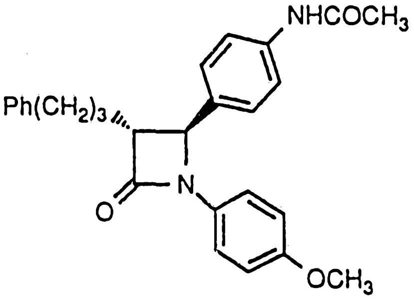
Add methanesulfonyl chloride (0.05 mL, 0.67 mmoL) to a 0°C solution of the product of Example 8B (0.26, 0.67 mmol), pyridine(3 drops) in CH_2Cl_2 (5 mL). Stir the mixture overnight. Monitor by TLC (50% EtOAc/hexanes). Upon consumption of starting material, dilute with CH_2Cl_2, wash with 0.5M HCl, 5% $NaHCO_3$, water and brine, dry over anhydrous sodium sulfate, filter and concentrate to a residue. Chromatogaph the residue (SiO_2, 50% EtOAc/hexanes) to afford 0.18g (58% yield) of the title compound, FAB MS (M+1) = 465.

By substantially the same procedure, the following compounds can be prepared:

Example 25A	Example 25B
	
mp 170.5-171.5°C	mp 175-176°C

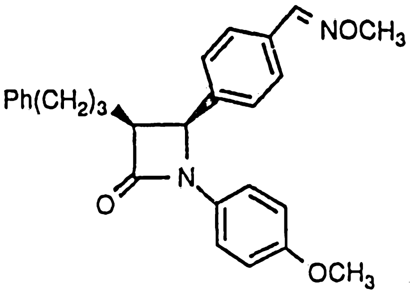
Example 25C  EI MS (M) = 542	

Example 26

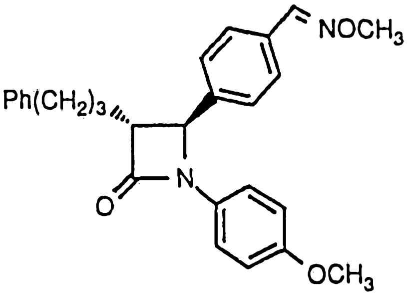


Add acetyl chloride (0.04 mL, 0.57 mmoL) to a solution of the product of Example 8C (0.20, 0.52 mmol) and triethylamine(0.11 mL, 0.79) in CH_2Cl_2 (3 mL) at room temperature . Monitor by TLC (50% EtOAc/hexanes). Upon consumption of starting material (~3h), dilute with CH_2Cl_2, wash with 5% $NaHCO_3$, water and brine, dry over anhydrous Na_2SO_4, filter and concentrate to afford 0.19g, (85% yield) of the title compound, mp 153-154 °C.

Example 27

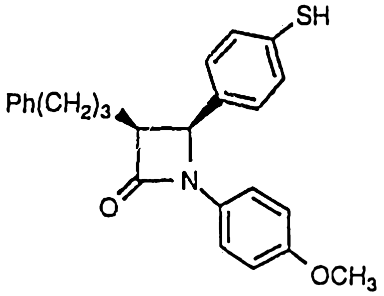


Reflux a suspension of the product of Example 16 (0.6g, 1.5 mmol), hydroxylamine hydrochloride (0.4g, 4.5 mmoL), sodium acetate (0.4g 4.5 mmol), methanol (12mL) and water (5mL) overnight. Monitor by TLC (50% EtOAc/hexanes). Upon consumption of starting material, evaporate to dryness, partition the residue between water and ethyl acetate, extract with EtOAc, combine the extracts, wash with water and brine, dry over anhydrous Na_2SO_4, filter and concentrate to a residue. Chromatograph the residue (silica gel, 20% EtOAc/hexanes) to provide the title compound mp 98-99 °C; and Example 27A:



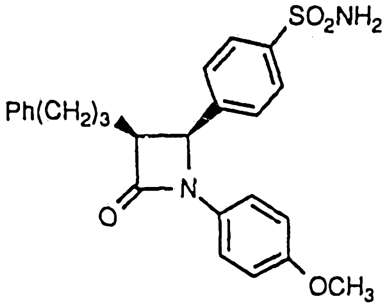
mp 63-64° C

Example 28



Reflux a solution of the product of Example 17 (3.2g, 7.38 mmol), CH_2Cl_2 (15 mL) trifluoracetic anhydride (15 mL) for 15 min. Monitor the reaction by TLC (100% EtOAc). Upon consumption of starting material, distill to remove most of solvent, cool to room temperature, and evaporate to a residue. Dissolve the residue in 50% triethylamine/methanol solution (30 mL) stir for 15 min., evaporate to dryness on a rotovap. Redissolve in CH_2Cl_2, wash with NH_4Cl (sat.), dry over anhydrous Na_2SO_4, filter and concentrate onto enough silica gel (1g SiO_2/ mmol substrate) that a free flowing powder results. Load the powder onto a chromatography column packed with silica gel and 30 % EtOAc/hexanes. Elute with 30-60% EtOAc/hexanes to provide 2.65g (89%) of a residue. Recrystallize from Et_2O/CH_2Cl_2 to give the title compound, mp 134-135°C.

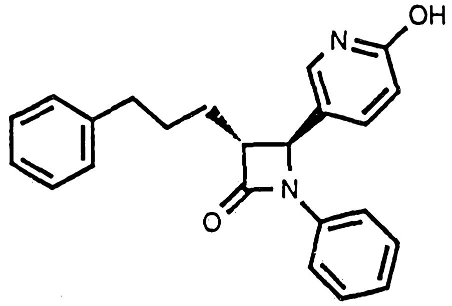
Example 29



Dissolve the product of Example 28 (1.81g, 4.49 mmol) in THF (25 mL) cool to 0 °C. Add 1N NaOH (5.39 mL, 5.39 mmol), and a solution of aqueous ammonia (16.8 mL, 5.39 mmol), followed by cholorox (6.7 mL, 5.39 mmol). Monitor the reaction by TLC (50% EtOAc/hexane). Upon consumption of starting material, dilute with EtOAc, wash with water and brine, dry over anhydrous Na_2SO_4 and concentrate to provide the sulfinamine (1.88g).

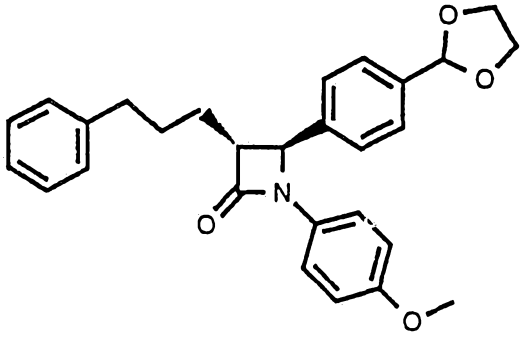
Dissolve the sulfinamine (1.88g, 4.49 mmol) in CH_2Cl_2 (50 mL), add m-chloroperbenzoic acid (1.70g, 9.88 mmol). Monitor the reaction by TLC (50% EtOAc/hexane). Upon consumption of starting material, quench with solid $Ca(OH)_2$ (1.78g, 24.0 mmol), stir for 20 min., filter and concentrate onto enough silica gel (1g SiO_2/ mmol substrate) that a free flowing powder results. Load the powder onto a chromatography column packed with silica gel and 50 % EtOAc/hexanes. Elute with 50% EtOAc/hexanes to provide 0.49g (24%) of the title compound, mp 174-176°C.

Example 30



Add BBr_3 (5.15 mL, 5.15 mmol, 1M in CH_2Cl_2) to a 0 °C solution of the compound of Example 70 (0.768g, 2.06 mmol) in CH_2Cl_2 (25 mL). Monitor the reaction by TLC (30% EtOAc). Upon consumption of starting material, quench with $NaHCO_3$ (sat.) and methanol, stir for 30 min., wash with $NaHCO_3$ (sat.) and water, dry over anhydrous Na_2SO_4, filter and concentrate onto enough silica gel (1g SiO2/ mmol substrate) such that a free flowing powder results. Load the powder onto a chromatography column packed with silica gel and 100% EtOAc. Elute with 100% EtOAc followed by 5% MeOH/EtOAc to provide 0.234g (32%) of the title compound, CI MS (M+1) = 359.

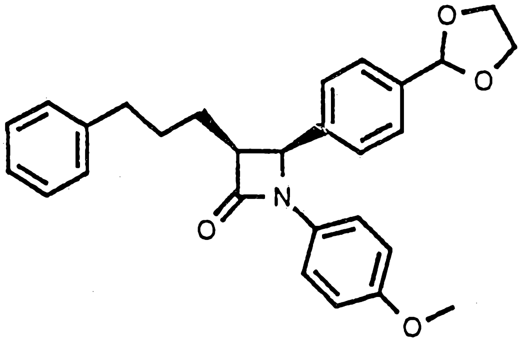
Example 31



Reflux a mixture of the product of Example 16 (0.23g, 0.6 mmol) ethylene glycol (0.2mL, 3.6 mmol), p-toluene sulfonic acid and toluene (5 mL) overnight. Monitor by 1H NMR and TLC (50% EtOAc/hexanes). Cool to room temperature, wash with $NaHCO_3$(sat.), water and brine, dried over anhydrous Na_2SO_4, and concentrate to give 0.27g (100%) of the title compound, EI MS (M) = 443.

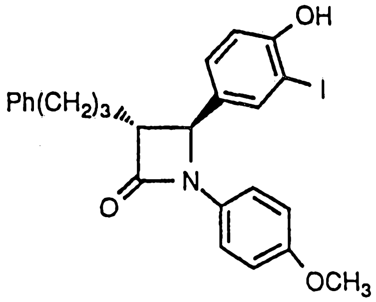
The following compound can be prepared by substantially the same procedure:

Example 31A

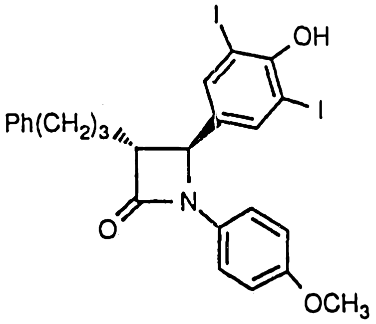


EI MS (M) = 443

Example 32

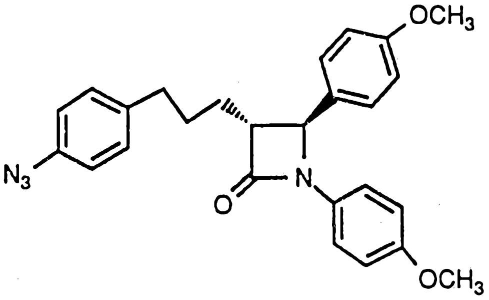


Stir a solution of 388mg (1.00 mmol) of the compound of Example 8F, and 180mg (1.20 mmol) chloramine-T NaI in 4.6 mL DMF. Add 377mg (1.2mmol) and stir for 18h at room temperature. Partition the reaction between 30 mL 1N HCl and 30 mL ethyl acetate. Wash the organic layer with 10% aqueous Na_2SO_3 and dry the organic solution with $MgSO_4$. Concentrate in vacuo and chromatograph the residue over (silica gel, 40% ethyl acetate-hexane) to give 170mg of the title compound, CI MS (M+1) = 514, and 41mg of the diodo analog (Example 32A):



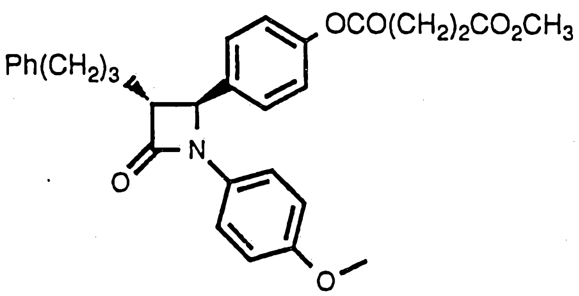
CI MS (M+1) = 640

Example 33



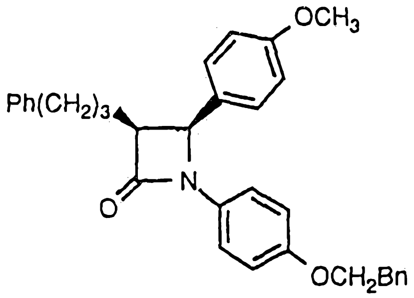
Stir 400 mg (0.96 mmol) of the compound of Example 8E, in 25 mL acetic acid and 5mL water at 0°C and add 133 mg (1.92 mmol) $NaNO_2$ in 4.7 mL water. Stir for 20 min. at 0°C add 212 mg (3.26 mmol) NaN_3 in 9 mL water and stir for 3h while warming to room temperature. Dilute with ethyl acetate and neutralize with NH_4OH. Dry the ethyl acetate layer with $MgSO_4$ and concentrate to a residue. Recrystallize the residue from ether-hexanes to give the titled compound, mp = 80 - 84°C.

Example 34



Dissolve 300 mg (0.77 mmol) of the compound of Example 8F, in 3 mL CH_2Cl_2 and add 98 µL (120 mg, 0.80 mmol) 3-carbomethoxypropionyl chloride and 146 µL (109 mg, 0.84 mmol) Hünig's base. Stir at room temperature for 1.5h. Add another full portion of acid chloride and Hünig's base and stir for an additional hour. Partition the reaction between ethyl acetate and 1N HCl. Dry the ethyl acetate layer with $MgSO_4$ and concentrate to a residue. Chromatograh the residue (SiO_2, 40% ethyl acetate-hexane) and filter through grade I basic alumina eluting with 50%ethyl acetate-hexane to give 334 mg (86%) of the title compound, EI MS (M+) = 501.25.

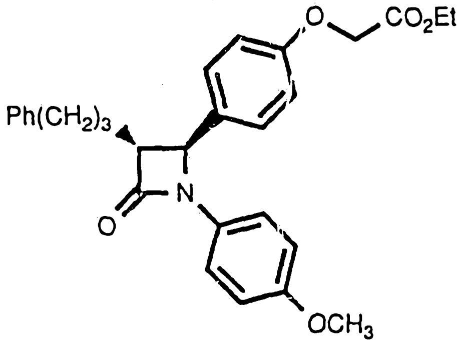
Example 35



Benzyl bromide (0.44 g) was added to a solution of the compound of Example 15B (1.0 g) in acetone (15 mL) containing K_2CO_3 (0.715 g). The reaction was heated at reflux for 26 h. The reaction mixture was then poured into water and the product extracted with ethyl acetate. The crude product was recrystallized from ethyl acetate/hexane to give (0.908 g, 74% yield) of the desired product, mp 115-116°C.

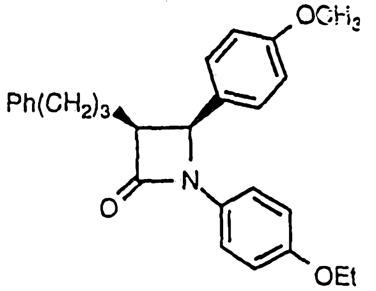
The following compounds were prepared via substantially the same procedure:

Example 35A



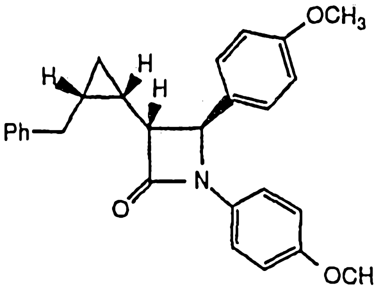
CI MS (M+1) = 474

Example 35B



Elemental analysis:
calculated for $C_{27}H_{29}NO_3$:
C, 78.04; H, 7.03; N 3.37
Found: C, 78.00; H, 7.02; N, 3.55

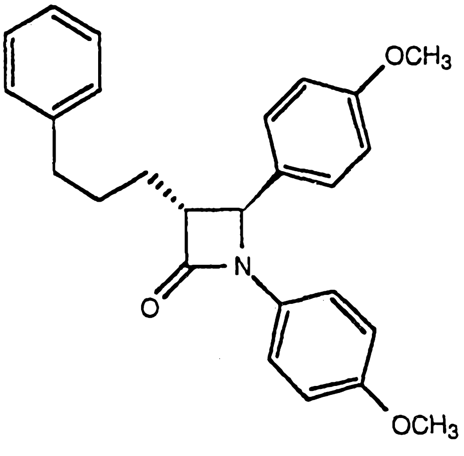
Example 36



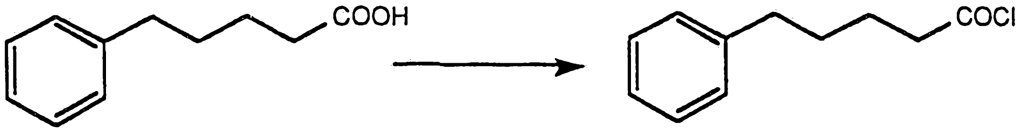
The compound of Example 7AI (0.19 g) was cooled to -20°C. To this ws added a solution of diethyl zinc in toluene(4.3 mL of a 1.1 M solution) followed by diiodomethane (2.56 g). The reaction mixture was slowly allowed to warm to ambient temperature over three hours. Then the reaction mixture was warmed to 45°C for 5 min. After cooling the reaction mixture was treated with aqueous NH_4Cl and product extracted with diethyl ether. The organic layer was washed with water, brine and concentrated to a residue. The residue was purified by chromatography (SiO_2, ethyl acetate/hexane (3:7)) to give the title compound (0.17 g, 88% yield), Elemental analysis:

calculated - C, 78.42; H, 6.58; N, 3.39
found- C, 78.32; H, 6.48; N, 3.61.

Example 37

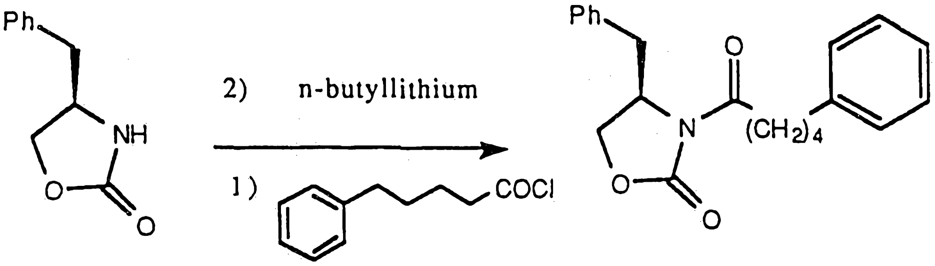


step (a)



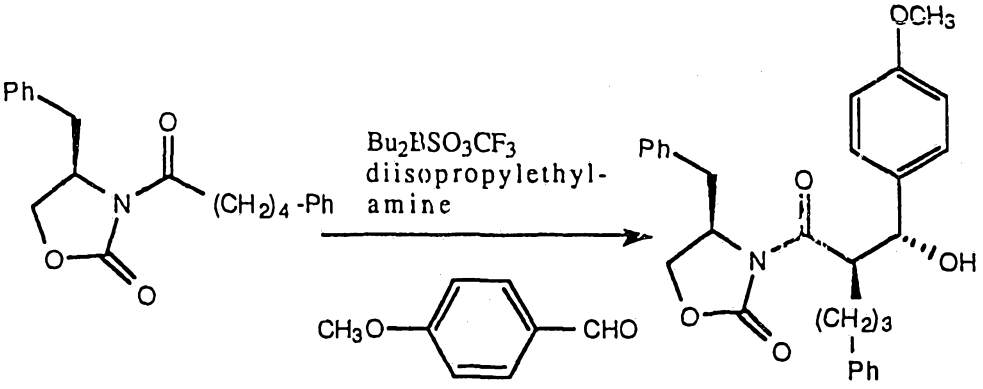
Combine 5-phenylvaleric acid (89.9 g, 0.504 mol) and $SOCl_2$ (89.3 mL, 1.225 mol) in a 500 mL round bottom flask equipped with a condenser and drying tube. Heat the flask to 70°C and maintain the reaction at reflux for 1h. Vacuum distill (50 - 100 mm Hg) the excess $SOCl_2$ and add 200 mL of dry toluene to the remaining mixture. Vacuum distill a second time to remove the toluene and any residual $SOCl_2$. Add 188 mL of dry THF to the crude acid chloride remaining in the reaction vessel and use the resulting solution directly in the next step.

step (b)



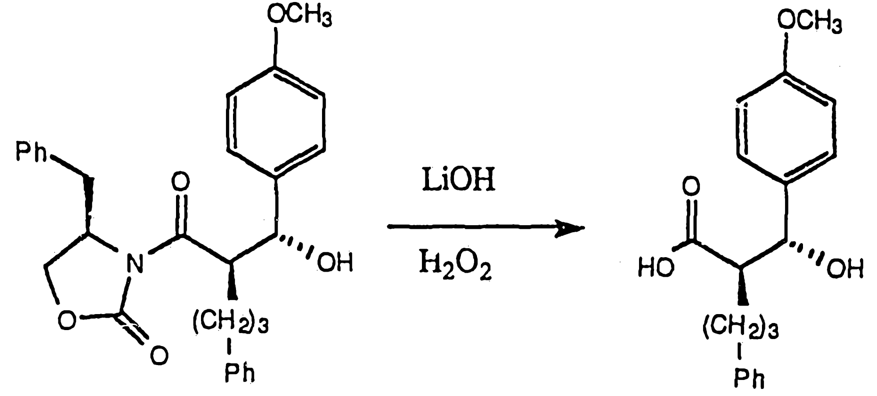
Combine 76 g (0.4289 mol) of R-(+)-4-benzyl-oxazolidinone and 1.3 L of dry THF under dry nitrogen atmosphere. Cool the resulting solution to -78°C and add 278 mL of a 1.6 M solution of n-butyllithium in hexane over a period of 30-40 minutes. Stir the mixture for an additional 30 minutes following the addition. Add the solution of 5-phenylvaleroyl chloride from step (a) over a period of 45 minutes. Allow the mixture to warm to 0°C and stir for 1 h. Quench the reaction mixture by adding 673.6 mL of K_2CO_3 (1 M aqueous solution) and stir for 1 h. Distill off the THF under vacuum at 30-35°C. Dilute the residue with 1 L of water and extract with three 800 mL portions of CH_2Cl_2. Combine the organic extracts and wash with 800 mL of water, then with 800 mL of brine. Dry the organic extracts over $MgSO_4$, filter, then concentrate *in vacuo* to an oil. Dissolve the oil in 200 mL of hexane, then distill off the hexane under vacuum. Repeat the hexane treatment two more times, then dissolve the oil in 1.7 mL of CH_2Cl_2. The resulting solution is used directly in the next step.

step (c)



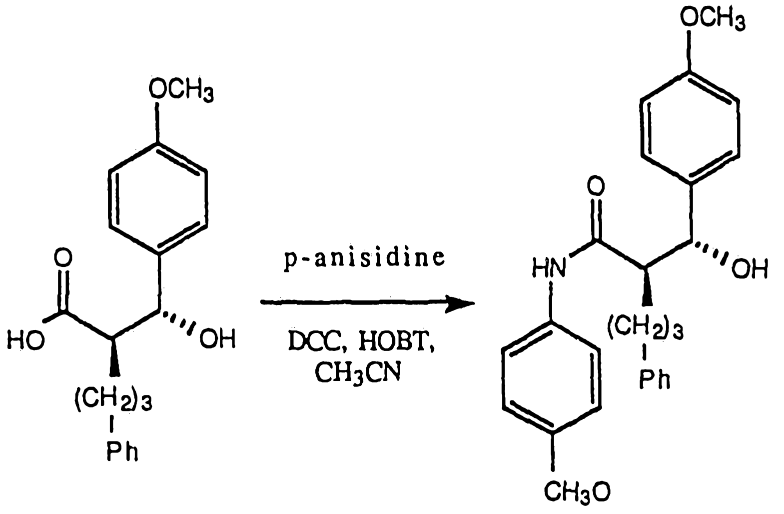
Cool the solution of the product from step (b) to -5°C to 0°C, under dry nitrogen atmosphere. Add 129.8 mL of di-n-butylboron triflate at a rate that maintains the temperature of the reaction mixture at -6°C to -3°C. Following the addition, stir the mixture for 10 minutes, then add 97.12 mL of diisopropylethylamine at a rate that maintains the temperature of the reaction mixture at -6°C to -3°C. Following the addition, stir the mixture at 0°C for 30 minutes, then cool the mixture to -78°C and stir for 30 minutes. Add 57.4 mL of p-anisaldehyde and stir the mixture at -78°C for 30 minutes, then at 0°C for 1 h. While maintaining the temperature at 0°C to 5°C, quench the mixture by adding 688.2 mL of a pH 7 buffer solution (68 g KH_2PO_4, 12 g NaOH and 800 mL of water), then add 473 mL of 30% H_2O_2 and stir the resulting mixture at 0°C for 1 h. Extract the mixture with three 600 mL portions of hexane:ethyl actetate (1:1). Combine the organic extracts and wash with 800 mL of saturated $NaHCO_3$ (aqueous), then with 800 mL of brine. Dry the organic extracts over $NaSO_4$, filter, and evaporate to an oil. Crystallize the oil from hexane/ethyl acetate (1:1) to give 176 g of the product as a white solid.

step (d)



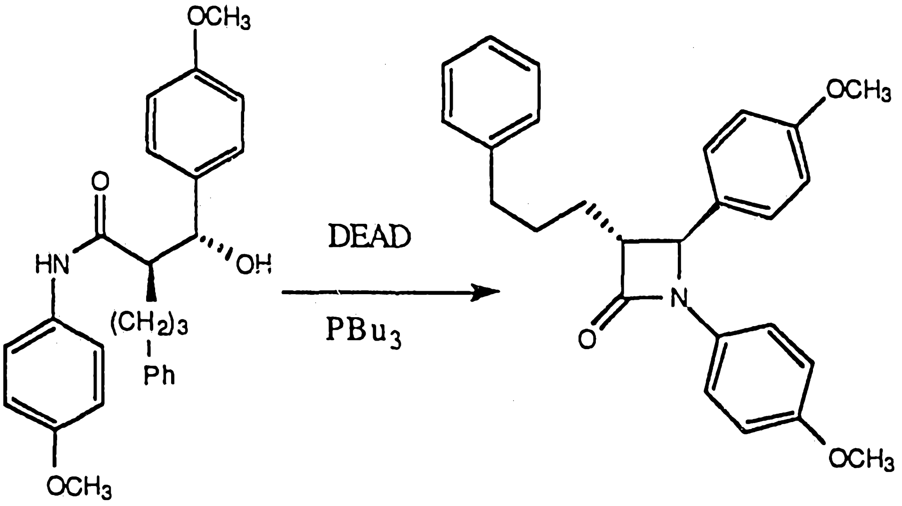
Combine the product of step (c) (170 g, 0.36 Mol), 1595 mL of THF and 400 mL of water, stir the mixture and cool to about 3°C. Add 226 mL (2.156 Mol) of 30% H_2O_2 to the mixture over 15 minutes, then add a solution of LiOH (36.2 g, 0.862 Mol) in 400 mL of water over a period of 30 minutes. Stir the reaction mixture at 0°C to 5°C for 3 h. Add a solution of 272 g of Na_2SO_3 in 850 mL of water over 70 minutes while keeping the temperature under 27°C. Distill off the bulk of the solvent under vacuum and add 7 L of water. Extract with four 1.7 L portions of toluene. Acidify the aqueous layers to pH 2.4 with 3 N HCl. Extract with one 2.6 L portion and two 1.7 L portions of ethyl acetate. Combine the ethyl acetate extracts, wash with brine, dry over $NaSO_4$, filter, then evaporate to give the product as a white solid. . 12 g.

step (e)



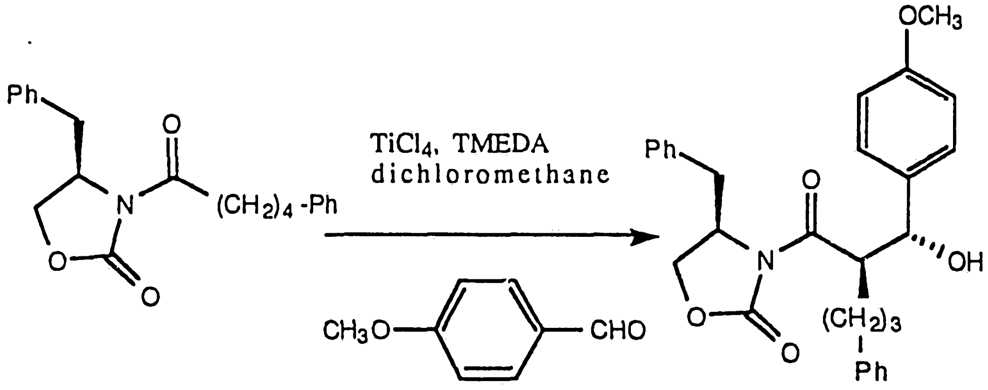
Combine the product of step (d) (19.47 g, 62 mmol), 400 mL of acetonitrile, 9.49 g (62 mmol) of 1-hydroxybenzotriazole (HOBT), 22.91 g (186 mmol) of p-anisidine and 14.05 g (68.2 mmol) of dicyclohexylcarbodiimide (DCC). Stir the reaction mixture at 40°C for 4 h and confirm the consumption of starting material by TLC (6:4 hexane/ ethyl acetate). Concentrate the mixture to 1/3 its volume and partition between 300 mL of water and 300 mL of ethyl acetate. Filter the organic layer, then wash with 200 mL of 1 N HCl, then with two 100 mL portions of saturated $NaHCO_3$, and two 100 mL portions of brine. Dry the organic layer over $NaSO_4$ and concentrate to give the product as a solid, 24 g.

step (f)



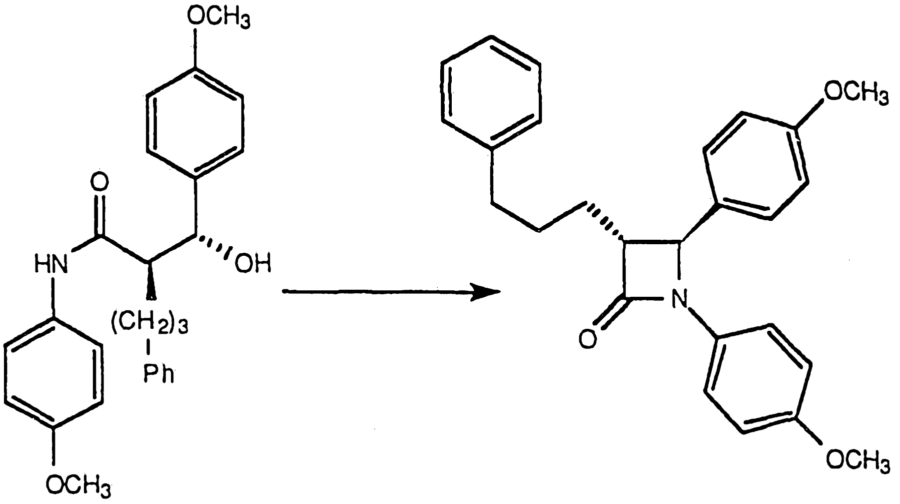
Combine the product of step (e) (115 g, 0.2745 Mol) and 2.3 L of THF under dry nitrogen atmosphere and cool to -70°C. Stir the mixture and simultaneously add a solution of 137 mL (0.551 Mol) of tri-n-butylphosphine in 113 mL THF, and 163 mL (1.03 Mol) of diethylazodicarboxylate (DEAD) over 2 h. Allow the mixture to warm to room temperature and stir overnight. Remove the solvent under vacuum. Filter the residue through a plug of silica gel using CH_2Cl_2/ hexane/ ethyl acetate (70:24:6) as the eluant. Evaporate the solvent and purify the residue by preparative HPLC (silica gel, 15% ethyl actetate/ hexane) to give 88 g (80% yield) of the β-lactam product.

Example 38

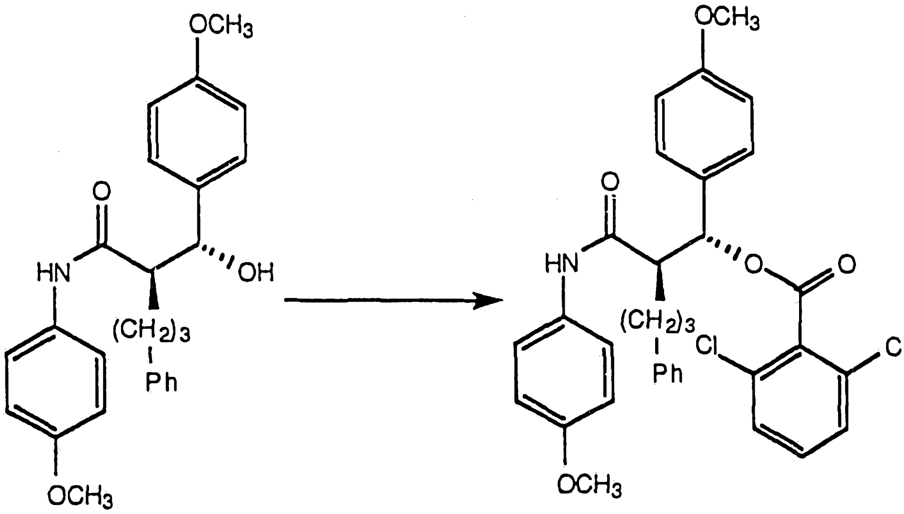


Cool a solution of 33.7 g (0.1 mol) of the product of Example 37, step (b), in 200 mL of CH_2Cl_2 to -20°C. Stir the cold solution and add 11 mL (0.1 mol) of $TiCl_4$. Stir the mixture for 10 min. at -20°C, then slowly add 30 mL (2 equiv.) of tetramethylethylenediamine (TMEDA) over a period of 10 min., while keeping the temperature below -10°C. Stir the mixture at -15° to -10°C for 70 min., then add 24 mL (2 equiv.) of p-anisaldehyde. Stir at -15° to -10°C for 1 hour, then allow the mixture to warm to 10°C while stirring for 40 min. Quench the reaction by adding 600 mL of 10% aqueous tartaric acid, then add 600 mL of ethyl acetate. Agitate well, then separate the layers, extracting the aqueous layer with another 200 mL of ethyl acetate. Combine the organic extracts and wash successively with water, saturated $NaHCO_3$ (aqueous) and brine. Dry the organic solution over anhydrous Na_2SO_4, filter, then concentrate to a residue. Crystallize the residue from a mixture of 100 mL of ethyl acetate + 210 mL of hexane to give 36.8 g of the desired compound, which can be used in step (d) of Example 37.

Example 39

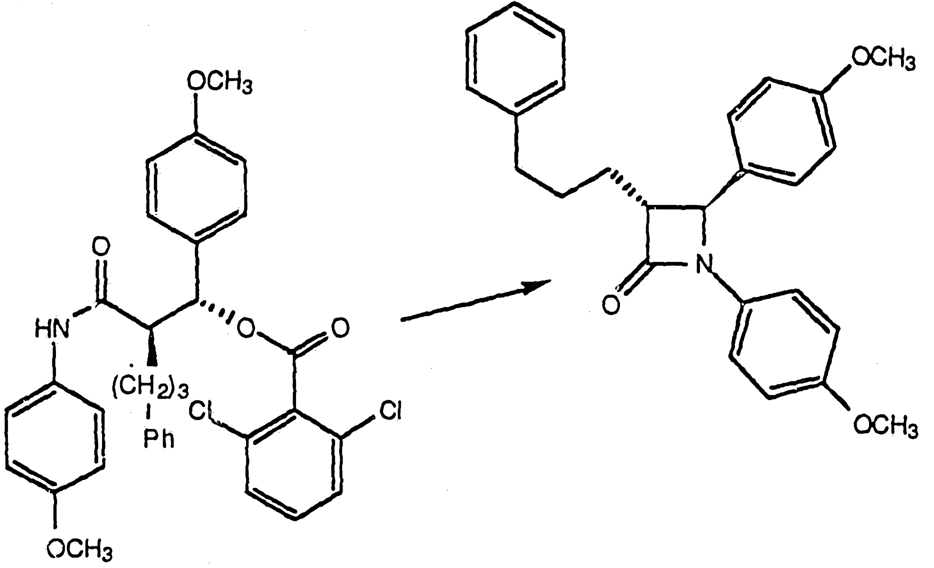


Step (a)



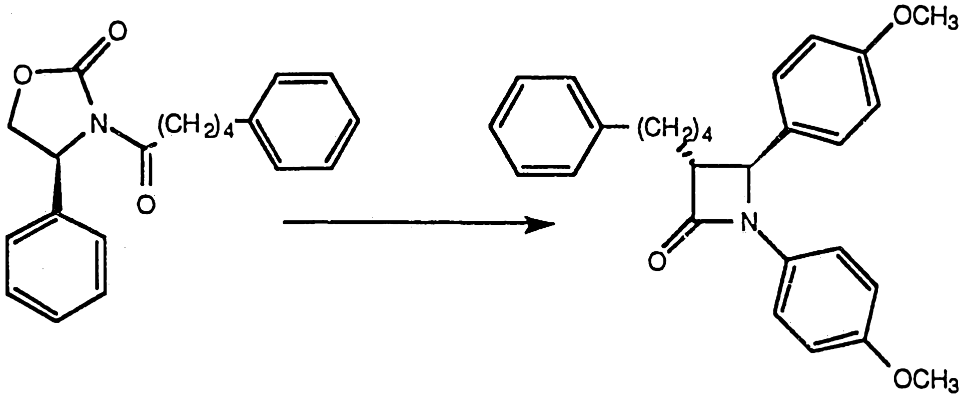
Dissolve 500 g (0.85 mol) of the product of Example 37, step(e), in 1700 mL of CH_2Cl_2, then add 4.0 g (12 mmol) of tera-n-butylammonium hydrogen sulfate. Stir the mixture while cooling to 10° to 20°C and add 50% aqueous NaOH (200 g). Slowly add 60 g (285 mmol) of 2,6-dichlorobenzoyl chloride to the stirred mixture over a period of 30 min. Continue stirring at 15° to 20°C for 3 h., then pour the mixture into 2000 mL of cold water. Separate the layers and wash the organic layer with water until neutral pH is attained. Distill the methylene chloride solution to reduce the volume to 800 mL. Heat the solution to reflux and add 800 mL of heptane. Cool the hot solution to 0°C to crystallize. Collect the product by filtration to give 116 g of the dichlorobenzoate product.

Step (b)

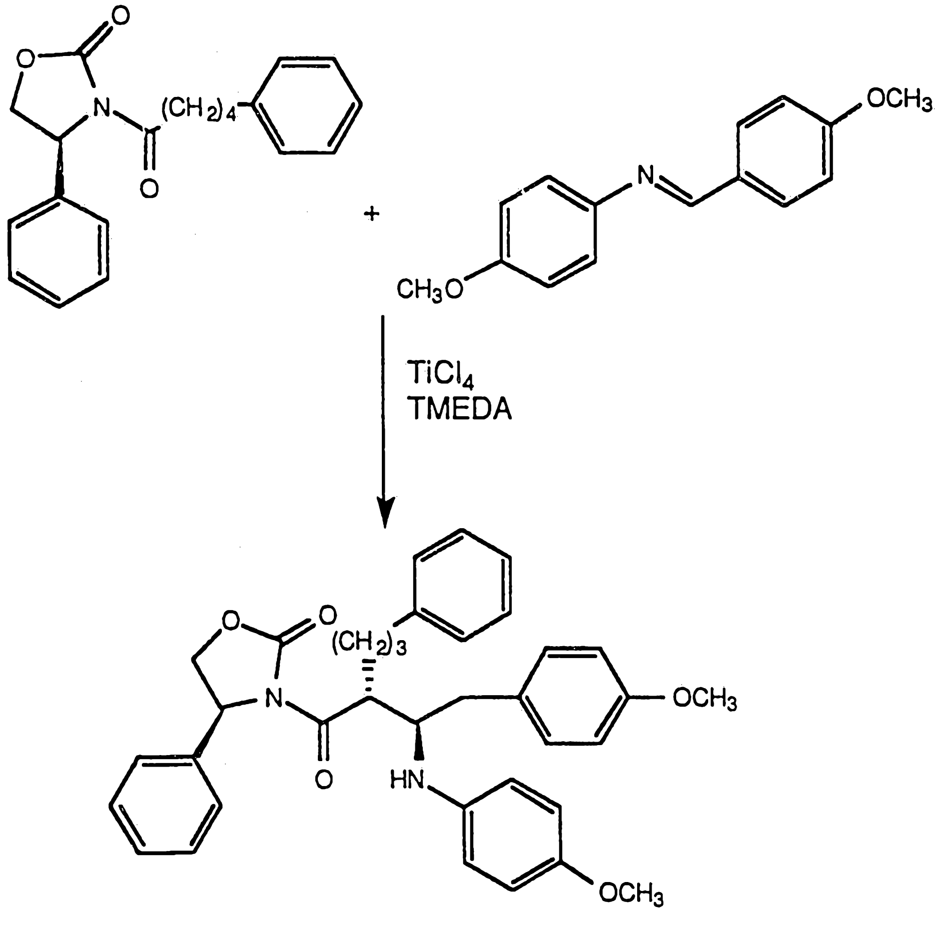


Combine 500 g (0.85 mol) of the product of step (a) with 250 g (1.1 mol) of benzyltriethylammonium chloride, 2000 mL of CH_2Cl_2 and 8000 mL of methyl t-butyl ether. Stir the mixture while cooling to 15° to 20°C, then add 1000 mL of 50% aqueous NaOH over a period of 10 min. Stir the mixture for 4 h., then pour into 5000 mL of water and 4 kg of ice. Separate the layers and wash the organic layer with water until the pH is neutral. Distill the solvent to reduce the volume to 2000 mL, then filter. Evaporate the filtrate to a residue and purify the residue by chromatography on silica gel to obtain the crude product. Crystallize the product from 6 volumes of a 1:2 mixture of methyl t-butyl ether and heptane at 0°C to give the product (240 g).

Example 40

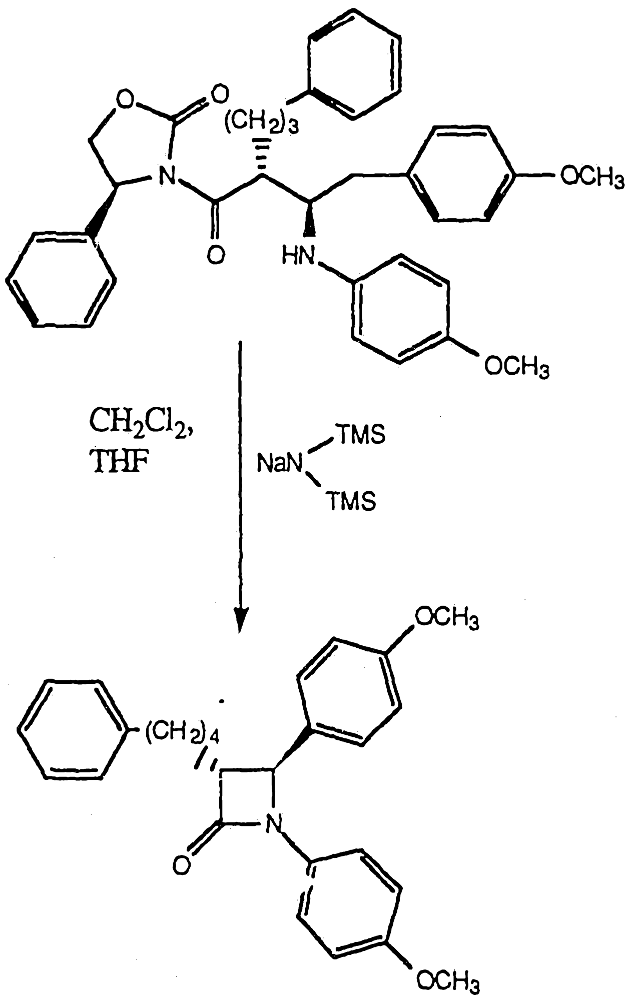


5 Step (a):



Dissolve 3.23 g (10 mmol) of the product of Example 37, step (b), in 50 mL of CH_2Cl_2, then stir under nitrogen atmosphere while cooling to -20°C. Add 10 mL (10 mmol) of a 1M solution of $TiCl_4$ in CH_2Cl_2, stir the mixture for 5 min., then add 1.5 mL (10 mmol) of TMEDA. Stir the mixture at -25° to -20°C for 1 h., then slowly add 4.8 g (20 mmol) of the Schiff's base derived from anisaldehyde and p-anisidine as a solution in 50 mL of CH_2Cl_2 over a period of 30 min. Stir the mixture at -20°C for 30 min, then gradually warm to 0°C. The reaction is monitored by HPLC (Zorbax® Sil column, 1:4 ethyl acetate/hexane), while stirring at 0°C, until complete. Quench the mixture by pouring into 50 mL of 10% aqueous tartaric acid. Extract with ethyl acetate, then wash the organic extract successively with saturated $NaHCO_3$ (aqueous) and brine. Dry the organic solution over anhydrous Na_2SO_4, filter, then concentrate to give the crude product. Crystallize from ethyl acetate/hexane to give the purified product.

Step (b):



A solution of 0.505 g (0.89 mmol) of the product of step (a) in 25 mL of CH_2Cl_2 is stirred at 0°C, then treated with 1.77 mL (1.77 mmol) of a 1M solution of sodium bistrimethylsilylamide in THF. Stir the mixture while warming to room temperature, then continue stirring until the starting material is gone as determined by HPLC (typically 1 to 1 1/2 h.) Quench the mixture into 10% tartaric acid (aqueous). Wash the organic layer successively with saturated $NaHCO_3$ (aqueous) and brine, then dry over anhydrous Na_2SO_4. Filter and concentrate to give the title compound.

The following formulations exemplify some of the dosage forms of this invention. In each the term "active compound" designates a compound of formula I or II, preferably (3R,4S)-1,4-bis-(4-methoxyphenyl)-3-(3-phenylpropyl)-2-azetidinone. However, this compound may be replaced by an equally effective amount of other compounds of formula I or II.

EXAMPLE A

Tablets

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B
Capsules

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70
4	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

Using the test procedures described above, the following in vitro and in vivo data were obtained for the preferred compounds, which are referred to in the following table by the corresponding example numbers. For the in vitro ACAT data, negative percent inhibition denotes apparent stimulation, while positive numbers denote inhibition. For the in vivo results, data is reported as percent change versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

Ex.	ACAT (in vitro)			% Reduction (in vivo)		
	IC50 (mM)	% Inhib.	Conc. (mM)	Serum Cholest.	Cholest. Esters	Dose mg/kg
1	---	38	10	-45	-95	50
				-17	-55	10
				0	0	5
1A	7.5	83	25	-10	-26	100
1B	---	28	10	0	0	50
1C	---	22	10	-6	-15	50
1D	---	39	10	0	0	50
1E	---	3	10	---	---	---
1F	---	61	10	0	20	50
1G	---	21	10	-11	0	50
1H	---	57	10	-21	-51	50
1I	4.5	81	10	---	---	---
1J	3.0	86	10	---	---	---
1K	---	-70	10	0	0	50
1L	---	20	10	-31	-75	50
				-22	-34	10
				-25	-30	5
1M	7.0	80	10	-11	-31	25
1P	---	39	10	-19	-54	50
1S	---	-19	10	0	-32	85
1T	---	-11	10	0	0	50
1U	19	58	10	0	0	50
1V	---	64	10	---	---	---
1W	---	9	10	---	---	---
1X	---	9	10	-12	0	50
1Y	---	50	10	---	---	---
1Z	---	-15	10	-15	-39	50
1AA	--	-36	10	---	---	---
1AB	---	17	10	---	---	---
1AC	---	40	10	-16	-33	50

1AD	---	-5	10	---	---	---
1AE	---	-7	10	---	---	---
1AF	---	0	10	---	---	---
1AG	---	-3	10	-16	-29	50
1AH	---	4	10	---	---	---
1AI	---	27	10	---	---	---
1AJ	---	-17	10	0	0	50
1AK	---	-33	10	---	---	---
1AL	---	-43	10	0	0	50
1AM	---	---	---	-12	-29	50
1AN	---	---	---	-34	-85	50
1AO	---	---	---	-33	-78	50
1AP	---	---	---	-51	-95	50
1AQ	---	---	---	-20	-22	50
1AR	---	-41	10	-22	-25	50
1AS	1.0	83	10	0	-19	50
1AT	5.0	70	10	0	-28	50
1AU	---	44	10	0	-21	50
1AV	---	7	10	15	0	50
1AW	---	68	10	-14	-16	50
1AX	---	---	---	-16	-52	50
1AY	---	---	---	-28	-78	50
1AZ	---	---	---	-37	-91	50
1BA	---	---	---	0	-0	50
1BB	---	-16	10	0	0	50
1BC	---	-2	10	0	0	50
1BD	---	17	10	0	-25	50
1BE	---	30	10	-10	-21	50
1BF	---	-17	10	0	-23	50
1BG	---	3	10	12	0	50
1BH	---	50	10	0-	0	50
1BI	---	59	10	-17	-45	50
1BJ	---	56	10	0	0	50
1BK	---	55	10	0	0	50

1BL	---	42	10	-10	0	50
1BM	---	38	10	0	-21	50
1BN	7.0	---	---	-16	0	50
1BO	5.4	79	10	-48	-93	50
1BP	---	58	10	-9	0	50
1BQ	---	35	10	0	-17	50
1BR	---	---	---	-15	-70	50
1BS	---	---	---	0	-43	50
1BT	---	---	---	0	0	50
1BU	---	---	---	-39	-95	50
1BV	---	---	---	-11	0	50
1BW	---	---	---	-9	-29	50
1BX	---	---	---	0	0	50
1BY	---	---	---	-18	-72	50
1BZ	---	---	---	-9	0	50
1CA	---	---	---	-12	0	50
1CB	---	33	10	0	0	50
1CC	---	46	10	0	0	50
1CD	7.0	84	10	0	-23	50
1CE	---	15	10	-19	-17	50
1CF	---	53	10	-23	-47	50
1CG	---	8	10	-30	-61	50
1CH	---	---	---	-49	-95	50
				-41	-90	10
				-24	-80	3
1CI	---	26	10	-8	-23	50
1CJ	---	---	---	0	0	50
1CK	---	-12	10	0	-28	50
1CL	---	89	10	0	-18	50
1CM				0	0	50
1CN	---	-28	10	0	0	50
2	6.0	82	10	-15	-37	5
				-28	-69	10
2A	25	---	---	0	0	50

3	---	56	10	0	0	50
3A	---	33	10	-12	-29	50
3B	6.0	84	10	-11	-16	50
3C	---	-18	10	---	---	---
3D	12	42	10	0	0	50
3E	---	-24	10	0	0	50
3F	1.7	82	10	0	-31	50
3G	5.0	74	10	9	0	50
3H	---	66	10	-10	31	50
3I	---	43	10	-9	0	50
3J	---	45	10	0	-16	50
3K	---	19	10	0	0	50
3L	---	53	10	0	0	25
3M	---	13	10	0	0	50
3N	---	62	10	0	0	50
3O	---	-28	10	0	0	50
3Q	---	3	10	-6	0	50
3R	---	-8	10	0	0	50
3T	---	-9	10	---	---	---
3U	---	46	10	0	0	50
3V	6.5	60	10-	0	0	50
3W	---	56	10	0	0	50
3X	---	3	10	---	---	---
3Y	---	-33	10	0	0	50
4	---	16	10	---	---	---
5	18	33	10	-29	-77.5	50
				-20	-72	25
				-21	-60	10
5A	---	-70	10	---	---	---
5C	---	21	10	-17	-24	50
5D	---	---	---	-38	-95	50
				-41	-94	30
				-24	-77	10
5E	---	---	---	-38	-91	50

5F	---	---	---	-44	-98	50
				-15	-59	30
				-13	-25	10
5G	---	---	---	-44	-93	50
5H	---	---	---	-57	-96	50
5I	---	---	---	-26	-70	50
5J	---	---	---	-38	-90	50
5K	---	---	---	-28	-49	50
5L	---	---	---	-50	-95	10
				-39	-84	3
				-54	-64	1
5M	---	---	---	-8	-36	10
				-12	0	3
				-20	-50	50
5N	---	-23	10	-17	-55	50
5P	---	53	10	-11	-33	50
5Q	---	-36	10	0	-19	50
5R	---	18	10	-20	-21	50
5S	---	28	10	-52	-98	50
5T	---	---	---	-15	-48	50
5U	---	---	---	-48	-86	50
5V	---	---	---	-37	-77	50
5W	---	-16	10	0	-19	50
5X	---	38	10	0	-39	50
5Y	---	---	---	-29	0	50
5Z	---	---	---	-16	0	50
5AA	---	---	---	-53	-93	50
5AB	---	30	10	-28	-72	50
6	5	59	10	14	0	50
7	---	---	---	-49	-95	40
				-41	-89.5	10
				-30	-50	3
7A	---	---	---	-22	-54	50
7B	---	---	---	-13	-45	50

7C	---	---	---	-51	-95	50
7D	---	---	---	-35	-74	50
7E	---	---	---	-52	-93	50
7F	---	---	---	0	-26	50
7J	---	---	---	-21	-27	50
7K	---	---	---	0	-32	50
7L	--	---	---	0	0	50
7M	---	---	---	-38	-94	50
7N	---	---	---	-11	0	50
7O	---	---	---	-14	-20	50
7P	---	---	---	-40	-95	50
7Q	---	---	---	-16	0	50
7R	---	---	---	-35	-80	50
7S	---	---	---	-27	-82	50
7T	---	---	---	-49	-93	50
7U	---	---	---	-29	-60	50
7V	---	---	---	0	0	50
7W	---	---	---	12	0	50
7X	---	---	---	-26	-78	50
7Y	---	---	---	-53	-94	50
				-27	-79	10
				-22	-55	3
7Z	---	---	---	-21	-39	50
7AA	---	---	---	-10	-42	50
7AC	---	31	10	0	0	50
7AD	---	-22	10	-12	-12	50
7AE	---	-95	10	-17	-10	50
7AF	---	53	10	23	-15	50
7AG	---	---	---	0	-15	50
7AH	---	-5	10	16	16	50
7AI	---	---	---	-63	-95	50
				-20	-73	10
				-11	-46	3
7AJ	---	---	---	0	-18	50

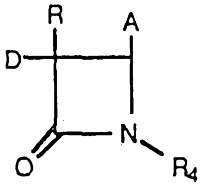
7AK	---	---	---	12	-28	50
7AL	---	---	---	-13	0	50
7AM	---	---	---	-24	-70	50
7AN	---	---	---	-12	-42	50
7AO	---	---	---	-41	-90	50
7AP	---	---	---	-24	-82	50
7AQ	---	---	---	-52	-91	50
7AR	---	---	---	-32	-88	50
7AS	---	---	---	0	-20	50
7AT	---	---	---	-10	-32	50
8	---	-12	10	---	---	---
8A	---	-17	10	0	0	50
8B	---	-5	10	-9	-35	50
8C	---	63	10	0	0	50
8E	---	---	---	0	-32	50
8F	---	8	10	-16	-48	50
				-20	-45	25
9	26	30	20	-43	-93	10
				-21.5	-66	5
				-25	-68	3
10A	---	-37	10	-19	-58	50
11	---	---	---	-8	0	50
12	---	---	---	-12	0	50
12A	---	---	---	-14	-39	50
12B	---	---	---	0	-26	50
12C	---	---	---	0	0	50
12D	---	---	---	0	0	50
13	---	---	---	-18	0	50
14	---	---	---	30	-87	50
14A	---	---	---	31	-78	50
14B	---	---	---	0	0	50
14C	---	---	---	0	0	50
15	---	-6	10	-21	-46	50
15A	---	2	10	0	0	50

15B	---	-55	10	0	-18	50
16	---	42	10	-25	-29	50
16A	---	55	10	-30	-53	50
17	---	25	10	-17	-52	50
17A	---	38	10	-11	-25	50
17B	---	---	---	0	-39	50
18	---	---	---	0	0	50
19	---	24	10	-20	-51	50
19A	---	64	10	-20	-34	50
19B	---	53	10	-26	-31	50
19C	---	---	---	-9	-46	50
19D	---	---	---	-15	-18	50
19E	---	---	---	-19	-30	50
20	---	---	---	12	0	50
21	---	---	---	-27	-56	50
21A	---	---	---	0	-25	50
22	---	---	---	-17	-33	50
22A	---	---	---	-16	-22	50
23	---	---	---	-22	-40	50
24	---	---	---	-17	0	50
24A	---	---	---	-21	-76	50
25	---	---	---	-8	-34	50
25A	---	---	---	-13	0	50
25B	---	---	---	0	0	50
25C	---	---	---	-8	-46	50
26	---	---	---	-4	-26	50
27	---	---	---	-12	-36	50
27A	---	---	---	-15	-42	50
28	---	---	---	-19	0	50
29	---	---	---	-22	-24	50
31	---	---	---	-19	-52	50
31A	---	---	---	0	0	50
32	---	---	---	0	0	50
32A	---	---	---	0	0	50

33	---	---	---	0	0	50
34	---	---	---	-39	-94	50
35	---	18	10	-15	-32	50
35A	---	---	---	-34	-84	50
35B	---	65	10	-53	-99	50
36	---	---	---	-53	-94	50

We claim:

1. A compound having the structural formula



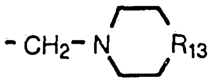
wherein

A is -CH=CH-B;

-C≡C-B;

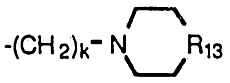
$-(CH_2)_p-X-B$, wherein p is 0, 1 or 2 and X is a bond, -NH- or $-S(O)_{0-2}-$;

heteroaryl, benzofused heteroaryl, W-substituted heteroaryl or W-substituted benzofused heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, and wherein W is 1-3 substituents on the ring carbon atoms selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, $-NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, halogeno, $-NHC(O)OR_5$, $-NHC(O)R_5$, R_6O_2SNH-, $(R_6O_2S)_2N-$, $-S(O)_2NH_2$, $-S(O)_{0-2}R_{10}$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$ and



, and wherein the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, $-C(O)OR_5$, $-C(O)R_5$, OH, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, $-S(O)_2NH_2$ and 2-(trimethylsilyl)ethoxymethyl;

-C(O)-B; or



, wherein k is 1 or 2;

D is B'-$(CH_2)_m$C(O)-, wherein m is 1, 2, 3, 4 or 5;

B'-$(CH_2)_q$-, wherein q is 2, 3, 4, 5 or 6;

B'-$(CH_2)_e$-Z-$(CH_2)_r$-, wherein Z is -O-, -C(O)-, phenylene, -NR_8- or -$S(O)_{0-2}$-, e is 0, 1, 2, 3, 4 or 5 and r is 1, 2, 3, 4 or 5, provided that the sum of e and r is 1, 2, 3, 4, 5 or 6;

B'-(C_2-C_6 alkenylene)-; B'-(C_4-C_6 alkadienylene)-;

B'-$(CH_2)_t$-Z-(C_2-C_6 alkenylene)-, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

B'-$(CH_2)_f$-V-$(CH_2)_g$-, wherein V is C_3-C_6 cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

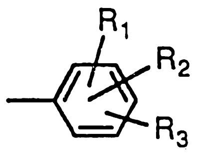
B'-$(CH_2)_t$-V-(C_2-C_6 alkenylene)- or B'-(C_2-C_6 alkenylene)-V-$(CH_2)_t$-, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

B'-$(CH_2)_a$-Z-$(CH_2)_b$-V-$(CH_2)_d$-, wherein Z and V are as defined above and a ,b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6;

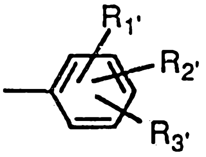
T-$(CH_2)_s$-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 1, 2, 3, 4, 5 or 6; or

naphthylmethyl, heteroarylmethyl, or W-substituted heteroarylmethyl, wherein heteroaryl and W are as defined above;

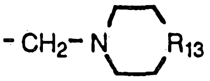
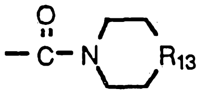
B is

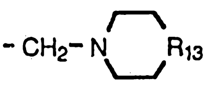
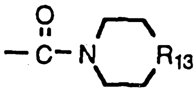


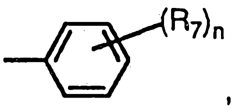
B' is naphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is as defined above, or



R is hydrogen, fluoro, C_1-C_{15} alkyl, C_1-C_{15} alkenyl, C_1-C_{15} alkynyl, or B-$(CH_2)_h$ -, wherein h is 0, 1, 2, or 3;

R_1, R_2 and R_3 are independently selected from the group consisting of H, lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, $-NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, o-halogeno, m-halogeno, $-NHC(O)OR_5$, $-NHC(O)R_5$, R_6O_2SNH-, $(R_6O_2S)_2N$-, $-S(O)_2NH_2$, $-S(O)_{0\text{-}2}R_{10}$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$,  and  , or R_1 is hydrogen and R_2 and R_3, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

$R_{1'}$, $R_{2'}$ and $R_{3'}$ are independently selected from the group consisting of H, lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, $-NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, halogeno, $-NHC(O)OR_5$, $-NHC(O)R_5$, R_6O_2SNH-, $(R_6O_2S)_2N$-, $-S(O)_2NH_2$, $-S(O)_{0\text{-}2}R_{10}$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$,  and  , or $R_{1'}$ is hydrogen and $R_{2'}$ and $R_{3'}$, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R_4 is , wherein n is 0, 1, 2 or 3, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl or quinolyl;

R_5 is lower alkyl, phenyl, R_{14}-phenyl, benzyl or R_{14}-benzyl;

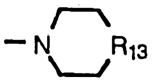
R_6 is OH, lower alkyl, phenyl, benzyl, R_{14}-phenyl or R_{14}-benzyl;

R_7 is lower alkyl, lower alkoxy, OH, halogeno, $-NR_{10}R_{11}$, $-NHC(O)OR_5$, $-NHC(O)R_5$, NO_2, -CN, $-N_3$, -SH, $-S(O)_{0-2}$-(lower alkyl), $-COOR_9$, $-CONR_{10}R_{11}$, $-COR_{12}$, phenoxy, benzyloxy, $-OCF_3$, or tert-butyldimethylsilyloxy, and where n is 2 or 3, the R_7 groups can be the same or different;

R_8 is H, lower alkyl, phenyl lower alkyl, or $-C(O)R_9$;

R_9 is H, lower alkyl, phenyl or phenyl lower alkyl;

R_{10} and R_{11} are independently selected from H and lower alkyl;

R_{12} is H, OH, alkoxy, phenoxy, benzyloxy, , $-NR_{10}R_{11}$, lower alkyl, phenyl or R_{14}-phenyl;

R_{13} is -O-, $-CH_2-$, -NH- or -N(lower alkyl)-; and

R_{14} is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO_2, $-NR_{10}R_{11}$, OH or halogeno;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein R is hydrogen.

3. A compound of claim 1 or 2 wherein D is $B'-(CH_2)_q-$, $B'-(CH_2)_e-Z-(CH_2)_r-$, $B'-(C_2-C_6$ alkenylene)- or $B'-(CH_2)_f-V-(CH_2)_g-$, wherein B', Z, V, q, e, r, f, and g are as defined in claim 1.

4. A compound of claim 3 wherein D is $B'-(CH_2)_q-$ wherein B' is phenyl and q is 3 or 4; $B'-(CH_2)_e-Z-(CH_2)_r-$ wherein B' is p-fluorophenyl or p-methoxyphenyl, e is zero, Z is -O-, and r is 2; $B'-(C_2-$

C_6 alkenylene)- is 3-phenyl-1-propenyl; or B'-$(CH_2)_f$-V-$(CH_2)_g$- wherein B' is phenyl, f is 1, V is cyclopropylene, and g is zero.

5. A compound of claim 1, 2, 3 or 4 wherein A is -$(CH_2)_p$-X-B wherein wherein X, B and p are as defined in claim 1.

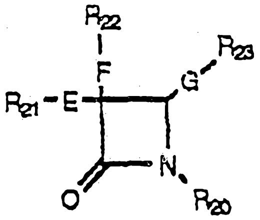
6. A compound of claim 5 wherein p is zero and X is a bond.

7. A compound of claim 6 wherein R_1, R_2 and R_3 are selected from the group consisting of H, OH, lower alkoxy, NO_2, alkoxyalkoxy, m-halogeno, lower alkyl lower alkandioyl, $NR_{10}R_{11}$(lower alkoxy)-, allyloxy, phenoxy, alkoxycarbonylalkoxy and -C(O)R_{12}.

8. A compound of claim 1, 2, 3, 4, 5, 6 or 7 wherein R_4 is phenyl, R_7-substituted phenyl or indanyl.

9. A compound of claim 8 wherein R_7 is selected from the group consisting of lower alkyl, lower alkoxy, halogeno, -OCF_3, lower alkylthio, -$NR_{10}R_{11}$, -CN, OH, and -COR_{12}.

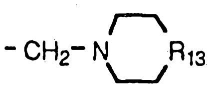
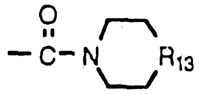
10. A pharmaceutical composition comprising a cholesterol-lowering effective amount of a compound having the structure



wherein

R_{20} is phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl and W-substituted benzofused heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof;

R_{21}, R_{22} and R_{23} are independently selected from H or R_{20};

W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy-, $-CF_3$, $-OCF_3$, benzyl, R_{14}-benzyl, benzyloxy, R_{14}-benzyloxy, phenoxy, R_{14}-phenoxy, dioxolanyl, NO_2, $-NR_{10}R_{11}$, $NR_{10}R_{11}$(lower alkyl)-, $NR_{10}R_{11}$(lower alkoxy)-, OH, halogeno, $-NHC(O)OR_5$, $-NHC(O)R_5$, R_6O_2SNH-, $(R_6O_2S)_2N-$, $-S(O)_2NH_2$, $-S(O)_{0-2}R_{10}$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$,  and ;

E, F and G are independently a bond; C_3-C_6 cycloalkylene; C_1-C_{10} alkylene; C_1-C_{10} alkenylene; C_1-C_{10} alkynylene; an alkylene, alkenylene or alkynylene chain as defined substituted by one or more substituents independently selected from the group consisting of phenyl, W-substituted phenyl, heteroaryl and W-substituted heteroaryl, wherein heteroaryl is as defined above; an alkylene, alkenylene or alkynylene chain as defined interrupted by one or more groups independently selected from the group consisting of -O-, -S-, -SO-, $-SO_2-$, $-NR_8$, -C(O)-, C_3-C_6 cycloalkylene, phenylene, W-substituted phenylene, heteroarylene and W-substituted heteroarylene; or an interrupted alkylene, alkenylene or alkynylene chain as defined substituted by one or more substituents independently selected from the group consisting of phenyl, W-substituted phenyl, heteroaryl and W-substituted heteroaryl; or one of R_{21}-E and R_{22}-F is selected from the group consisting of halogeno, OH, lower alkoxy, $-OC(O)R_5$, $-NR_{10}R_{11}$, -SH or -S(lower alkyl);

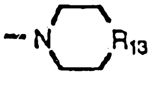
R_5 is lower alkyl, phenyl, R_{14}-phenyl, benzyl or R_{14}-benzyl;

R_6 is OH, lower alkyl, phenyl, benzyl, R_{14}-phenyl or R_{14}-benzyl;

R_8 is H, lower alkyl, phenyl lower alkyl or $-C(O)R_9$;

R_9 is H, lower alkyl, phenyl or phenyl lower alkyl;

R_{10} and R_{11} are independently selected from H and lower alkyl;

R_{12} is H, OH, alkoxy, phenoxy, benzyloxy,  , $-NR_{10}R_{11}$, lower alkyl, phenyl or R_{14}-phenyl;

R_{13} is -O-, $-CH_2-$, -NH- or -N(lower alkyl)-;

R_{14} is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO_2, $-NR_{10}R_{11}$, OH or halogeno;

provided that when G is a bond, R_{23} is not H, and provided that when R_{23} is W-substituted phenyl, W is not p-halogeno;

or a phamaceutically acceptable salt thereof;

in a pharmaceutically acceptable carrier.

11. A compound of claim 1 selected from those prepared in examples 1, 1A-1M, 1P, 1AM-1AZ, 1BA-1BZ, 1CA-1CI, 1CM-1CO, 3, 3A-3O, 5, 5B-5M, 5O-5Z, 5AA-5AB, 7, 7A-7I, 7M-7Z, 7AA, 7AB, 7AE, 7AI-7AK, 7AM-7AU, 8B-8F and 8H.

12. A compound of claim 1 or 11 selected from those listed in Table 1.

13. A compound of claim 1, 11 or 12 which is (3R,4S)-1,4-bis-(4-methoxyphenyl)-3-(3-phenylpropyl)-2-azetidinone.

14. A composition of claim 10 wherein the compound administered is selected from those prepared in examples 1-40..

15. The use of a compound of claim 1 for the manufacture of a medicament for lowering serum cholesterol.

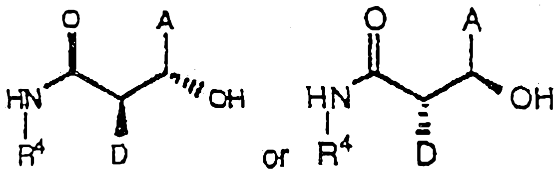
16. The use of a compound of claim 1 for the manufacture of a medicament for inhibiting the enzyme acyl CoA:cholesterol acyl transferase.

17. A process for the preparation of a pharmaceutical composition as claimed in claim 10 which comprises admixing a compound as defined in claim 10 with a pharmaceutically acceptable carrier.

18. A method of lowering serum cholesterol levels in a mammal in need of such treatment comprising administering an effective amount of a composition of claim 10.

19. A method of inhibiting the enzyme acyl CoA:cholesterol acyl transferase by administering an effective amount of a composition of claim 10 to a mammal in need of such treatment.

20. A process for producing a compound of claim 1, wherein R is H, and D and A have trans relative stereochemistry, comprising cyclizing a hydroxyamide of the formula



wherein D, A and R^4 are defined in claim 1, by treating with:

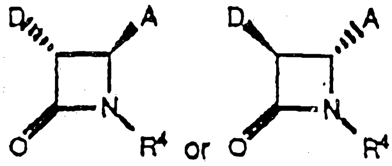
(i) a dialkylazodicarboxylate and a trialkylphosphine; or

(ii) a di- or tri-chlorobenzoyl chloride, an aqueous base and a phase transfer catalyst, then treating the resulting di- or tri-chlorobenzoate with an aqueous base and a phase transfer catalyst; or

(iii) a dialkylchlorophosphate, an aqueous base and a phase transfer catalyst; or

(iv) a di- or tri-chlorobenzoyl chloride and an alkali metal hydride.

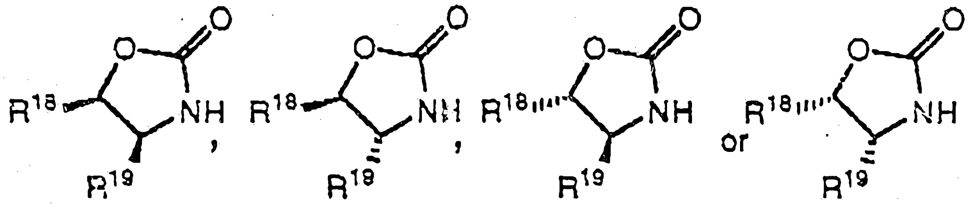
21. A process for producing a compound of claim 1 having the formula



wherein D, A and R^4 are as defined in claim 1, comprising:

(a) reacting a carboxylic acid of the formula DCH_2-COOH, wherein D is as defined above, with a chlorinating agent;

(b) deprotonating a chiral oxazolidinone of the formula



wherein R^{18} and R^{19} are independently selected from the group consisting of: hydrogen, C_1-C_6 alkyl, phenyl, naphthyl, substituted phenyl, substituted naphthyl, and benzyl; with a strong base and treating the resulting anion with the product of step (a);

(c) enolizing the product of step (b) with either:

(i) a dialkylboron triflate and a tertiary amine base;

(ii) $TiCl_4$ and tetramethylethylenediamine (TMEDA) or a mixture of TMEDA and triethylamine;

then condensing with an aldehyde of the formula A-CHO, wherein A is as defined above;

(d) hydrolyzing the product of step (c) with a base and hydrogen peroxide;

(e) condensing the product of step (d) with an amine of the formula R^4NH_2, wherein R^4 is as defined above, by treating with a dehydrative coupling agent, optionally adding an activating agent; and

(f) cyclizing the product of step (e) by treating with:

(i) a dialkylazodicarboxylate and a trialkylphosphine; or

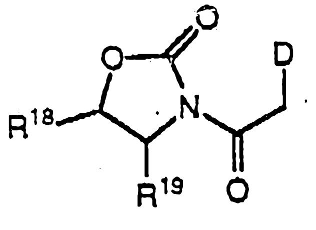
(ii) a di- or tri-chlorobenzoyl chloride, an aqueous base and a phase transfer catalyst, then treating the resulting di- or tri-chlorobenzoate with an aqueous base and a phase transfer catalyst; or

(iii) a dialkylchlorophosphate, an aqueous base and a phase transfer catalyst; or

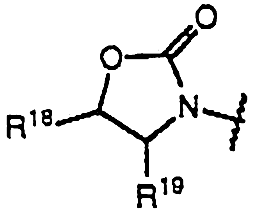
(iv) a di- or tri-chlorobenzoyl chloride and an alkali metal hydride.

22. A process for producing a compound of claim 1, wherein R is hydrogen, and D and A have trans relative stereochemistry, comprising:

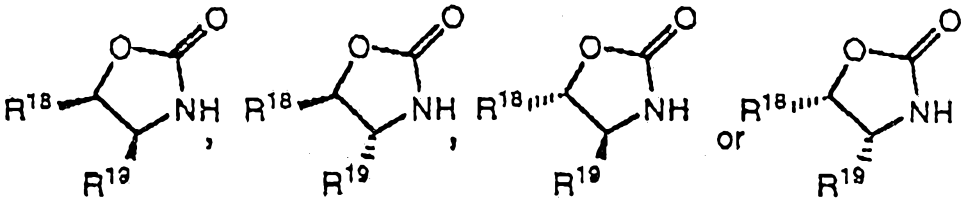
(a) enolizing a compound of the formula



with TiCl4 and tetramethylethylenediamine (TMEDA), then condensing with an imine of the formula A-CH=N-R^4, wherein A and R^4 are as defined above, and wherein the group



represents an chiral auxiliary of the formula



wherein R^{18} and R^{19} are independently selected from the group consisting of: hydrogen, C_1-C_6 alkyl, phenyl, naphthyl, substituted phenyl, substituted naphthyl, and benzyl; and

(b) cyclizing the product of step (a) by treating with a strong non-nucleophilic base.

23. A process for preparing compounds of claim 1 comprising:

(a) treating an ester of the formula D-CH(R)-C(O)OR^{17}, wherein R^{17} is lower alkyl, menthyl, or 10-(siisopropylsulfonamido)-isobornyl, with a strong base, and then with an imine of the formula A-CH=N-R^4, wherein A and R^4 are as defined in claim 1; or

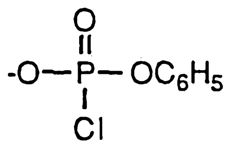
(b) for preparing a compound of claim 1 wherein R is not hydrogen, reacting a compound of claim 1, wherein R is hydrogen, with a strong base and an alkylating agent or an acylating agent; or

(c) for preparing a compound of claim 1, wherein R is hydrogen, and D and A have cis relative stereochemistry, reacting a compound of claim 1, wherein R is hydrogen, and D and A have trans relative stereochemistry, with a strong base at -80° to -40°C, and then with a proton source; or

(d) for preparing a compound of claim 1, wherein R is hydrogen, and D and A have trans relative stereochemistry, reacting a compound of claim 1, wherein R is hydrogen, and D and A have cis relative stereochemistry, with an alkali metal t-butoxide, then quenching with acid; or

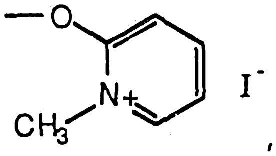
(e) reacting a carboxylic acid derivative of the formula D-CH(R)-C(O)-Z, wherein D and R are as defined in claim

1, and Z is Cl,



$-O-\underset{\underset{Cl}{|}}{\overset{\overset{O}{\|}}{P}}-OC_6H_5$

, or



, with an imine of the formula A-CH=N-R^4, wherein A and R^4 are as defined in claim 1, in the presence of a tertiary amine base.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/05972

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D205/08; C07D205/085; C07D401/04; C07D403/04
C07D405/10; C07D405/04; C07D409/04; A61K31/395

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0 199 630 (MERCK & CO., INC.) 29 October 1986 see claims	1-9, 22-30
X	EP,A,0 337 549 (MERCK & CO., INC.) 18 October 1989 see claims	1-9, 22-30
A	EP,A,0 365 364 (TAISHO PHARMACEUTICAL CO.) 25 April 1990 see claims	1-9, 22-30
A	EP,A,0 375 527 (CNRS) 27 June 1990 see claims	1-9, 22-30
P,A	EP,A,0 462 667 (MERCK & CO., INC.) 27 December 1991 see claims	1-9, 22-30

-/--

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step .
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

1

IV. CERTIFICATION

Date of the Actual Completion of the International Search 15 OCTOBER 1992	Date of Mailing of this International Search Report 23. 11. 92
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer CHOULY J.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,A	EP,A,0 481 671 (MERCK & CO., INC.) 22 April 1992 see claims -----	1-9, 22-30

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9205972
SA 62862

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 15/10/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0199630	29-10-86	US-A-	4680391	14-07-87
		JP-A-	61289074	19-12-86
EP-A-0337549	18-10-89	AU-A-	1858292	10-09-92
		AU-A-	3263089	12-10-89
		JP-A-	2006471	10-01-90
EP-A-0365364	25-04-90	CA-A-	2000437	20-04-90
		JP-A-	2191249	27-07-90
		US-A-	4952689	28-08-90
EP-A-0375527	27-06-90	FR-A-	2640621	22-06-90
		AU-A-	4691789	21-06-90
		CA-A-	2005759	19-06-90
		JP-A-	3034966	14-02-91
		US-A-	5030628	09-07-91
EP-A-0462667	27-12-91	US-A-	5120729	09-06-92
		CA-A-	2044906	21-12-91
EP-A-0481671	22-04-92	AU-A-	8583391	19-12-91

nternational application No.

PCT/US92/05972

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 25,26 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.