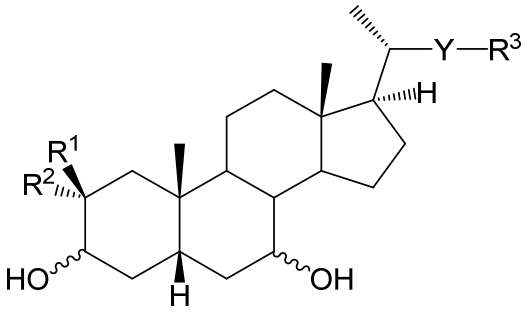
CLAIMS

1. A compound of general formula (I):



(I)

wherein

one of R^1 and R^2 is F and the other of R^1 and R^2 is H or F;

Y is a bond, or a C_{1-20} alkylene, C_{2-20} alkenylene or C_{2-20} alkynylene linker group;

R^3 is $C(O)OR^{12}$, $C(O)NR^{12}R^{13}$, $S(O)_2R^{12}$, $OS(O)_2R^{12}$, $S(O)_2OR^{12}$, $OS(O)_2OR^{12}$, $S(O)_2NR^{12}R^{13}$, $C(O)NR^{12}S(O)_2R^{13}$, $NHC(O)NR^{12}S(O)_2R^{13}$, $OP(O)(OR^{12})_2$, $C(O)NR^{12}[CH(R^{15})]_nR^{16}$ or $C(O)NR^{12}C(O)CH_2NR^{12}[CH(R^{15})]_nR^{16}$;

each R^{12} is independently H or C_{1-6} alkyl optionally substituted by one or more substituents selected from halo, OR^{10}, $NR^{10}R^{11}$, R^{16} and aryl;

each R^{10} and R^{11} is independently H or C_{1-6} alkyl;

R^{13} is H, C_{1-6} alkyl optionally substituted by one or more substituents selected from halo and aryl; or a 3- to 8-membered carbocyclic ring or heterocyclic ring, wherein said carbocyclic or heterocyclic ring is optionally substituted with one or more substituents selected from =O and R^{16}; or a phenyl or 5- or 6-membered heteroaryl ring, wherein said phenyl or heteroaryl ring is optionally substituted with a substituent R^{16}; or

when R^3 is $C(O)NR^{12}R^{13}$ or $S(O)_2NR^{12}R^{13}$, R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 3- to 8-membered heterocyclic ring which optionally contains one or more further hetero atoms selected from N, O and S; and is optionally substituted with one or more substituents selected from $CH_2C(O)OH$, $C(O)OH$, C_{1-6} alkyl, $C(O)OC_{1-6}$ alkyl, $S(O)_2OH$, =O and =N-OH; and is optionally fused to a phenyl group which is unsubstituted or substituted with one or more substituents selected from halo and nitro;

n is 1, 2 or 3;

each R^{15} is independently H or C_{1-6} alkyl optionally substituted by one or more substituents selected from halo, phenyl and 5- or 6-membered heteroaryl; a 3- to 8-membered cycloalkyl group; or a group R^{14}, where R^{14} is a side chain of an amino acid; or

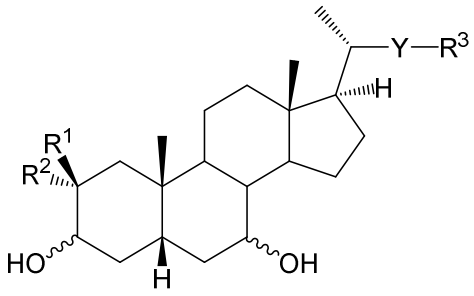
when n is 2 or 3, two R^{15} groups together with the carbon atoms to which they are attached, and optionally an intervening carbon atom where present, can combine to form $-(CH_2)_p-$ such that the group $[CH(R^{15})]_n$ is a 3- to 8 membered carbocyclic ring;

p is 1, 2, 3, 4, 5 or 6;

R^{16} is selected from $C(O)OH$, $S(O)_2OH$, $S(O)_2(C_{1-6}$ alkyl), $OS(O)_2OH$ and $P(O)(OH)_2$;

or a pharmaceutically acceptable salt or isotopic variant thereof.

2. A compound of general formula (I'):



(I')

wherein

one of R^1 and R^2 is F and the other of R^1 and R^2 is H or F;

Y is a bond, or a C_{1-20} alkylene, C_{2-20} alkenylene or C_{2-20} alkynylene linker group;

R^3 is $C(O)OR^{12}$, $C(O)NR^{12}R^{13}$, $S(O)_2R^{12}$, $OS(O)_2R^{12}$, $S(O)_2OR^{12}$, $OS(O)_2OR^{12}$, $S(O)_2NR^{12}R^{13}$, $C(O)NR^{12}S(O)_2R^{13}$, $NHC(O)NR^{12}S(O)_2R^{13}$, $OP(O)(OR^{12})_2$, $C(O)NR^{12}[CH(R^{15})]_nR^{16}$ or $C(O)NR^{12}C(O)CH_2NR^{12}[CH(R^{15})]_nR^{16}$

each R^{12} is independently H or C_{1-6} alkyl optionally substituted by one or more halo or aryl groups;

R^{13} is H, C_{1-6} alkyl optionally substituted by one or more halo or aryl groups or a 5- or 6-membered carbocyclic ring optionally substituted with a substituent R^{16}; or

R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring optionally containing a further nitrogen atom,

optionally substituted with one or more substituents selected from $CH_2C(O)OH$, $C(O)OH$, $S(O)_2OH$, =O or =N-OH groups and optionally fused to a phenyl group which is unsubstituted or substituted with one or more substituents selected from halo and nitro;

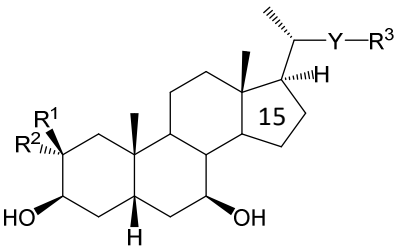
each R^{15} is independently H or C_{1-6} alkyl optionally substituted by one or more halo or aryl groups or a group R^{14}, where R^{14} is a side chain of an amino acid;

n is 1, 2 or 3;

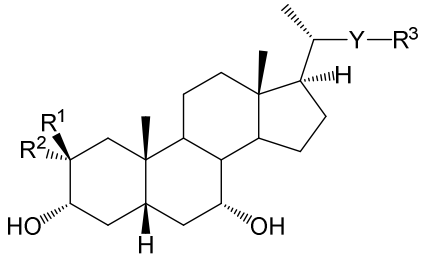
R^{16} is selected from $C(O)OH$, $S(O)_2OH$, $OS(O)_2OH$ and $P(O)(OH)_2$;

or a pharmaceutically acceptable salt or isotopic variant thereof.

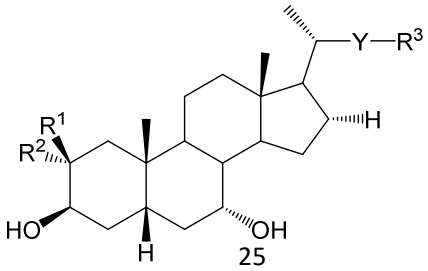
3. A compound according to claim 1 or claim 2 which is a compound of general formula (IA), (IB), (IC) or (ID):



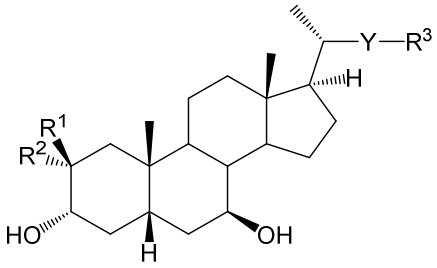
(IA)



(IB)



(IC)



(ID)

wherein R^1, R^2, Y and R^3 are as defined above for general formula (I).

4. A compound according to claim 3 which is a compound of general formula (IA).

5. A compound according to claim 3 which is a compound of general formula (IB).

6. A compound according to any one of claims 1 to 5 wherein both R^1 and R^2 are F.

7. A compound according to any one of claims 1 to 6 wherein Y is a bond, or a C_{1-3} alkylene or C_{2-3} alkenylene linker group.

8. A compound according to claim 7, wherein Y is $-CH_2CH_2-$.

9. A compound according to any one of claims 1 to 8 wherein:
R^3 is $C(O)OR^{12}$, $C(O)NR^{12}CH(R^{14})C(O)OH$ or $C(O)NR^{12}CH(R^{15})CH(R^{15})S(O)_2OH$, wherein R^{12} and R^{14} are as defined in claim 1 and R^{15} is H or C_{1-6} alkyl optionally substituted by one or more halo or aryl groups; or
R^3 is $C(O)OR^{12}$, $(C(O)N(R^{12})(R^{13})$ or $C(O)NR^{12}[CH(R^{15})]_nR^{16}$;
wherein R^{12}, R^{13}, R^{15}, R^{16} and n are as defined in claim 1.

10. A compound according to any one of claims 1 to 9 wherein
R^{12} is H or methyl or ethyl optionally substituted with R^{16} or $N(R^{10})(R^{11})$; or
R^3 is $C(O)NR^{12}S(O)_2R^{13}$, $NHC(O)NR^{12}S(O)_2R^{13}$, $C(O)NR^{12}[CH(R^{15})]_nR^{16}$ or $C(O)NR^{12}C(O)CH_2NR^{12}[CH(R^{15})]_nR^{16}$; and R^{12} is H or methyl; and/or

R^{13}, when present, is suitably a 5- or 6-membered carbocyclic ring or heterocyclic ring optionally substituted with R^{16} or =O; or phenyl optionally substituted with R^{16}; or

R^3 is $C(O)NR^{12}R^{13}$ or $S(O)_2NR^{12}R^{13}$ and R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring optionally substituted with one or more substituents selected from R^{16} and =O and optionally comprising one or more further heteroatoms selected from O, N and S; and/or

R^{16}, when present, is $C(O)OH$, $S(O)_2OH$, $S(O)_2(C_{1-6}$ alkyl) or $OS(O)_2OH$; or

R^{16}, when present, is $C(O)OH$, $S(O)_2OH$, $OS(O)_2OH$ or $P(O)(OH)_2$ and the compound is in the form of a pharmaceutically acceptable salt.

11. A compound according to any one of claims 1 to 10 wherein R^3 is $C(O)OR^{12}$ or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 11 wherein R^{12} is H, CH_2R^{16} or $-CH_2CH_2R^{16}$ where R^{16} is as defined above.

13. A compound according to any one of claims 1 to 10 wherein R^3 is $C(O)NR^{12}[CH(R^{15})]_nR^{16}$ or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 13 wherein R^{12} is H, methyl or methyl substituted with R^{16}.

15. A compound according to claim 13 or claim 14 wherein R^3 is $C(O)NR^{12}CH(R^{14})C(O)OH$ or $C(O)NR^{12}CH(R^{15})CH(R^{15})S(O)_2OH$, wherein R^{14} is a side chain of an amino acid and R^{15} is H or C_{1-6} alkyl optionally substituted by one or more halo or aryl groups

16. A compound according to claim 15 wherein:
R^3 is $C(O)NR^{12}CH(R^{14})C(O)OH$, wherein R^{12} is H or methyl and R^{14} is H; or
R^3 is $C(O)NR^{12}CH(R^{15})CH(R^{15})S(O)_2OH$, wherein R^{12} is H or methyl and both R^{15} moieties are H.

17. A compound according to claim 13 or claim 14 wherein:
each R^{15} is independently H or C_{1-4} alkyl optionally substituted as set out in claim 1; or
n is 2 or 3 and two R^{15} groups combine with the carbon atoms to which they are attached, and optionally with an intervening carbon atom where present, to form a 5- to 7 membered carbocyclic ring.

18. A compound according to any one of claims 1 to 10 wherein R^3 is $C(O)NR^{12}R^{13}$ or a pharmaceutically acceptable salt thereof.

19. A compound according to claim 18 wherein R^{12} is H or C_{1-3} alkyl substituted with a single R^{16} substituent, wherein R^{16} is as defined in claim 1.

20. A compound according to claim 18 or claim 19, wherein R^{13} is phenyl, or a 5- to 7-membered cycloalkyl or heterocyclyl group, any of which is optionally substituted with a single R^{16} substituent and where cycloalkyl and heterocyclyl groups are substituted with one or more =O substituents.

21. A compound according to claim 1 selected from:
2β-fluorochenodeoxycholic acid (Compound 1);
2β-fluoro-3β,7α-dihydroxy-5β-cholanic acid (Compound 2);
2α-fluoro-3β,7α-dihydroxy-5β-cholanic acid (Compound 3);
2α-fluoro-3β,7β-dihydroxy-5β-cholanic acid (Compound 4);
2α-fluoro-3α,7α-dihydroxy-5β-cholanic acid (Compound 5);

2α-fluoro-3α,7β-dihydroxy-5β-cholanic acid (Compound 6);

2,2-difluoro-3β,7β-dihydroxy-5β-cholanic acid (Compound 7);

2,2-difluoro-3α,7α-dihydroxy-5β-cholanic acid (Compound 8);

2,2-difluoro-3α,7β-dihydroxy-5β-cholanic acid (Compound 9);

N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-amide)-ethylsulfonic acid (Compound 10);

N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-amide)-propanoic acid (Compound 11);

N-(methyl),*N*-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-amide)-acetic acid (Compound 12);

N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-amide)-*trans*-2-cyclohexane carboxylic acid (Compound 13);

1-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl)-piperidine-3-carboxylic acid (Compound 14);

3-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-amide)-4-thiazolidine-carboxylic acid (Compound 15);

N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl)-morpholine (Compound 16);

N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-amide)-methylcarboxylic acid (Compound 17)

N-(carboxymethyl)-*N*-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl)-2-amino acetic acid (Compound 18);

N-(methyl)-*N*-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-amide) ethylsulfonic acid (Compound 19);

3-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl) amino-propanesulfonic acid (Compound 20);

N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-amide) methanesulfonic acid (Compound 21);

N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl)-2-aminoethyl sulfuric acid (Compound 22);

O-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl)-2-hydroxy ethyl sulfonic acid (Compound 23);

N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl) aniline-2-sulfonic acid (Compound 24);

N-(cyclohexyl)-*N*-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl)-3-amino-propanesulfonic acid (Compound 25);

N-(cyclohexyl)-*N*-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl)-2-amino-ethanesulfonic acid (Compound 26);

N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl) 2-aminoethyl methyl sulfone (Compound 27);

N-(ethyl)-*N*-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl)-3-amino-tetrahydrothiophene dioxide (Compound 28);
N-(2-(diisopropylamino)ethyl)-*N*-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl)-3-amino-tetrahydrothiophene dioxide (Compound 29);
N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl)-thiomorpholine-dioxide (Compound 30);
N-(2,2-difluoro-3β,7β-dihydroxy-5β-cholan-24-oyl) 1,1-dioxidotetrahydro-2H-thiopyran-3-ylamine (Compound 31); and
pharmaceutically acceptable salts thereof (where appropriate), especially metal salts, such as sodium or potassium salts, particularly sodium salts or (for Compound 18) the disodium salt.

22. A compound according to any one of claims 1 to 21 for use in medicine, for example for use in the treatment or prevention of a neurodegenerative disorder.

23. The use of a compound according to any one of claims 1 to 21 in the manufacture of a medicament for the treatment or prevention of a neurodegenerative disorder.

24. A compound for use according to claim 22 or a use according to claim 23, wherein the neurodegenerative disorder is Parkinson's disease, mild cognitive impairment, dementia (including Alzheimer's disease, vascular dementia and dementia with Lewy bodies), Huntington's disease, amyotrophic lateral sclerosis (motor neurone disease), progressive supranuclear palsy or Wilson's disease.

25. A compound for use or a use according to claim 24, wherein the neurodegenerative disorder is Parkinson's disease and the compound is selected from compounds of general formula (IA) and (ID) as defined in claim 3.

26. A compound for use or a use according to claim 25, wherein the compound is selected from 2,2-difluoro-3β,7β-dihydroxy-5β-cholanic acid (Compound 7) and difluoro-3α,7β-dihydroxy-5β-cholanic acid (Compound 9).

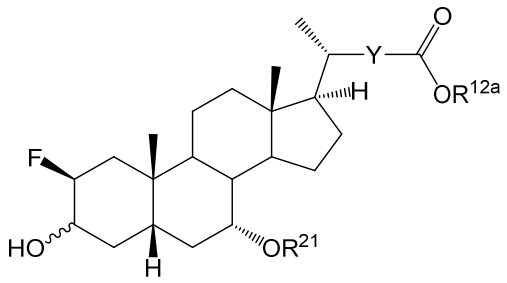
27. A compound for use or a use according to claim 25, wherein the neurodegenerative disorder is Alzheimer's disease and the compound is selected from compounds of general formula (IB) as defined in claim 3.

28. A compound for use or a use according to claim 27, wherein the compound is 2,2-difluoro-3α,7α-dihydroxy-5β-cholanic acid (Compound 8).

29. A pharmaceutical composition comprising a compound according to any one of claims 1 to 21 and a pharmaceutically acceptable excipient or carrier.

30. A process for the preparation of a compound according to any one of claims 1 to 21 comprising:

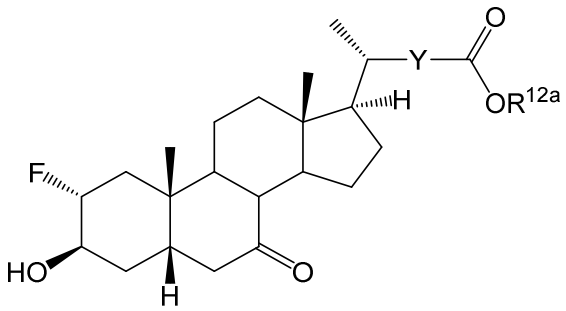
A. for a compound of general formula (IB) or (IC) as defined in claim 3 in which R^1 is F and R^3 is $C(O)OR^{12a}$: wherein R^{12a} is C_{1-6} alkyl optionally substituted by one or more halo or aryl groups:
treating with an acid a compound of general formula (II):



(II)

wherein Y and R^3 are as defined in claim 1; R^{12a} is C_{1-6} alkyl optionally substituted by one or more halo or aryl groups; and R^{21} is an OH protecting group which is acid labile;

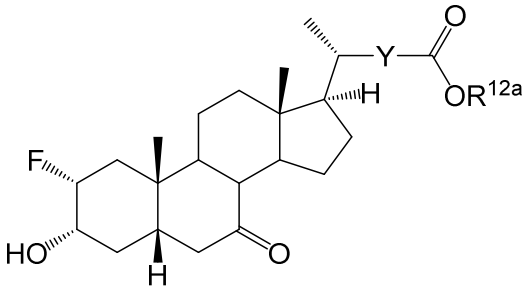
B. for a compound of general formula (IA) or (IC) as defined in claim 3 in which R^2 is F and R^3 is $C(O)OR^{12a}$, wherein R^{12a} is as defined for general formula (II):
reducing a compound of general formula (XIIa):



(XIIa)

wherein Y is as defined in claim 1 and R^{12a} is as defined for general formula (II);

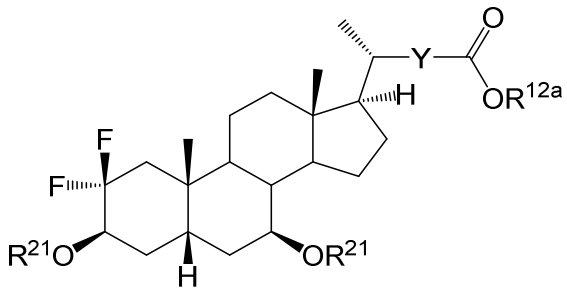
C. for a compound of general formula (IB) or (ID) as defined in claim 3 in which R^2 is F and R^3 is $C(O)OR^{12a}$, wherein R^{12a} is as defined for general formula (II):
reducing a compound of general formula (XIIb):



(XIIb)

wherein Y is as defined in claim 1 and R^{12a} is as defined for general formula (II);

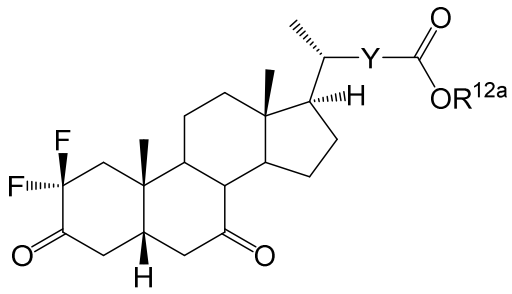
D. for a compound of general formula (IA) as defined in claim 3 in which both R^1 and R^2 are F and R^3 is $C(O)OR^{12a}$, wherein R^{12a} is as defined for general formula (II):
reacting with an acid a compound of general formula (XXI):



(XXI)

wherein Y is as defined in claim 1 and R^{12a} and R^{21} are as defined for general formula (II);

E. for a compound of general formula (IB) or (ID) as defined in claim 3 in which both R^1 and R^2 are F and R^3 is $C(O)OR^{12a}$, wherein R^{12a} is as defined for general formula (II):
reducing a compound of general formula (XXII):



(XXII)

wherein Y is as in claim 1 and R^{12a} and R^{21} are as defined for general formula (II);

F. for a compound of general formula (I) in which R^3 is C(O)OH:
hydrolysing a compound of general formula (I) in which R^3 is $C(O)R^{12a}$, wherein R^{12a} is as defined above for general formula (II);

G. for a compound of general formula (I) in which R^3 is $C(O)NR^{12}R^{13}$:
reacting a compound of general formula (I) in which R^3 is C(O)OH with an amine of general formula:

$$H\text{-}NR^{12}R^{13}$$

wherein R^{12} and R^{13} are as defined in claim 1;
in the presence of a coupling reagent and an amine;

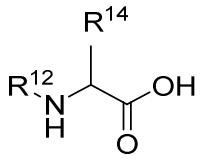
H. for a compound of general formula (I) in which R^3 is $C(O)NR^{12}[CH(R^{15})]_nR^{16}$:
reacting a compound of general formula (I) in which R^3 is C(O)OH with a compound of general formula (XL):

$$HNR^{12}[CH(R^{15})]_nR^{16}$$

(XL)

wherein R^{12}, R^{15}, n and R^{16} are as defined in claim 1;
in the presence of a coupling agent and an amine;

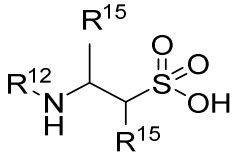
I. for a compound of general formula (I) in which R^3 is $C(O)NR^{12}CH(R^{14})C(O)OH$:
reacting a compound of general formula (I) in which R^3 is C(O)OH by reaction with an amino acid of general formula (XLI):



(XLI)

wherein R^{12} and R^{14} are as defined in claim 1;
in the presence of a coupling agent and an amine;

J. for a compound of general formula (I) in which R^3 is $C(O)NR^{12}CH(R^{15})CH(R^{15})S(O)_2OH$:
reacting a compound of general formula (I) in which R^3 is C(O)OH by reaction with a compound of general formula (XLII):



(XLII)

wherein R^{12} and R^{15} are as defined in claim 1;

in the presence of a coupling agent and an amine;

K. for a compound of general formula (I) in which R^3 is $C(O)NR^{12}S(O)_2R^{13}$:

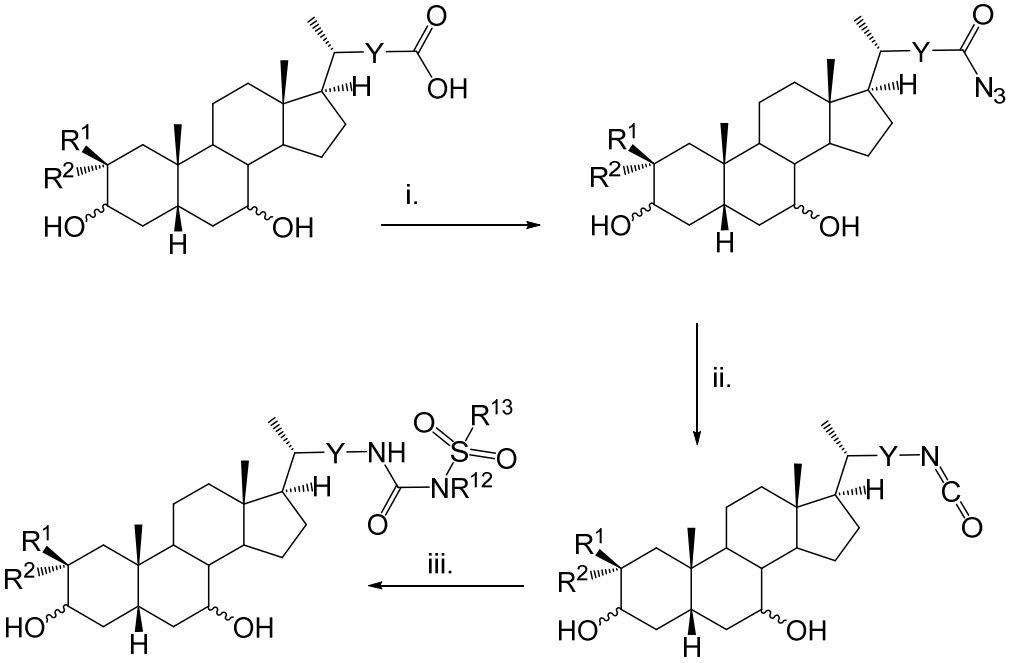
reacting a compound of general formula (I) in which R^3 is C(O)OH with a compound of formula:

$$NHR^{12}S(O)_2R^{13}$$

wherein R^{12} and R^{13} are as defined in claim 1, in the presence of a coupling reagent and an amine;

L. for a compound of general formula (I) in which R^3 is $NHC(O)NR^{12}S(O)_2R^{13}$:

reacting a compound of general formula (I) in which R^3 is C(O)OH as follows:



i diphenyl phosphoryl azide / triethylamine

ii heat

iii $R^{13}SO_2NHR^{12}$

wherein R^1, R^2, R^{12} and R^{13} are as defined in claim 1;

M. for a compound of general formula (I) in which R^3 is $S(O)_2OR^{12}$:
reacting a compound of general formula (I) in which R^3 is C(O)OH with a C_{1-6} alkanoyl or benzoyl chloride or with a C_{1-6} alkanoic anhydride to give a protected intermediate; and
converting the carboxylic acid group of the protected intermediate to OH by reduction with a hydride reducing agent to give a reduced intermediate; and
halogenating the reduced intermediate to give a halogenated intermediate in which the OH group is replaced with a halogen; and
reacting the halogenated intermediate with sodium sulphite in an alcoholic solvent;

N. for a compound of general formula (I) in which R^3 is $OS(O)_2R^{12}$:
reacting a compound of general formula (I) in which R^3 is $C(O)OR^{12}$ with a C_{1-6} alkanoyl or benzoyl chloride or with a C_{1-6} alkanoic anhydride to protect any OH groups; and
converting the $C(O)OR^{12}$ of the protected intermediate to OH by reduction with a hydride reducing agent to give a reduced intermediate; and
reacting the reduced intermediate with chlorosulfonic acid in the presence of a base to give a protected product; and
base hydrolysis of the protected product to remove the protecting groups;

O. for a compound of general formula (I) in which R^3 is $S(O)_2R^{12}$:
Reacting the reduced intermediate of (M) or (N) above with Lawesson's reagent followed by oxidation of the resultant product.