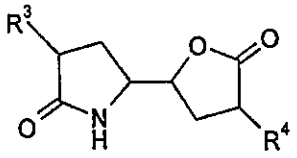
What is claimed is:

1. A compound of the formula (II)



(II)

wherein

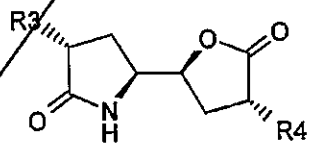
R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl; and

R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl,O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl;

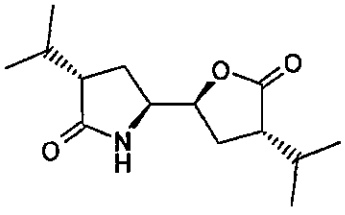
or a salt thereof.

2. The compound according to claim 1 wherein R^3 and R^4 are independently branched C_{3-6}alkyl.

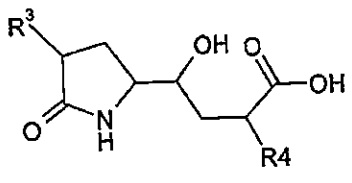
3. The compound according to claim 1 or 2 having the following stereochemistry:



4. The compound according to any of the preceding claims, having the formula



5. A compound of the formula (II')



(II')

wherein

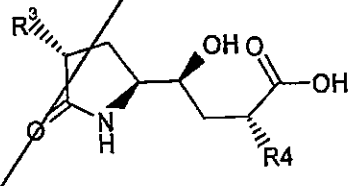
R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl; and

R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl,O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl;

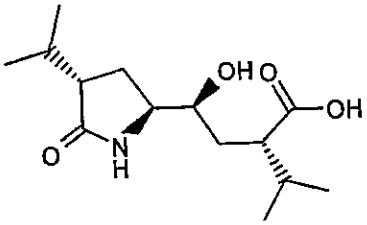
or a salt thereof.

6. The compound according to claim 5 wherein R^3 and R^4 are independently branched C_{3-6}alkyl.

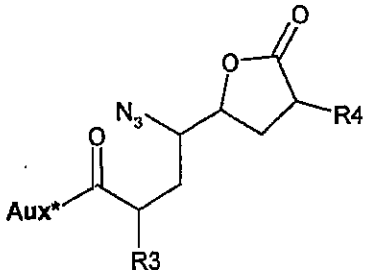
7. The compound according to claim 5 or 6 having the following stereochemistry:



8. The compound according to any one of claims 5 to 7, having the formula



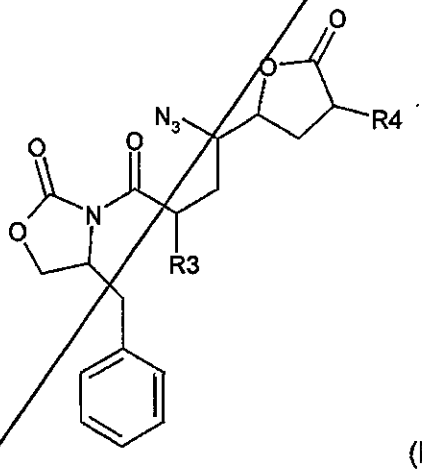
9. A method for preparing a compound of formula (II) according to any one of claims 1 to 4, said method comprising subjecting a compound of formula (I')



(I')

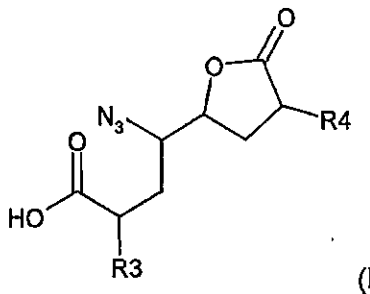
wherein R^3 and R^4 are as defined for a compound of formula (II) and Aux* is an auxiliary able to form an ester or amide with the carbonyl functionality, or a salt thereof, to hydrogenation to convert the azide moiety to an amine and to effect lactam ring closure.

10. A method according to claim 9, wherein the compound of formula (I') is a compound of formula (I)



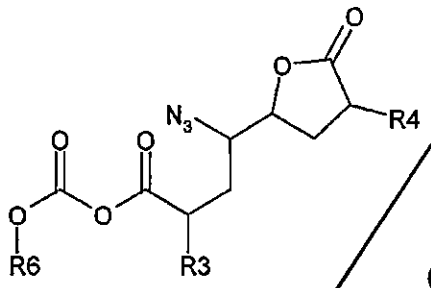
(I).

11. A method for preparing a compound of formula (II) according to any one of claims 1 to 4, said process comprising subjecting a compound of formula (III)



(III)

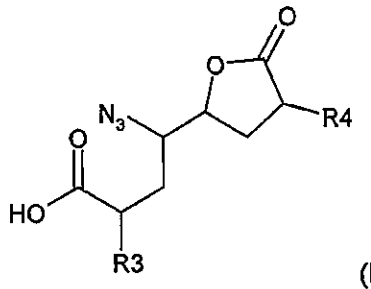
wherein R^3 and R^4 are as defined for a compound of formula (II), or a salt thereof, to conversion to an anhydride of formula (IV)



(IV)

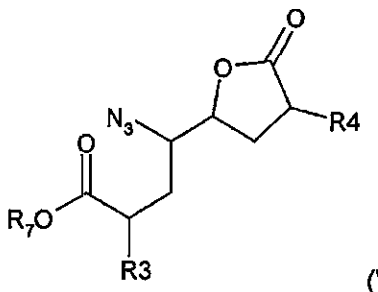
wherein R^3 and R^4 are as defined for a compound of formula (II) and R^6 is C_{1-7}alkyl or C_{3-8}cycloalkyl, or a salt thereof; to activate the acid moiety followed by hydrogenation to convert the azide moiety to an amine and to effect lactam ring closure.

12. A method for preparing a compound of formula (II) according to any one of claims 1 to 4, said process comprising subjecting a compound of formula (III)



(III)

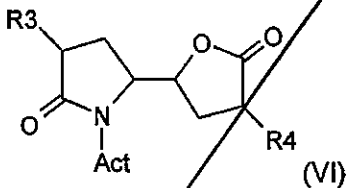
wherein R^3 and R^4 are as defined for a compound of formula (II), or a salt thereof, to conversion to an ester of formula (V)



(V)

wherein R^3 and R^4 are as defined for a compound of formula (II) and R^7 is C_{1-7}alkyl or C_{3-8}cycloalkyl, or a salt thereof; followed by hydrogenation to convert the azide moiety to an amine and to effect lactam ring closure.

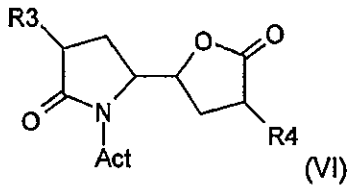
13. A method for preparing a compound of formula (VI)



(VI)

wherein R^3 and R^4 are as defined for a compound of formula (II) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof; comprising introducing the activating group at the nitrogen of a compound of formula (II) as given in any one of claims 1 to 4, or a salt thereof.

14. A compound of formula (VI)



(VI)

wherein

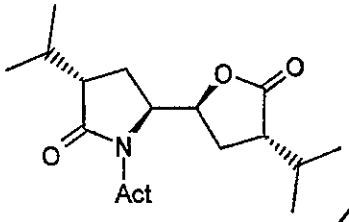
R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl;

R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, pheny-l or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl,O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl; and

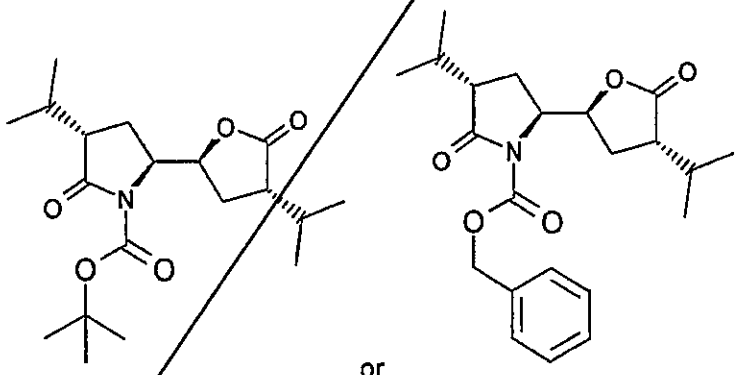
Act is an activating group selected from an amino protecting group, in particular a carbamate;

or a salt thereof.

15. The compound according to claim 14, having the formula

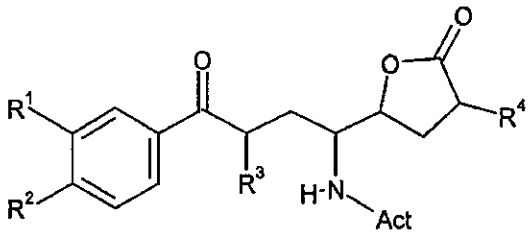


16. The compound according to claim 14 or 15, having the formula



or

17. A method for preparing a compound of formula (VIII)

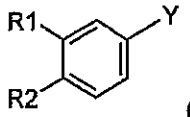


(VIII)

wherein R^3 and R^4 are as defined for a compound of formula (II) and Act is an activating group selected from an amino protecting group, in particular a carbamate, R^1 is halogen,

hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl; R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy, or a salt thereof;

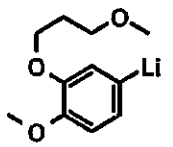
comprising the step of lactam ring opening of the N-activated lactam lactone of formula (VI) or a salt thereof defined above with a compound of formula (VII)



(VII)

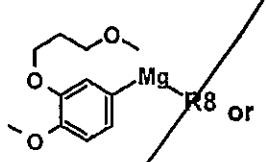
wherein Y is a metal containing group such as -Li, -MgX, -magnesate, aryl magnesium species, alkyl magnesium species, -MnX, $(alkyl)_3MnLi$-, or $-CeX_2$ wherein X is halogen such as Cl, I or Br, more preferably Br; and R^1 and R^2 are as defined for a compound of formula (VIII).

18. The method according to claim 17 wherein the N-activated lactam lactone of formula (VI) is reacted with a compound of the following formula:



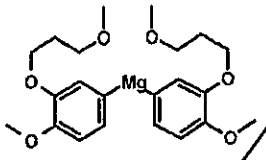
(VIIa)

or



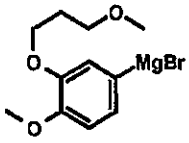
or

(VIIb) **R8 = C_{1-7} alkyl, preferably branched C1-7 alkyl**



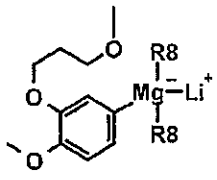
(VIIc)

or



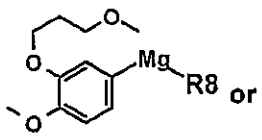
(VIId)

or

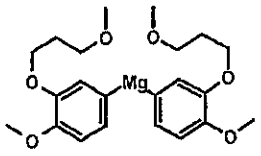


(VIIe)

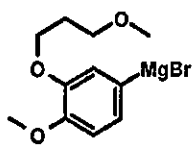
19. The compound having the following formula:



(VIIb) R8 = C_{1-7} alkyl, preferably branched C1-7 alkyl

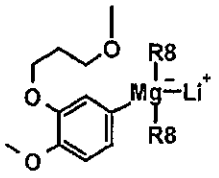


(VIIc)



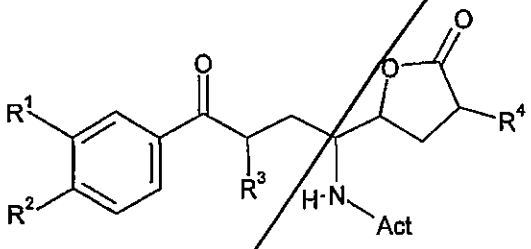
(VIId)

or



(VIIe)

20. A compound of formula (VIII)



(VIII)

wherein

R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl;

R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl,O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl;

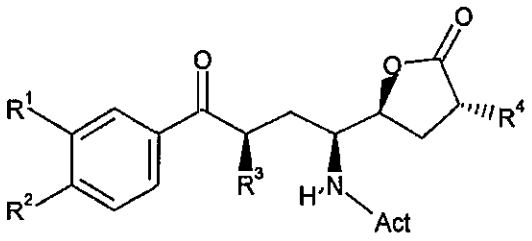
R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl;

R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy; and

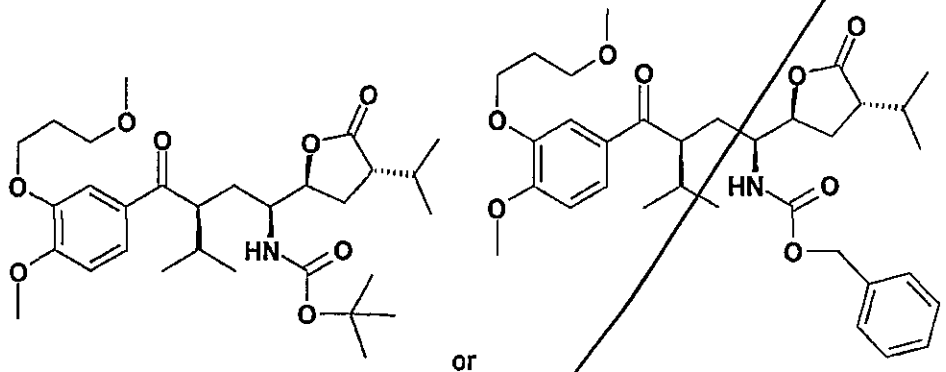
Act is an activating group selected from an amino protecting group, in particular a carbamate;

or a salt thereof.

21. The compound according to claim 20, having the formula

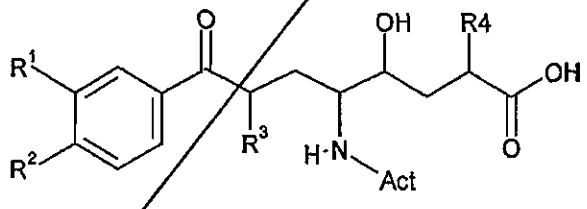


22. The compound according to claim 20 or 21, having the formula



or

23. A compound of formula (VIII')



(VIII')

wherein

R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl;

R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl,O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl;

R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl;

R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy; and

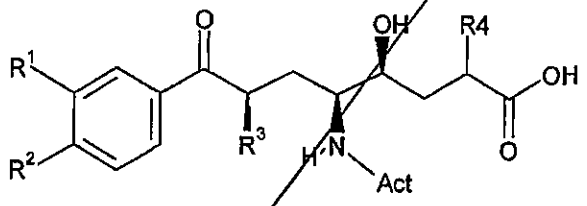
Act is an activating group selected from an amino protecting group, in particular a carbamate;

or a salt thereof.

24. The compound according to claim 23 in the form of a salt.

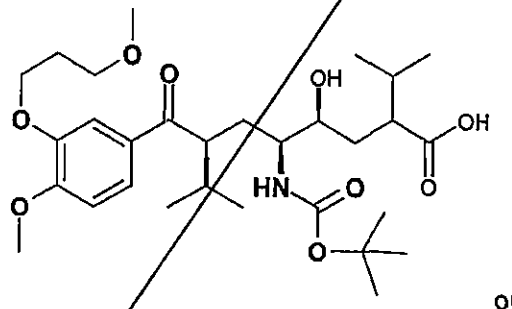
25. The compound according to claims 23 or 24 in the form of the Li, Na, K, Mg, Ca, primary, secondary or tertiary amine salt.

26. The compound according to any one of claims 23 to 25, having the formula

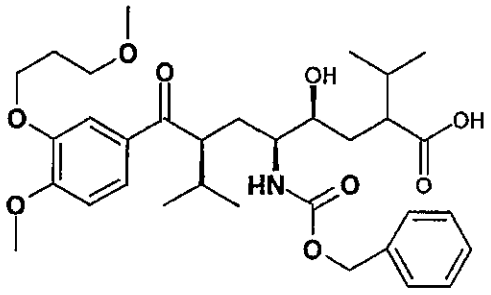


or preferably a salt thereof.

27. The compound according to any one of claims 23 to 26, having the formula

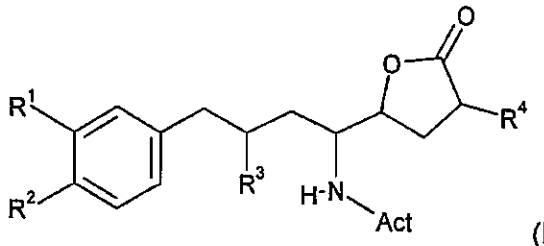


or



or preferably a salt thereof.

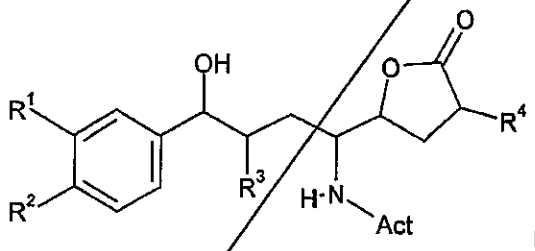
28. A method for preparing a compound of formula (IX)



(IX)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, comprising reduction of the benzylic carbonyl of the compound of formula (VIII) as defined in claims 20 to 22 or a compound of formula (VIII') as defined in claim 23 to 27 to a methylene moiety.

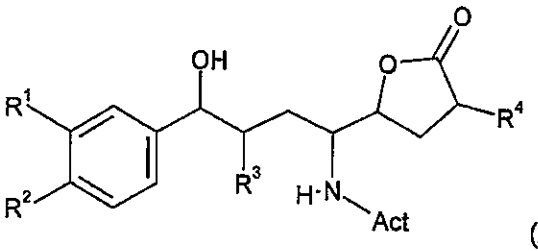
29. A method for preparing a compound of formula (X)



(X)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, comprising reduction of the benzylic carbonyl of the compound of formula (VIII) as defined in claims 20 to 22 to a hydroxyl moiety.

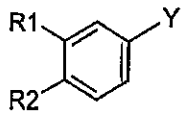
30. A method for preparing a compound of formula (X)



(X)

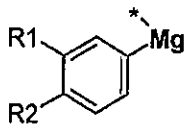
wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, comprising as a one-pot synthesis the steps of

- lactam ring opening of the N-activated lactam lactone of formula (VI) or a salt thereof as defined in claims 14 to 16 with a compound of formula (VII)



(VII)

wherein Y is a metal containing group such as -Li, -MgX, -magnesates, aryl magnesium species such as



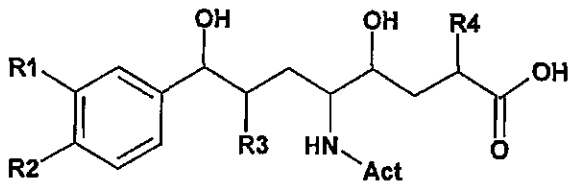
, wherein R1 and R2 are as defined herein,

alkyl magnesium species,such as branched C_{1-7}alkyl-Mg-, -MnX, $(alkyl)_3MnLi$-, or $-CeX_2$ wherein X is halogen such as Cl, I or Br, more preferably Br; and R^1 and R^2 are as defined for a compound of formula (X), to obtain a compound of formula (VIII'), or a salt thereof, as defined in claims 23 to 27 ,

- followed by reduction of the benzylic carbonyl group of the compound of formula (VIII') or a salt thereof to obtain a compound of formula (X'), or a salt thereof, as defined in claims 32 to 37, and

- lactonization of the compound of formula (X') to obtain a compound of formula (X).

31. A method for preparing a compound of formula (X')

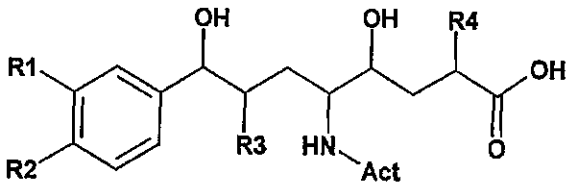


(X')

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, comprising reduction

of the benzylic carbonyl of the compound of formula (VIII') as defined in claim 23 to 27 to a hydroxyl moiety.

32. A compound of formula (X')



(X')

wherein

R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl;

R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl,O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl;

R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl;

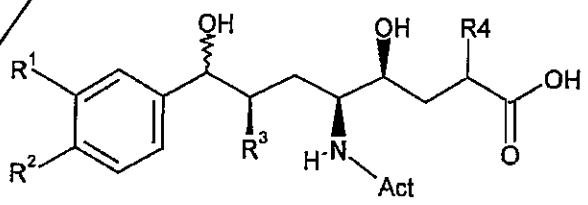
R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy; and

Act is an activating group selected from an amino protecting group, in particular a carbamate; or a salt thereof.

33. The compound according to claim 32 in the form of a salt.

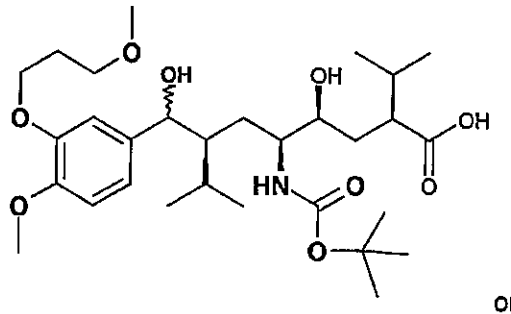
34. The compound according to claims 32 or 33 in the form of the Li, Na, K, Mg, Ca, primary, secondary or tertiary amine salt.

35. The compound according to any one of claims 32 to 34, having the formula

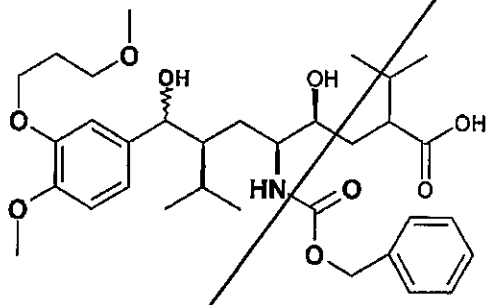


or preferably a salt thereof.

36. The compound according to any one of claims 32 to 36, having the formula

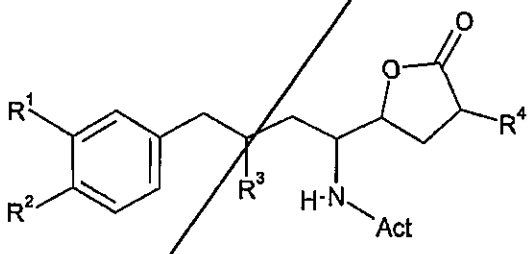


or



or preferably a salt thereof.

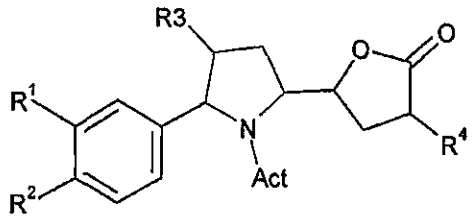
37. A method for preparing a compound of formula (IX)



(IX)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, said method comprising a method for preparing a compound of formula (X) as set forth in claim 29 or a compound of formula (X') as set forth in claim 31 and then hydrogenation of the compound of formula (X) or (X') to a compound of formula (IX).

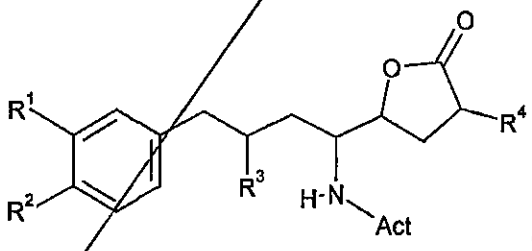
38. A method for preparing a compound of formula (XI)



(XI)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, said method comprising cyclisation of the benzylic alcohol and the amine moieties of the compound of formula (X) as defined in claim 30 to a pyrrolidine moiety.

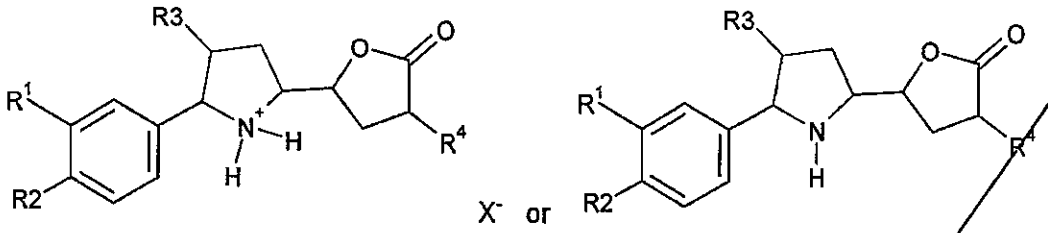
39. A method for preparing a compound of formula (IX)



(IX)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, said method comprising a method for preparing a compound of formula (XI) as set forth in claim 38 and then hydrogenation or reduction of the pyrrolidine moiety of the compound of formula (XI) to ring-open and to obtain the methylene moiety in position 8.

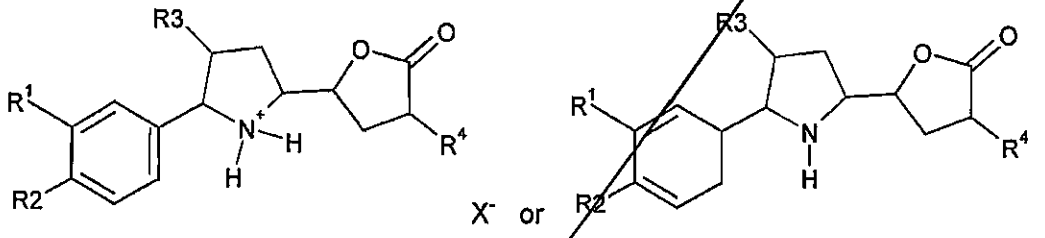
40. The method according to claim 39, wherein the compound of formula (XI) is converted to a pyrrolidine salt of formula (XI') or a pyrrolidine free base of formula (XI'')



(XI') X⁻ or (XI'')

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and X^- is an anion such as halide, trifluoroacetate, sulfate, nitrate, oxalate, sulfonate, triflate, phosphonate or phosphate.

41. A compound of formula (XI'):



(XI') X⁻ or (XI'')

wherein

R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl;

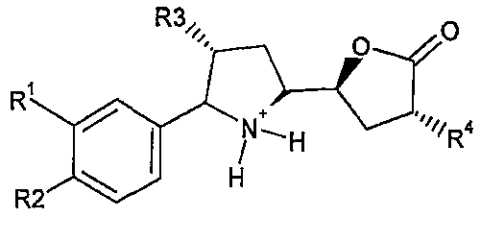
R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, pheny-l or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl,O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl;

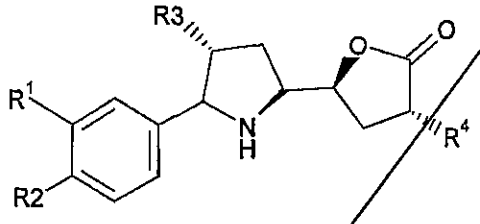
R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl;

R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy, and

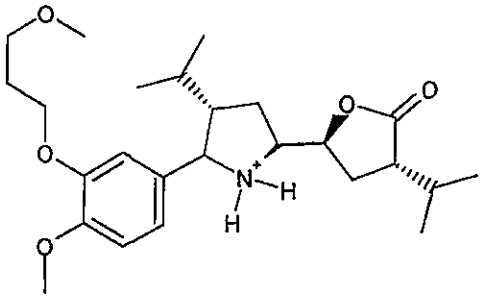
X^- is an anion such as halide, trifluoroacetate, sulfate, nitrate, oxalate, sulfonate, triflate, phosphonate or phosphate.

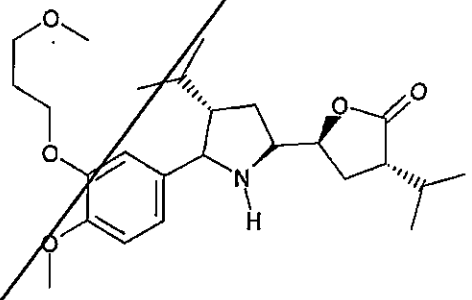
42. The compound according to claim 41, having the formula



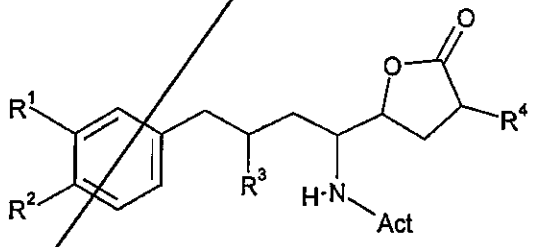
or


43. The compound according to claim 41 or 42, having the formula



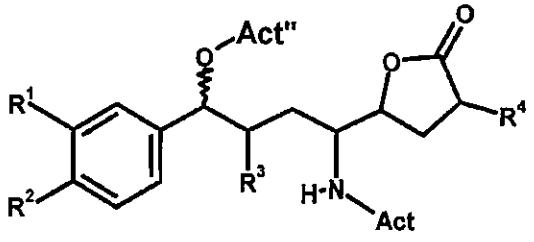
or


44. A method for preparing a compound of formula (IX)



(IX)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, said method comprising the preparation a compound of formula (X")



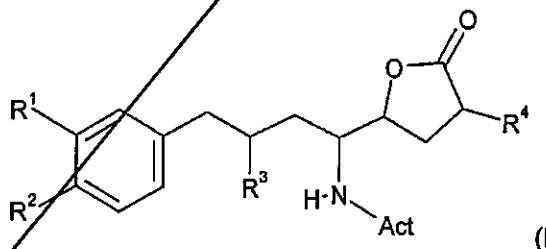
(X")

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII), Act is an activating group selected from an amino protecting group, in particular a carbamate, and Act" is an electron-withdrawing group, or a salt thereof, by conversion of the benzylic alcohol of the compound of formula (X) as defined in claim 30 to an activated alcohol moiety, wherein the compound of formula (X) is prepared as set forth in claim 29.

45. The method according to claim 44, said method comprising hydrogenation or reduction of the activated alcohol moiety of the compound of formula (X') as defined in claim 44 to obtain the methylene moiety in position 8.

46. The method according to claim 44 or 45, wherein Act" is -(C=O)-R^9, where R^9 can be substituted alkyl, alkyl-oxy-R^{10}, substituted aralkyl, substituted aryl, substituted or unsubstituted O-alkyl, substituted O-aryl, NH-R^{10} , where R^{10} can be substituted alkyl, substituted aryl, substituted aralkyl, such as substituted benzyl, benzoyl, substituted sulfonyl, wherein the substituent is in each case one or more electon-withdrawing moiety such as F or CF_3.

47. A method for preparing a compound of formula (IX)

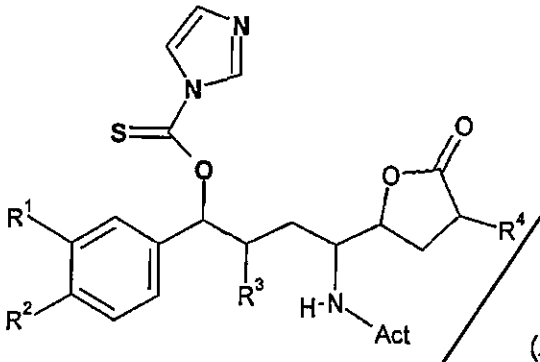


(IX)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, said method comprising the transformation of the compound of formula (X) as defined in claim 30 to a thiocarbonyl derivative and subsequently subjecting same to radical-based reduction to obtain the compound of formula (IX).

48. The method according to claim 47, wherein the thiocarbonyl derivative is selected from the group consisting of thionocarbamates, such as imidazolyl derivatives, thiocarbonyls, such as xanthates, and thionocarbonates.

49. The method according to claim 47 or 48 wherein the thiocarbonyl derivative is a thionocabamate of formula (XV)

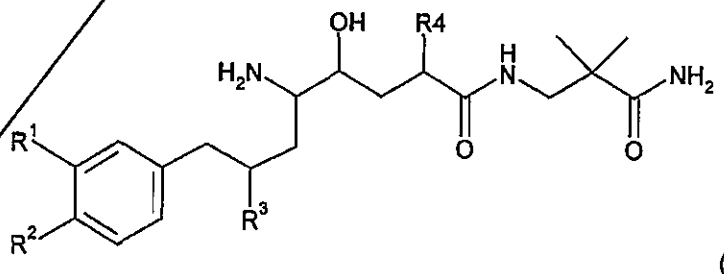


(XV)

wherein R^3 and R^4 are as defined for a compound of formula (II) and Act is an activating group selected from an amino protecting group, in particular a carbamate, R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl; R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy, or a salt thereof.

50. The method according to any one of claims 47 to 49, wherein the thiocarbonyl derivative is reacted with Bu_3SnH or tris(trimethylsilyl)-silane.

51. A method for preparing a compound of formula (XIV)

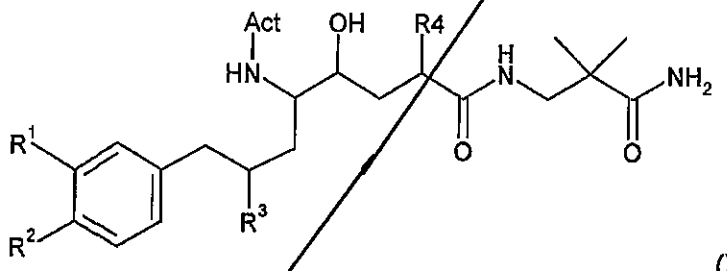


(XIV)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and and R^2 are as defined for a compound of formula (VIII), or a salt thereof, comprising one or more of the following steps either individually or in any combination:

- the manufacture of a compound of the formula II according to one of claims 9, 10, 11 or 12, or a salt thereof,
- the manufacture of a compound of the formula VI according to claim 13, or a salt thereof,
- the manufacture of a compound of the formula VIII according to claim 17, or a salt thereof, and
- the manufacture of a compound of the formula IX according to claim 28, or a salt thereof.

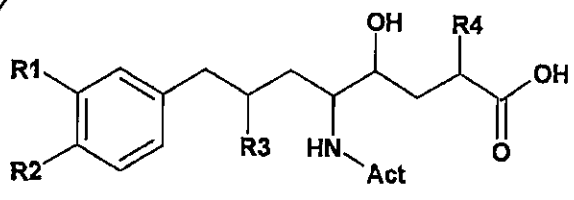
52. A method for preparing a compound of formula (XII)



(XII)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, comprising reacting a compound of the formula IX as defined in claim 28

or a compound of formula (IX')



(IX')

wherein

R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl;

R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl,O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl;

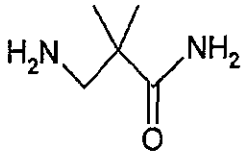
R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl;

R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy; and

Act is an activating group selected from an amino protecting group, in particular a carbamate,

or a salt thereof,

with an amine of the formula XIII,



(XIII)

(wherein the amido nitrogen can also be protected if desired and the protecting group then be removed in the corresponding protected compound of the formula XII),

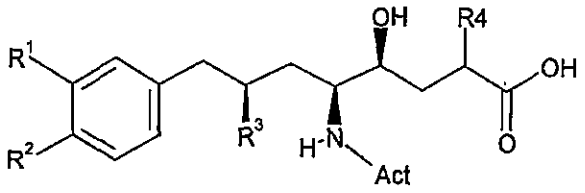
or a salt thereof and

comprising the steps of

- the manufacture of a compound of the formula II according to one of claims 9 or 12, or a salt thereof,
- the manufacture of a compound of the formula VI according to claim 13, or a salt thereof, and/or
- the manufacture of a compound of the formula VIII according to claim 17, or a salt thereof.

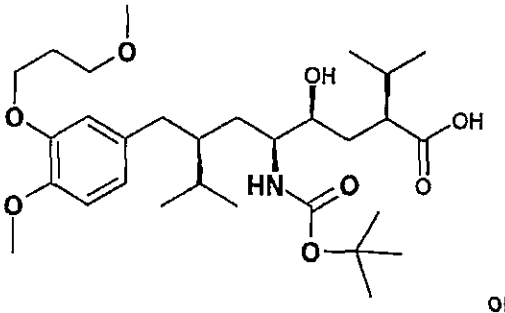
53. A method according to claim 52 wherein the salt of the compound of formula (IX') is in the form of the Li, Na, K, Mg, Ca, primary, secondary or tertiary amine salt.

54. A method according to claim 52 or 53 wherein the compound of formula (IX') has the formula

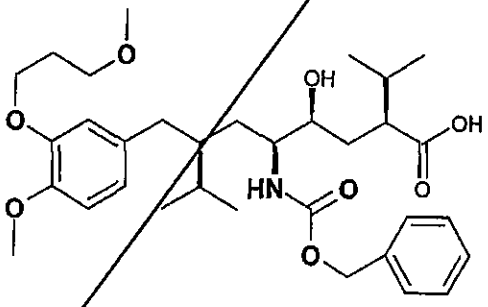


or preferably a salt thereof.

55. A method according to any one of claims 52 to 54 wherein the compound of formula (IX') has the formula



or



or preferably a salt thereof.

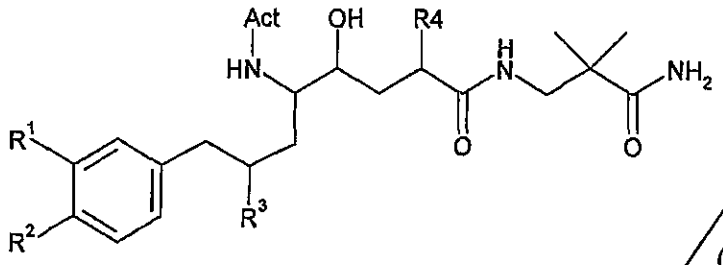
56. A method according to claim 51 comprising the steps of

- the manufacture of a compound of the formula II according to one of claims 9, or a salt thereof, and/or
- the manufacture of a compound of the formula VI according to claim 13, or a salt thereof.

57. A method according to claim 56 comprising the steps of

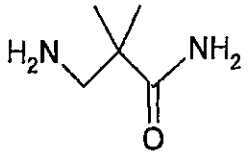
- the manufacture of a compound of the formula II according to one of claims 12, or a salt thereof, and/or
- the manufacture of a compound of the formula VI according to claim 13, or a salt thereof.

58. A method for preparing a compound of formula (XII)



(XII)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, comprising reacting a compound of the formula IX as defined in claim 30 or a compound of formula (IX') as defined in any one of claims 52-55, with an amine of the formula XIII,



(XIII)

(wherein the amido nitrogen can also be protected if desired and the protecting group then be removed in the corresponding protected compound of the formula XII), or a salt thereof.

and further comprising the steps of

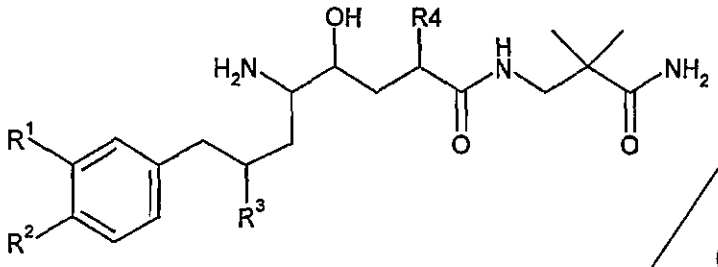
- the manufacture of a compound of the formula VIII according to claim 17, or a compound of the formula VIII' according to claim 23, or a salt of these,
- the manufacture of a compound of the formula IX according to claim 28, or a compound of the formula IX' according to claim 52, or a salt of these.

59. A method according to claim 58 comprising the steps of

- the manufacture of a compound of the formula X according to claim 29, or a compound of the formula X' according to claim 31, or a salt of these, and/or

- the manufacture of a compound of the formula IX according to claim 33, or a compound of the formula IX' according to claim 52, or a salt of these.

60. A method for preparing a compound of formula (XIV)



(XIV)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and and R^2 are as defined for a compound of formula (VIII), or a salt thereof, comprising one or more of the following steps either individually or in any combination:

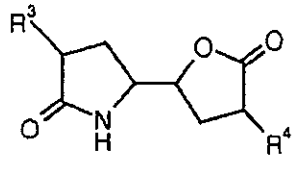
- the manufacture of a compound of the formula II according to one of claims 9, 10, 11 or 12, or a salt thereof,
- the manufacture of a compound of the formula VI according to claim 15, or a salt thereof,
- the manufacture of a compound of the formula X according to claim 30, or a salt thereof, and
- the manufacture of a compound of the formula IX according to claim 37, or a salt thereof.

61. A method according to claim 39 comprising the steps of

- the manufacture of a compound of the formula II according to claim 9, or a salt thereof,
- the manufacture of a compound of the formula VI according to claim 15, or a salt thereof, and/or
- the manufacture of a compound of the formula X according to claim 30, or a salt thereof.

Claims

1. A compound of the formula (II)

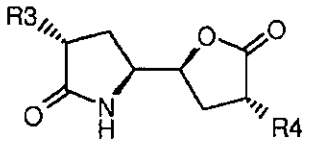


(II)

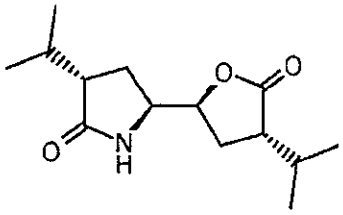
wherein
R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl; and
R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl,O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl; or a salt thereof.

2. The compound according to claim 1, wherein R^3 and R^4 are independently branched C_{3-6}alkyl.

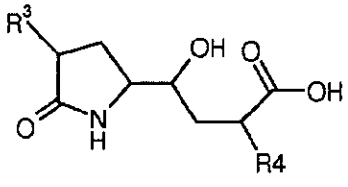
3. The compound according to claim 1 or 2, having the following stereochemistry:



4. The compound according to any of the preceding claims, having the formula



5. A compound of the formula (II')

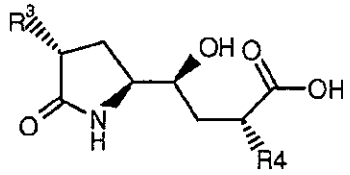


(II')

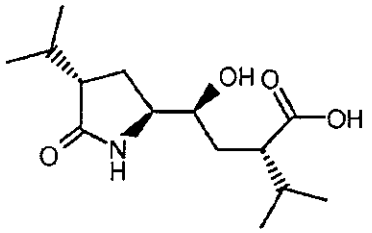
wherein
R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl; and
R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl, O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl; or a salt thereof.

6. The compound according to claim 5, wherein R^3 and R^4 are independently branched C_{3-6}alkyl.

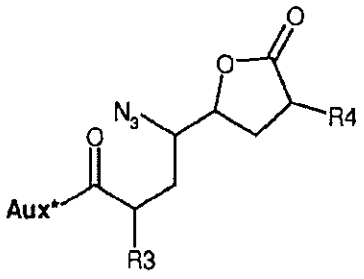
7. The compound according to claim 5 or 6, having the following stereochemistry:



8. The compound according to any of claims 5 to 7, having the formula



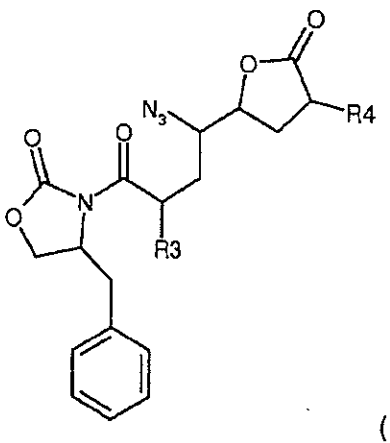
9. A method for preparing a compound of formula (II) according to any of claims 1 to 4, said method comprising subjecting a compound of formula (I')



(I')

wherein R^3 and R^4 are as defined for a compound of formula (II) and Aux* is an auxiliary able to form an ester or amide with the carbonyl functionality, or a salt thereof, to hydrogenation to convert the azide moiety to an amine and to effect lactam ring closure.

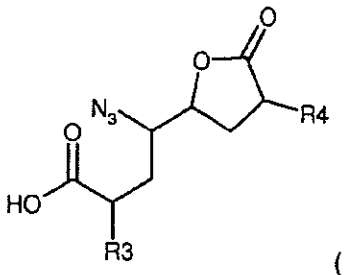
10. A method for preparing a compound of formula (II) according to any of claims 1 to 4, said method comprising subjecting a compound of formula (I)



(I)

wherein R^3 and R^4 are as defined for a compound of formula (II), or a salt thereof, to hydrogenation to convert the azide moiety to an amine and to effect lactam ring closure.

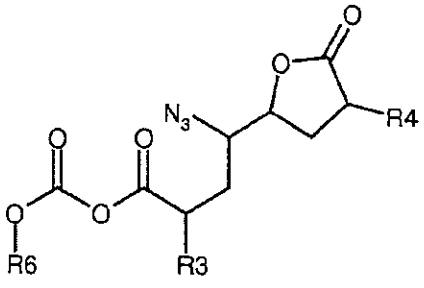
11. A method for preparing a compound of formula (II) according to any of claims 1 to 4, said process comprising subjecting a compound of formula (III)



(III)

wherein R^3 and R^4 are as defined for a compound of formula (II), or a salt thereof, to conversion

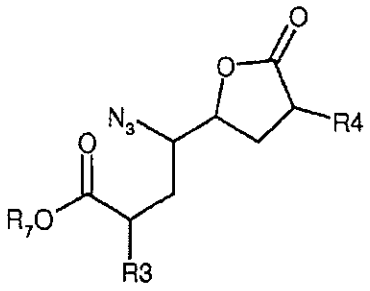
(a) to an anhydride of formula (IV)



(IV)

wherein R^3 and R^4 are as defined for a compound of formula (II) and R^6 is C_{1-7}alkyl or C_{3-8}cycloalkyl, or a salt thereof; to activate the acid moiety followed by hydrogenation to convert the azide moiety to an amine and to effect lactam ring closure;
or

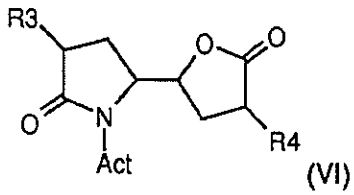
(b) to an ester of formula (V)



(V)

wherein R^3 and R^4 are as defined for a compound of formula (II) and R^7 is C_{1-7}alkyl or C_{3-8}cycloalkyl, or a salt thereof; followed by hydrogenation to convert the azide moiety to an amine and to effect lactam ring closure.

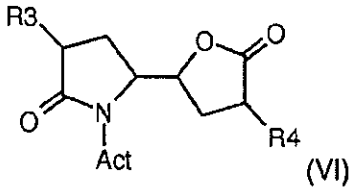
12. A method for preparing a compound of formula (VI)



(VI)

wherein R^3 and R^4 are as defined for a compound of formula (II) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof; comprising introducing the activating group at the nitrogen of a compound of formula (II) as given in any of claims 1 to 4, or a salt thereof.

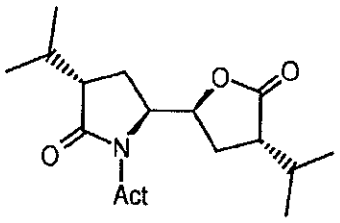
13. A compound of formula (VI)



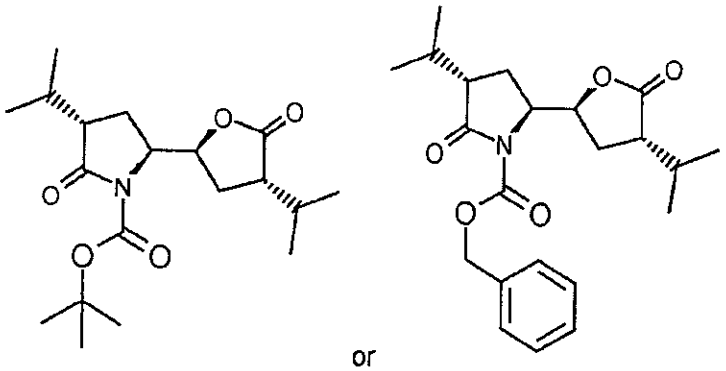
(VI)

wherein
R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl;
R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl, O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl; and
Act is an activating group selected from an amino protecting group, in particular a carbamate;
or a salt thereof.

14. The compound according to claim 13, having the formula

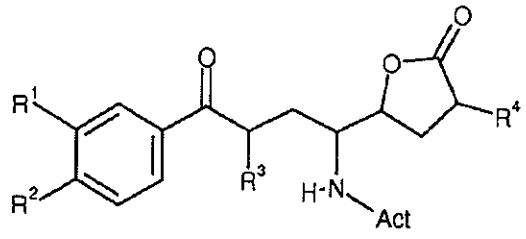


15. The compound according to claim 13 or 14, having the formula



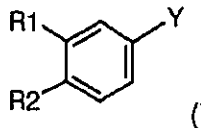
or

16. A method for preparing a compound of formula (VIII)



(VIII)

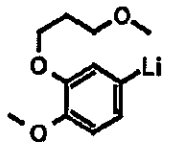
wherein R^3 and R^4 are as defined for a compound of formula (II); Act is an activating group selected from an amino protecting group, in particular a carbamate; R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl; and R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy, or a salt thereof;
comprising the step of lactam ring opening of the N-activated lactam lactone of formula (VI) or a salt thereof as defined in any of claims 13 to 15 with a compound of formula (VII)



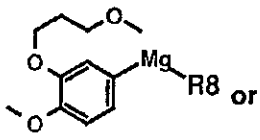
(VII)

wherein Y is a metal containing group such as -Li, -MgX, -magnesate, aryl magnesium species, alkyl magnesium species, -MnX, $(alkyl)_3MnLi$-, or $-CeX_2$ wherein X is halogen such as Cl, I or Br, more preferably Br; and R^1 and R^2 are as defined for a compound of formula (VIII).

17. The method according to claim 16 wherein the N-activated lactam lactone of formula (VI) is reacted with a compound of the following formula:

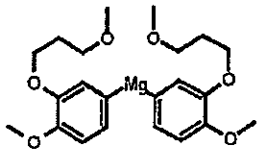


or

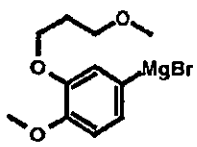


or

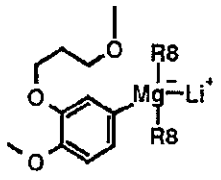
(VIIa) (VIIb) **R8 = C_{1-7} alkyl, preferably branched C1-7 alkyl**



or

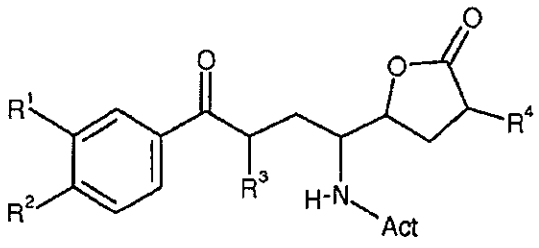


or



(VIIc) (VIId) (VIIe)

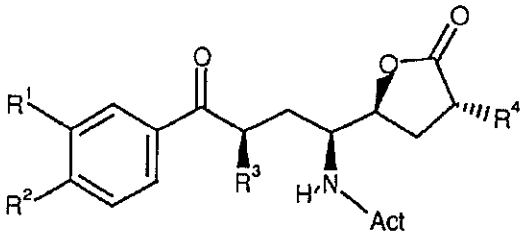
18. A compound of formula (VIII)



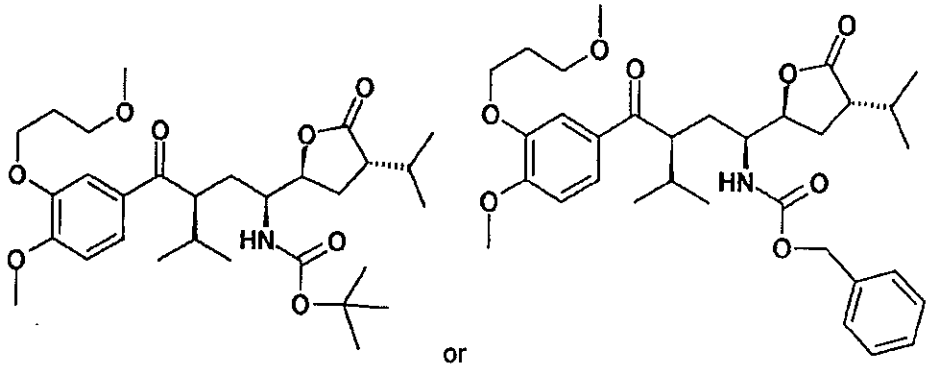
(VIII)

wherein
R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl;
R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl, O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl;
R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl; R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy; and
Act is an activating group selected from an amino protecting group, in particular a carbamate;
or a salt thereof.

19. The compound according to claim 18, having the formula

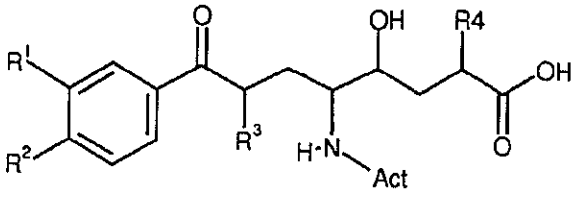


20. The compound according to claim 18 or 19, having the formula



or

21. A compound of formula (VIII')



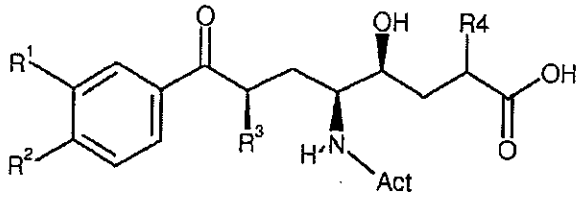
(VIII')

wherein
R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl;
R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl, O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl;
R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl; R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy; and
Act is an activating group selected from an amino protecting group, in particular a carbamate;
or a salt thereof.

22. The compound according to claim 21 in the form of a salt.

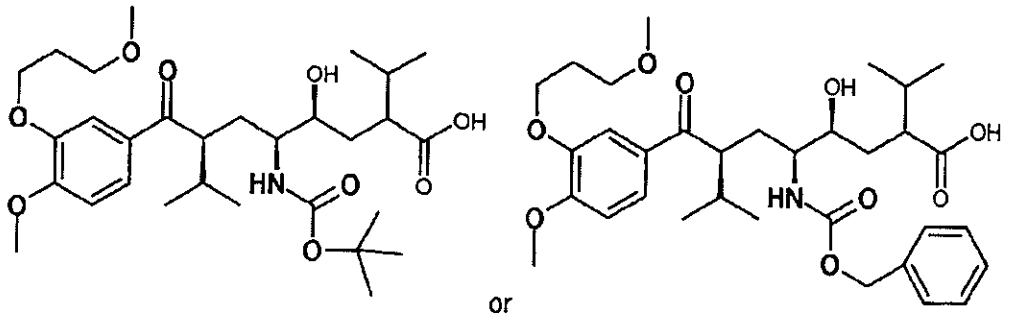
23. The compound according to claims 21 or 22 in the form of the Li, Na, K, Mg, Ca, primary, secondary or tertiary amine salt.

24. The compound according to any of claims 21 to 23, having the formula



or preferably a salt thereof.

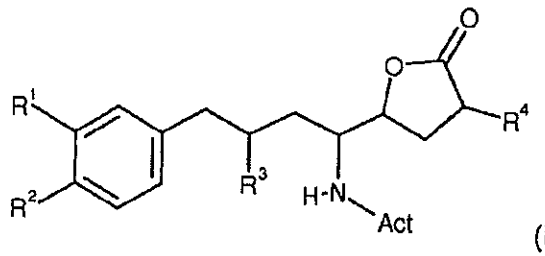
25. The compound according to any of claims 21 to 24, having the formula



or

or preferably a salt thereof.

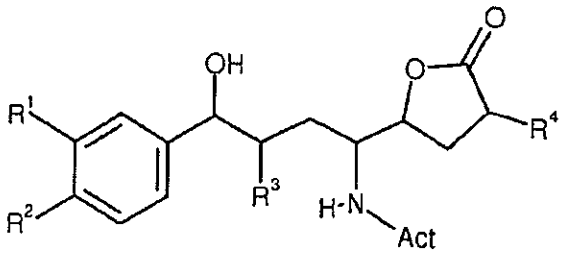
26. A method for preparing a compound of formula (IX)



(IX)

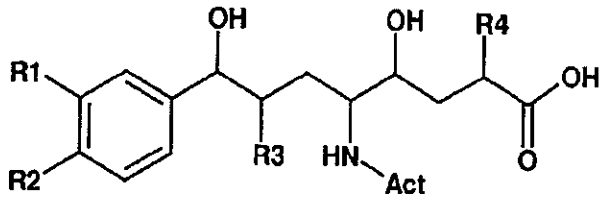
wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof,

(a) comprising reduction of the benzylic carbonyl of the compound of formula (VIII) as defined in any of claims 18 to 20, or a compound of formula (VIII') as defined in any of claims 21 to 25 to a methylene moiety;
or
(b) comprising a method for preparing a compound of formula (X)



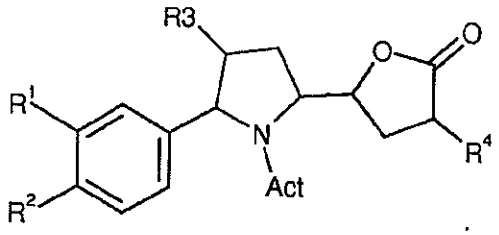
(X)

defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, said method comprising the reduction of the benzylic carbonyl of the compound of formula (VIII) as defined in any of claims 18 to 20 to a hydroxyl moiety,
and then hydrogenation of the compound of formula (X) to a compound of formula (IX); or
(c) comprising a method for preparing a compound of formula (X')



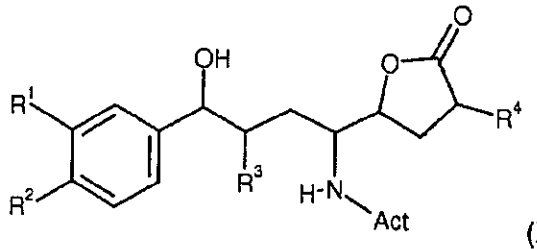
(X')

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, said method comprising reduction of the benzylic carbonyl of the compound of formula (VIII') as defined in any of claims 21 to 25 to a hydroxyl moiety,
and then hydrogenation of the compound of formula (X') to a compound of formula (IX); or
(d) comprising a method for preparing a compound of formula (XI)



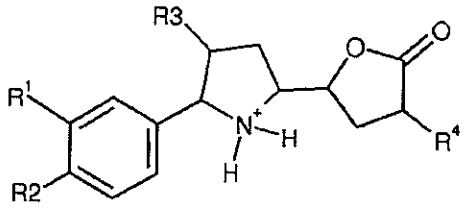
(XI)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof, said method comprising
the reduction of the benzylic carbonyl of the compound of formula (VIII) as defined in any of claims 18 to 20 to a hydroxyl moiety, then
cyclisation of the benzylic alcohol and the amine moieties of the compound of formula (X)

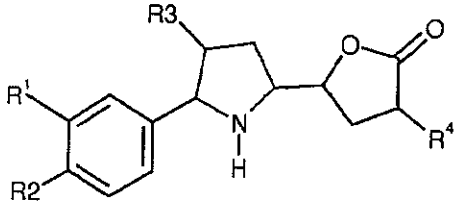


(X)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof,
to a pyrrolidine moiety,
and then hydrogenation or reduction of the pyrrolidine moiety of the compound of formula (XI) to ring-open and to obtain the methylene moiety in position 8 to form a compound of formula (IX),
wherein in method (d) the compound of formula (XI) is optionally converted to a pyrrolidine salt of formula (XI') or a pyrrolidine free base of formula (XI")

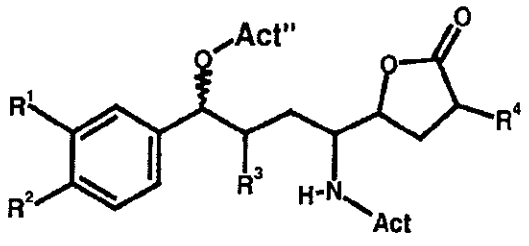


X⁻ or



(XI') (XI")

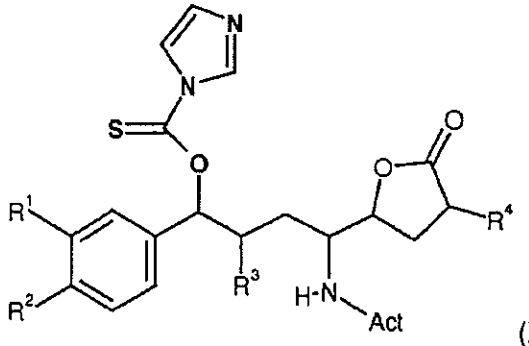
wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and X^- is an anion such as halide, trifluoroacetate, sulfate, nitrate, oxalate, sulfonate, triflate, phosphonate or phosphate;
or
(e) comprising the preparation a compound of formula (X")



(X'')

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII), Act is an activating group selected from an amino protecting group, in particular a carbamate, and Act" is an electron-withdrawing group, or a salt thereof, by
reduction of the benzylic carbonyl of the compound of formula (VIII) as defined in any of claims 18 to 20 to a hydroxyl moiety, then
conversion of the benzylic alcohol of the compound of formula (X) wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII), Act is an activating group selected from an amino protecting group, in particular a carbamate, to an activated alcohol moiety,
followed by hydrogenation or reduction of the activated alcohol moiety of the compound of formula (X") wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula

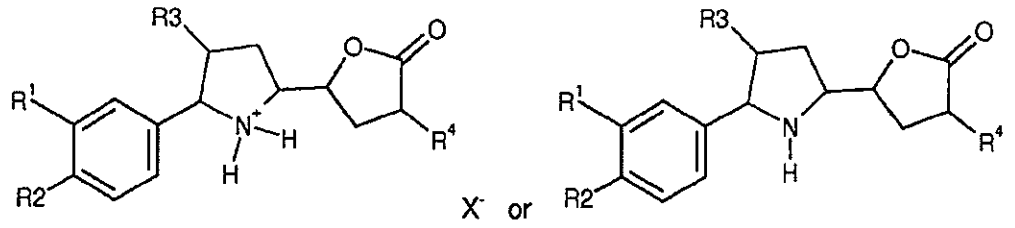
(VIII), Act is an activating group selected from an amino protecting group, in particular a carbamate, and Act'' is an electron-withdrawing group, or a salt thereof,to obtain the methylene moiety in position 8,
wherein in the method (e) Act'' is optionally -(C=O)-R^9, where R^9 can be substituted alkyl, alkyl-oxy-R^{10}, substituted aralkyl, substituted aryl, substituted or unsubstituted O-alkyl, substituted O-aryl, NH-R^{10} , where R^{10} can be substituted alkyl, substituted aryl, substituted aralkyl, such as substituted benzyl, benzoyl, substituted sulfonyl, wherein the substituent is in each case one or more electon-withdrawing moiety such as F or CF_3; or
(f) comprising
the reduction of the benzylic carbonyl of the compound of formula (VIII) as defined in any of claims 18 to 20 to a hydroxyl moiety, then
the transformation of the compound of formula (X) wherein R^1 and R^2 are as defined for a compound of formula (VIII), Act is an activating group selected from an amino protecting group, in particular a carbamate, to a thiocarbonyl derivative and subsequently subjecting the same to radical-based reduction to obtain the compound of formula (IX),
wherein the thiocarbonyl derivative is optionally selected from the group consisting of thionocarbamates, such as imidazolyl derivatives, thiocarbonyls, such as xanthates, and thionocarbonates, or
wherein the thiocarbonyl derivative is optionally a thionocabamate of formula (XV)



(XV)

wherein R^3 and R^4 are as defined for a compound of formula (II); Act is an activating group selected from an amino protecting group, in particular a carbamate, R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl; R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy, or a salt thereof; or
wherein the thiocarbonyl derivative is optionally reacted with Bu_3SnH or tris(trimethylsilyl)-silane.

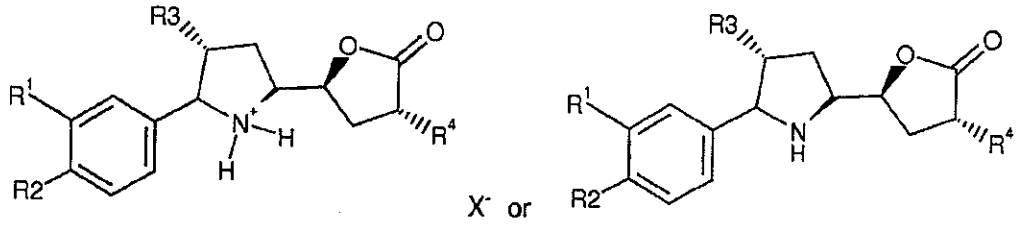
27. A compound of formula (XI'), or a compound of formula (XI''):



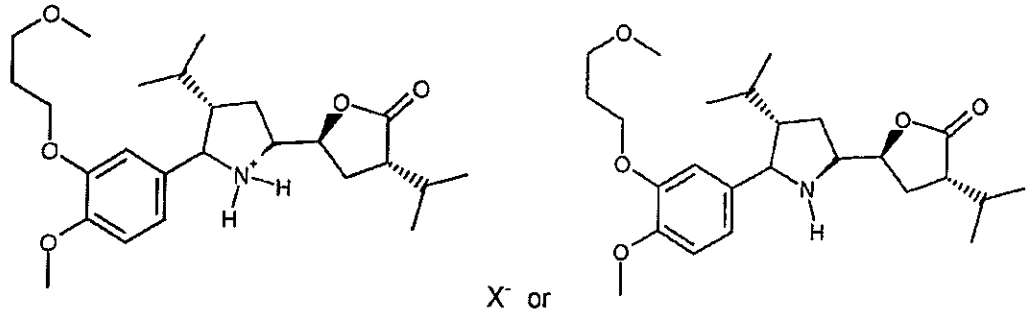
(XI') (XI'')

wherein
R^3 is C_{1-7}alkyl or C_{3-8}cycloalkyl;
R^4 is C_{1-7}alkyl, C_{2-7}alkenyl, C_{3-8}cycloalkyl, phenyl- or naphthyl-C_{1-4}alkyl each unsubstituted or mono-, di- or tri-substituted by C_{1-4}alkyl,O-C_{1-4}alkyl, OH, C_{1-4}alkylamino, di-C_{1-4}alkylamino, halogen and/or by trifluoromethyl;
R^1 is halogen, hydroxyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy-C_{1-6}alkyloxy or C_{1-6}alkoxy-C_{1-6}alkyl; R^2 is halogen, hydroxyl, C_{1-4}alkyl or C_{1-4}alkoxy; and
X^- is an anion such as halide, trifluoroacetate, sulfate, nitrate, oxalate, sulfonate, triflate, phosphonate or phosphate.

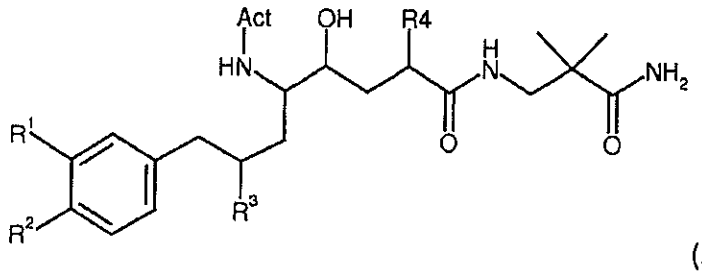
28. The compound according to claim 27, having the formula



29. The compound according to claim 27 or 28, having the formula



30. A method for preparing a compound of formula (XII)



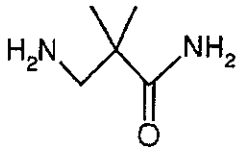
(XII)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof,

comprising

preparing a compound of the formula (IX) according to a method according to claim 26; followed by reacting the compound of the formula (IX)

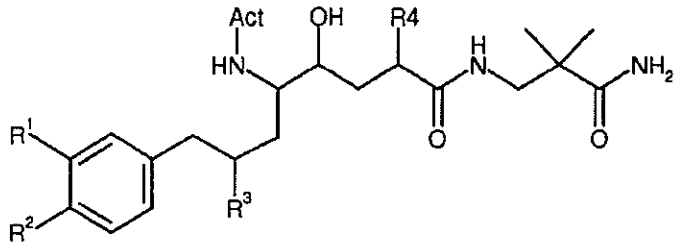
with an amine of the formula XIII,



(XIII)

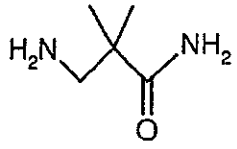
(wherein the amido nitrogen can also be protected if desired and the protecting group then be removed in the corresponding protected compound of the formula XII), or a salt thereof.

31. A method for preparing a compound of formula (XII)



(XII)

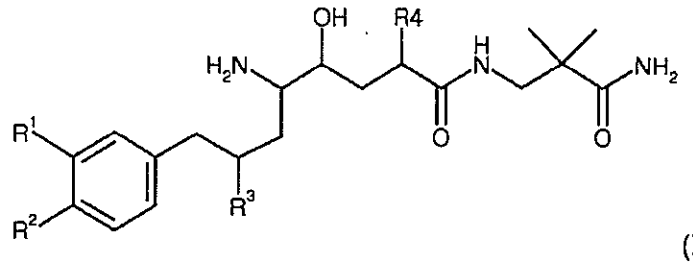
wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII) and Act is an activating group selected from an amino protecting group, in particular a carbamate, or a salt thereof,
comprising
preparing a compound of the formula (IX) according to a method according to claim 26; converting the compound of the formula (IX) to a compound of formula (IX'),
and then reacting the compound of formula (IX')
with an amine of the formula XIII,



(XIII)

(wherein the amido nitrogen can also be protected if desired and the protecting group then be removed in the corresponding protected compound of the formula XII), or a salt thereof.

32. A method for preparing a compound of formula (XIV)



(XIV)

wherein R^3 and R^4 are as defined for a compound of formula (II), R^1 and R^2 are as defined for a compound of formula (VIII), or a salt thereof, comprising one or more of the following steps either individually or in any combination:

- the manufacture of a compound of the formula II according to one of claims 9, 10, 11, or a salt thereof,
- the manufacture of a compound of the formula VI according to claim 12, or a salt thereof,
- the manufacture of a compound of the formula VIII according to claim 16, or a salt thereof, and
- the manufacture of a compound of the formula IX according to claim 26, or a salt thereof.

33. A method according to claim 32, wherein the compound of formula (XIV) is aliskiren.