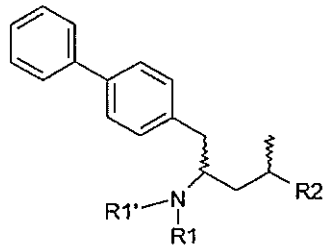
Claims

1. A process for producing a compound according to formula (i),

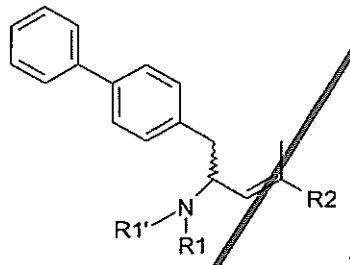


(i)

or salt thereof,

wherein R1 and R1' independently are hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group,

comprising reacting a compound according to formula (ii)



(ii)

or salt thereof,

wherein R1, R1' and R2 are defined as above,

with hydrogen in the presence of a transition metal catalyst and a chiral ligand, wherein the transition metal is selected from group 7, 8 or 9 of the periodic table.

2. A process according to claim 1, wherein the reaction is carried out as a homogenous catalysis.

3. A process according to claim 1 or 2, wherein the transition metal catalyst comprises rhodium or ruthenium.

4. A process according to any of the preceding claims, wherein the transition metal catalyst comprises a dimer complex, preferably a dimer ruthenium complex.

5. A process according to any of the preceding claims, wherein the transition metal catalyst comprises $[RuI_2(p\text{-cymene})]_2$.

6. A process according to any of claims 1 to 3, wherein the transition metal catalyst comprises $Rh(nbd)_2BF_4$.

7. A process according to any of the preceding claims, wherein the chiral ligand is a chiral phosphine.

8. A process according to any of the preceding claims, wherein the chiral ligand is a chiral ferrocene.

9. A process according to any of the preceding claims, wherein the chiral ligand is a Mandyphos ligand, a Walphos ligand, a Josiphos ligand or a Solphos ligand.

10. A process according to any of the preceding claims, wherein the chiral ligand is selected from Mandyphos SL-M001-1, Mandyphos SL-M002-1, Mandyphos SL-M004-1 Mandyphos SL-M004-2, Josiphos SL-J002-1, Josiphos SL-J003-1, Josiphos SL-J009-1, Walphos SL-W001-2, Walphos SL-W003-1, Walphos SL-W008-1 or Solphos SL-A001-1.

11. A process according to claim to 3, wherein the transition metal catalyst comprises rhodium and wherein the chiral ligand is selected from Mandyphos SL-M004-1, Josiphos SL-J003-1, Josiphos SL-J009-1, Walphos SL-W001-2, Walphos SL-W003-1, Walphos SL-W008-1 or Solphos SL-A001-1.

12. A process according to claim 11 wherein the transition metal catalyst comprises $Rh(nbd)_2BF_4$.

13. A process according to claims 11 or 12, wherein the chiral ligand is Walphos SL-W008-1.

14. A process according to claim 3, wherein the transition metal catalyst comprises ruthenium and wherein the chiral ligand is selected from Mandyphos SL-M001-1, Mandyphos SL-M002-1, Mandyphos SL-M004-1 Mandyphos SL-M004-2 or Josiphos SL-J002-1.

15. A process according to claim 14 wherein the transition metal catalyst comprises $[RuI_2(p\text{-cymene})]_2$.

16. A process according to claims 14 or 15, wherein the chiral ligand is selected from Mandyphos SL-M001-1, Mandyphos SL-M004-1 or Josiphos SL-J002-1.

17. A process according to claims 14 or 15, wherein the chiral ligand is Mandyphos SL-M004-2.

18. A process according to claims 14 or 15, wherein the chiral ligand is Mandyphos SL-M004-1.

19. A process according to any of the preceding claims, wherein the molar ratio of the compound of formula (ii), or salt thereof, to "active catalyst" (S/C) is 100 or higher, preferably from 1 000 to 30 000.

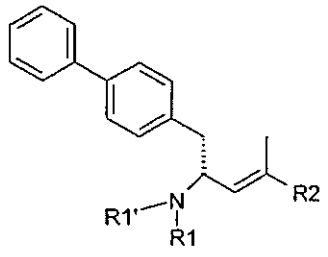
20. A process according to any of the preceding claims, wherein a hydrogen pressure of from 5 bar to 25 bar is applied.

21. A process according to any of the preceding claims, wherein R1 and R1' are independently hydrogen or an amine protective group selected from the group consisting of C_{1-6}alkyl which is mono-, di- or trisubstituted by C_{6-10}aryl, wherein the aryl ring is unsubstituted or substituted by one, two or three, residues selected from the group consisting of C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, nitro, cyano and CF_3; C_{6-10}aryl-C_{1-6}alkyl, cumyl, phenyl-C1-C2-alkoxycarbonyl, allyl, cinnamyl, 9-fluorenylmethyloxycarbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethoxycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), C_{1-10}alkenyloxycarbonyl, silyl, sulfonyl, sulfenyl, succinimidyl, C_{2-6}alkanoyl, C_{6-10}aryl-carbonyl, C_{1-6}alkoxy-carbonyl and C_{6-10}aryl-C_{1-6}alkoxycarbonyl.

22. A process according to any of the preceding claims, wherein R1 is a t-butoxycarbonyl group.

23. A process according to any of the preceding claims, wherein R2 is –COOH or –COOR3, wherein R3 is C_{1-6}alkyl.

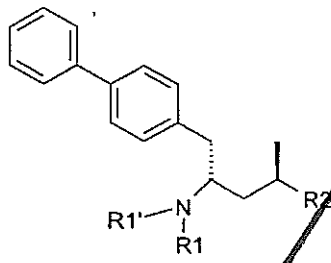
24. A process according to any of the preceding claims, wherein a compound according to formula (ii-a), or salt thereof, is reacted:



(ii-a),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

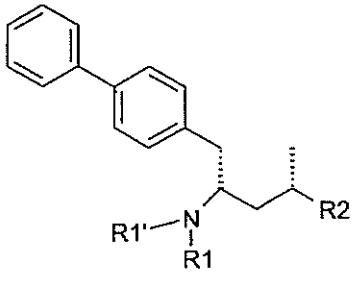
25. A process according to claim 24, wherein a compound according to formula (i-a), or salt thereof, is produced:



(i-a),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

26. A process according to claim 24, wherein a compound according to formula (i-b), or salt thereof, is produced:



(i-b),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

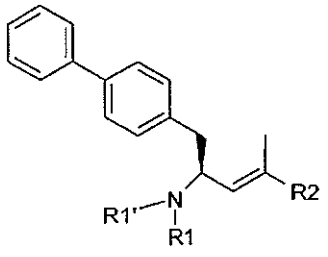
27. A process according to claim 24, wherein a composition comprising compounds according to formulae (i-a) and (i-b), or salts thereof, is produced and wherein the molar ratio of compounds according to formula (i-a) to compounds according to formula (i-b) is at least 88 : 12.

28. A process according to claim 24, wherein a composition comprising compounds according to formulae (i-a) and (i-b), or salts thereof, is produced and wherein the molar ratio of compounds according to formula (i-b), or salts thereof, to compounds according to formula (i-a), or salts thereof, is at least 65 : 35.

29. A process according to claim 27, wherein the compounds according to formula (i-a), or salts thereof, are separated from the composition by means of crystallisation.

30. A process according to claim 29, wherein isopropylacetate and heptane are used as solvents.

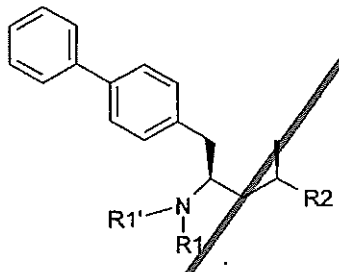
31. A process according to any of the preceding claims, wherein a compound according to formula (ii-b), or salt thereof, is reacted:



(ii-b),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or ester group.

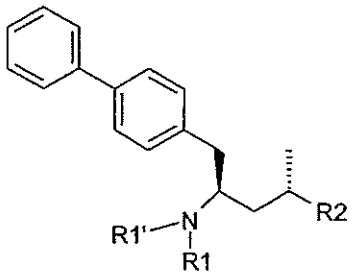
32. A process according to claim 31, wherein a compound according to formula (i-c), or salt thereof, is produced:



(i-c),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

33. A process according to claim 31, wherein a compound according to formula (i-d), or salt thereof, is produced:

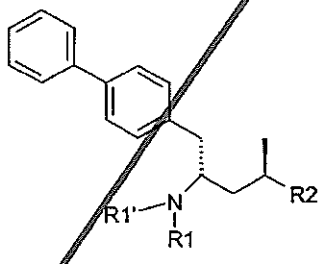


(i-d),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

34. A process according to claim 31, wherein a composition comprising compounds according to formulae (i-c) and (i-d), or salts thereof, is produced and wherein the molar ratio of compounds according to formula (i-c), or salts thereof, to compounds according to formula (i-d), or salts thereof, is at least 88 : 12.

35. A compound according to formula (i-a)



(i-a)

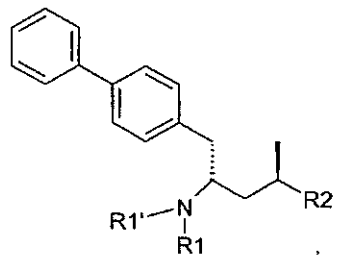
or salt thereof,
in crystalline form,

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

36. A compound according to claim 35, wherein the crystal system is monoclinic.

37. A compound according to claim 36, wherein the space group is P21.

38. A compound according to formula (i-a),



(i-a)

or salt thereof,

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group, provided that it is not the ethyl ester if R1 is BOC and R1' is hydrogen.

39. A compound according to claims 36 to 39, wherein R2 is COOH.

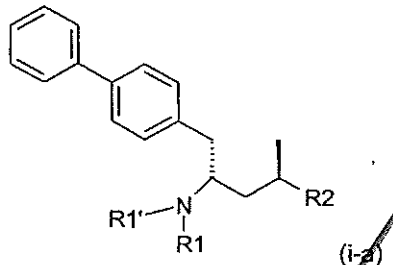
40. A process according to claims 1 to 35, wherein the compound according to formula (i), or salt thereof, is further reacted to obtain an NEP-inhibitor or a prodrug thereof.

41. A process according to claims 1 to 35, wherein the compound according to formula (i), or salt thereof, is further reacted to obtain an NEP-inhibitor or a prodrug thereof, comprising a γ-amino-δ-biphenyl-α-methylalkanoic acid, or acid ester, backbone.

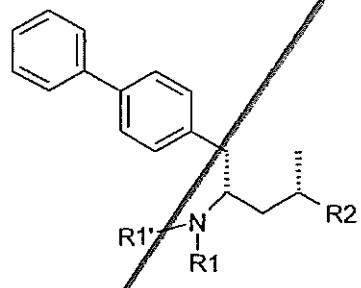
42. A process according to claims 40 or 41, wherein the NEP-inhibitor is N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid or a salt or a prodrug thereof.

43. A process according to claims 40 or 41, wherein the NEP-inhibitor prodrug is N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester or a salt thereof.

44. A composition comprising compounds according to formula (i-a) and (i-b),



(i-a)



(i-b)

or salts thereof,
wherein the molar ratio (i-a) to (i-b) is at least 88 : 12 and wherein R1 and R1' independently are hydrogen or an amine protecting group. and R2 is a carboxyl group or an ester group.

45. The composition according to claim 44 wherein R2 is COOH.

46. Use of a transition metal catalyst and a chiral ligand in the synthesis of a NEP inhibitor, or a prodrug thereof, wherein the transition metal is selected from group 7, 8 or 9 of the periodic table.

47. Use according to claim 46, wherein the NEP inhibitor, or a prodrug thereof, comprises a γ-amino-δ-biphenyl-α-methylalkanoic acid, or acid ester, backbone.

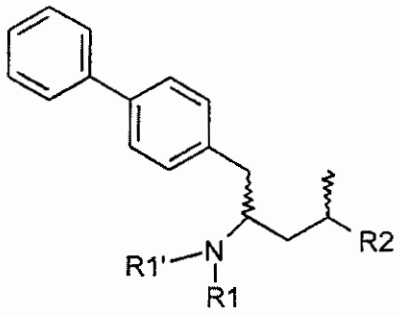
48. Use according to claim 47, wherein the transition metal catalyst and the chiral ligand are used in a hydrogenation step.

49. Use according to claim 48 wherein the reaction gives two diastereomers having a diastereomeric ratio of at least 88 : 12.

50. Use according to any of claims 47 to 49, wherein the NEP-inhibitor prodrug is N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester, or a salt thereof.

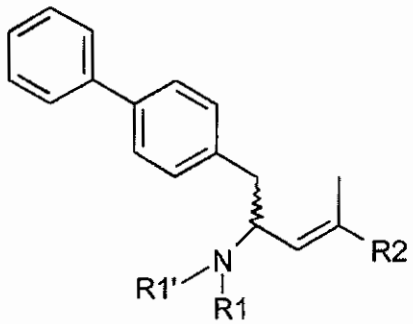
Claims

1. A process for producing a compound according to formula (i),



(i)

or salt thereof,
wherein R1 and R1' independently are hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group,
comprising reacting a compound according to formula (ii)



(ii)

or salt thereof,
wherein R1, R1' and R2 are defined as above,
with hydrogen in the presence of a transition metal catalyst and a chiral ligand, wherein the transition metal is selected from group 7, 8 or 9 of the periodic table.

2. A process according to claim 1, wherein the reaction is carried out as a homogenous catalysis.

3. A process according to claim 1 or 2, wherein the transition metal catalyst comprises rhodium or ruthenium.

4. A process according to any of the preceding claims, wherein the transition metal catalyst comprises a dimer complex, preferably a dimer ruthenium complex.

5. A process according to any of the preceding claims, wherein the transition metal catalyst comprises $[RuI_2(p\text{-cymene})]_2$.

6. A process according to any of claims 1 to 3, wherein the transition metal catalyst comprises $Rh(nbd)_2BF_4$.

7. A process according to any of the preceding claims, wherein the chiral ligand is a chiral phosphine.

8. A process according to any of the preceding claims, wherein the chiral ligand is a chiral ferrocene.

9. A process according to any of the preceding claims, wherein the chiral ligand is a Mandyphos ligand, a Walphos ligand, a Josiphos ligand or a Solphos ligand.

10. A process according to any of the preceding claims, wherein the chiral ligand is selected from Mandyphos SL-M001-1, Mandyphos SL-M002-1, Mandyphos SL-M004-1 Mandyphos SL-M004-2, Josiphos SL-J002-1, Josiphos SL-J003-1, Josiphos SL-J009-1, Walphos SL-W001-2, Walphos SL-W003-1, Walphos SL-W008-1 or Solphos SL-

A001-1.

11. A process according to claim to 3, wherein the transition metal catalyst comprises rhodium and wherein the chiral ligand is selected from Mandyphos SL-M004-1, Josiphos SL-J003-1, Josiphos SL-J009-1, Walphos SL-W001-2, Walphos SL-W003-1, Walphos SL-W008-1 or Solphos SL-A001-1.

12. A process according to claim 11 wherein the transition metal catalyst comprises $Rh(nbd)_2BF_4$.

13. A process according to claims 11 or 12, wherein the chiral ligand is Walphos SL-W008-1.

14. A process according to claim 3, wherein the transition metal catalyst comprises ruthenium and wherein the chiral ligand is selected from Mandyphos SL-M001-1, Mandyphos SL-M002-1, Mandyphos SL-M004-1 Mandyphos SL-M004-2 or Josiphos SL-J002-1.

15. A process according to claim 14 wherein the transition metal catalyst comprises $[RuI_2(p\text{-cymene})]_2$.

16. A process according to claims 14 or 15, wherein the chiral ligand is selected from Mandyphos SL-M001-1, Mandyphos SL-M004-1 or Josiphos SL-J002-1.

17. A process according to claims 14 or 15, wherein the chiral ligand is Mandyphos SL-M004-2.

18. A process according to claims 14 or 15, wherein the chiral ligand is Mandyphos SL-M004-1.

19. A process according to any of the preceding claims, wherein the molar ratio of the compound of formula (ii), or salt thereof, to "active catalyst" (S/C) is 100 or higher, preferably from 1 000 to 30 000.

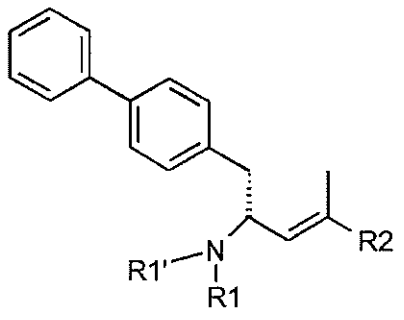
20. A process according to any of the preceding claims, wherein a hydrogen pressure of from 5 bar to 25 bar is applied.

21. A process according to any of the preceding claims, wherein R1 and R1' are independently hydrogen or an amine protective group selected from the group consisting of C_{1-6}alkyl which is mono-, di- or trisubstituted by C_{6-10}aryl, wherein the aryl ring is unsubstituted or substituted by one, two or three, residues selected from the group consisting of C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, nitro, cyano and CF_3; C_{6-10}aryl-C_{1-6}alkyl, cumyl, phenyl-C1-C2-alkoxy-carbonyl, allyl, cinnamyl, 9-fluorenylmethyloxycarbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethxoycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), C_{1-10}alkenyloxycarbonyl, silyl, sulfonyl, sulfenyl, succinimidyl, C_{2-6}alkanoyl, C_{6-10}aryl-carbonyl, C_{1-6}alkoxy-carbonyl and C_{6-10}aryl-C_{1-6}alkoxycarbonyl.

22. A process according to any of the preceding claims, wherein R1 is a t-butoxycarbonyl group.

23. A process according to any of the preceding claims, wherein R2 is -COOH or - COOR3, wherein R3 is C_{1-6}alkyl.

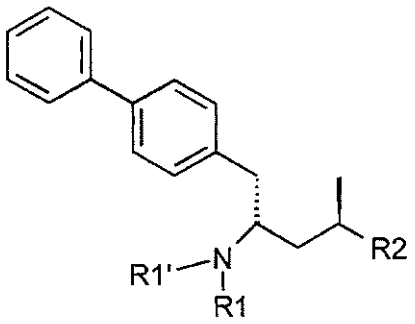
24. A process according to any of the preceding claims, wherein a compound according to formula (ii-a), or salt thereof, is reacted:



(ii-a),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

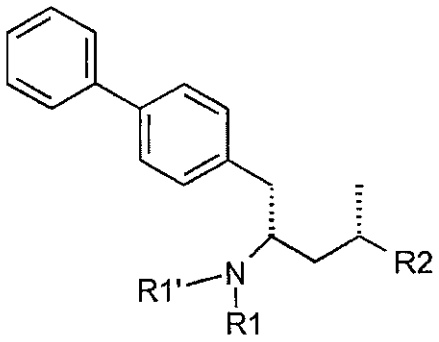
25. A process according to claim 24, wherein a compound according to formula (i-a), or salt thereof, is produced:



(i-a),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

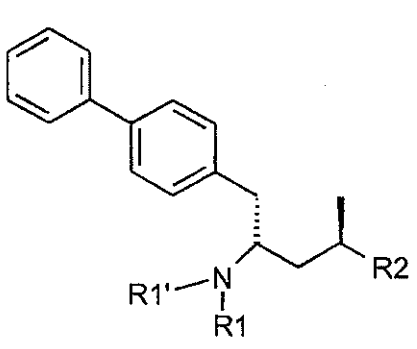
26. A process according to claim 24, wherein a compound according to formula (i-b), or salt thereof, is produced:



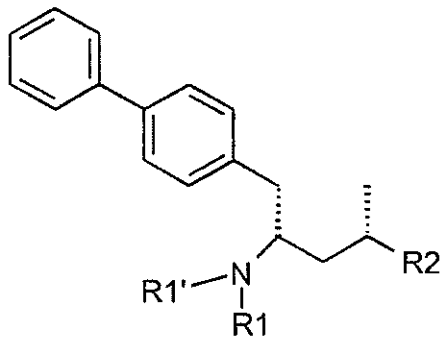
(i-b),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

27. A process according to claim 24, wherein a composition comprising compounds according to formulae (i-a) and (i-b), or salts thereof,



(i-a),

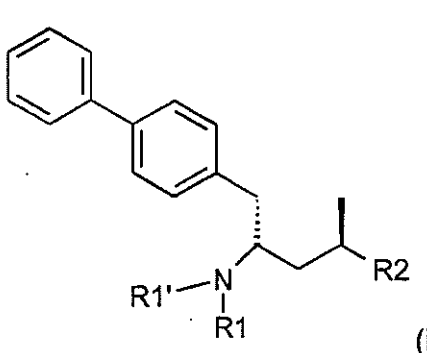


(i-b),

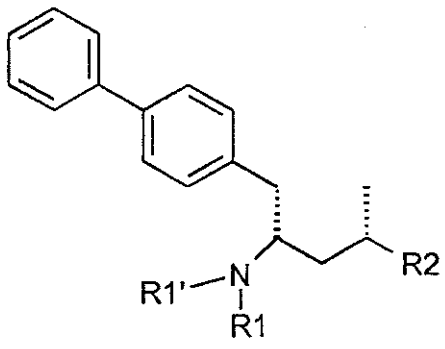
wherein R1, R1' and R2 are as defined in claim 24, is produced and wherein the molar ratio of compounds according to formula (i-a) to compounds according to formula (i-b) is at least 88 : 12.

28. A process according to claim 24, wherein a composition comprising compounds according to formulae (i-a) and (i-

b), or salts thereof,



(i-a),



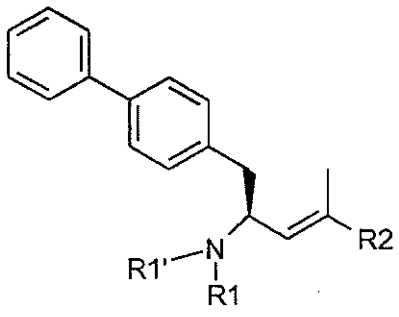
(i-b),

wherein R1, R1' and R2 are as defined in claim 24, is produced and wherein the molar ratio of compounds according to formula (i-b), or salts thereof, to compounds according to formula (i-a), or salts thereof, is at least 65 : 35.

29. A process according to claim 27, wherein the compounds according to formula (i-a), or salts thereof, are separated from the composition by means of crystallisation.

30. A process according to claim 29, wherein isopropylacetate and heptane are used as solvents.

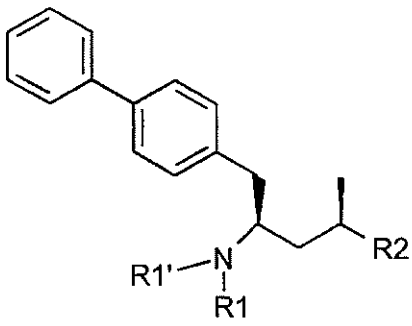
31. A process according to any of the preceding claims, wherein a compound according to formula (ii-b), or salt thereof, is reacted:



(ii-b),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or ester group.

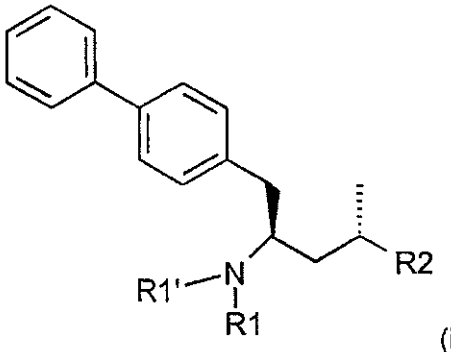
32. A process according to claim 31, wherein a compound according to formula (i-c), or salt thereof, is produced:



(i-c),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

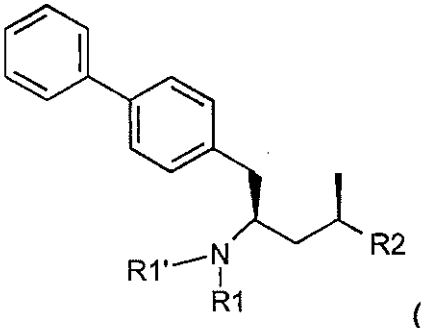
33. A process according to claim 31, wherein a compound according to formula (i-d), or salt thereof, is produced:



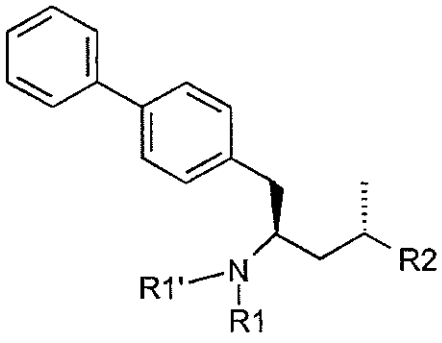
(i-d),

wherein R1 and R1' are independently hydrogen or an amine protecting group and R2 is a carboxyl group or an ester group.

34. A process according to claim 31, wherein a composition comprising compounds according to formulae (i-c) and (i-d), or salts thereof,



(i-c),



(i-d),

wherein R1, R1' and R2 are as defined in claim 31, is produced and wherein the molar ratio of compounds according to formula (i-c), or salts thereof, to compounds according to formula (i-d), or salts thereof, is at least 88 : 12.

35. A process according to claims 1 to 34, wherein the compound according to formula (i), or salt thereof, is further reacted to obtain a NEP-inhibitor.

36. A process according to claims 1 to 34, wherein the compound according to formula (i), or salt thereof, is further reacted to obtain a NEP-inhibitor comprising a γ-amino-δ-biphenyl-α-methylalkanoic acid, or acid ester, backbone.

37. A process according to claims 35 or 36, wherein the NEP-inhibitor is N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid or a salt thereof.

38. A process according to claims 1 or 34, wherein the compound according to formula (i), or salt thereof, is further reacted to obtain the NEP-inhibitor pro-drug N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester or a salt thereof.