



(43) International Publication Date
2 March 2017 (02.03.2017)

(10) International Publication Number
WO 2017/033128 A1

(51) International Patent Classification:

A61K 31/215 (2006.01) C07C 237/06 (2006.01)
C07C 219/06 (2006.01) C07C 53/42 (2006.01)
C07C 327/22 (2006.01)

(21) International Application Number:

PCT/IB2016/055027

(22) International Filing Date:

23 August 2016 (23.08.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

PCT/CN2015/087975

25 August 2015 (25.08.2015)

CN

(71) Applicant (for all designated States except US): **NO-VARTIS AG** [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).

(72) Inventors; and

(71) Applicants (for US only): **HOOK, David** [GB/CH]; c/o Novartis Pharma AG, Postfach, 4002 Basel (CH). **KU, Jie** [CN/CN]; c/o Suzhou Novartis Pharma Technology Co., Ltd., #18 Tonglian Road, Riverside Industrial Park, Changshu Economic Development Zone, Changshu, Jiangsu 215537 (CN). **ZHOU, Jianguang** [CN/CN]; c/o Suzhou Novartis Pharma Technology Co., Ltd., #18 Tonglian Road, Riverside Industrial Park, Changshu Economic Development Zone, Changshu, Jiangsu 215537 (CN).

(74) Agent: **LARBIG, Karen D.**; c/o Novartis Pharma AG, Patent Department, 4002 Basel (CH).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- with amended claims (Art. 19(1))

(54) Title: BIPHENYL-SUBSTITUED 4-AMINO-BUTYRIC ACID DERIVATIVES AND THEIR USE IN THE SYNTHESIS OF NEP INHIBITORS

(57) Abstract: The invention relates to a novel process, novel process steps and novel intermediates useful in the synthesis of pharmaceutically active compounds, in particular neutral endopeptidase (NEP) inhibitors and prodrugs thereof.



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BIPHENYL-SUBSTITUED 4-AMINO-BUTYRIC ACID DERIVATIVES AND
THEIR USE IN THE SYNTHESIS OF NEP INHIBITORS

Field of the invention

The invention relates to a novel process, novel process steps and novel intermediates useful
5 in the synthesis of pharmaceutically active compounds, in particular neutral endopeptidase
(NEP) inhibitors or prodrugs thereof.

Background of the invention

The present invention relates to a method to prepare key intermediates in the synthesis of
10 pharmaceutically active compounds, in particular neutral endopeptidase (NEP) inhibitors,
such as those described in U.S. Patent No. 4,722,810, U.S. Patent No. 5,223,516, U.S.
Patent No. 4,610,816, U.S. Patent No. 4,929,641, South African Patent Application 84/0670,
UK 69578, U.S. Patent No. 5,217,996, EP 00342850, GB 02218983, WO 92/14706, EP
0034391 1, JP 06234754, EP 00361365, WO 90/09374, JP 07157459, WO 94/15908, U.S.
15 Patent No. 5,273,990, U.S. Patent No. 5,294,632, U.S. Patent No. 5,250,522, EP 00636621,
WO 93/09101, EP 00590442, WO 93/10773, WO2008/031567 and U.S. Patent No.
5,217,996, particularly in the preparation of *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-
phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester, or a salt thereof.

Endogenous atrial natriuretic peptides (ANP), also called atrial natriuretic factors (ANF), have
20 diuretic, natriuretic and vasorelaxant functions in mammals. The natural ANF peptides are
metabolically inactivated, in particular by a degrading enzyme which has been recognized to
correspond to the enzyme neutral endopeptidase (NEP, EC 3.4.24.11), which is also
responsible for e.g. the metabolic inactivation of enkephalins.

In the art biaryl substituted phosphonic acid derivatives are known which are useful as neutral
25 endopeptidase (NEP) inhibitors, e.g. as inhibitors of the ANF-degrading enzyme in mammals
so as to prolong and potentiate the diuretic, natriuretic and vasodilator properties of ANF in
mammals by inhibiting the degradation thereof to less active metabolites. NEP inhibitors are
thus particularly useful for the treatment of conditions and disorders responsive to the
inhibition of neutral endopeptidase (EC 3.4.24.11), particularly cardiovascular disorders such
30 as hypertension, renal insufficiency including edema and salt retention, pulmonary edema
and congestive heart failure.

Processes for preparing NEP-inhibitors are known.

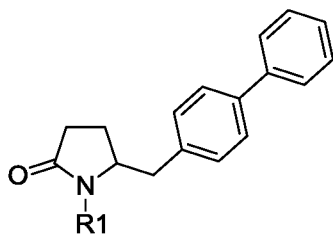
US 5,217,996 describes biaryl substituted 4-amino-butyric acid amide derivatives which are
useful as neutral endopeptidase (NEP) inhibitors, e.g. as inhibitors of the ANF-degrading

enzyme in mammals. As a preferred embodiment US 5,217,996 discloses *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester and a method for its preparation.

Several dicarboxylic acid dipeptide neutral endopeptidase (NEP) inhibitors are further described by G.M. Ksander *et al.* in *J. Med. Chem.* **1995**, *38*, 1689-1700, "Dicarboxylic Acid Dipeptide Neutral Endopeptidase Inhibitors". Among others, *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester and a method for its preparation are disclosed.

WO2008/083967 describes a method for producing NEP inhibitors or prodrugs thereof, in particular *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester, or a salt thereof, via intermediates such as:

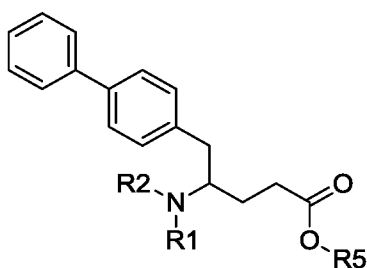
- a compound according to formula (2*), or a tautomer, or a salt thereof,



(2*)

wherein R1 is hydrogen or a nitrogen protecting group;

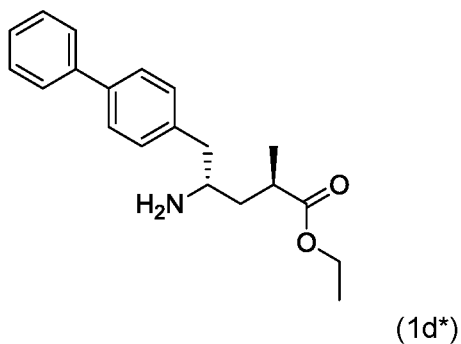
- a compound of formula (3*), or a salt thereof,



(3*)

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, and R5 is hydrogen or C₁-C₇-alkyl; and, in particular,

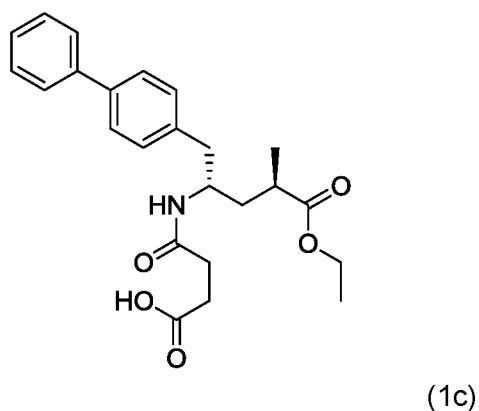
- a compound of formula (1d*)



or a salt thereof.

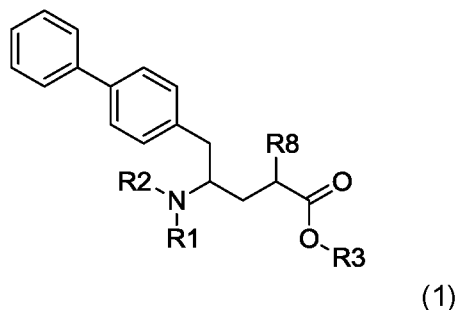
The conversion of the compound of formula (1d) into *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester (known in the art as AHU377), or a salt thereof, has been described, for example, in Subsection B-3 in WO2008/083967.

It is an object of the present invention to provide an alternative reaction route in a process for producing NEP inhibitors or prodrugs thereof. In particular it is an object to provide an alternative reaction route in a process for producing *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester, or a salt thereof, according to formula (1c)

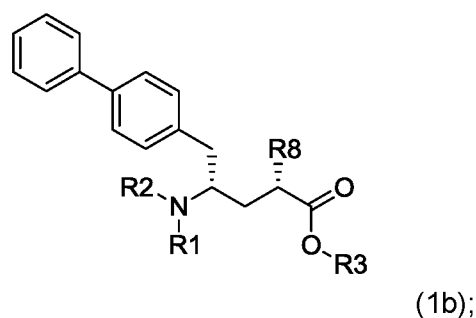
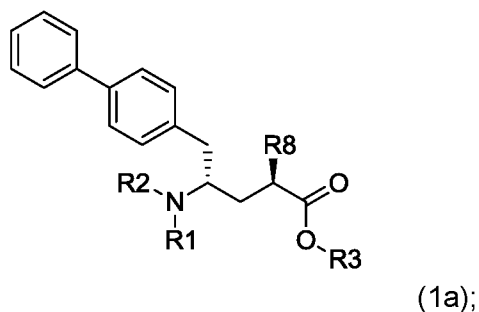


Summary of the invention:

This invention provides new methods for preparing a compound according to the formula (1), or a salt thereof,



preferably having a configuration according to formula (1a) or (1b), more preferably (1a),



5 wherein

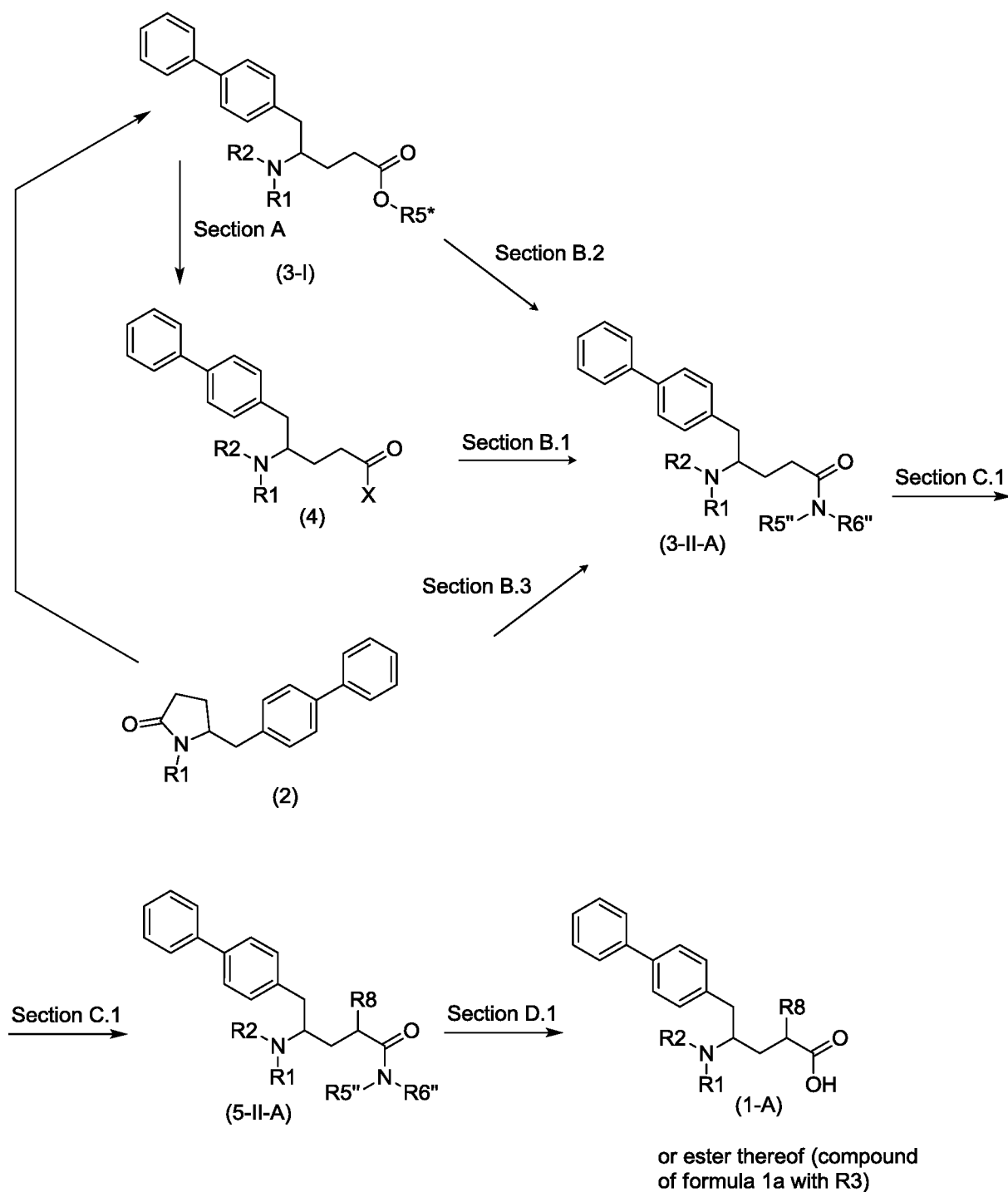
R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 10 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R3 is hydrogen or C₁-C₇-alkyl; preferably hydrogen or ethyl, and

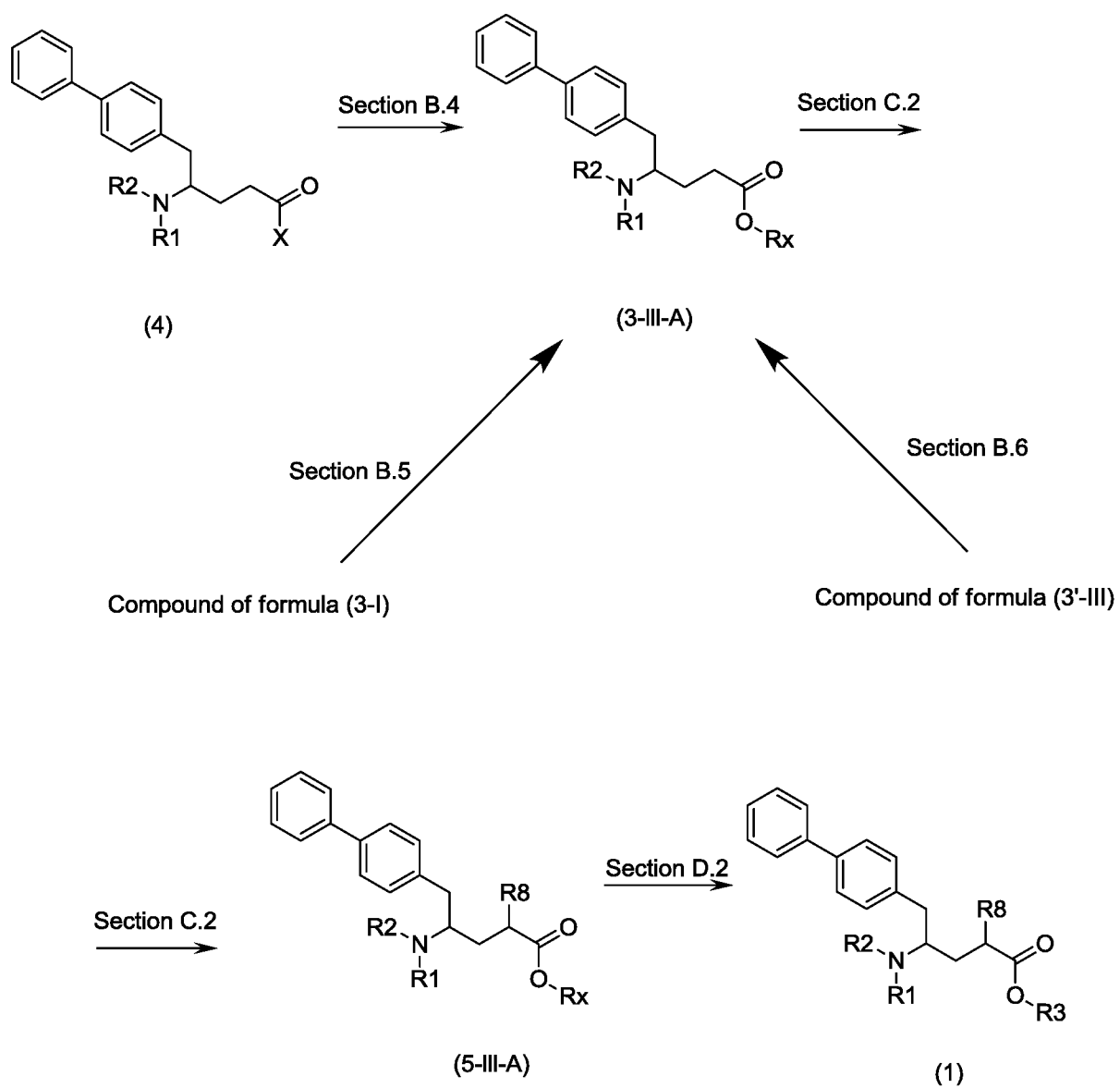
R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl.

15 New processes, according to the present invention, for producing a compound according to formula (1), are summarized in the following Schemes 1 to 5

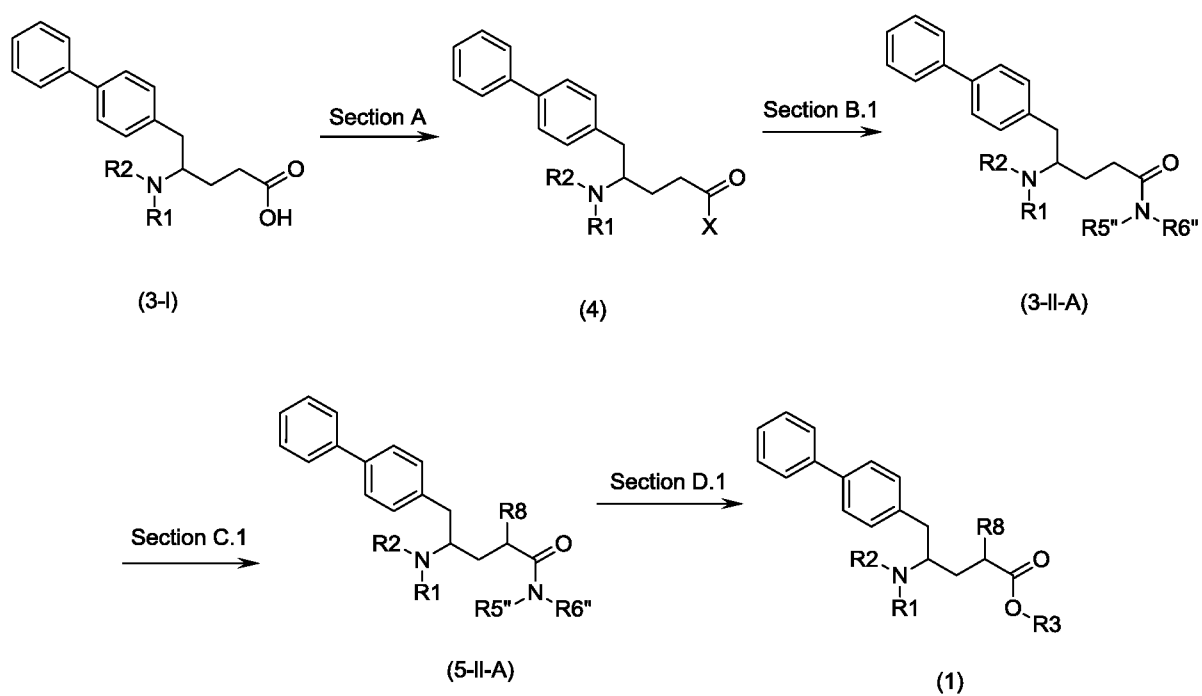
Scheme 1: formation of amide/alkylated amide/hydrolysis to (1-A)



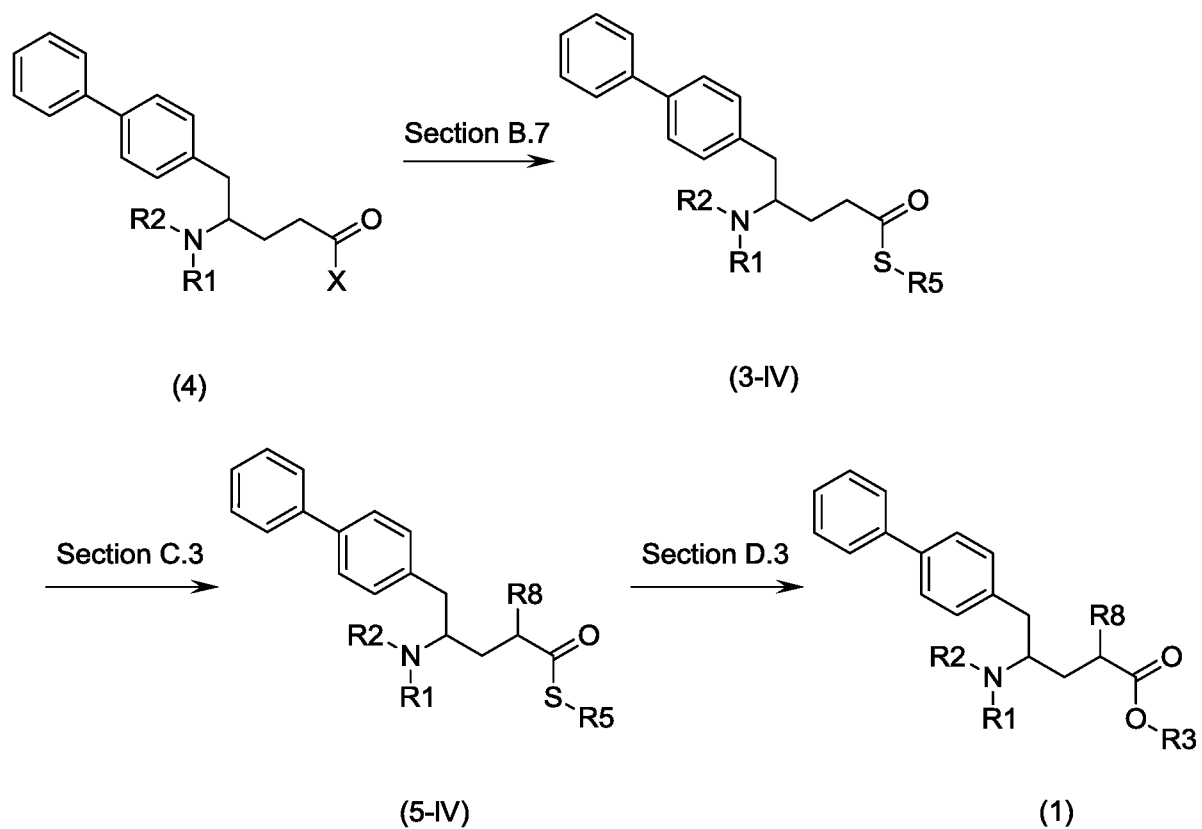
Scheme 2: formation of ester/alkylated ester/hydrolysis to (1):



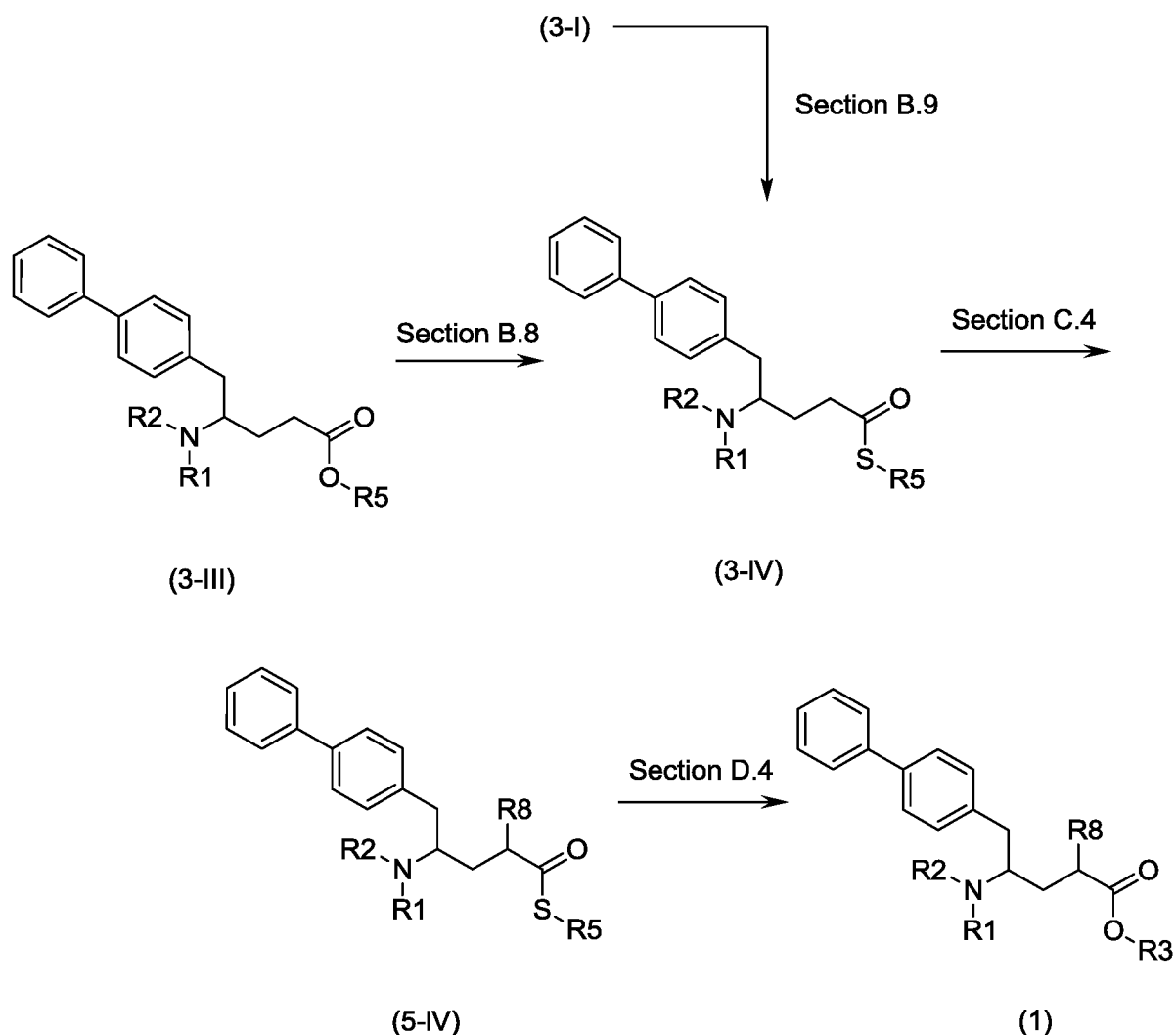
Scheme 3: formation of acid chloride/amide/alkylated amide/hydrolysis to (1):



Scheme 4: formation of thioester/alkylated thioester/hydrolysis to (1):



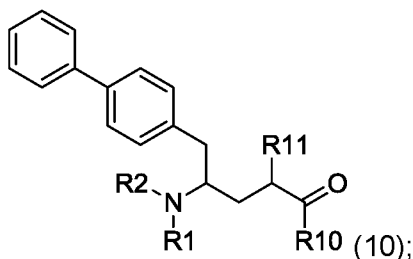
Scheme 5: formation of thioester/alkylated thioester/hydrolysis to (1):



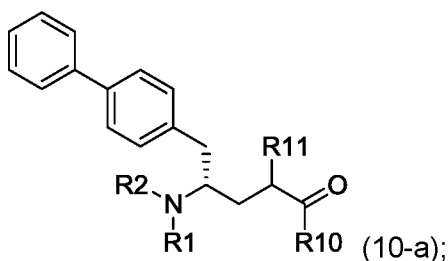
The conversion of a compound of formula (1) or salt thereof, as described above, in particular wherein R1 is H, R2 is *t*-butoxycarbonyl, R8 is methyl and R3 is ethyl, into a NEP inhibitor or prodrug thereof, in particular into *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester, or a salt thereof, has been described, for example by G.M. Ksander *et al.* in *J. Med. Chem.* **1995**, 38, 1689-1700 and the patent documents cited hereinbefore, the disclosure for each of which is incorporated by reference.

- 10 In the above schemes, where R3 in a compound of formula (1) is H, the corresponding compound is also called compound of formula (1-A). The compound of formula (3-I*) is a compound of formula (3-I) in which R5* is hydrogen, C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl.

Furthermore, the present also claims novel intermediates, in particular a compound of formula (10), or a salt thereof,



preferably having a configuration according to formula (10-a)



wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

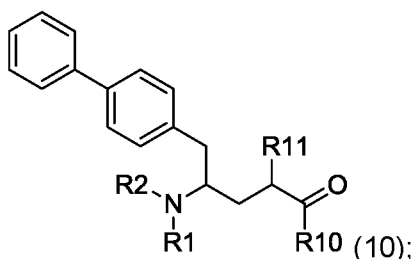
R10 is selected from

- X, wherein X is halo, preferably chloro;
- a group –NR^{5''}R^{6''}, wherein R^{5''} and R^{6''} are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R^{5''} and R^{6''} form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R^{5''} and R^{6''} together with the nitrogen to which they are attached form a chiral moiety;
- a group –O-R_x, wherein R_x together with the oxygen to which it is attached forms a chiral moiety; and

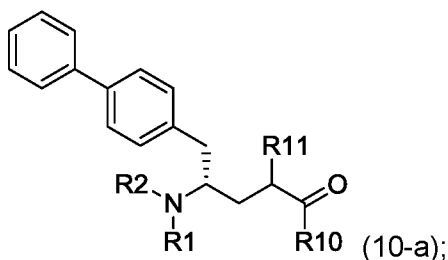
- a group $-S-R_5$, wherein R_5 is C_1 - C_7 -alkyl, C_6 - C_{10} -aryl, or C_6 - C_{10} -aryl- C_1 - C_7 -alkyl;

R_{11} is either hydrogen or a group R_8 which is C_1 - C_7 -alkyl or C_6 - C_{10} -aryl- C_1 - C_7 -alkyl, preferably methyl.

- 5 In one embodiment thereof, the invention relates to a compound of formula (10), or a salt thereof,



preferably having a configuration according to formula (10-a)



- 10 wherein

R_1 and R_2 are, independently of each other, hydrogen or a nitrogen protecting group, or R_1 and R_2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C_1 - C_7 -alkyl, C_1 - C_7 -alkoxy, halo, carboxyl and oxo, and

R_{10} is selected from

- X, wherein X is halo, preferably chloro;

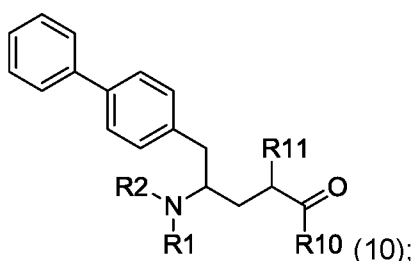
- 20 • a group $-NR_5''R_6''$, wherein R_5'' and R_6'' are, independently of each other, C_1 - C_7 -alkyl, C_6 - C_{10} -aryl, C_6 - C_{10} -aryl- C_1 - C_7 -alkyl, C_3 - C_7 -cycloalkyl or R_5'' and R_6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted
- 25

with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety;

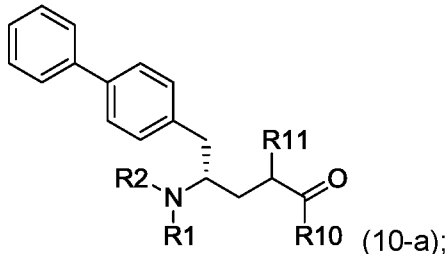
- a group –O-Rx, wherein Rx together with the oxygen to which it is attached forms a chiral moiety; and
- a group –S-R5, wherein R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl;

and R11 is hydrogen.

In another embodiment, the present invention relates to a compound of formula (10), or a salt thereof,



preferably having a configuration according to formula (10-a)



wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R10 is selected from

- a group –NR5''R6'', wherein R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably

4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5" and R6" together with the nitrogen to which they are attached form a chiral moiety;

- a group –O-Rx, wherein Rx together with the oxygen to which it is attached forms a chiral moiety; and
- a group –S-R5, wherein R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl;

and R11 is a group R8 which is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl.

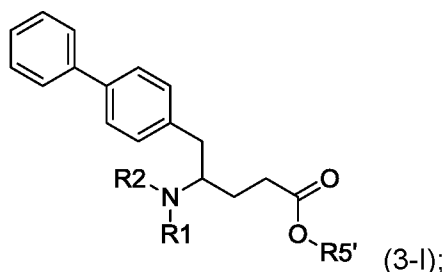
The compounds and moieties are defined preferably as indicated in the following.

Detailed description of the invention:

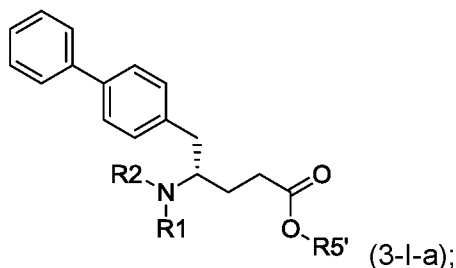
In the following, specific embodiments of the invention are presented.

Preparation of a compound of formula (3-I):

A compound of formula (3-I), or a salt thereof,



preferably having a configuration according to formula (3-I-a)

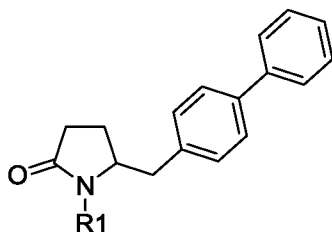


wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as

nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

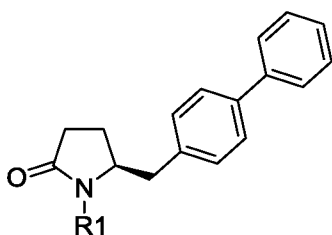
and R₅' is hydrogen, or further C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl (then being
5 a compound of the formula 3-I* wherein instead of R₅' R₅* is present),

is prepared by reacting a compound of formula (2), or a tautomer, or a salt thereof,



(2);

preferably having a configuration according to formula (2-a)



(2-a);

10 wherein R₁ is hydrogen or a nitrogen protecting group,
with a ring opening agent.

Examples for ring opening agents are selected from

- metal hydroxides, for example alkali metal or alkaline earth metal hydroxides (e.g. lithium hydroxide, sodium hydroxide);
- 15 - hydrogen peroxides, for example alkali metal hydrogen peroxides (e.g. lithium hydrogenperoxide);
- metal alcoholates of formula MOR₅, wherein M is an alkali metal or alkaline earth metal and R₅ is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl (e.g. lithium ethoxide, sodium methoxide, sodium ethoxide);
- 20 - mineral acids such as sulfuric acid, hydrobromic acid, perchloric acid and hydrochloric acid in the presence of a nucleophile or a nucleophilic solvent (e.g. water);
- sulfonic acids such as *p*-toluenesulfonic acid in the presence of a nucleophile or a nucleophilic solvent (e.g. water); and

- polymer-bound acids such as Amberlyst® in the presence of a nucleophile or a nucleophilic solvent (e.g. water).

In one embodiment the ring opening agent is selected from sodium ethoxide or lithium hydroxide. Preferably metal hydroxides or metal alcoholates are used in the presence of water, alcohols, such as methanol or ethanol, or THF.

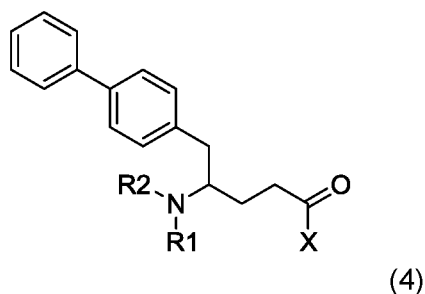
In another embodiment the ring opening agent is hydrochloric acid. Preferably acids are used in the presence of water or an alcohol (such as methanol or ethanol).

The ring opening agent can be used catalytically or stoichiometrically. Preferably, the lactam ring opening agent is used in an amount from 1 to 10 equivalents. Preferably, less than 1 equivalent, more preferably 0.1 equivalents or less than 0.1 equivalents.

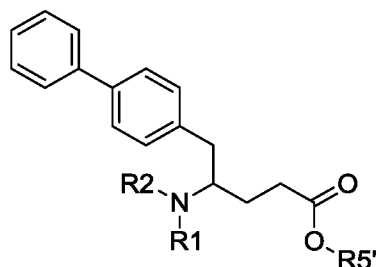
Alternatively, a compound of formula (3-I), preferably having a configuration according to formula (3-I-a), is prepared as described in WO2008/083967.

SECTION A. Preparation of acyl halide intermediates:

- 15 In one embodiment, the present invention relates to a method for preparing a compound of formula (4), or a salt thereof,



- wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and
- 25 X is halo, such as chloro,
- comprising reacting a compound of formula (3-I), or a salt thereof,



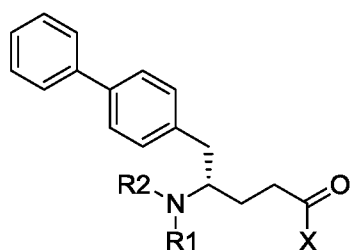
(3-I)

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5' is hydrogen

10 with an acyl halide generating reagent to provide the compound of formula (4).

In a preferred embodiment, the present invention relates to a method for preparing a compound of formula (4-a), or a salt thereof,



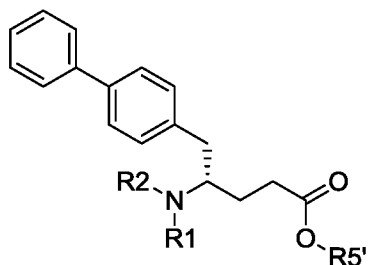
(4-a)

wherein

15 R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

X is halo, such as chloro,

comprising reacting a compound of formula (3-I-a), or a salt thereof,



(3-I-a)

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

and R5' is hydrogen

with an acyl halide generating reagent to provide the compound of formula (4-a).

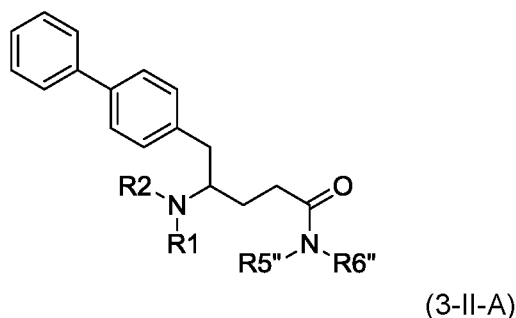
Suitable acyl halide generating reagents are for example vinyl halides, C₁-C₇-alkyl halides and halogenated phosphines. Suitable acyl halide generating reagents are for example selected from thionyl chloride, thionyl bromide, PCl₃, PCl₅, oxalyl chloride, Me₂C=C(Cl)NMe₂, CCl₄Ph₃P, PhCOCl, PBr₃, PBr₅, Ph₃PBr₂, oxalyl bromide or Me₂C=C(Br)NMe₂.

Acyl halide generating reaction conditions are well known in the art and are for example described by Allen, C., Barker W. in *Organic Syntheses*, Coll. Vol. 2, 1943, p. 156 (product of equation 1); by Adams, R., Jenkins, R. in *Organic Syntheses*, Coll. Vol. 1, 1941, p. 394 (product of equation 1); by Newcomb, M., Burchill, M., Deeb, T. in *J. Am. Chem. Soc.* **1988**, *110*, 6528–6535 (intermediate of equation 1 on p. 6529); by Devos, A., Remion, J., Frisque-Hesbain, A., Colens, A., Ghosez, L. in *Chem. Commun.* **1979**, 1180 (compound 2); by Lee, J. in *J. Am. Chem. Soc.* **1966**, *88*, 3440–3441 (product of equation 1 on p. 3340); by Brown, H. in *J. Am. Chem. Soc.* **1938**, *60*, 1325–1328 (table I and table II on p. 1326); by Adams, R., Ulich, L. in *J. Am. Chem. Soc.* **1920**, 599–611 (product of equation 3 on p. 601, product of equation 1 on p. 602); by Jesus Mari, A., Palomo, C. in *Synthesis* **1982**, 684–687 (compound 2 on p. 684, compounds 10 and 11 in table 1 on p. 685).

SECTION B. Preparation of starting materials for the alkylation step:

Section B.1. Preparation of amide intermediates of formula (3-II-A):

In another embodiment the present invention relates to a method for preparing a compound of formula (3-II-A), or a salt thereof,

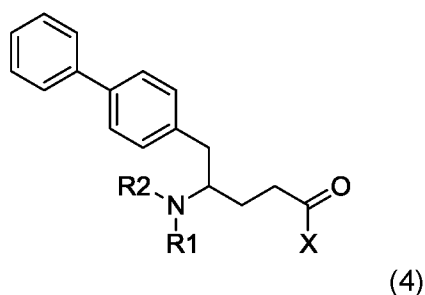


wherein

- 5 R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or
- 10 three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

- R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which
- 15 cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety,

- 20 comprising reacting a compound of formula (4), or a salt thereof,



wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

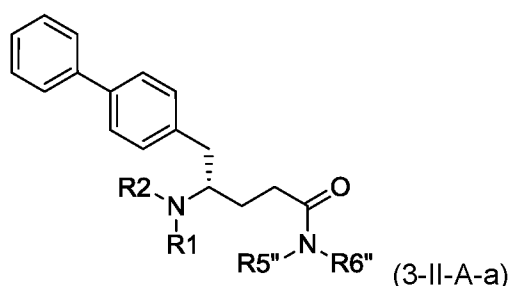
X is halo, such as chloro,

with an amine of formula HNR^{5''}R^{6''}, wherein R^{5''} and R^{6''} are as defined for the compound of formula (3-II-A),

optionally in the presence of an amine coupling reagent,

to provide the compound of formula (3-II-A).

In a preferred embodiment the present invention relates to a method for preparing a compound of formula (3-II-A-a), or a salt thereof,



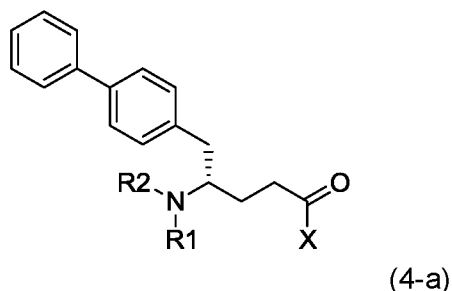
wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R^{5''} and R^{6''} are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R^{5''} and R^{6''} form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-

alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5" and R6" together with the nitrogen to which they are attached form a chiral moiety,

comprising reacting a compound of formula (4-a), or a salt thereof,



5 wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 10 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

X is halo, such as chloro,

with an amine of formula HNR5"R6", wherein R5" and R6" are as defined for the compound of
 15 formula (3-II-A),

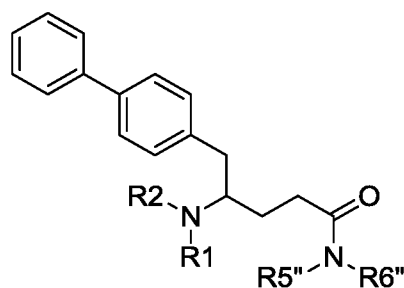
optionally in the presence of an amine coupling reagent,

to provide the compound of formula (3-II-A-a).

Coupling reagents are commonly used to prepare amides, esters and acid anhydrides from carboxylic acids. Typical examples of suitable amine coupling reagents can be found in Valeur,
 20 E., Bradley, M. *Chem. Soc. Rev.* **2009**, 38, 606-631. Preferred examples of suitable coupling reagents are selected from DCC (*N,N'*-dicyclohexylcarbodiimide), EDC (*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide), CDI (1,1'-carbonyldiimidazole), HATU (*N,N,N',N'*-tetramethyluronium hexafluorophosphate), HOBt (6-chloro-1-hydroxybenzotriazol) and mixtures thereof.

Section B.2. Preparation of amide intermediates of formula (3-II-A):

In another embodiment the present invention relates to a method for preparing a compound of formula (3-II-A), or a salt thereof,



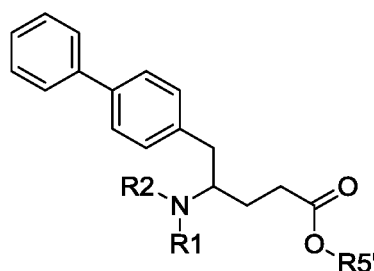
(3-II-A)

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety,

comprising reacting a compound of formula (3-I), or a salt thereof,



(3-I)

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as

nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R^{5'} is hydrogen

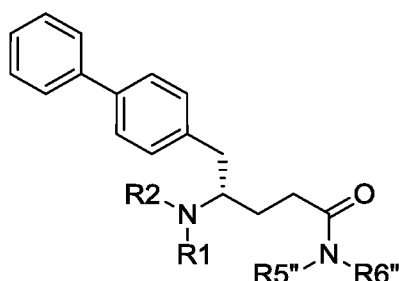
- 5 with an amine of formula HNR^{5''}R^{6''}, wherein R^{5''} and R^{6''} are as defined for the compound of formula (3-II-A),

in the presence of an amine coupling reagent,

to provide the compound of formula (3-II-A).

In a preferred embodiment the present invention relates to a method for preparing a

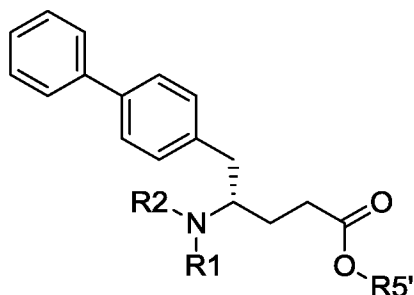
- 10 compound of formula (3-II-A-a), or a salt thereof,



(3-II-A-a)

wherein

- R¹ and R² are, independently of each other, hydrogen or a nitrogen protecting group, or R¹ and R² form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and
- 15 R^{5''} and R^{6''} are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R^{5''} and R^{6''} form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R^{5''} and R^{6''} together with the nitrogen to which they are attached form a chiral moiety,
- 20 comprising reacting a compound of formula (3-I-a), or a salt thereof,
- 25



(3-I-a)

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or
 5 unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5' is hydrogen

10 with an amine of formula HNR5''R6'', wherein R5'' and R6'' are as defined for the compound of formula (3-II-A),

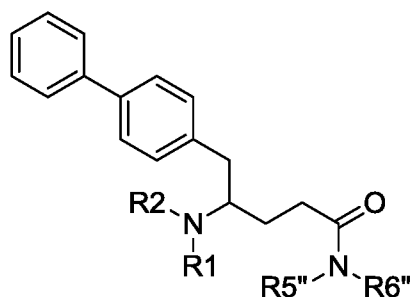
in the presence of an amine coupling reagent,

to provide the compound of formula (3-II-A-a).

Typical examples of suitable amine coupling reagents can be found in Valeur, E., Bradley, M.
 15 *Chem. Soc. Rev.* **2009**, 38, 606-631. Preferred examples of suitable coupling reagents are selected from DCC (*N,N'*-dicyclohexylcarbodiimide), EDC (*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide), CDI (1,1'-carbonyldiimidazole), HATU (*N,N,N',N'*-tetramethyluronium hexafluorophosphate), HOBt (6-chloro-1-hydroxybenzotriazol) and mixtures thereof.

20 **Section B.3. Preparation of amide intermediates of formula (3-II-A):**

In another embodiment the present invention relates to a method for preparing a compound of formula (3-II-A), or a salt thereof,



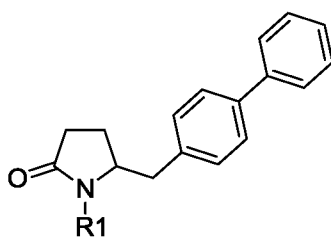
(3-II-A)

wherein

R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R_{5''} and R_{6''} are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R_{5''} and R_{6''} form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R_{5''} and R_{6''} together with the nitrogen to which they are attached form a chiral moiety,

comprising reacting a compound of formula (2), or a tautomer, or a salt thereof,

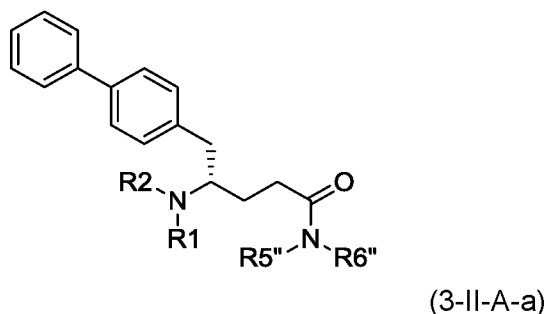


(2);

with an amine of formula HNR_{5''}R_{6''}, wherein R_{5''} and R_{6''} are as defined for the compound of formula (3-II-A), and wherein R₁ is hydrogen or a nitrogen protecting group,

in the presence of an ionic salt, to provide the compound of formula (3-II-A).

In a preferred embodiment the present invention relates to a method for preparing a compound of formula (3-II-A-a), or a salt thereof,

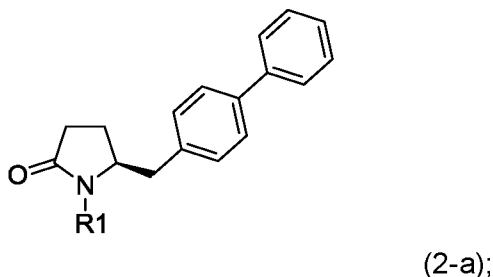


wherein

- 5 R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or
 10 three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

- R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which
 15 cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety,

- 20 comprising reacting a compound of formula (2-a) (which is also a compound of formula 2), or a tautomer, or a salt thereof,



with an amine of formula HNR5''R6'', wherein R5'' and R6'' are as defined for the compound of formula (3-II-A),

in the presence of an ionic salt to provide the compound of formula (3-II-A-a).

Preferred examples of ionic salts are alkali metal alkoxides, such as sodium methoxylate or sodium ethoxylate, or alkali metal hexafluorophosphate salts, such as lithium hexafluorophosphate.

- 5 Preferably the reaction is carried out in a polar, aprotic organic solvent, preferably THF at a temperature in the range from 0-40 °C, preferably 10-30 °C, not preferably 15-25 °C.

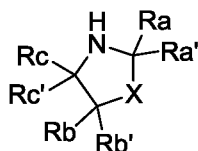
Preferably the reaction is carried out in an organic solvent at room temperature, for example, the reaction is performed in tetrahydrofuran at room temperature.

- 10 In one embodiment the ionic salts that are metal alkoxides are used in a catalytic amount, preferably 0.1 equivalents of sodium methoxylate is used.

In one embodiment the amine of formula HNR⁵R⁶ is, for example, pyrrolidine, morpholine or dimethylamine.

Where chiral moieties are mentioned, they are based on the chiral molecules described anywhere in the present description.

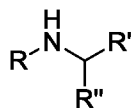
- 15 In a preferred embodiment of the invention the amine of formula HNR⁵R⁶ is a chiral amine, for example, of the formula:



- wherein Ra', Ra, Rb, Rb', Rc, Rc' and X are, for example, as described in Evans, D. A. *Aldrichimica Acta* **1982**, 15, 23-32, in particular as described in Scheme VI on page 25 therein, which is incorporated herein by reference; or in Kawanami, Y., Ito, Y., Kitagawa, T., Taniguchi, Y., Katsuki, T., Yamaguchi, M. *Tetrahedron Lett.* **1984**, 25, 857-860, in particular as described in Table 1 on page 858 therein, which is incorporated herein by reference; or in Askin, D., Wallace, M., Vacca, J., Reamer, R., Volante, R., Shinkai, I. *J. Org. Chem.* **1992**, 57, 2771-2773, in particular as described in Example 1 on page 2771 herein, which is incorporated herein by reference.
- 20
- 25

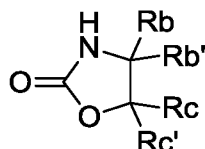
Specifically, (S)-prolinol or (R)-prolinol can be used as the chiral amine.

In another preferred embodiment the chiral amine is of the formula



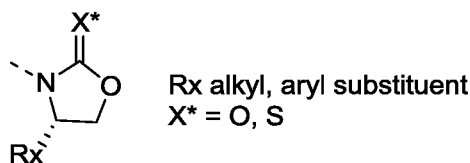
wherein R, R', and R'' are, for example, as described in Blaser, H.-U. *Chem. Rev.* **1992**, 92, 935-952, in particular as described in Table on 4 page 937 therein, which is incorporated herein by reference; in Myers, A. G., Yang, B. H., Chen, H., McKinstry, L., Kopecky, D. J., Gleason, J. L. *J. Am. Chem. Soc.* **1997**, 119, 6496-6511, in particular as described in Table 2 on page 6498 therein, which is incorporated herein by reference; in Jullian, V., Quirion, J., Husson, H. *Synthesis* **1997**, 1091-1097, in particular as described in Examples 1a-b on page 109 therein, which are incorporated herein by reference. For example, R is Me, R' is Me and R'' is Ph or C(OH)Ph; or R is methyl, R' is phenyl and R'' is CH₂OH.

10 In one embodiment the chiral amine is of the formula

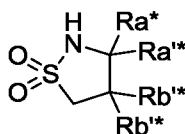


wherein Rb, Rb', Rc and Rc' are, for example, as described in Evans, D. A. *Aldrichimica Acta* **1982**, 15, 23-32, in particular as described in Schemes X and XI on page 27 therein, which are incorporated herein by reference; in Davies, S., Sangane, H. *Tetrahedron Asymmetry* **1995**, 6, 671-674, in particular as described in Examples 3a-d on page 672 therein, which are incorporated herein by reference. For example, Rb is CH₂Ph, *i*Pr, or Me and Rb' = Rc' = hydrogen and Rc is hydrogen or Ph; or Rb is methyl, phenyl or CH₂Ph, *i*Pr, Rb' is hydrogen, Rc = Rc' = methyl; or Rb is CH₂Ph, *i*Pr, or Me and Rb' = Rc' = Rc = hydrogen. Preferably, Rb is CH₂Ph, *i*Pr, or Me and Rb' = Rc' = Rc = hydrogen. Particularly suitable are (*R*)-4-benzyl-oxazolidin-2-one or (*R*)-4-isopropyl-oxazolidin-2-one.

Particularly preferred is a chiral amine inserting a moiety NR⁵R⁶ of the formula



In one embodiment the chiral amine is of the formula



wherein Ra^* , Ra'^* , Rb^* , Rb'^* are, for example, as described in Oppolzer, W., Poli, G., Kingma, A., Starkemann, C., Bernardinelli, G. *Helv. Chim. Acta* **1987**, 70, 2201-2214, in particular camphorsultam as described in Example 8 on page 2204 therein, which is incorporated herein by reference. Additional examples as described in Lee, A.W.M., Chan, W.H., Zhang, S-J.,
 5 Zhang, H-K., *Cur. Org. Chem* **2007**, 11, 213-228 and references cited therein.

Alternatively, particularly preferred is a chiral amine inserting a moiety NR^5R^6 of the formula



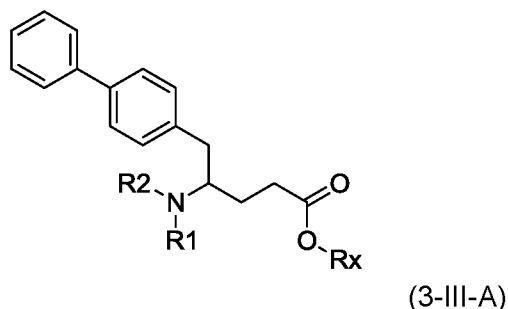
R^* monodentate ligand such as in (*R*)- or (*S*)-2-phenethylamine or other chiral amine or a bidentate ligand such as amino alcohol, amino acid, amino ester, such as prolinol or oxidized form, or protected form thereof such as sultam, camphor in chiral form; R' = hydrogen or alkyl

In one embodiment the chiral amine is (*S*)-methyl-(1-phenylethyl)amine, (*R*)-methyl-(1-phenylethyl)amine or (1*R*,2*R*)-pseudoephedrine.

10 In a preferred embodiment the chiral amine is (1*R*,2*R*)-pseudoephedrine.

Section B.4. Preparation of ester intermediates of formula (3-III-A):

In another embodiment the present invention relates to a method for preparing a compound of formula (3-III-A), or a salt thereof,

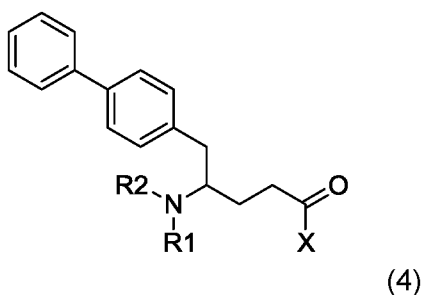


5 wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 10 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

Rx is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or (preferably) Rx together with the oxygen to which it is attached forms a chiral moiety,

15 comprising reacting a compound of formula (4), or a salt thereof,



wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 20 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or

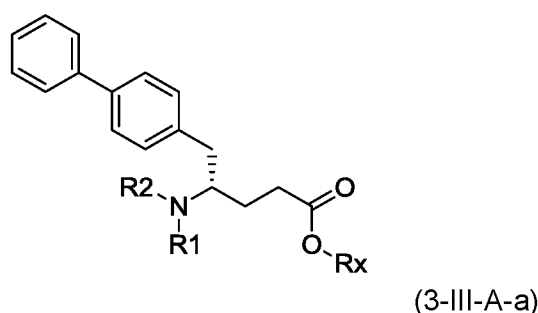
three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

X is halo, such as chloro,

with an alcohol of formula HOR_x, wherein R_x is as defined for the compound of formula (3-III-A),

optionally in the presence of a coupling reagent, to provide the compound of formula (3-III-A).

In a preferred embodiment the present invention relates to a method for preparing a compound of formula (3-III-A-a), or a salt thereof,

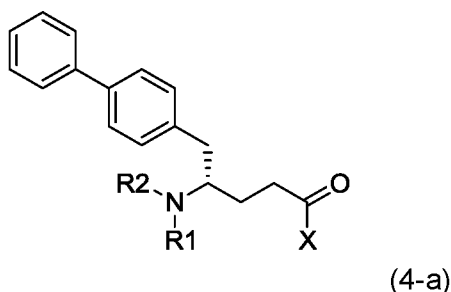


wherein

R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R_x is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or (preferably) R_x together with the oxygen to which it is attached forms a chiral moiety,

comprising reacting a compound of formula (4-a), or a salt thereof,



wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

X is halo, such as chloro,

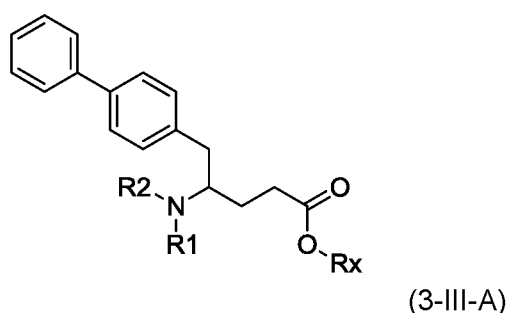
with an alcohol of formula HOR_x, wherein R_x is as defined for the compound of formula (3-III-A-a),

optionally in the presence of a coupling reagent, to provide the compound of formula (3-III-A-a).

Coupling reagents (see also the definition above) are commonly used to prepare amides, esters and acid anhydrides from carboxylic acids. Typical examples of suitable coupling reagents can be found in Valeur, E., Bradley, M. *Chem. Soc. Rev.* **2009**, 38, 606-631. Preferred examples of suitable coupling reagents are selected from DCC (*N,N'*-dicyclohexylcarbodiimide), EDC (*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide), CDI (1,1'-carbonyldiimidazole), HATU (*N,N,N',N'*-tetramethyluronium hexafluorophosphate), HOBt (6-chloro-1-hydroxybenzotriazol) and mixtures thereof.

Section B.5. Preparation of ester intermediates of formula (3-III-A):

In another embodiment the present invention relates to a method for preparing a compound of formula (3-III-A), or a salt thereof,



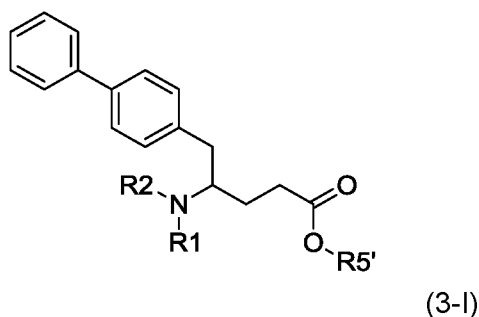
wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as

nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R_x is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or (preferably) R_x together with the oxygen to which it is attached forms a chiral moiety,

comprising reacting a compound of formula (3-I), or a salt thereof,



wherein

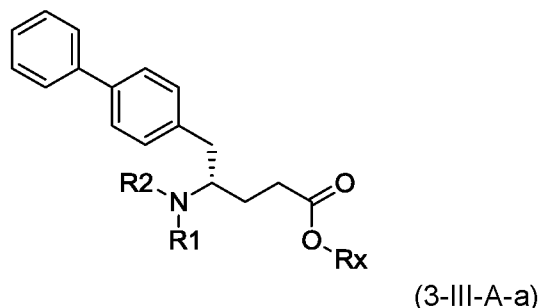
R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R₅' is hydrogen

with an alcohol of formula HOR_x or with a halogenide of formula R_x-X wherein R_x is as defined for the compound of formula (3-III-A) and wherein X is as defined above in formula (4), such as bromo or chloro,

optionally in the presence of a coupling reagent, to provide the compound of formula (3-III-A).

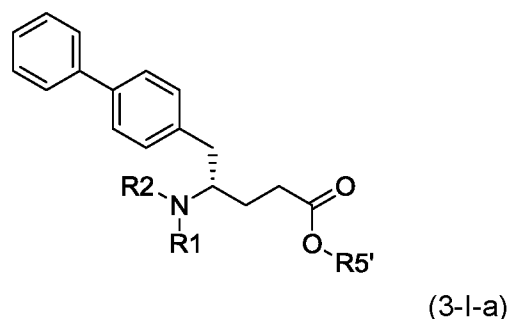
In a preferred embodiment the present invention relates to a method for preparing a compound of formula (3-III-A-a), or a salt thereof,



wherein

- R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and
- 10 Rx is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or Rx together with the oxygen to which it is attached forms a chiral moiety,

comprising reacting a compound of formula (3-I-a), or a salt thereof,



wherein

- 15 R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,
- 20 and R5' is hydrogen

with an alcohol of formula HOR_x or with a halogenide of formula Rx-X wherein Rx is as defined for the compound of formula (3-III-A) and wherein X is as defined above in formula (4), such as bromo or chloro,

optionally in the presence of a coupling reagent,

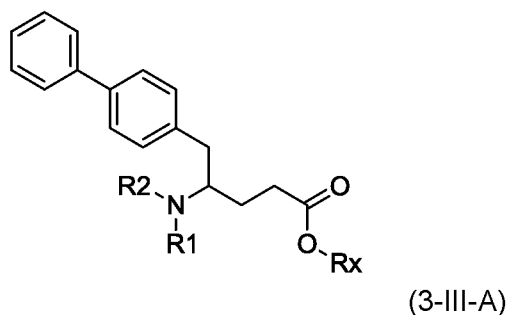
- 5 to provide the compound of formula (3-III-A).

Coupling reagents are commonly used to prepare amides, esters and acid anhydrides from carboxylic acids. Typical examples of suitable coupling reagents can be found in Valeur, E., Bradley, M. *Chem. Soc. Rev.* **2009**, 38, 606-631. Preferred examples of suitable coupling reagents are selected from DCC (*N,N'*-dicyclohexylcarbodiimide), EDC (*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide), CDI (1,1'-carbonyldiimidazole), HATU (*N,N,N',N'*-tetramethyluronium hexafluorophosphate), HOBt (6-chloro-1-hydroxybenzotriazol) and mixtures thereof.

The formation of esters is a reaction well known in the art.

15 **Section B.6. Preparation of ester intermediates of formula (3-III-A):**

In another embodiment the present invention relates to a method for preparing a compound of formula (3-III-A), or a salt thereof,

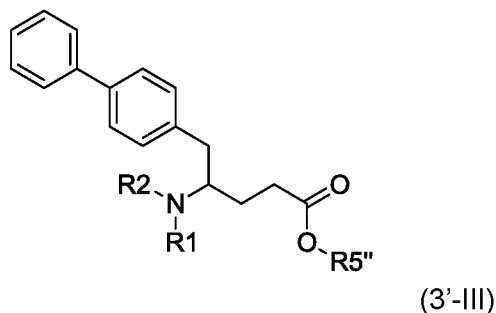


wherein

- 20 R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or
- 25 three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R_x is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or R_x together with the oxygen to which it is attached forms a chiral moiety,

comprising reacting a compound of formula (3'-III), or a salt thereof,



wherein

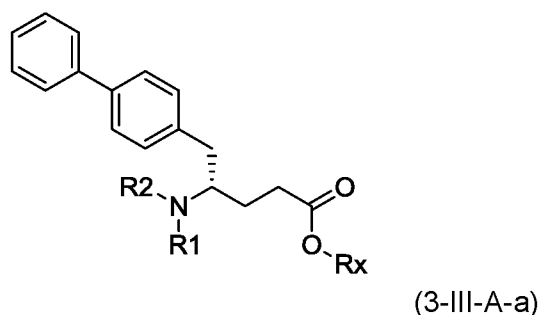
R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5'' is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, under the proviso that R5'' is other than Rx

with an alcohol of formula HORx, wherein Rx is as defined for the compound of formula (3-III-A), optionally in the presence of an acid or a base,

to provide the compound of formula (3-III-A).

In a preferred embodiment the present invention relates to a method for preparing a compound of formula (3-III-A-a), or a salt thereof,



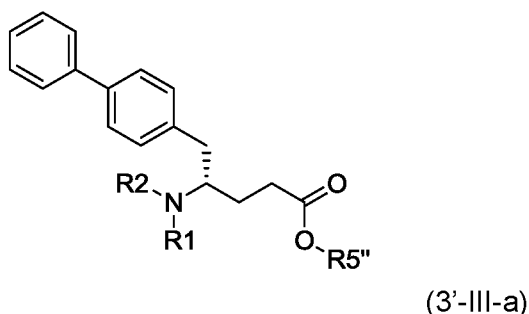
wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or

unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

- 5 Rx is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or Rx together with the oxygen to which it is attached forms a chiral moiety,

comprising reacting a compound of formula (3'-III-a), or a salt thereof,



wherein

- 10 R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or
- 15 three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R5'' is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, under the proviso that R5'' is other than Rx

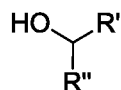
- with an alcohol of formula HOR_x, wherein Rx is as defined for the compound of formula (3-III-A), optionally in the presence of an acid or a base
- 20 to provide the compound of formula (3-III-A-a).

- Transesterifications are well known in the art. Preferably, transesterifications are performed by heating esters in alcohols in the presence of catalytic amounts of acid or alkali. Typical conditions for transesterifications are e.g. described by Riemenschneider, W.; Bolt, H. M. in
- 25 *Ullmann's Encyclopedia of Industrial Chemistry* **2012**, 245-266.

In one embodiment the alcohol is of formula HOR_x, wherein Rx is methyl, ethyl, *p*-methylphenyl or benzyl.

In one embodiment Rx of the halogenide Rx-X is methyl, ethyl, *p*-methylphenyl or benzyl. Preferably Rx-X is benzylbromide.

In a preferred embodiment of the invention the alcohol of formula HOR_x is a chiral alcohol, for example, of the following formula:



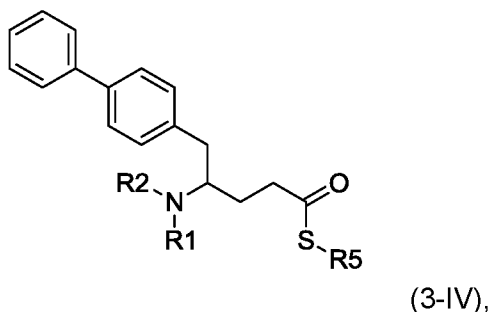
5

wherein R' and R'' are, for example, as described by Blaser, H.-U. in *Chem. Rev.* **1992**, 92, 935-952, in particular as described in Table 3 on page 937 therein, which is incorporated herein by reference; by Oertling, H., Reckziegel, A., Surburg, H., Bertram, H. in *Chem. Rev.* **2007**, 107, 2136-2164, in particular as described in Examples 1a-e on page 2138 therein, which are
10 incorporated herein by reference; by Hultin, P., Earle, M., Sudharshan, M. in *Tetrahedron* **1997**, 53, 14823-14870, in particular as described in Examples 111 and 117 on pages 14843-14844 therein, which are incorporated herein by reference; and by Kunz, H., Ruck, K. in *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 336-358, in particular as described in Example 17 on page 339 therein, which is incorporated herein by reference. For example, R' is Me and R'' is Ph (cf. (a) Leemhuis, M.; Van Steenis, J. H.; Van Uxem, M. J.; Van Nostrum, C. F.; Hennink, W. E. *Eur. J. Org. Chem.* 2003, 3344-3349; (b) Neradovic; Van Steenberg; Vansteelant; Meijer; Van Nostrum; Hennink *Macromolecules* 2003, 36, 7491-7498). Alternatively, in particular, the alcohol of formula HOR_x is L-menthol or D-menthol (cf. (a) Zheng, S.-L.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* 2002, 889-892; (b) Maegawa, Y.; Agura, K.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Synlett* 2012, 137-141; (c)
15 Iwasaki, T.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *J. Org. Chem.* 2008, 5147-5150; (d) Meth-Cohn, O. *J. Chem. Soc. Chem. Comm.* 1986, 695-697). Additionally, in particular the reaction is performed in an organic solvent, such as tetrahydrofuran, at room temperature. Chiral moieties formed from Rx with the binding oxygen are preferably those wherein Rx thus correspond to an enantiomeric menthyl or 2-phenylethyl moiety.

25

Section B.7. Preparation of thioester intermediates of formula (3-IV):

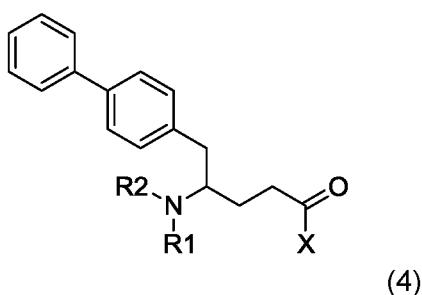
In another embodiment the present invention relates to a method for preparing a compound of formula (3-IV), or a salt thereof,



5 wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 10 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably a chiral moiety, comprising reacting a compound of formula (4), or a salt thereof,



15

wherein

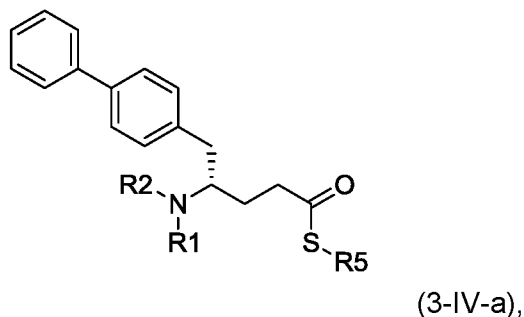
R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 20 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

X is halo, such as chloro,

with a thiol of formula HSR₅, wherein R₅ is as defined for the compound of formula (3-IV), optionally in the presence of a coupling reagent,

to provide the compound of formula (3-IV).

- 5 In a preferred embodiment the present invention relates to a method for preparing a compound of formula (3-IV-a), or a salt thereof,

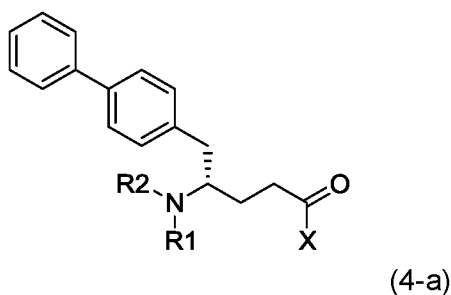


wherein

- R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R₅ is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl,

comprising reacting a compound of formula (4-a), or a salt thereof,



wherein

- R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or

unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

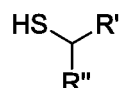
5 X is halo, such as chloro, or is hydroxy

with a thiol of formula HSR₅, wherein R₅ is as defined for the compound of formula (3-IV-a), optionally in the presence of a coupling reagent,

to provide the compound of formula (3-IV-a).

In one embodiment the thiol is of formula HSR₅, wherein R₅ is 4-methylbenzyl.

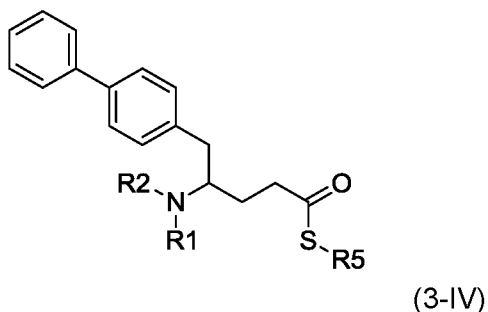
10 Preferably, the thiol of formula HSR₅ is a chiral thiol, for example, of the formula:



wherein R' and R'' are, for example, as described by Blaser, H.-U. in *Chem. Rev.* **1992**, 92, 935-952, in particular as described in Table 3 on page 937 therein, which is incorporated herein by reference; by Oertling, H., Reckziegel, A., Surburg, H., Bertram, H. in *Chem. Rev.* **2007**, 107, 2136-2164, in particular as described in Examples 1a-e on page 2138 therein, which are incorporated herein by reference; by Hultin, P., Earle, M., Sudharshan, M. in *Tetrahedron* **1997**, 53, 14823-14870, in particular as described in Examples 111 and 117 on pages 14843-14844 therein, which are incorporated herein by reference; and by Kunz, H., Ruck, K. in *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 336-358, in particular as described in Example 17 on page 339 therein, which is incorporated herein by reference. For example, R' is Me and R'' is Ph (cf. (a) Alajarin, M.; Ortin, M.-M.; Sanchez-Andrada, P.; Vidal, A.; Bautista, D. *Org. Lett.* 2005, 7, 5281-5284; (b) EP1264547 A1, 2002; (c) Corey, E. J.; Cimprich, K. A. *Tet. Lett.* 1992, 33, 4099-4102). Alternatively, in particular, the alcohol of formula HSR_x is the thio analogue of L-menthol or D-menthol. Chiral moieties formed from R_x with the binding sulfur are preferably those wherein
25 R_x thus correspond to an enantiomeric menthyl or 2-phenylethyl moiety.

Section B.8. Preparation of thioester intermediates of formula (3-IV):

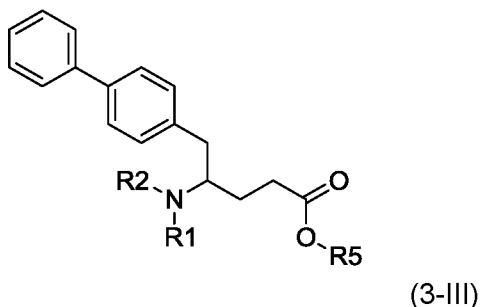
In another embodiment the present invention relates to a method for preparing a compound of formula (3-IV), or a salt thereof,



5 wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 10 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably a chiral moiety, comprising reacting a compound of formula (3-III), or a salt thereof,



15

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or
 20 unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or

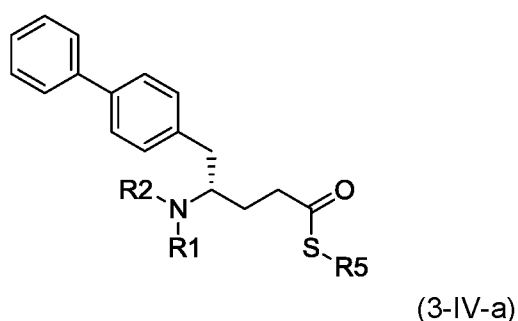
three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R₅ is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl,

with a compound of formula MSR₅, wherein R₅ is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl and M is a metal,

e.g. an alkali metal or aluminium, to provide the compound of formula (3-IV).

In a preferred embodiment the present invention relates to a method for preparing a compound of formula (3-IV-a), or a salt thereof,

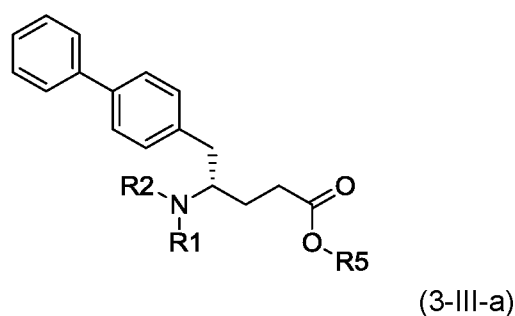


10 wherein

R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R₅ is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl,

comprising reacting a compound of formula (3-III-a), or a salt thereof,



20

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl,

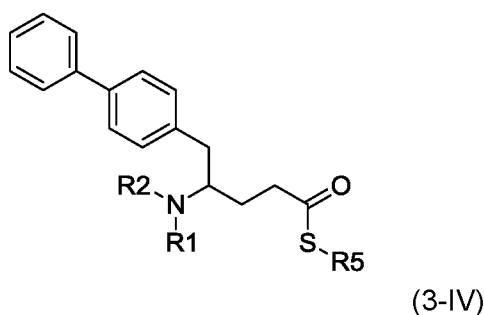
with a compound of formula MSR5, wherein R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, and M is an alkali metal, to provide the compound of formula (3-IV-a).

The formation of thioesters by transesterification is well-known in the art (cf. e.g. (a) US5948917 A1; (b) Gennari, C.; Carcano, M.; Donghi, M.; Mongelli, N.; Vanotti, E.; Vulpetti, A. *J. Org. Chem.* **1997**, *62*, 4746-4755; (c) Trost, B. M.; O'Boyle, B. M. *Org. Lett.* **2008**, *10*, 1369-1372.

The (e.g. chiral) moieties and the compounds of formula MSR5 are preferably as described for moieties in compounds of the formula HSR5.

Section B.9. Preparation of thioester intermediates of formula (3-IV):

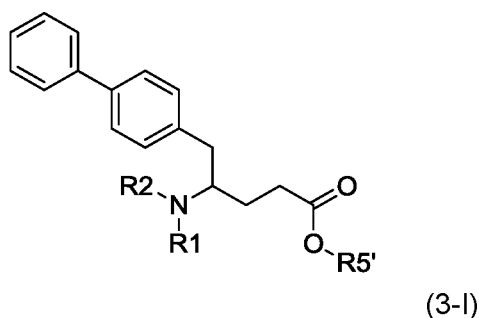
In another embodiment the present invention relates to a method for preparing a compound of formula (3-IV), or a salt thereof,



wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably a chiral moiety, comprising reacting a compound of formula (3-I), or a salt thereof,



wherein

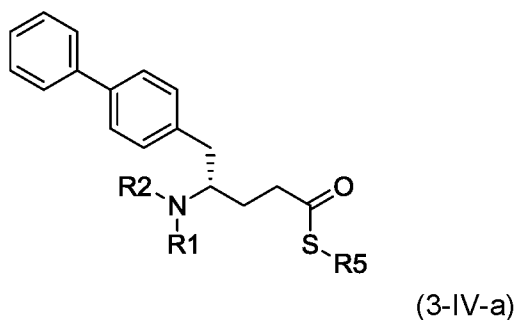
- 5 R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or
- 10 three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5' is hydrogen

with a thiol of formula HSR₅, wherein R₅ is as defined for the compound of formula (3-IV), optionally in the presence of a coupling reagent,

- 15 to provide the compound of formula (3-IV).

In a preferred embodiment the present invention relates to a method for preparing a compound of formula (3-IV-a), or a salt thereof,



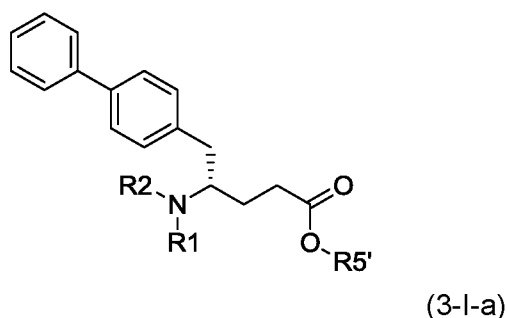
wherein

- 20 R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as

nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R₅ is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably a chiral moiety,

- 5 comprising reacting a compound of formula (3-I-a), or a salt thereof,



wherein

- R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

- 15 R₅' is hydrogen

with a thiol of formula HSR₅, wherein R₅ is as defined for the compound of formula (3-IV), optionally in the presence of a coupling reagent,

to provide the compound of formula (3-IV-a).

- Coupling reagents are commonly used to prepare amides, esters and acid anhydrides from carboxylic acids. Typical examples of suitable coupling reagents can be found in Valeur, E., Bradley, M. *Chem. Soc. Rev.* **2009**, 38, 606-631. Preferred examples of suitable coupling reagents are selected from DCC (*N,N'*-dicyclohexylcarbodiimide), EDC (*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide), CDI (1,1'-carbonyldiimidazole), HATU (*N,N,N',N'*-tetramethyluronium hexafluorophosphate), HOBt (6-chloro-1-hydroxybenzotriazol) and mixtures thereof.

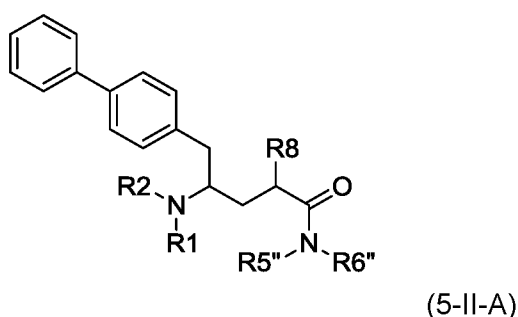
The formation of thioesters is a reaction well known in the art (cf. e.g. for thio menthol (a) Porto, S.; Seco, J. M.; Ortiz, A.; Quinoa, E.; Riguera, R. *Org. Lett.* **2007**, 9, 5015-5018; (b) Louzao, I.; Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Comm.* **2010**, 46, 7903-7905; for 1-

phenylthioethanol): Shoda, S.-i.; Mukaiyama, T. *Chem. Lett.* **1980**, 391-392). Preferably, R5 of thiol of formula HSR5 is 4-methylphenyl, whereby the reaction with compound according to formula (3-I-a) whereby R1 and R2 are benzyl is performed in an organic solvent, such as dichloromethane, at room temperature, in the presence of a suitable coupling reagent such as CDI.

SECTION C. The alkylation step:

Section C.1. Alkylation of amide intermediates:

In another embodiment the present invention relates to a method for preparing a compound of formula (5-II-A), or a salt thereof,



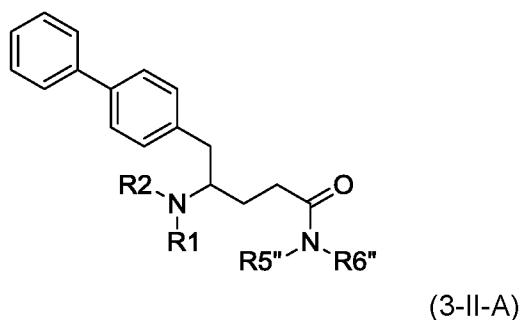
wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety, and

R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,

comprising reacting a compound of formula (3-II-A), or a salt thereof,



wherein

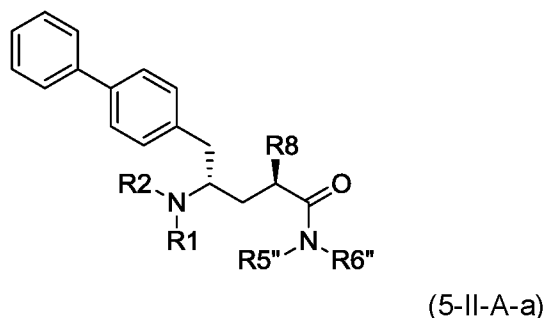
R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety,

with a base and an C₁-C₇-alkyl ating reagent selected from

- (R8)₃O⁺Z⁻, wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and Z⁻ is an anion (such as tetrafluoroborate);
 - R8X wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and X is a leaving group such as halo (such as chloride, bromide, iodide) or a sulfonate (e.g. triflate, tosylate or mesylate); and
 - (R8)₂SO₄, wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl,
- optionally in the presence of an additive,
- to provide the compound of formula (5-II-A).

In a preferred embodiment the present invention relates to a method for preparing a compound of formula (5-II-A-a), or a salt thereof,

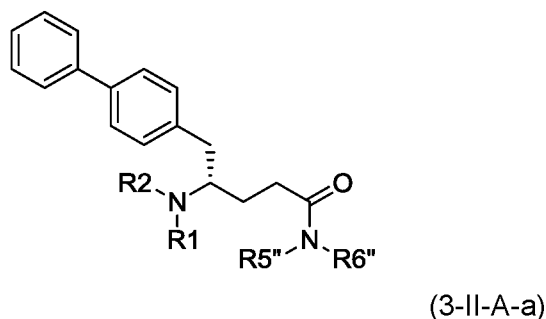


wherein

- 5 R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or
- 10 three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

- R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which
- 15 cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety, and

- 20 R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,
- comprising reacting a compound of formula (3-II-A-a), or a salt thereof,



wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or
5 unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5" and R6" are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5" and R6" form, together with the nitrogen to which they are attached, a 3
10 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5" and R6" together with the nitrogen to which they are attached
15 form a chiral moiety,

with a base and an alkylating reagent selected from

- (R8)₃O⁺Z⁻, wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and Z⁻ is an anion (such as tetrafluoroborate);
 - 20 - R8X wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and X is a leaving group such as halo (such as chloride, bromide, iodide) or a sulfonate (e.g. triflate, tosylate or mesylate); and
 - (R8)₂SO₄, wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl,
- optionally in the presence of an additive,

25 to provide the compound of formula (5-II-A-a).

Preferably, the alkylating reagent is methyl iodide, dimethylsulfonate, benzyl bromide or isopropyl iodide, most preferably methyl iodide or dimethylsulfonate.

Suitable additives are compounds that improve the solubility of the formed products or help to deaggregate the base, thereby making it more reactive, for example, as described in the
30 relevant chapters in Carey, F. A., Sundberg, R. J. *Organische Chemie*, VCH, Weinheim, 1995, such as hexamethylphosphoramide (HMPA), N,N'-dimethylpropyleneurea (DMPU), tetramethylethylenediamine (TMEDA), dimethylsulfoxide (DMSO), NMP (N-methylpyrrolidinone) or mixtures thereof. Crown ethers or chiral crown ethers, for example as described by Shirakawa, S., Yamamoto, K., Kitamura, M., Ooi, T., Maruoka, K. in *Angew. Chem.*

Int. Ed. **2005**, *44*, 625-628, in particular as described in Scheme 1 on page 626 therein, which is incorporated herein by reference; by Weber, B., Seebach, D. in *Tetrahedron* **1994**, *50*, 7473-7484, in particular as described in Table 1 on page 7476 therein, which is incorporated herein by reference, are also suitable for this purpose.

5 Suitable bases are, for example, selected from the formula

- R_mR_nNM, wherein R_m and R_n are independently selected from C₁-C₇-alkyl, cycloalkyl, heterocyclyl or silyl and M is an alkali metal such as Na, Li or K; for example lithium bis(trimethylsilyl)amide (LHMDS), sodium bis(trimethylsilyl)amide (NaHMDS), potassium bis(trimethylsilyl)amide (KHMDS), lithium diisopropylamide (LDA) or potassium diisopropylamide;
10
- R_mM, wherein R_m is selected from C₁-C₇-alkyl or aryl and M is an alkali metal such as Na, Li or K; for example methyl lithium, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium or phenyllithium;
- MH, wherein M is an alkali metal such as Na, Li or K; for example sodium hydride or
15 potassium hydride;
- or mixtures thereof.

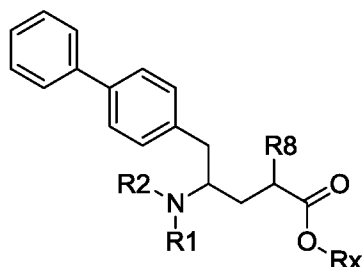
Preferably the base is NaHMDS, LDA or KHMDS.

The alkylation reaction may be performed in the presence of a solvent. Suitable solvents include ethers, such as diethyl ether, *tert*-butylmethylether, tetrahydrofuran or 2-methyltetrahydrofuran;
20 aromatic solvents, such as toluene or xylene or aliphatic hydrocarbons, such as pentane, hexane or heptane. Any mixture of two or more of said solvents is also within the scope of the present invention. Preferably the alkylation reaction is performed at less than room temperature, preferably at or less than -10 °C. More preferably the alkylation reaction is performed at a temperature between -10 °C and -78 °C. Most preferably, the alkylation reaction is performed
25 at a temperature between -60 °C and -78 °C.

Chiral moieties are as defined above for NR⁵"R⁶".

Section C.2. Alkylation of ester intermediates:

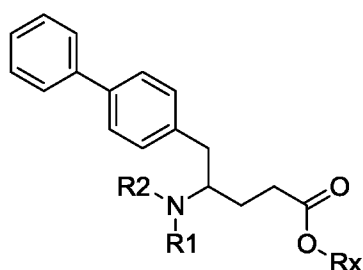
In another embodiment the present invention relates to a method for preparing a compound of
30 formula (5-III-A), or a salt thereof,



(5-III-A)

wherein

- R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,
- 10 Rx is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, or (preferably) Rx together with the oxygen to which it is attached forms a chiral moiety, and
- R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,
- comprising reacting a compound of formula (3-III-A), or a salt thereof,



(3-III-A)

- 15 wherein
- R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
- 20 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

Rx is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or (preferably) Rx together with the oxygen to which it is attached forms a chiral moiety,

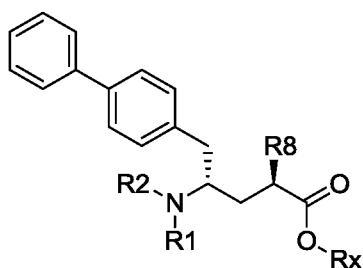
with a base and an alkylating reagent selected from

- (R₈)₃O⁺Z⁻, wherein R₈ is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and Z⁻ is an anion (such as tetrafluoroborate);
- R₈X wherein R₈ is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and X is a leaving group such as halo (such as chloride, bromide, iodide) or a sulfonate (e.g. triflate, tosylate or mesylate); and
- (R₈)₂SO₄, wherein R₈ is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl,

optionally in the presence of an additive,

to provide the compound of formula (5-III-A).

In another embodiment the present invention relates to a method for preparing a compound of formula (5-III-A-a), or a salt thereof,



(5-III-A-a)

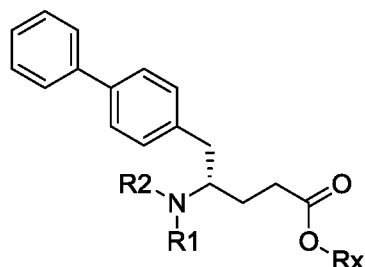
wherein

R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

Rx is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or (preferably) Rx together with the oxygen to which it is attached forms a chiral moiety, and

R₈ is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,

comprising reacting a compound of formula (3-III-A-a), or a salt thereof,



(3-III-A-a)

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

Rx is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or (preferably) Rx together with the oxygen to which it is attached forms a chiral moiety,

with a base and an alkylating reagent selected from

- (R8)₃O⁺Z⁻, wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and Z⁻ is an anion (such as tetrafluoroborate);
- R8X wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and X is a leaving group such as halo (such as chloride, bromide, iodide) or a sulfonate (e.g. triflate, tosylate or mesylate); and
- (R8)₂SO₄, wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, optionally in the presence of an additive,

to provide the compound of formula (5-III-A-a).

Suitable alkylating reagents are, for example, as defined in Section C.1 herein above.

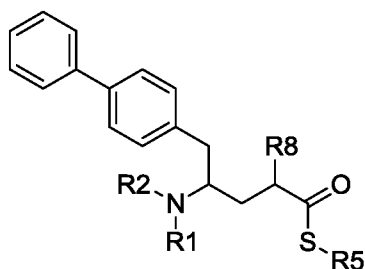
Suitable additives are, for example, as defined in Section C.1 herein above.

Suitable bases are, for example, as defined in Section C.1 herein above.

Suitable solvents are, for example, as defined in Section C.1 herein above.

Section C.3 and C4. Alkylation of thioester intermediates:

In another embodiment the present invention relates to a method for preparing a compound of formula (5-IV), or a salt thereof,



(5-IV),

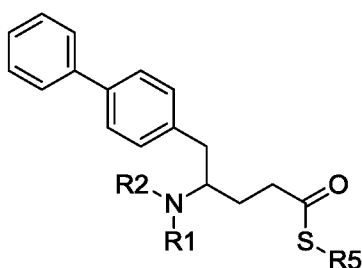
5 wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably a chiral moiety, and

R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,

15 comprising reacting a compound of formula of formula (3-IV), or a salt thereof,



(3-IV),

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or

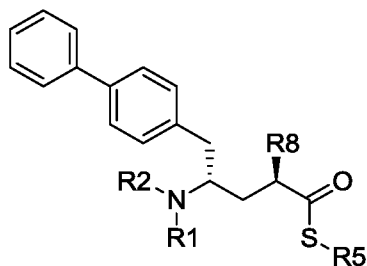
three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R₅ is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably a chiral moiety,

with a base and an alkylating reagent selected from

- 5 - (R₈)₃O⁺Z⁻, wherein R₈ is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and Z⁻ is an anion (such as tetrafluoroborate);
 - R₈X wherein R₈ is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and X is a leaving group such as halo (such as chloride, bromide, iodide) or a sulfonate (e.g. triflate, tosylate or mesylate); and
 - 10 - (R₈)₂SO₄, wherein R₈ is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, optionally in the presence of an additive,
- to provide the compound of formula (5-IV).

In a preferred embodiment the present invention relates to a method for preparing a compound of formula (5-IV-a), or a salt thereof,



(5-IV-a),

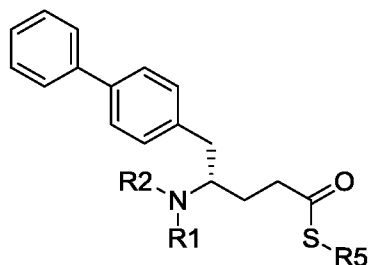
wherein

R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R₅ is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, and

R₈ is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,

comprising reacting a compound of formula of formula (3-IV-a), or a salt thereof,



(3-IV-a),

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably a chiral moiety,

with a base and an alkylating reagent selected from

- (R8)₃O⁺Z⁻, wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and Z⁻ is an anion (such as tetrafluoroborate);
- R8X wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl, and X is a leaving group such as halo (such as chloride, bromide, iodide) or a sulfonate (e.g. triflate, tosylate or mesylate); and
- (R8)₂SO₄, wherein R8 is C₁-C₇-alkyl (such as methyl or ethyl) or C₆-C₁₀-aryl-C₁-C₇-alkyl,

optionally in the presence of an additive,

to provide the compound of formula (5-IV-a).

Suitable alkylating reagents are, for example, as defined in Section C.1 herein above.

Suitable additives are, for example, as defined in Section C.1 herein above.

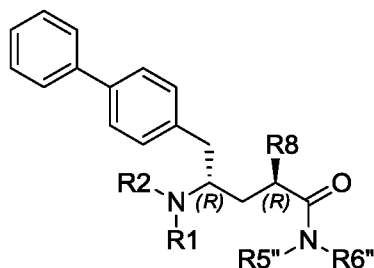
Suitable bases are, for example, as defined in Section C.1 herein above.

Suitable solvents are, for example, as defined in Section C.1 herein above.

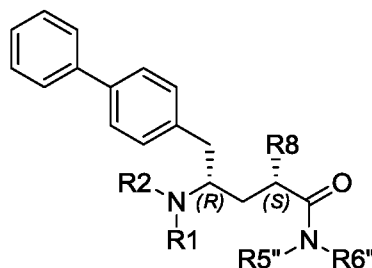
Chiral moieties are preferably as defined above for compounds of the formula HSR5.

In one aspect of the present invention, a compound according to formula 3-II-A-a is treated with a base, preferably NaHMDS, and an alkylating agent, preferably methyl iodide, in the presence of a solvent, preferably tetrahydrofuran, to afford a compound according to the formula 5-II-A-a

and its corresponding diastereomer of formula 5-II-A-b. Preferably, the ratio of 5-II-A-a to 5-II-A-b is 77:23, more preferably 84:16, even more preferably 90:10, yet more preferably 97:3. Most preferably, the ratio of 5-II-A-a to 5-II-A-b is 99:1.



(5-II-A-a)



(5-II-A-b)

- 5 In another aspect of the present invention, a compound according to formula 3-II-A-a is treated with a base, preferably KHMDS, and an alkylating agent, preferably methyl iodide, in the presence of a solvent, preferably tetrahydrofuran, to afford a compound according to the formula 5-II-A-a and its corresponding diastereomer of formula 5-II-A-b. Preferably, the ratio of 5-II-A-a to 5-II-A-b is 41:59, more preferably 23:77, most preferably, the ratio of 5-II-A-a to 5-II-A-b is
- 10 >1:99.

- In another aspect of the present invention, a compound according to formula 3-II-A-a is treated with a base, preferably LDA, and an alkylating agent, preferably ethyl iodide, in the presence of a solvent, preferably tetrahydrofuran, to afford a compound according to the formula 5-II-A-a and its corresponding diastereomer of formula 5-II-A-b. Preferably, the ratio of 5-II-A-a to 5-II-A-b
- 15 is 79:21 or higher.

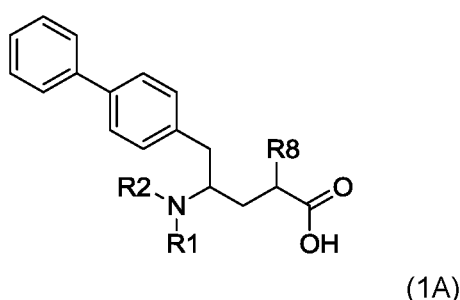
- In still another aspect of the present invention, a compound according to formula 3-II-A-a is treated with a base, preferably LDA, and an alkylating agent, preferably isopropyl iodide, in the presence of a solvent, preferably tetrahydrofuran, to afford a compound according to the formula 5-II-A-a and its corresponding diastereomer of formula 5-II-A-b. Preferably, the ratio of 5-II-A-a to 5-II-A-b is 72:28, or higher.
- 20

- In still another aspect of the present invention, a compound according to formula 3-II-A-a is treated with a base, preferably NaHMDS, and an alkylating agent, preferably benzyl bromide, in the presence of a solvent, preferably tetrahydrofuran, to afford a compound according to the formula 5-II-A-a and its corresponding diastereomer of formula 5-II-A-b. Preferably, the ratio of
- 25 5-II-A-a to 5-II-A-b is >99:1.

SECTION D. Conversion of intermediates of the present invention into a compound of formula (1) (known intermediate described in WO 2008/083967):

Section D.1. Alkylated amide intermediates:

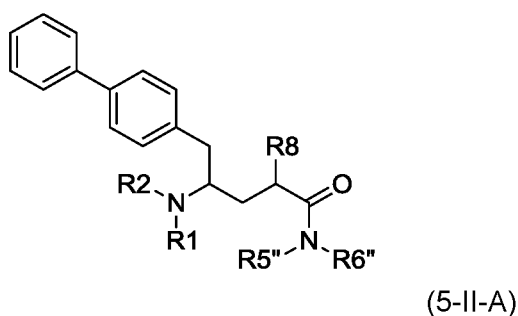
In another embodiment the present invention relates to a method for preparing a compound of
5 formula (1A), or a salt thereof,



wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered,
10 preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

15 R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,
comprising reacting a compound of formula (5-II-A), or a salt thereof,



wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered,
20 preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as

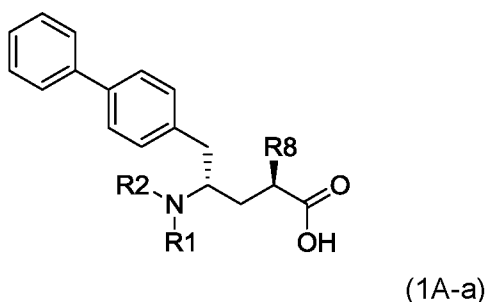
nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R₈ is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl, and

- 5 R₅'' and R₆'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R₅'' and R₆'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one,
 10 two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R₅'' and R₆'' together with the nitrogen to which they are attached form a chiral moiety,

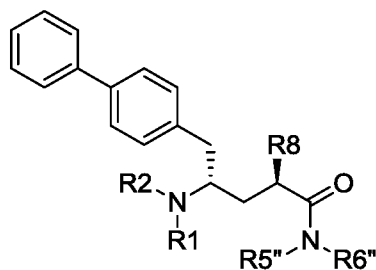
with an inorganic acid to provide the compound of formula (1A).

- 15 In a preferred embodiment the present invention relates to a method for preparing a compound of formula (1A-a), or a salt thereof,



wherein

- R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or
 20 unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and
- 25 R₈ is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl, comprising reacting a compound of formula (5-II-A-a), or a salt thereof,



(5-II-A-a)

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl, and

R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety,

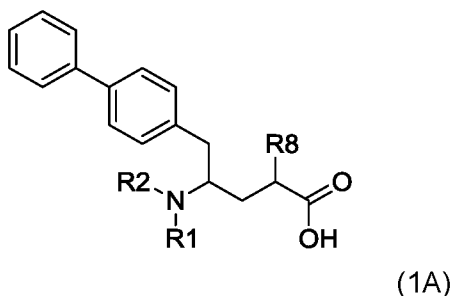
with an inorganic acid to provide the compound of formula (1A-a).

Suitable inorganic acids are, for example, mineral or Brønsted acids, such as hydrochloric acid, sulfuric acid or phosphoric acid. Typically, the use of HCl is, for example, as described by Kawanami, Y., Ito, Y., Kitagawa, T., Taniguchi, Y., Katsuki, T., Yamaguchi, M. in *Tetrahedron Lett.* **1984**, 25, 857-860 on page 860, line 3.

Chiral moieties NR5''R6'' are preferably as defined herein above.

Section D.2. Alkylated ester intermediates:

In another embodiment the present invention relates to a method for preparing a compound of formula (1A), or a salt thereof,

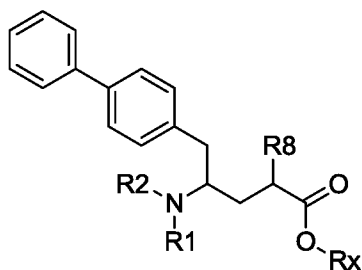


5 wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 10 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,

comprising reacting a compound of formula (5-III-A), or a salt thereof,



15

(5-III-A)

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or
 20 unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or

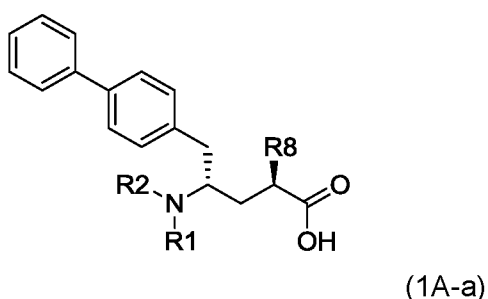
three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R₈ is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl, and

5 Rx is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or preferably Rx together with the oxygen to which it is attached forms a chiral moiety,

with an inorganic acid to provide the compound of formula (1A).

In a preferred embodiment the present invention relates to a method for preparing a compound of formula (1A-a), or a salt thereof,

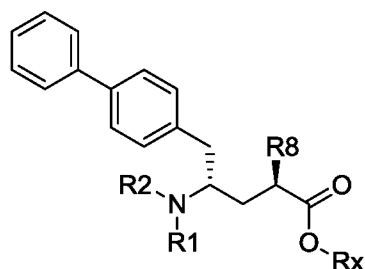


10 wherein

R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 15 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R₈ is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,

comprising reacting a compound of formula (5-III-A-a), or a salt thereof,



20

(5-III-A-a)

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl, and

Rx is C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, or preferably Rx together with the oxygen to which it is attached forms a chiral moiety,

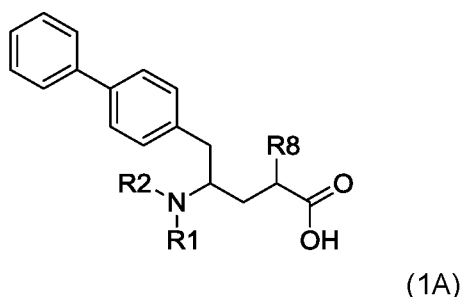
with an inorganic acid to provide the compound of formula (1A-a).

Suitable inorganic acids are, for example, mineral or Brønsted acids, such as hydrochloric acid, sulfuric acid or phosphoric acid. Typically, the use of HCl is, for example, as described by Ullrich, A., Chai, Y., Pistorius, D., Elnakady, Y., Herrmann, J., Weissman, K., Kazmaier, U., Muller, R. in *Angew. Chem. Int. Ed. Engl.* **2009**, 48, 4422-4425 in Scheme 3 on page 4424.

Chiral moieties formed from Rx together with the binding oxygen are preferably as defined herein above.

Section D.3 and D.4. Alkylated thioester intermediates:

In another embodiment the present invention relates to a method for preparing a compound of formula (1A), or a salt thereof,



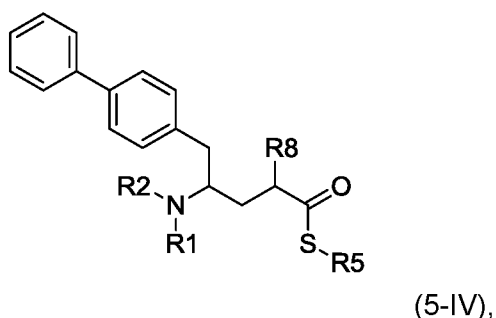
wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as

nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R₈ is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,

- 5 comprising reacting a compound of formula (5-IV), or a salt thereof,



wherein

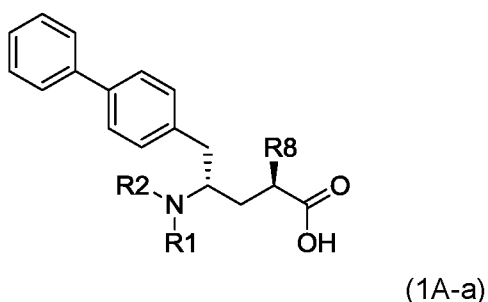
- 10 R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

- 15 R₅ is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably a chiral moiety, and

R₈ is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,

under oxidative conditions to provide the compound of formula (1A).

In a preferred embodiment the present invention relates to a method for preparing a compound of formula (1A-a), or a salt thereof,



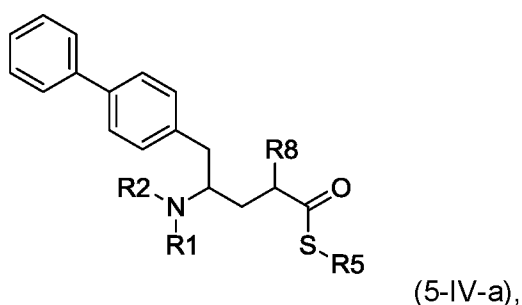
20

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,

comprising reacting a compound of formula (5-IV-a), or a salt thereof,



wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably a chiral moiety, and

R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl,

under oxidative conditions to provide the compound of formula (1A).

Suitable oxidative conditions refer, for example, to the use of an oxidizing reagent, such as H₂O₂, under basic conditions (e.g. in the presence of an alkali metal base such as NaOH, LiOH or KOH). Typically, oxidative conditions are, for example, as described by Gierasch, T; Shi, Z.; Verdine, G. in *Org. Lett.* **2003**, 5, 621-624 in Scheme 2 on page 622.

The chiral moieties are preferably as defined above for thiols or resulting from using thiols of the formula HSR5.

The formation of a compound of the formula I (esterification with R³-OH wherein R³ is as defined for a compound of the formula I other than hydrogen) (especially R³ = ethyl) can be achieved according to well known esterification conditions, e.g. as described in WO 2008/083967 e.g. in Examples 51, 43, 44 or 42.

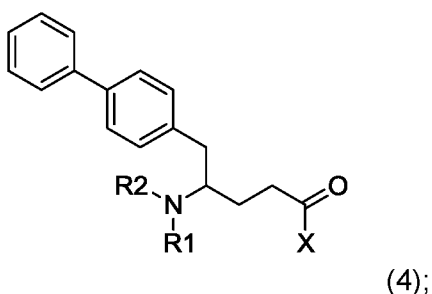
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Section E: Novel and Inventive Compounds Occurring in the Preceding Sections and especially in the Examples

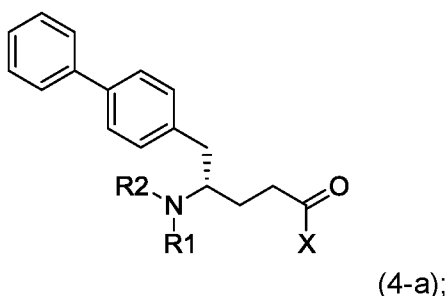
In the processes shown above several novel and inventive compounds are involved.

10 Consequently, further subjects of the present invention are the compounds shown below.

A compound of formula (4), or a salt thereof,



preferably having a configuration according to formula (4-a)

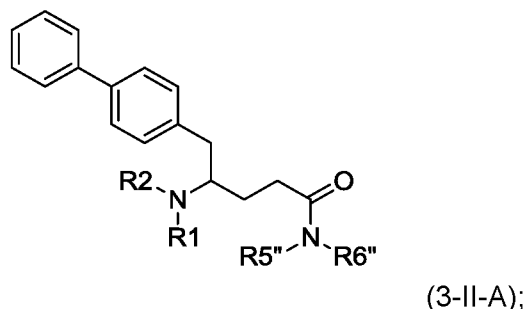


15 wherein

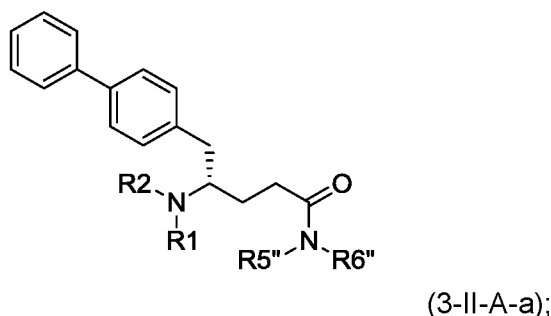
R¹ and R² are, independently of each other, hydrogen or a nitrogen protecting group, or R¹ and R² form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 20 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

X is halo, such as chloro.

A compound of formula (3-II-A), or a salt thereof,



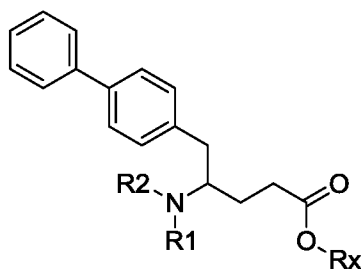
- 5 preferably having a configuration according to formula (3-II-A-a)



wherein

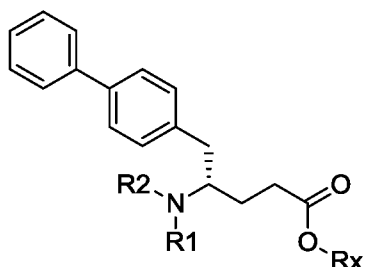
- R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and
- 15 R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety, especially as defined elsewhere herein.
- 20

A compound of formula (3-III-A), or a salt thereof,



(3-III-A)

preferably having a configuration according to formula (3-III-A-a)



(3-III-A-a);

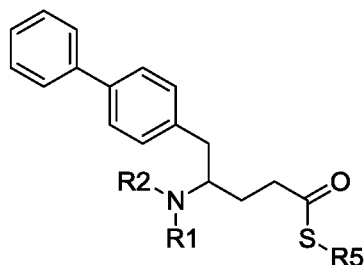
5

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or
 10 unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

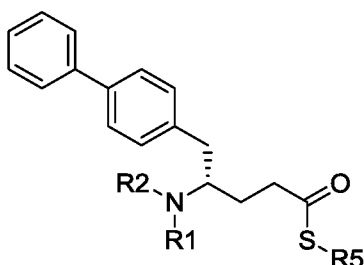
Rx together with the oxygen to which it is attached forms a chiral moiety, preferably as defined
 15 elsewhere herein.

A compound of formula (3-IV), or a salt thereof,



(3-IV);

preferably having a configuration according to formula (3-IV-a)



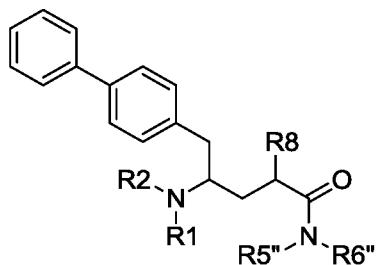
(3-IV-a);

wherein

- 5 R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or
- 10 three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

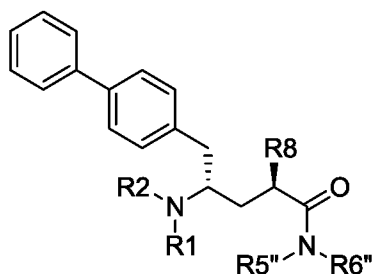
R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, especially a chiral moiety, preferably as defined elsewhere herein.

- 15 A compound of formula (5-II-A), or a salt thereof,



(5-II-A);

preferably having a configuration according to formula (5-II-A-a)

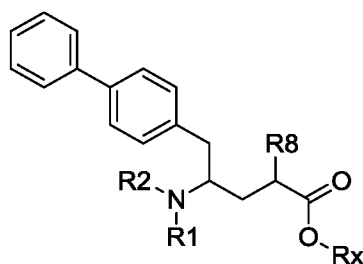


(5-II-A-a);

wherein

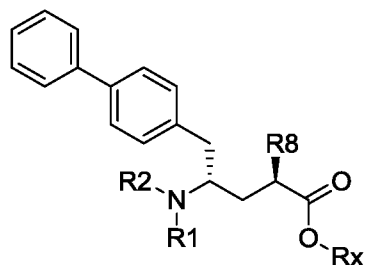
- R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,
- 10 R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one,
- 15 two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety, preferably as defined elsewhere herein, and
- R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl.

- 20 A compound of formula (5-III-A), or a salt thereof,



(5-III-A),

preferably having a configuration according to formula (5-III-A-a),

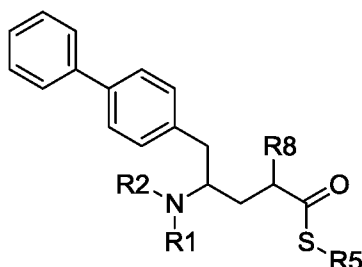


(5-III-A-a),

wherein

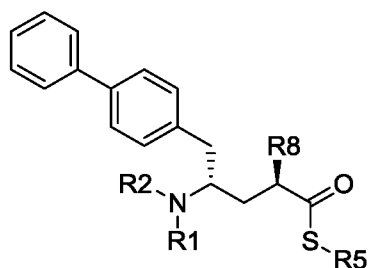
- R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and
- 10 Rx together with the oxygen to which it is attached forms a chiral moiety, preferably as defined elsewhere herein.

A compound of formula (5-IV), or a salt thereof,



(5-IV),

- 15 preferably having a configuration according to formula (5-IV-a),



(5-IV-a),

wherein

R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or
5 unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably a chiral moiety as defined
10 elsewhere herein, and

R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl.

((cf. scheme 1)) In a further aspect, the present invention relates to a method for converting a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a), as defined
15 herein or a salt thereof, comprising

- i) the method in Section B.2 to convert a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt thereof, into a compound of formula (3-II-A), preferably a compound of formula (3-II-A-a), as defined herein or a
20 salt thereof;
- ii) the method in Section C.1 to convert a compound of formula (3-II-A), preferably a compound of formula (3-II-A-a), as defined herein or a salt thereof, into a compound of formula (5-II-A), preferably a compound of formula (5-II-A-a) as defined herein or a salt thereof;
- 25 iii) the method in Section D.1 to convert a compound of formula (5-II-A), preferably a compound of formula (5-II-A-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a) as defined herein or a salt thereof;

((cf. scheme 3)) In another aspect, the present invention relates to a method for converting a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a), as defined
30 herein or a salt thereof, comprising

- i) the method in Section A to convert a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt thereof, into a compound of formula (4), preferably a compound of formula (4-a) as defined herein or a salt thereof;
- 5 ii) the method in Section B.1 to convert a compound of formula (4), preferably a compound of formula (4-a), as defined herein or a salt thereof, into a compound of formula (3-II-A), preferably a compound of formula (3-II-A-a) as defined herein or a salt thereof;
- 10 iii) the method in Section C.1 to convert a compound of formula (3-II-A), preferably a compound of formula (3-II-A-a), as defined herein or a salt thereof, into a compound of formula (5-II-A), preferably a compound of formula (5-II-A-a) as defined herein or a salt thereof;
- iv) the method in Section D.1 to convert a compound of formula (5-II-A), preferably a compound of formula (5-II-A-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a) as defined herein or a salt thereof;

15 ((cf. scheme 1)) In another aspect, the present invention relates to a method for converting a compound of formula (2), preferably a compound of formula (2-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a), as defined herein or a salt thereof, comprising

- 20 i) the method in Section B.3 to convert a compound of formula (2), preferably a compound of formula (2-a), as defined herein or a salt thereof, into a compound of formula (3-II-A), preferably a compound of formula (3-II-A-a) as defined herein or a salt thereof;
- 25 ii) the method in Section C.1 to convert a compound of formula (3-II-A), preferably a compound of formula (3-II-A-a), as defined herein or a salt thereof, into a compound of formula (5-II-A), preferably a compound of formula (5-II-A-a) as defined herein or a salt thereof;
- 30 iii) the method in Section D.1 to convert a compound of formula (5-II-A), preferably a compound of formula (5-II-A-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a) as defined herein or a salt thereof;

((cf. scheme 2)) In a further aspect, the present invention relates to a method for converting a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt

thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a), as defined herein or a salt thereof, comprising

- i) the method in Section B.5 to convert a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt thereof, into a compound of formula (3-III-A), preferably a compound of formula (3-III-A-a), as defined herein or a salt thereof;
- ii) the method in Section C.2 to convert a compound of formula (3-III-A), preferably a compound of formula (3-III-A-a), as defined herein or a salt thereof, into a compound of formula (5-III-A), preferably a compound of formula (5-III-A-a) as defined herein or a salt thereof;
- iii) the method in Section D.2 to convert a compound of formula (5-III-A), preferably a compound of formula (5-III-A-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a) as defined herein or a salt thereof;

((cf. scheme 1 variant including Section A) In another aspect, the present invention relates to a method for converting a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a), as defined herein or a salt thereof, comprising

- i) the method in Section A to convert a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt thereof, into a compound of formula (4), preferably a compound of formula (4-a) as defined herein or a salt thereof;
- ii) the method in Section B.1 to convert a compound of formula (4), preferably a compound of formula (4-a), as defined herein or a salt thereof, into a compound of formula (3-II-A), preferably a compound of formula (3-II-A-a), as defined herein or a salt thereof;
- iii) the method in Section C.1 to convert a compound of formula (3-II-A), preferably a compound of formula (3-II-A-a), as defined herein or a salt thereof, into a compound of formula (5-II-A), preferably a compound of formula (5-II-A-a) as defined herein or a salt thereof;
- iv) the method in Section D.1 to convert a compound of formula (5-II-A), preferably a compound of formula (5-II-A-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a) as defined herein or a salt thereof;

((cf. scheme 2)) In another aspect, the present invention relates to a method for converting a compound of formula (3'-III), preferably a compound of formula (3'-III-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a), as defined herein or a salt thereof, comprising

- 5 i) the method in Section B.6 to convert a compound of formula (3'-III), preferably a compound of formula (3'-III-a), as defined herein or a salt thereof, into a compound of formula (3-III-A), preferably a compound of formula (3-III-A-a), as defined herein or a salt thereof;
- 10 ii) the method in Section C.2 to convert a compound of formula (3-III-A), preferably a compound of formula (3-III-A-a), as defined herein or a salt thereof, into a compound of formula (5-III-A), preferably a compound of formula (5-III-A-a) as defined herein or a salt thereof;
- 15 iii) the method in Section D.2 to convert a compound of formula (5-III-A), preferably a compound of formula (5-III-A-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a) as defined herein or a salt thereof;

((cf. scheme 1 + scheme 4)) In another aspect, the present invention relates to a method for converting a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined
20 herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a), as defined herein or a salt thereof, comprising

- i) the method in Section A to convert a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt thereof, into a compound of formula (4), preferably a compound of formula (4-a) as defined herein or a salt thereof;
- 25 ii) the method in Section B.7 to convert a compound of formula (4), preferably a compound of formula (4-a), as defined herein or a salt thereof, into a compound of formula (3-IV), preferably a compound of formula (3-IV-a), as defined herein or a salt thereof;
- 30 iii) the method in Section C.3 to convert a compound of formula (3-IV), preferably a compound of formula (3-IV-a), as defined herein or a salt thereof, into a compound of formula (5-IV), preferably a compound of formula (5-IV-a) as defined herein or a salt thereof;
- 35 iv) the method in Section D.3 to convert a compound of formula (5-IV), preferably a compound of formula (5-IV-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a) as defined herein or a salt thereof;

((cf. scheme 5)) In another aspect, the present invention relates to a method for converting a compound of formula (3-III), preferably a compound of formula (3-III-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a), as defined herein or a salt thereof, comprising

i) the method in Section B.8 to convert a compound of formula (3-III), preferably a compound of formula (3-III-a), as defined herein or a salt thereof, into a compound of formula (3-IV), preferably a compound of formula (3-IV-a), as defined herein or a salt thereof;

ii) the method in Section C.4 to convert a compound of formula (3-IV), preferably a compound of formula (3-IV-a), as defined herein or a salt thereof, into a compound of formula (5-IV), preferably a compound of formula (5-IV-a) as defined herein or a salt thereof;

iii) the method in Section D.4 to convert a compound of formula (5-IV), preferably a compound of formula (5-IV-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a) as defined herein or a salt thereof;

((cf. scheme 5)) In another aspect, the present invention relates to a method for converting a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a), as defined herein or a salt thereof, comprising

i) the method in Section B.9 to convert a compound of formula (3-I), preferably a compound of formula (3-I-a), as defined herein or a salt thereof, into a compound of formula (3-IV), preferably a compound of formula (3-IV-a), as defined herein or a salt thereof;

ii) the method in Section C.4 to convert a compound of formula (3-IV), preferably a compound of formula (3-IV-a), as defined herein or a salt thereof, into a compound of formula (5-IV), preferably a compound of formula (5-IV-a) as defined herein or a salt thereof;

iii) the method in Section D.4 to convert a compound of formula (5-IV), preferably a compound of formula (5-IV-a), as defined herein or a salt thereof, into a compound of formula (1-A), preferably a compound of formula (1-A-a) as defined herein or a salt thereof;

The invention specially relates to any one of the processes described in each section. The invention likewise relates, independently, to every single step described in a process sequence within the corresponding section. Therefore, each and every single step of any process consisting of a sequence of steps described herein is itself an embodiment of the present invention. Thus, the invention also relates to those embodiments of the process, according to which a compound obtainable as an intermediate in any step of the process is used as a starting material.

Especially preferred are any reactions (process steps) in which a moiety R8 as defined for the respective compounds herein is introduced where in the rest of the molecule chiral moieties (e.g. NR5''R6'', ORx or OR5) are present as this allows for a stereochemically selective synthesis.

The products of the processes of the present invention can be used in the synthesis of NEP inhibitors or prodrugs thereof, in particular they can be used in the synthesis of NEP inhibitors comprising a γ -amino- δ -biphenyl- α -methylalkanoic acid, or acid ester, backbone.

In one embodiment the products of the processes of the present invention can be used in the synthesis of the NEP inhibitor prodrug *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methylbutanoic acid ethyl ester or its active metabolite, the NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methylbutanoic acid.

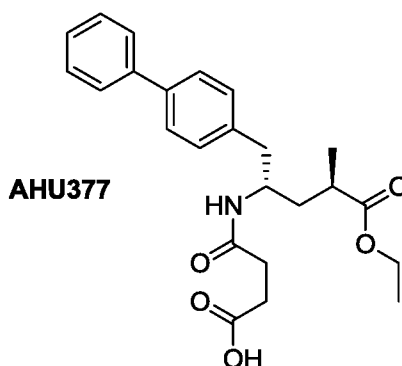
The term "NEP inhibitor" describes a compound which inhibits the activity of the enzyme neutral endopeptidase (NEP, EC 3.4.24.11). In the present invention the terms "NEP-inhibitor" (which also in all embodiments can include a prodrug) or "NEP-inhibitors prodrug" relates to the substances as such or to salts thereof, preferably pharmaceutically acceptable salts thereof. Examples are sodium, potassium, magnesium, calcium or ammonium salts. Calcium salts are preferred.

The term "prodrug" describes a pharmacological substance which is administered in an inactive (or less active) form. Once administered, the prodrug is metabolised in the body in vivo into the active compound.

One embodiment of the process of the present invention comprises one or more additional steps wherein the compound according to formula (1-A), or a salt thereof, is further reacted to obtain a NEP-inhibitor or a prodrug thereof, in particular a NEP-inhibitor or a prodrug thereof comprising a γ -amino- δ -biphenyl- α -methylalkanoic acid, or acid ester, backbone.

Preferably compounds according to formula (1-A), or a salts thereof, are further reacted to obtain a NEP-inhibitor or a prodrug thereof, in particular a NEP-inhibitor or a prodrug thereof comprising a γ -amino- δ -biphenyl- α -methylalkanoic acid, or acid ester, backbone.

In a preferred embodiment a compound according to formula (1-A) preferably a compound of formula (1-A-a), as defined herein or a salt thereof, is further reacted to obtain the NEP inhibitor prodrug *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methylbutanoic acid ethyl ester (known in the art as AHU377) or a salt thereof.



Generally, the present invention comprises any pharmaceutically acceptable salt of *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methylbutanoic acid ethyl ester.

The NEP inhibitor prodrug *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methylbutanoic acid ethyl ester optionally is further reacted to obtain the active NEP inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methylbutanoic acid.

General Terms:

Listed below are definitions of various terms used to describe the present invention. These definitions, either by replacing one, more than one or all general expressions or symbols used in the present disclosure and thus yielding preferred embodiments of the invention, preferably apply to the terms as they are used throughout the specification unless they are otherwise limited in specific instances either individually or as part of a larger group.

In the present application the term "nitrogen protecting group" generally comprises any group which is capable of reversibly protecting a nitrogen functionality, preferably an amino and/or amide functionality.

Preferably the nitrogen protecting group is an amine protecting group and/or an amide protecting group. Suitable nitrogen protecting groups are conventionally used in peptide

chemistry and are described e.g. in the relevant chapters of standard reference works such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, and in "*Methoden der organischen Chemie*" (Methods of Organic Chemistry), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974.

Preferred nitrogen protecting groups generally comprise:

- C₁-C₆-alkyl, preferably C₁-C₄-alkyl, more preferably C₁-C₂-alkyl, most preferably C₁-alkyl which is optionally mono-, di- or tri-substituted by tri-C₁-C₇-alkylsilyl-C₁-C₇-alkoxy (eg. trimethylsilyethoxy) C₆-C₁₀-aryl, preferably phenyl, or an heterocyclic group, preferably pyrrolidinyl, wherein the aryl ring or the heterocyclic group is unsubstituted or substituted by one or more, e.g. two or three, residues, e.g. selected from the group consisting of C₁-C₇-alkyl, hydroxy, C₁-C₇-alkoxy, C₂-C₈-alkanoyl-oxy, halogen, nitro, cyano, and CF₃; or
- C₆-C₁₀-aryl-C₁-C₂-alkoxycarbonyl (preferably phenyl-C₁-C₂-alkoxycarbonyl eg. benzyloxycarbonyl); C₁-C₁₀-alkenyloxycarbonyl; C₁-C₆-alkylcarbonyl (eg. acetyl or pivaloyl); C₆-C₁₀-arylcarbonyl; C₁-C₆-alkoxycarbonyl (eg. *tert*-butoxycarbonyl); C₆-C₁₀-aryl-C₁-C₆-alkoxycarbonyl; allyl or cinnamyl; sulfonyl or sulfenyl; succinimidyl group, a silyl group according to the formula SiR_AR_A^{*}R_A^{**}, wherein R_A, R_A^{*} and R_A^{**} are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl-C₁-C₂-alkyl or C₆-C₁₀-aryl. Preferred examples for R_A, R_A^{*} and R_A^{**} are methyl, ethyl, isopropyl, t-butyl or phenyl.

Examples of preferred nitrogen protecting groups are acetyl, benzyl, cumyl, benzhydryl, trityl, benzyloxycarbonyl (Cbz), 9-fluorenylmethyloxycarbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyl-oxy-methyl (POM), trichloroethoxycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), allyl, allyloxycarbonyl, trimethylsilyl, *tert*-butyl-dimethylsilyl, triethylsilyl (TES), triisopropylsilyl, trimethylsilyethoxymethyl (SEM), *tert*-butoxycarbonyl (BOC), *tert*-butyl, 1-methyl-1,1-dimethylbenzyl, (phenyl)methylbenzene, pyrrolidinyl and pivaloyl. Most preferred nitrogen protecting groups are acetyl, benzyl, benzyloxycarbonyl (Cbz), triethylsilyl (TES), trimethylsilyethoxymethyl (SEM), *tert*-butoxycarbonyl (BOC), pyrrolidinylmethyl and pivaloyl.

Preferred nitrogen protecting groups are benzyl, phthalyl, and *tert*-butoxycarbonyl BOC.

Further examples of preferred nitrogen protecting groups are pivaloyl, pyrrolidinylmethyl, t-butoxycarbonyl, benzyl and silyl groups, particularly silyl groups (eg. triethylsilyl).

If an embodiment requires the removal of the nitrogen protecting group, as defined above, the removal usually can be carried out by using known methods. Preferably, the nitrogen protecting group, as defined above, is removed by using acidic or basic conditions. Examples for acidic

conditions are hydrochloric acid, trifluoroacetic acid, sulfuric acid. Examples of basic conditions are lithium hydroxide, sodium ethoxide. Nucleophiles such as sodium borohydride can be used.

In the case of *N*-benzyl as nitrogen protecting group it can be removed by hydrogenation or by the use of some suitable oxidizing agents, e.g. ceric ammonium nitrate (CAN) or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ).

Alkyl (being a radical or part of a radical such as aralkyl or alkoxy) is a straight or branched (one or, if desired and possible, more times) carbon chain, and is especially C₁-C₇-alkyl, or C₁-C₆-alkyl such as C₁-C₄-alkyl, in particular branched C₁-C₄-alkyl, such as isopropyl. The term "lower" or "C₁-C₇-" defines a moiety with up to and including maximally 7, especially up to and including maximally 4, carbon atoms, said moiety being branched (one or more times) or straight-chained and bound via a terminal or a non-terminal carbon. Lower or C₁-C₇-alkyl, for example, is *n*-pentyl, *n*-hexyl or *n*-heptyl or preferably C₁-C₄-alkyl, such as methyl, ethyl, *n*-propyl, *sec*-propyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, in particular methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl. In particular, C₁-C₇-alkyl is methyl, ethyl, propyl, or isopropyl. In one embodiment C₁-C₇-alkyl is methyl or ethyl.

Aryl, as a radical or part of a radical such as aralkyl, for example is a mono- or bicyclic substituted or unsubstituted aryl with 6 to 10 carbon atoms, such as phenyl, indenyl, indanyl or naphthyl, in particular phenyl. Substituted C₆₋₁₀aryl is, for example, C₆₋₁₀aryl substituted by one or more substituents (for example one to three substituents) independently selected from, for example, C₁-C₇-alkyl, C₁-C₇-alkoxy-C₁-C₇-alkyl, C₁-C₇-alkoxy and halo. In one embodiment, substituted C₆₋₁₀aryl is C₆₋₁₀aryl substituted by halo, such as para-chlorophenyl. In one embodiment, aryl is unsubstituted C₆₋₁₀aryl.

Cycloalkyl is, for example, C₃-C₇-cycloalkyl and is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cyclopentyl and cyclohexyl are preferred.

Acyl as a radical or part of a radical is, for example, unsubstituted or substituted C₆₋₁₀arylcarbonyl, unsubstituted or substituted C₆₋₁₀arylsulfonyl, unsubstituted or substituted heterocyclylcarbonyl or unsubstituted or substituted heterocyclylsulfonyl; wherein preferred substituents are selected from the group consisting of halo, C₁-C₇-alkyl, halo-C₁-C₇-alkyl, C₁-C₇-alkoxy, halo-C₁-C₇-alkoxy, such as trifluoromethoxy and C₁-C₇-alkoxy-C₁-C₇-alkoxy. Preferably acyl is unsubstituted or substituted C₆₋₁₀arylcarbonyl; or unsubstituted or substituted heterocyclylcarbonyl; wherein preferred substituents are selected from the group consisting of halo, C₁-C₇-alkyl, halo-C₁-C₇-alkyl, C₁-C₇-alkoxy, halo-C₁-C₇-alkoxy, such as trifluoromethoxy and C₁-C₇-alkoxy-C₁-C₇-alkoxy.

The term arylalkyl refers to C₆-C₁₀-aryl-C₁-C₇-alkyl, wherein aryl is as defined herein. In one embodiment arylalkyl is for example benzyl.

The term carboxyl refers to $\text{-CO}_2\text{R}$, wherein R is either hydrogen or $\text{C}_1\text{-C}_7\text{-alkyl}$.

Aryloxy refers to a Aryl-O- wherein aryl is as defined above.

Heterocyclyl is a mono- or polycyclic, preferably a mono-, bi- or tricyclic-, most preferably mono-, unsaturated, partially saturated, saturated or aromatic ring system with preferably 3 to 14 (more preferably 5 to 14) ring atoms and with one or more, preferably one to four, heteroatoms independently selected from nitrogen, oxygen, sulfur, S(=O)- or S(=O)_2 .

Alkoxy, as a radical or part of a radical, is, for example, $\text{C}_1\text{-C}_7\text{-alkoxy}$ and is, for example, methoxy, ethoxy, *n*-propyloxy, isopropyloxy, *n*-butyloxy, isobutyloxy, *sec*-butyloxy, *tert*-butyloxy and also includes corresponding pentyloxy, hexyloxy and heptyloxy radicals. $\text{C}_1\text{-C}_4\text{alkoxy}$ is preferred.

Where a "cycle" is referred to, e.g. in the case of a cycle formed from R1 and R2 together with the binding nitrogen, this includes mono- or bicyclic cyclic moieties, e.g. benzo-fused ring systems. Where cycles are mentioned which, e.g. together with the nitrogen to which they are attached, may be saturated or unsaturated and may optionally contain one or more, preferable one, two or three additional heteroatoms, such as nitrogen, oxygen or sulfur, whereby the cycle contains 3 to 10, preferably 4 to 7 ring atoms; these cycles may also carry one or more substituents, preferably one, two or three substituents, independently selected from such substituents as hydroxyl, $\text{C}_1\text{-C}_7\text{-alkyl}$, $\text{C}_1\text{-C}_7\text{-alkoxy}$, halo, carboxyl and oxo.

Where "one or more" is mentioned, e.g. in the case of heteroatoms, this preferably refers to 1 to 4 (1, 2, 3, 4), 1 to 3 (1, 2, 3) or 1 or 2. The respective substituents or heteroatoms can then be selected independently of each other and need not be identical.

Halo or halogen is preferably fluoro, chloro, bromo or iodo, most preferably bromo or especially chloro.

The term "alkali metal" refers to metals on the 1st column of the periodic table, such as Li, Na or K.

In the formulae of the present application the term "" on a C-sp^3 indicates the absolute stereochemistry, either (*R*) or (*S*).

In the formulae of the present application the term "" on a C-sp^3 indicates the absolute stereochemistry, either (*R*) or (*S*).

In the formulae of the present application the term "" on a C-sp^3 represents a stereochemical (e.g. racemic) mixture, thus it means a chiral center wherein the (*S*) stereoisomer and the (*R*) stereoisomer are both present, e.g. in a 50:50 ratio.

The term "chiral", as used herein, refers to molecules which have the property of non-superimposability on their mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. Any possible pure enantiomer or mixture of enantiomers, pure diastereoisomer or mixture of diastereomer are encompassed by the present invention. In one embodiment the term chiral refers to an enantiomerically enriched mixture of enantiomers. The term "enantiomerically enriched", as used herein, refers to a mixture of enantiomers wherein the amount of one enantiomer is higher than 50%. In another embodiment the term chiral refers to a diastereomerically enriched mixture of diastereomers. The term "diastereomerically enriched", as used herein, refers to a mixture of diastereomers wherein the amount of one diastereomer is higher than 50%.

The term "reflux" refers to the temperature at which the reaction mixture boils, preferably a temperature up to the actual reflux temperature or 180 °C, preferably up to 140 °C.

As used herein, the term "room temperature" or "ambient temperature" means a temperature of from 20 to 35 °C, such as of from 20 to 25 °C.

In view of the close relationship between the compounds and intermediates in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the compounds or a salts thereof, any reference to "compounds", "starting materials" and "intermediates" hereinbefore and hereinafter, is to be understood as referring also to one or more salts thereof or a mixture of a corresponding free compound, intermediate or starting material and one or more salts thereof, each of which is intended to include also any solvate, metabolic precursor such as ester or amide, or a salt of any one or more of these, as appropriate and expedient and if not explicitly mentioned otherwise. Different crystal forms may be obtainable and then are also included.

Salts can be formed where salt forming groups, such as basic or acidic groups, are present that can exist in dissociated form at least partially, e.g. in a pH range from 4 to 10 in aqueous solutions, or can be isolated especially in solid, especially crystalline, form.

In the presence of basic groups (e.g. imino or amino), salts may be formed preferably with organic or inorganic acids. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, lactic acid, fumaric acid, succinic acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, benzoic acid, methane- or ethane-sulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, *N*-cyclohexylsulfamic acid, *N*-methyl-, *N*-ethyl- or *N*-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

In the presence of negatively charged radicals, such as carboxy or sulfo, salts may be formed with bases, e.g. metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example triethylamine or tri(2-hydroxyethyl)amine, or heterocyclic bases, for example *N*-ethyl-piperidine or *N,N'*-dimethyl-piperazine.

When a basic group and an acid group are present in the same molecule, internal salts may also be formed.

Particularly useful salts include the hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric, lactic acid, fumaric acid, succinic acid, oxalic acid, malic acid, malonic acid, tartaric acid, tolyltartaric acid, benzoyltartaric acid, orotic acid, nicotinic acid, methane-sulfonic acid or 4-methylbenzenesulfonic acid salts of compounds of the present invention and the like formed from reaction with the above reagents. Methods to prepare acid addition salts are described in the literature, for example, in the relevant chapters of "CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation", D. Kozma, CRC Press 2002, in *Acta Cryst.* **2006**, B62, 498-505 and in *Synthesis* **2003**, 13, 1965-1967.

Where the plural form is used for compounds, starting materials, intermediates, salts, pharmaceutical preparations, diseases, disorders and the like, this is intended to mean one (preferred) or more single compound(s), salt(s), pharmaceutical preparation(s), disease(s), disorder(s) or the like, where the singular or the indefinite article ("a", "an") is used, this is not intended to exclude the plural, but only preferably means "one".

The term "prodrug," as used herein, represents in particular compounds which are transformed *in vivo* to the parent compound, for example, by hydrolysis in blood, for example as described in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; H Bundgaard, ed, Design of Prodrugs, Elsevier, 1985; and Judkins, et al. *Synthetic Communications* **1996**, 26, 4351-4367, and "The Organic Chemistry of Drug Design and Drug Action", 2nd Edition, R B Silverman (particularly Chapter 8, pages 497 to 557), Elsevier Academic Press, 2004.

Prodrugs therefore include drugs having a functional group which has been transformed into a reversible derivative thereof. Typically, such prodrugs are transformed to the active drug by hydrolysis. As examples may be mentioned the following:

Functional Group	Reversible derivative
<i>Carboxylic acid</i>	<i>Esters, including e.g. alkyl esters</i>

<i>Alcohol</i>	<i>Esters, including e.g. sulfates and phosphates as well as carboxylic acid esters</i>
<i>Amine</i>	<i>Amides, carbamates, imines, enamines,</i>
<i>Carbonyl (aldehyde, ketone)</i>	<i>Imines, oximes, acetals/ketals, enol esters, oxazolidines and thiazoxolidines</i>

Prodrugs also include compounds convertible to the active drug by an oxidative or reductive reaction. As examples may be mentioned:

Oxidative activation

- *N*- and *O*-dealkylation
- Oxidative deamination
- *N*-oxidation
- Epoxidation

Reductive activation

- Azo reduction
- Sulfoxide reduction
- Disulfide reduction
- Bioreductive alkylation
- Nitro reduction.

Each of the above described reactions and/or reaction steps can be used individually or in combination in a method to prepare a NEP-inhibitor or a prodrug thereof, such as a NEP inhibitor or prodrug thereof comprising a γ -amino- δ -biphenyl- α -methylalkanoic acid, or acid ester, such as alkyl ester, backbone. In particular the NEP-inhibitor is *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methylbutanoic acid or a salt thereof or a prodrug thereof.

EXAMPLE SECTION

Particular embodiments of the invention are provided in the following Examples. These Examples serve to illustrate the invention without limiting the scope thereof, while they on the other hand represent preferred embodiments of the reaction steps, intermediates and/or the process of the present invention.

Abbreviations:

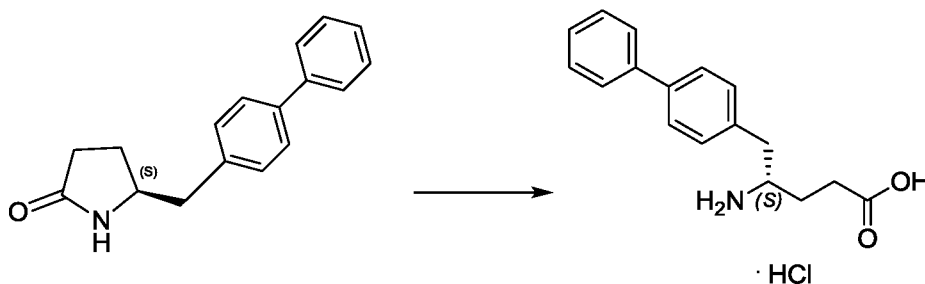
δ	chemical shift
μ l	microlitre
μ m	micrometre
AcOH	acetic acid

	aliph	aliphatic
	arom	aromatic
	Bn	benzyl
	Boc	<i>tert</i> -butoxycarbonyl
5	br. s.	Based on recovered starting material
	<i>n</i> -BuLi	<i>n</i> -butyl Lithium
	BOC ₂ O	di- <i>tert</i> -butyl carbonate
	CDCl ₃	deuterated chloroform
	CDI	<i>N,N</i> -carbonyldiimidazole
10	CH ₂ Cl ₂	dichloromethane
	(COCl) ₂	oxalyl chloride
	d	doublet
	dd	doublet of doublet
	DCM	dichloromethane
15	DMF	dimethylformamide
	de	diastereomeric excess
	dr	diastereomeric ratio
	EDC·HCl	<i>N</i> -(3-dimethylaminopropyl)- <i>N</i> -ethylcarbodiimide hydrochloride
	DEA	Diethylamine
20	DMF = dmf	<i>N,N</i> -dimethylformamide
	DMSO	dimethylsulfoxide
	DMSO- <i>d</i> ₆	dimethylsulfoxide deuterated
	<i>d</i> ₆ -DMSO	dimethylsulfoxide deuterated
	ee	enantiomeric excess
25	ES	electrospray
	ESI	electrospray ionisation
	Et	ethyl
	EtOAc	ethyl acetate
	EtOH	ethanol
30	FTIR	Fourier transform infrared
	h	hour(s)
	HCl	hydrochloric acid
	H ₂ SO ₄	sulfuric acid
	HOBt	6-chloro-1-hydroxybenzotriazol
35	HNMR	proton nuclear magnetic resonance
	HPLC	high performance liquid chromatography
	H ₃ PO ₄	phosphoric acid
	iPr	isopropyl

	iPrOAc	isopropyl acetate
	iPrOH	isopropanol
	IR	infra red
	<i>J</i>	coupling constant
5	K ₂ CO ₃	potassium carbonate
	KHMDS	Potassium bis(trimethylsilyl)amide
	L	litre
	LDA	lithium diisopropylamide
	LiOH	lithium hydroxide
10	LC-MS	liquid chromatography-mass spectrometry
	LHMDS	lithium bis(trimethylsilyl)amide
	M	molarity
	m	multiplet
	m/e	mass-to-charge ratio
15	m/z	mass-to-charge ratio
	Me	methyl
	MeOH	methanol
	mg	milligram
	min	minute(s)
20	Mel	methyl iodide
	ml	millilitre
	mmol(s)	millimole(s)
	mol(s)	mole(s)
	MS	mass spectrometry
25	N	nitrogen atom
	N ₂	nitrogen gas
	nm	nanometre
	NaH	sodium hydride
	NaOH	sodium hydroxide
30	NaHCO ₃	sodium bicarbonate
	NaHMDS	sodium bis(trimethylsilyl)amide
	NH ₄ Cl	ammonium chloride
	nm	nanometre
	NMR	nuclear magnetic resonance
35	Ph	phenyl
	pH	hydrogen ion concentration
	ppm	parts per million
	q	quartet

	RT = rt	room temperature
	s	singlet
	SM	starting material
	t	triplet
5	TBME	<i>tert</i> -butyl methyl ether
	TEA	triethylamine
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TLC	thin layer chromatography
10	Tol	toluene
	t _R	retention time

Example 1: (S)-4-Amino-5-biphenyl-4-yl-pentanoic acid hydrochloride

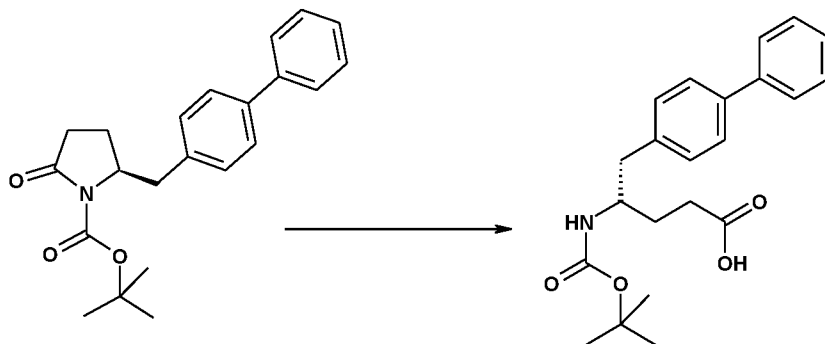


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(S)-5-biphenyl-4-ylmethyl-pyrrolidin-2-one (40.0 g, 0.159 mol) is suspended in 6N HCl (250 mL), the mixture is refluxed for 2 h and then is allowed to cool to room temperature. After filtration, the solid is collected and dried to give (S)-4-amino-5-biphenyl-4-yl-pentanoic acid hydrochloride. ¹H NMR (DMSO): 1.80 (2H, m), 2.45 (2H, m), 2.81 (1H, m), 3.05 (1H, m), 3.57 (1H, m), 7.36~7.71 (9H, m, aromatic), 8.21 (2H, s), 12.23 (1H, s).

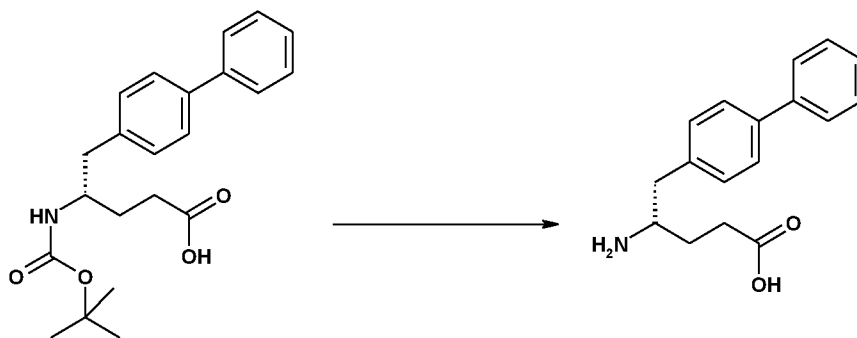
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Example 2: (S)-5-(Biphenyl-4-yl)-4-(*tert*-butoxycarbonylamino)pentanoic acid



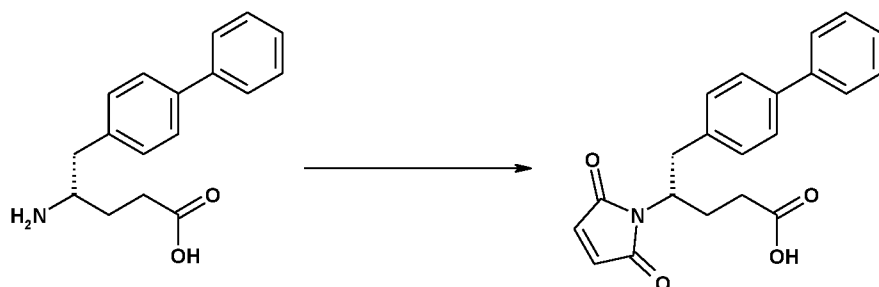
To a mixture of tetrahydrofuran (150 ml) and water (50 ml) is added (S)-2-biphenyl-4-ylmethyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (20 g, 56 mmol). A solution of lithium hydroxide (6 g) dissolved in water (100 ml) is then added to the mixture. The resulting mixture is then stirred vigorously for 14 h. 1 M hydrochloric acid solution is added to the mixture until a pH of less than 7 is achieved. The tetrahydrofuran solvent is then removed from the mixture under reduced pressure. Ethyl acetate (100 ml) is then added and the two phases separated. The organic phase is washed with 1 M hydrochloric acid solution (40 ml) and brine solution (40 ml). The organic layer is dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford (S)-5-(biphenyl-4-yl)-4-(tert-butoxycarbonylamino) pentanoic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.3 (s, 9 H) 1.4 - 1.8 (m, 2 H) 2.1 - 2.3 (m, 2 H) 2.7 (d, *J*=7.0 Hz, 2 H) 3.5 - 3.7 (m, 1 H) 6.7 (d, *J*=8.8 Hz, 1 H) 7.2 - 7.7 (m, 9 H) 12.0 (br. s., 1 H); ESI+ MS *m/z* 369.5 ([*M*+*H*]⁺, 370.5).

Example 3: (S)-4-Amino-5-(biphenyl-4-yl)pentanoic acid



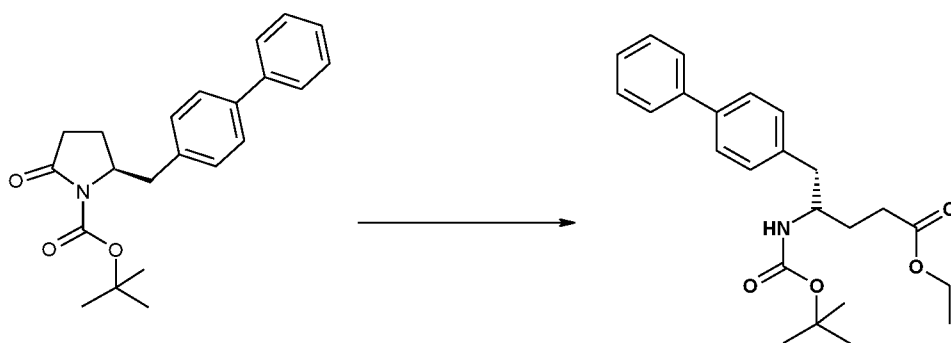
(S)-5-(biphenyl-4-yl)-4-(tert-butoxycarbonylamino)pentanoic acid (6.512 g, 17 mmol) is added to dichloromethane (20 ml). Trifluoroacetic acid (10 ml) is added to the mixture. The mixture is stirred at room temperature until effervescence ceases, then the mixture is stirred for an additional 40 minutes at 50°C. The mixture is then concentrated under reduced pressure. Ethyl acetate (120 ml) is then added. The mixture is washed with water (3×40 ml) and brine solution (40 ml). The organic layer is dried over anhydrous sodium sulfate, filtered and the volatiles removed under reduced pressure to afford (S)-4-amino-5-(biphenyl-4-yl)pentanoic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.7 - 1.9 (m, 2 H) 2.3 - 2.5 (m, 2 H) 2.8 - 3.0 (m, 2 H) 3.4 - 3.6 (m, 1 H) 7.3 (d, *J*=8.0 Hz, 3 H) 7.4 (t, *J*=7.6 Hz, 2 H) 7.6 (dd, *J*=7.6, 4.4 Hz, 4 H) 7.9 (br. s., 3 H); ESI+ MS *m/z* 269.3 ([*M*+*H*]⁺, 270.3).

Example 4: (S)-5-(Biphenyl-4-yl)-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)pentanoic acid



Maleic anhydride (820 mg, 8.3 mmol) is added to tetrahydrofuran (40 ml). A mixture of (S)-4-amino-5-(biphenyl-4-yl)pentanoic acid (2.131 g, 6.9 mmol) in tetrahydrofuran (8 ml) is then added. The reaction mixture is stirred at room temperature for 3 h. The mixture is then concentrated to dryness and toluene (50 ml) is added. Zinc(II) bromide (1.550 g, 6.9 mmol) is then added in a single portion and the resulting mixture is stirred rigorously and heated to 80°C. A solution of hexamethyldisilazane (2.6 ml, 12.4 mmol) in toluene (15 ml) is added in three separate portions over a period of 30 min. The reaction is stirred overnight at 80°C. The reaction mixture is evaporated to dryness. The resulting oil is washed with saturated sodium carbonate solution (2×20 ml) and brine solution (40 ml). Ethyl acetate (40 ml) is added. The organic layers is dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to afford (S)-5-(biphenyl-4-yl)-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)pentanoic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.9 - 2.0 (m, 1 H) 2.1 - 2.3 (m, 3 H) 2.9 - 3.2 (m, 2 H) 4.1 - 4.3 (m, 1 H) 6.8 (s, 2 H) 7.0 - 7.7 (m, 9 H) 12.1 (br. s., 1 H); ESI+ MS *m/z* 349.4 ([M+H]⁺, 350.4).

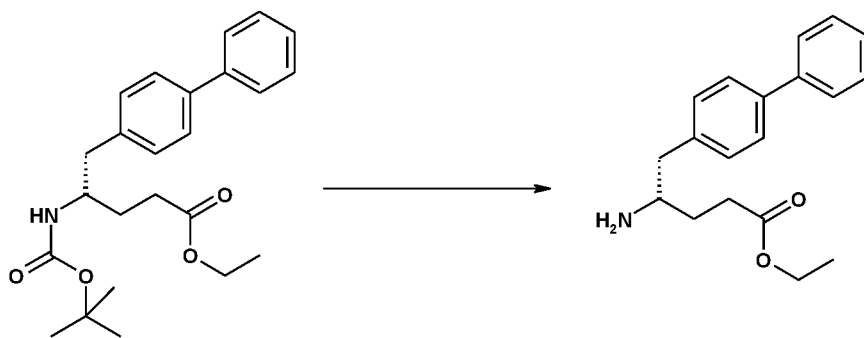
Example 5: (S)-5-Biphenyl-4-yl-4-tert-butoxycarbonylamino-pentanoic acid ethyl ester



To a solution of (S)-2-biphenyl-4-ylmethyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (5.9 g) in ethanol (10 mL) is added sodium ethoxide (1.14 g) at room temperature. After 30 min the solution is poured into brine and extracted with TBME. The combined organic extracts are dried and concentrated to give (S)-5-biphenyl-4-yl-4-tert-butoxycarbonylamino-pentanoic acid ethyl ester. ¹H NMR (CDCl₃): 1.22~1.26 (3H, t), 1.40 (9H, s), 1.62~1.68 (1H, m),

1.86~1.94 (1H, m), 2.36~2.41 (2H, m), 2.76~2.87 (2H, m), 3.86 (1H, s), 4.11~4.23 (2H, q), 3.38~3.41 (1H, m), 7.24~7.58 (9H, m, aromatic).

Example 6: (S)-Ethyl 4-amino-5-(biphenyl-4-yl)pentanoate



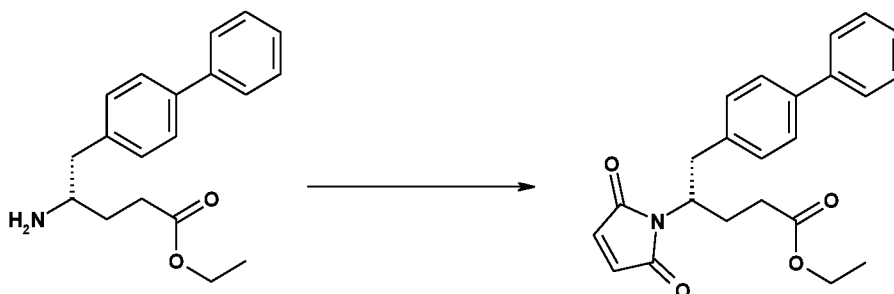
5

(S)-Ethyl 5-(biphenyl-4-yl)-4-(tert-butoxycarbonylamino)pentanoate (5 g, 12.6 mmol) is dissolved in dichloromethane (20 ml). Trifluoroacetic acid (8 ml) is added to the mixture. The mixture is stirred at room temperature until effervescence ceases, then the mixture is stirred for an additional 40 minutes at 50°C. The mixture is then concentrated under reduced pressure.

10 Ethyl acetate (120 ml) is then added. The resulting mixture is washed with saturated sodium carbonate solution (2×40 ml) and brine solution (40 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the volatiles removed under reduced pressure to afford (S)-ethyl 4-amino-5-(biphenyl-4-yl)pentanoate. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.5 (t, *J*=7.1 Hz, 3 H) 2.1 - 2.3 (m, 2 H) 2.7 - 3.0 (m, 2 H) 3.2 - 3.5 (m, 2 H) 3.8 - 4.0 (m, 1 H) 4.4 (q, *J*=7.0 Hz, 2 H) 7.6 - 8.2 (m, 9 H) 8.5 (br. s., 3 H); ESI+ MS *m/z* 297.4 ([*M*+*H*]⁺, 298.4).

15

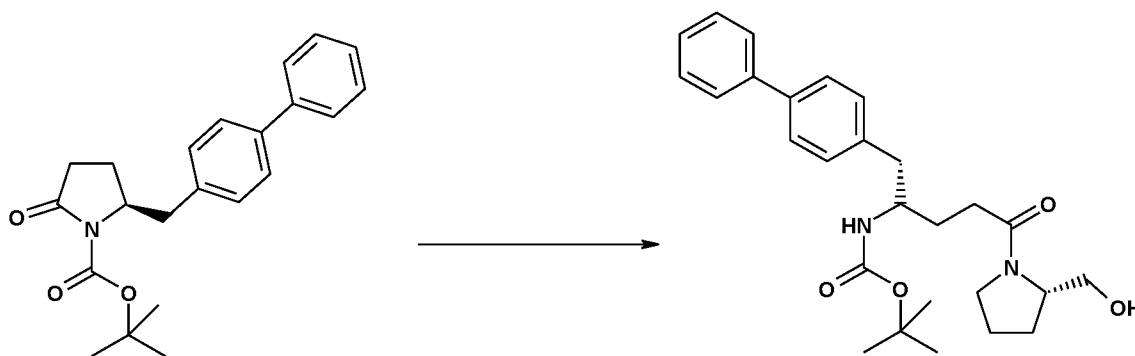
Example 7: (S)-Ethyl-5-(biphenyl-4-yl)-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)pentanoate



20 Maleic anhydride (1.28 g, 13.0 mmol) is added to tetrahydrofuran (60 ml) at room temperature. (S)-Ethyl 4-amino-5-(biphenyl-4-yl)pentanoate. (3.226 g, 10.9 mmol) in tetrahydrofuran (12 ml) is then added to the mixture. The resulting mixture is stirred at room temperature for 3 h. The mixture is then concentrated to dryness and toluene (80 ml) is added. Zinc(II) bromide (2.443g,

10.9 mmol) is then added in a single portion and the resulting mixture is stirred rigorously and heated to 80°C. A solution of hexamethyldisilazane (4.1 ml, 19.5 mmol) in toluene (25 ml) is added in three separate portions over a period of 30 min. The reaction is stirred overnight at 80°C. The reaction mixture is evaporated to dryness. Ethyl acetate (50 ml) is added and the mixture is washed with saturated sodium carbonate solution (2×40 ml) and brine solution (40 ml). The organic layer is dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The residue is purified by chromatography (1% methanol in dichloromethane) to afford (S)-ethyl-5-(biphenyl-4-yl)-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)pentanoate. ¹H NMR (400 MHz, DMSO-*d*₆) 1.1 (t, *J*=7.1 Hz, 3 H) 1.9 - 2.4 (m, 4 H) 2.9 - 3.2 (m, 2 H) 4.0 (q, *J*=7.1 Hz, 2 H) 4.1 - 4.3 (m, 1 H) 6.9 (s, 2 H) 7.0 - 7.7 (m, 9 H); ESI+ MS *m/z* 377.4 ([*M*+*H*]⁺, 378.4); IR (FTIR) cm⁻¹ 3454 (C=O), 3099 (CH. arom), 2977 (CH. aliph), 1728, 1702 (C=O imide + ester), 1400, 1371 (C-N).

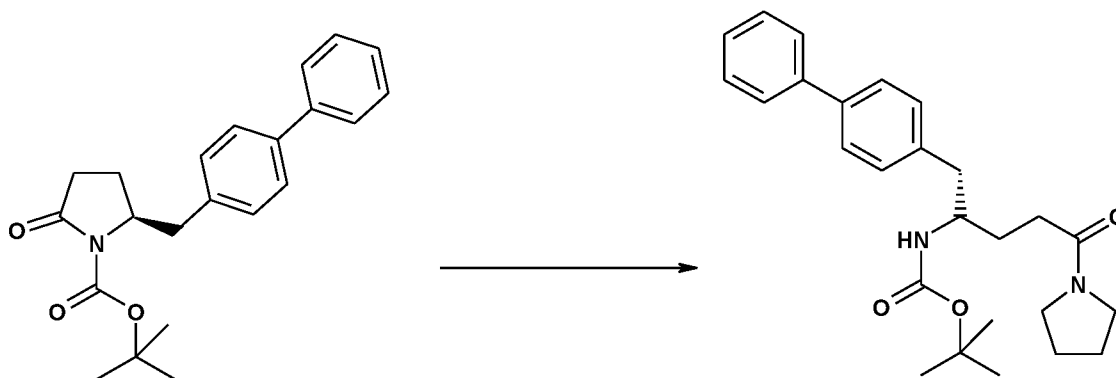
Example 8: [(S)-1-Biphenyl-4-ylmethyl-4-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-4-oxo-butyl]-carbamic acid tert-butyl ester



Sodium methoxide (54 mg, 1 mmol) is added to the mixture of (S)-2-biphenyl-4-ylmethyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (3.5 g, 10 mmol) and (S)-(+)-prolinol (1.11 g, 11 mmol) in 50mL dry THF and stirred for 3h. Then ammonium chloride aqueous solution is added, the mixture is extracted with ethyl acetate and the organic extracts are combined and dried. Purification of the residue by column chromatography gives [(S)-1-biphenyl-4-ylmethyl-4-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-4-oxo-butyl]-carbamic acid tert-butyl ester. ¹H NMR (CDCl₃): 1.40 (9H, s, (CH₃)₃), 1.80 (2H, m, 3-CH₂), 1.90 (4H, m, CH₂CH₂), 2.36 (2H, m, 2-CH₂), 2.85 (2H, m, 5-CH₂), 3.42 (1H, m, 4-CH), 3.45 (2H, m, CH₂), 3.58 (2H, m, CH₂), 4.18 (1H, m, CH), 4.93 (1H, s, OH), 7.40~7.60 (9H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150×4.6mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (90 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 0.7 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 11.2 min

Example 9: [(S)-1-Biphenyl-4-ylmethyl-4-oxo-4-pyrrolidin-1-yl-butyl]-carbamic acid tert-butyl ester

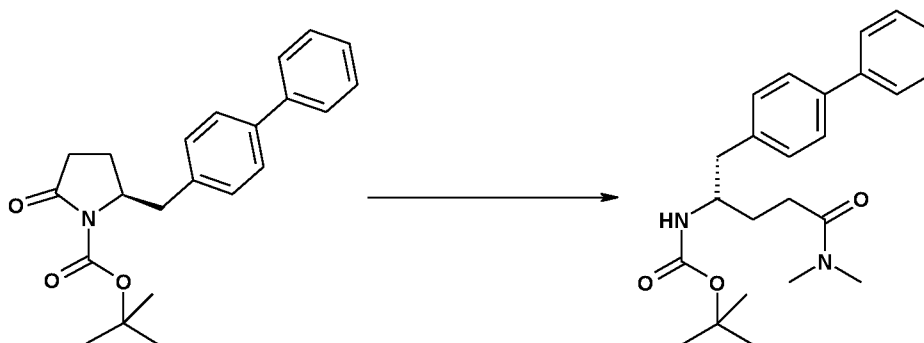


- 5 Sodium methoxide (16 mg, 0.3mmol) is added to the mixture of (S)-2-Biphenyl-4-ylmethyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (1.05 g, 3 mmol) and pyrrolidine (0.23 g, 3.3 mmol) in 15 mL dry THF and stirred for 3 h. Ammonium chloride aqueous solution is added, the mixture is extracted with ethyl acetate and the organic layers are combined and concentrated. Purification of the residue by column chromatography affords [(S)-1-biphenyl-4-ylmethyl-4-oxo-4-pyrrolidin-1-yl-butyl]-carbamic acid tert-butyl ester. ¹H NMR (CDCl₃): 1.40 (9H, s, (CH₃)₃), 1.82 (2H, m, 3-CH₂), 1.90 (4H, m, CH₂CH₂), 2.32 (2H, m, 2-CH₂), 2.78 (2H, m, 5-CH₂), 2.90 (1H, m, 4-CH), 3.36 (2H, t, CH₂), 3.44 (2H, t, CH₂), 7.20~7.60 (9H, m, aromatic).
- 10

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (90 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 0.7ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 13.2 min

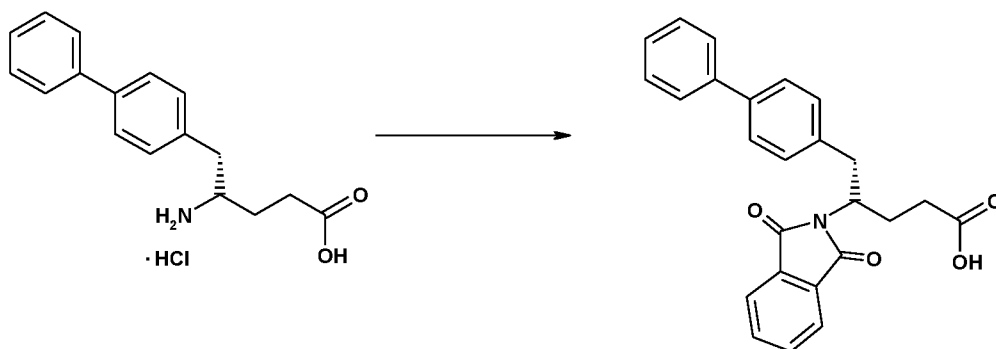
15

Example 10: (S)-tert-Butyl -1-(biphenyl-4-yl)-5-(dimethylamino)-5-oxopentan-2-ylcarbamate



To a mixture of (S)-2-biphenyl-4-ylmethyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (351 mg, 1 mmol) and lithium hexafluorophosphate (152 mg, 1 mmol) in tetrahydrofuran (5 ml) is added dimethylamine (2 M THF solution) (5 ml, 10 mmol). The mixture is stirred at ambient temperature for 30 min. The mixture is then concentrated under vacuum and ethyl acetate is added (20 ml). The mixture is washed with saturated sodium carbonate solution (2×20 ml) followed by brine solution (20 ml). The organic layer is dried over anhydrous sodium sulfate, filtered and the volatile materials removed under reduced pressure. The resulting residue is purified by column chromatography, to afford (S)-tert-butyl-1-(biphenyl-4-yl)-5-(dimethylamino)-5-oxopentan-2-ylcarbamate. ¹H NMR (400 MHz, d₆-DMSO): 1.3 (s, 9 H) 1.5 - 1.8 (m, 2 H) 2.3 (t, *J*=7.5 Hz, 2 H) 2.7 (d, *J*=5.8 Hz, 2 H) 2.8 (s, 3 H) 2.9 (s, 3 H) 3.6 (br. s., 1 H) 6.8 (d, *J*=8.8 Hz, 1 H) 7.2 - 7.7 (m, 9 H); ESI+ MS *m/z* 369.5 ([*M*+*H*]⁺, 370.5); IR (FTIR) cm⁻¹ 3255 (N-H), 3005, 2981 (CH. arom), 2968, 2944 (CH. aliph), 1714 (C=O. Boc), 1619 (C=O. amide).

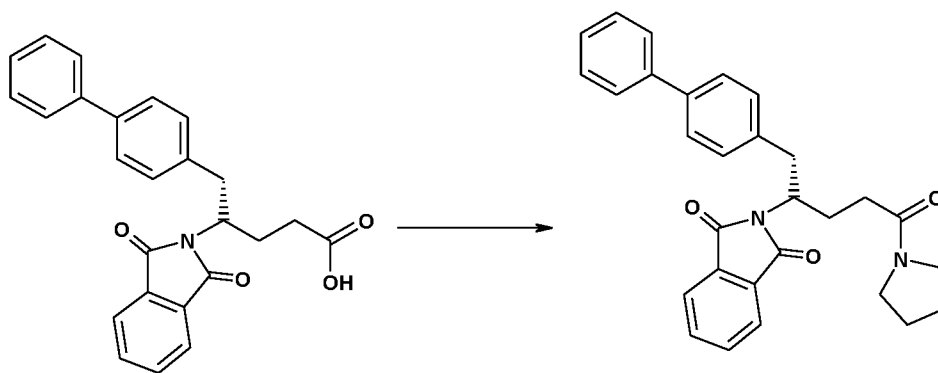
Example 11: (S)-5-Biphenyl-4-yl-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid



To a solution of (S)-4-Amino-5-biphenyl-4-yl-pentanoic acid hydrochloride (30.0 g, 98 mmol) in THF (300 mL) is added triethylamine (27.4 mL, 197 mmol) followed by 1,3-dioxo-1,3-dihydro-isoindole-2-carboxylic acid ethyl ester (25.2 g, 103 mmol). The reaction mixture is refluxed for 12 hours. The solvent is then removed under vacuum, 200 mL of 2 N HCl is added, stirred for 0.5 h, filtered, the cake is washed with 2 N HCl and n-heptane, then dried to obtain (S)-5-biphenyl-4-yl-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid, as determined by HPLC. ¹H NMR (CDCl₃): 2.15(1H, m, 3-CH), 2.36 (2H, m, 2-CH₂), 2.54 (1H, m, 3-CH), 4.56 (1H, m, 4-CH), 7.20~7.80 (13H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 7.8 min

Example 12: 2-((S)-1-Biphenyl-4-ylmethyl-4-oxo-4-pyrrolidin-1-yl-butyl)-isoindole-1,3-dione

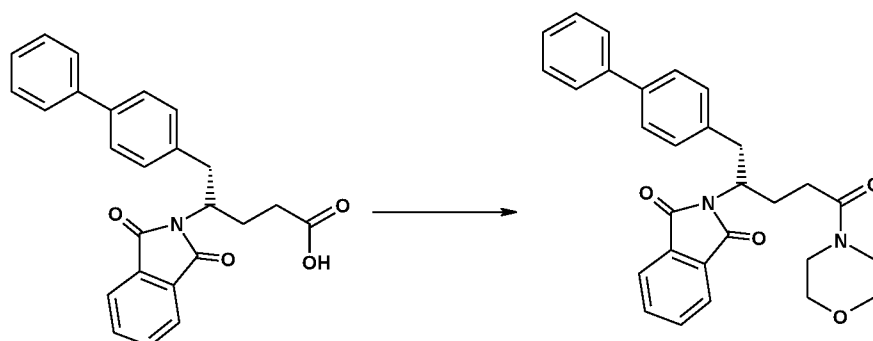


To a solution of 2-((S)-1-biphenyl-4-ylmethyl-4-morpholin-4-yl-4-oxo-butyl)-isoindole-1,3-dione (5 g, 12.52 mmol) in dry THF (30 mL) is added EDC·HCl (2.88 g, 15.03 mmol), HOBt (2.03 g, 15.03 mmol), TEA (7 mL, 50.08 mmol) and pyrrolidine (0.98 g, 13.77 mmol) at room temperature. The reaction mixture is stirred vigorously for 12h, then ethyl acetate (100 mL) is added to the reaction mixture. The organic phase is separated, washed sequentially with 1N HCl (50 mL), saturated NaHCO₃ solution (50 mL) and brine (50 mL), dried and concentrated. The resulting residue is purified by flash column chromatography to give 2-((S)-1-biphenyl-4-ylmethyl-4-oxo-4-pyrrolidin-1-yl-butyl)-isoindole-1,3-dione. ¹H NMR (CDCl₃): 1.78 (2H, m), 1.85 (2H, m), 2.23 (2H, m), 2.63 (1H, m), 3.30 (6H, m), 4.72 (1H, m), 7.20~7.78 (13H, m, aromatic). MS (ESI, m/e) 453 (MH⁺).

2-((S)-1-Biphenyl-4-ylmethyl-4-oxo-4-pyrrolidin-1-yl-butyl)-isoindole-1,3-dione is a crystalline solid and can be characterised by X-ray powder patterns. The most intensive reflections in the X-ray diffraction pattern show the following interlattice plane intervals (average 2θ in [°] are indicated with error limit of ±0.2): 2θ in [°]: 3.7, 9.6, 10.5, 11.2, 14.7, 15.7, 16.4, 19.6, 20.1, 21.2, 26.2.. Data taken using a Bruker D8 Advance diffractometer using Cu-Kα radiation.

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 9.4 min

Example 13: 2-((S)-1-Biphenyl-4-ylmethyl-4-morpholin-4-yl-4-oxo-butyl)isoindole-1, 3-dione

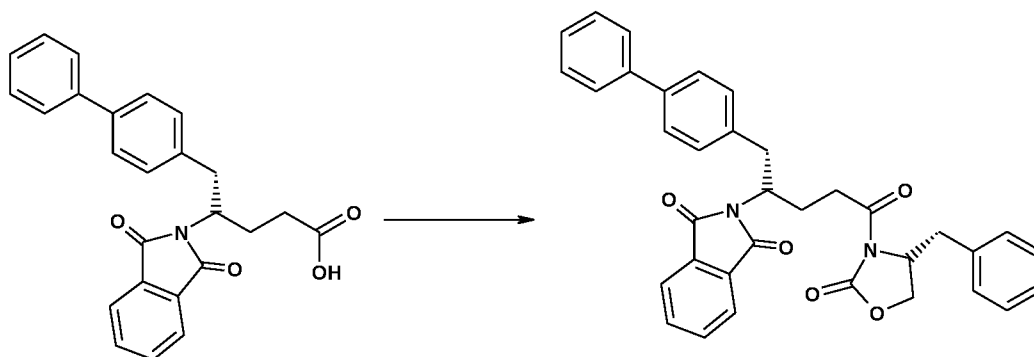


To a solution of (S)-5-biphenyl-4-yl-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid (5 g, 12.52 mmol) in dry THF (30 mL) is added EDC·HCl (2.88 g, 15.03 mmol), HOBt (2.03 g, 15.03 mmol), TEA (7 mL, 50.08 mmol) and morpholine (1.20 g, 13.77 mmol) at room temperature. The reaction mixture is stirred vigorously for 12 h, then ethyl acetate (100 mL) is added. The organic phase is washed sequentially with 1 N HCl (50 mL), saturated NaHCO₃ solution (50 mL) and brine (50 mL), dried and concentrated. The resulting residue is purified by flash column chromatograph to give 2-((S)-1-biphenyl-4-ylmethyl-4-morpholin-4-yl-4-oxo-butyl)-isoindole-1,3-dione. ¹H NMR (CDCl₃): 1.24 (2H, m), 2.21~2.29 (1H, m), 2.31~2.40 (2H, m), 2.52~2.57 (1H, m), 3.18~3.21 (1H, m), 3.23(2H, m), 3.24~3.32 (2H, m), 3.53~3.57 (3H, m), 7.23 ~7.75 (13H, m, aromatic). MS (ESI, m/e) 469 (MH⁺).

2-((S)-1-Biphenyl-4-ylmethyl-4-morpholin-4-yl-4-oxo-butyl)isoindole-1, 3-dione is a crystalline solid and can be characterised by X-ray powder patterns. The most intensive reflections in the X-ray diffraction pattern show the following interlattice plane intervals (average 2θ in [°] are indicated with error limit of ±0.2): 2θ in [°]: 3.6, 9.5, 10.8, 12.6, 13.1, 14.5, 15.9, 16.9, 18.5, 19.3, 20.4, 22.5, 23.1, 24.1, 25.9, 27.2, 27.9. Data taken using a Bruker D8 Advance diffractometer using Cu-Kα radiation.

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 7.9 min

Example 14: 2-[(S)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione



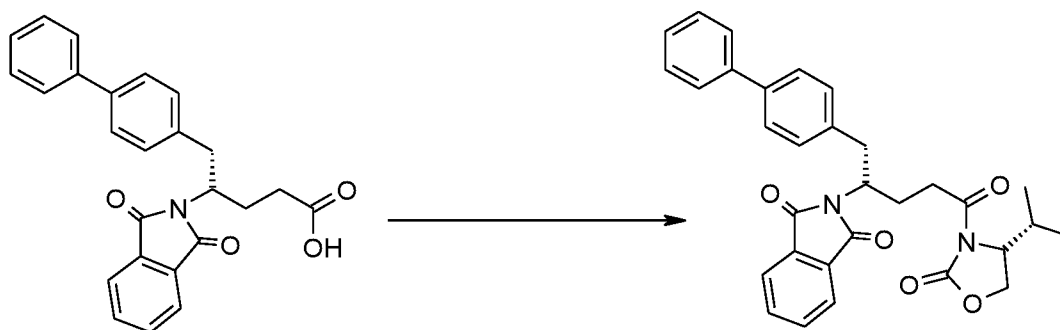
To a solution of (S)-5-biphenyl-4-yl-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)pentanoic acid (1.00 g, 2.95 mmol) in 10 mL of anhydrous DCM is added 1 drop of DMF, cooled to 0 °C, then (COCl)₂ (0.75 g, 5.89 mmol) is added dropwise. The mixture is stirred for 1 h, then excess (COCl)₂ is distilled. In a separate flask, NaH (142 mg, 3.24 mmol) is suspended in 10 mL of anhydrous THF, cooled to 0 °C, (R)-4-Benzyl-oxazolidin-2-one (0.57 g, 3.24 mmol) is added, stirred at 0 °C for 1 h, then the preformed acid chloride is added. The reaction mixture is stirred at 0 °C for 30 min, then saturated NH₄Cl is added, extraction with DCM and washed with water, the organic

extracts is washed with 5 % NaHCO₃ and brine, dried and concentrated. The resulting crude material is crystallized to give 2-[(S)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione. ¹H NMR (CDCl₃): 2.28 (1H, m), 2.25 (1H, m), 2.67 (1H, m), 2.95 (2H, m), 3.27 (2H, m), 3.50 (1H, m), 4.15 (1H, m), 4.23 (1H, m), 7.15 ~7.80 (18H, m, aromatic). m/z : 559 (MH⁺).

2-[(S)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione is a crystalline solid and can be characterised by X-ray powder patterns. The most intensive reflections in the X-ray diffraction pattern show the following interlattice plane intervals (average 2θ in [°] are indicated with error limit of ±0.2): 2θ in [°]: 4.4, 8.6, 9.4, 10.7, 12.3, 14.2, 14.6, 15.9, 16.9, 18.1, 19.6, 20.4, 20.7, 21.3, 21.7, 22.1, 23.2, 23.7, 24.2, 24.8, 25.1, 26.4. Data taken using a Bruker D8 Advance diffractometer using Cu-Kα radiation.

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (10 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 11.5 min

Example 15: 2-[(S)-4-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione

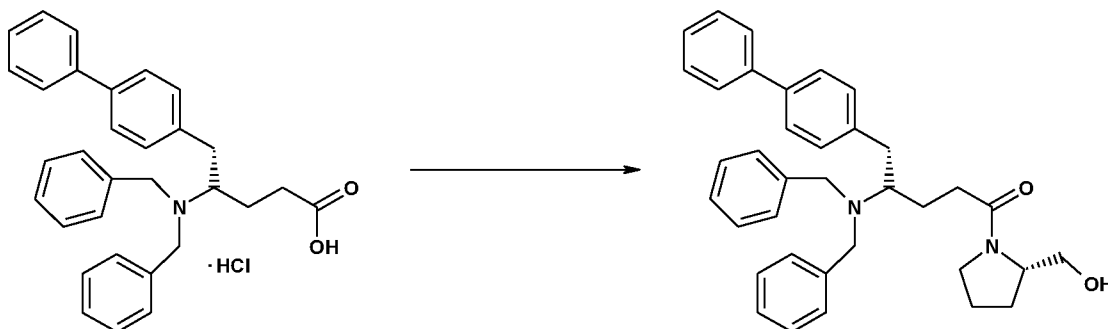


To a solution of (S)-5-biphenyl-4-yl-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid (1.00 g, 2.95 mmol) in 10 mL of anhydrous CH₂Cl₂ is added 1 drop of DMF, cooled to 0 °C, then (COCl)₂ (0.75 g, 5.89 mmol) is added dropwise. The mixture is stirred for 1 h, then excess (COCl)₂ is distilled. In a separate flask, NaH (142 mg, 3.24 mmol) is suspended in 10 mL of anhydrous THF, cooled to 0 °C, (R)-4-isopropyl-oxazolidin-2-one (418 mg, 3.24 mmol) is added, stirred at 0 °C for 1 h, then the preformed acid chloride is added. The reaction mixture is stirred at 0 °C for 30 min, then saturated NH₄Cl is added, extraction with DCM and washed with water, the organic extracts is washed with 5 % NaHCO₃ and brine, dried and concentrated. The resulting crude material is purified by column chromatography to give 2-[(S)-4-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione. ¹H NMR (CDCl₃):

0.8 (6H, d), 2.26 (2H, m), 2.54 (1H, m), 2.90 (1H, m), 3.01 (1H, m), 3.20 (1H, m), 3.45 (1H, m), 4.10 (2H, dd), 4.27 (1H, m), 4.60 (1H, m), 7.20 ~7.80 (13H, m, aromatic). m/z : 400 (MH⁺).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention times: 9.8 min

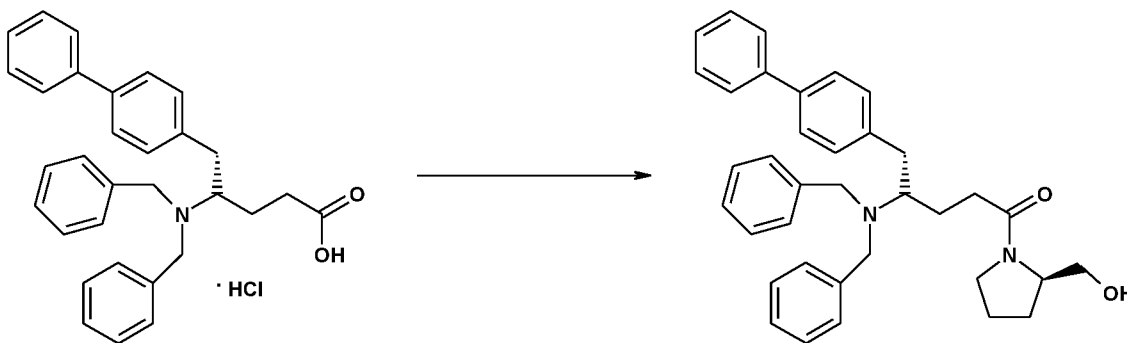
Example 16: (S)-5-Biphenyl-4-yl-4-dibenzylamino-1-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-pentan-1-one



The suspension (S)-5-biphenyl-4-yl-4-dibenzylamino-pentanoic acid hydrochloride (4.86g
 5 10mmol) in 100 mL of CH₂Cl₂ is added (S)-(+)-prolinol (1.11g, 11mmol), EDC·HCl (2.3 g, 12
 mmol), HOBt (1.62 g, 12 mmol) and TEA (5 g, 50 mmol) sequentially and the mixture is stirred
 at room temperature for 12 h. The reaction mixture is washed with water, dried and
 concentrated. The resulting residue is purified by column chromatography (ethyl
 acetate/heptane = 1/2) to give (S)-5-biphenyl-4-yl-4-dibenzylamino-1-((S)-2-hydroxymethyl-
 10 pyrrolidin-1-yl)-pentan-1-one. ¹H NMR (CDCl₃): 1.69 (1H, m, 3-CHH), 1.75 (1H, m, 3-CHH),
 1.94 (4H, m, CH₂CH₂), 2.50 (1H, m, 2- CHH), 2.55 (2H, m, 5-CH₂), 2.79 (1H, m, 2- CHH), 3.17
 (1H, dd, 4-CH), 3.31 (2H, m, CH₂), 3.54 (2H, d, CH₂), 3.58 (2H, m, CH₂), 3.88 (2H, d, CH₂), 4.09
 (1H, m, CH), 5.14 (1H, s, OH), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150×4.6mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄)
 15 in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 %
 B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 9.6 min

Example 17: (S)-5-Biphenyl-4-yl-4-dibenzylamino-1-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-pentan-1-one

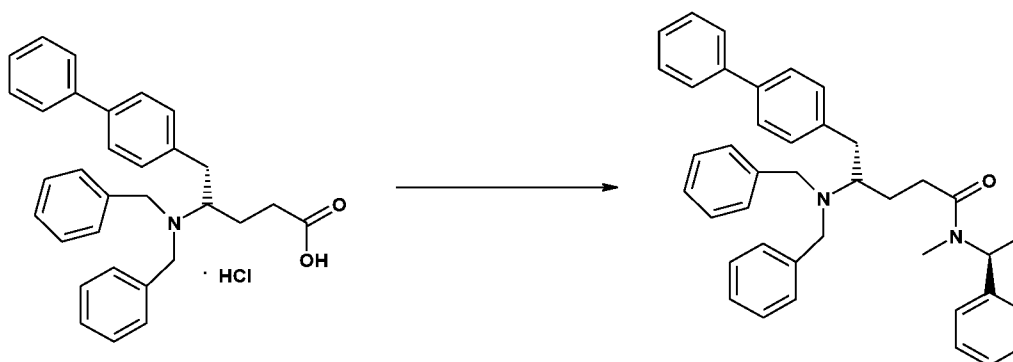


The suspension of (S)-5-biphenyl-4-yl-4-dibenzylamino-pentanoic acid hydrochloride (4.86 g
 10 mmol) in 100mL of CH₂Cl₂ is added (R)-(-)-prolinol (1.11 g, 11 mmol), EDC·HCl (2.3 g, 12
 mmol), HOBt (1.62 g, 12 mmol) and TEA (5 g, 50 mmol) sequentially and the mixture is stirred

at room temperature for 12 h. The reaction mixture is washed with water, dried and concentrated. The resulting residue is purified by column chromatography (ethyl acetate/heptane = 1/2) to give (S)-5-biphenyl-4-yl-4-dibenzylamino-1-((R)-2-hydroxymethylpyrrolidin-1-yl)-pentan-1-one. ¹H NMR (CDCl₃): 1.69 (1H, m, 3-CHH), 1.75 (1H, m, 3-CHH), 1.94 (4H, m, CH₂CH₂), 2.50 (1H, m, 2-CHH), 2.55 (2H, m, 5-CH₂), 2.79 (1H, m, 2-CHH), 3.18 (1H, dd, 4-CH), 3.31 (2H, m, CH₂), 3.54 (2H, d, CH₂), 3.57 (2H, m, CH₂), 3.87 (2H, d, CH₂), 4.12 (1H, m, CH), 5.12 (1H, d, OH), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 9.5 min

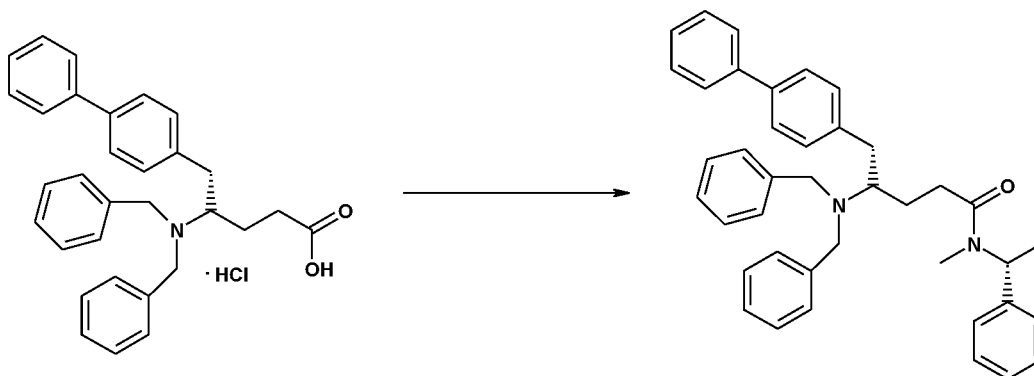
Example 18: (S)- 5-Biphenyl-4-yl-4-dibenzylamino-pentanoic acid methyl-((S)-1-phenyl-ethyl)-amide



The suspension of (S)-5-biphenyl-4-yl-4-dibenzylamino-pentanoic acid hydrochloride (4.86 g 10 mmol) in 10 mL of CH₂Cl₂ is added (S)-methyl-(1-phenyl-ethyl)-amine (0.19 g, 1.36 mmol), EDC·HCl (0.29 g, 1.5 mmol), HOBt (0.21 g, 1.5 mmol) and TEA (0.63 g, 6.2 mmol) sequentially and the mixture is stirred at room temperature for 12 h. The reaction mixture is washed with water, dried and concentrated. The resulting residue is purified by column chromatography (ethyl acetate/heptane=1/5) to give (S)-5-biphenyl-4-yl-4-dibenzylamino-pentanoic acid methyl-((S)-1-phenyl-ethyl)-amide. ¹H NMR (CDCl₃): 1.40 (3H, d, CH₃), 1.74 (1H, m, 3-CHH), 1.90 (1H, m, 3-CHH), 2.50 (3H, s, CH₃), 2.60 (2H, m, 2-CH₂), 2.80 (2H, m, 5-CH₂), 3.20 (1H, dd, 4-CH), 3.57 (2H, d, CH₂), 3.89 (2H, d, CH₂), 6.02 (1H, q, CH), 7.10~7.50 (24H, m, aromatic).

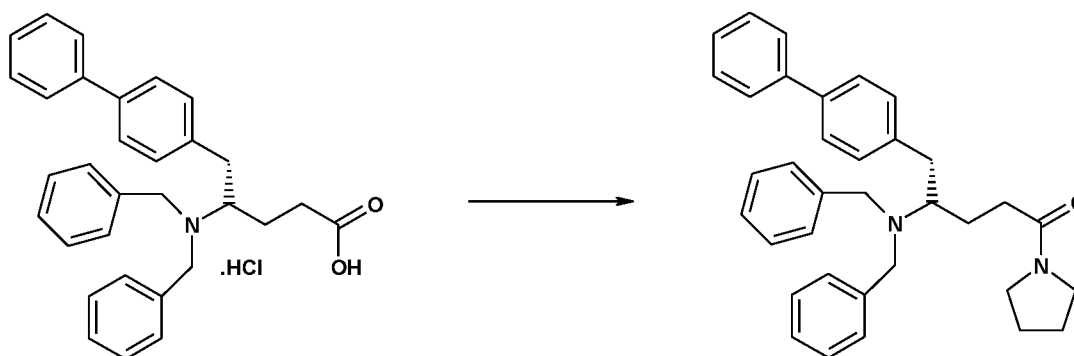
HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 11.1 min

Example 19: (S)- 5-Biphenyl-4-yl-4-dibenzylamino-pentanoic acid methyl-((R)-1-phenyl-ethyl)-amide



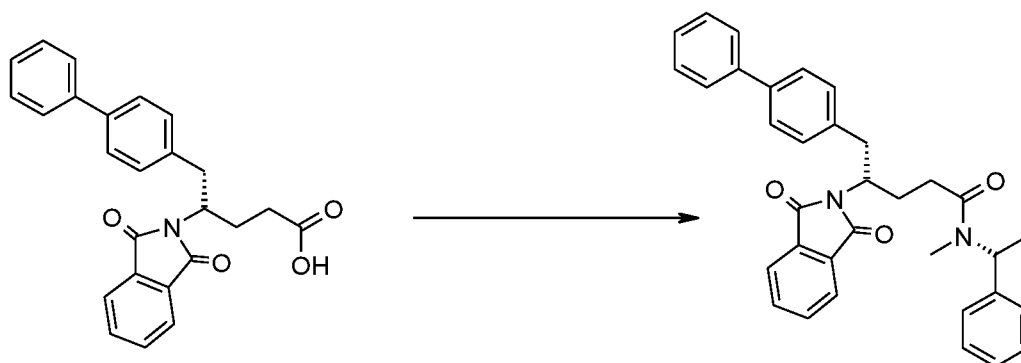
The suspension of (S)-5-biphenyl-4-yl-4-dibenzylamino-pentanoic acid hydrochloride (4.86 g
 5 10 mmol) in 10 mL of CH₂Cl₂ is (R)-methyl-(1-phenyl-ethyl)-amine (0.19 g, 1.36 mmol),
 EDC·HCl (0.29 g, 1.5 mmol), HOBt (0.21 g, 1.5 mmol) and TEA (0.63 g, 6.2 mmol) sequentially
 and the mixture is stirred at room temperature for 12 h. The reaction mixture is washed with
 water, dried and concentrated. The residue is purified by column chromatography (ethyl
 acetate/heptane = 1/5) to give (S)- 5-biphenyl-4-yl-4-dibenzylamino-pentanoic acid methyl-((S)-
 10 1-phenyl-ethyl)-amide. ¹H NMR (CDCl₃): 1.45 (3H, d, CH₃), 1.73 (1H, m, 3-CHH), 1.90 (1H, m,
 3-CHH), 2.51 (3H, s, CH₃), 2.63 (2H, m, 2- CH₂), 2.79 (2H, m, 5-CH₂), 3.20 (1H, dd, 4-CH),
 3.54 (2H, q, CH₂), 3.87 (2H, q, CH₂), 6.02 (1H, q, CH), 7.10~7.50 (24H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄)
 in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 %
 15 B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 11.0
 minz

Example 20: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-1-pyrrolidin-1-yl-pentan-1-one

To a solution of 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid hydrochloride (1.46 g, 3 mmol) in CH_2Cl_2 is added triethylamine (0.34 g, 3.3 mmol), followed by CDI (0.73 g, 4.5 mmol) and the mixture is stirred for 15 min at room temperature,. pyrrolidine (0.43 g, 6 mmol) is then added. After stirring for 30 min, the reaction mixture is diluted with water and the organic layer is dried and concentrated to give 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-pyrrolidin-1-yl-pentan-1-one. ^1H NMR (CDCl_3): 1.80 (2H, m, 3- CH_2), 1.88 (2H, m, CH_2), 1.98 (2H, m, CH_2), 2.53 (2H, m, 2- CH_2), 2.81 (2H, m, 5- CH_2), 3.20 (1H, dd, 4-CH), 3.26(2H, m, CH_2), 3.38 (2H, m, CH_2), 3.54 (2H, d, CH_2), 3.84 (2H, d, CH_2), 7.10~7.4 (19H, m, aromatic).

HPLC method: Column: Waters Xbridge-Phenyl; 150×3.0mm; 3.5 μm . Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (90 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 0.7 ml min^{-1} . Wavelength: 210 nm. Temperature: 30 $^\circ\text{C}$. Retention time: 11.2 min

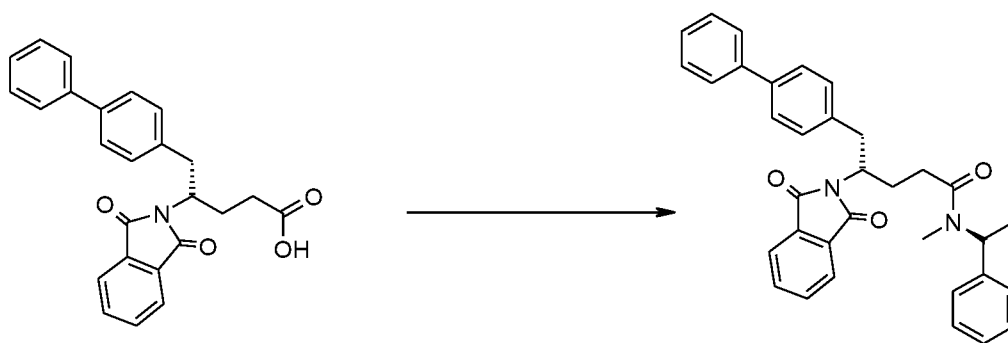
Example 21: (S)-5-Biphenyl-4-yl-4-(1,3-dihydro-isoindol-2-yl)-pentanoic acid methyl-(R-1-phenyl-ethyl)-amide

To a solution of (S)-5-biphenyl-4-yl-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid (4.0 g, 10 mmol) in 100 mL CH_2Cl_2 is added N-methyl-(R-1-phenyl-ethyl)amine (1.48g, 11mmol), EDC·HCl (2.3g, 12mmol), HOBt (1.62 g, 12 mmol) and TEA (5 g, 50 mmol) sequentially and the mixture is stirred at room temperature for 12 h. After that the mixture is washed with water,

dried and concentrated. The residue is purified by column chromatography (ethyl acetate/heptane = 1/2) to give (S)-5-biphenyl-4-yl-4-(1,3-dihydro-isoindol-2-yl)-pentanoic acid methyl-(R-1-phenyl-ethyl)-amide. ¹H NMR (CDCl₃): 1.39 (3H, d), 2.34 (3H, m), 2.51 (3H, s), 2.60 (1H, m), 3.24 (1H, m), 3.46 (1H, m), 4.65 (1H, m), 5.99 (1H, m), 7.20~7.80 (18H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1% H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml/min. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 9.9 min

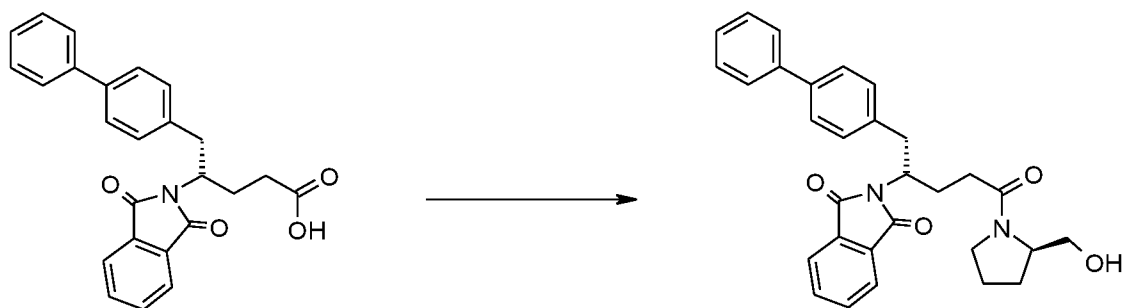
Example 22: (S)-5-Biphenyl-4-yl-4-(1,3-dihydro-isoindol-2-yl)-pentanoic acid methyl-(S-1-phenyl-ethyl)-amide



To a solution of (S)-5-biphenyl-4-yl-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid (4.0 g 10 mmol) in 100 mL of CH₂Cl₂ is added N-methyl-(S-1-phenyl-ethyl)amine (1.48 g, 11 mmol), EDC·HCl (2.3g, 12mmol), HOBT (1.62 g, 12 mmol) and TEA (5 g, 50 mmol) sequentially and the mixture is stirred at room temperature for 12 h. After that the mixture is washed with water, dried and concentrated. The residue is purified by column chromatography (ethyl acetate/heptane = 1/2) to give (S)-5-biphenyl-4-yl-4-(1,3-dihydro-isoindol-2-yl)-pentanoic acid methyl-(S-1-phenyl-ethyl)-amide. ¹H NMR (CDCl₃): 1.39 (3H, d), 2.34 (3H, m), 2.51 (3H, s), 2.60 (1H, m), 3.24 (1H, m), 3.46 (1H, m), 4.65 (1H, m), 5.99 (1H, m), 7.20~7.80 (18H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 9.9 min

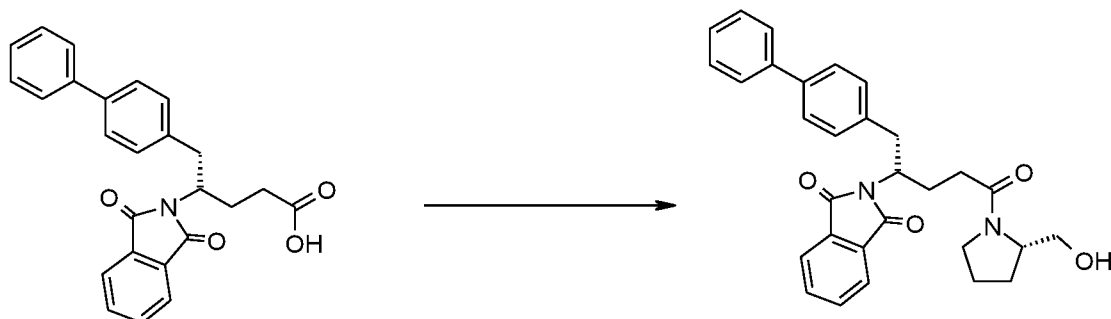
Example 23: 2-(S)-1-biphenyl-4-yl methyl-4(R)-2-hydroxymethyl-pyrrolidin-1-yl)-4-oxo-butyl)-isoindole-1,3-dione



To a solution of (S)-5-biphenyl-4-yl-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid (4.0 g, 10 mmol) in 100 mL of CH₂Cl₂ is added (R)-prolinol (1.12 g, 11 mmol), EDC·HCl (2.3 g, 12 mmol), HOBT (1.62 g, 12 mmol) and TEA (5 g, 50 mmol) sequentially and the mixture is stirred at room temperature for 12 h. After that the reaction mixture is washed with water, dried and concentrated. The residue is purified by column chromatography to give 2-(S)-1-biphenyl-4-yl methyl-4(R)-2-hydroxymethyl-pyrrolidin-1-yl-4-oxo-butyl-isoindole-1,3-dione. ¹H NMR (CDCl₃): 1.57 (1H, m), 1.78 (1H, m), 1.93 (2H, m), 2.24 (1H, m), 2.30 (2H, m), 2.57 (1H, m), 3.1-3.6 (5H, m), 3.72 (1H, m), 3.95 (1H, m), 4.60 (1H, m), 7.20~7.80 (13H, m, aromatic).

- 10 HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 7.6 min

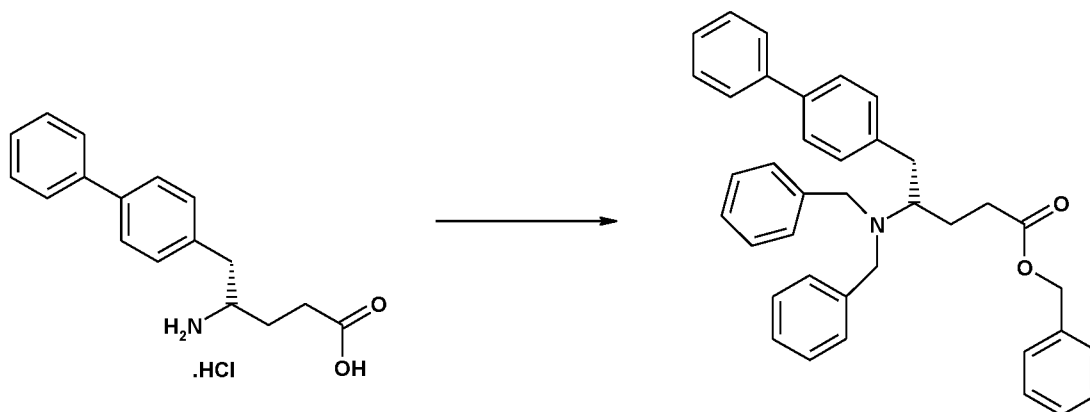
Example 24: 2-(S)-1-biphenyl-4-yl methyl-4(S)-2-hydroxymethyl-pyrrolidin-1-yl-4-oxo-butyl-isoindole-1,3-dione



To a solution of (S)-5-biphenyl-4-yl-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid (4.0 g, 10 mmol) in 100 mL of CH₂Cl₂ is added (S)-prolinol (1.12 g, 11 mmol), EDC·HCl (2.3 g, 12 mmol), HOBT (1.62 g, 12 mmol) and TEA (5 g, 50 mmol) sequentially and the mixture is stirred at room temperature for 12 h. The reaction mixture is then washed with water, dried and concentrated. The residue is purified by column chromatography to give 2-(S)-1-biphenyl-4-yl methyl-4(S)-2-hydroxymethyl-pyrrolidin-1-yl-4-oxo-butyl-isoindole-1,3-dione. ¹H NMR (CDCl₃): 1.53 (1H, m), 1.83 (2H, m), 1.98 (1H, m), 2.22 (1H, m), 2.32 (2H, m), 2.59 (1H, m), 3.22 (1H, dd), 3.30-3.50 (4H, m), 3.56 (1H, m), 4.13 (1H, m), 7.20~7.80 (13H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 7.5 min

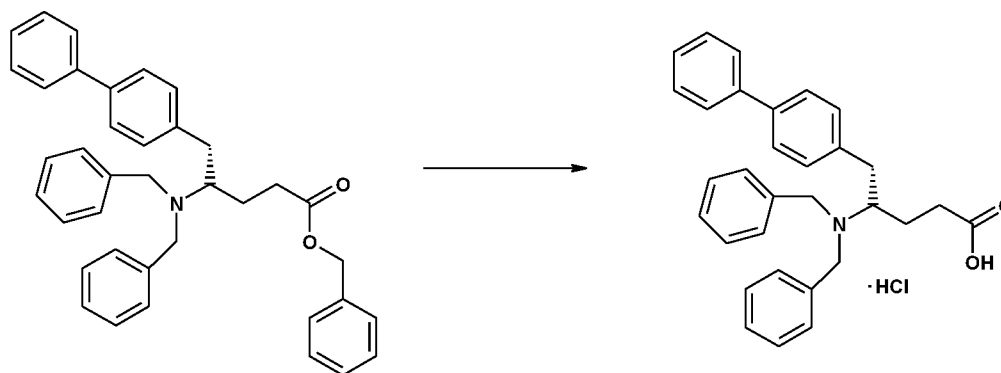
5 **Example 25: (S)-5-Biphenyl-4-yl-4-dibenzylamino-pentanoic acid benzyl ester**



To a suspension of (S)-4-amino-5-biphenyl-4-yl-pentanoic acid hydrochloride (10g, 32.7mmol) in 200 mL water is added benzylbromide (22.4g, 130.8mmol), K₂CO₃ (18.1g, 130.8mmol) and NaOH (3.9g, 98mmol) and the mixture is heated to refluxed for 4 h. Then concentrated HCl is added and the pH is adjusted to 4-5, extracted with ethyl acetate, and the organic layer is washed with water, dried and concentrated to give (S)-5-biphenyl-4-yl-4-dibenzylamino-pentanoic acid benzyl ester. ¹H NMR (CDCl₃): 1.70 (1H, m, 3-CHH), 1.90 (1H, m, 3-CHH), 2.20 (1H, m, 2-CHH), 2.46 (1H, m, 5-CHH), 2.63 (1H, m, 2-CHH), 2.83 (1H, m, 5-CHH), 3.18 (1H, dd, 4-CH), 3.52 (2H, d, CH₂), 3.85 (2H, d, CH₂), 4.98 (2H, s, CH₂), 7.10~7.50 (24H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 12.7 min

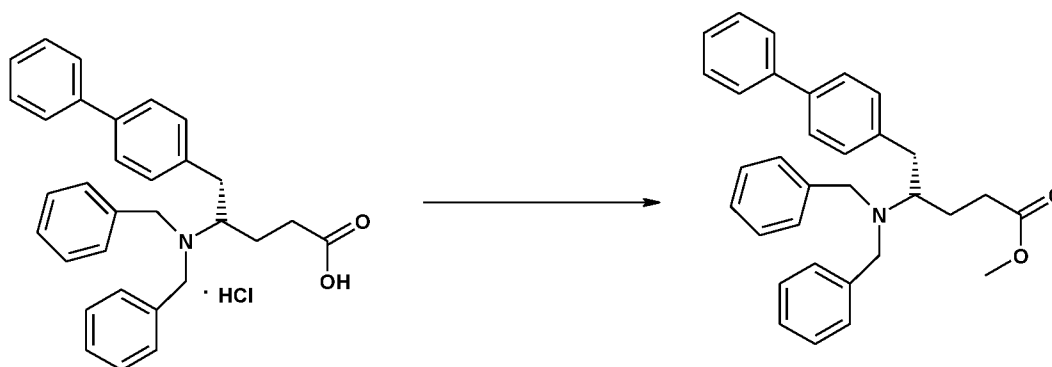
Example 26: (S)-5-Biphenyl-4-yl-4-dibenzylamino-pentanoic acid hydrochloride



To a suspension of (S)-5-biphenyl-4-yl-4-dibenzylamino-pentanoic acid benzyl ester (14.5g, 32.3mmol) in water is added 3.9 g of NaOH, the mixture is refluxed for 3 h, after being cooled to room temperature, the mixture is extracted with heptane, and the aqueous layer is treated with concentrated HCl to adjust pH to 4-5, then the mixture is extracted with ethyl acetate, and the organic layer is washed with water, dried and concentrated. The resulting residue is treated with HCl in ethyl acetate, the solid formed is filtered and dried to give (S)-5-biphenyl-4-yl-4-dibenzylamino-pentanoic acid hydrochloride. ¹H NMR (DMSO-d₆): 1.75 (1H, m, 3-CHH), 1.92 (1H, m, 3-CHH), 2.21 (1H, m, 2-CHH), 2.47 (1H, m, 5-CHH), 2.65 (1H, m, 2-CHH), 2.84 (1H, m, 5-CHH), 3.20 (1H, dd, 4-CH), 3.54 (2H, d, CH₂), 3.86 (2H, d, CH₂), 7.10~7.50 (19H, m, aromatic), 10.8 (1H, s, COOH).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B); 8 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 10.4 min

Example 27: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid methyl ester

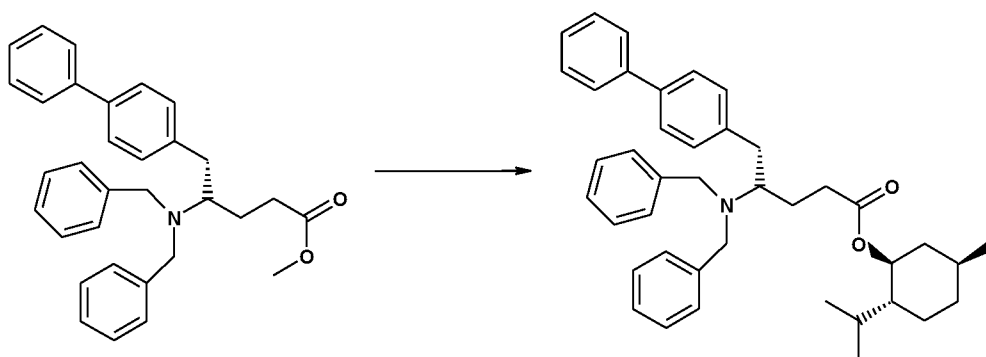


To the mixture of 4.9 g of 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid hydrochloride in 50 mL MeOH is added concentrated H₂SO₄ (0.1 mL). The reaction mixture is heated to reflux for 12 h. After removal of MeOH, the residue is dissolved in 50 mL ethyl acetate, washed with NaHCO₃, water, and dried. The solvent is removed and 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid methyl ester is obtained. ¹H NMR (CDCl₃): 1.65 (1H, m, 3-CHH), 1.87 (1H, m,

3-CHH), 2.13 (1H, m, 2-CH₂), 2.46 (1H, m, 2-CH₂), 2.60 (1H, m, 5-CH₂), 2.81 (1H, m, 5-CH₂), 3.19 (1H, dd, 4-CH), 3.52 (2H, d, CH₂), 3.55 (3H, s, OCH₃), 3.86 (2H, d, CH₂), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (90 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 0.7 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 13.9 min

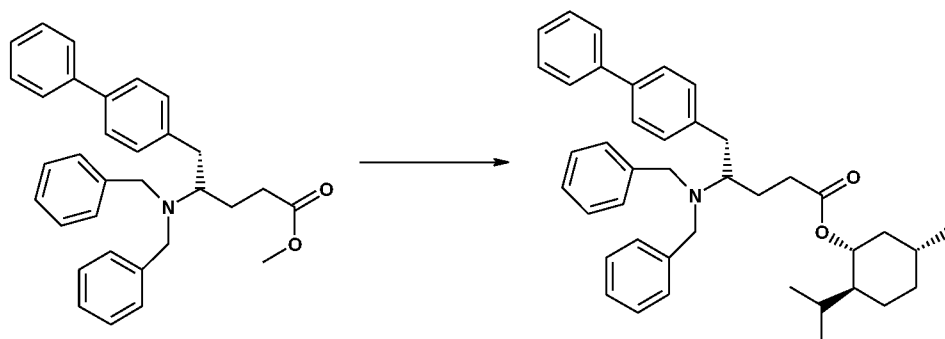
Example 28: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid L-menthyl ester



Under N₂ atmosphere, n-BuLi (1.6 M, 0.9 mL, 1.44 mmol) is added to the solution of L-menthol in 10 mL dry THF. 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid methyl ester in 5 mL THF is then added, the mixture is stirred for 2h at room temperature. The reaction mixture is diluted with saturated ammonium chloride aqueous solution, extracted with ethyl acetate. The organic extracts are combined and concentrated, the resulting residue is purified by column chromatography (ethyl acetate/heptane = 1/15) to give 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid L-menthyl ester. ¹H NMR (CDCl₃): 0.67 (3H, d, CH₃), 0.79 (3H, d, CH₃), 0.86 (3H, d, CH₃), 1.26 (4H, m, CH₂-CH₂), 1.56 (2H, m, CH₂), 1.60 (1H, m, CH), 1.71 (1H, m, CH), 1.73 (1H, m, 3-CHH), 1.87 (1H, m, 3-CHH), 2.14 (1H, m, 2-CHH), 2.47 (1H, m, 2-CHH), 2.59 (1H, m, 5-CHH), 2.78 (1H, m, 5-CHH), 3.17 (1H, dd, 4-CH), 3.54 (2H, d, CH₂), 3.87 (2H, d, CH₂), 4.56 (3H, m, OCH), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (60 % B); 30 min (95 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 210 nm. Temperature: 35 °C. Retention time: 27.3 min

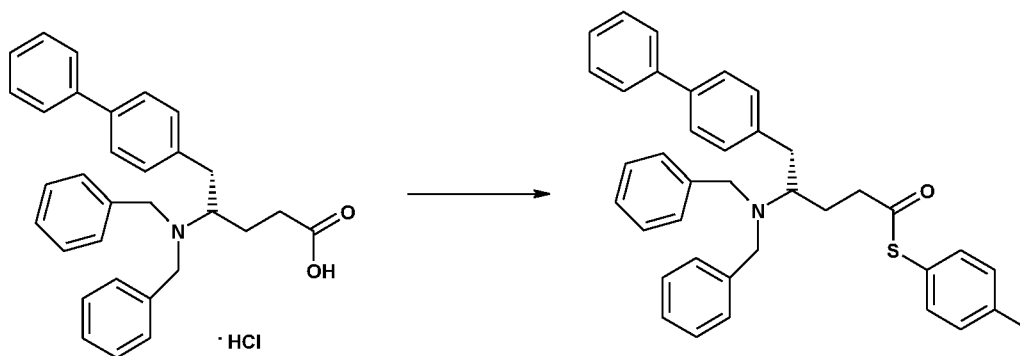
Example 29: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid D-menthyl ester



Under N₂ atmosphere, n-BuLi (1.6 M, 0.9 mL, 1.44 mmol) is added to the mixture of D-menthol in 10 mL dry THF. 5-Biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid methyl ester in 5mL THF is then added, the mixture is stirred for 2h at room temperature. The reaction mixture is diluted with saturated ammonium chloride aqueous solution, extracted with ethyl acetate. The organic extracts are combined and concentrated, the resulting residue is purified by column chromatography (ethyl acetate/heptane = 1/15) to give 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid L-menthyl ester. ¹H NMR (CDCl₃): 0.71 (3H, d, CH₃), 0.87 (6H, d, CH₃), 1.26 (4H, m, CH₂-CH₂), 1.55 (2H, m, CH₂), 1.64 (1H, m, CH), 1.78 (1H, m, CH), 1.88 (2H, m, 3-CH₂), 2.04 (1H, m, 2-CHH), 2.46 (1H, m, 2-CHH), 2.62 (1H, m, 5-CHH), 2.80 (1H, m, 5-CHH), 3.16 (1H, dd, 4-CH), 3.55 (2H, d, CH₂), 3.85 (2H, d, CH₂), 4.60 (3H, m, OCH), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (60 % B); 30 min (95 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 210 nm. Temperature: 35 °C. Retention time: 22.9 min

Example 30: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid S-p-tolyl ester

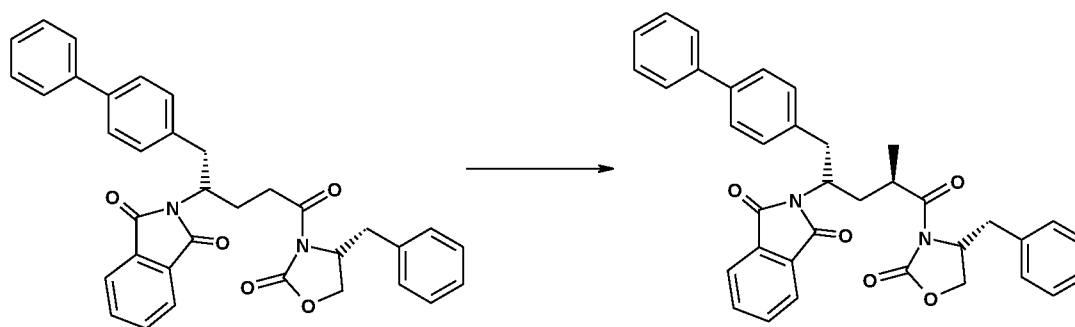


To a solution of 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid hydrochloride (1.46 g, 3mmol) in CH₂Cl₂ is added triethylamine (0.34g, 3.3mmol) followed by CDI (0.73 g, 4.5mmol). The reaction mixture is stirred for 15min at room temperature, 4-methyl-benzenethiol (0.74 g, 6 mmol) is then added. After 30min, the reaction mixture is washed with water and concentrated, the resulting residue is purified by column chromatography (ethyl acetate/heptane = 1/25) to

give 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid S-p-tolyl ester. ^1H NMR (CDCl_3): 1.72 (1H, m, 3-CHH), 1.95 (1H, m, 3-CHH), 2.34 (3H, s, CH_3), 2.43 (2H, m, 2- CH_2), 2.79 (1H, m, 5- CH_2), 2.95 (1H, m, 5- CH_2), 3.17 (1H, dd, 4-CH), 3.52 (2H, d, CH_2), 3.86 (2H, d, CH_2), 7.10~7.40 (23H, m, aromatic).

5 HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm . Mobile Phase A (0.1 % H_3PO_4) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (90 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 0.7 ml min^{-1} . Wavelength: 210 nm. Temperature: 30 $^\circ\text{C}$. Retention time: 14.8 min

10 **Example 31: 2-[(1S,3R)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione**



Method 1:

To a -78 $^\circ\text{C}$ solution of NaHMDS (6.5mL, 6.5 mmol) in 20 mL of anhydrous THF is added 2-[(S)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione (3.00 g, 5.38 mmol) in dry THF. The reaction mixture is stirred for 1 h, then iodomethane (3.82 g, 26.90 mmol) is added to the reaction mixture. After 12 h, the reaction mixture is allowed to warm to room temperature, saturated NH_4Cl (25 ml) is added, the mixture is extracted with TBME. The combined organic extracts are washed with brine, dried and concentrated, the residue is crystallized from TBME and heptane to afford 2-[(1S,3R)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione, diastereomeric ratio (2R, 4S) : (2S, 4S) = 97 : 3 as determined by HPLC. This material can be recrystallized from TBME and heptane to give (2R, 4S) : (2S, 4S) >99:1 as determined by HPLC. ^1H NMR (CDCl_3): 1.35 (3H, d), 2.28 (1H, m), 2.25 (1H, m), 2.67 (1H, m), 2.95 (2H, m), 3.27 (2H, m), 3.50 (1H, m), 4.15 (1H, m), 4.23 (1H, m), 7.15 ~7.80 (18H, m, aromatic). MS (ESI, m/e) 573 (MH^+).

2-[(1S,3R)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione is a crystalline solid and can be characterised by X-ray powder patterns. The most intensive reflections in the X-ray diffraction pattern show the following interlattice plane

intervals (average 2θ in $^{\circ}$) are indicated with error limit of ± 0.2): 2θ in $^{\circ}$: 7.5, 9.5, 10.9, 16.9, 19.1, 21.4, 22.9, 24.9, 26.2, 27.6, 29.6, 30.9. Data taken using a Bruker D8 Advance diffractometer using Cu-K α radiation.

Method 2:

- 5 To a -60 $^{\circ}$ C solution of NaHMDS (2.1 mL, 2.1 mmol) in 5 mL of anhydrous THF is added 2-[(S)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione (1 g, 1.8 mmol) in dry THF. The reaction mixture is stirred for 1 h, then iodomethane (1.2 g, 8.5 mmol) is added to the reaction mixture. After 12 h, the reaction mixture is allowed to warm to room temperature, saturated NH_4Cl (10 mL) is added, the mixture is extracted with TBME. The
- 10 combined organic extracts are washed with brine, dried and concentrated, the residue is crystallized from TBME and heptane to afford 2-[(1S,3R)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione, diastereomeric ratio (2R, 4S) : (2S, 4S) = 95 : 5 as determined by HPLC.

Method 3:

- 15 To a -40 $^{\circ}$ C solution of NaHMDS (2.1 mL, 2.1 mmol) in 5 mL of anhydrous THF is added 2-[(S)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione (1 g, 1.8 mmol) in dry THF. The reaction mixture is stirred for 1 h, then iodomethane (1.2 g, 8.5 mmol) is added to the reaction mixture. After 12 h, the reaction mixture is allowed to warm to room temperature, saturated NH_4Cl (10 mL) is added, the mixture is extracted with TBME. The
- 20 combined organic extracts are washed with brine, dried and concentrated, the residue is crystallized from TBME and heptane to afford 2-[(1S,3R)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione, diastereomeric ratio (2R, 4S) : (2S, 4S) = 94 : 6 as determined by HPLC.

Method 4:

- 25 To a -10 $^{\circ}$ C solution of NaHMDS (2.1 mL, 2.1 mmol) in 5 mL of anhydrous THF is added 2-[(S)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione (1 g, 1.8 mmol) in dry THF. The reaction mixture is stirred for 1 h, then iodomethane (1.2 g, 8.5 mmol) is added to the reaction mixture. After 12 h, the reaction mixture is allowed to warm to room temperature, saturated NH_4Cl (10 mL) is added, the mixture is extracted with TBME. The
- 30 combined organic extracts are washed with brine, dried and concentrated, the residue is crystallized from TBME and heptane to afford 2-[(1S,3R)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione, diastereomeric ratio (2R, 4S) : (2S, 4S) = 90 : 10 as determined by HPLC.

Method 5:

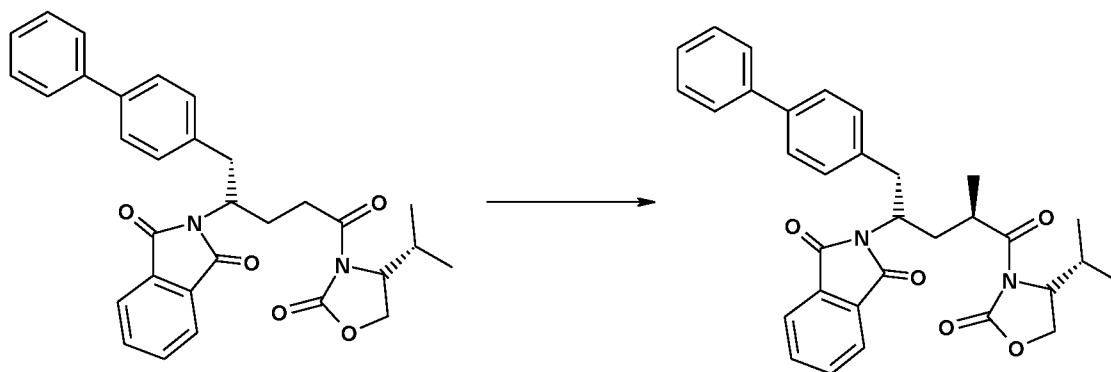
To a -78 °C solution of NaHMDS (2.1mL, 2.1 mmol) in 5 mL of anhydrous toluene is added 2-[(S)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione (1 g, 1.8 mmol) in dry THF. The reaction mixture is stirred for 1 h, then iodomethane (1.2 g, 8.5 mmol) is added to the reaction mixture. After 12 h, the reaction mixture is allowed to warm to room temperature, saturated NH₄Cl (10 ml) is added, the mixture is extracted with TBME. The combined organic extracts are washed with brine, dried and concentrated, the residue is crystallized from TBME and heptane to afford 2-[(1S,3R)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione, diastereomeric ratio (2R, 4S) : (2S, 4S) = 77 : 23 as determined by HPLC.

10 **Method 6:**

To a -78 °C solution of KHMDS (2.1mL, 2.1 mmol) in 5 mL of anhydrous THF is added 2-[(S)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione (1 g, 1.8 mmol) in dry THF. The reaction mixture is stirred for 1 h, then iodomethane (1.2 g, 8.5 mmol) is added to the reaction mixture. After 12 h, the reaction mixture is allowed to warm to room temperature, saturated NH₄Cl (10 ml) is added, the mixture is extracted with TBME. The combined organic extracts are washed with brine, dried and concentrated, the residue is crystallized from TBME and heptane to afford 2-[(1S,3R)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione, diastereomeric ratio (2R, 4S) : (2S, 4S) = 41 : 59 as determined by HPLC.

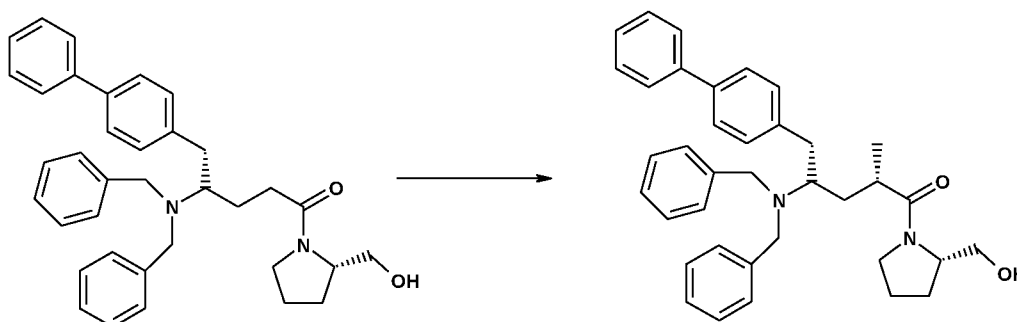
20 HPLC method : Column: Phenomenex Gemini C18; 150 × 3.0 mm; 3.0 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (30 % B) 30 min (95 % B); 35 min (95 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 210 or 254 nm. Temperature: 30 °C. Retention times: SM 25.0 min, (2S, 4S) 26.1 min, (2R, 4S) 26.9 min

Example 32: 2-[(S)-4-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione



- To a -78 °C solution of NaHMDS (6.5mL, 6.5 mmol) in 20 mL of anhydrous THF is added 2-[(S)-4-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione (2.74 g, 5.38 mmol) in dry THF. The reaction mixture is stirred for 1 h, then iodomethane (3.82 g, 26.90 mmol) is added to the reaction mixture. After 12h, the reaction mixture is allowed to warm to room temperature, saturated NH₄Cl (25 ml) is added, the mixture is extracted with TBME. The combined organic extracts are washed with brine, dried and concentrated to give 2-[(S)-4-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione, diastereomeric ratio (2R, 4S):(2S, 4S) = 99.6:0.4 is determined by HPLC. ¹H NMR (CDCl₃): 0.9(6H, d), 1.2 (3H, d), 2.31 (3H, m), 3.12 (1H, m), 3.45 (1H, m), 3.75 (1H, m), 4.17 (1H, m), 4.41 (1H, m), 4.47 (1H, m), 4.54 (1H, m), 7.15 ~7.70 (13H, m, aromatic). MS (ESI, m/e) 400 (MH⁺).
- HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (10 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 1.0 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention times: 10.5 min

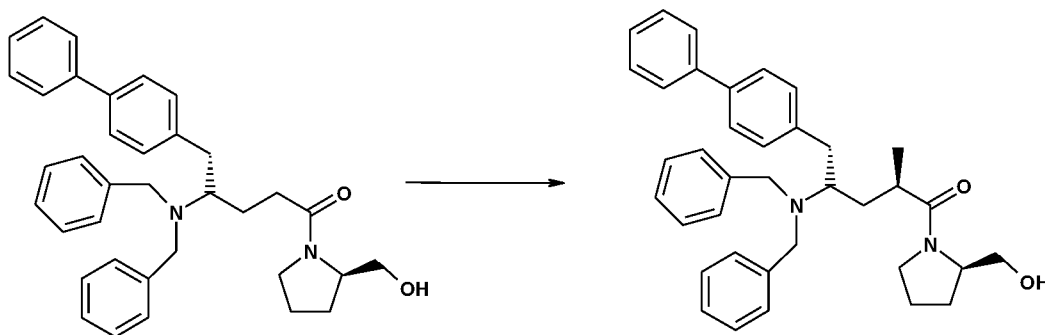
Example 33: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-1-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-(S)-2-methyl-pentan-1-one



Under N₂ atmosphere, 2.5 mL of LDA (1.0 M in THF) is added to the mixture of 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-pentan-1-one (0.53 g, 1 mmol) in 15 mL dry THF at -70 °C. The mixture is stirred for another 1 h, MeI (0.2 g, 1.4 mmol) is then added. The resulting mixture is warmed slowly to room temperature and stirred for 3 h, saturated ammonium chloride solution is added, the aqueous layer is extracted with ethyl acetate and concentrated to obtain 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-(S)-2-methyl-pentan-1-one. The ratio of diastereomers by HPLC analysis: (2R, 4S):(2S, 4S) = 23:77. ¹H NMR (CDCl₃): 1.04 (3H, d, CH₃), 1.48 (1H, m, 3-CHH), 1.80 (4H, m, CH₂CH₂), 1.90 (1H, m, 3-CHH), 2.45 (1H, m, 5-CHH), 2.60 (1H, m, 5-CHH), 2.96 (1H, m, 2-CHH), 3.08 (1H, m, 4-CH), 3.20 (2H, m, CH₂), 3.62 (2H, m, CH₂), 3.57 (2H, m, CH₂), 3.86 (2H, d, CH₂), 4.05 (1H, m, CH), 5.07 (1H, d, OH), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (55 % B); 30 min (55 % B); 30.1 min (95 % B); 35 min (95 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 210 nm. Temperature: 35 °C. Retention time: (2R, 4S): 22.6 min; (2S, 4S): 20.0 min

Example 34: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-1-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-(R)-2-methyl-pentan-1-one

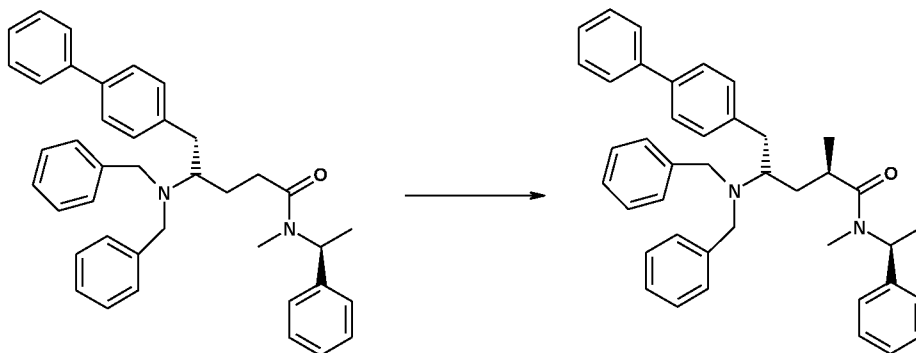


Under N₂ atmosphere, 2.5 mL of LDA (1.0 M in THF) is added to the mixture of 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-pentan-1-one (0.53 g, 1 mmol) in 15 mL dry THF at -70 °C. The mixture is stirred for another 1 h, MeI (0.2 g, 1.4 mmol) is then added. The resulting mixture is warmed slowly to room temperature and stirred for 3 h, saturated ammonium chloride solution is added, the aqueous layer is extracted with ethyl acetate and concentrated to obtain 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-(R)-2-methyl-pentan-1-one. The ratio of diastereomers by HPLC analysis: (2R, 4S):(2S, 4S) = 84:16. ¹H NMR (CDCl₃): 0.99 (3H, d, CH₃), 1.42 (1H, m, 3-CHH), 1.70 (4H, m, CH₂CH₂), 1.91 (2H, m, 3-CH₂), 2.50 (1H, m, 5-CHH), 2.60 (1H, m, 2-CHH), 2.92 (1H, m, 4-CH), 3.00 (2H, m, CH₂), 3.28 (2H, m, CH₂), 3.60 (2H, m, CH₂), 3.71 (2H, d, CH₂), 4.11 (1H, m, CH), 5.12 (1H, d, OH), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (50 % B); 20 min (50 % B); 30 min (60 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 210 nm. Temperature: 50 °C. Retention time: (2R, 4S): 30.1 min; (2S, 4S): 30.8 min

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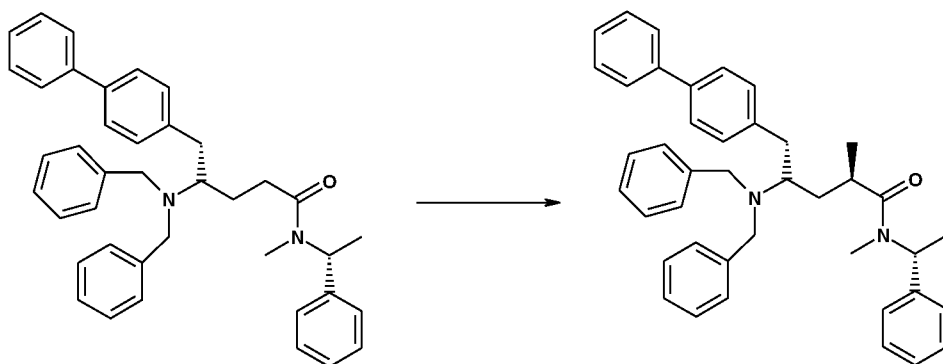
Example 35: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid (S)-methyl-(1-phenyl-ethyl)-amide



Under N₂ atmosphere, 2.5 mL of LDA (1.0 M in THF) is added to the mixture of 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-pentan-1-one (0.53 g, 1 mmol) in 15 mL dry THF at -70 °C. The mixture is stirred for another 1 h, MeI (0.2 g, 1.4 mmol) is then added. The resulting mixture is warmed slowly to room temperature and stirred for 3 h, saturated ammonium chloride solution is added, the aqueous layer is extracted with ethyl acetate and concentrated to obtain 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid (S)-methyl-(1-phenyl-ethyl)-amide. The ratio of diastereomers by HPLC analysis: (2R,4S): (2S, 4S) = 63:37. ¹H NMR (CDCl₃): 1.00 (3H, d, CH₃), 1.38 (3H, d, CH₃), 1.87 (2H, m, 3-CH₂), 2.30 (3H, s, CH₃), 2.60 (1H, m, 2-CH₂), 2.98 (2H, m, 5-CH₂), 3.55 (1H, dd, 4-CH), 3.58 (2H, d, CH₂), 3.70 (2H, d, CH₂), 6.00 (1H, m, CH), 7.10~7.50 (24H, m, aromatic).

HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (65 % B); 30 min (65 % B); 30.1 min (95 % B), 35 min (95 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 210 nm. Temperature: 35 °C. Retention time: (2R, 4S): 20.4 min; (2S, 4S): 19.3 min

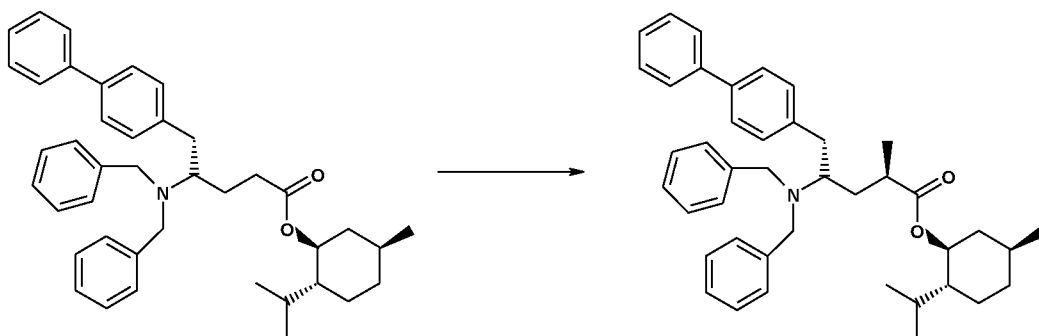
Example 36: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid (R)-methyl-(1-phenyl-ethyl)-amide



Under N₂ atmosphere, 2.5 mL of LDA (1.0 M in THF) is added to the mixture of 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-pentan-1-one (0.53 g, 1 mmol) in 15 mL dry THF at -70 °C. The mixture is stirred for another 1 h, MeI (0.2 g, 1.4 mmol) is then added. The resulting mixture is warmed slowly to room temperature and stirred for 3 h, saturated ammonium chloride solution is added, the aqueous layer is extracted with ethyl acetate and concentrated to obtain 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid (R)-methyl-(1-phenyl-ethyl)-amide. The ratio of diastereomers by HPLC analysis: (2R,4S): (2S, 4S) = 75: 25. ¹H NMR (CDCl₃): 1.03 (3H, d, CH₃), 1.37 (3H, d, CH₃), 1.82 (1H, m, 3-CHH), 1.92 (1H, m, 3-CHH), 2.41 (3H, s, CH₃), 2.63 (1H, m, 2-CH₂), 2.99 (2H, m, 5-CH₂), 3.57 (1H, m, 4-CH), 3.59 (2H, m, CH₂), 3.70 (2H, d, CH₂), 6.00 (1H, m, CH), 7.10~7.50 (24H, m, aromatic).

HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (60 % B); 40 min (60 % B); 40.1 min (95 % B), 45 min (95 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 210 nm. Temperature: 35 °C. Retention time: (2R, 4S) : 33.4 min; (2S, 4S): 34.6 min

Example 37: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methylpentanoic acid L-menthyl ester

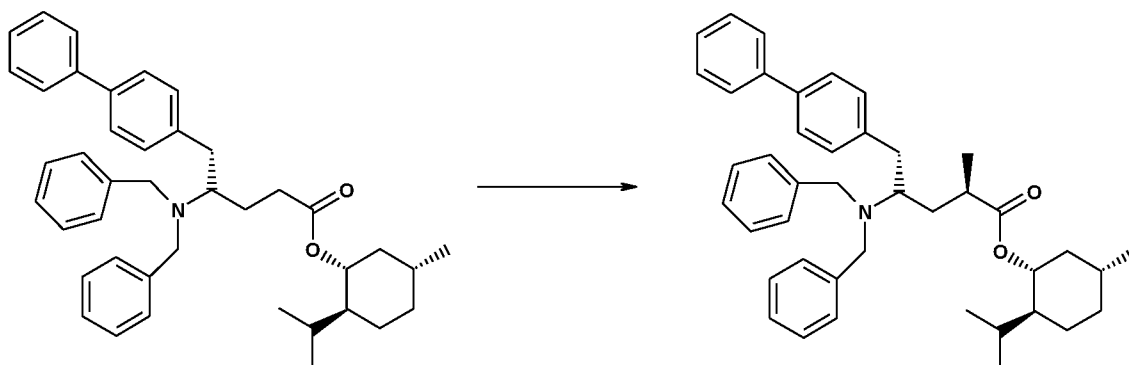


Under N₂ atmosphere, LDA (1.0 M in THF, 0.6 mL) is added to the mixture of 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid L-menthyl ester (0.3g, 0.5mmol) in 15 mL dry THF at -70 °C. After 1h, MeI (0.04 mL, 0.6mmol) is added and the reaction mixture is warmed slowly to room temperature and stirred for 3h. The mixture is diluted with saturated ammonium chloride

aqueous solution, then extracted with ethyl acetate. The organic extracts are combined and concentrated to obtain 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methylpentanoic acid L-menthyl ester. According to HPLC analysis, the ratio of diastereomers (2R,4S): (2S, 4S) is 57: 43. ¹H NMR (CDCl₃): 0.68 (3H, d, CH₃), 0.99 (3H, d, CH₃), 0.80 (3H, d, CH₃), 0.85 (3H, d, CH₃), 1.27 (4H, m, CH₂-CH₂), 1.55 (2H, m, CH₂), 1.62 (1H, m, CH), 1.73 (1H, m, CH), 1.75 (1H, m, 3-CHH), 1.86 (1H, m, 3-CHH), 2.15 (1H, m, 2-CH), 2.60 (1H, m, 5-CHH), 2.79 (1H, m, 5-CHH), 3.18 (1H, dd, 4-CH), 3.56 (2H, d, CH₂), 3.85 (2H, d, CH₂), 4.57 (3H, m, OCH), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (60 % B); 30 min (95 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 210 nm. Temperature: 35 °C. Retention time: (2R, 4S): 32.1 min; (2S, 4S): 31.7 min

Example 38: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methylpentanoic acid D-menthyl ester

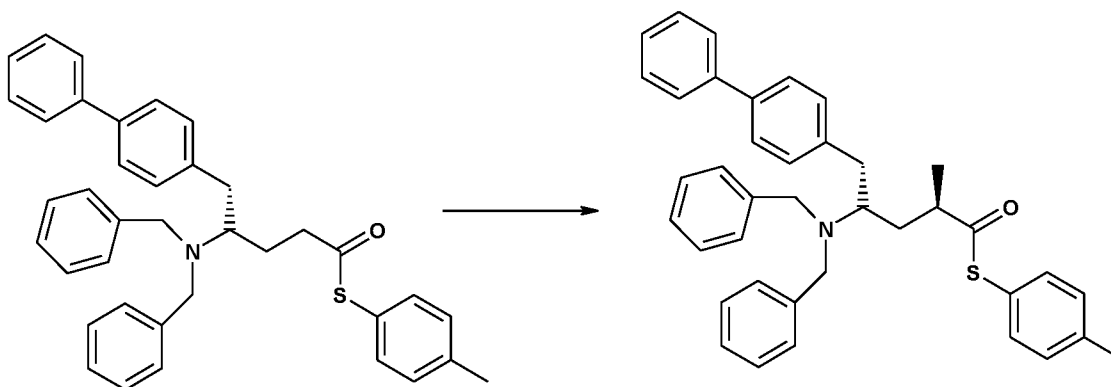


Under N₂ atmosphere, LDA (1.0 M in THF, 0.6 mL) is added to the mixture of 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid D-menthyl ester (0.3 g, 0.5 mmol) in 15 mL dry THF at -70 °C. After 1h, MeI (0.04 mL, 0.6mmol) is added and the reaction mixture is warmed slowly to room temperature and stirred for 3 h. The mixture is diluted with saturated ammonium chloride aqueous solution, extracted with ethyl acetate. The organic extracts are combined and concentrated to give 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methylpentanoic acid D-menthyl ester. According to HPLC analysis, the ratio of diastereomers (2R,4S): (2S, 4S) is 64: 36. ¹H NMR (CDCl₃): 0.70(3H, d, CH₃), 0.85(6H, d, CH₃), 0.98(3H, d, CH₃), 1.25(4H, m, CH₂-CH₂), 1.56(2H, m, CH₂), 1.65(1H, m, CH), 1.79(1H, m, CH), 1.89(2H, m, 3-CH₂), 2.08(1H, m, 2-CH), 2.63 (1H, m, 5-CHH), 2.79(1H, m, 5-CHH), 3.17(1H, dd, 4-CH), 3.57(2H, d, CH₂), 3.86 (2H, d, CH₂), 4.62(3H, m, OCH), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (60 % B); 30 min (95 % B). Flow

rate: 0.5 ml min⁻¹. Wavelength: 210 nm. Temperature: 35 °C. Retention time: (2R, 4S): 23.4 min; (2S, 4S): 23.8 min

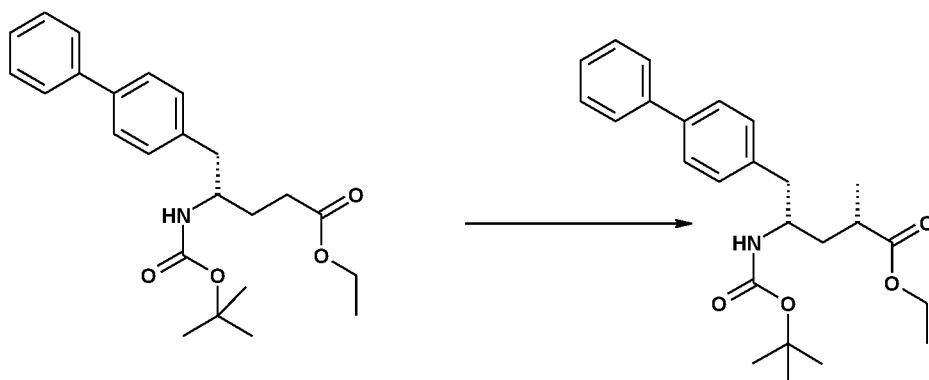
Example 39: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methylpentanoic acid S-p-tolyl ester



Under N₂ atmosphere, LDA (1.0 M in THF, 2.8 mL) is added to the mixture of 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid S-p-tolyl ester (1.11g, 2mmol) in 20 mL dry THF at -70 °C. After 1h, MeI (0.19 mL, 3 mmol) is added and the mixture is warmed slowly to room temperature and stirred for 3h. The mixture is diluted with ammonium chloride solution, extracted with ethyl acetate. The organic extracts are combined and concentrated to give 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methylpentanoic acid S-p-tolyl ester. According to HPLC analysis, the ratio of diastereomers (2R,4S): (2S, 4S) is 66: 34. ¹H NMR (CDCl₃): 1.13(3H, d, CH₃), 1.68 (1H, m, 3-CHH), 1.87 (1H, m, 3-CHH), 2.34 (3H, s, CH₃), 2.54 (1H, m, 2-CH₂), 2.91 (1H, m, 5-CH₂), 3.07 (1H, m, 5-CH₂), 3.19 (1H, dd, 4-CH), 3.52 (2H, d, CH₂), 3.86 (2H, d, CH₂), 7.10~7.40 (23H, m, aromatic).

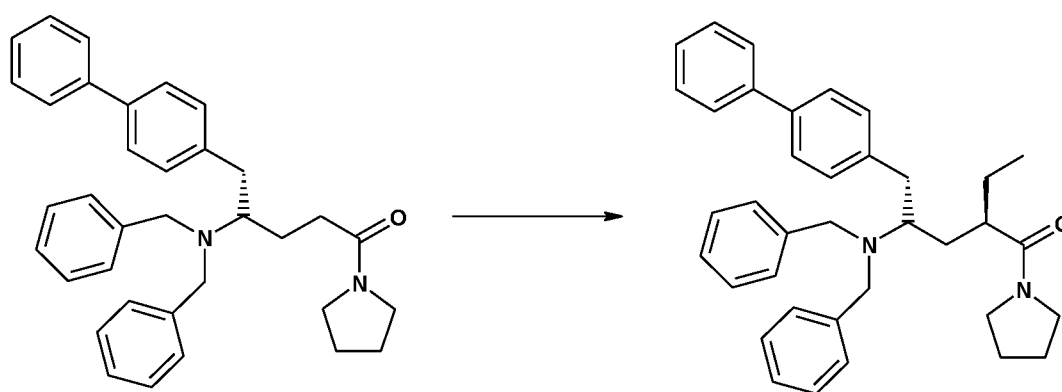
HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (60 % B); 30 min (95 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 210 nm. Temperature: 35 °C. Retention time: (2R, 4S): 20.1 min; (2S, 4S): 20.5 min

Example 40: (2S,4S)-5-Biphenyl-4-yl-4-tert-butoxycarbonylamino-2-methyl-pentanoic acid ethyl ester



(S)-5-biphenyl-4-yl-4-tert-butoxycarbonylamino-pentanoic acid ethyl ester (2 g) is added to tetrahydrofuran (18 ml) at room temperature. The resulting mixture is then cooled to -78 °C. Lithium bis(trimethylsilyl)amide (13.1 ml, 1 M solution in tetrahydrofuran) is added. The mixture is then stirred for 45 min at -78 °C. Methyl iodide (1.56 ml) is then added and the mixture stirred at -78 °C for 2 h. 1 N aqueous hydrochloric acid (20 ml) and ethyl acetate (10 ml) are added. The phases are separated and the organic layer washed with 1 N aqueous hydrochloric acid (10 ml) and then with brine (20 ml). The organic phase is then dried over magnesium sulfate and concentrated under reduced pressure to afford (2S,4S)-5-biphenyl-4-yl-4-tert-butoxycarbonylamino-2-methyl-pentanoic acid ethyl ester. ¹H NMR (CDCl₃): 0.98 (3H), 1.09 (3H), 1.23 (9H), 1.38-1.43 (1H), 1.58-1.66 (1H), 2.31-2.36 (1H), 2.59-2.70 (2H), 3.76 (1H), 3.97 (2H), 4.19 (1H), 7.10 (2H), 7.17 (1H), 7.27 (2H), 7.37 (2H), 7.41 (2H).

Example 41: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-ethyl-1-pyrrolidin-1-yl-pentan-1-one

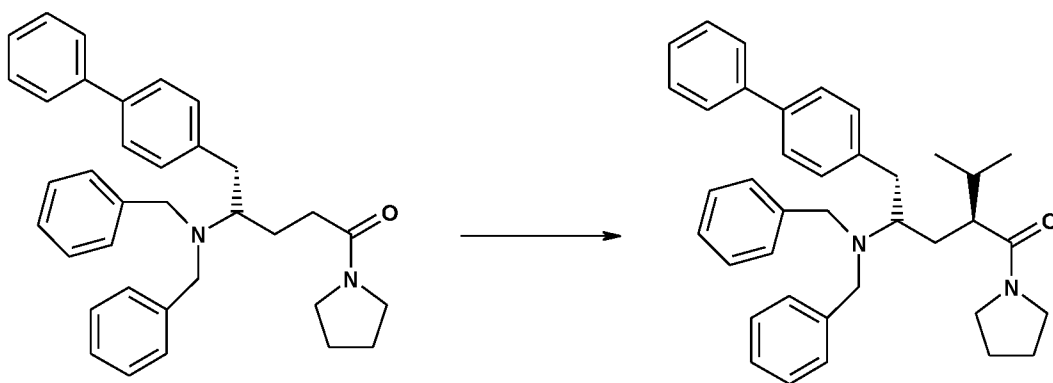


Under N₂ atmosphere, LDA (1.0 M in THF, 2.8 mL) is added to the solution of 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-pyrrolidin-1-yl-pentan-1-one (1.0 g, 2 mmol) in 20 mL dry THF at -70 °C. After 1 h iodoethane (0.45g, 3mmol) is added at -70 °C, and the reaction mixture is warmed slowly to room temperature. After 3 h at room temperature, the mixture is diluted with sodium chloride solution, extracted with ethyl acetate and concentrated to dryness to obtain 5-biphenyl-

4-yl-(S)-4-dibenzylamino-(R)-2-ethyl -1-pyrrolidin-1-yl-pentan-1-one. According to HPLC analysis, the ratio of diastereomers (2R, 4S): (2S, 4S) is 79: 21. ¹H NMR (CDCl₃): 0.77 (3H, m), 1.40-2.00 (8H, m), 2.39 (1H, m), 2.61 (1H, m), 3.04 (2H, m), 3.35 (4H, m), 3.7-3.9 (4H, m), 7.10~7.4 (19H, m, aromatic).

- 5 HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (60 % B); 30 min (95% B). Flow rate: 0.5 ml min⁻¹ . Wavelength: 210 nm. Temperature: 35 °C. Retention time: (2R, 4S) : 12.6 min; (2S, 4S): 12.2 min

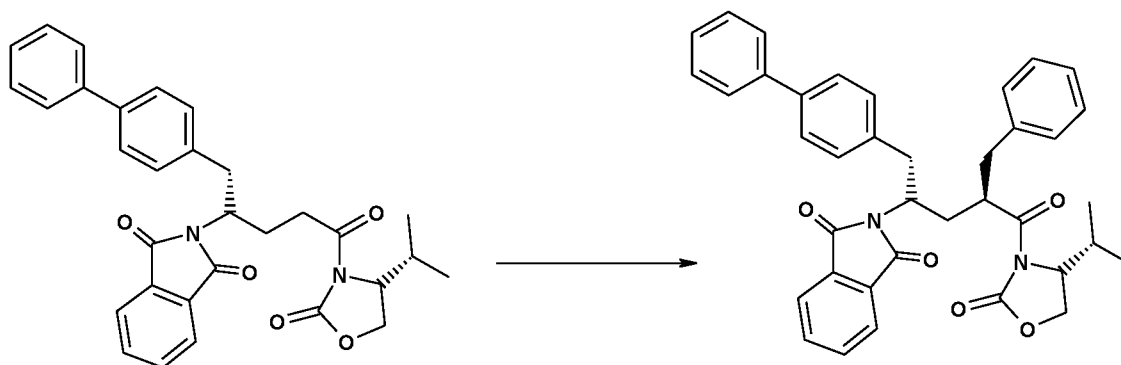
10 **Example 42: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-isopropyl-1-pyrrolidin-1-yl-pentan-1-one**



- Under N₂ atmosphere, LDA (1.0 M in THF, 2.8 mL) is added to the solution of 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-pyrrolidin-1-yl-pentan-1-one (1.0 g, 2 mmol) in 20 mL dry THF at -70 °C, the mixture is stirred for another 1h at -70 °C, 2-iodo-propane (0.51 g, 3 mmol) is then added, and the reaction mixture is warmed slowly to room temperature and stirred for 3 h. Saturated ammonium chloride solution is added, the mixture is extracted with ethyl acetate and the combined organic extracts is concentrated to obtain 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-isopropyl-1-pyrrolidin-1-yl-pentan-1-one. According to HPLC analysis, the ratio of diastereomers (2R, 4S): (2S, 4S) is 72: 28. ¹H NMR (CDCl₃): 0.68(3H, d, CH₃), 0.74(3H, d, CH₃), 1.62 (2H, m, 3-CH₂), 1.68 (2H, m, CH₂), 1.78 (2H, m, CH₂), 2.29(1H, m, CH), 2.44 (1H, m, 2-CH₂), 2.81 (2H, m, 5-CH₂), 3.16 (1H, dd, 4-CH), 3.26(2H, m, CH₂), 3.47(2H, m, CH₂), 3.57 (2H, d, CH₂), 3.77 (2H, d, CH₂), 7.10~7.40 (19H, m, aromatic).

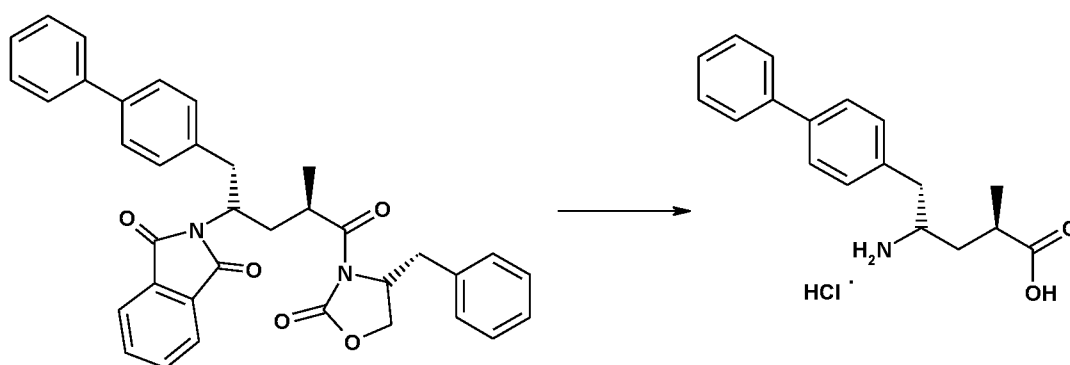
- HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (60 % B); 30 min (95 % B). Flow rate: 0.5 ml min⁻¹ . Wavelength: 210 nm. Temperature: 35 °C. Retention time: (2R, 4S):13.8 min; (2S, 4S):13.1 min

Example 43: 2-[(S)-4-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-benzenemethyl-4-oxo-butyl]-isoindole-1,3-dione



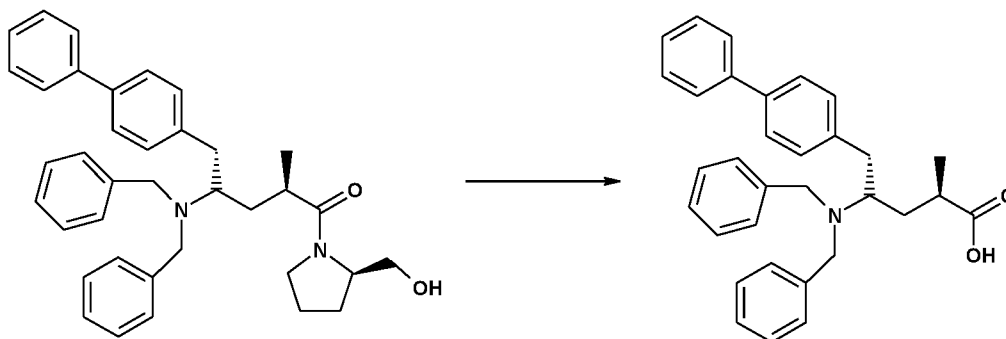
- To a -78 °C solution of NaHMDS (6.5 mL, 6.5 mmol) in 20 mL of anhydrous THF is added 2-
 5 [(S)-4-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-4-oxo-butyl]-isoindole-1,3-dione (2.74 g, 5.38 mmol) in dry THF. The reaction mixture is stirred for 1 h, then benzyl bromide (3.82 g, 22.30 mmol) is added to the reaction mixture. After 12 h, the reaction mixture is allowed to warm to room temperature, saturated NH₄Cl (25 mL) is added, the mixture is extracted with TBME. The combined organic extracts is washed with brine, dried and concentrated to give 2-
 10 [(1S,3R)-3-benzyl-1-(biphenyl-4-ylmethyl)-4-((4R)-4-isopropyl-2-oxo-1,3-oxazolidin-3-yl)-1H-isoindole-1,3(2H)-dione. According to HPLC analysis, the ratio of diastereomers (2R,4S): (2S, 4S) is >99:1. ¹H NMR (CDCl₃): 0.5-1.0 (6H, d), 2.11(1H, m), 2.31 (1H, m), 2.61(1H, m), 2.80 (3H, m), 2.91 (1H, m), 3.11 (1H, m), 3.43 (1H, m), 4.0-4.5 (5H, m), 7.05 ~7.70 (18H, m, aromatic). MS (ESI, m/e) 400 (MH⁺).
- 15 HPLC method: Column: Waters Xbridge-Phenyl, 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (60 % B); 25 min (60 % B), 30 min (95 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 210 nm. Temperature: 35 °C. Retention time: (2R, 4S) : 16.7 min; (2S, 4S): 16.0 min

20 Example 44: (2R,4S)-4-Amino-5-biphenyl-4-yl-2-methyl-pentanoic acid hydrochloride



To a solution of 2-[(1S,3R)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione (100 mg, 0.175 mmol) in 10 mL of THF is added 2.5 mL of water at 0 °C, then LiOH·H₂O (15 mg, 0.350 mmol) is added. After stirring for 12 h, 2 mL of concentrated HCl is added, the mixture is then refluxed for 2 h before being cooled to room temperature. The resulting precipitation is filtered, dried under high vacuum to afford (2R,4S)-4-amino-5-biphenyl-4-yl-2-methyl-pentanoic acid hydrochloride (43 mg). *m/z* : 283 (MH⁺). Spectroscopic data as described in Example 7 in WO2008/083967.

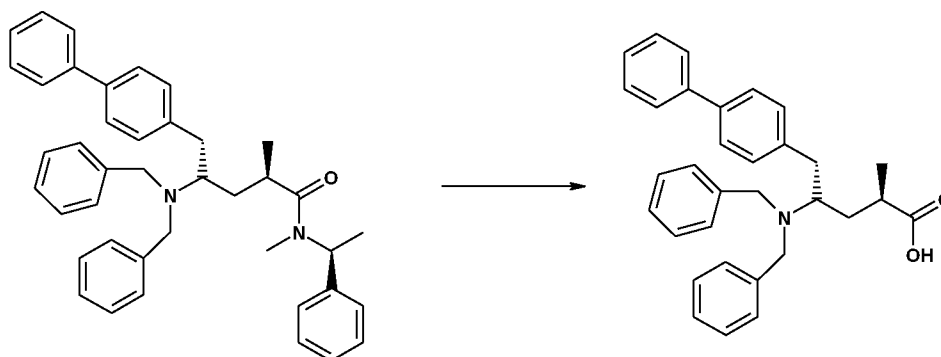
Example 45: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid



The mixture of 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-2-methyl-pentan-1-one (0.5 g, 0.9 mmol) in 10 mL 6N HCl is heated to reflux for 6 h. Then water is removed, the resulting residue is dissolved in 20 mL ethyl acetate, washed with NaHCO₃, water. The organic phase is concentrated to give 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid. ¹H NMR (CDCl₃): 0.88 (3H, d, CH₃), 1.65 (1H, m, 3-CHH), 1.82 (1H, m, 3-CHH), 2.55 (1H, m, 2-CH), 2.65 (1H, m, 4-CH), 3.14 (2H, m, 5-CH₂), 3.59 (2H, d, CH₂), 3.85 (2H, m, CH₂), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (90 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 0.7 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 11.2 min

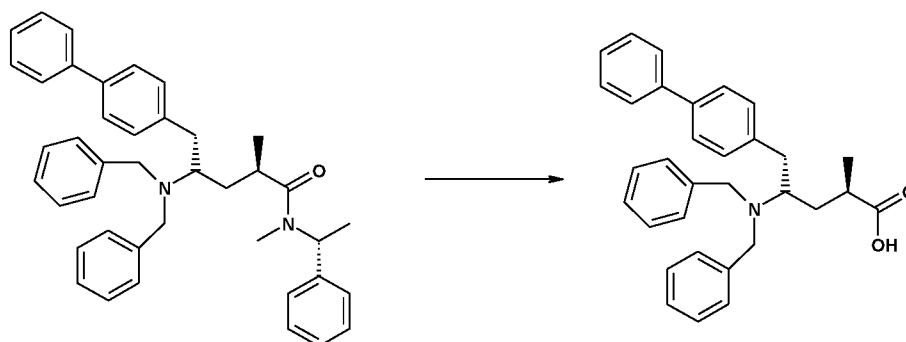
Example 46: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid



The mixture of 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid-(S)-methyl-(1-phenyl-ethyl)-amide (0.5 g, 0.9 mmol) in 10 mL 6N HCl is heated to reflux for 6 h. Then water is removed, the resulting residue is dissolved in 20 mL ethyl acetate, washed with NaHCO₃, water. The organic phase is concentrated to give 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid. ¹H NMR (CDCl₃): 0.88 (3H, d, CH₃), 1.65 (1H, m, 3-CHH), 1.82 (1H, m, 3-CHH), 2.55 (1H, m, 2-CH), 2.65 (1H, m, 4-CH), 3.14 (2H, m, 5-CH₂), 3.59 (2H, d, CH₂), 3.85 (2H, m, CH₂), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (90 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 0.7 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 11.2 min

Example 47: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid

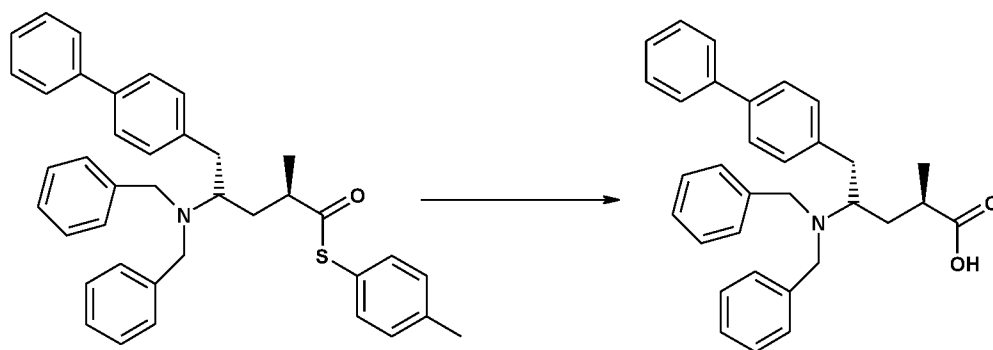


The mixture of 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid-(R)-methyl-(1-phenyl-ethyl)-amide (0.5 g, 0.9 mmol) in 10 mL 6N HCl is heated to reflux for 6h. Then water is removed, the resulting residue is dissolved in 20 mL ethyl acetate, washed with NaHCO₃, water. The organic phase is concentrated to give 0.3 g of 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid. ¹H NMR (CDCl₃): 0.88 (3H, d, CH₃), 1.65 (1H, m, 3-CHH), 1.82 (1H, m, 3-CHH), 2.55 (1H, m, 2-CH), 2.65 (1H, m, 4-CH), 3.14 (2H, m, 5-CH₂), 3.59 (2H, d, CH₂), 3.85 (2H, m, CH₂), 7.10~7.50 (19H, m, aromatic).

HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (90 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 0.7 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 11.2 min

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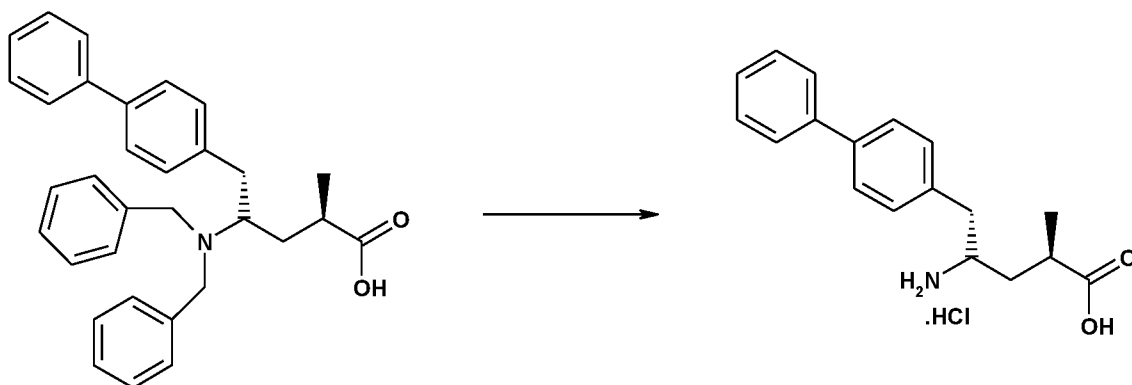
Example 48: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid



To a mixture of tetrahydrofuran (2 ml) and water (5 ml) is added 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methylpentanoic acid-S-p-tolyl ester (200 mg, 0.35 mmol). Then lithium hydroxide (20 mg) is added to the mixture. The resulting mixture is then stirred at room temperature for 12 h. 1 M hydrochloric acid solution is added to the mixture becomes acidic. The tetrahydrofuran solvent is then removed from the mixture. Ethyl acetate (5 ml) is then added and the two phases separated. The organic layer is combined and dried to give 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid. ¹H NMR (CDCl₃): 0.88 (3H, d, CH₃), 1.65 (1H, m, 3-CHH), 1.82 (1H, m, 3-CHH), 2.55 (1H, m, 2-CH), 2.65 (1H, m, 4-CH), 3.14 (2H, m, 5-CH₂), 3.59 (2H, d, CH₂), 3.85 (2H, m, CH₂), 7.10~7.50 (19H, m, aromatic).

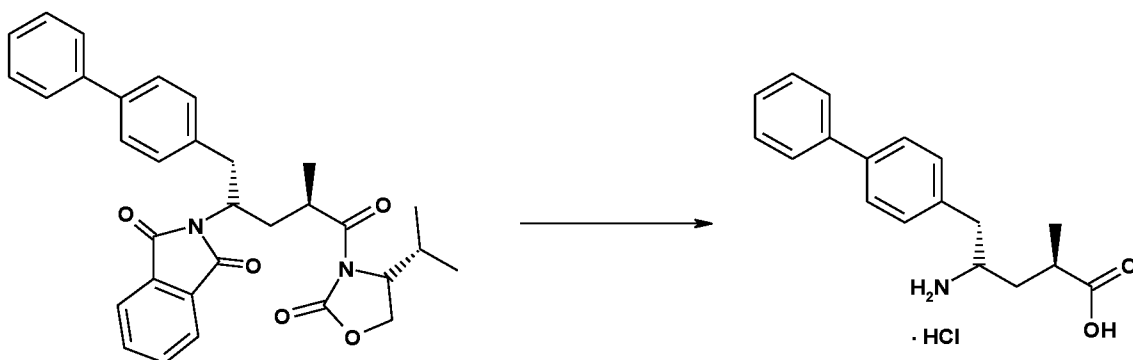
HPLC method: Column: Eclipse XDB-C18; 150 × 4.6 mm; 5 μm. Mobile Phase A (0.1 % H₃PO₄) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (90 % B); 10 min (95 % B); 15 min (95 % B). Flow rate: 0.7 ml min⁻¹. Wavelength: 210 nm. Temperature: 30 °C. Retention time: 11.2 min

Example 49: 5-biphenyl-(S)-4-amino-4-yl-(R)-2-methylpentanoic acid hydrochloride



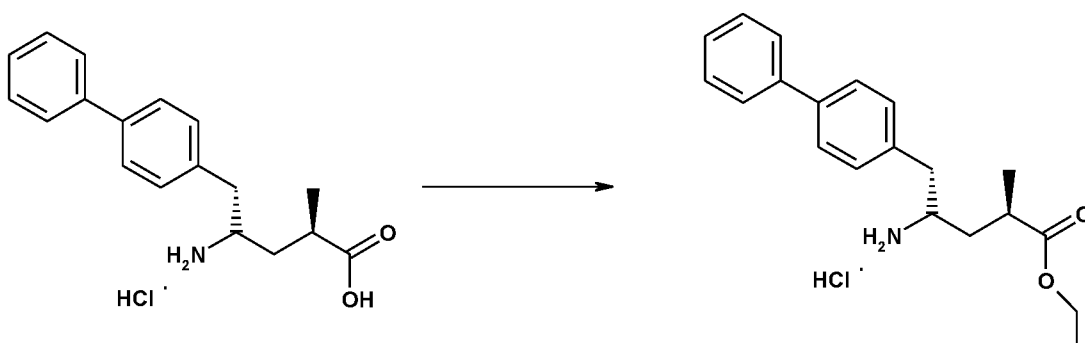
Under H₂ atmosphere, the mixture of 0.3 g of 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid, 0.1 g of palladium on carbon in 10 mL AcOH is heated to 50 °C and stirred for 12 h. The reaction mixture is filtered, and concentrated. To the resulting residue is added 3 M HCl in ethyl acetate, the precipitation is filtered and and dried to give 5-biphenyl-(S)-4-amino-4-yl-(R)-2-methylpentanoic acid hydrochloride. Spectroscopic data as described in Example 7 in WO2008/083967.

Example 50: (2R,4S)-4-amino-5-biphenyl-4-yl-2-methyl-pentanoic acid hydrochloride



To a solution of 2-[(S)-4-((R)-4-isopropyl-2-oxo-oxazolidin-3-yl)-1-biphenyl-4-ylmethyl-3-methyl-4-oxo-butyl]-isoindole-1,3-dione (102 mg, 0.2 mmol) in 10 mL of THF is added 2.5 mL of water at 0°C followed by LiOH·H₂O (15 mg, 0.350 mmol). After 12 h, 2 mL of concentrated HCl is added, then the mixture is refluxed for 2 h. The reaction mixture is allowed to cool to room temperature, filtered and dried to give (2R, 4S)-4-amino-5-biphenyl-4-yl-2-methyl-pentanoic hydrochloride. Spectroscopic data as described in Example 7 in WO2008/083967

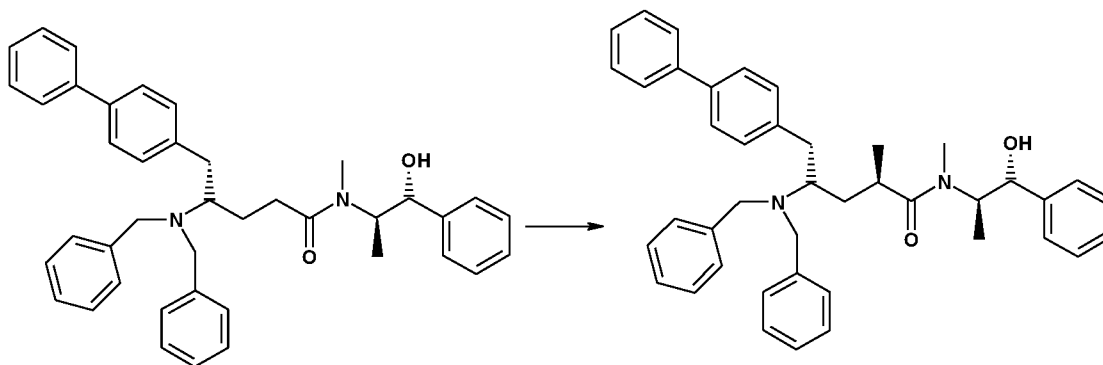
Example 51: (2R,4S)-4-Amino-5-biphenyl-4-yl-2-methyl-pentanoic acid ethyl ester



A suspension of (2R,4S)-4-amino-5-biphenyl-4-yl-2-methyl-pentanoic acid hydrochloride (100 mg, 0.32 mmol) in 10 mL of 3~4 M HCl / EtOH is stirred at room temperature for 12 h. The reaction mixture is concentrated under vacuum to give (2R,4S)-4-amino-5-biphenyl-4-yl-2-

methyl-pentanoic acid ethyl ester. Spectroscopic data as described in Example 9-1 in WO2008/083967.

Example 52: 5-Biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid ((R)-2-hydroxy-(R)-1-methyl-2-phenyl-ethyl)-methyl-amide

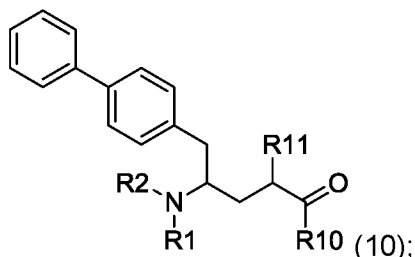


Under N₂ atmosphere, LiCl (500 mg, 0.84 mmol) is suspended in THF (3 mL) and cooled to -70 °C, then diisopropylamine (0.53 mL, 3.8 mmol) is added to the suspension followed by dropwise addition of n-BuLi (2.2 mL, 1.6 M in hexanes, 3.50 mmol). After 30 min, a solution of 5-biphenyl-4-yl-(S)-4-dibenzylamino-pentanoic acid ((R)-2-hydroxy-(R)-1-methyl-2-phenyl-ethyl)-methyl-amide (0.99 g, 1.67 mmol) in THF (4 mL) is added to a solution of 5-biphenyl-4-yl-(S)-4-dibenzylamino-1-((S)-2-hydroxymethyl-pyrrolidin-1-yl)-pentan-1-one (0.53 g, 1 mmol) in dry THF (4 mL) at -70 °C. After 1 h, MeI (470 mg, 3.34 mmol) is added, and the reaction mixture is stirred for 30 min. NH₄Cl (3 mL, saturated aqueous solution) is then added. The resulting mixture is warmed slowly to room temperature, the aqueous layer is extracted with TBME (10 mL). The organic layer is dried and concentrated to obtain 5-biphenyl-4-yl-(S)-4-dibenzylamino-(R)-2-methyl-pentanoic acid ((R)-2-hydroxy-(R)-1-methyl-2-phenyl-ethyl)-methyl-amide. The ratio of diastereomers by HPLC analysis: (2R, 4S):(2S, 4S) = 99:1. ¹H NMR (DMSO-D₆): 0.83-.89 (3H, m), 1.23-1.29 (3 H, m), 1.43-1.65 (2 H, m), 2.62-3.07 (8 H, m), 3.47-3.69 (4 H, m), 4.38-4.58 (1 H, m), 5.39-5.42 (1 H, m), 7.08~7.67 (24 H, m).

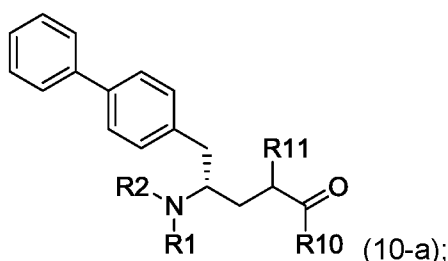
HPLC method: Column: Waters Xbridge-Phenyl; 150 × 3.0 mm; 3.5 μm. Mobile Phase A (0.1 % DEA) in water; Mobile Phase B (Acetonitrile). Gradient: 0 min (60 % B); 20 min (95 % B); 25 min (95 % B); 35 min (95 % B). Flow rate: 0.5 ml min⁻¹. Wavelength: 254 nm. Temperature: 35 °C. Retention time: (2R, 4S): 16.7 min; (2S, 4S): 17.2 min.

Claims:

1. A compound of formula (10), or a salt thereof,



5 preferably having a configuration according to formula (10-a)



wherein R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R₁₀ is selected from

- X, wherein X is halo, preferably chloro;
- a group -NR₅^{''}R₆^{''}, wherein R₅^{''} and R₆^{''} are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R₅^{''} and R₆^{''} form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R₅^{''} and R₆^{''} together with the nitrogen to which they are attached form a chiral moiety;
- a group -O-R_x, wherein R_x together with the oxygen to which it is attached forms a chiral moiety; and

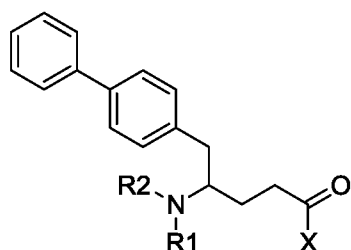
- a group $-S-R_5$, wherein R_5 is C_1-C_7 -alkyl, C_6-C_{10} -aryl, or C_6-C_{10} -aryl- C_1-C_7 -alkyl;

R_{11} is either hydrogen or a group R_8 which is C_1-C_7 -alkyl or C_6-C_{10} -aryl- C_1-C_7 -alkyl, preferably methyl.

- 5 2. The compound of formula (10) according to claim 1 wherein when R_{11} is R_8 which is C_1-C_7 -alkyl or C_6-C_{10} -aryl- C_1-C_7 -alkyl, preferably methyl, then R_{10} is selected from

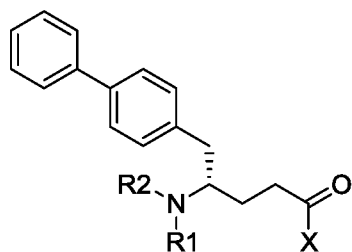
- a group $-NR_5''R_6''$, wherein R_5'' and R_6'' are, independently of each other, C_1-C_7 -alkyl, C_6-C_{10} -aryl, C_6-C_{10} -aryl- C_1-C_7 -alkyl, C_3-C_7 -cycloalkyl or R_5'' and R_6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C_1-C_7 -alkyl, C_1-C_7 -alkoxy, halo, carboxyl and oxo, preferably R_5'' and R_6'' together with the nitrogen to which they are attached form a chiral moiety;
- a group $-O-R_x$, wherein R_x together with the oxygen to which it is attached forms a chiral moiety; and
- a group $-S-R_5$, wherein R_5 is C_1-C_7 -alkyl, C_6-C_{10} -aryl, or C_6-C_{10} -aryl- C_1-C_7 -alkyl.

- 20 3. The compound of formula (10) according to claim 1 wherein the compound is of formula (4), or a salt thereof,



(4);

preferably having a configuration according to formula (4-a)



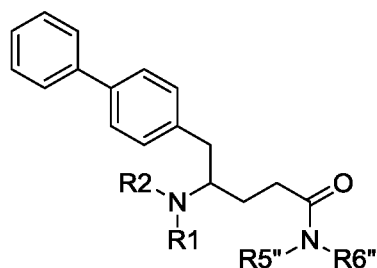
(4-a);

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or
 5 unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

X is halo, preferably chloro.

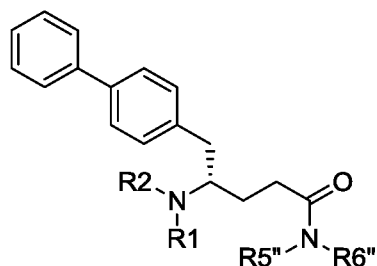
10

4. The compound of formula (10) according to claim 1 wherein the compound is of formula (3-II-A), or a salt thereof,



(3-II-A);

preferably having a configuration according to formula (3-II-A-a)



(3-II-A-a);

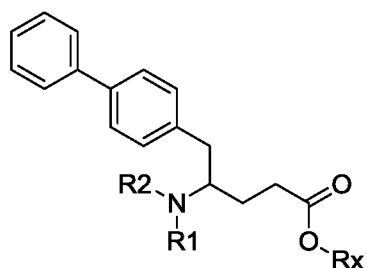
15

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or

unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

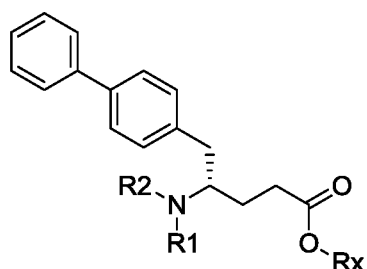
- 5 R^{5''} and R^{6''} are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R^{5''} and R^{6''} form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R^{5''} and R^{6''} together with the nitrogen to which they are attached form a chiral moiety.

5. The compound of formula (10) according to claim 1 wherein the compound is of formula (3-III-A), or a salt thereof,



(3-III-A);

preferably having a configuration according to formula (3-III-A-a)



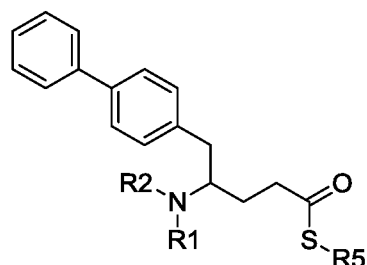
(3-III-A-a);

- wherein R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or

three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

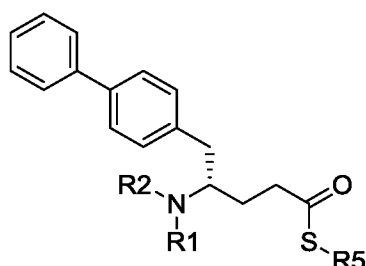
Rx together with the oxygen to which it is attached forms a chiral moiety.

- 5 6. The compound of formula (10) according to claim 1 wherein the compound is of formula (3-IV), or a salt thereof,



(3-IV);

preferably having a configuration according to formula (3-IV-a)

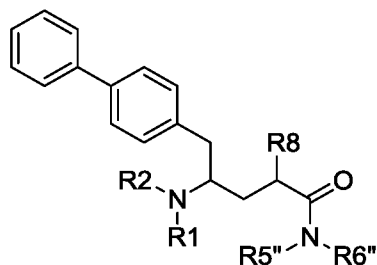


(3-IV-a);

- 10 wherein R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group, or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or
- 15 three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

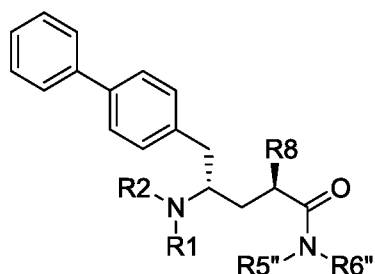
R₅ is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl.

7. The compound of formula (10) according to claim 1 wherein the compound is of formula (5-II-A), or a salt thereof,
- 20



(5-II-A);

preferably having a configuration according to formula (5-II-A-a)



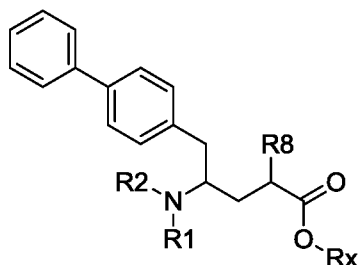
(5-II-A-a);

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group,
 5 or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo,
 10 carboxyl and oxo,

R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional
 15 heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, preferably R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety, and

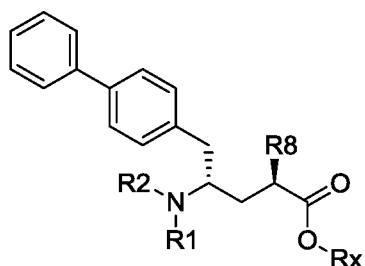
R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl.

8. The compound of formula (10) according to claim 1 wherein the compound is of formula (5-III-A), or a salt thereof,



(5-III-A),

preferably having a configuration according to formula (5-III-A-a),

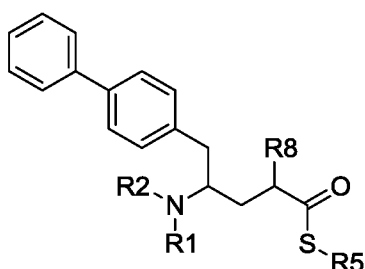


(5-III-A-a),

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group,
 5 or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered,
 preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or
 unsaturated and may optionally contain one, two or three additional heteroatoms, such as
 nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or
 three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo,
 10 carboxyl and oxo, and

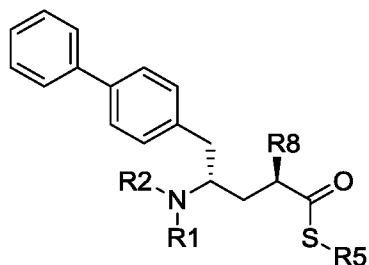
Rx together with the oxygen to which it is attached forms a chiral moiety.

9. The compound of formula (10) according to claim 1 wherein the compound is of formula (5-IV), or a salt thereof,



(5-IV),

preferably having a configuration according to formula (5-IV-a),



(5-IV-a),

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5 is C₁-C₇-alkyl, C₆-C₁₀-aryl, or C₆-C₁₀-aryl-C₁-C₇-alkyl, and

R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl.

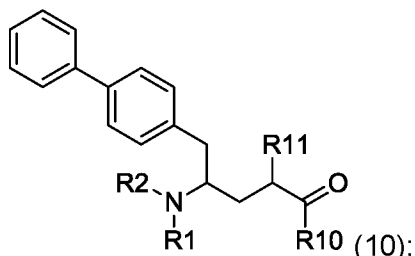
10. The use of a compound according to any one of claims 1 to 9, in the synthesis of the NEP-inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methylbutanoic acid or a salt thereof, or the NEP inhibitor prodrug *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester or a salt thereof.

11. A process for preparing *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid, or a salt thereof, or *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester, or a salt thereof, comprising the manufacture of a compound, or a salt thereof, as defined in any one of claims 1 to 7.

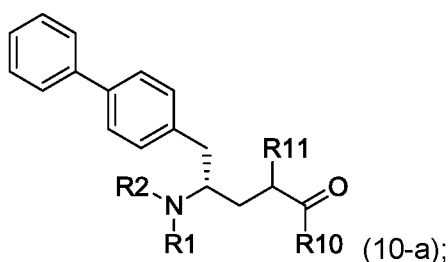
AMENDED CLAIMS

received by the International Bureau on 21 December 2016 (21.12.2016)

1. A compound of formula (10), or a salt thereof,



5 preferably having a configuration according to formula (10-a)



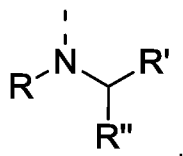
wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R10 is selected from

- X, wherein X is halo, preferably chloro;
- a group –NR^{5''}R^{6''}, wherein R^{5''} and R^{6''} are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R^{5''} and R^{6''} form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, or R^{5''} and R^{6''} together with the nitrogen to which they are attached form a chiral moiety selected from (S)-prolinol,

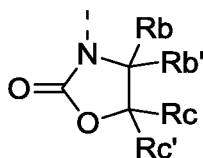
(R)-prolinol,

a compound of the formula



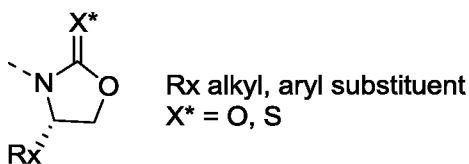
wherein R is methyl, R' is methyl and R'' is phenyl or C(OH)-phenyl; or R is methyl, R' is phenyl and R'' is CH₂OH,

a compound of formula



wherein Rb is CH₂Phenyl, *i*Propyl, or Methyl and Rb' = Rc' = hydrogen and Rc is hydrogen or Ph; or Rb is methyl, phenyl or CH₂Phenyl, *i*Propyl, Rb' is hydrogen, Rc = Rc' = methyl; or Rb is CH₂Phenyl, *i*Propyl, or Methyl and Rb' = Rc' = Rc = hydrogen,

a compound of formula



camphorsultam,

(*S*)-methyl-(1-phenylethyl)amine,

(*R*)-methyl-(1-phenylethyl)amine and

(1*R*,2*R*)-pseudoephedrine; and

- a group –O-Rx, wherein Rx is an enantiomeric menthyl moiety;

R11 is either hydrogen or a group R8 which is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl.

2. The compound of formula (10) according to claim 1 wherein when R11 is R8 which is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl, then R10 is selected from

- a group –NR^{5''}R^{6''}, wherein R^{5''} and R^{6''} are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R^{5''} and R^{6''} form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted

with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, or R^{5''} and R^{6''} together with the nitrogen to which they are attached form a chiral moiety

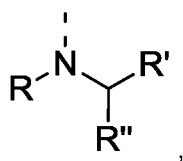
selected from

5

(S)-prolinol,

(R)-prolinol,

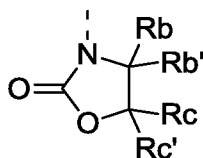
a compound of the formula



wherein R is methyl, R' is methyl and R'' is phenyl or C(OH)-phenyl; or R is methyl, R' is phenyl and R'' is CH₂OH,

10

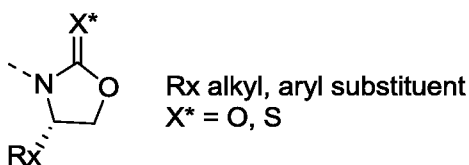
a compound of formula



wherein Rb is CH₂Phenyl, *i*Propyl, or Methyl and Rb' = Rc' = hydrogen and Rc is hydrogen or Ph; or Rb is methyl, phenyl or CH₂Phenyl, *i*Propyl, Rb' is hydrogen, Rc = Rc' = methyl; or Rb is CH₂Phenyl, *i*Propyl, or Methyl and Rb' = Rc' = Rc = hydrogen,

15

a compound of formula



camphorsultam,

20

(S)-methyl-(1-phenylethyl)amine,

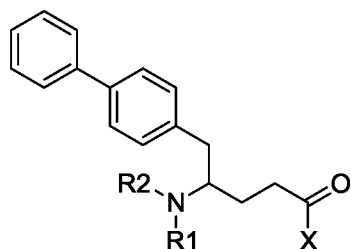
(R)-methyl-(1-phenylethyl)amine and

(1*R*,2*R*)-pseudoephedrine; and

- a group -O-Rx, wherein Rx is an enantiomeric menthyl moiety.

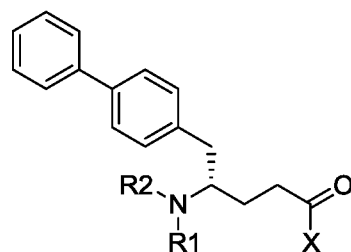
25

3. The compound of formula (10) according to claim 1 wherein the compound is of formula (4), or a salt thereof,



(4);

preferably having a configuration according to formula (4-a)

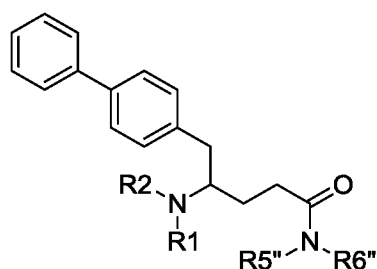


(4-a);

wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group,
 5 or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo,
 10 carboxyl and oxo, and

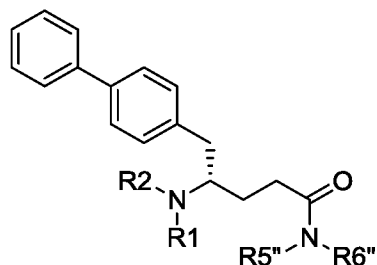
X is halo, preferably chloro.

4. The compound of formula (10) according to claim 1 wherein the compound is of formula (3-II-A), or a salt thereof,



(3-II-A);

preferably having a configuration according to formula (3-II-A-a)



(3-II-A-a);

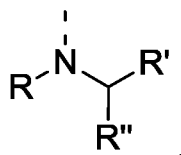
wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, or R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety selected from

(S)-prolinol,

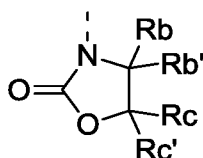
(R)-prolinol,

a compound of the formula



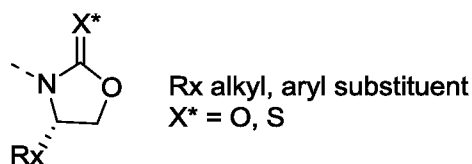
wherein R is methyl, R' is methyl and R'' is phenyl or C(OH)-phenyl; or R is methyl, R' is phenyl and R'' is CH₂OH,

a compound of formula



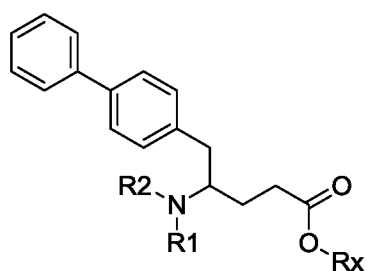
wherein Rb is CH₂Phenyl, *i*Propyl, or Methyl and Rb' = Rc' = hydrogen and Rc is hydrogen or Ph; or Rb is methyl, phenyl or CH₂Phenyl, *i*Propyl, Rb' is hydrogen, Rc

= R_c' = methyl; or R_b is CH₂Phenyl, *i*Propyl, or Methyl and R_b' = R_c' = R_c = hydrogen,
a compound of formula



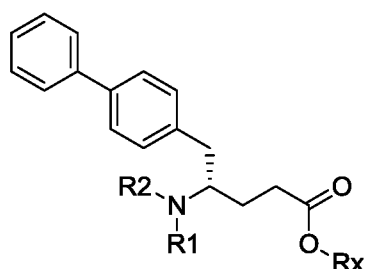
- 5 camphorsultam,
(*S*)-methyl-(1-phenylethyl)amine,
(*R*)-methyl-(1-phenylethyl)amine and
(1*R*,2*R*)-pseudoephedrine.

- 10 5. The compound of formula (10) according to claim 1 wherein the compound is of formula (3-III-A), or a salt thereof,



(3-III-A);

preferably having a configuration according to formula (3-III-A-a)

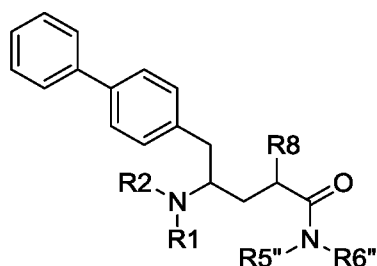


(3-III-A-a);

- 15 wherein R₁ and R₂ are, independently of each other, hydrogen or a nitrogen protecting group,
or R₁ and R₂ form, together with the nitrogen to which they are attached, a 3 to 10-
membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated
or unsaturated and may optionally contain one, two or three additional heteroatoms, such as
nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or
20 three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo,
carboxyl and oxo, and

Rx is an enantiomeric menthyl moiety.

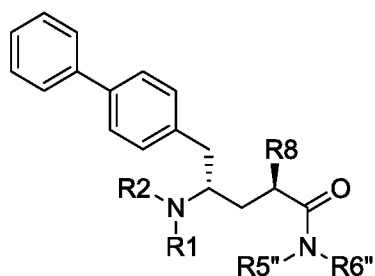
6. The compound of formula (10) according to claim 1 wherein the compound is of formula (5-II-A), or a salt thereof,



5

(5-II-A);

preferably having a configuration according to formula (5-II-A-a)



(5-II-A-a);

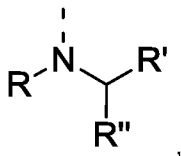
wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo,

R5'' and R6'' are, independently of each other, C₁-C₇-alkyl, C₆-C₁₀-aryl, C₆-C₁₀-aryl-C₁-C₇-alkyl, C₃-C₇-cycloalkyl or R5'' and R6'' form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, or R5'' and R6'' together with the nitrogen to which they are attached form a chiral moiety selected from

(S)-prolinol,

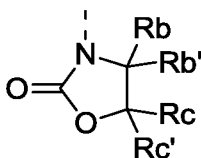
(R)-prolinol,

a compound of the formula



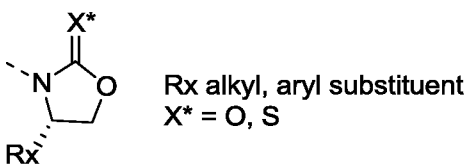
wherein R is methyl, R' is methyl and R'' is phenyl or C(OH)-phenyl; or R is methyl, R' is phenyl and R'' is CH₂OH,

a compound of formula



wherein Rb is CH₂Phenyl, *i*Propyl, or Methyl and Rb' = Rc' = hydrogen and Rc is hydrogen or Ph; or Rb is methyl, phenyl or CH₂Phenyl, *i*Propyl, Rb' is hydrogen, Rc = Rc' = methyl; or Rb is CH₂Phenyl, *i*Propyl, or Methyl and Rb' = Rc' = Rc = hydrogen,

a compound of formula



camphorsultam,

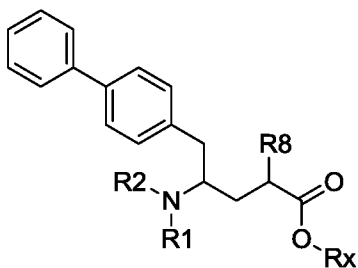
(S)-methyl-(1-phenylethyl)amine,

(R)-methyl-(1-phenylethyl)amine and

(1*R*,2*R*)-pseudoephedrine, and

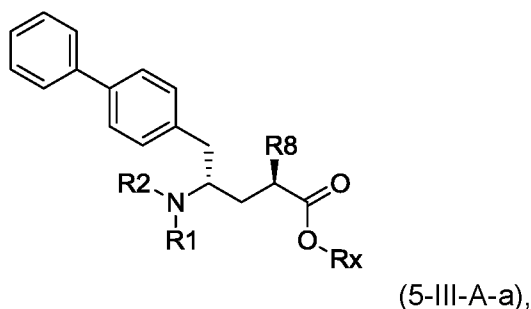
R8 is C₁-C₇-alkyl or C₆-C₁₀-aryl-C₁-C₇-alkyl, preferably methyl.

7. The compound of formula (10) according to claim 1 wherein the compound is of formula (5-III-A), or a salt thereof,



(5-III-A),

preferably having a configuration according to formula (5-III-A-a),



wherein R1 and R2 are, independently of each other, hydrogen or a nitrogen protecting group, or R1 and R2 form, together with the nitrogen to which they are attached, a 3 to 10-membered, preferably 4 to 7-membered, mono- or bicyclic cycle which cycle may be saturated or unsaturated and may optionally contain one, two or three additional heteroatoms, such as nitrogen, oxygen or sulphur, and which may be unsubstituted or substituted with one, two or three substituents independently selected from hydroxyl, C₁-C₇-alkyl, C₁-C₇-alkoxy, halo, carboxyl and oxo, and

Rx is an enantiomeric menthyl moiety.

8. The use of a compound according to any one of claims 1 to 7, in the synthesis of the NEP-inhibitor *N*-(3-carboxy-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methylbutanoic acid or a salt thereof, or the NEP inhibitor prodrug *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester or a salt thereof.

9. A process for preparing *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid, or a salt thereof, or *N*-(3-carboxyl-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-(2*R*)-methyl butanoic acid ethyl ester, or a salt thereof, comprising the manufacture of a compound, or a salt thereof, as defined in any one of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/055027

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/215 C07C219/06 C07C327/22 C07C237/06 C07C53/42
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	Page 17, line 7 - page 18, line 7; claims 1-90; examples 37,42-47, -----	1-11
X	WO 2014/198195 A1 (SHANGHAI HANSOH BIOMEDICAL CO LTD [CN]; JIANGSU HANSOH PHARMACEUTICAL) 18 December 2014 (2014-12-18)	6,9-11
Y	page 32, example 16; page 33 and 34, examples 17 and 18; abstract -----	1-11
X	EP 1 903 027 A1 (NOVARTIS AG [CH]) 26 March 2008 (2008-03-26) paragraphs [0079] - [0094]; claims 1-36 -----	1,2,5,8, 10,11
	-/--	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 October 2016

Date of mailing of the international search report

02/11/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Kleidernigg, Oliver

INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	GARY M KSANDER ET AL: "Dicarboxylic Acid Dipeptide Neutral Endopeptidase Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US , vol. 38, no. 10 1 May 1995 (1995-05-01), pages 1689-1700, XP008154341, ISSN: 0022-2623, DOI: 10.1021/JM00010A014 Retrieved from the Internet: URL: http://pubs.acs.org/journals/jmcmar/index.html [retrieved on 1995-05-01] page 1691, compounds 18-21; table 4 -----	1,2,5,8, 10,11

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International application No

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International application No

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