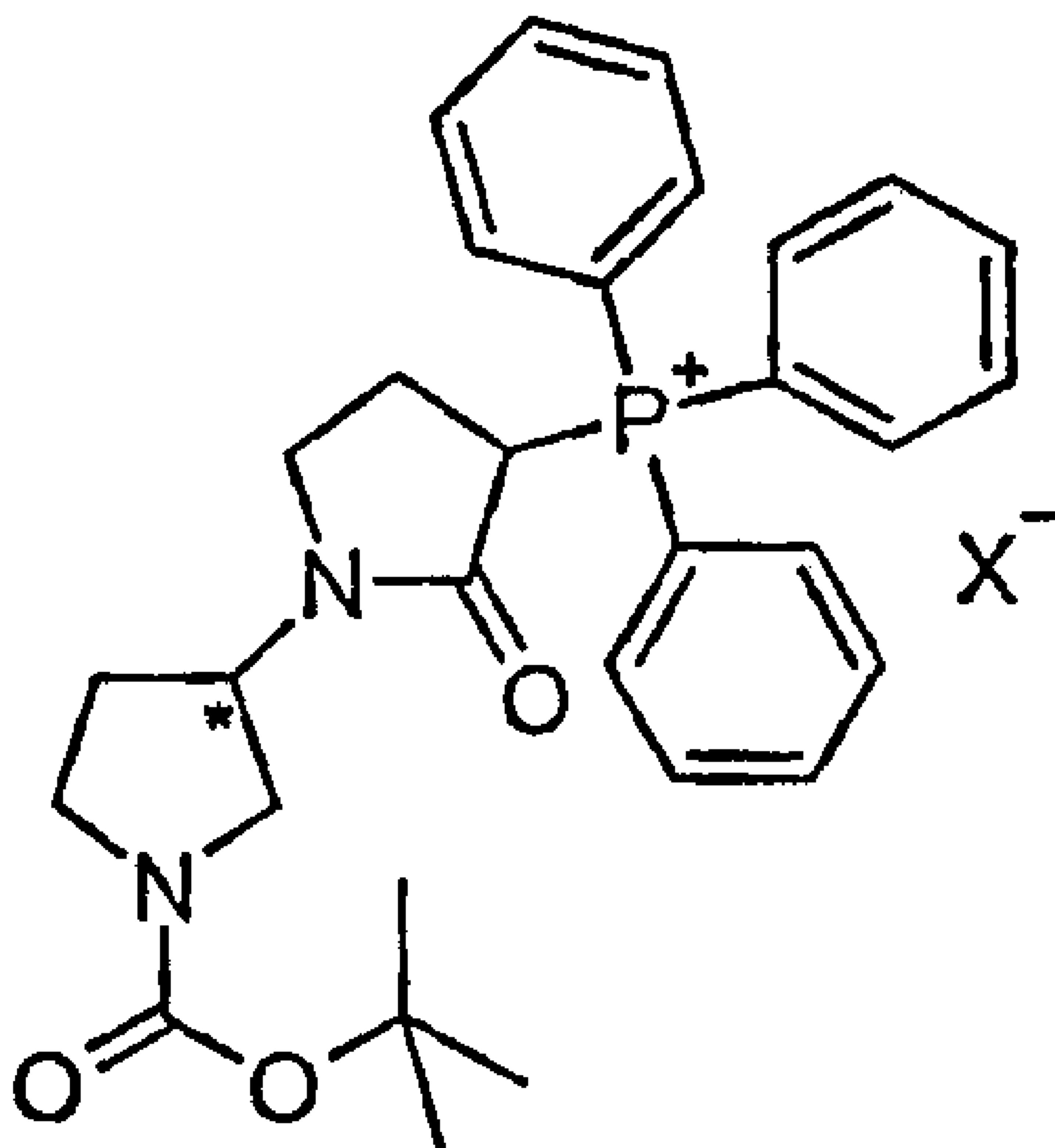




(86) Date de dépôt PCT/PCT Filing Date: 2001/08/06
(87) Date publication PCT/PCT Publication Date: 2002/02/21
(45) Date de délivrance/Issue Date: 2011/03/22
(85) Entrée phase nationale/National Entry: 2003/02/11
(86) N° demande PCT/PCT Application No.: EP 2001/009059
(87) N° publication PCT/PCT Publication No.: 2002/014332
(30) Priorité/Priority: 2000/08/14 (EP00117525.6)

(51) Cl.Int./Int.Cl. *C07F 9/6558* (2006.01),
C07D 207/14 (2006.01), *C07D 207/26* (2006.01),
C07D 207/273 (2006.01), *C07D 207/416* (2006.01),
C07D 501/00 (2006.01), *C07F 9/572* (2006.01)
(72) Inventeur/Inventor:
ROGERS-EVANS, MARK, CH
(73) Propriétaire/Owner:
BASILEA PHARMACEUTICA AG, CH
(74) Agent: BORDEN LADNER GERVAIS LLP

(54) Titre : PREPARATION DE SELS DE PHOSPHONIUM SUBSTITUES PAR 3-PYRROLIDINE-LACTAME N-PROTEGE
(54) Title: PREPARATION OF N-PROTECTED-3-PYRROLIDINE-LACTAM SUBSTITUTED PHOSPHONIUM SALTS



(57) Abrégé/Abstract:

New process for the preparation of bipyrrolidinyl compounds of formula I wherein * signifies an asymmetric centre with an (R) or (S) configuration and X represents chlorine, bromine or iodine. The compounds of formula I are important building blocks for the

(57) **Abrégé(suite)/Abstract(continued):**

production of useful products in the chemical and in the pharmaceutical industry. In particular they are useful for the production of antibacterial substances for example like vinylpyrrolidinone-cephalosporin derivatives.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
21 February 2002 (21.02.2002)

PCT

(10) International Publication Number
WO 02/14332 A1(51) International Patent Classification⁷: **C07F 9/6558**,
C07D 207/26, 501/00

(21) International Application Number: PCT/EP01/09059

(22) International Filing Date: 6 August 2001 (06.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00117525.6 14 August 2000 (14.08.2000) EP(71) Applicant (for all designated States except US):
BASILEA PHARMACEUTICA AG [CH/CH]; c/o
Rudolf Maag, 11 Neuhofweg, CH-4102 Binningen (CH).

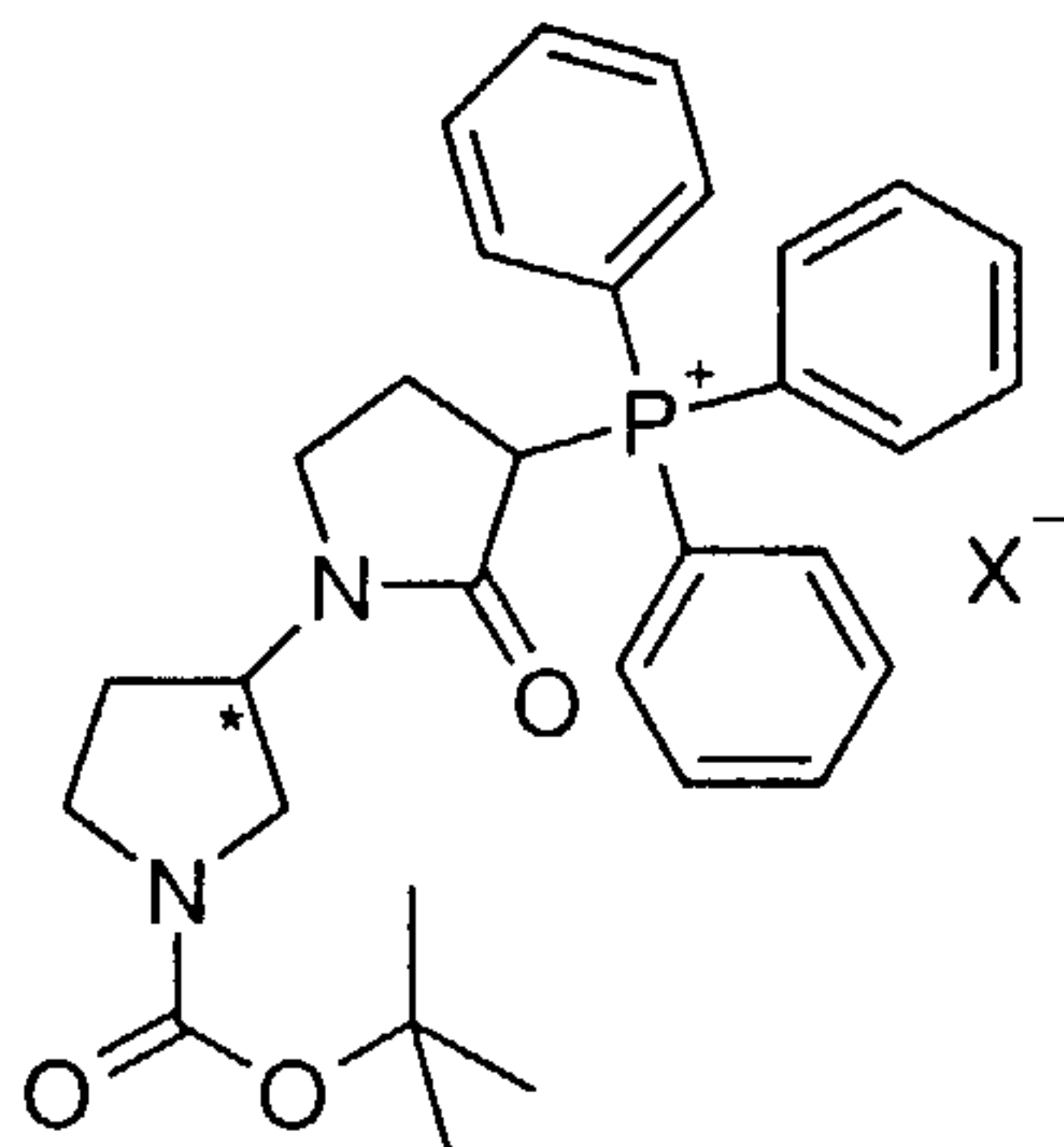
(72) Inventor; and

(75) Inventor/Applicant (for US only): **ROGERS-EVANS**,
Mark [GB/CH]; 1 Hauptstrasse, CH-4102 Binningen
(CH).(81) Designated States (national): AE, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, CA, CH, CN, CO, CU, CZ, DE, DK,EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA,
UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).**Published:**

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PREPARATION OF N-PROTECTED-3-PYRROLIDINE-LACTAM SUBSTITUTED PHOSPHONIUM SALTS



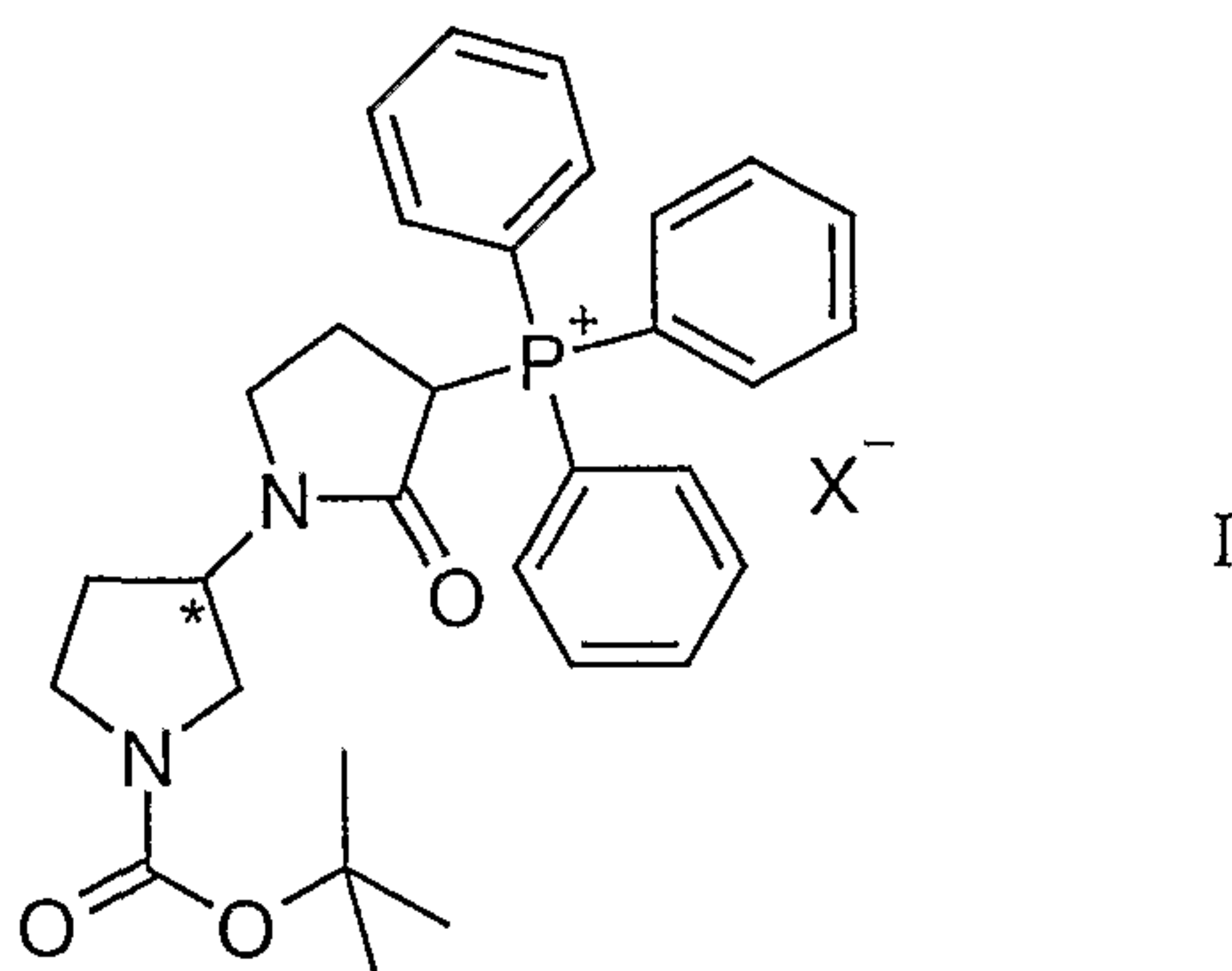
(I)

(57) Abstract: New process for the preparation of bipyrrolidinyl compounds of formula I wherein * signifies an asymmetric centre with an (R) or (S) configuration and X represents chlorine, bromine or iodine. The compounds of formula I are important building blocks for the production of useful products in the chemical and in the pharmaceutical industry. In particular they are useful for the production of antibacterial substances for example like vinylpyrrolidinone-cephalosporin derivatives.

WO 02/14332 A1

PREPARATION OF N-PROTECTED-3-PYRROLIDINE-LACTAM SUBSTITUTED PHOSPHONIUM SALTS

The invention relates to a new process for the preparation of (1'-tert-butoxycarbonyl-2-oxo-[1,3']-bipyrrolidinyl-3-(R,S)-yl)-triphenyl-phosphonium
 5 halogenide compounds of formula I

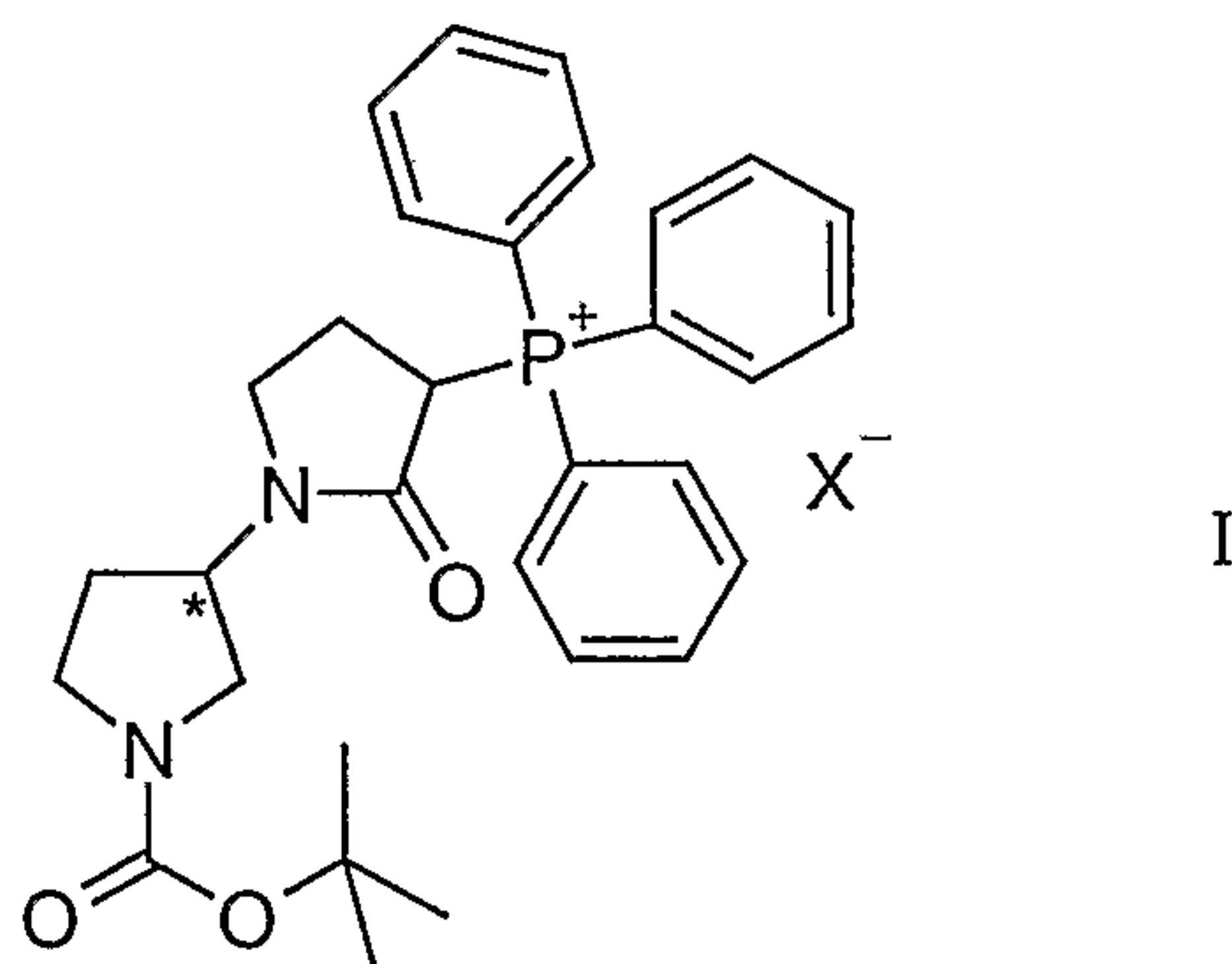


wherein * signifies an asymmetric center with an (R) or (S) configuration and X represents chlorine, bromine or iodine.

10 The compounds of formula I are known from EP-A 0 849 269 and can be obtained through multiple-step synthesis of the corresponding allyloxycarbonyl (ALLOC) protected [1,3']bipyrrolidinyl-2-oxo derivative by removal of the allyloxycarbonyl protecting group and protection reaction with a tert-butoxycarbonyl moiety to yield tert-butoxycarbonyl (t-BOC) protected [1,3']bipyrrolidinyl-2-oxo compounds of formula I.

15 It has now been found that the compounds of formula I can be manufactured in an improved and shortened way by the process of the present invention. The new process for the preparation of (1'-tert-butoxycarbonyl-2-oxo-[1,3']-bipyrrolidinyl-3-(R,S)-yl)-triphenyl-phosphonium halogenide compounds of formula I

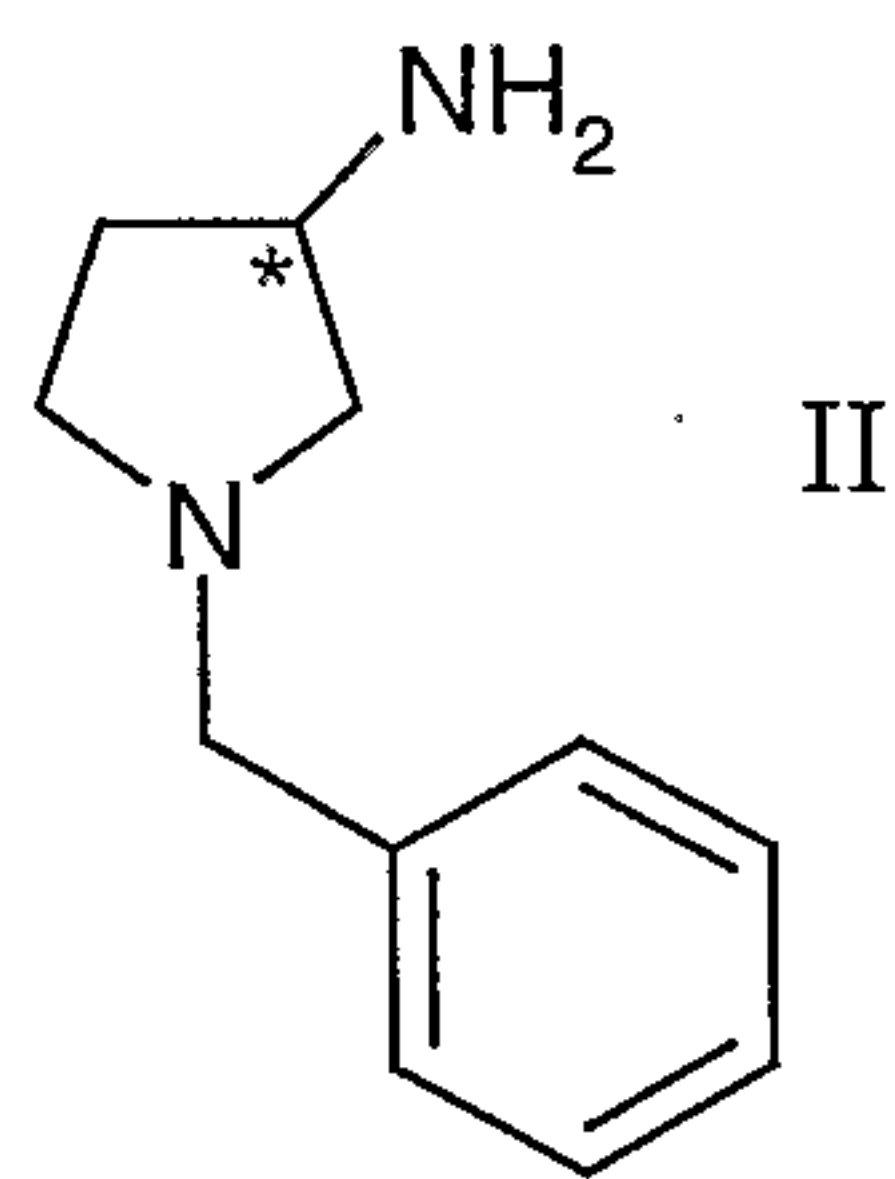
- 2 -



wherein * signifies an asymmetric center with an (R) or (S) configuration and X represents chlorine, bromine or iodine;

comprises

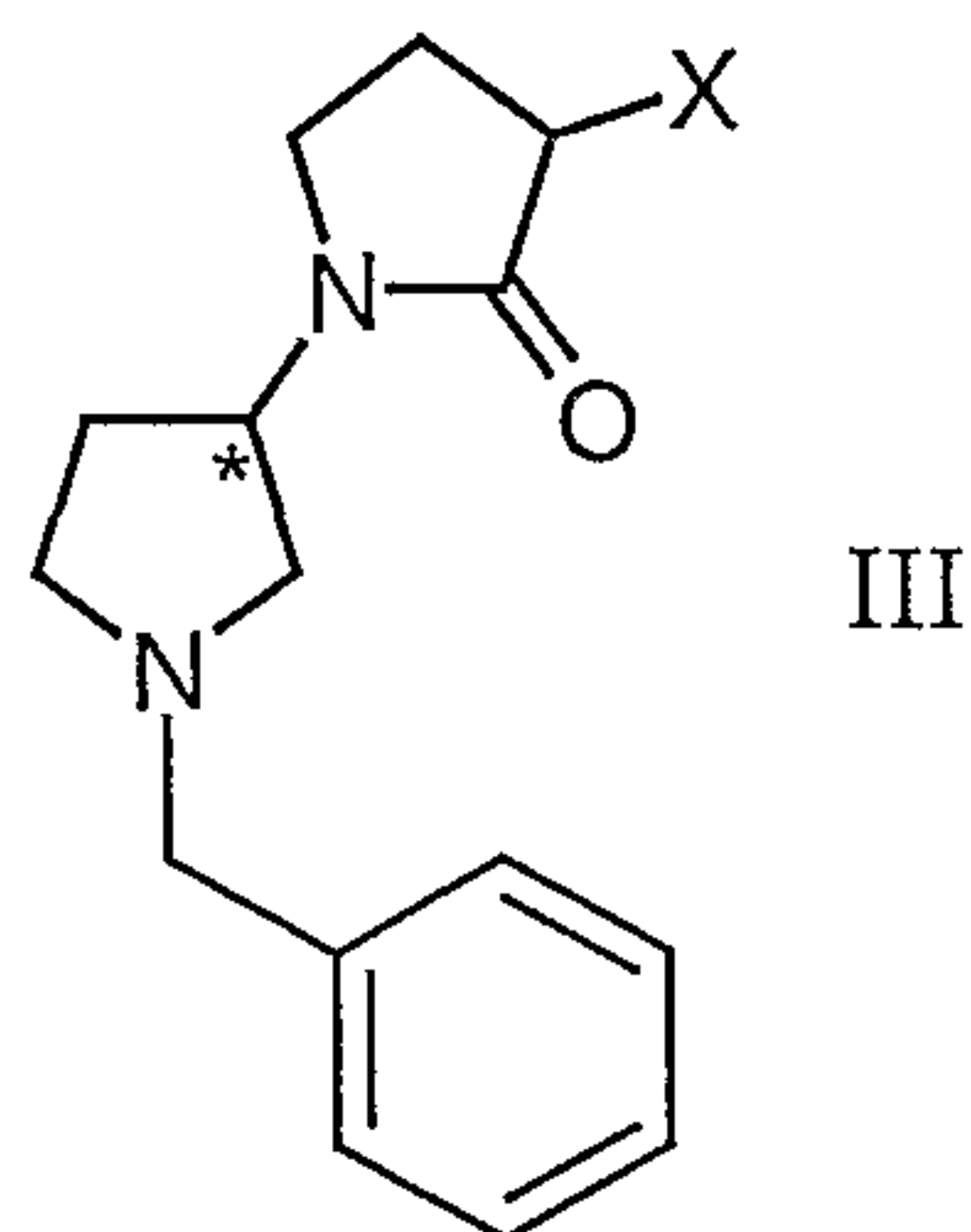
5 step 1) coupling N-benzyl-3-pyrrolidinamine of formula II



wherein * is as defined above

with a compound of formula $X(CH_2)_2CH(X)COX$

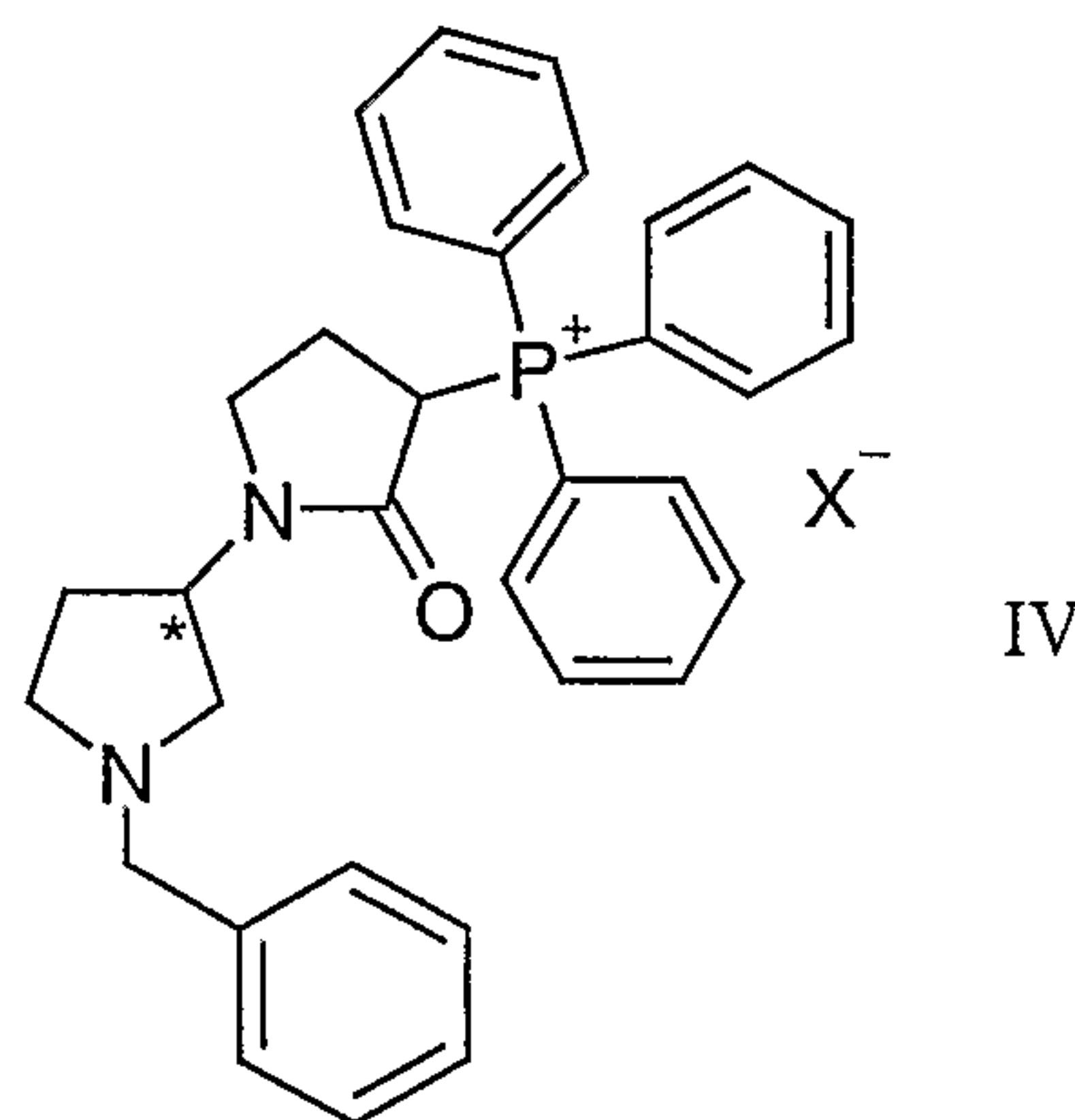
10 wherein X is independently of each other chlorine, bromine or iodine; and subsequent cyclization in the presence of a base to obtain a compound of formula III



wherein * and X are as defined above;

15 step 2) reacting the compound of formula III with triphenylphosphine to obtain the phosphonium salt of formula IV

- 3 -



wherein * and X are as defined above; and

step 3) reacting the phosphonium salt of formula IV with di-tert.-butyl-dicarbonate under hydrogenation conditions to obtain the compounds of formula I.

5 Surprisingly, it has been found that the N-benzyl-3-pyrrolidinamine of formula II undergoes the reaction sequence described above to yield the compounds of formula I, despite the expected instability of intermediate III. The corresponding t-Boc and Alloc protected derivatives of starting material of formula II are not available through the described process

10 In the structural formulae of the compounds given throughout this application, a wedged bond ($\blacktriangle$) indicates a substituent which is above the plane of the paper.

In the structural formulae of the compounds given throughout this application, a dotted bond ($\cdots$) indicates a substituent which is below the plane of the paper.

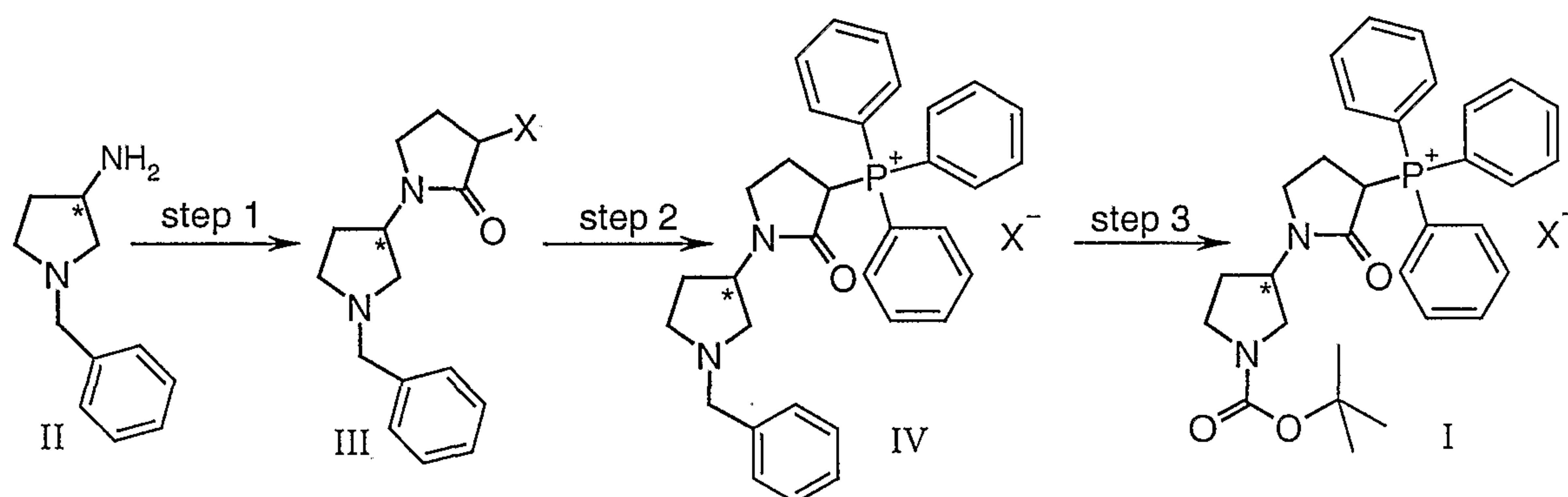
The compounds of the present process invention exhibit stereoisomerism and can be any stereoisomer. The compounds of the present process invention having one asymmetric carbon atom may be obtained as racemic mixtures of stereoisomers which can be resolved, at the appropriate steps in the process of this invention by methods well known in the art to obtain a given stereoisomer or pure enantiomer having a desired stereoconfiguration. Alternatively, the desired isomers may be directly synthesized by methods known in the art.

20 The asymmetric carbon atom in the compound of the present invention is denoted as "*". The stereoconfiguration of the asymmetric carbon atom denoted as "*" can be designated according to the particular stereoisomer it represents. Compounds of the present invention include those compounds wherein the carbon atom denoted as "*" have the S, R or R,S-configuration, preferably the R-configuration.

25 The term halogen stands for chlorine, bromine and iodine, more preferred chlorine or bromine, most preferred halogen is bromine.

The compounds of the present invention are prepared as shown in the reaction scheme 1.

Reaction scheme 1:



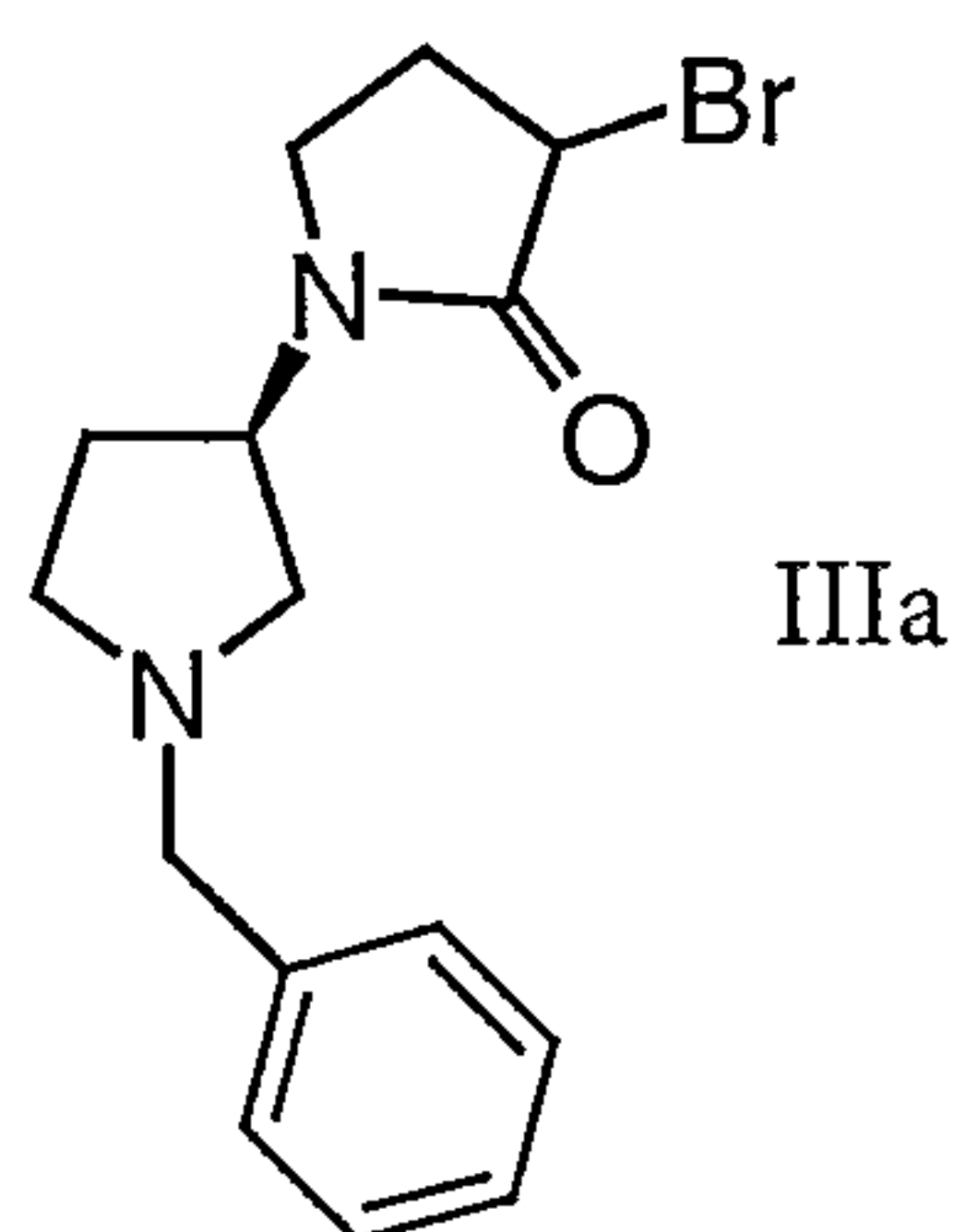
5 wherein * and X are as defined above.

In the 1st step of the reaction the compound of formula II is coupled with 1-4 equivalents, preferably 1-2 equivalents of $X(CH_2)_2CH(X)COX$ wherein X is independently of each other chlorine or bromine or iodine, preferably bromine (preparation see below) in the presence of bases such as Na_3PO_4 , K_2CO_3 , Na_2CO_3 , KOH or NaOH, preferably
 10 Na_3PO_4 and an appropriate solvent. Appropriate solvents are polar aprotic solvents such as acetonitrile (CH_3CN), dimethylsulfoxide (DMSO), dimethylacetamide or N,N-dimethylformamide (DMF), preferably CH_3CN . The reaction is carried out at a reaction temperature between about $-20^\circ C$ and about $30^\circ C$, preferably at a reaction temperature between about $-10^\circ C$ and about $10^\circ C$. Subsequently, a cyclization reaction is carried out
 15 with the intermediate coupling product to obtain compounds of formula III. The cyclization reaction is carried out in the presence of 1-3 equivalents, preferably 2-2.5 equivalents of a base, such as K_2CO_3 , Na_2CO_3 , KOH or NaOH, preferably NaOH in aqueous solution, at a reaction temperature between about $-10^\circ C$ and about $50^\circ C$, preferably between about $10^\circ C$ and about $30^\circ C$.

20 Compounds of formula $X(CH_2)_2CH(X)COX$ wherein X is independently of each other chlorine or bromine or iodine are commercially available or are synthesized according to methods known from textbooks. For example the compound of formula $X(CH_2)_2CH(X)COX$ wherein X is chlorine is prepared according to Mathew, K. K. et al. Indian J. Chem., Sect. B (1981), 20B(4), 340-2. The compound of formula
 25 $X(CH_2)_2CH(X)COX$ wherein X is bromine is prepared according to Marinelli, E. R. et al. Tetrahedron (1996), 52(34), 11177-11214. The compound of formula $X(CH_2)_2CH(X)COX$ wherein X is iodine can be obtained by reacting the tribromide ($X=Br$) with NaI in CH_3CN .

- 5 -

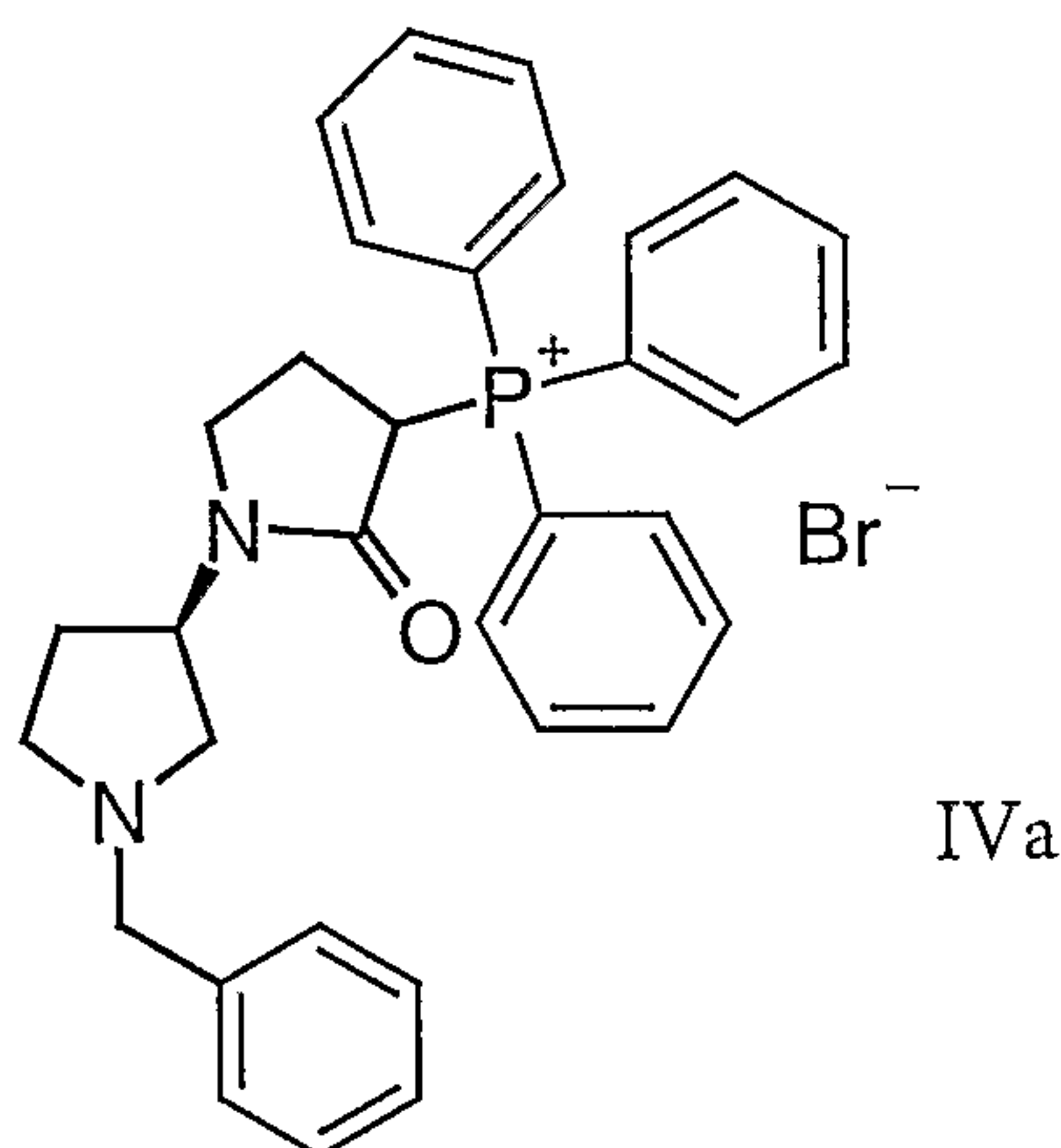
In a preferred embodiment of the invention the compound of formula IIIa



is formed according to the above described 1st step of the reaction. The compound of formula IIIa is new and therefore part of the present invention.

5 In the 2nd step of the process the compound of formula III is reacted with 1-5 equivalents, preferably 2-4 equivalents of triphenylphosphine to obtain the phosphonium salt of formula IV. The reaction is carried out in an aromatic solvent such as toluene, o-xylene, m-xylene, p-xylene or benzene, preferably toluene at a reaction temperature between about 20°C and about 180°C, preferably between about 80°C and about 140°C.

10 In a preferred embodiment of the invention the compound of formula IVa



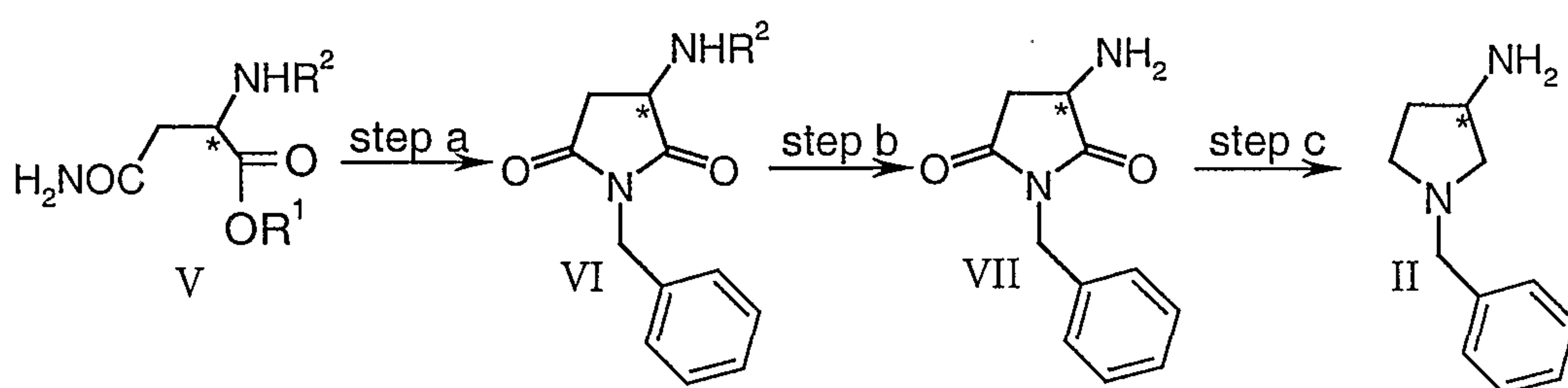
is formed according to the above described 2nd step of the reaction. The compound of formula IVa is new and therefore part of the present invention.

15 In the 3rd step of the process the phosphonium salt of formula IV is reacted with 1-5 equivalents, preferably 2-4 equivalents of di-tert.-butyl-dicarbonate (commercially available from Fluka) under hydrogenation conditions in the presence of a catalyst such as Pd/C (commercially available from Degussa) preferably with 10% Pd on activated carbon, to obtain compounds of formula I. The reaction is carried out in an alcoholic solvent such as methanol, ethanol or isopropanol, preferably in methanol at a reaction temperature
20 between about 10°C and about 100°C, preferably between about 40°C and about 80°C.

In a preferred embodiment of the invention steps 1-3 are carried out for compounds wherein * signifies an asymmetric center with (R) configuration and X is chlorine or bromine, preferably bromine.

Compounds of formula II, used as starting material in the present process is prepared according reaction steps a→b→c as shown in reaction scheme 2. The preparation of the compound of formula II is also part of the present invention.

Reaction scheme 2:



wherein R¹ is alkyl, R² is an amino protecting group and * is as defined above.

The terms which have already been mentioned and will be mentioned in the description of the invention are defined as follows:

The term "alkyl" as used herein denotes an optionally substituted straight or branched chain hydrocarbon residue containing 1 to 12 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert.-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and its isomers.

Alkyl in R¹ is preferably unsubstituted straight or branched chain hydrocarbon residue containing 1 to 4 carbon atoms, more preferred methyl or ethyl, and most preferred methyl.

The term "amino protecting group" as used herein refers to groups such as those employed in peptide chemistry, such as an allyloxycarbonyl group (ALLOC), a lower alkoxy carbonyl group such as tert-butoxycarbonyl (t-BOC) and the like, a substituted lower alkoxy carbonyl group such as trichloroethoxycarbonyl, an optionally substituted aryloxy carbonyl group for example p-nitrobenzyloxycarbonyl or benzyloxycarbonyl (Z), an arylalkyl group such as triphenylmethyl (trityl), benzhydryl or benzyl, an alkanoyl group such as formyl, acetyl or benzoyl, a halogen-alkanoyl group such as trifluoroacetyl, or a silyl protective group such as the tert-butyldimethylsilyl group.

Preferred amino protecting groups are benzyloxycarbonyl, tert-butoxycarbonyl or allyloxycarbonyl.

An especially preferred amino protecting for R² is the benzyloxycarbonyl group.

The term "lower alkoxy" signifies an alkyl group as defined above which is bonded via an oxygen atom. Examples are methoxy, ethoxy, propyloxy, butoxy, tert. butoxy and the like.

The term "aryl" as used herein denotes an optionally substituted phenyl group (Ph) in which one or more aryl hydrogen atoms can be substituted by one or more phenyl groups, alkyl groups, lower alkoxy groups, halogenated alkyl groups, halogen atoms or nitro. Examples are phenyl, o-tolyl, m-tolyl, p-tolyl, o-methoxyphenyl, m-methoxyphenyl, p-methoxyphenyl, o-trifluoromethylphenyl, m-trifluoromethylphenyl, p-trifluoromethylphenyl, o-trichloromethylphenyl, m-trichloromethylphenyl, p-trichloromethylphenyl, p-fluorophenyl p-chlorophenyl, p-bromophenyl, p-nitrophenyl.

The term "aryloxy" signifies an aryl group as defined above which is bonded via an oxygen atom. Examples are phenyloxy, benzyloxy and the like.

The term "lower alkoxycarbonyl" denotes lower alkoxy residues as defined, attached to a carbonyl group ($-C(=O)$). Examples are methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl and the like.

The term "aryloxycarbonyl" denotes aryloxy residues as defined, attached to carbonyl group ($-C(=O)$). Examples are phenyloxycarbonyl and benzyloxycarbonyl.

The term "arylalkyl" as used herein denotes a hydrocarbon group in which one or more alkyl hydrogen atoms are substituted by an aryl group as defined. Examples are trityl, benzhydryl or benzyl.

The term "hydroxy protecting group" as used herein denotes an alkyl group, a cycloalkyl group or an arylalkyl group. A preferred hydroxy protecting group is an arylalkyl group, especially preferred is a triphenylmethyl (trityl) group.

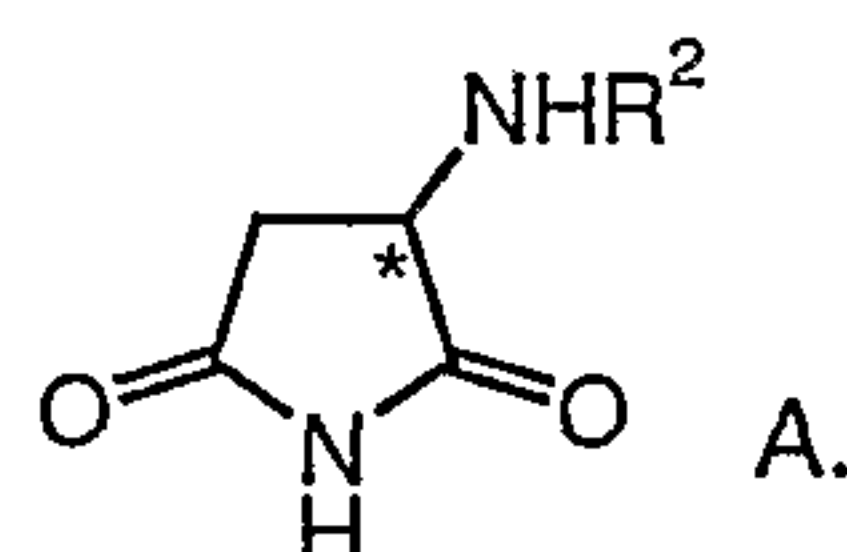
The term "carboxylic acid protecting group" includes protecting groups which are usually used to replace a proton of the carboxyl group. Examples of such groups are described in Green T. Protective Groups in Organic Synthesis, Chapter 5, John Wiley and Sons, Inc. (1981), pp. 152-192. Examples of such protecting groups are: benzhydryl, tert.-butyl, p-nitrobenzyl, p-methoxybenzyl, methoxymethyl and the like. Benzhydryl is a preferred carboxylic acid protecting group.

The term "cycloalkyl" as used herein denotes a 3-6 membered saturated carbocyclic moiety, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, preferably cyclohexyl.

In step (a) of the reaction the asparagine derivatives of formula V (preparation see below) is treated with 0.5 - 2.0 equivalents, preferably 1.0 - 1.5 equivalents of a base such as

- 8 -

NaH, NaOH or KOH, preferably with NaH, in an appropriate solvent to obtain the cyclic intermediate of formula A



wherein * and R² are as defined above.

5 Appropriate solvents for the cyclization reaction are ethers such as tetrahydrofuran, diethyl ether, dioxane or a mixture of the mentioned solvents, preferably tetrahydrofuran. Then, in a preferred embodiment of the invention, the intermediate of formula A is reacted with commercially available benzyl bromide in the presence of an appropriate solvent to obtain the 3-amino protected benzyl-2,5-dioxo-pyrrolidine of formula VI. Appropriate
10 solvents are polar aprotic solvents such as dimethylsulfoxide (DMSO), dimethylacetamide or N,N-dimethylformamide (DMF), preferably DMF. The reaction is carried out at a temperature between about 0°C and about 50°C, preferably between about 10°C and about 40°C.

In another embodiment of the invention the intermediate of formula A is reacted
15 with commercially available p-methoxybenzylbromide, 3,4-dimethoxybenzylbromide, trityl chloride, methoxy methyl chloride or allyl bromide under above-described reaction conditions or alternatively according to methods known from textbooks on organic chemistry (e.g. J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons) to obtain the corresponding 1-N-substituted 3-
20 amino protected-2,5-dioxo-pyrrolidine of formula VI.

The reaction of step (a) can optionally be carried via a two step procedure. First, the asparagine derivatives of formula V is treated with 0.5 - 2.0 equivalents, preferably 1.0 - 1.5 equivalents of a base such as NaH, NaOH or KOH, preferably with NaH in an appropriate solvent to obtain the cyclic compound of formula A. Appropriate solvents for this first step
25 are ethers such as tetrahydrofuran, diethyl ether, dioxane or a mixture of the mentioned solvents, preferably tetrahydrofuran. The reaction is carried out at a temperature between about -10°C and about 30°C, preferably starting at 0°C; during the reaction the temperature is increased to room temperature. After the reaction, the reaction mixture is acidified to a pH in the range between 3.0 and 5.0, preferably between 3.5 and 4.5, and
30 then the organic solvent is evaporated. Secondly, the compound of formula A is treated with a base such as NaH, NaOH or KOH, preferably with NaH in ethers such as tetrahydrofuran, diethyl ether, dioxane or a mixture of the mentioned solvents, preferably in tetrahydrofuran.

Then, in a preferred embodiment of the invention, the mixture is reacted with commercially available benzyl bromide in the presence of an appropriate solvent to obtain the 3-amino protected benzyl-2,5-dioxo-pyrrolidine of formula VI. Appropriate solvents for the reaction are polar aprotic solvents such as dimethylsulfoxide (DMSO),
5 dimethylacetamide or N,N-dimethylformamide (DMF), preferably DMF. The reaction is carried out at a temperature between about -10°C and about 30°C, preferably starting at 0°C; during the reaction the reaction temperature is increased to room temperature. After the reaction, the product is worked-up in a manner known in the art for example quenched with H₂O and extracted with an aromatic solvent such as toluene, o-xylene, m-
10 xylene, p-xylene or benzene preferably toluene, dried over anhydrous magnesium sulfate, sodium sulfate, calcium chloride, preferably magnesium sulfate and finally the organic solvent is evaporated.

In another embodiment of the invention the mixture is reacted with commercially available p-methoxybenzylbromide, 3,4-dimethoxybenzylbromide, trityl chloride, methoxy
15 methyl chloride or allyl bromide under above-described reaction conditions or alternatively according to methods known from textbooks on organic chemistry (e.g. J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons) to obtain the corresponding 1-N-substituted 3-amino protected-2,5-dioxo-pyrrolidine of formula VI.

20 Asparagine derivatives of formula V are commercially available or can be synthesized according to methods known from textbooks on organic chemistry (e.g. J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons) for example starting with D- or L-asparagine (Fluka) protection of the free amino function and subsequent esterification to obtain the corresponding asparagine derivatives
25 of formula V.

The advantage of carrying out the reaction of step (a) via a two step procedure is that the compounds of formula VI are obtained in higher yield. The two step procedure is also a part of the present invention.

In step (b) of the process the amino protecting group (R²) of the compounds of
30 formula VI is removed under condition described below. Preferred amino protecting groups for R² are benzyloxycarbonyl, tert-butoxycarbonyl or allyloxycarbonyl, most preferred benzyloxycarbonyl. The benzyloxycarbonyl amino protecting group is for example removed under hydrogenation conditions in the presence of a catalyst such as Pd/C (commercially available from Degussa) preferably with 10% Pd on activated carbon.
35 The deprotection reactions are carried out in the presence of acetic acid, trifluoroacetic

- 10 -

acid, ethanolic HCl, methanesulphonic acid or fluorosulphonic acid to obtain the corresponding amino salt of formula VII which is more stable than the free base and therefore can be stored without degradation. In a preferred embodiment acetic acid is used to prepare the acetic acid salt of formula VII. The reaction is carried out at a temperature
5 between about 10°C and about 50°C, preferably between about 20°C and about 40°C.

Depending on the amino protecting groups the deprotection is carried out as follows:

The amino protecting groups may be cleaved off by acid hydrolysis (e.g. the tert-butoxycarbonyl or trityl group), e.g. aqueous formic acid, trifluoroacetic acid or by basic
10 hydrolysis (e.g. the trifluoroacetyl group). Further protecting groups may be cleaved off by hydrazinolysis (e.g. the phthalimido group). The allyloxycarbonyl group may be cleaved off by Pd catalysed transfer to nucleophiles. The chloroacetyl, bromoacetyl and iodoacetyl groups are cleaved off by treatment with thiourea.

Amino protecting groups which are cleavable by acid hydrolysis are preferably
15 removed with the aid of a lower alkanecarboxylic acid which may be halogenated. In particular, formic acid or trifluoroacetic acid is used. The reaction is carried out in the acid or in the presence of a co-solvent such as a halogenated lower alkane, e.g. methylene chloride. The acid hydrolysis is generally carried out at room temperature, although it can be carried out at a slightly higher or slightly lower temperature (e.g. a temperature in the
20 range of about -30°C to 40°C). Protecting groups which are cleavable under basic conditions are generally hydrolyzed with dilute aqueous caustic alkali at 0°C to 30°C. The chloroacetyl, bromoacetyl and iodoacetyl protecting groups can be cleaved off using thiourea in acidic, neutral or alkaline medium at about 0°C to 30°C.

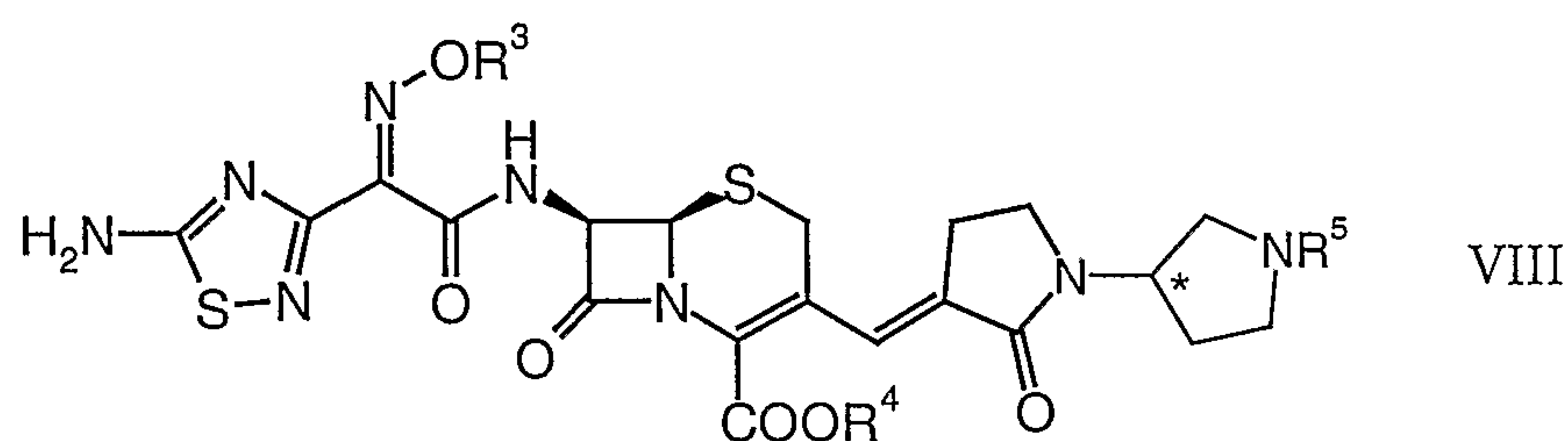
In step (c) of the process the amino salt compound of formula VII is treated with a
25 base such as NaOH, KOH, Na₂CO₃ or K₂CO₃ preferably with NaOH in aqueous solution to adjust the pH in the ranges from 7.0 to 9.0, preferably in the range from 7.5 to 8.5 in the presence of a halogenated hydrocarbon such as monochloromethane or dichloromethane, preferably dichloromethane, to remove the acid and to obtain the intermediate acid free compound of formula VII. The intermediate is then worked-up by extraction with a
30 halogenated hydrocarbon such as monochloromethane or dichloromethane, preferably dichloromethane and then the organic solvent is evaporated. Subsequently, the acid free derivative of formula VII is reduced with a reducing agent such as Vitride®, NaBH₄, LiBH₄, LiAlH₄, BH₃•THF, preferably with Vitride®, to obtain the amino pyrrolidine of formula II. The reducing agents are commercially available from Aldrich or Fluka. The
35 reaction is carried out in an aromatic solvent such as toluene, o-xylene, m-xylene, p-xylene

or benzene, preferably with toluene at a reaction temperature between about -10°C and about 100°C, preferably starting at 0°C; during the reaction the temperature is increased to 80°C. Then, the mixture is cooled to a temperature between about -20°C and about 20°C, preferably to a temperature between about -10°C and about 10°C and treated with a base
 5 such as sodium hydroxide in aqueous solution.

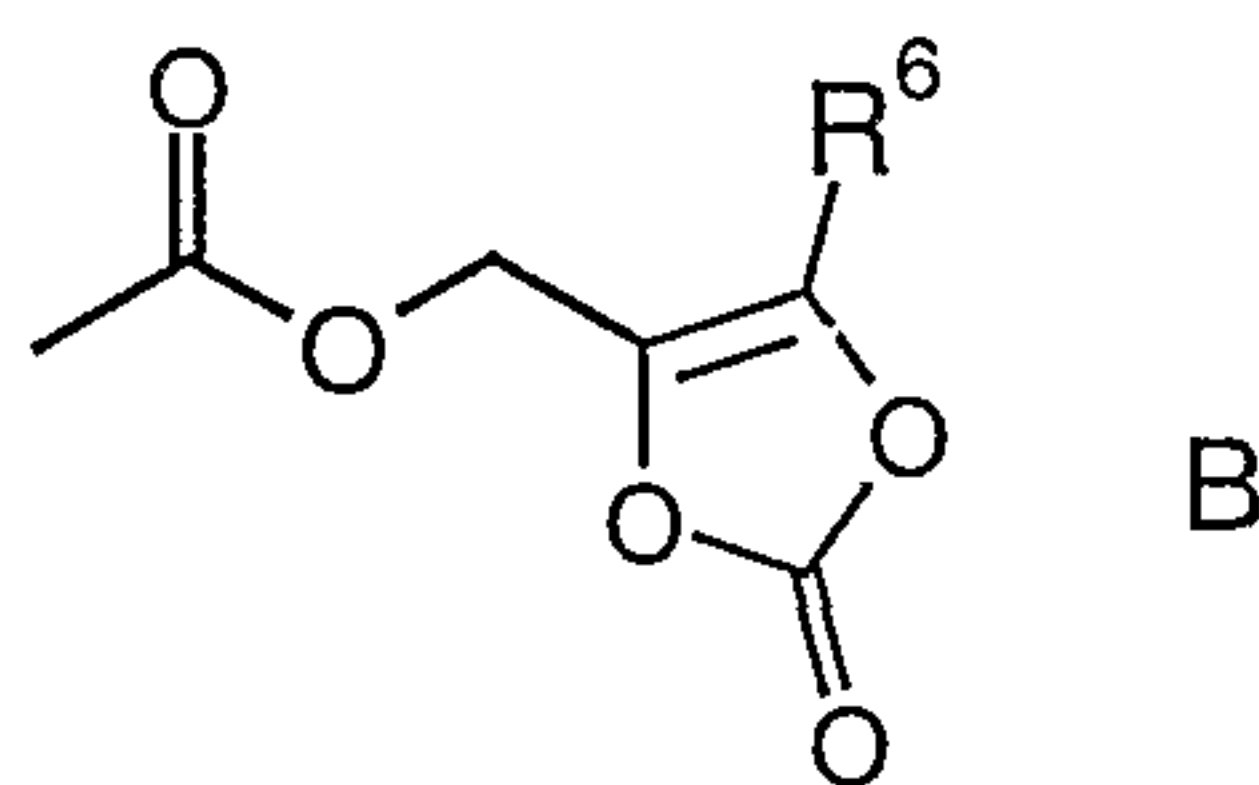
In a preferred embodiment of the process steps a-c are carried out for compounds wherein * signifies an asymmetric center with (R) configuration and R¹ is methyl or ethyl, preferably methyl and R² is benzyloxycarbonyl, tert-butoxycarbonyl or allyloxycarbonyl, preferably benzyloxycarbonyl and X is chlorine or bromine, preferably bromine.

10 The compounds of formula I-VII are important building blocks for the production of useful products in the chemical and pharmaceutical industry. In particular they are useful for the production of antibacterial substances for example vinylpyrrolidinone-cephalosporin derivatives as described in EP-A 0 849 269. Preferably compounds of formula I-VII are useful for the preparation of compounds of formula VIII

15



wherein R³ is a hydroxy protecting group, R⁴ is a carboxylic acid protecting group,
 * is as defined above and R⁵ is an amino protecting group preferably a tert-
 20 butoxycarbonyl group or a group of formula B



wherein R⁶ is preferably an unsubstituted straight chain or branched alkyl group containing 1 to 4 carbon atoms, more preferred methyl, ethyl or isopropyl and most
 25 preferred methyl.

The preparation of compounds of formula VIII is described in EP-A 0 849 269.

- 12 -

In the following examples the abbreviations used have the following signification's.

	ISP-MS	ion spray positive mass spectroscopy
	EI-MS	electron impact mass spectroscopy
5	GC	gas chromatography
	SFC	super critical fluid chromatography
	NMR	nuclear magnetic resonance spectroscopy
	IR	infrared spectroscopy
	TLC	thin layer chromatography
10	HPLC	high performance liquid chromatography
	HV	high vacuum
	FID	flame ionization detector
	THF	tetrahydrofurane
	DMF	N,N-dimethylformamide
15	DMSO	dimethylsulfoxide
	TBME	tert.-butyl methyl ether
	TFA	trifluoracetic acid
	TBAHS	tetrabutylammonium hydrogen sulfate
	min	minute(s)
20	h	hour(s)
	rt	room temperature

- 13 -

Example 1Preparation of (R)-(1-benzyl-2,5-dioxo-pyrrolidin-3-yl)-carbamic acid benzyl ester

1.1 (via one step): A suspension of 1.12 g of 60 % NaH in 75 ml of THF is treated with 7.50 g of Z-(D)-asparagine methyl ester (99.9% (R)-isomer) (synthesized according to J. Liq. Chromatogr. (1994), 17(13), 2759 or for example starting with D-asparagine (Fluka) and protecting the free amino function with a benzyloxycarbonyl group and subsequent esterification to the corresponding methyl ester asparagine derivative of formula I; the reactions are carried out according to textbook of organic chemistry e.g. J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons) over 5 min at rt. After 20 min, 3.57 ml of benzyl bromide (commercially available from Fluka) was added, followed by 120 ml of DMF. After 3 h, the conversion was completed (indicated by HPLC). The reaction was quenched with 150 ml H₂O and extracted three times with 120 ml of toluene. The organic layer was washed with H₂O, dried over MgSO₄, filtered and the filtrate was evaporated to dryness. The residue was triturated in 100 ml of TBME, the resultant suspension filtered and dried (35°C/10 mbar) to give 8.13 g (90 %) of (R)-(1-benzyl-2,5-dioxo-pyrrolidin-3-yl)-carbamic acid benzyl ester as white crystals: m.p. 143.3-144.5°C. Optically pure material could be obtained from crystallization from CH₂Cl₂ / n-hexane, 72% recovery; m.p. 145.9-146.7°C; 99.9% (R)-isomer.

1.2.1 (via two steps; 1st step): A suspension of 856 mg of 60% NaH in 50 ml THF at 0°C was treated with 5.0 g of Z-(D)-asparagine methyl ester 3 (99.9% (R)-isomer) and stirred at rt for 90 min whereupon TLC indicated complete consumption of the starting material. The reaction mixture was acidified to pH 4 with 6.0 ml of AcOH and the THF distilled away. The remaining aqueous layer was extracted three times with 20 ml of TBME and the combined organic phases washed with 20 ml of brine, dried over MgSO₄ and concentrated to give 4.66 g of a white sticky solid (105 % contains ~5% w/w AcOH) of (R)-(2,5-dioxo-pyrrolidin-3-yl)-carbamic acid benzyl ester as a white sticky solid which was used directly for the second step (example 1.2.2) below. Digestion in EtOAc / n-hexane gave 3.47 g (75%) of (R)-(2,5-dioxo-pyrrolidin-3-yl)-carbamic acid benzyl ester as white crystals, m.p. 117.2-117.8°C.

1.2.2 (via two steps; 2nd step): A suspension of 48.4 mg of 60% NaH in 3 ml of THF was treated with 300 mg of (R)-(2,5-dioxo-pyrrolidin-3-yl)-carbamic acid benzyl ester at 0°C followed by 161.3 µL of benzyl bromide. After 30 min the resulting precipitate was warmed to rt and treated with 3 ml of DMF to give after 15 min a solution which was stirred for 16 h at rt then quenched with 60 ml of H₂O and extracted with 40 ml of

- 14 -

toluene. The combined organic layers were dried over MgSO_4 and concentrated to give 409 mg (74%) of the (R)-(2,5-dioxo-pyrrolidin-3-yl)-carbamic acid benzyl ester as white crystals; m.p. 145.1-145.5°C. Overall yield for the two step process: 78%.

5

Example 2

Preparation of 3-(R)-amino-1-benzyl-pyrrolidin-2,5-dione acetic acid (1:2)

A solution of 7.80 g of (R)-(1-benzyl-2,5-dioxo-pyrrolidin-3-yl)-carbamic acid benzyl ester (93 % (R)-isomer) in 160 ml of acetic acid was treated with 0.78 g of 10% Pd/C (commercially available from Degussa; 1835) and hydrogenated at 30°C for 20 min whereupon TLC and HPLC indicated completion of the reaction. The reaction mixture was filtered, evaporated and the residue crystallized from EtOAc and n-hexane to give 5.80 g (78%) of 3-(R)-amino-1-benzyl-pyrrolidin-2,5-dione acetic acid (1:2) as white crystals; HPLC (100%): HP 1050, nucleosil 100-5 C18 column, CH_3CN , H_2O , TFA system buffered with TBAHS; GC (99.8% as free amine): J and W, DB-1, 15 m x 0.32 mm, carrier gas He, program: 50-320°C (5°C/min); injector temp. 250°C; FID: 320°C; 91 % (R)-isomer, analyzed as the corresponding trifluoroacetamide by GC (BGB-177): 15 m x 0.25 mm, carrier gas: He; program: 150°C-200°C at 1°C / min; injector temp. 210°C; FID: 220°C; NMR (CDCl_3 , 400 MHz; 1.6 eq AcOH) 7.32 (m, 5H, H-ar), 5.64 (bs, 4H, NH), 4.65 (s, 2H, PhCH_2O), 3.92 (dd, $J=5.4$ and 7.8, 1H, NCH), 3.05 (dd, $J=7.8$ and 18, COCH_2 , 1H), 2.50 (dd, $J=18$ and 5.4, COCH_2 , 1H), 2.08 (s, 2 x CH_3CO_2 , 6H).

20

Example 3

Preparation of (R)-1-(phenylmethyl)-3-pyrrolidinamine

A solution of 10.87 g of 3-(R)-amino-1-benzyl-pyrrolidine-2,5-dione acetic acid (1:2) in 100ml of H_2O was treated with 100 ml of CH_2Cl_2 followed by 67.60 ml of 1 N NaOH at rt to pH 8.0. After saturation with NaCl, the mixture was extracted seven times with 100 ml of CH_2Cl_2 , dried over MgSO_4 and evaporated at 35°C / 10mbar to give 6.32 g (97%) of the NMR clean free base as a pale yellow solid. NMR (CDCl_3 , 250 MHz): 7.30 (m, 5H, H-ar), 4.64 (s, 2H, PhCH_2), 3.88 (dd, $J=5$ and 7.5, 1H, NCH), 3.04 (dd, $J=7.5$ and 17.5, 1H, COCH_2), 2.43 (dd, $J=5$ and 17.5, 1H, COCH_2).

30

5.90 g of this yellow oil was treated at 0°C over 20 min with 33 ml of a 3.5 M solution of Vitride® in toluene and the resultant yellow-orange solution was warmed to 80°C for 30 min (MS indicated completion of the reaction), cooled to 0°C and treated with 80 ml of 1 N NaOH solution. The phases were separated and the aqueous phase extracted with two

- 15 -

further portions of 15ml toluene. The combined organic phases were washed with 76 ml 1N NaOH, 70 ml brine, dried and evaporated to give 4.42g (87%) of (R)-1-(phenylmethyl)-3-pyrrolidinamine, as a light brown oil. GC: (97%, J and W, DB-1, conditions as described for example 2; 93 % (R)-isomer, analyzed as the corresponding trifluoroacetamide by GC: (BGB-177), conditions as described for example 2; MS (Ion Spray): 177.1 ($M + H^+$); 1H -NMR ($CDCl_3$, 250 MHz): 7.28 (m, 5H, H-ar), 3.63 and 3.56 (2 x d, $J=12.5$, 2H, $PhCH_2N$), 2.69 (m, 2H, NCH_2CHNH_2 and $NCH_2CH_2CHNH_2$), 2.44 (m, 1H, $NCH_2CH_2CHNH_2$), 2.24 (dd, $J=4.5$ and 9.5 , 1H, NCH_2CHNH_2), 2.15 (m, 1H, $NCH_2CH_2CHNH_2$), 1.45 (bm, 3H, NH_2 and $NCH_2CH_2CHNH_2$); IR (Film): (NH) 3357 (m), (NCH) 2789 (s).

Example 4

Preparation of (R)-(1'-benzyl-3-bromo-[1,3']bipyrrolidinyl-2-one)

A solution of 5.0 g of (R)-1-(phenylmethyl)-3-pyrrolidinamine in 50.0 ml CH_3CN was treated at rt with 2.72 g of Na_3PO_4 . The resulting fine light yellow suspension was cooled to $0^\circ C$ and treated with a solution of 10.07 g of 2,4-dibromobutyrylbromide (prepared according to Marinelli, E. R.; Arunachalam, T.; Diamantidis, G.; Emswiler, J.; Fan, H.; Neubeck, R.; Pillai, K. M. R.; Wagler, T. R.; Chen, C.-K.; et al. Tetrahedron (1996), 52(34), 11177-11214) in 5.0 ml of CH_3CN over 20 min. After 30 min the very fine suspension was filtered and concentrated to a volume of 30 ml, and then treated with 130.1 ml of 0.497 M NaOH solution at room temperature. The resultant turbid orange solution was stirred for 2 h, concentrated and the resultant aqueous phase extracted with three portions of 50 ml of TBME. The combined organic phases were washed with H_2O until neutral, dried over $MgSO_4$ and concentrated to give 5.79g (63%) of (R)-(1'-benzyl-3-bromo-[1,3']bipyrrolidinyl-2-one) as yellow waxy crystals.

The fine suspension from above was triturated with 100 ml CH_3CN , filtered, concentrated to a volume of 40 ml and treated with 50 ml of 0.497 m NaOH, then stirred at rt for 1 h. The CH_3CN was distilled away and the resultant aqueous phase worked up as above to give a further 2.57g (28%) of product. The total yield 8.36g (91%). 1H -NMR ($CDCl_3$, 400 MHz, 14:1 mixture of diastereomers) 7.32 (m, 5H, H-ar), 4.65 (m, 1H, NCH), 4.39 (dd, 1H, CHBr), 3.60 (2d, 2H, $PhCH_2N$), 3.52 (m, 2H, $CONCH_2$), 2.92 (ddd, 1H, $PhCH_2NCH_2CH_2$), 2.71 (dd, 1H, $PhCH_2NCH_2CHNCO$), 2.49 (m, 2H, $COCHBrCH_2$ and $PhCH_2NCH_2CH$), 2.25 (m, 3H, $PhCH_2NCH_2CH_2$, $COCHBrCH_2$ and $PhCH_2NCH_2CH_2$), 1.70 (m, 1H, $PhCH_2NCH_2CH_2$).

- 16 -

Example 5Preparation of (R)-(1'-benzyl-2-oxo-[1,3']bipyrrolidinyl-3-yl)-triphenyl-phosphonium; bromide

A suspension of 800 mg of 1'-benzyl-3-bromo-[1,3']bipyrrolidinyl-2-one in 1.0 ml
5 toluene was treated with 1.95 g of Ph₃P and stirred at 110°C for 30 min whereupon TLC
indicated the reaction was complete. The brown two phase mixture was diluted with 10 ml
EtOAc and the organic phase was extracted with three portions of 10 ml of saturated NaBr
solution. The combined aqueous phases were washed three times with 10 ml EtOAc (to
remove Ph₃P), and then extracted seven times with 15 ml CH₂Cl₂, the combined organic
10 phases dried over MgSO₄ and concentrated to give 1.13g (78%) of (R)-(1'-benzyl-2-oxo-
[1,3']bipyrrolidinyl-3-yl)-triphenyl-phosphonium bromide as a light brown foam. ¹H-
NMR (250 MHz; CDCl₃, ~1:1 mixture of diastereomers): 7.32-8.04 (m, 5H), 7.50-7.82 (m,
10H), 7.19-7.40 (m, 5H), 6.44-6.64 (m, 1H), 4.39-4.50 (m, 1H), 3.10-3.88 (m, 5H), 2.85-
3.00 (m, 0.5 H), 2.62-2.80 (m, 1H), 2.32-2.5 (m, 0.5 H), 1.72-2.32 (m, 5H).

15

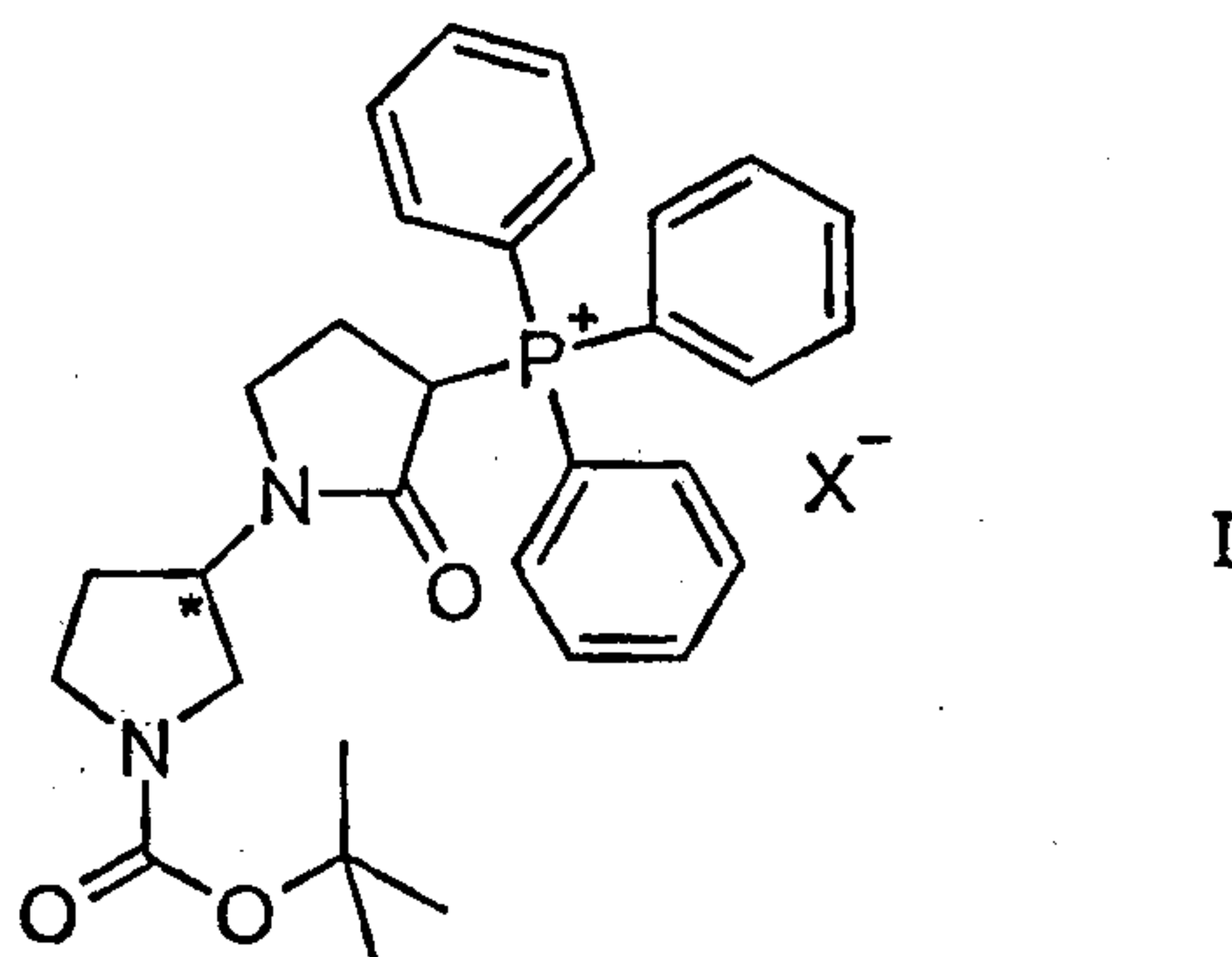
Example 6Preparation of (1'-tert-butoxycarbonyl-2-oxo-[1,3']-(R)-bipyrrolidinyl-3-(R,S)-yl)-triphenyl-phosphonium; bromide

A solution of the mixture of 880 mg of (R)-(1'-benzyl-2-oxo-[1,3']bipyrrolidinyl-3-
20 yl)-triphenyl-phosphonium bromide and 820 mg of di-tert.-butyl-dicarbonate
(commercially available from Fluka) in 5.5 ml MeOH was treated with 880 mg of 10 %
Pd/C (commercially available from Degussa; 1835) and hydrogenated at 60°C for 3 d and
then filtered and evaporated to give 627 mg (70 %) of (1'-tert-butoxycarbonyl-2-oxo-
[1,3']-(R)-bipyrrolidinyl-3-(R,S)-yl)-triphenyl-phosphonium; bromide as a beige foam.
25 ¹H-NMR (CDCl₃, 250 MHz; mixture of diastereomers and rotamers): 7.82-8.01 (m, 5H),
7.55-7.81 (m, 10H), 6.71-6.88 (m, 1H), 4.22-4.51 (m, 1H), 3.70-3.91 (m, 1H), 3.35-3.50 (m,
1H), 2.61-3.32 (m, 4H), 1.90-2.20 (m, 2H), 1.64-1.80 (m, 2H), 1.44 (s, 9H).

- 17 -

Claims

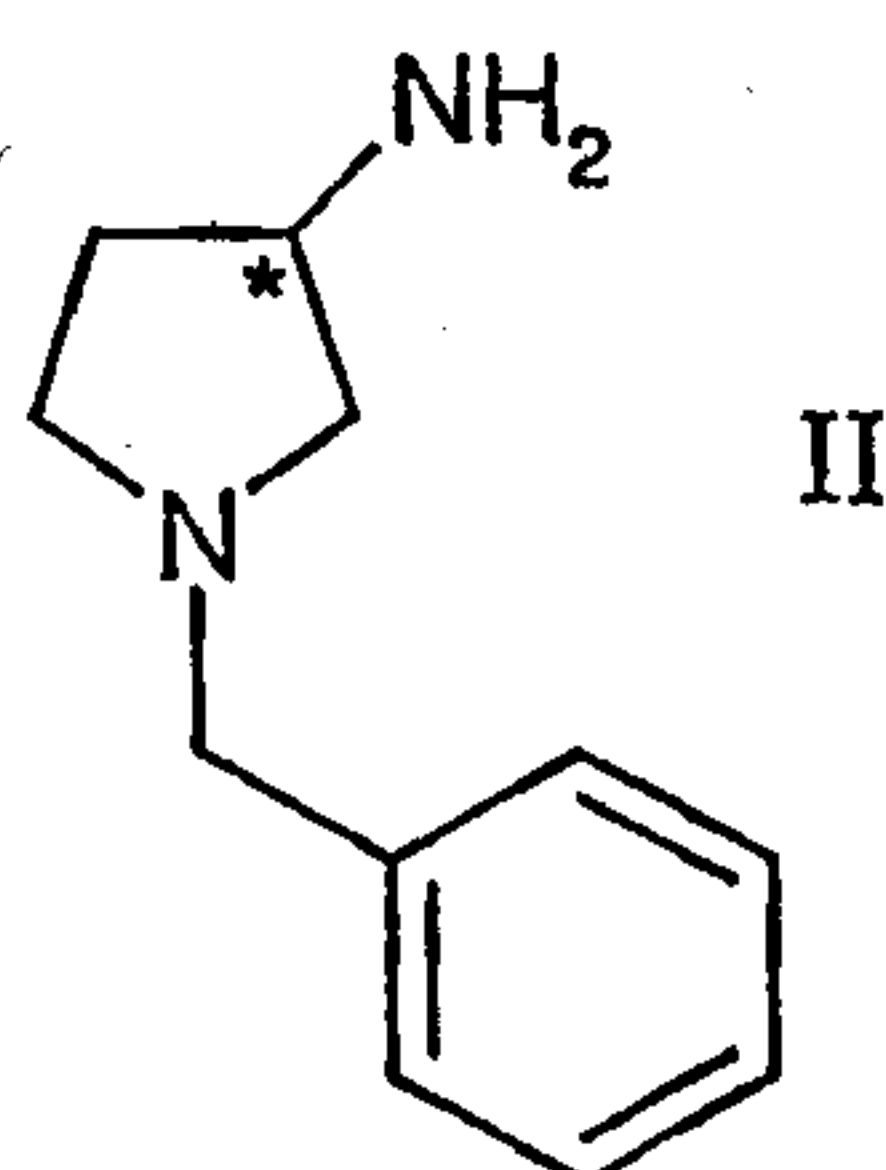
1. A process for the preparation of bipyrrolidinyl compounds of formula I



wherein * signifies an asymmetric center with an (R) or (S) configuration and X represents chlorine, bromine or iodine;

comprises

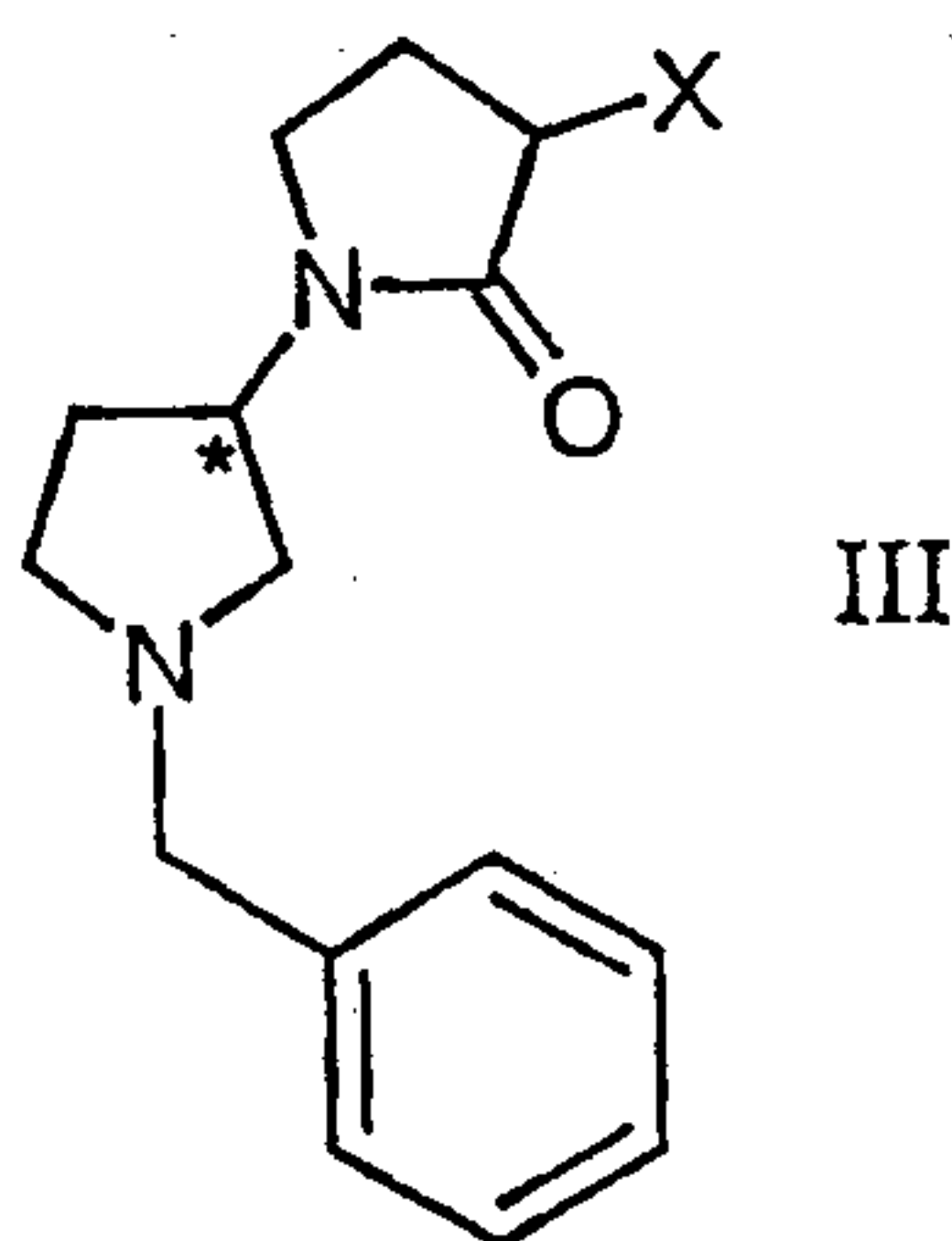
step 1) coupling the compound of formula II



wherein * is as defined above

with a compound of formula $X(CH_2)_2CH(X)COX$

wherein X is independently of each other chlorine, bromine or iodine; and subsequent cyclization in the presence of a base to obtain a compound of formula III

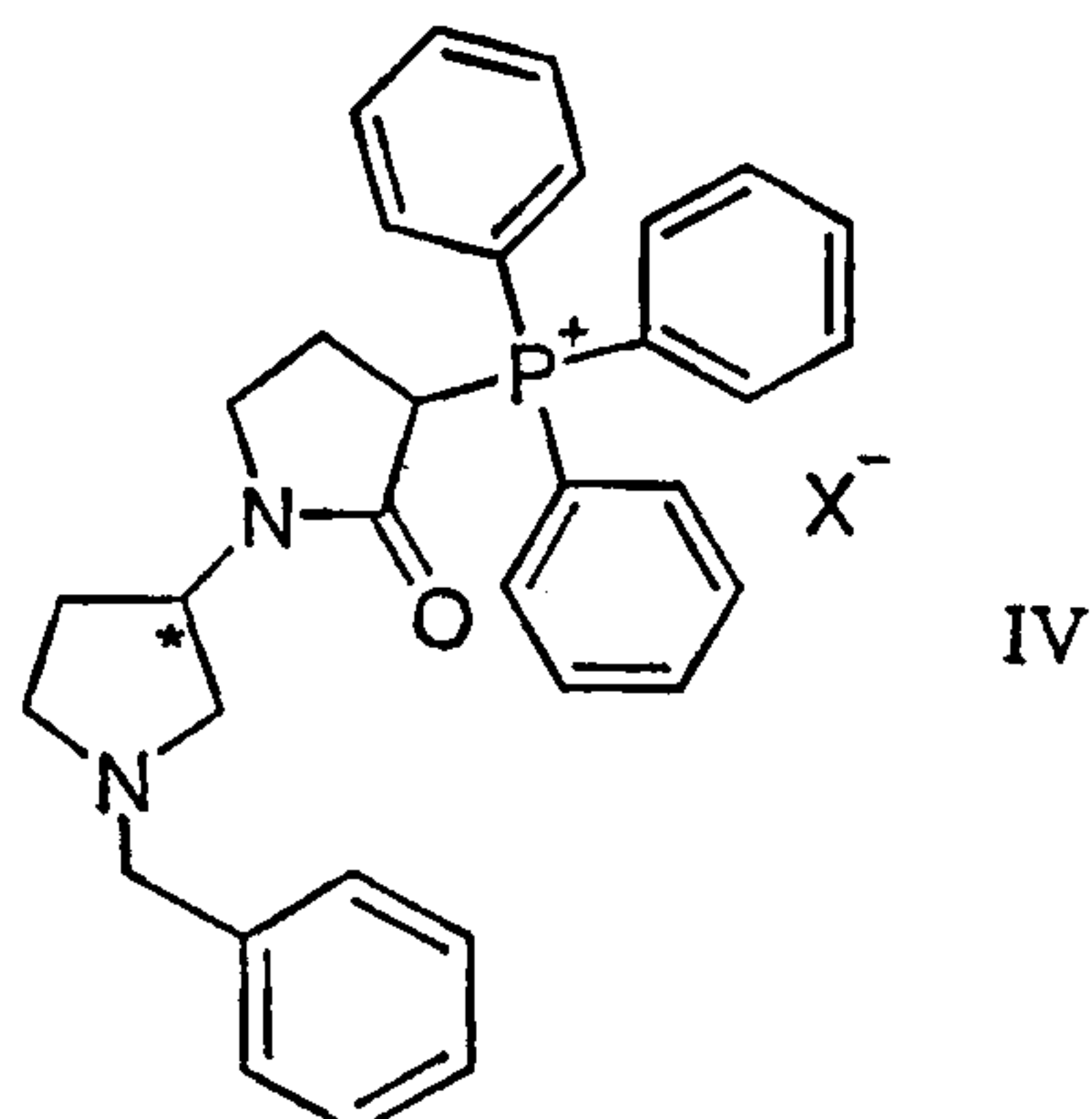


wherein * and X are as defined above;

step 2) reacting the compound of formula III with triphenylphosphine

- 18 -

to obtain the phosphonium salt of formula IV



wherein * and X are as defined above; and

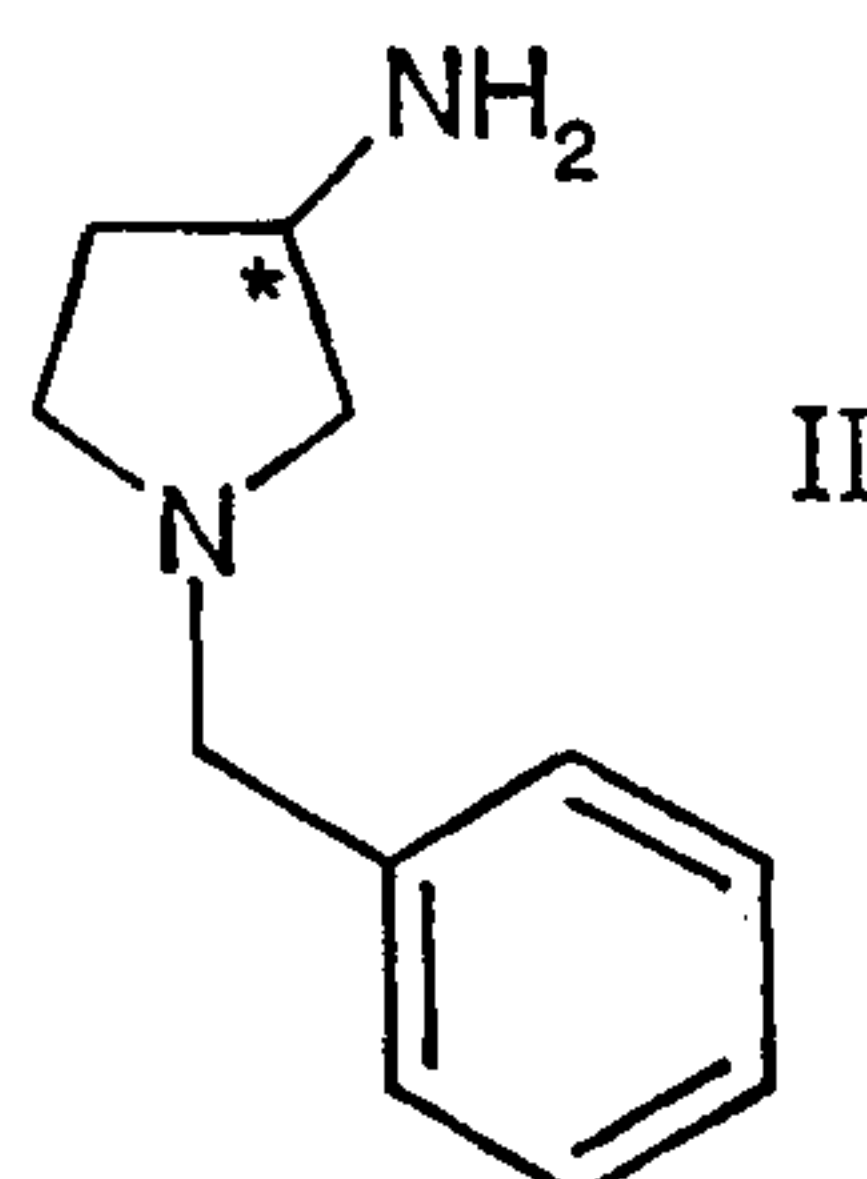
step 3) reacting the phosphonium salt of formula IV with di-tert.-butyl-dicarbonate under hydrogenation conditions to obtain the compounds of formula I.

2. The process as claimed in claim 1 characterized in that step 1 is carried out in the presence of Na_3PO_4 and the subsequent cyclization reaction is carried out in the presence of sodium hydroxide.

3. The process as claimed in any one of claims 1 to 2 characterized in that step 2 is carried out in an aromatic solvent.

4. The process as claimed in any one of claims 1 to 3 characterized in that step 3 is carried out in methanol and the hydrogenation is carried out in the presence of palladium on activated carbon.

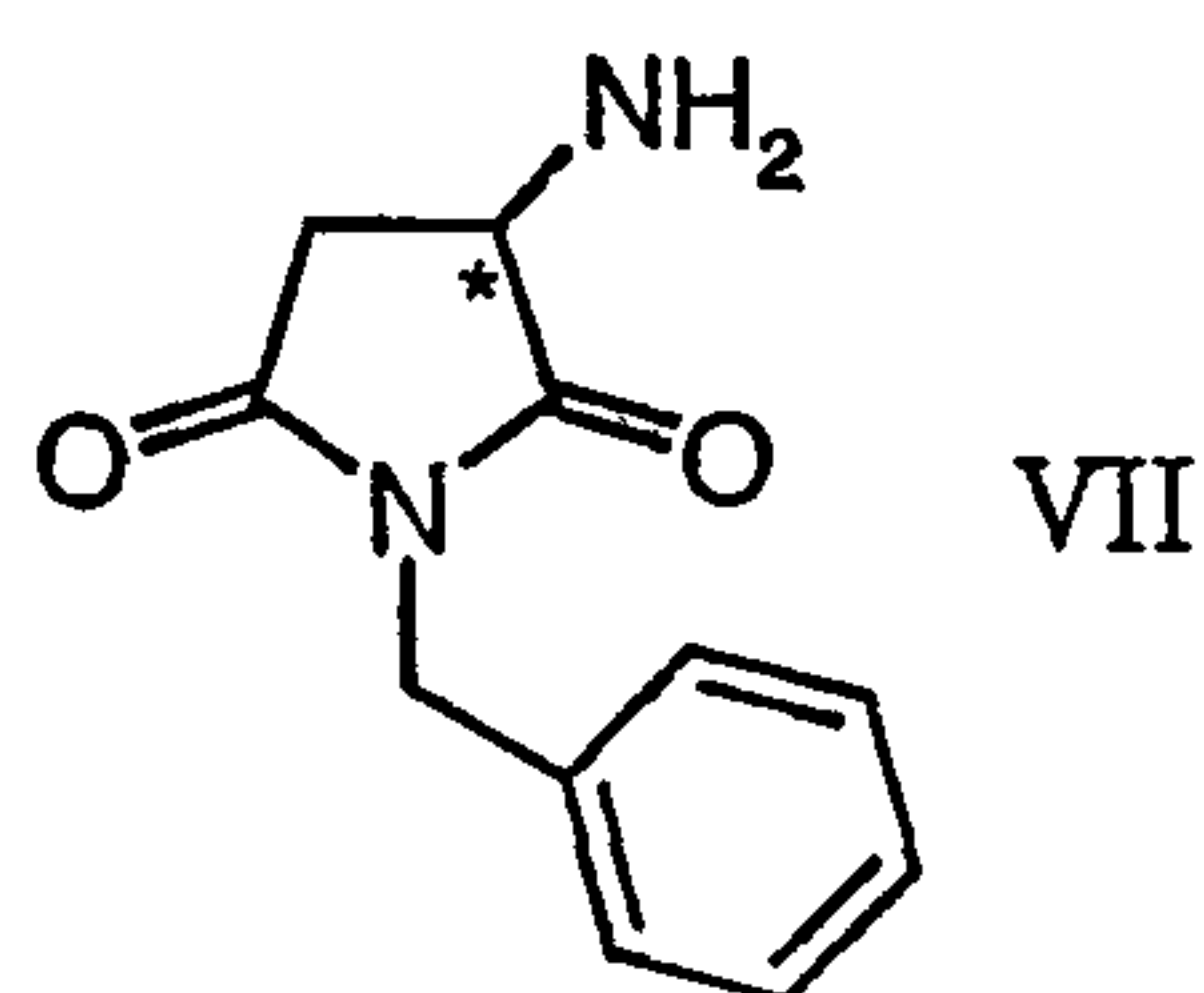
5. The process for the preparation of bipyrrrolidiny compounds of formula I according to claim 1 characterized in that compound of formula II



wherein * is as defined above

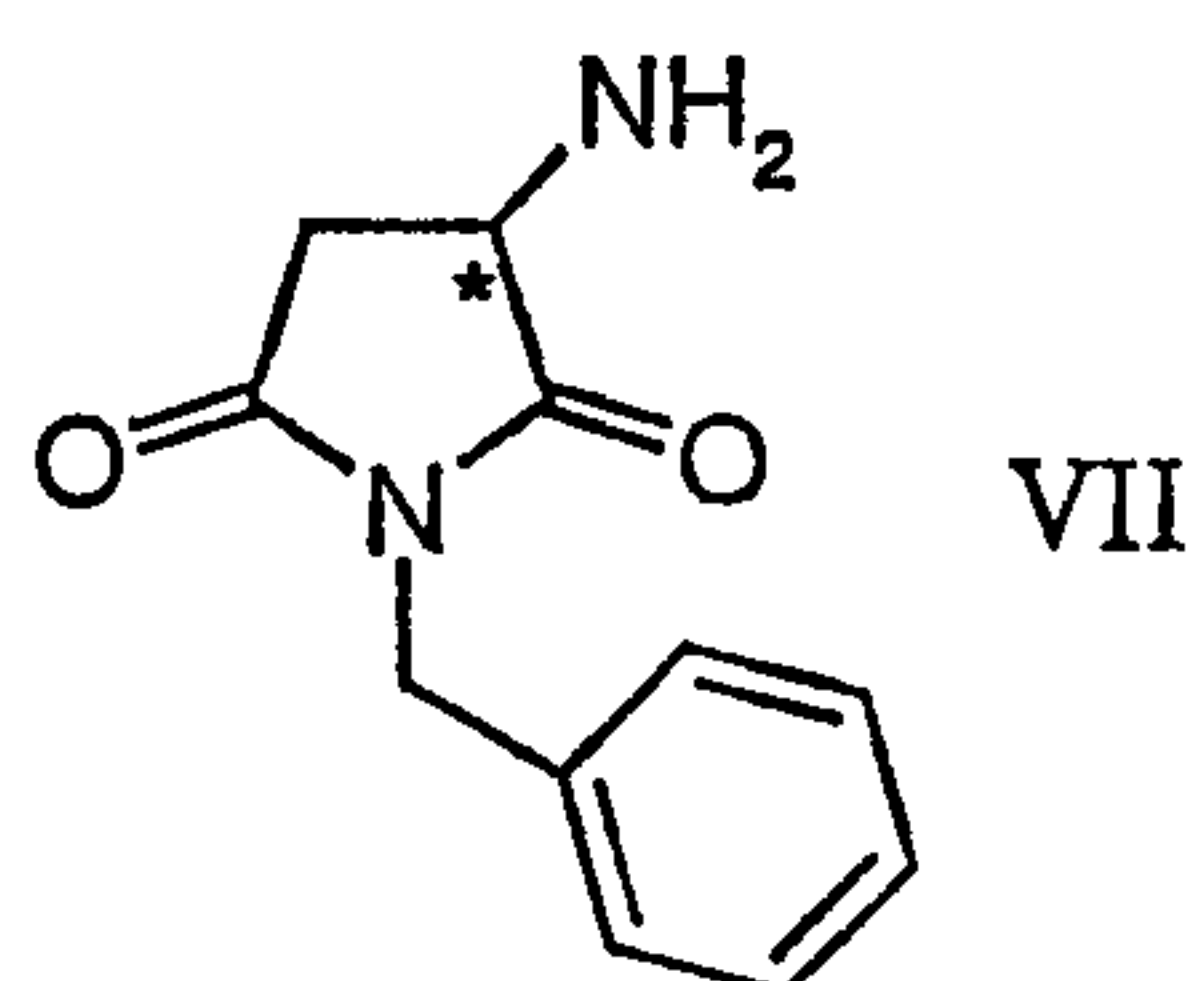
is prepared by reaction of the compound of formula VII

- 19 -

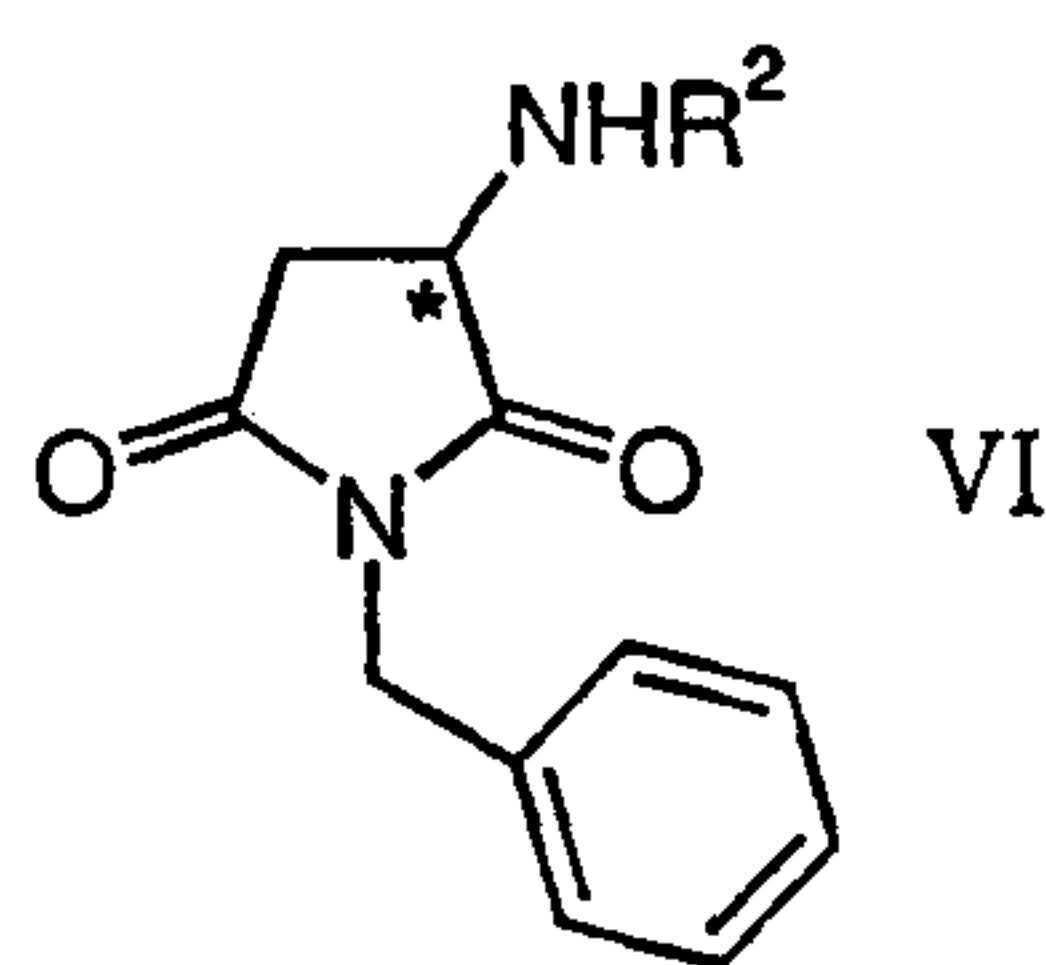


wherein * is as defined above
 with a base; and the subsequent reduction reaction is carried out with a reducing agent to obtain the amino pyrrolidine compound of formula II.

6. The process for the preparation of bipyrrrolidinyll compounds of formula I according to claim 5 characterized in that the compound of formula VII

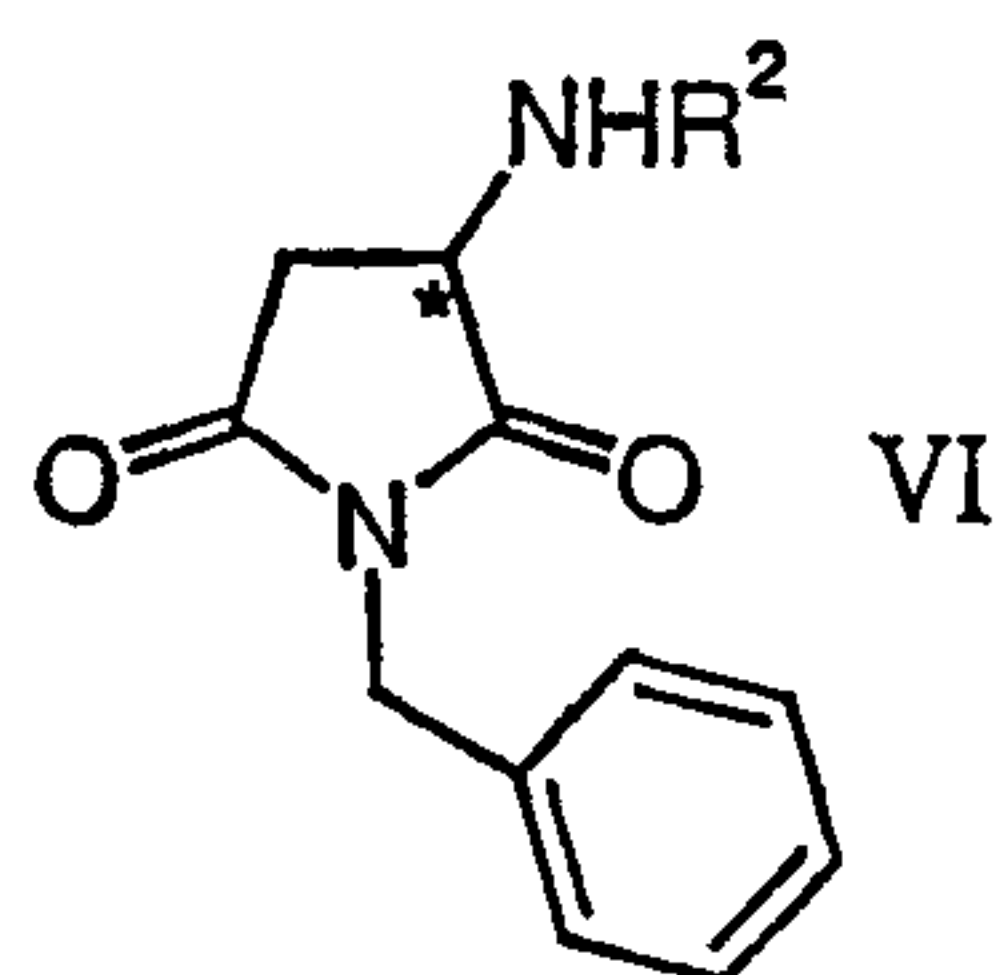


wherein * is as defined above
 is prepared by removal of the amino protecting group of compounds of formula VI



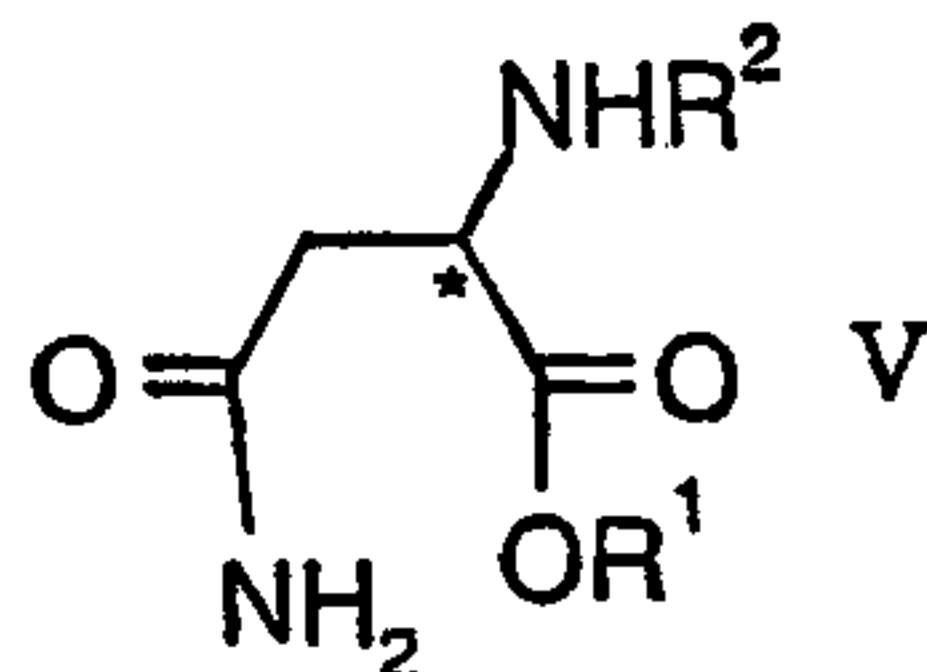
wherein * is as defined above and R² is an amino protecting group
 in the presence of an acid to obtain the amino salt of compound of formula VII.

7. The process for the preparation of bipyrrrolidinyll compounds of formula I according to claim 6 characterized in that compounds of formula VI



- 20 -

wherein * and R^2 are as defined above
 is prepared by cyclization reaction of compounds of formula V



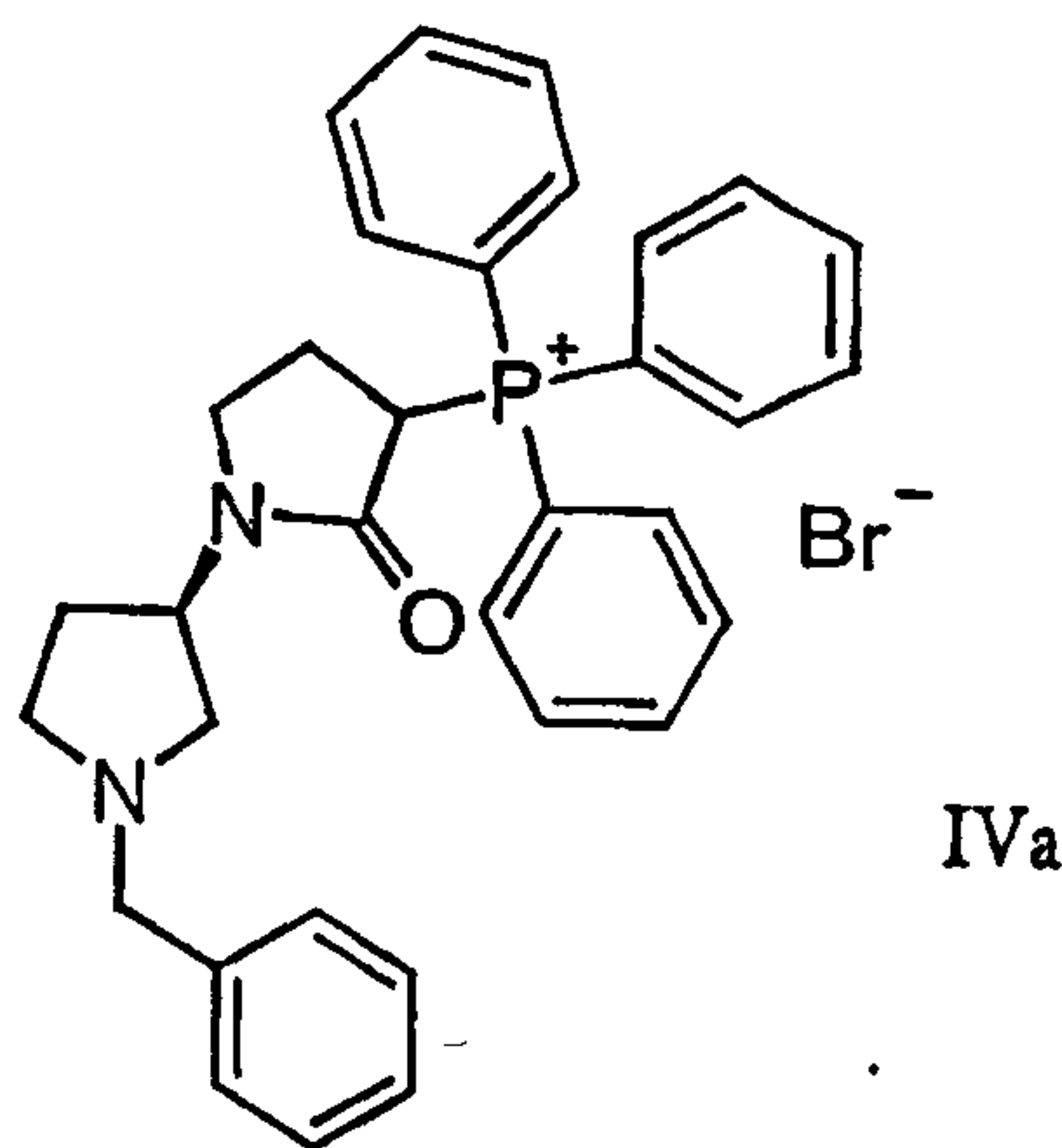
wherein R^1 is an alkyl group and * and R^2 are as defined above
 in the presence of a base; and subsequent reaction with benzyl bromide to obtain a
 compound of formula VI.

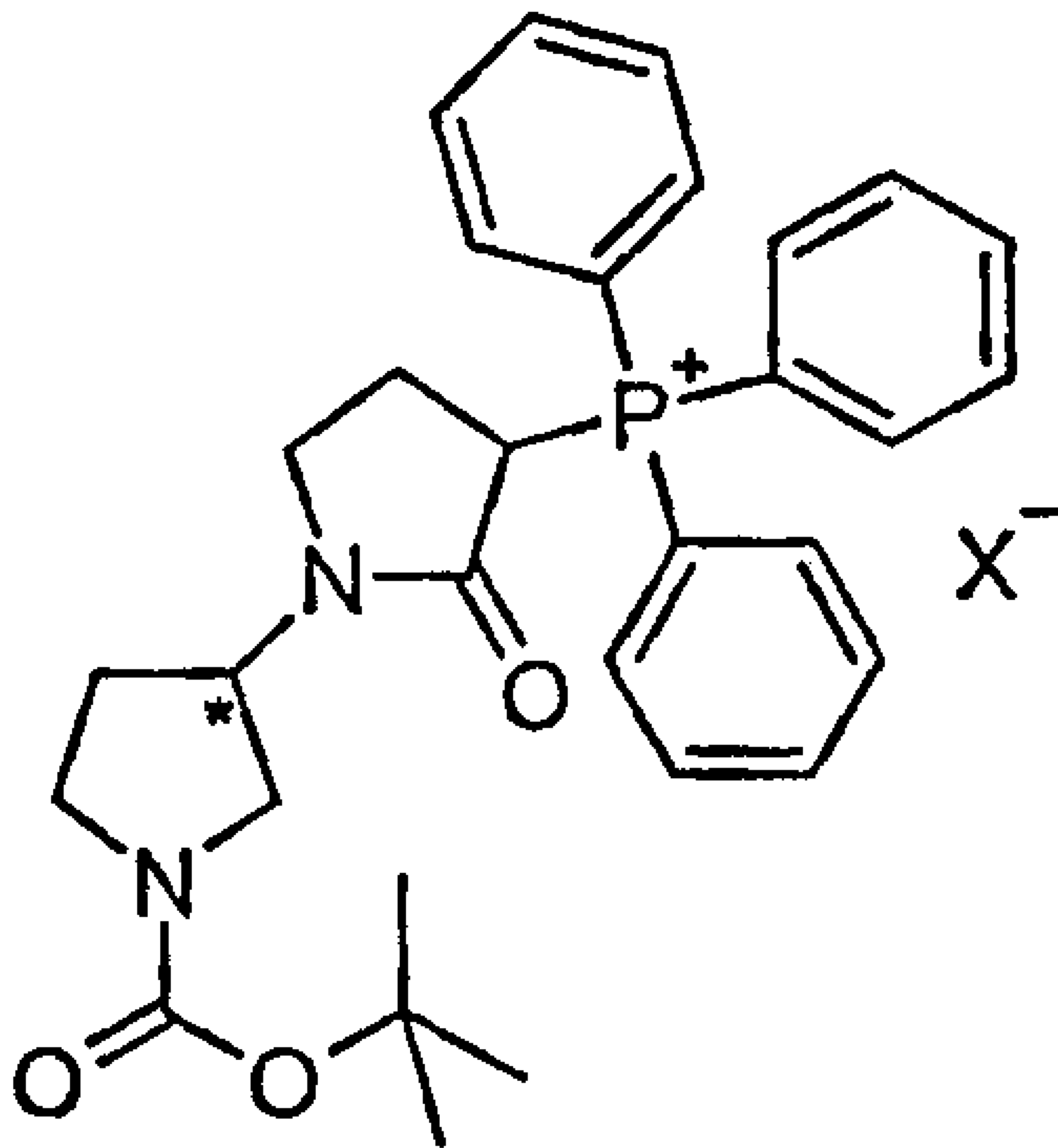
8. The process as claimed in any one of claims 1-7 characterized in that * signifies an asymmetric center with (R) configuration and R^1 is methyl or ethyl, R^2 is benzyloxycarbonyl, tert-butoxycarbonyl or allyloxycarbonyl and X is chlorine or bromine.

9. The process as claimed in any one of claims 1-8 characterized in that R^1 is methyl, R^2 is benzyloxycarbonyl and X is bromine.

10. The compound of formula IIIa (R)-(1'-benzyl-3-bromo-[1,3']bipyrrolidinyl-2-one).

11. The compound of formula IVa:





I