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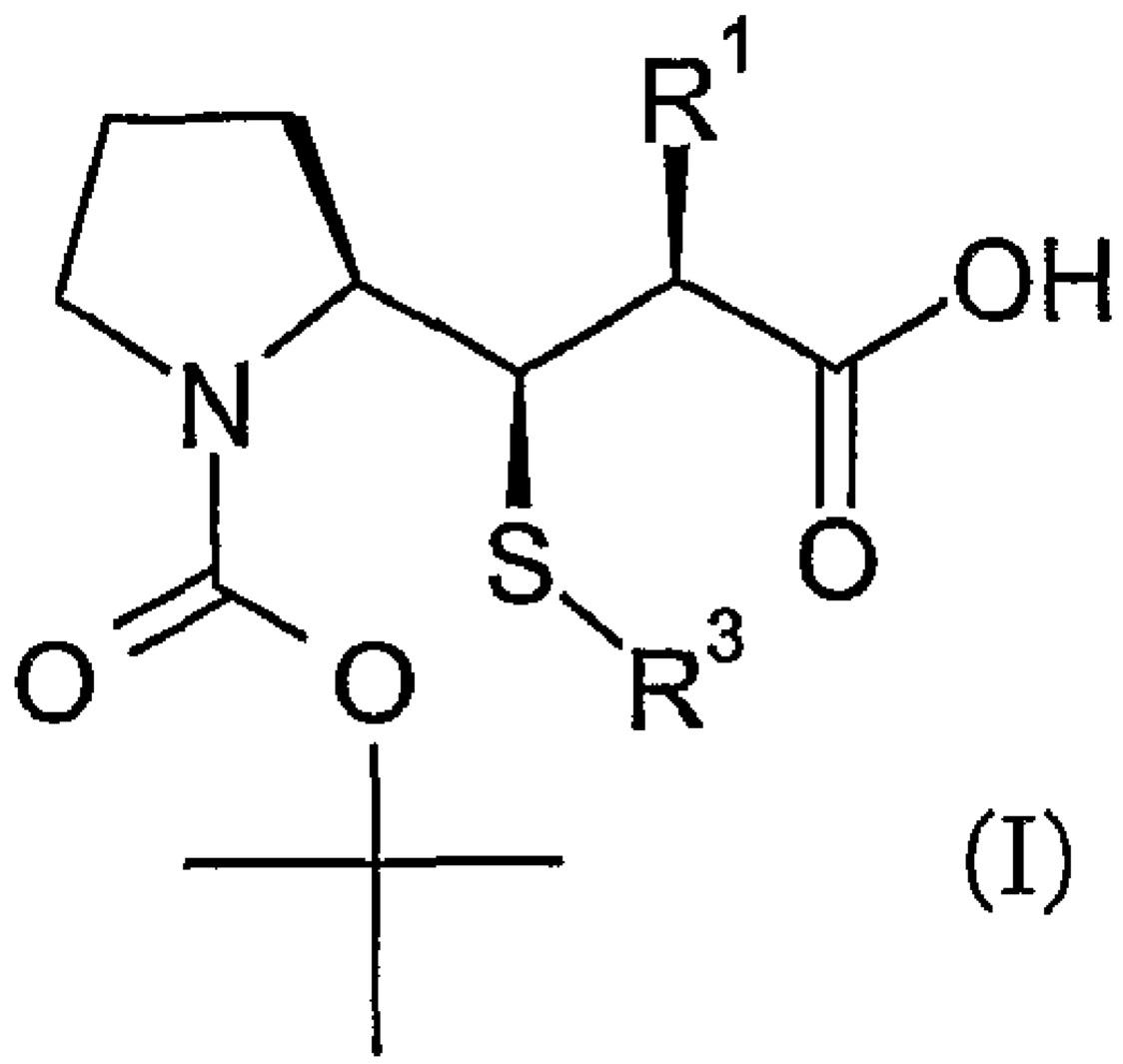
(54) Titre : NOUVEAU PROCEDE POUR LA FABRICATION DE DERIVES D'ACIDE 3-PYRROLIDIN-2-YL-PROPIONIQUE
(54) Title: NOVEL PROCESS FOR THE MANUFACTURE OF 3-PYRROLIDIN-2-YL-PROPIONIC ACID DERIVATIVES



(I)

(57) Abrégé/Abstract:
The present invention relates to the manufacture of the compounds of formula (I) said compounds of formula (I) being valuable intermediates in the manufacture of Dolastatin 10 analogues, which are useful in the treatment of cancer.

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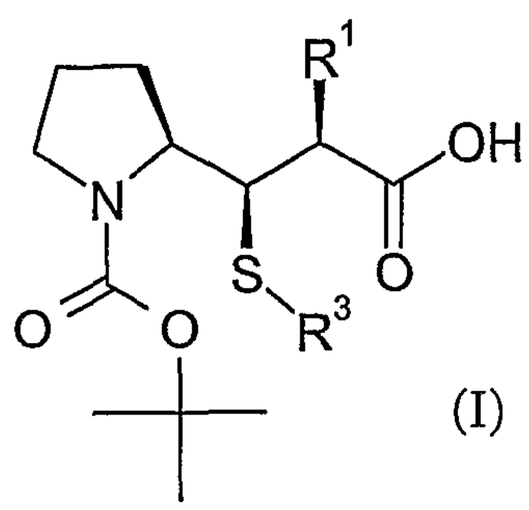


(I)

(57) Abstract: The present invention relates to the manufacture of the compounds of formula (I) said compounds of formula (I) being valuable intermediates in the manufacture of Dolastatin 10 analogues, which are useful in the treatment of cancer.

WO 2006/063706 A1

NOVEL PROCESS FOR THE MANUFACTURE OF 3-PYRROLIDIN-2-YL-PROPIONIC ACID DERIVATIVES

The present invention relates to a new process for the manufacture of derivatives of 3-pyrrolidin-2-yl-propionic acid. According to the present invention, said derivatives are obtainable using two different reaction sequences A) and B) which require the same starting material.

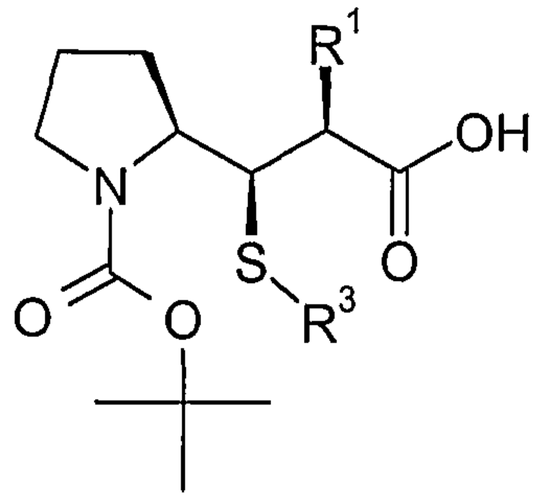
The compounds obtainable by the process according to the present invention are valuable intermediates in the manufacture of Dolastatin 10 analogues. Dolastatin 10 is known to be a potent antimitotic peptide, isolated from the marine mollusk *Dolabella auricularia*, which inhibits tubulin polymerization and is a different chemical class from taxanes and vincas (*Curr. Pharm. Des. 1999, 5: 139-162*). Preclinical studies of Dolastatin 10 have demonstrated activities against a variety of murine and human tumors in cell cultures and animal models. Dolastatin 10 and two synthetic dolastatin derivatives, Cemadotin and TZT-1027 are described in *Drugs of the future 1999, 24(4): 404-409.*

Subsequently it had been found that certain Dolastatin 10 derivatives having various thio-groups at the dolaproine part show significantly improved anti-tumor activity and therapeutic index in human cancer xenograft models (WO 03/008378). However the synthesis disclosed in WO 03/008378 suffers from low yields, mainly due to laborious separation of the diastereoisomer mixtures, obtained in the *β-addition* reaction (s. **scheme 1**, below), by chromatography. Therefore it remains a need to provide new and improved processes.

The present invention addresses this problem by providing a new, improved process for the manufacture of compounds of the general formula (I), which are key fragments in the synthesis of the above-mentioned Dolastatin 10 derivatives. More precisely, it has now surprisingly been found that the process of the present invention provides an improved diastereoisomer ratio and an improved yield of the compounds of formula (I), which is subsequently retained in the synthesis of said Dolastatin 10 derivatives. Furthermore the

process according to the present invention avoids the laborious separation of the diastereoisomer mixtures by chromatography.

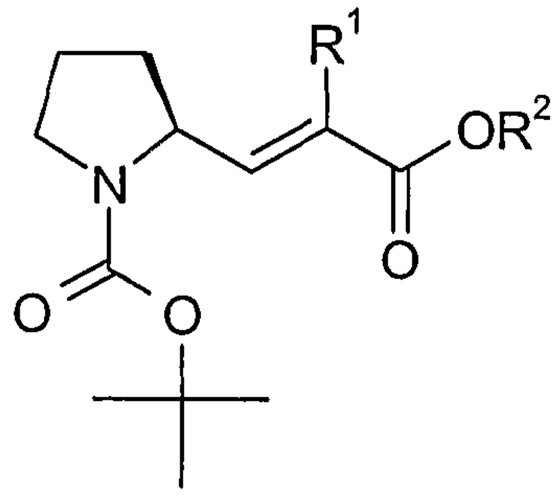
In particular the present invention relates to the manufacture of the compounds of formula (I)



(I)

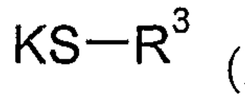
whereby

A) a compound of formula (II)



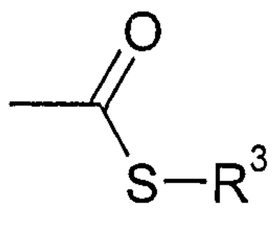
(II)

is reacted with a compound of formula (III)



(III),

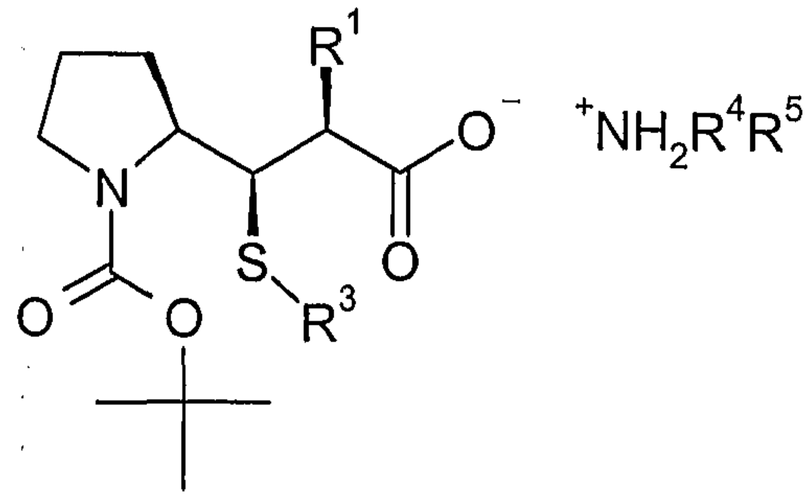
in the presence of triethylammonium chloride in a suitable solvent, whereby said compound of formula (III) is being used as such or can be generated *in situ* by reacting a compound of formula (III-A)



(III-A)

in the presence of potassium bases; and

the compounds of formula (I) are obtained by cleavage of R^2 in the $-COOR^2$ ester group, followed by the addition of an amine of the formula NHR^4R^5 to the resulting carboxylic acid, to form an ammonium salt of formula (IV)

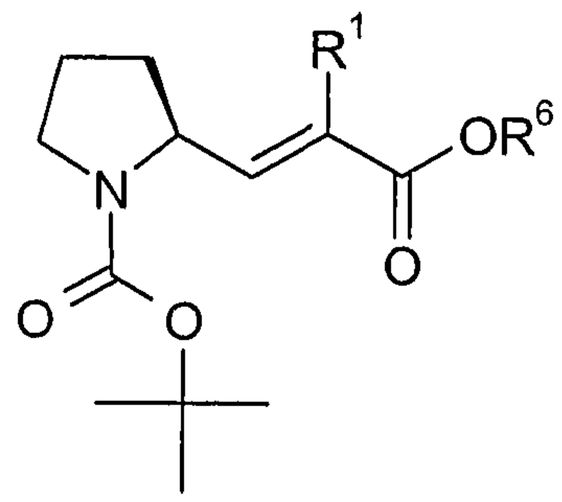


(IV)

and decomposition of said salt of formula (IV);

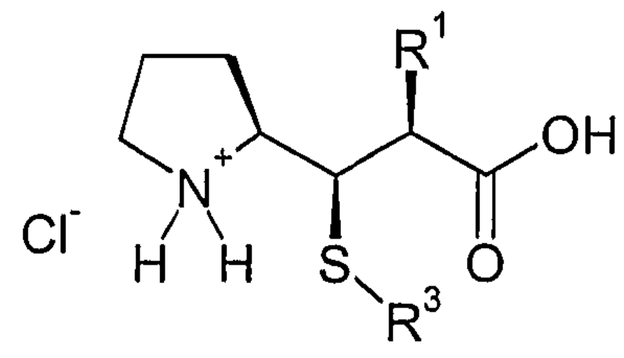
or

B) a compound of formula (V)



(V)

is reacted with a compound of formula (III), or (III-A) together with a potassium base as described above; and the compounds of formula (I) are obtained from the reaction product by addition of hydrochloric acid to form a compound of formula (VI)



(VI)

followed by re-protection of the N-atom by reaction with a *tert*-butoxycarbonyl-delivering reagent;

and wherein

R^1, R^3 and R^6 independently from each other represent alkyl;

R^2 is benzyl or substituted benzyl; and

R^4 and R^5 are independently selected from cycloalkyl or alkyl, which alkyl can be unsubstituted or substituted one, two or three times with hydroxy, alkoxy, amino, mono- or di-alkylamino, acetoxy, alkylcarbonyloxy, carbamoyloxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyloxy, halogen, cycloalkyl or phenyl.

The compounds of the general formulae (IV) and (VI) are new and a further embodiment of the present invention.

The term "alkyl" as used herein means a straight-chain or branched-chain hydrocarbon group containing a maximum of 8, preferably a maximum of 5, carbon atoms, e.g., methyl, ethyl, n-propyl, 2-methylpropyl (iso-butyl), 1-methylethyl (iso-propyl), n-butyl, 1,1-dimethylethyl (t-butyl or *tert*-butyl) or t-pentyl, and more preferably a maximum of 4 carbon atoms. The alkyl group may be unsubstituted or may be substituted with one or more substituents, preferably with one to three substituents, most preferably with one substituent. The substituents are selected from the group consisting of hydroxy, alkoxy, amino, mono- or di-alkylamino, acetoxy, alkylcarbonyloxy, carbamoyloxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyloxy, halogen, cycloalkyl or phenyl.

The term "alkoxy" means –O-alkyl, wherein "alkyl" has the meaning given above.

The term "acetoxy" refers to the group –O-C(O)-CH_3.

The term "cycloalkyl" as used herein means a saturated mono- or bicyclic hydrocarbon group, containing from 3 to 10, preferably from 3 to 7 and more preferably 5 or 6 carbon-atoms. Examples of such cycloalkyls are cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or decahydro-naphthalene.

The term "carbamoyl" refers to the group –CO-NH_2 and the term "carbamoyloxy" to the group –O–C(O)–NH.

The term "alkylcarbamoyloxy" refers to an alkyl group as defined above attached to a parent structure via a carbymoyloxy radical, such as alkyl-NH-C(O)-O-.

The term "alkylcarbonyloxy" refers to an alkyl group as defined above attached to a parent structure via a carbonyloxy radical, such as alkyl-C(O)-O-.

The term "halogen" refers to fluorine, bromine, iodine and chlorine.

The term "substituted benzyl" as used herein means a benzyl group, wherein the phenyl ring is one, two or three times substituted with a substituent independently selected from methyl, methoxy, phenyl, nitro, halogen or methylene-dioxy. Especially preferred are the following substitution patterns: 2,4,6-trimethyl, 3-methoxy, 4-methoxy, 2,4-dimethoxy, 3,4-dimethoxy, 3,5-dimethoxy, 2-nitro, 4-nitro, 2,4-dinitro, 4-bromo, 4-phenyl and 3,4-methylene-dioxy.

The term "potassium bases" as used herein means basic potassium compounds, which are generally well known to the skilled artisan. Such potassium bases are for example potassium amides, –alkoxides or potassium hydroxide. Especially preferred according to the present invention is the use of potassium ethoxide.

The term "*tert*-butoxycarbonyl-delivering reagent" as used herein means a reagent for the introduction of the *N-Boc* group as described below. Such "*tert*-butoxycarbonyl-delivering reagents" are well known to the skilled artisan and for example described in "Protective Groups in Organic Synthesis, 3rd. Edition; Eds. T.W. Greene, P.G.M-Wuts, John Wiley & Sons, Inc., New York (1999); p.518. A preferred "*tert*-butoxycarbonyl-delivering reagent" according to the present invention is di-*tert*-butyl dicarbonate.

The term "suitable solvent" as used herein needs to be differentiated according to the different reaction sequences A) and B) as well as the different reaction steps within each sequence, according to scheme 1 further below. In particular, the following solvents are "suitable" according to the various reaction steps of each sequence:

<u>sequence A)</u>

The *β-addition* is preferably carried out in ethers, such as tetrahydrofuran, methyl-tetrahydrofuran, *tert*-butyl methyl ether, dimethylether, diethylether and at temperatures from -20°C to the reflux temperature of the respective solvent, most preferably between 0°C to room temperature.

The *ester cleavage* is preferably carried out by hydrogenolysis in alcohols such as ethanol, methanol, isopropanol and the like; esters such as ethyl acetate, methyl acetate or isopropyl acetate; hydrocarbons such as toluene; or mixtures of the above solvents. This reaction requires temperatures between 0°C to reflux temperature of the respective solvent, preferably from 0°C to room temperature, whereby room temperature is most preferred.

The *ammonium salt formation* preferably takes place in solvents which provide suitable solubilities for compounds of formulae (I), NHR^4R^5 and (IV). In this connection ethers such as *tert*-butyl methyl ether, tetrahydrofuran, methyl-tetrahydrofuran, dimethylether, diethylether; alkanes such as hexane, cyclohexene, heptane; or aromatic solvents such as toluene, xylene; or mixtures of all the above-mentioned solvents are especially preferred. The temperature can vary between -20°C and 50°C, whereby the crystallization preferably occurs at temperatures between room temperature and -20°C; most preferred at temperatures between 0°C and -20°C.

The *final decomposition of the isolated salt* can take place under basic or acidic conditions. If basic conditions are used, inorganic bases such as alkali-hydroxides, -hydrogencarbonates or -carbonates are especially preferred. If acidic conditions are used, mineral acids such as hydrochloric acid, sulfuric acid are especially preferred. Said decomposition is carried out in any inert organic solvent immiscible with water, preferably in *tert*-butyl methyl ether, toluene or ethyl acetate and at temperatures between 0°C and room temperature, most preferably at room temperature.

<u>sequence B)</u>

The solvents for the *β-addition* are as defined above under sequence A).

The *reaction with hydrochloric acid* takes place in solvents wherein the compounds of formula (VI) crystallize, preferably in esters, ethers or haloalkanes such as dichloromethane, more preferably in esters such as ethyl acetate; and at temperatures from 50°C to -20°C, preferably from room temperature to -20°C. The crystallization preferably occurs at temperatures between 0°C and -20°C.

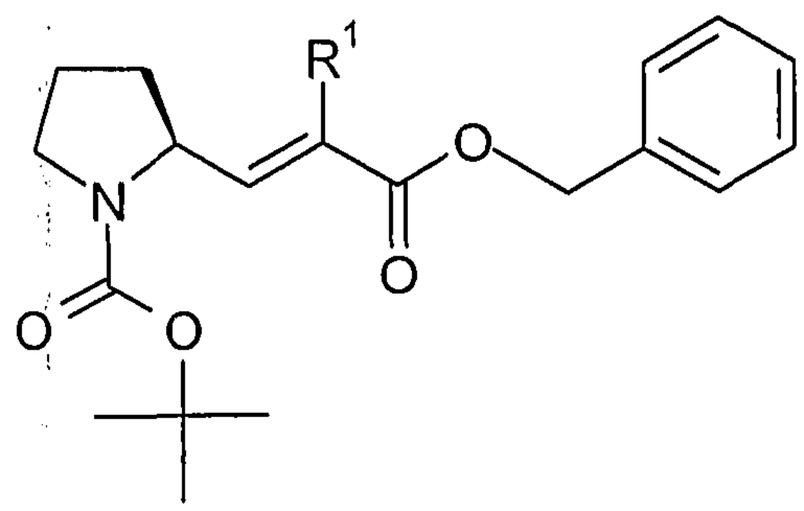
The subsequent *N-bocylation* can be carried out with a *tert*-butoxycarbonyl-delivering reagent as defined above. A preferred method for the introduction of the N-Boc group involves the use of di-*tert*-butyl dicarbonate as reagent in the presence of a base, e.g. an inorganic base such as alkali metal hydroxide, -hydrogencarbonate, -carbonate; or tertiary amine bases such as trialkylamines, e.g. triethylamine. Suitable solvents for this reaction are polar solvents, especially water; alcohols; ethers such as tetrahydrofuran, dioxane and the like; haloalkanes such as dichloromethane; acetonitrile etc. The

temperature can range from 0°C to 50°C, whereby room temperature is especially preferred.

An embodiment of the present invention, is the process for the manufacture of the compounds of formula (I)

whereby

the compounds of formula (II-A)



(II-A)

are reacted with a compound of formula (III), or (III-A) together with a potassium base as defined above, in the presence of triethylammonium chloride in tetrahydrofuran; and

the compounds of formula (I) are obtained by benzyl-ester cleavage from the product of said reaction, followed by addition of an amine of the formula NHR^4R^5 to the resulting carboxylic acid, and further followed by base addition and subsequent addition of mineral acids; and

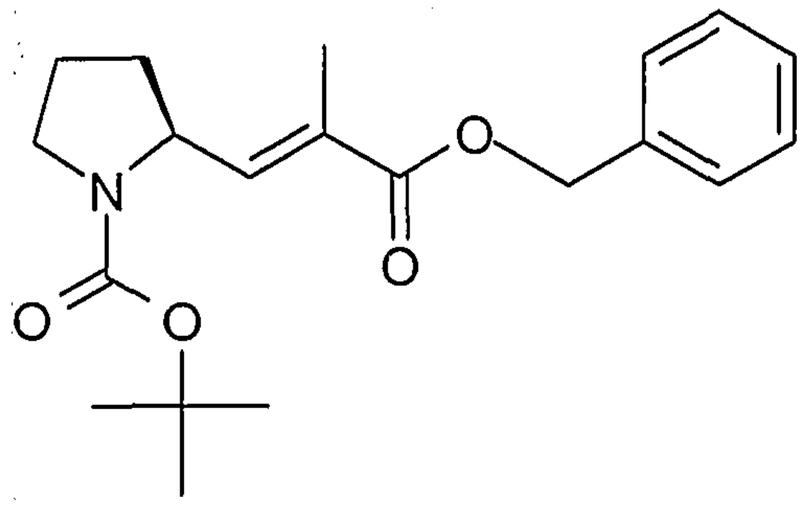
R^1, R^4 and R^5 have the meanings given herein before.

Another embodiment of the present invention is the process as described above, wherein the amines of formula NHR^4R^5 are selected from

dicyclohexylamine, diisopropylamine, *(R)*-α-phenylethylamine, benzyl-*(R)*-α-phenylethylamine and *(R)*-α-cyclohexylethylamine.

Still another embodiment of the present invention, is the process as described above,

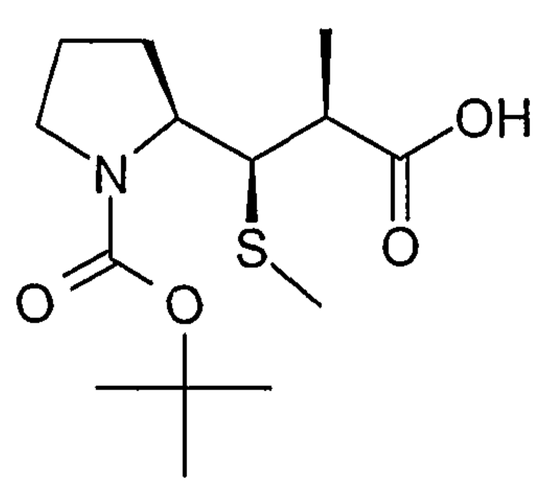
whereby the compound of formula (2)



(2)

is reacted with S-methyl thioacetate together with potassium ethoxide, in the presence of triethylammonium chloride in tetrahydrofuran; and

the compound of formula (1a)



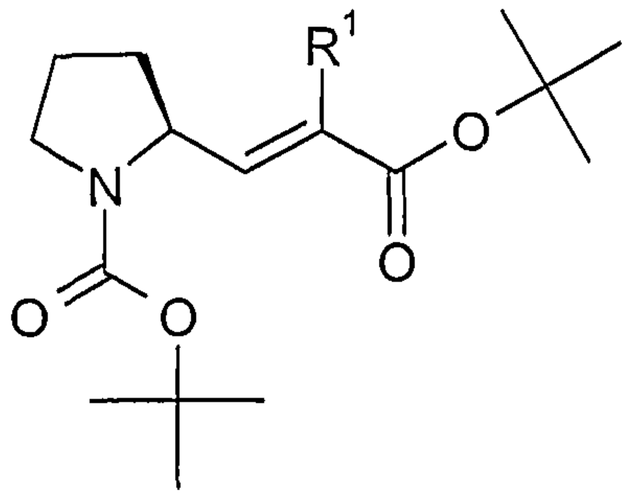
(1a)

is obtained by benzyl-ester cleavage from the product of said reaction, followed by addition of dicyclohexylamine, and further followed by sodium carbonate addition and subsequent addition of sulfuric acid.

Yet another embodiment of the present invention, is the process for the manufacture of the compounds of formula (I)

whereby

a compound of formula (V-A)



(V-A)

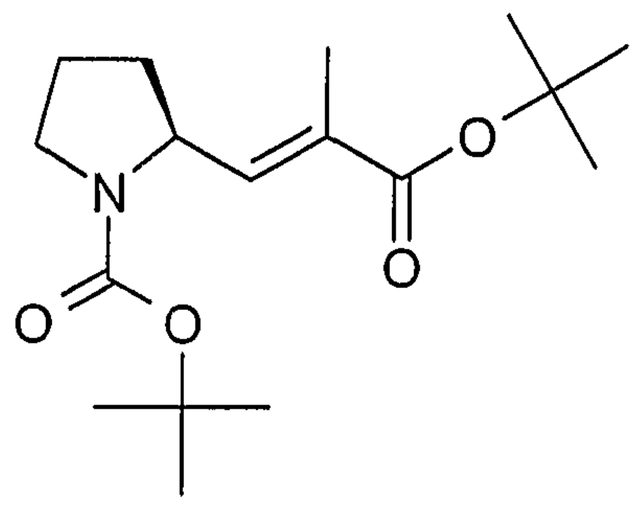
is reacted with a compound of formula (III), or (III-A) together with a potassium base as defined above, in the presence of triethylammonium chloride in tetrahydrofuran, and

the compounds of formula (I) are obtained by further reacting the product of the above reaction with dry hydrochloric acid in ethyl acetate, followed by addition of sodium carbonate and subsequent reaction with di-*tert*-butyl dicarbonate; and wherein

R^1 is as defined above.

Still another embodiment of the present invention is the process as described above, wherein

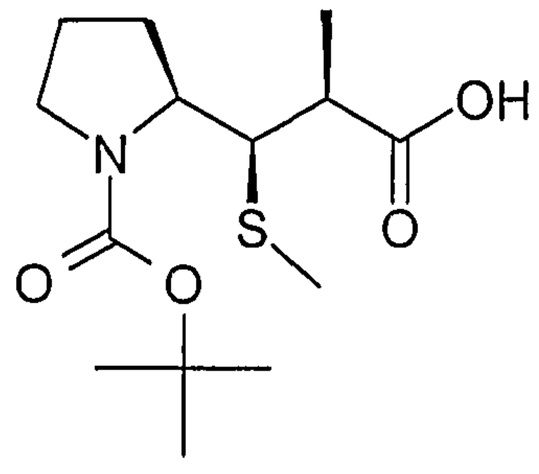
a compound of formula (4)



(4)

is reacted with S-methyl thioacetate together with potassium ethoxide, in the presence of triethylammonium chloride in tetrahydrofuran, and

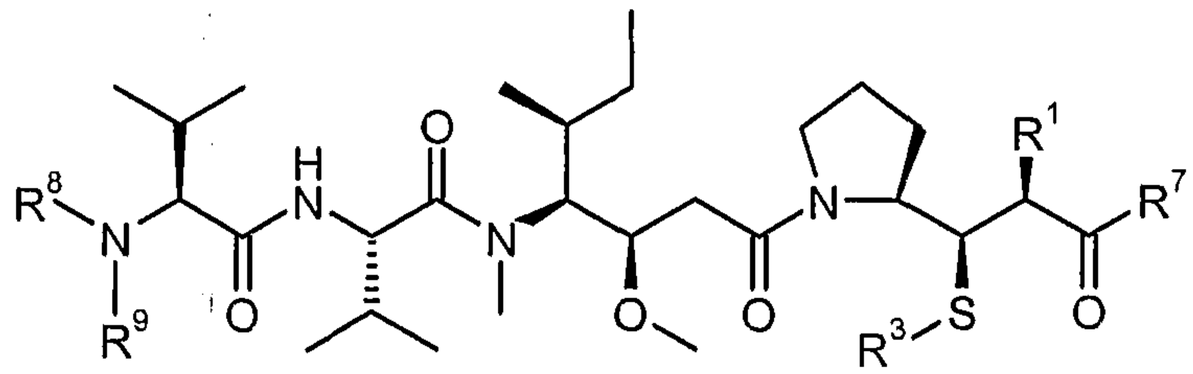
the compound of formula (1a)



(1a)

is obtained by further reacting the product of the above reaction with dry hydrochloric acid in ethyl acetate, followed by addition of sodium carbonate and subsequent reaction with di-*tert*-butyl dicarbonate.

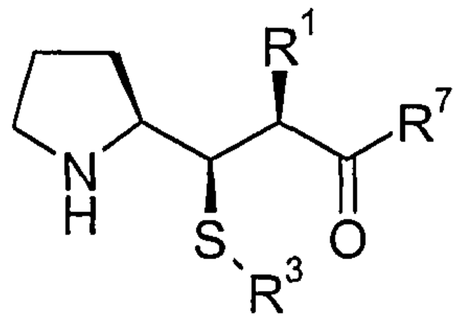
Still another embodiment of the present invention is the process as described above, wherein the compounds of formula (I) are further reacted to give the compounds of formula (A),



(A),

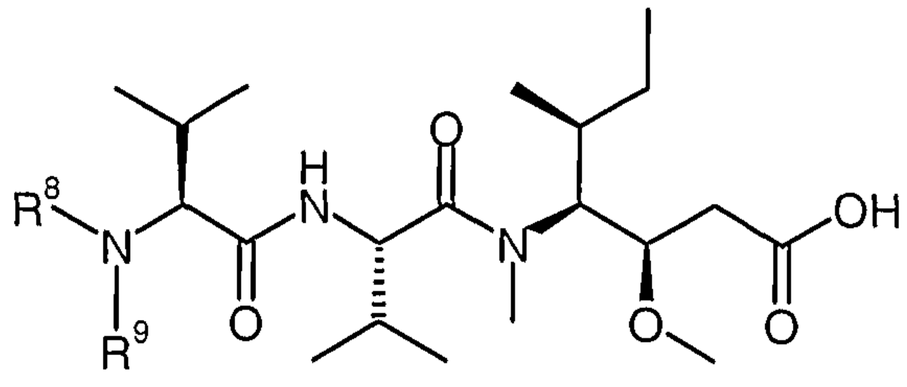
wherein

a) the compounds of formula (I) are reacted with an alcohol or an amine, followed by cleavage of the *tert*-butoxycarbonyl group at the pyrrolidine N-atom, to give the compounds of formula (B)



(B); and

b) the compounds of formula (B) are further reacted with the compounds of formula (C)



(C),

to give the compounds of formula (A); and

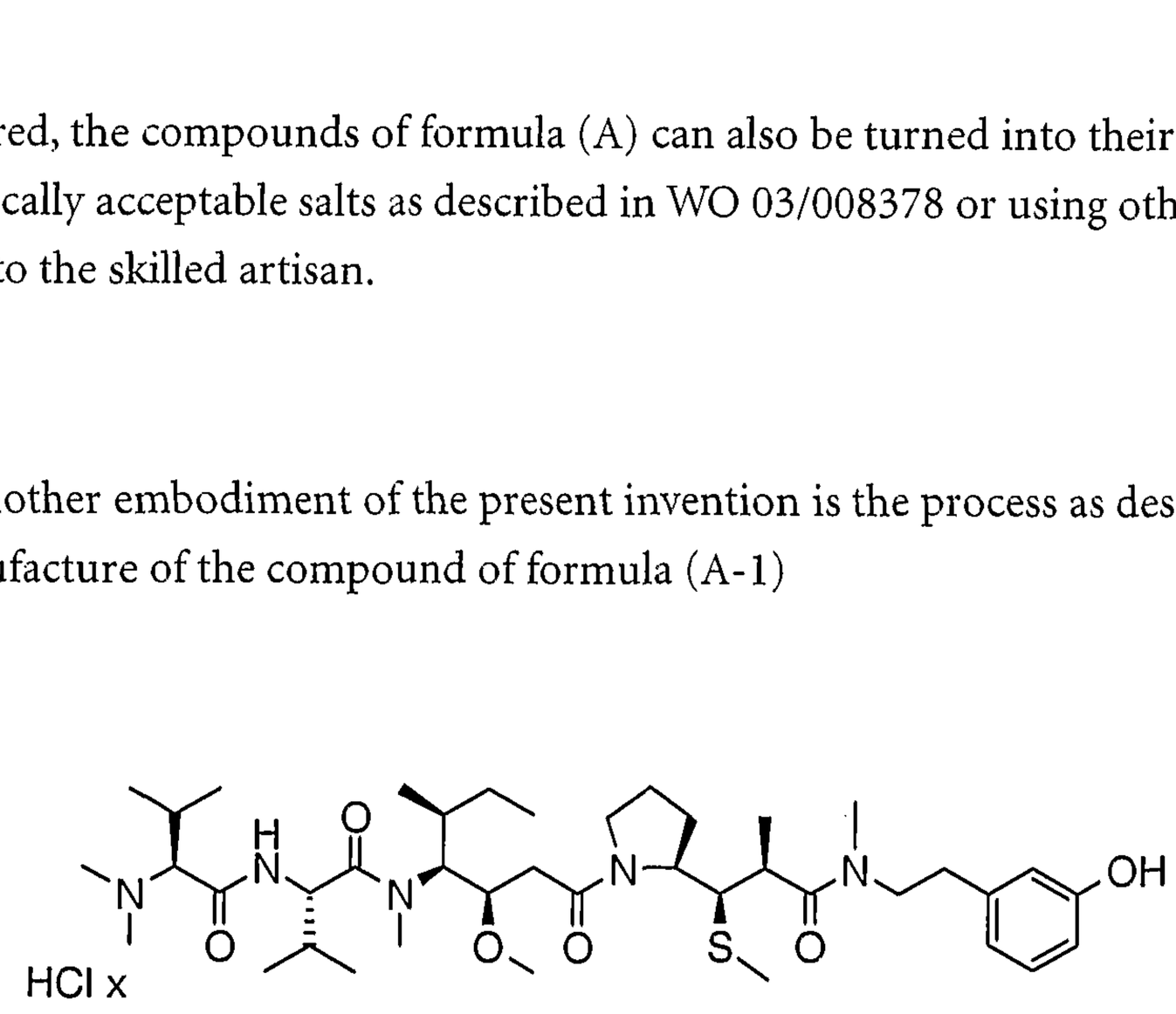
R^1 and R^3 are as defined herein before;

R^8 and R^9 independently from each other represent alkyl; and

R^7 is phenylalkyl-, or phenyldialkylamino or phenylalkyloxy, having (C_1-C_4)-alkylene and wherein the phenyl group optionally may be substituted with one, two or three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, carbamoyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, 1,3-dioxolyl, 1,4-dioxolyl, amino and benzyl.

If desired, the compounds of formula (A) can also be turned into their pharmaceutically acceptable salts as described in WO 03/008378 or using other methods well known to the skilled artisan.

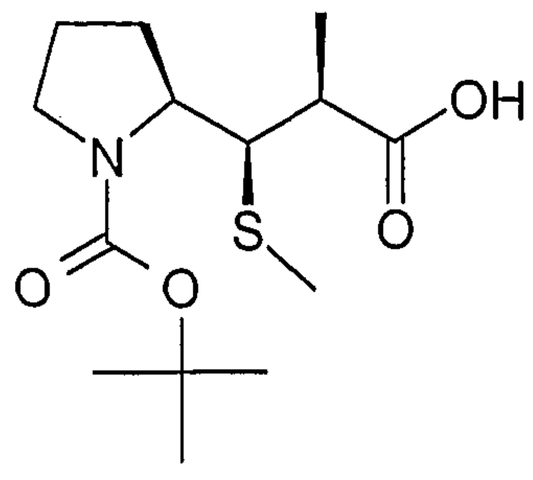
Still another embodiment of the present invention is the process as described above for the manufacture of the compound of formula (A-1)



(A-1),

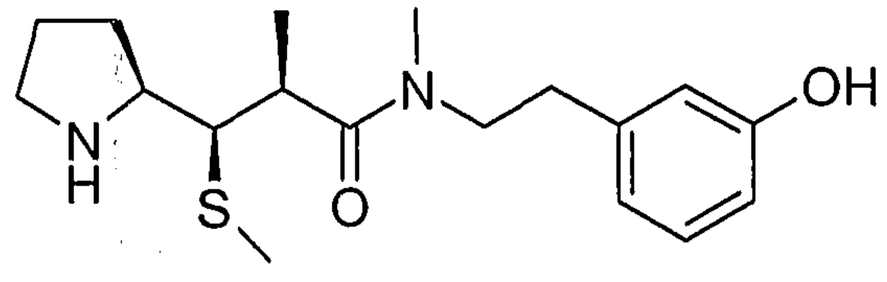
wherein

a) the compound of formula (1a)



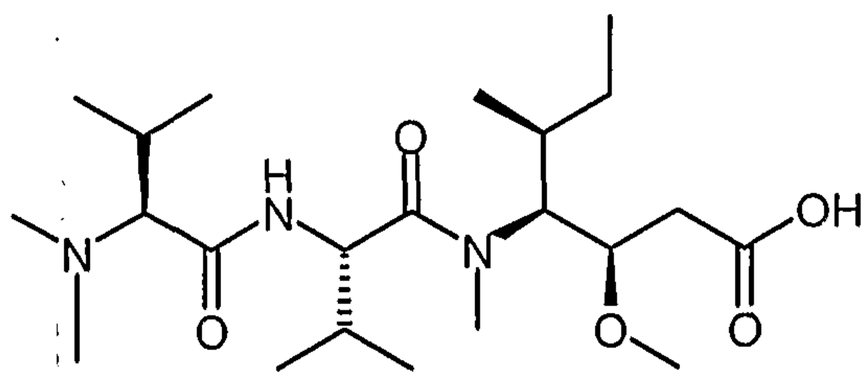
(1a)

is reacted with 3-(2-methylamino-ethyl)-phenol, followed by cleavage of the *tert*-butoxycarbonyl group at the pyrrolidine N-atom, to give the compound of formula (B-1)



(B-1); and

b) the compound of formula (B-1) is further reacted with the compound of formula (C-1)



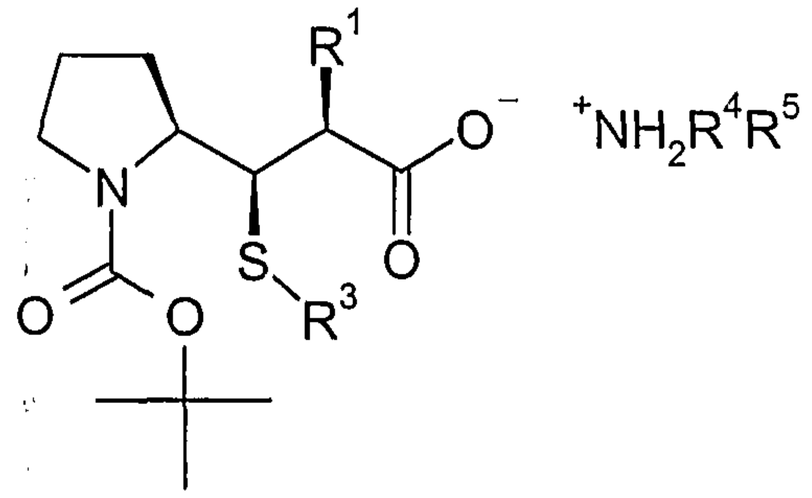
(C-1),

to give the compound of formula (A-1).

Yet another embodiment of the present invention is the use of the process according to the present invention in the manufacture of the compounds of formula (A) as defined above.

Yet another embodiment of the present invention is the use of the process according to the present invention in the manufacture of the compound of formula (A-1) as defined above.

In another embodiment of the present invention, there are provided the compounds of formula (IV)



(IV),

wherein

R^1 and R^3 independently from each other represent alkyl; and

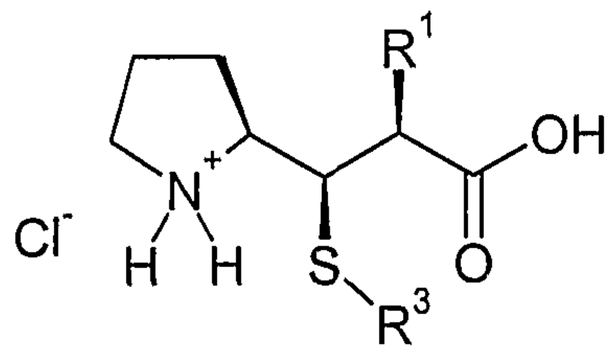
R^4 and R^5 independently represent cycloalkyl or alkyl, which alkyl can be unsubstituted, or substituted one, two or three times with hydroxy, alkoxy, amino, mono- or di-alkylamino, acetoxy, alkylcarbonyloxy, carbamoyloxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyloxy, halogen, cycloalkyl or phenyl.

In yet another embodiment of the present invention, there are provided the compounds as defined above, wherein

R^1 and R^3 are methyl; and

the group $^+NH_2R^4R^5$ represents a cation selected from dicyclohexylammonium, diisopropylammonium, *(R)*-α-phenylethylammonium, benzyl-*(R)*-α-phenylethylammonium or *(R)*-α-cyclohexylethylammonium.

In still another embodiment of the present invention, there are provided the compounds of formula (VI):



(VI),

wherein

R^1 and R^3 independently from each other represent alkyl.

In still another embodiment of the present invention, there are provided the compounds as described above, wherein

R^1 and R^3 are methyl.

Yet another embodiment of the present invention is the compound

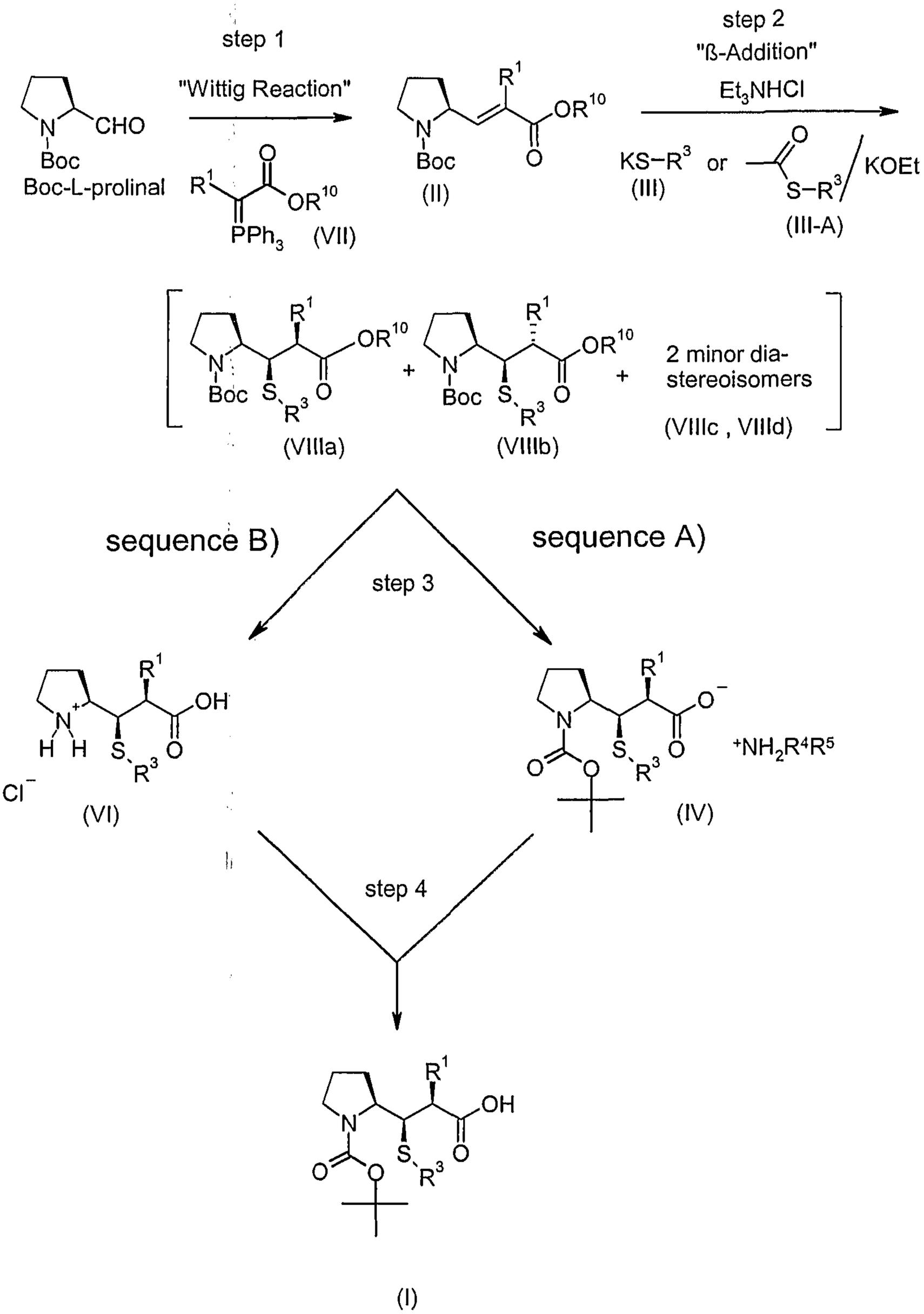
(*S*)-2-((*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**1a**).

Consequently, a further embodiment of the present invention is the use of a compound of the formulae (IV), (VI) or (**1a**) as defined above in a process as described herein before.

Still another embodiment of the present invention is the use of a compound of the formulae (IV), (VI) or (**1a**) as defined above in the manufacture of the compounds of formula (A) as defined herein before

Still another embodiment of the present invention is the use of a compound of the formula (IV), wherein R^1 and R^3 are methyl, or formula (**1a**) as defined above in the manufacture of the compound of formula (A-1) as defined herein before.

The process of the present invention can be performed according to the following general reaction scheme (scheme 1), wherein unless explicitly otherwise stated R^1, R^3, R^4 and R^5 have the significances given herein before. R^{10} is benzyl, substituted benzyl or alkyl, preferably benzyl or *tert*-butyl.



scheme 1

Step 1: This step represents a *Wittig reaction* starting from commercially available *tert*-butoxycarbonyl protected L-prolinal (Boc-L-prolinal) with the ylide (VII)and using methods known to the skilled artisan (see e.g. *Heterocycles*, 36 (9), 1993, 2073-2080 and WO 03/008378). Said ylide wherein R^1 is methyl and R^{10} is benzyl can be obtained according to the synthesis described in "Y. Ito, M. Okano, R.Oda, *Tetrahedron*, 23, 1967, 2137."

Said ylide wherein R^1 is methyl and R^{10} is *tert*-butyl can be obtained according to the synthesis described in "Y. Guindon, L. Murtagh, V. Caron, S.R. Landry, G. Jung, M. Bencheqroun, A.-M. Faucher, B. Guerin, *J. Org. Chem.*, 66, 2001, 5427" or "P.L. Stotter, K.A. Hill, *Tetrahedron Lett.*, 16, 1975, 1679."

Step 2: This reaction is a *β-addition* of alkyl-mercaptanes, especially methyl mercaptane, wherein the potassium salts of formula (III) can be used as such, or generated *in situ* by adding the compounds of formula (III-A) in the presence of potassium bases, especially potassium ethoxide. According to the present invention, improvement of diastereoselectivity in this addition reaction is achieved by using triethylammonium chloride (Et_3N x HCl) as the proton source, compared to other common proton sources tested (see *Table 1*).

Table 1: Diastereoselectivity of β-Addition: Influence of Proton Source

Proton Source (X-H)	AcSMe/KOEt/ X-H equiv.	3a / 3b [a)]
		2 h
phenol	6 / 6 / 3	70 : 30
succinimide	6 / 6 / 3	83 : 17
N-hydroxysuccinimide	6 / 6 / 3	85 : 15
Et_3N x HCl	6 / 6 / 3	85 : 15
Et_3N x HCl	3 / 3 / 1.5	90 : 10
CH_3SH	6 / 3 [b)]	88 : 12
Et_3N x HCl	3 / 1.5 / 1.0 [c)]	89 : 11

a) Ratio determined by GC analysis.

b) Methyl mercaptan (6 equiv.) used instead of S-methyl thioacetate (III-A, scheme 1), no additional proton source.

c) Methyl mercaptan (3 equiv.) used instead of S-methyl thioacetate (III-A, scheme 1); Et_3N x HCl (1.0 equiv.) as additional proton source.

Step 3:

With respect to reaction sequence A), the crude ester (mixture of VIII a, b, c and d, scheme 1 with R^{10} being benzyl or substituted benzyl) is now hydrogenolyzed, preferably in the presence of 20% Pd-C (30% w/w) in ethanol. According to the present invention, further treatment with the amines mentioned herein before, especially dicyclohexylamine in *tert*-butyl methyl ether, furnish the respective ammonium salts in good diastereoisomeric purities and high yields.

With respect to reaction sequence B) the crude ester (mixture of VIII a, b, c and d, scheme 1 with R^{10} being alkyl, preferably *tert*-butyl) can also be treated with dry hydrochloric acid in ethyl acetate at room temperature. The hydrochloride of the desired diastereoisomer precipitates directly from the reaction mixture in high diastereoisomeric purity and yield.

Step 4: The compounds of formula (I) can finally be obtained by standard decomposition methods of the salts obtained from step 3a) or by N-bocylation of the salts obtained from step 3b). Such decomposition and bocylation methods are well known to the skilled artisan.

The salts of formula (IV), as obtained from step 3 of reaction sequence A) can be decomposed in the presence of an inorganic base, such as for example but not limited to an alkali metal hydroxide, -hydrogencarbonate or –carbonate, preferably in the presence of sodium carbonate; followed by removal of the amine base by extraction with an organic solvent; followed by addition of a mineral acid, preferably sulfuric acid, to the remaining aqueous phase and extraction of the compounds of formula (I) into an organic solvent. Alternatively said decomposition can be achieved by direct addition of said mineral acid to the reaction mixture containing the compounds of formula (IV), followed by extraction of the compounds of formula (I) into an organic solvent.

The salts of formula (VI), as obtained from step 3 of reaction sequence B) can be further N-bocylated using methods well known to the skilled artisan, preferably in the presence of an inorganic base, such as for example but not limited to an alkali metal hydroxide or –carbonate, more preferably in the presence of sodium carbonate, followed by further reaction with di-*tert*-butyl dicarbonate; or alternatively with di-*tert*-butyl dicarbonate in dichloromethane and in the presence of amine bases such as triethylamine.

Subsequently to each of the aforementioned procedures the compounds of formula (I) can finally be obtained and/or purified by crystallization from organic solvents, preferably from hexane or heptane.

The following examples are provided to aid the understanding of the present invention. It is understood that modifications can be made without departing from the spirit of the invention.

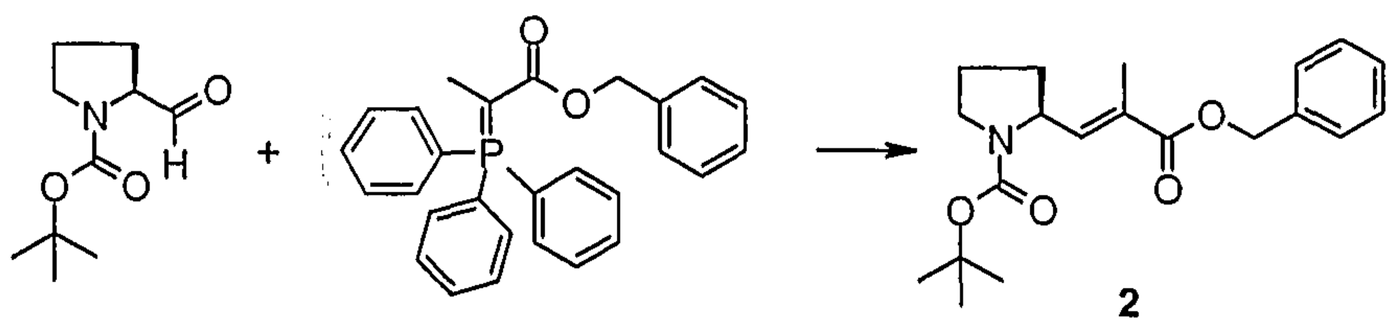
If not explicitly otherwise stated, the following abbreviations are used:

min	minute(s)
h	hour(s)
rt	room temperature
NMR	nuclear magnetic resonance
GC	gas chromatography
TLC	thin layer chromatography
HPLC	high performance liquid chromatography
dr	distereosiomer ratio
er	enantiomer ratio
ee	enantiomeric excess
mp	melting point

Reaction Sequence A)

Example 1

Synthesis of (*S*)-2-(2-Benzyloxycarbonyl-propenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2) (Synthesis with Preformed *Wittig* Ylide)



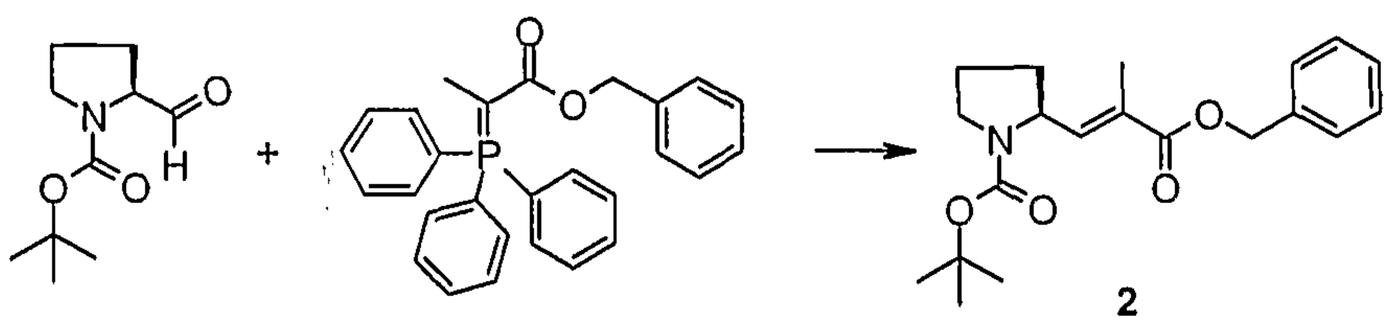
a) The *Wittig* ylide (benzyl 2-(triphenylphosphoranylidene)propionate) can be obtained according to the synthesis disclosed in "Y. Ito, M. Okano, R. Oda, *Tetrahedron*, 23, 1967, 2137".

b) To a solution of 135.7 g benzyl 2-(triphenylphosphoranylidene)propionate (320 mmol) in 440 ml *tert*-butyl methyl ether was added at rt a solution of 45.5 g Boc-L-prolinal (228.4 mmol) in 62 ml *tert*-butyl methyl ether. The yellow solution was heated under reflux for 1.5 h upon which a white precipitate of triphenylphosphine oxide formed. From the suspension 230 ml of *tert*-butyl methyl ether solvent were removed by distillation using a Dean-Stark trap. Then 360 ml heptane were added drop by drop at reflux temperature to further promote the triphenylphosphine oxide precipitation. The suspension was cooled to rt, stirred at rt overnight, then cooled to 0-5°C and stirred at this temperature for 30 min. The suspension was filtered over a pre-cooled (0-5°C) G3 glass filter funnel and the filter cake washed portion-wise with 250 ml pre-cooled (0-5°C) heptane. The yellow filtrate and the wash solution were combined and evaporated (40°C/10 mbar) to provide 86.8 g of yellow oil as the crude product. GC: 4.67% *Z*-2, 91.55% *E*-2, 3.78% triphenylphosphine oxide; *E/Z* = 95.15 : 4.85. Of this material 86.6 g were filtered over 434 g silica gel using ca. 3 l hexane/ethyl acetate (2:1) as the eluent to provide, after evaporation and drying *in vacuo*, 81.38 g (103% w/w) of the title compound (2) as light yellow oil. The material by GC analysis contained 4.59% *Z*-2, 90.58% *E*-2, and 1.12% triphenylphosphine oxide; *E/Z* = 95.2 : 4.8. The material by chiral HPLC analysis contained 4.19% *Z*-2, 0.31% *ent*-*E*-2, and 95.50% *E*-2; er = 99.7 : 0.3; *E/Z* = 95.7 : 4.3.

^{1}H-NMR: (400 MHz, $CDCl_3$): 7.4-7.3 (m, 5 arom. H); 6.65 (br. d, J = 7, vinyl. H of (*E*)-2); 5.9-5.8 (br., vinyl. H of (*Z*)-2); 5.3-5.1 (br. m, $PhCH_2O$); 4.7-4.4 (br. m, 1 H); 3.6-3.35 (br. m, 2 H); 2.13 (m, 1 H); 2.0-1.3 [m, in total 15 H, with 1.43 (br. s, tBu)].

Example 2

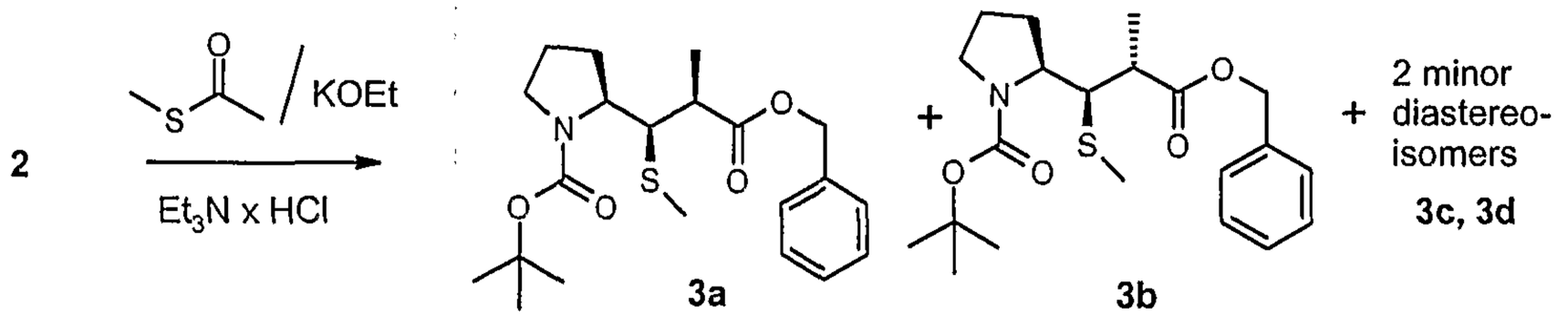
Synthesis of (*S*)-2-(2-Benzyloxycarbonyl-propenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2); (Synthesis with *in situ* Formation of *Wittig* Ylide)



A solution of 378 g (1-benzyloxycarbonyl-ethyl)-triphenylphosphonium bromide (82.9%, 619.9 mmol) in 1.45 l dichloromethane was azeotropically distilled while keeping the volume constant by addition of 1.20 l dichloromethane. To the solution was added slowly at an internal temperature of 10-12.5°C a solution of 71.0 g potassium *tert*-butoxide (98%, 620 mmol) in 640 ml tetrahydrofuran. The yellowish turbid solution was allowed to attain rt and stirred at rt for 75 min. Then, a solution of 127.4 g Boc-L-prolinal (97%, 620.3 mmol) in 640 ml tetrahydrofuran was added, whereby the reaction temperature rose to 25 °C. The yellow solution was heated under reflux for 18 h upon which a white precipitate of triphenylphosphine oxide formed. The tetrahydrofuran/dichloromethane solvent mixture was exchanged for 3.6 l heptane. The suspension was then cooled to 0°C, stirred at 0°C for 1 h, and the triphenylphosphine oxide was filtered and washed with 1 l heptane (pre-cooled at 0°C). The combined yellow filtrate and wash solution were washed with 2 x 2.5 l, a total of 5 l water and evaporated (40°C/100 mbar) to provide as crude product 233.9 g of the title compound (2) as yellow oil. This material by HPLC analysis contained 89.6% *E*-2 and 5.4% *Z*-2; *E*/*Z* = 94.3 : 5.7. The material by chiral HPLC analysis contained 5.5% *Z*-2, 0.0% *ent*-*E*-2, and 94.50% *E*-2; er = 100 : 0; *E*/*Z* = 94.5 : 5.5.

Example 3

Synthesis of (*S*)-2-((*1R,2S*)-2-Benzyloxycarbonyl-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3a) in mixture with (*S*)-2-((*1R,2R*)-2-Benzyloxycarbonyl-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3b) and two further diastereoisomers of (*S*)-2-(2-Benzyloxycarbonyl-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester of partially undetermined configuration (3c and 3d)

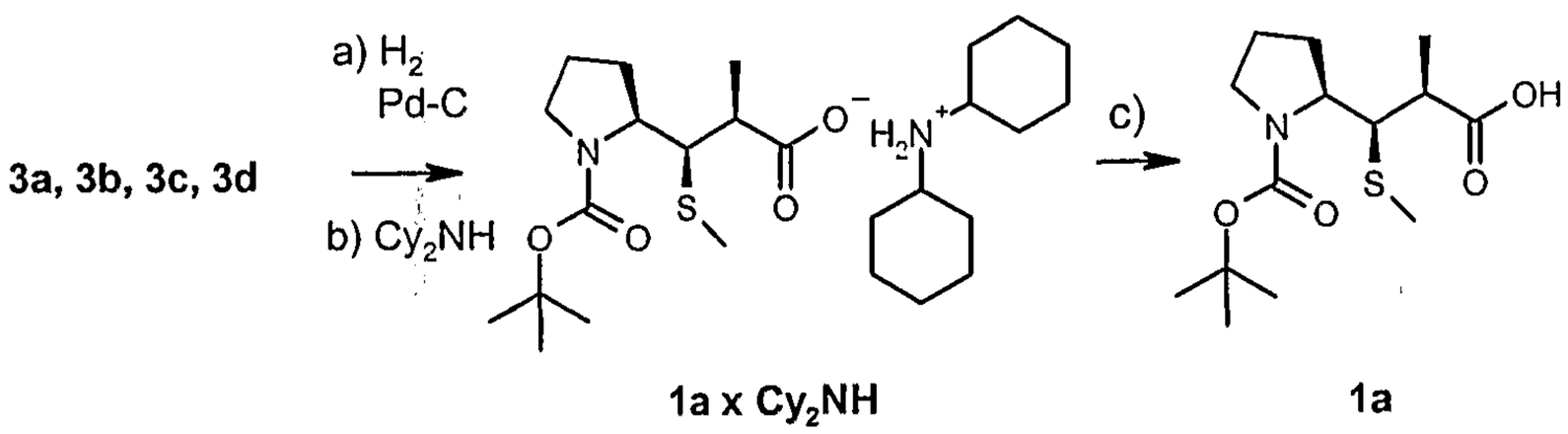


S-methyl thioacetate (64.09 g , 703 mmol) was dissolved under argon with stirring in 700 ml tetrahydrofuran. To the clear colorless solution potassium ethoxide (59.16 g, 703 mmol) was added as solid with the aid of a glass funnel and the funnel was rinsed with 100 ml tetrahydrofuran. The temperature of the yellow-orange suspension rose to 41°C then returned to rt within 30 min. The suspension was stirred at rt for 2.75 h. After a total reaction time of 3.25 h, 48.39 g triethylamine hydrochloride (351.5 mmol) were added at once followed by dropwise addition of a solution of 80.97 g (*S*)-2-(2-benzyloxycarbonyl-propenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2, from example 1) in 344 ml tetrahydrofuran. The yellow-orange suspension was stirred at rt for 5 h. For work-up 344 ml ethyl acetate and 690 ml 5M ammonium chloride solution were added at rt to the reaction mixture. The two phase system was stirred at rt for 2 min, and then transferred into a separatory funnel. The phases were separated, and the organic phase was dried over sodium sulfate, filtered and evaporated (40°C/10 mbar) to yield 93.91 g of the crude product as yellow oil. Subsequently, 93.0 g of the crude product were subjected to filtration over 465 g silica gel with ca. 2 l heptane/ethyl acetate 1:1 mixture. Evaporation and drying *in vacuo* afforded 91.8 g of the title compound (3) as clear yellow oil. This material by GC analysis contained 1.2% (*E*)-2, 84.1% 3a, 1.4% 3c, 1.5% 3d and 8.7% 3b; dr 3a/3b/3c/3d = 87.8 : 9.1 : 1.5 : 1.6.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.45-7.25 (m, 5 arom. H); 5.3-5.05 (br. m, $PhCH_2O$); 4.2-3.8 (br. m, 1 H); 3.75-3.15 (br. m, 3 H); 2.6 (br. m, 1 H); 2.07 (s, SCH_3); 1.9 (m, 3 H); 1.7 (m, 1 H); 1.46 and 1.43 (2 s, tBu of 2 rotamers); 1.34 (d, J = 6.5, CH_3).

Example 4:

Synthesis of (*S*)-2-((*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1a)



a) Synthesis of (*S*)-2-((*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1a) in mixture with (*S*)-2-((*1R,2R*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1b) and two further diastereoisomers of (*S*)-2-(2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester of partially undetermined configuration (1c and 1d)

91.8 g (*S*)-2-(2-Benzyloxycarbonyl-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3, diastereoisomer mixture, see example 3; derived from 224.5 mmol Boc-L-prolinal) were dissolved under argon in an Erlenmeyer flask in 920 ml ethanol and treated with 46.0 g Raney-Ni. The suspension was stirred at rt for 1 h, then filtered and the filter cake was thoroughly washed with 360 ml ethanol. The combined filtrate and wash solutions were divided in two parts of roughly equal volume (ca. 640 ml) which were hydrogenated separately over 13.75 g, a total of 27.5 g 20% Pd on charcoal with hydrogen at 10 bar pressure and at 30°C for 18 h. The hydrogen uptake was 2.74 l and 2.41 l (theor. 2 x 2.82 l). The black suspensions of the two runs were filtered and the filter cakes were washed each with 300 ml, a total of 600 ml ethanol. The filtrates and wash solutions of both runs were combined and the solution was divided in two parts of exactly equal volumes. One part was evaporated (40 °C/10 mbar/4 h) to provide, after drying *in vacuo*, 33.85 g of light yellow oil. The other part was concentrated to a volume of ca 150 ml, filtered to remove some traces of charcoal, and then evaporated to provide, after drying *in*

vacuo, 33.13 g of light yellow oil. Combined yield 66.98 g of crude acid **1** (diastereoisomer mixture). This material by GC analysis contained 84.4% **1a**, 1.4% **1c**, 8.8% **1b** and 1.65% **1d**; dr **1a/1b/1c/1d** = 87.7 : 9.2 : 1.5 : 1.6. Assays of 78.1% **1a** and of 7.1% **1b** were determined by HPLC with internal standard.

^{1}H-NMR (300 MHz, $CDCl_3$): ca. 10 (br. s, COOH); 4.15-3.95 (br. m, 1 H); 3.65-3.1 (br. m, 3 H); 2.6 (br. m, 1 H); 2.12 (s, SCH_3); 2.0-1.65 (m, 4 H); 1.46 and 1.43 (2 s, tBu of 2 rotamers), 1.39 (d, J = 6.5, CH_3).

b) Formation of (*S*)-2-((*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester; compound with dicyclohexylamine (1a x Cy_2NH)

A quantity of 33.5 g crude acid [**1**, diastereoisomer mixture from a), derived from 112.3 mmol Boc-L-prolinal] was dissolved in 170 ml *tert*-butyl methyl ether. The solution was filtered to remove some residual solid (charcoal), and then treated with 23.73 ml dicyclohexylamine (119 mmol). The solution was cooled to 0-5°C under stirring whereby a white solid started to precipitate at ca. 8°C. The suspension was stirred at 0-5°C for 3 h. The solid was collected by filtration over a pre-cooled glass filter funnel, washed with 100 ml pre-cooled (0-5°C) *tert*-butyl methyl ether and dried (40°C/10 mbar/4 h) to furnish 38.55 g (70.8%, based on Boc-L-prolinal) of the title compound (**1a** x Cy_2NH) as white powder; m.p. 141-142°C; $[\alpha]_D^{20}$ -20.56 (c 1.04, ethanol). The composition of this material as derived from GC analysis was 44.6% Cy_2NH, 54.1% **1a**, 0.33% **1c**, 0.69% **1b** and 0.13% **1d**; dr **1a/1b/1c/1d** = 97.9 : 1.25 : 0.6 : 0.25. An assay of 61% **1a** (theor. 62.6%) was determined by HPLC with internal standard. Chiral HPLC analysis showed **1a** to be enantiomerically pure (*ent*-**1a** not detectable).

^{1}H-NMR ($CDCl_3$, 400 MHz): 8.55 (br. s, NH_2^+); 4.2-4.0 (br. m, 1 H); 3.75-3.2 (br. m, 3 H); 2.87 (m, 1 H); 2.27 (m, 1 H); 2.2-1.1 [m, total 39 H, with 2.12 (s, SCH_3), 1.48 and 1.44, (2 s, tBu of 2 rotamers)].

c) Isolation and Crystallization of (*S*)-2-(*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1a)

A quantity of 38.5 g **1a** x Cy_2NH (derived from 112.1 mmol Boc-L-prolinal) was treated with 160 ml *tert*-butyl methyl ether and 160 ml 1M sodium carbonate solution. The organic phase was separated and extracted with 160 ml 1M sodium carbonate solution. The combined aqueous phases were acidified to pH 2 by addition of 175 ml 2M sulfuric acid and the resulting mixture was extracted 3 times with 175 ml, a total of 525 ml *tert*-butyl methyl ether. The combined extracts were dried over ca. 90 g sodium sulfate, filtered

and evaporated (40°C/10 mbar/ 0.5 h) to provide 24.16 g of crude acid 1a as colorless viscous oil. Assays of 95.2% 1a and of 1.2% 1b were determined by HPLC with internal standard. The crude acid 1a was dissolved at rt in 120 ml hexane and the solution stirred at -20°C for 16 h. The white precipitate was filtered over a pre-cooled (-20°C) glass filter funnel, washed portion-wise with 60 ml hexane (pre-cooled at -20°C) and dried (40°C/10 mbar/2 h) to furnish 19.94 g (58.5 % based on Boc-L-prolinal) of the title compound (1a) as white crystals; m.p. 64.5-66°C. The material by GC analysis contained 97.9% 1a, 0.53% 1c, 0.98% 1b and 0.13% 1d; dr 1a/1b/1c/1d = 98.4 : 1.0 : 0.5 : 0.1. Chiral HPLC analysis showed 1a to be enantiomerically pure (*ent*-1a not detectable).

^{1}H-NMR (400 MHz, $CDCl_3$): 4.15-3.95 (br. m, 1 H); 3.65-3.15 (br. m, 3 H); 2.6 (br. m, 1 H); 2.12 (s, SCH_3); 1.94 (br. m, 3 H); 1.75 (m, 1 H); 1.47 and 1.45 (2 s, tBu of 2 rotamers), 1.39 (d, J = 6.5, CH_3).

Example 5

(*S*)-2-((*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester; compound with (*R*)-1-phenyl-ethylamine (1a x (PhEt)NH_2)

Analogously to the salt formation described in example 4b) the (*R*)-1-phenylethyl-ammonium salt was obtained:

A quantity of 30.34 g of the crude acid **1** [diastereoisomer mixture, dr **1a/1b/1c/1d** = 87.7 : 9.2 : 1.5 : 1.6, see example 4a), derived from 101.7 mmol Boc-L-prolinal] was dissolved in 166.9 ml heptane, resulting in a slightly turbid, greenish solution. Then 12.98 g (105 mmol) (*R*)-(+)-1-phenyl-ethylamine were injected in one portion from a syringe resulting in a temperature increase from 25 to 35°C. The reaction mixture was stirred overnight (16 h) at rt. The precipitated crystals were separated by filtration, washed with heptane and dried *in vacuo* at rt, yielding 31.43 g of the crude (*R*)-1-phenylethylammonium salt of 1a. The crude product was purified by recrystallization from diisopropyl ether leading to 27.4 g (63% based on Boc-L-prolinal) white crystals; m.p. 99-100°C. The material contained, as derived from GC analysis, 97.7 % 1a, 0.9 % 1b, and 0.2 and 0.1 % of the minor diastereoisomers 1c and 1d. A sample for analysis was obtained by further recrystallization, white crystals; m.p. 103-104°C; $[\alpha]_D^{20}$ -22.4 (c 1.04, ethanol).

^{1}H-NMR: (300 MHz, $CDCl_3$): 7.5-7.2 (m, NH_3^+ and 5 arom. H); 4.33 (q, J = 6.8, PhCH(Me)); 3.97 (br. m, 1H); 3.50 (br. t, J = 8, 1 H); 3.24 (m, 2 H); 2.45-1.15 [m, in total

23 H with 2.03 (s, SCH_3), 1.58 (d, J = 6.8, PHCH-$\underline{CH_3}$), 1.34 (s, tBu), 1.20 (d, J = 6.5, $\underline{CH_3}$CH-COO^-)].

The isolation and crystallization of **1a** can be carried out analogously to the description given in example 4c).

Example 6

(*S*)-2-((*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester; compound with diisopropyl-amine (1a x $(iPr)_2NH$)

Analogously to the salt formation described in examples 4b) or 5 the diisopropyl-ammonium salt was obtained:

A quantity of 1.10 g of the crude acid **1** [diastereoisomer mixture with assays of 69.9% **1a** and 8.0% **1b** as determined by HPLC with internal standard; cf. example 4a)] and 370 mg (3.62 mmol) of diisopropylamine were dissolved at 60°C in 10 ml cyclohexane. The hot solution was allowed to cool to rt overnight while stirring. The precipitated white crystals were collected by filtration, washed with cyclohexane and dried at rt *in vacuo* to yield 700 mg (68.5%) of the diisopropyl ammonium salt of **1a** as white crystals; m.p. 125-128 °C; $[\alpha]_D^{20}$ -26.9 (c 1.98, ethanol).

^{1}H-NMR: (300 MHz, $CDCl_3$): 8.42 (br. s, NH_2^+); 4.1 (br. s, 1 H); 3.7-3.3 (br. m, 3 H); 3.24 (septet, J = 6.5, 2 C$\underline{H}Me_2$); 2.25 (m, 1 H); 2.15-1.2 [m, in total 31 H, with 2.11 (s, SCH_3), 1.46 and 1.44 (2 s, tBu of 2 rotamers), 1.26 (d, J = 6.5, 2 CH($\underline{CH_3}$)$_2$].

The isolation and crystallization of **1a** can be carried out analogously to the description given in example 4c).

Example 7

(*S*)-2-((*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester; compound with (*R*)-1-cyclohexyl-ethylamine (1a x (CyEt)NH_2)

and

(*S*)-2-((*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester; compound with benzyl-((*R*)-1-phenyl-ethyl)-amine (1a x (Bn)(PhEt)NH)

Analogously to the salt formation described in examples 4b), 5 and 6 the respective (*R*)-1-cyclohexyl-ethylammonium salt or benzyl-((*R*)-1-phenyl-ethyl)-ammonium salt can be obtained. These salts were obtained as reference examples by adding the respective amine to the pure acid (**1a**), which was dissolved under argon in a mixture of *tert*-butyl methyl ether and heptane (1:1). Stirring for 18 h at rt yields the crystalline ammonium salt which is separated by filtration, washed with heptane and dried *in vacuo* for about 4 h.

a) The respective (*R*)-1-cyclohexyl-ethylammonium salt is obtained as white crystals with a melting point of 132-133 °C; $[\alpha]_D^{20}$ -23.2 (c 1.06, ethanol).

^{1}H-NMR: (300 MHz, $CDCl_3$): 7.29 (br. s, NH_3^+); 4.0 (br. m, 1 H); 3.55 (br. t, J = 8, 1 H); 3.4-3.2 (m, 2 H); 3.06 (qui, J = 6, 1 H); 2.4-1.0 [m, in total 42 H with 2.09 (s, SCH_3), 1.43 (s, tBu), 1.35 (d, J = 7, 1 CH_3), 1.27 (d, J = 7, 1 CH_3)].

b) The respective benzyl-((*R*)-1-phenyl-ethyl)-ammonium salt is obtained as white crystals with a melting point of 71-73 °C; $[\alpha]_D^{20}$ -5.1 (c 1.09, ethanol).

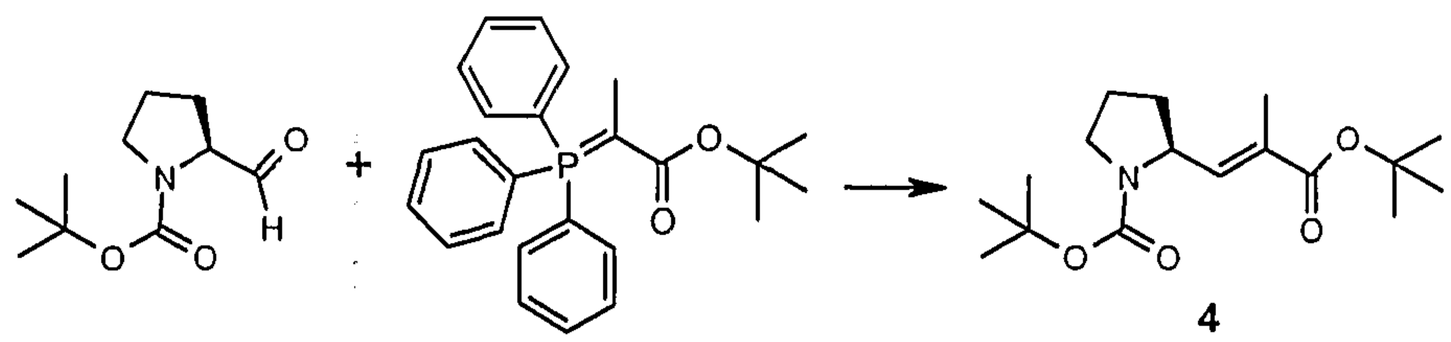
^{1}H-NMR: (300 MHz, $CDCl_3$): 7.4-7.2 (m, 10 arom. H); 6.97 (br. s, NH_2^+); 3.99 (q, J = 5.5, 1 H); 3.90 (q, J = 7, 1 H); 3.75 and 3.65 (AB, J = 13; $PhCH_2$-); 3.65-3.15 (br m, 3 H); 2.47 (m, 1 H); 2.11 (s, SCH_3); 2.0-1.25 [m, in total 19 H, with 1.46 (s, tBu), 1.36 (d, J = 7, 1 CH_3)].

The isolation and crystallization of **1a** can be carried out analogously to the description given in example 4c).

Reaction sequence B)

Example 8

Synthesis of (*S*)-2-(2-*tert*-Butoxycarbonyl-propenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4) (Synthesis with preformed *Wittig* Ylide)



a) The *Wittig* Ylide ((2-triphenylphosphoranylidene)-propionic acid *tert*-butyl ester) can be obtained according to the synthesis described in "Y. Guindon, L. Murtagh, V. Caron, S.R. Landry, G. Jung, M. Bencheqroun, A.-M. Faucher, B. Guerin, *J. Org. Chem.*, 66, 2001, 5427" or

"P.L. Stotter, K.A. Hill, *Tetrahedron Lett.*, 16, 1975, 1679."

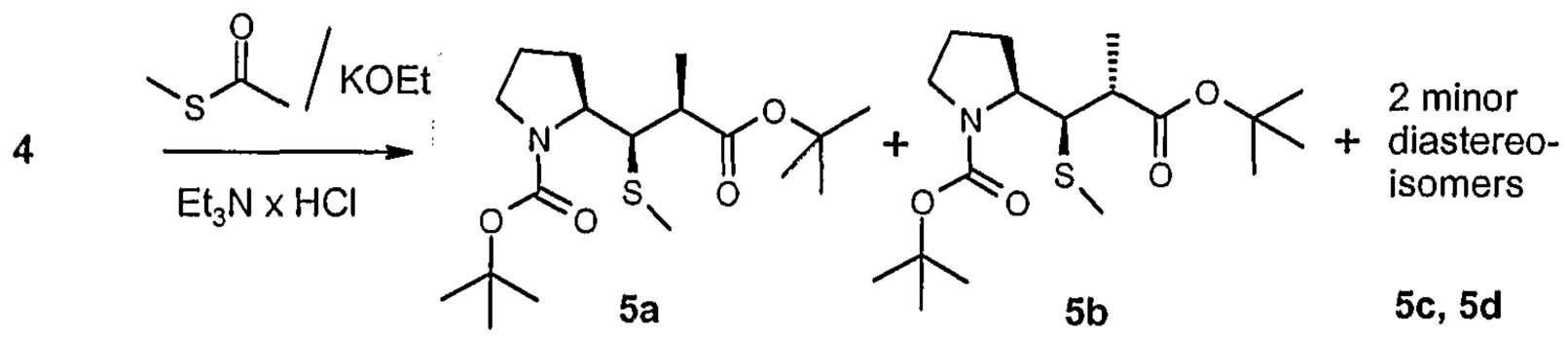
b) A quantity of 56.0 g (2-triphenylphosphoranylidene)-propionic acid *tert*-butyl ester (143.4 mmol) was suspended under argon and with stirring in 160 ml *tert*-butyl methyl ether. A solution of 21.0 g Boc-L-prolinal (105.4 mmol) in 50 ml *tert*-butyl methyl ether was added drop by drop. The yellowish suspension was stirred at 50°C for 3.5 h. After complete conversion, the suspension was transferred with dichloromethane into a 1 l round bottomed flask. The solvent was removed by evaporation and final drying *in vacuo* (0.1 mbar/rt/15 min). The residue was taken up in 400 ml heptane, the resulting yellowish suspension stirred at rt for 30 min and the white precipitate of triphenylphosphine oxide removed by filtration over ca. 20 g decalite speed plus (diatomaceous filter-aid). The filter residue was washed 3 times with 50 ml, a total of 150 ml heptane and the combined filtrate and wash solutions were evaporated. The residue was dried (0.1 mbar/rt/2 h) to afford 34.4 g of the crude product. The material by GC analysis contained 5.5% *(Z)*-4, 91.7% *(E)*-4 and 1.8% triphenylphosphine. The crude product was dissolved in ca. 20 ml hexane/ethyl acetate (9:1 mixture) and flash-filtered over 150 g silica gel using a pressure of ca. 0.5 bar.

The product was eluted with ca. 2 l hexane/ethyl acetate 9:1 mixture. Evaporation afforded as the filtered product 32.4 g (98.7% based on Boc-L-prolinal) of the title compound (4) as a light yellowish oil. The material by GC analysis contained 5.6% *(Z)*-4, 92.8% *(E)*-4 and 1.4% triphenylphosphine; *E/Z* = 94:6. The material by chiral HPLC analysis contained 0.05% (*R,E*)-4 and 99.95% (*S,E*)-4; ee = 99.9%.

^{1}H-NMR: (300 MHz, $CDCl_3$): 6.5 (br. d, J = 7, vinyl. H of (*E*)-4); 5.75 and 5.95 (2 br. s, vinyl. H of 2 rotamers of (*Z*)-4); 4.65-4.35 (br. m, 1 H); 3.6-3.35 (br. m, 2 H); 2.15 (m, 1H); 2.0-1.3 (m, in total 24 H, with 1.48 (s, tBu), 1.41 (br. s, tBu)].

Example 9

Synthesis of (*S*)-2-((*1R,2S*)-2-*tert*-Butoxycarbonyl -1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (5a) in mixture with (*S*)-2-((*1R,2R*)-2- *tert*-Butoxycarbonyl-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (5b) and two further diastereoisomers of (*S*)-2-(2-*tert*-Butoxycarbonyl-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester of partially undetermined configuration (5c and 5d)



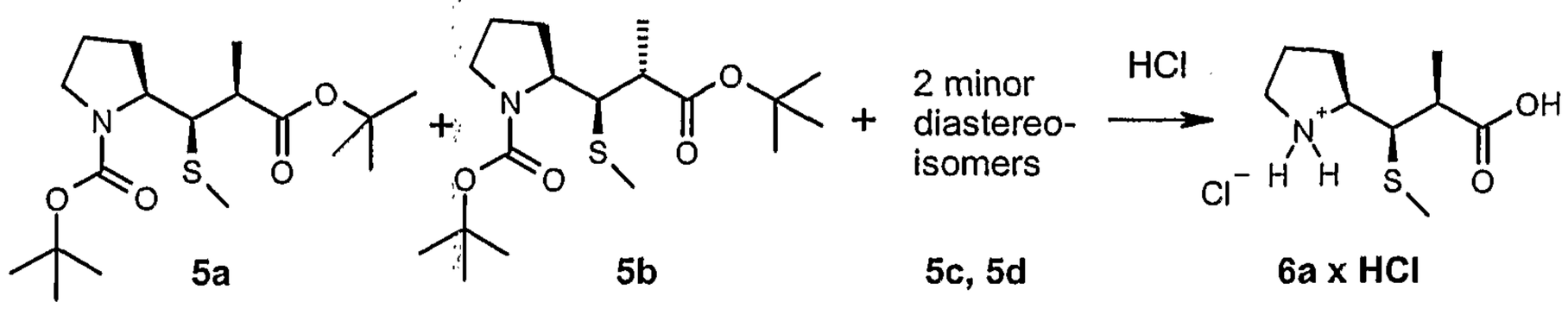
54.6 g S-methyl thioacetate (606 mmol) were dissolved under argon with stirring in 310 ml tetrahydrofuran. To the clear colorless solution 50.4 g potassium ethoxide (599 mmol) were added at once as a yellow solid with the aid of a glass funnel. The funnel was rinsed with 50 ml tetrahydrofuran. The suspension was stirred at rt for an additional 4 h. After a total reaction time of 5 h, 41.3 g triethylamine hydrochloride were added at once followed by dropwise addition of a solution of 31.1 g (*S*)-2-(2-*tert*-butoxycarbonyl-propenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (100 mmol, see example 8) in 160 ml tetrahydrofuran. The yellow suspension was stirred at rt for 22 h. After 22 h, 120 ml ethyl acetate and 350 ml 5M ammonium chloride solution were added to the reaction mixture. The two phase-system was stirred at rt for 10 min, then transferred into a separatory funnel and the phases were separated. The aqueous phase was extracted with 100 ml ethyl

acetate. The combined organic phases were dried over ca. 40 g sodium sulfate, filtered and evaporated to yield 37.7 g of the crude product. The material by GC analysis contained 1.3% (*Z*)-4, 3.3% (*E*)-4, 81.8% 5a, 2.0% 5c and 9.5% of the co-eluting 5b and 5d. The crude product was dissolved in 20 ml hexane/ethyl acetate (9:1 mixture) and flash-filtered over 100 g silica gel using a pressure of ca. 0.5 bar. The product was eluted with ca. 2 l hexane/ethyl acetate 9:1 mixture. Evaporation and drying (0.1 mbar/rt/2 h) afforded as the filtered product 35.5 g of the title product 5 (99% based on Boc-L-prolinal) as a clear yellow oil. This material consisted by GC analysis of 1.3% (*Z*)-4, 2.6% (*E*)-4, 82.5% 5a, 2.2% 5c, 7.5% 5b and 2.2% 5d; dr 5a/5b/5c/5d = 87.4. 8.0 : 2.3 : 2.3.

^{1}H-NMR: (300 MHz, $CDCl_3$): 4.2-3.1 (br. m, 4 H); 2.45 (m, 1 H); 2.3-1.15 (m, in total 28 H, with 2.11 (s, SCH_3), 1.48 and 1.46 (2 s, tBu of 2 rotamers), 1.29 (br. d, J = 6.5, CH_3)].

Example 10

Synthesis of (*S*)-2-((*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidinium chloride (6a x HCl)

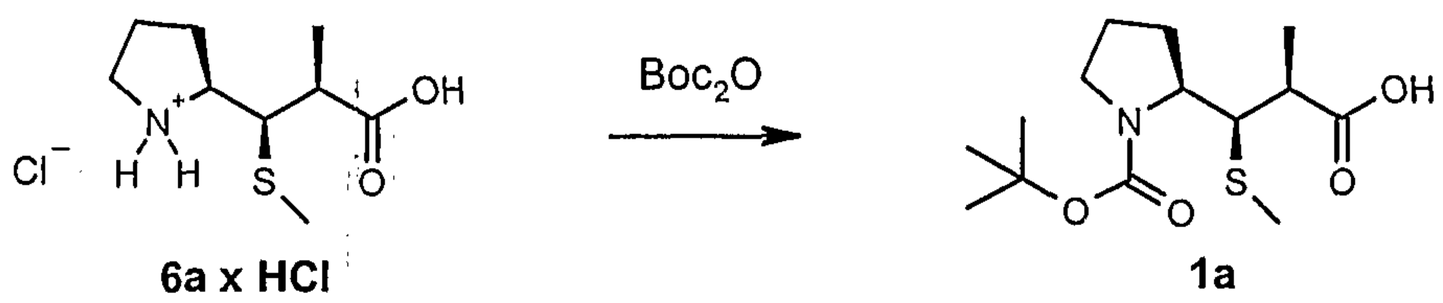


A quantity of 33.5 g (*S*)-2-(2-*tert*-butoxycarbonyl-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (5, 93.3 mmol, from example 9; diastereoisomer mixture, **5a/5b/5c/5d** = 87.4 : 8.0 : 2.3 : 2.3) was dissolved under argon with stirring in 185 ml of a 4.44M solution of dry hydrochloric acid in ethyl acetate (821 mmol). The solution was stirred at rt for 30 min, then seed crystals were added whereby crystallization started. The suspension was stirred at rt for 2 h and at 0°C for 2 h. The precipitate was isolated by filtration, washed two times with 10 ml, a total of 20 ml cold ethyl acetate (0°C) and dried *in vacuo* (0.1 mbar) at rt for about 18 h to afford 15.5 g (69% based on 5) of the title compound (1a x HCl) as white crystals; m.p. 169-170°C.

^{1}H-NMR (300 MHz, d_6-DMSO): 12.5 (br. s, COOH); 9.9 and 8.9 (2 br. s, NH_2^+); 3.57 (q, J = 6.7, 1 H); 3.34 (dxd, J = 9 and 4.5, 1 H); 3.21 (m, 2 H); 2.86 (m, 1 H); 2.25 (m, 1 H); 2.19; (s, SCH_3); 2.0-1.65 (m, 3 H); 1.15 (d, J = 6.9, CH_3).

Example 11

Synthesis of (*S*)-2-(*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1a)



6a x HCl **1a**

A quantity of 15.2 g (*S*)-2-((*1R,2S*)-2-carboxy-1-methylsulfanyl-propyl)-pyrrolidinium chloride (**6a x HCl**, 63.4 mmol, from example 10) was suspended under argon with stirring in 280 ml dioxane. A solution of 9.4 g sodium carbonate (89 mmol) in 205 ml deionized water was added. Upon addition of approximately half of the volume, a clear solution formed which after completion of the addition turned into a milky solution. Then 17.3 g di-*tert*-butyl dicarbonate (79.3 mmol) were added and the slightly turbid solution was stirred at rt for 5.5 h. For work-up 100 ml *tert*-butyl methyl ether/heptane 1:1 mixture were added and the two phases were separated. The organic phase was evaporated to afford 4.4 g of a colorless oil containing product by TLC and HPLC. The aqueous phase was overlaid with 150 ml *tert*-butyl methyl ether and acidified under stirring with 57.5 ml 2N hydrochloric acid to pH 2. After phase separation, the water phase was extracted 3 times with 40 ml, a total of 120 ml *tert*-butyl methyl ether. The combined organic phases were washed 2 times with 40 ml, a total of 80 ml saturated sodium chloride solution, dried over ca. 40 g sodium sulfate, filtered and evaporated. The residue was taken up in little dichloromethane and combined with the 4.4 g material obtained above. The solution was evaporated and the residue dried *in vacuo* (0.1 mbar) at a temperature of 70°C for 2 h to yield 21.5 g of crude product as thick colorless oil. The material by GC analysis consisted of 96.0% **1a**, 0.35% **1c**, 0.43% **1b** and 0.17% **1d**; dr **1a/1b/1c/1d** = 99.0 : 0.5 : 0.4 : 0.1. HPLC analysis with internal standard indicated an assay of 85.0 w% **1a**. For crystallization the crude material was dissolved in 60 ml heptane at 70°. The clear solution was stirred and allowed to cool to rt whereby crystallization started after ca. 20 min. The suspension was stirred at 0°C for 3h, and the resulting thick suspension placed in the refrigerator at 4°C for

24 h and finally in the freezer at -18°C for 72 h. The precipitate was isolated by filtration, washed 2 times with 10 ml, a total of 20 ml cold heptane and dried *in vacuo* (0.1 mbar) at rt for 2h to afford as the 1st crop product 15.6 g (81%) of **1a** as white crystals; m.p. 71-72°C. The material by GC analysis consisted of 98.9% **1a**, 0.25% **1c**, 0.04% **1b** and 0.00 % **1d**; dr **1a/1b/1c/1d** = 99.7 : 0.05 : 0.25 : 0.0.

^{1}H-NMR (300 MHz, $CDCl_3$): ca. 10 (br. s, COOH); 4.15-3.95 (br. m, 1 H); 3.65-3.1 (br. m, 3 H); 2.6 (br. m, 1 H); 2.12 (s, SCH_3); 2.0-1.65 (br. m, 4 H); 1.46 (br. s, tBu), 1.39 (br. d, J = 6.5, CH_3).

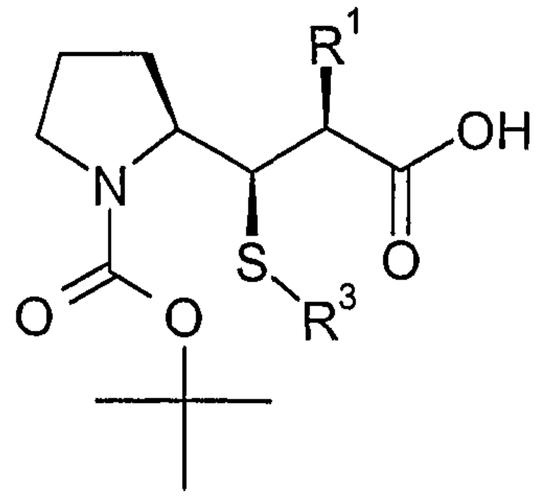
Microanalysis calc. for $C_{14}H_{25}NO_4S$ (303.42): C 55.42, H 8.30, N 4.62, S 10.57;
found: C 55.34/55.25, H 7.88/7.88, N 4.64/4.64, S 10.56/10.59.

The residue from the mother liquor (4.3 g, colorless oil) was dissolved in a round bottom flask in 9 ml heptane at 70°, and the solution was allowed to cool to rt. Seed crystals from the 1st crop were added and the flask was placed in a freezer at -18° for 48 h. Filtration and drying as described above afforded as the 2nd crop product 1.04 g (5.4%) of **1a** as white crystals; m.p. 70-71°C. The material by GC analysis consisted of 98.2% **1a**, 0.60% **1c**, 0.13% **1b** and 0.10 % **1d**; dr **1a/1b/1c/1d** = 99.2 : 0.1 : 0.6 : 0.1.

^{1}H-NMR (300 MHz, $CDCl_3$): identical with ^{1}H-NMR of 1st crop material.
Combined yield: 16.64 g **1a** (86.5%)

Claims

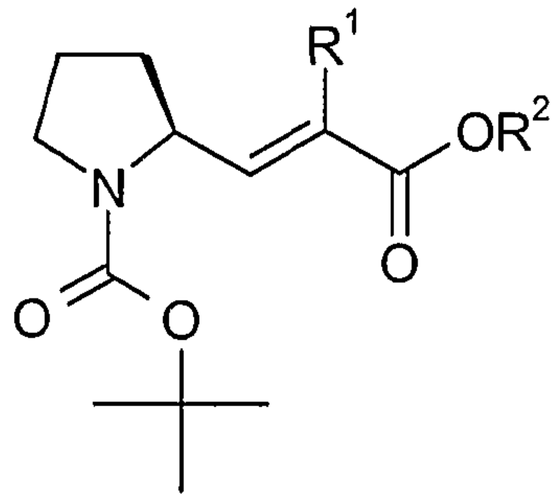
1. A process for the manufacture of the compounds of formula (I)



(I)

whereby

A) a compound of formula (II)

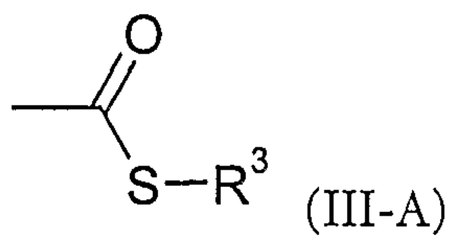


(II)

is reacted with a compound of formula (III)

$$KS-R^3 \quad \text{(III)},$$

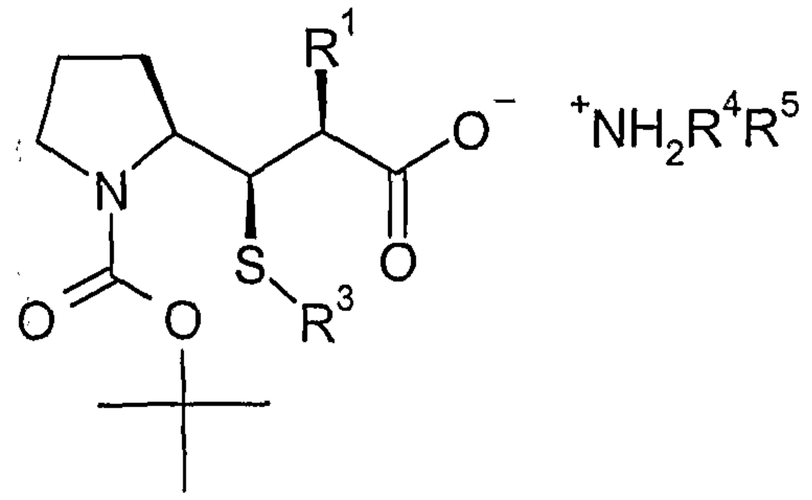
in the presence of triethylammonium chloride in a suitable solvent, whereby said compound of formula (III) is being used as such or can be generated *in situ* by reacting a compound of formula (III-A)



(III-A)

in the presence of potassium bases; and

the compounds of formula (I) are obtained by cleavage of R^2 in the $-COOR^2$ ester group, followed by the addition of an amine of the formula NHR^4R^5 to the resulting carboxylic acid, to form an ammonium salt of formula (IV)

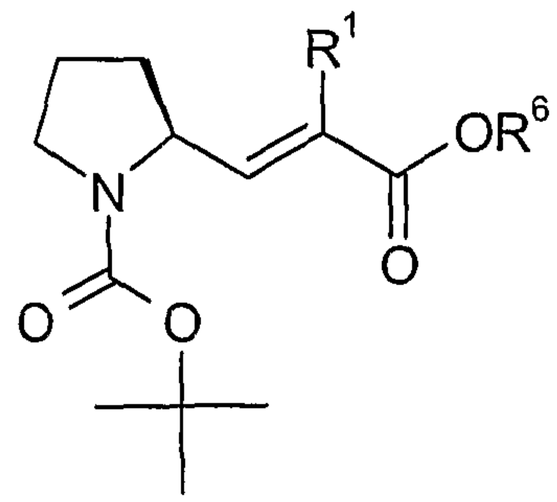


(IV)

and decomposition of said salt of formula (IV);

or

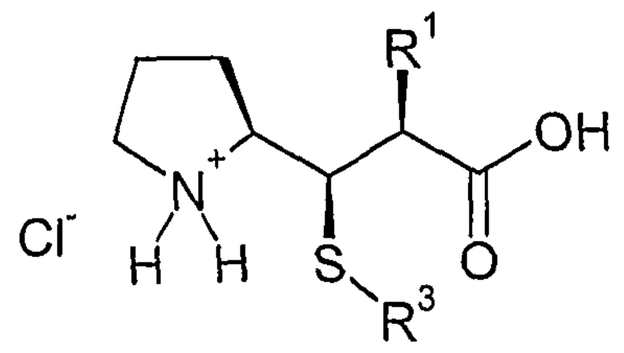
B) a compound of formula (V)



(V)

is reacted with a compound of formula (III), or (III-A) together with a potassium base as described above; and the compounds of formula (I) are obtained from the reaction product by addition of hydrochloric acid to form a compound of formula

(VI)



(VI)

followed by re-protection of the N-atom by reaction with a *tert*-butoxycarbonyl-delivering reagent;

and wherein

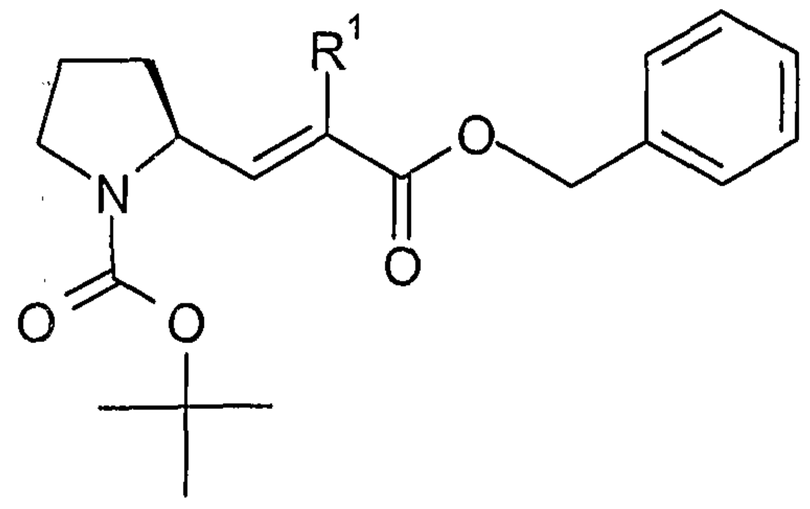
R^1, R^3 and R^6 independently from each other represent alkyl;

R^2 is benzyl or substituted benzyl; and

R^4 and R^5 are independently selected from cycloalkyl or alkyl, which alkyl can be unsubstituted or substituted one, two or three times with hydroxy, alkoxy, amino, mono- or di-alkylamino, acetoxy, alkylcarbonyloxy, carbamoyloxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyloxy, halogen, cycloalkyl or phenyl.

2. The process according to claim 1, whereby

the compounds of formula (II-A)



(II-A)

are reacted with a compound of formula (III), or (III-A) together with a potassium base as defined above, in the presence of triethylammonium chloride in tetrahydrofuran; and

the compounds of formula (I) are obtained by benzyl-ester cleavage from the product of said reaction, followed by addition of an amine of the formula NHR^4R^5 to the resulting carboxylic acid, and further followed by base addition and subsequent addition of mineral acids; and

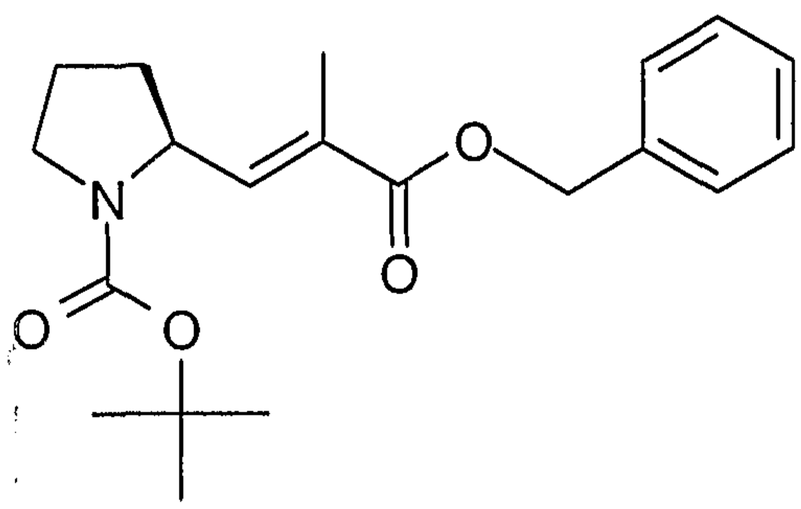
R^1, R^4 and R^5 have the meanings given herein before.

3. The process according to claim 1 or 2, wherein the amines of formula NHR^4R^5 are selected from

dicyclohexylamine, diisopropylamine, *(R)*-α-phenylethylamine, benzyl-*(R)*-α-phenylethylamine and *(R)*-α-cyclohexylethylamine.

4. The process according to claim 3, whereby

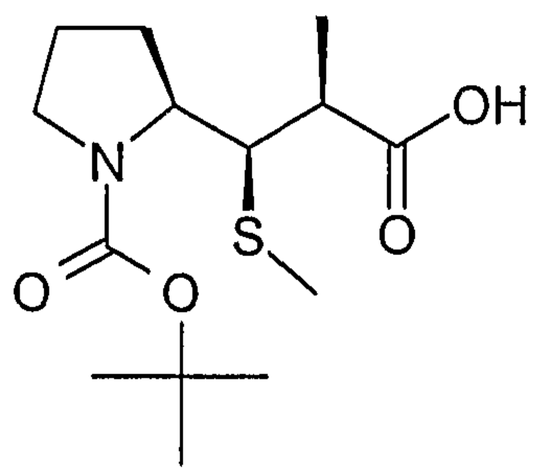
the compound of formula (2)



(2)

is reacted with S-methyl thioacetate together with potassium ethoxide, in the presence of triethylammonium chloride in tetrahydrofuran; and

the compound of formula (1a)

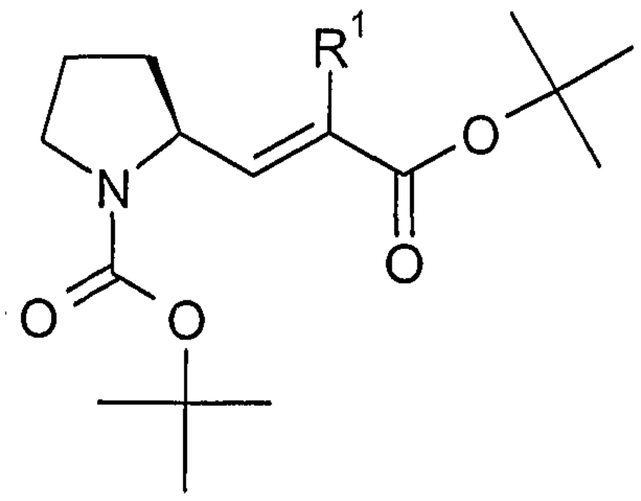


(1a)

is obtained by benzyl-ester cleavage from the product of said reaction, followed by addition of dicyclohexylamine, and further followed by sodium carbonate addition and subsequent addition of sulfuric acid.

5. The process according to claim 1, whereby

a compound of formula (V-A)



(V-A)

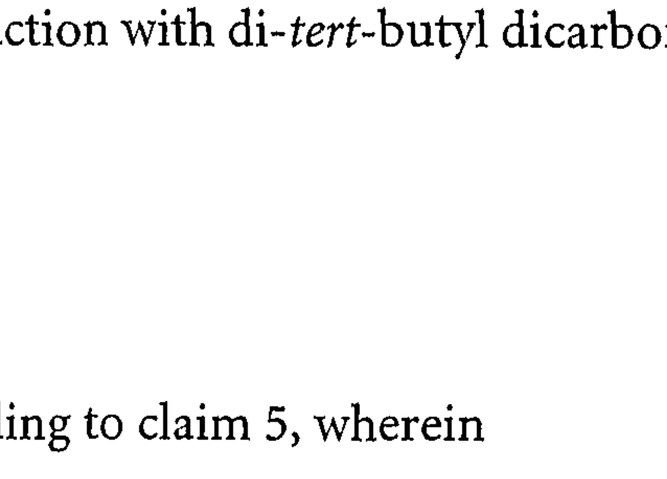
is reacted with a compound of formula (III), or (III-A) together with a potassium base as defined above, in the presence of triethylammonium chloride in tetrahydrofuran, and

the compounds of formula (I) are obtained by further reacting the product of the above reaction with dry hydrochloric acid in ethyl acetate, followed by addition of sodium carbonate and subsequent reaction with di-*tert*-butyl dicarbonate; and wherein

R^1 is as defined above.

6. The process as according to claim 5, wherein

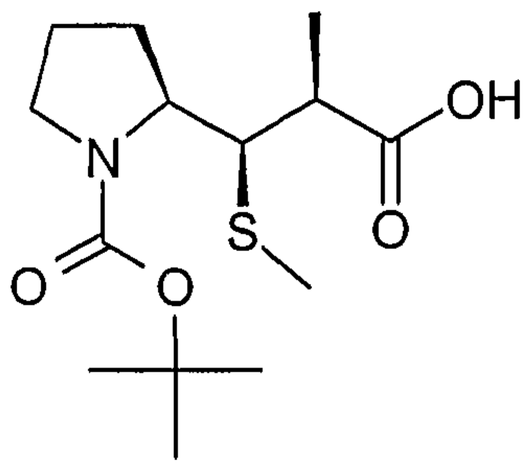
a compound of formula (4)



(4)

is reacted with S-methyl thioacetate together with potassium ethoxide, in the presence of triethylammonium chloride in tetrahydrofuran, and

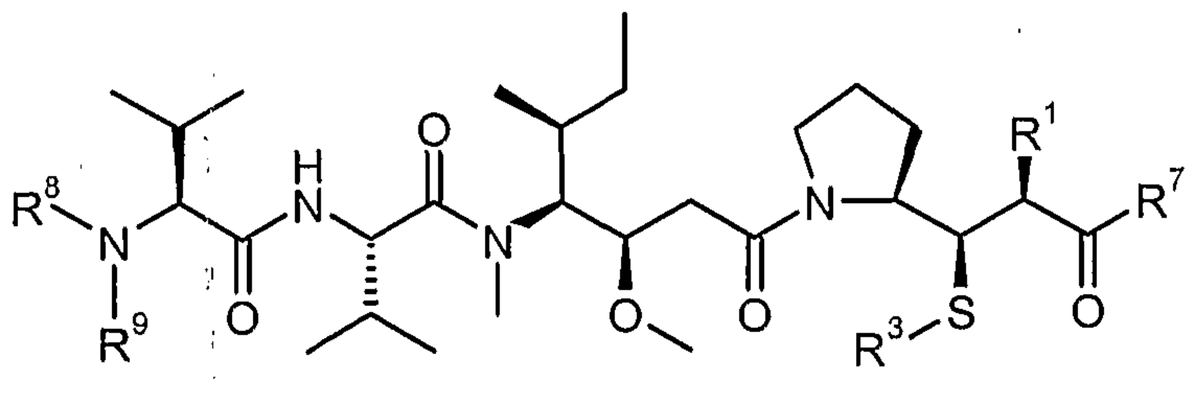
the compound of formula (1a)



(1a)

is obtained by further reacting the product of the above reaction with dry hydrochloric acid in ethyl acetate, followed by addition of sodium carbonate and subsequent reaction with di-*tert*-butyl dicarbonate.

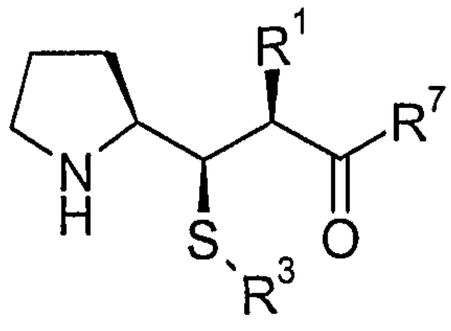
7. The process according to claim 1, wherein the compounds of formula (I) are further reacted to give the compounds of formula (A),



(A),

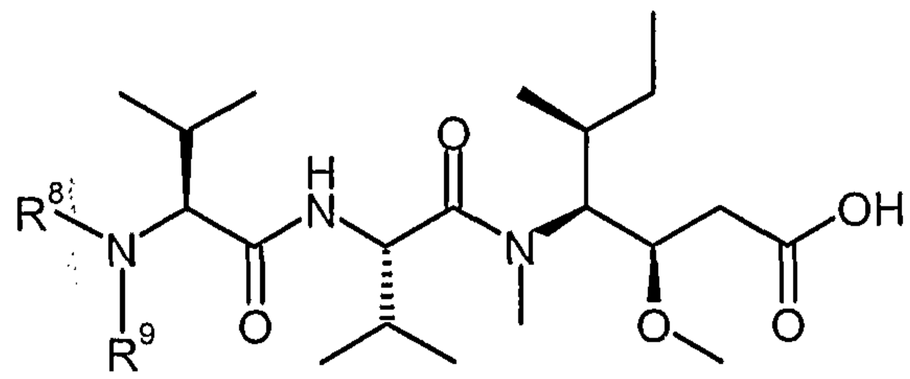
wherein

a) the compounds of formula (I) are reacted with an alcohol or an amine, followed by cleavage of the *tert*-butoxycarbonyl group at the pyrrolidine N-atom, to give the compounds of formula (B)



(B); and

b) the compounds of formula (B) are further reacted with the compounds of formula (C)



(C),

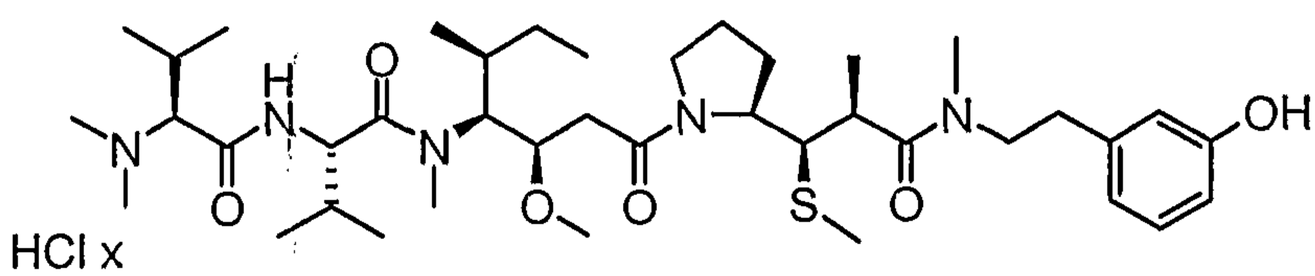
to give the compounds of formula (A); and

R^1 and R^3 are as defined in claim 1;

R^8 and R^9 independently from each other represent alkyl; and

R^7 is phenylalkyl-, or phenyldialkylamino or phenylalkyloxy, having (C_1-C_4)-alkylene and wherein the phenyl group optionally may be substituted with one, two or three substituents selected from the group consisting of halogen, alkoxycarbonyl, sulfamoyl, alkylcarbonyloxy, carbamoyloxy, cyano, mono- or di-alkylamino, alkyl, alkoxy, phenyl, phenoxy, trifluoromethyl, trifluoromethoxy, alkylthio, hydroxy, alkylcarbonylamino, 1,3-dioxolyl, 1,4-dioxolyl, amino and benzyl.

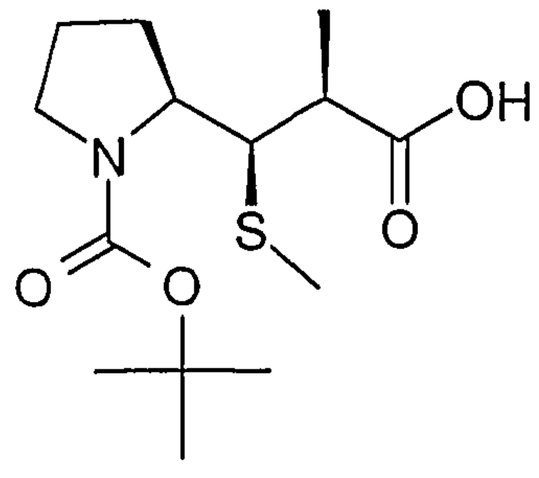
8. The process according to claim 7 for the manufacture of the compound of formula (A-1)



(A-1),

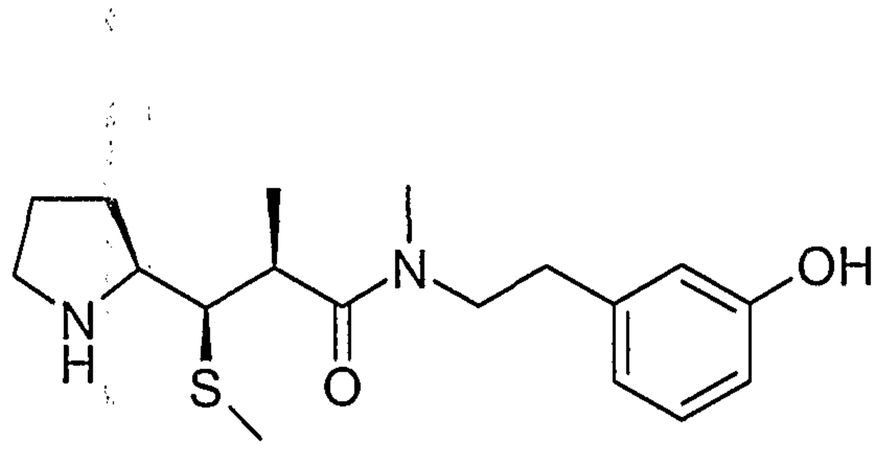
wherein

a) the compound of formula (1a)



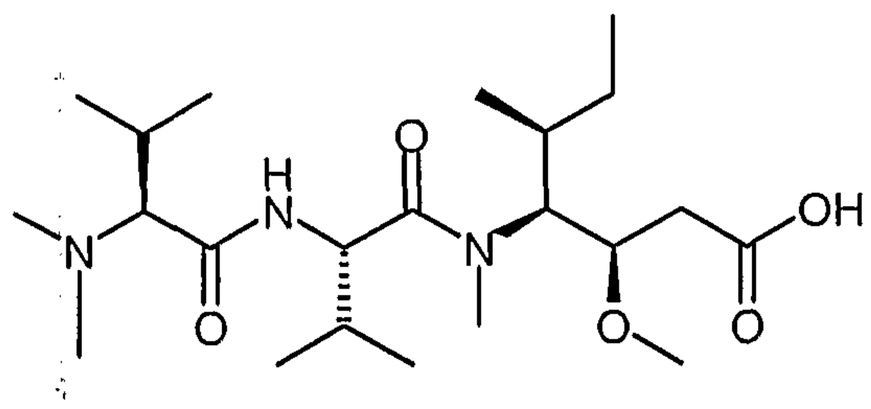
(1a)

is reacted with 3-(2-methylamino-ethyl)-phenol, followed by cleavage of the *tert*-butoxycarbonate group at the pyrrolidine N-atom, to give the compound of formula (B-1)



(B-1); and

b) the compound of formula (B-1) is further reacted with the compound of formula (C-1)



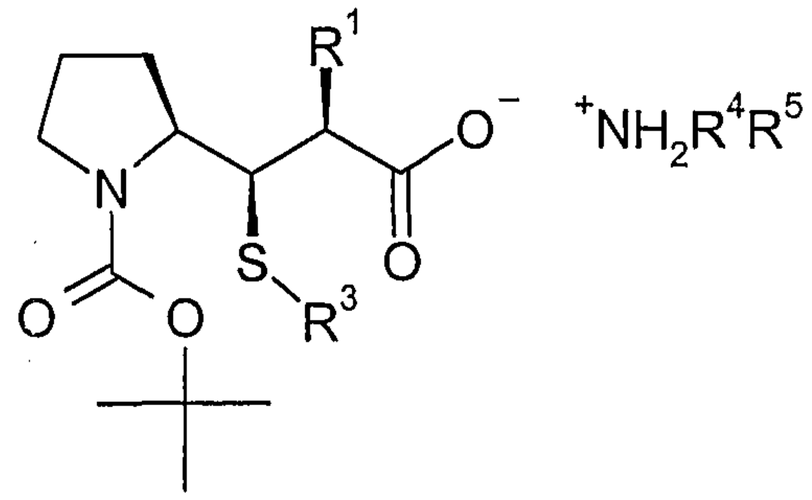
(C-1),

to give the compound of formula (A-1).

9. The use of the process according to claim 1 in the manufacture of the compounds of formula (A) according to claim 7.

10. The use of the process according to claim 1 in the manufacture of the compound of formula (A-1) according to claim 8.

11. The compounds of formula (IV)



(IV),

wherein

R^1 and R^3 independently from each other represent alkyl; and

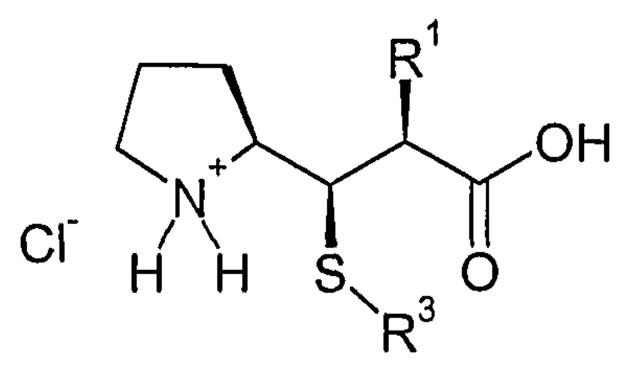
R^4 and R^5 are independently selected from cycloalkyl or alkyl, which alkyl can be unsubstituted, or substituted one, two or three times with hydroxy, alkoxy, amino, mono- or di-alkylamino, acetoxy, alkylcarbonyloxy, carbamoyloxy, alkoxycarbonyl, carbamoyl, alkylcarbamoyloxy, halogen, cycloalkyl or phenyl.

12. The compounds according to claim 11, wherein

R^1 and R^3 are methyl; and

the group $^+NH_2R^4R^5$ represents a cation selected from dicyclohexylammonium, diisopropylammonium, *(R)*-α-phenylethylammonium, benzyl-*(R)*-α-phenylethylammonium or *(R)*-α-cyclohexylethylammonium.

13. The compounds of formula (VI)



(VI),

wherein

R^1 and R^3 independently from each other represent alkyl.

14. The compound according to claim 13, wherein

R^1 and R^3 are methyl.

15. The compound

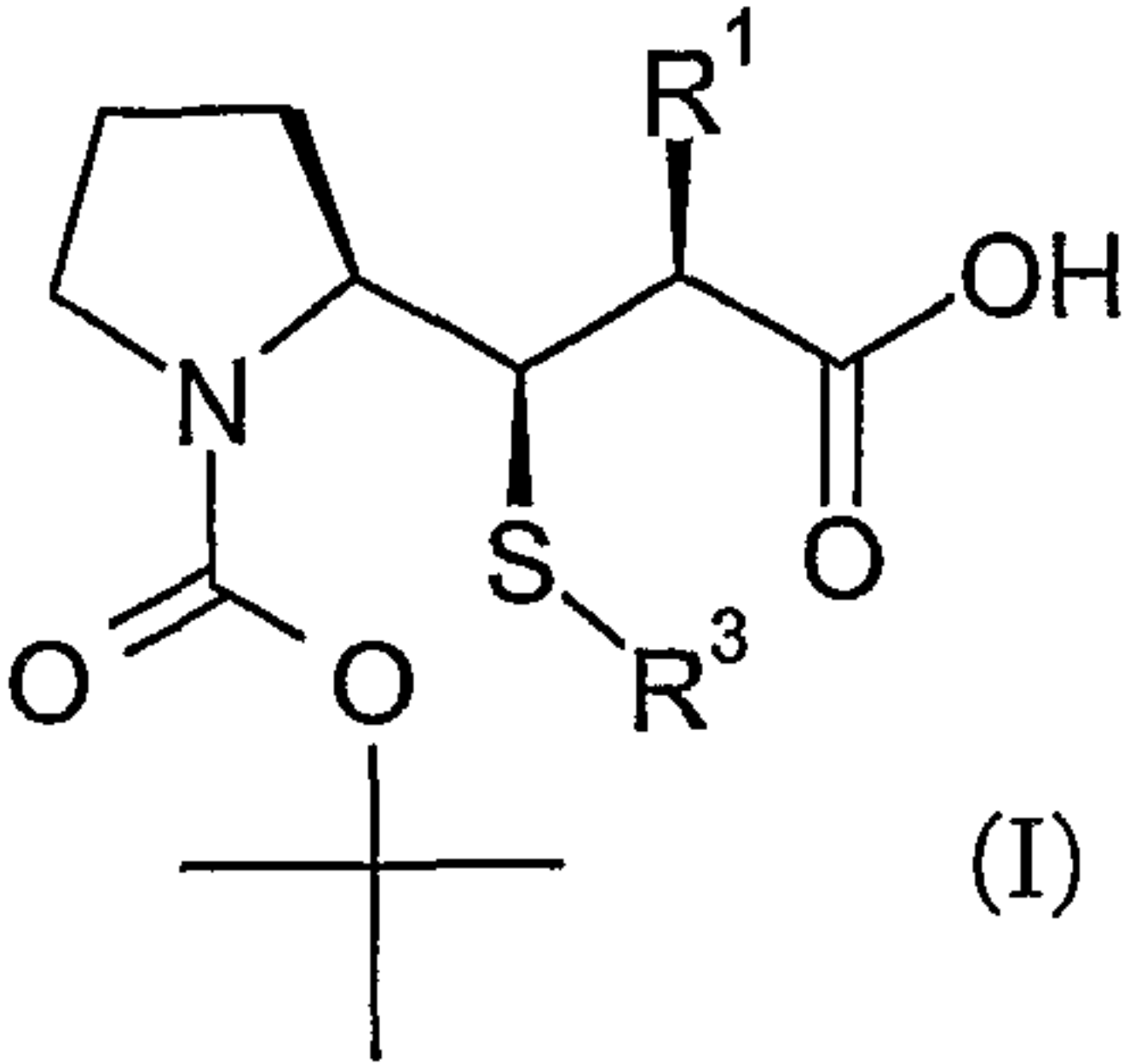
(*S*)-2-((*1R,2S*)-2-Carboxy-1-methylsulfanyl-propyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

16. The use of a compound as defined in any one of claims 11 to 15 in a process as defined in claim 1.

17. The use of a compound as defined in any one of claims 11 to 15 in the manufacture of the compounds of formula (A) according to claim 7.

18. The use of a compound according to claim 12 or 15 in the manufacture of the compound of formula (A-1) according to claim 8.

19. The novel processes, compounds and uses substantially as described herein before.



(I)