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(54) Title: STEREOSELECTIVE SYNTHESIS OF N-PROTECTED ALKOXY PROLINES

(57) Abstract: A process for preparing optically-active N-protected alkoxy prolines, including (2*R*,4*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester is disclosed. The N-protected alkoxy prolines are useful for preparing various serine protease factor Xa inhibitors, which are useful for treating diseases associated with abnormal thrombosis.

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STEREOSELECTIVE SYNTHESIS OF N-PROTECTED ALKOXY PROLINES

BACKGROUND OF THE INVENTION

FIELD OF INVENTION

[0001] This invention relates to materials and methods for preparing optically-active N-protected alkoxy prolines, including (2*R*,4*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester. The N-protected alkoxy prolines are useful for preparing various serine protease factor Xa inhibitors, which are thought to be useful for treating diseases associated with abnormal thrombosis.

DISCUSSION

[0002] U.S. Patent Application No. US 2003/0162787 A1 to Bigge et al. (the '787 application) describes a number of cyclic amino acid and proline derivatives that inhibit serine protease factor Xa. Factor Xa is involved in the formation of thrombin, which regulates a number of processes linked to thrombus generation, formation, and stabilization. Since inappropriate thrombus formation in blood vessels is associated with cardiovascular disease, it is thought that the administration of factor Xa inhibitors, including those described in the '787 application, may be useful for treating thrombus-related diseases. Such diseases include venous thrombosis, arterial thrombosis, pulmonary embolism, myocardial infarction, cerebral infarction, restenosis, angina, atrial fibrillation, and heart failure, among others.

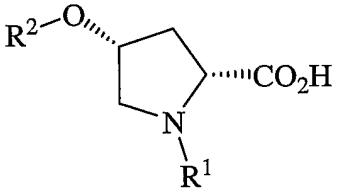
[0003] The '787 application describes a number of methods for preparing the cyclic amino acid and proline derivatives. Many of these methods employ, as chemical intermediates, optically active N-protected alkoxy prolines, including (2*R*,4*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester. As described in the '787 application, the N-protected alkoxy prolines are prepared from an appropriate optically active cyclic amino acid, such as (2*R*,4*R*)-4-hydroxy-pyrrolidine-2-carboxylic acid (cis-4-hydroxy-D-proline), using a rather involved, six-step synthesis. The complexity of the route is apparently due to concerns over loss of optical activity.

[0004] Although the individual steps in the preparation of the N-protected alkoxy prolines may be achieved in good yield, the large number of steps diminishes the overall yield. For instance, in Example 28 of the '787 application, (2*R*,4*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester is prepared from cis-4-hydroxy-D-proline in an overall yield of 57 %. Thus, improved methods for preparing N-protected alkoxy prolines would be desirable.

SUMMARY OF THE INVENTION

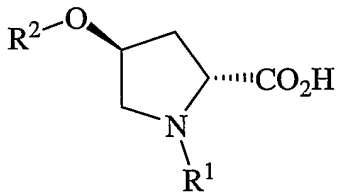
[0005] The present invention provides a comparatively short and efficient method for preparing N-protected alkoxy prolines from commercially available starting materials. For example, (2*R*,4*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester may be prepared from cis-4-hydroxy-D-proline in two steps with a yield of 85% or better. The N-protected alkoxy prolines are useful for preparing various serine protease factor Xa inhibitors, which are thought to be useful for treating diseases associated with abnormal thrombosis.

[0006] One aspect of the present invention provides a method of making a compound of Formula 1A,



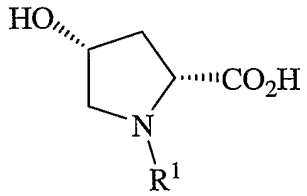
1A

or Formula 1B,



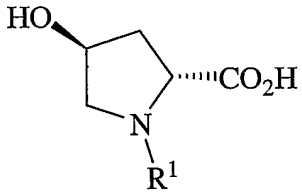
1B

or an opposite enantiomer of the compound of Formula 1A or Formula 1B, or salts thereof, wherein R^1 is an N-protecting group and R^2 is C_{1-6} alkyl, the method comprising reacting a compound of Formula 2A,



2A ,

or Formula 2B



2B ,

or an opposite enantiomer of the compound of Formula 2A or Formula 2B, or salts thereof, with a compound of Formula 3,

$$R^2—X$$

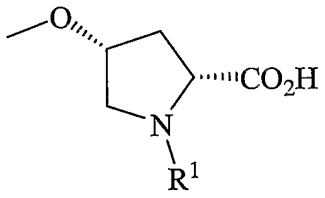
3 ,

in the presence of a base to give, respectively, the compound of Formula 1A or Formula 1B, or the opposite enantiomer of the compound of Formula 1A or Formula 1B, or salts thereof, wherein R^1 and R^2 in Formula 2A, Formula 2B, and Formula 3 are as defined in Formula 1A and Formula 1B, and X in Formula 3 is a leaving group.

[0007] Another aspect of the present invention provides a method of making a compound of Formula 1A or a salt thereof. The method comprises reacting a compound of Formula 2A or a salt thereof with a compound of Formula 3, in the presence of a base, to give the compound of Formula 1A or a salt thereof, where

Formula 1A, Formula 2A, and Formula 3, including their substituents, R^1, R^2, and X, are as defined above in the preceding paragraph.

[0008] A further aspect of the present invention provides a method of making a compound of Formula 5,



5 ,

or a salt thereof, wherein R^1 is an N-protecting group, the method comprising reacting a compound of Formula 2A, as defined above, or a salt thereof, with a compound of Formula 6,

Me—X

6 ,

in the presence of a base to give the compound of Formula 1A or a salt thereof, wherein Formula 2A is as defined above in the preceding paragraphs and X in Formula 6 is a leaving group.

[0009] The present invention includes all salts, whether pharmaceutically acceptable or not, solvates, hydrates, and polymorphic forms of the disclosed compounds. Certain compounds may contain an alkenyl or cyclic group, so that *cis/trans* (or *Z/E*) stereoisomers are possible, or may contain a keto or oxime group, so that tautomerism may occur. In such cases, the present invention generally includes all *Z/E* isomers and tautomeric forms, whether they are pure or mixtures.

DETAILED DESCRIPTION

DEFINITIONS AND ABBREVIATIONS

[0010] Unless otherwise indicated, this disclosure uses definitions provided below. Some of the definitions and formulae may include a "-" (dash) to indicate a bond between atoms or a point of attachment to a named or unnamed atom or group of atoms. Other definitions and formulae may include an "=" to indicate a double bond.

[0011] "Substituted" groups are those in which one or more hydrogen atoms have been replaced with one or more non-hydrogen atoms or groups, provided that valence requirements are met and that a chemically stable compound results from the substitution.

[0012] "Alkyl" refers to straight chain and branched saturated hydrocarbon groups, generally having a specified number of carbon atoms (i.e., C_{1-6} alkyl refers to an alkyl group having 1, 2, 3, 4, 5, or 6 carbon atoms). Examples of alkyl groups include, without limitation, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, *i*-butyl, *t*-butyl, pent-1-yl, pent-2-yl, pent-3-yl, 3-methylbut-1-yl, 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2,2-trimethyleth-1-yl, *n*-hexyl, and the like.

[0013] "Alkenyl" refers to straight chain and branched hydrocarbon groups having one or more unsaturated carbon-carbon bonds, and generally having a specified number of carbon atoms. Examples of alkenyl groups include, without limitation, ethenyl, 1-propen-1-yl, 1-propen-2-yl, 2-propen-1-yl, 1-buten-1-yl, 1-buten-2-yl, 3-buten-1-yl, 3-buten-2-yl, 2-buten-1-yl, 2-buten-2-yl, 2-methyl-1-propen-1-yl, 2-methyl-2-propen-1-yl, 1,3-butadien-1-yl, 1,3-butadien-2-yl, and the like.

[0014] "Alkanoyl" refers to alkyl-C(O)-, where alkyl is defined above, and generally includes a specified number of carbon atoms, including the carbonyl carbon. Examples of alkanoyl groups include, without limitation, formyl, acetyl, propionyl, butyryl, pentanoyl, hexanoyl, and the like.

[0015] "Alkoxy" and "alkoxycarbonyl" refer, respectively, to alkyl-O- and alkyl-O-C(O)-, where alkyl is defined above. Examples of alkoxy groups include, without limitation, methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *s*-butoxy, *t*-butoxy, *n*-pentoxy, *s*-pentoxy, and the like. Examples of alkoxycarbonyl groups include, without limitation, methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, *i*-propoxycarbonyl, *n*-butoxycarbonyl, *s*-butoxycarbonyl, *t*-butoxycarbonyl, *n*-pentoxycarbonyl, *s*-pentoxycarbonyl, and the like

[0016] "Halo," "halogen" and "halogeno" may be used interchangeably, and refer to fluoro, chloro, bromo, and iodo.

[0017] "Cycloalkyl" refers to saturated monocyclic and bicyclic hydrocarbon rings, generally having a specified number of carbon atoms that comprise the ring (i.e., C_{3-7} cycloalkyl refers to a cycloalkyl group having 3, 4, 5, 6 or 7 carbon atoms as ring members). The cycloalkyl may be attached to a parent group or to a substrate at any ring atom, unless such attachment would violate valence requirements. Likewise, the cycloalkyl groups may include one or more non-hydrogen substituents unless such substitution would violate valence requirements. Useful substituents include, without limitation, alkyl, alkoxy, alkoxycarbonyl, alkanoyl, and halo, as defined above, and hydroxy, mercapto, nitro, and amino.

[0018] Examples of monocyclic cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Examples of bicyclic cycloalkyl groups include, without limitation, bicyclo[1.1.0]butyl, bicyclo[1.1.1]pentyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl, bicyclo[3.1.0]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.0]heptyl, bicyclo[3.1.1]heptyl, bicyclo[4.1.0]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[4.1.1]octyl, bicyclo[3.3.0]octyl, bicyclo[4.2.0]octyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.0]nonyl, bicyclo[3.3.2]decyl, bicyclo[4.2.2]decyl, bicyclo[4.3.1]decyl, bicyclo[4.4.0]decyl, bicyclo[3.3.3]undecyl, bicyclo[4.3.2]undecyl, bicyclo[4.3.3]dodecyl, and the like.

[0019] "Cycloalkanoyl" refers to cycloalkyl-C(O)-, where cycloalkyl is defined above, and generally includes a specified number of carbon atoms, excluding the

carbonyl carbon. Examples of cycloalkanoyl groups include, without limitation, cyclopropanoyl, cyclobutanoyl, cyclopentanoyl, cyclohexanoyl, cycloheptanoyl, and the like.

[0020] "Aryl" and "arylene" refer to monovalent and divalent aromatic groups, respectively. Examples of aryl groups include, without limitation, phenyl, naphthyl, biphenyl, pyrenyl, anthracenyl, fluorenyl, and the like, which may be unsubstituted or substituted with 1 to 4 substituents. Such substituents include, without limitation, alkyl, alkoxy, alkoxycarbonyl, alkanoyl, cycloalkanoyl, and halo, as defined above, as well as nitro.

[0021] "Arylalkyl" refers to aryl-alkyl, where aryl and alkyl are defined above. Examples include, without limitation, benzyl, fluorenylmethyl, and the like.

[0022] "Leaving group" refers to any group that leaves a molecule during a fragmentation process, including substitution reactions, elimination reactions, and addition-elimination reactions. Leaving groups may be nucleofugal, in which the group leaves with a pair of electrons that formerly served as the bond between the leaving group and the molecule, or may be electrofugal, in which the group leaves without the pair of electrons. The ability of a nucleofugal leaving group to leave depends on its base strength, with the strongest bases being the poorest leaving groups. Common nucleofugal leaving groups include nitrogen (e.g., from diazonium salts), sulfonates (including tosylates, brosylates, nosylates, and mesylates), triflates, nonaflates, tresylates, halide ions, carboxylate anions, phenolate ions, and alkoxides. Some stronger bases, such as NH_2^- and OH^- can be made better leaving groups by treatment with an acid. Common electrofugal leaving groups include the proton, CO_2, and metals.

[0023] "Enantiomeric excess" or "ee" is a measure, for a given sample, of the excess of one enantiomer over a racemic sample of a chiral compound and is expressed as a percentage. Enantiomeric excess is defined as 100 x (er - 1) / (er + 1), where "er" is the ratio of the more abundant enantiomer to the less abundant enantiomer.

[0024] "Diastereomeric excess" or "de" is a measure, for a given sample, of the excess of one diastereomer over a sample having equal amounts of diastereomers and is expressed as a percentage. Diastereomeric excess is defined as 100 x (dr - 1) / (dr + 1), where "dr" is the ratio of a more abundant diastereomer to a less abundant diastereomer.

[0025] "Stereoselective," "enantioselective," "diastereoselective," and variants thereof, refer to a given process (e.g., hydrogenation) that yields more of one stereoisomer, enantiomer, or diastereoisomer than of another, respectively.

[0026] "High level of stereoselectivity," "high level of enantioselectivity," "high level of diastereoselectivity," and variants thereof, refer to a given process that yields products having an excess of one stereoisomer, enantiomer, or diastereoisomer, which comprises at least about 90% of the products. For a pair of enantiomers or diastereomers, a high level of enantioselectivity or diastereoselectivity would correspond to an ee or de of at least about 80%.

[0027] "Stereoisomerically enriched," "enantiomerically enriched," "diastereomerically enriched," and variants thereof, refer, respectively, to a sample of a compound that has more of one stereoisomer, enantiomer or diastereomer than another. The degree of enrichment may be measured by % of total product, or for a pair of enantiomers or diastereomers, by ee or de.

[0028] "Substantially pure stereoisomer," "substantially pure enantiomer," "substantially pure diastereomer," and variants thereof, refer, respectively, to a sample containing a stereoisomer, enantiomer, or diastereomer, which comprises at least about 95% of the sample. For pairs of enantiomers and diastereomers, a substantially pure enantiomer or diastereomer would correspond to samples having an ee or de of about 90% or greater.

[0029] A "pure stereoisomer," "pure enantiomer," "pure diastereomer," and variants thereof, refer, respectively, to a sample containing a stereoisomer, enantiomer, or diastereomer, which comprises at least about 99.5% of the sample.

For pairs of enantiomers and diastereomers, a pure enantiomer or pure diastereomer" would correspond to samples having an ee or de of about 99% or greater.

[0030] "Opposite enantiomer" refers to a molecule that is a non-superimposable mirror image of a reference molecule, which may be obtained by inverting all of the stereogenic centers of the reference molecule. For example, if the reference molecule has *S* absolute stereochemical configuration, then the opposite enantiomer has *R* absolute stereochemical configuration. Likewise, if the reference molecule has *S*,*S* absolute stereochemical configuration, then the opposite enantiomer has *R*,*R* stereochemical configuration, and so on.

[0031] "Pharmaceutically acceptable salts" refers to acid or base addition salts of claimed and disclosed compounds, which are within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use.

[0032] Table 1 lists abbreviations used throughout the specification.

TABLE 1. List of Abbreviations

Abbreviation	Description
Ac	acetyl
ACN	acetonitrile
Ac_2O	acetic anhydride
aq	aqueous
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bs	brosyl or *p*-bromo-benzenesulfonyl
Bn	benzyl
BnBr, BnCl	benzylbromide, benzylchloride
Bu	butyl
t-Bu	tertiary butyl
t-BuOK	potassium tertiary-butoxide

Abbreviation	Description
t-BuOLi	lithium tertiary-butoxide
Cbz	benzyloxycarbonyl
de	diastereomeric excess
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
Et	ethyl
Et_3N	triethyl-amine
EtOH	ethyl alcohol
Et_2O	diethyl ether
EtOAc	ethyl acetate
Fmoc	9-fluoroenylmethoxycarbonyl
h, min, s	hour(s), minute(s), second(s)
HOAc	acetic acid
KHMDS	potassium hexamethyldisilazane
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane
LTMP	2,2,6,6-tetramethylpiperidine
Me	methyl
$MeCl_2$	methylene chloride
MEK	methylethylketone or butan-2-one
MeOH	methyl alcohol
mp	melting point
Ms	mesyl or methanesulfonyl
Ph	phenyl
Pr	propyl
i-Pr	isopropyl
RT	room temperature (approximately 20°C to 25°C)
TEA	triethanolamine
Tf	trifyl or trifluoromethylsulfonyl

Abbreviation	Description
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tr	trityl or triphenylmethyl
Ts	tosyl or *p*-toluenesulfonyl

[0033] Some of the schemes and examples below may omit details of common reactions, including oxidations, reductions, and so on, which are known to persons of ordinary skill in the art of organic chemistry. The details of such reactions can be found in a number of treatises, including Richard Larock, *Comprehensive Organic Transformations* (1999), and the multi-volume series edited by Michael B. Smith and others, *Compendium of Organic Synthetic Methods* (1974-2003). Starting materials and reagents may be obtained from commercial sources or may be prepared using literature methods.

[0034] Generally, the chemical transformations described throughout the specification may be carried out using substantially stoichiometric amounts of reactants, though certain reactions may benefit from using an excess of one or more of the reactants. Additionally, many of the reactions disclosed throughout the specification may be carried out at about RT, but particular reactions may require the use of higher or lower temperatures, depending on reaction kinetics, yields, and the like. Many of the chemical transformations may also employ one or more compatible solvents, which depending on the nature of the reactants, may be polar protic solvents, polar aprotic solvents, non-polar solvents, or some combination. Although the choice of solvent or solvents may influence the reaction rate and yield, such solvents are generally considered to be inert (unreactive). Any reference in the disclosure to a stoichiometric range, a temperature range, a pH range, etc., includes the indicated endpoints.

[0035] This disclosure concerns materials and methods for preparing optically active N-protected alkoxy prolines and their salts. The N-protected alkoxy prolines

are represented by Formula 1A or Formula 1B (above and Scheme I), and by opposite enantiomers of the compounds of Formula 1A and Formula 1B. In Formula 1A and Formula 1B, R^1 is an N-protecting group and R^2 is C_{1-6} alkyl.

[0036] For a given compound, the N-protecting group prevents undesirable reaction of the amino functionality during chemical transformation of the compound and may influence other properties, such as solubility. Generally, R^1 may be any group used to protect an amine, including, but not limited to C_{1-6} alkyl, C_{2-6} alkenyl, and aryl C_{1-6} alkyl. Other useful R^1 include $-C(O)R^3$, $-CH_2OR^3$, $-CO_2R^3$, $-C(O)S_nR^3$, $-S(O)_nR^3$, $-NHR^3$, $-NR^3R^4$, $-NHC(O)R^3$, $-OC(O)NHR^3$, $-OC(O)NHC(O)R^3$, $-OC(O)NR^3R^4$, $-C(O)R^3Y$, $-COR^3Y$, $-CO_2R^3Y$, $-C(O)S_nR^3Y$, $-S(O)_nR^3Y$, $-NHR^3Y$, $-NHC(O)R^3Y$, $-OC(O)NHR^3Y$, or $-OC(O)NHC(O)R^3Y$, in which Y is $-Si(R^4)_3$, $-S(O)_nR^4$, $-OR^4$, -CN, $-NO_2$, halo, or $-P(O)(OR^4)_2$, and R^3 and R^4 are each, independently, C_{1-6} alkyl, C_{2-6} alkenyl, aryl or aryl C_{1-6} alkyl, and n is an integer between 0 and 2, inclusive. For a nonexclusive list of amine protecting groups, see T. W. Greene and P. G. Wuts, *Protecting Groups in Organic Chemistry* 494-653 (3d. ed. 1999), and P. Kocienski, *Protective Groups* 487-643 (3d. ed. 2003), as well as references cited therein.

[0037] Typical R^1 substituents include, but are not limited to, benzyl, Cbz, Boc, Fmoc, and trityl, and typical R^2 substituents include, but are not limited to methyl, ethyl, *n*-propyl, and *i*-propyl. Compounds of Formula 1A and Formula 1B may thus include, without limitation, (*R*,*R*)- and (4*S*,2*R*)-1-benzyl-4-methoxy-pyrrolidine-2-carboxylic acid; (*R*,*R*)- and (4*S*,2*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester; (*R*,*R*)- and (4*S*,2*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester; (*R*,*R*)- and (4*S*,2*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester; and (*R*,*R*)- and (4*S*,2*R*)-4-methoxy-1-trityl-pyrrolidine-2-carboxylic acid. Other useful N-protected alkoxy prolines include the opposite enantiomers of Formula 1A and Formula 1B, such as (*S*,*S*)- and (2*S*,4*R*)-1-benzyl-4-methoxy-pyrrolidine-2-carboxylic acid; (*S*,*S*)- and (2*S*,4*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester; (*S*,*S*)- and (2*S*,4*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester; (*S*,*S*)- and (2*S*,4*R*)-4-methoxy-pyrrolidine-1,2-

dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester; and (*S*,*S*)- and (2*S*,4*R*)-4-methoxy-1-trityl-pyrrolidine-2-carboxylic acid.

[0038] Scheme I shows a method for preparing optically active N-protected alkoxy prolines of Formula 1A or Formula 1B. As illustrated in Scheme I, the method includes installing a protecting group, R^1, on (*R*,*R*)-4-hydroxy-pyrrolidine-2-carboxylic acid (Formula 4A) or on (2*R*,4*S*)-4-hydroxy-pyrrolidine-2-carboxylic acid (Formula 4B) to give an N-protected, (*R*,*R*)-4-hydroxy-pyrrolidine-2-carboxylic acid (Formula 2A) or an N-protected, (2*R*,4*S*)-4-hydroxy-pyrrolidine-2-carboxylic acid (Formula 2B), which is subsequently reacted with an alkylating agent (Formula 3) to give the desired optically active N-protected alkoxy proline (Formula 1A or formula 1B). The opposite enantiomers of the compounds of Formula 1A and Formula 1B may be prepared by installing R^1 on (*S*,*S*)-4-hydroxy-pyrrolidine-2-carboxylic acid or on (4*R*,2*S*)-4-hydroxy-pyrrolidine-2-carboxylic acid, respectively, and then reacting the resulting N-protected intermediate with an alkylating agent (Formula 3). Besides the free acids, the above chemical transformations may be carried out using salts of the compounds represented by formula 1A, 1B, 2A, 2B, 4A, 4B, as well as their opposite enantiomers.

[0039] Depending on the nature of the protecting group, R^1 is installed using standard techniques such as acylation, alkylation, sulfonylation, and the like. Table II lists conditions for installing and removing representative protecting groups. For a more complete list of methods for installing and removing N-protecting groups, see T. W. Greene and P. G. Wuts, *Protecting Groups in Organic Chemistry*, and P. Kocienski, *Protective Groups*, as noted above. See also, M. Bodanszky & A. Bodanszky, *The Practice of Peptide Synthesis* (2d ed. 1994), and references cited therein.

Table II. Conditions for Protecting and De-protecting Amines

Protecting Group R^1	Formation	Cleavage
Ac	C_6F_5OAc, DMF, RT	HCl, reflux
	Ac_2O, 18-crown-6, Et_3N	TFA, reflux
allyloxycarbonyl	CH_2=$CHCH_2OC(O)Cl$, pyridine	$Rh(PPh_3)_3Cl$
	$(CH_2$=$CHCH_2OC(O))_2O$, dioxane, H_2O or $MeCl_2$, reflux	$Pd(PPh_3)_4$, Bu_3SnH, HOAc
		$Pd(PPh_3)_4$, dimedone, THF
		$Pd(PPh_3)_4$, HCO_2H, TEA
allyl	Allyl chloride, Cu(0), $Cu(ClO_4)_2 \cdot 6H_2O$, Et_2O	*t*-BuOK, DMSO, hydrolysis
	AllylOAc, $Pd(Ph_3P)_4$, diisopropylamine	$Pd(Ph_3P)_4$, N,N-dimethylbarbituric acid
		$Pd(Ph_3P)_4$, RSO_2Na, $MeCl_2$ or THF-MeOH
Bn	BnCl, aq K_2CO_3, reflux; H_2, Pd-C	Pd-C, HCOOH, MeOH, RT
	BnBr, EtOH, $NaCO_3$, H_2O, $MeCl_2$, reflux	20% $Pd(OH)_2$, EtOH, H_2
		Na, NH_3
		Convert to carbamate via Braun rxn, then like Cbz
Cbz	BnOC(O)Cl, Na_2CO_3, H_2O, 0°C	H_2, 10 % Pd/C
	BnOC(O)Cl, MgO, EtOAc, reflux	H_2, 10 % Pd/C, MeOH, NH_4OAc, -33°C
	$(BnOC(O))_2O$, dioxane, H_2O, NaOH or Et_3N, <50°C	HCO_2H, Pd/C

Protecting Group R^1	Formation	Cleavage
		Raney Ni
Boc	$(Boc)_2O$, NaOH, H_2O, RT	TFA, $MeCl_2$
	$(Boc)_2O$, TEA, MeOH or DMF, 40-50°C	HCl, EtOAc, RT
	$(Boc)_2O$, EtOH or MeOH, $NaHCO_3$, ultrasound	Me_3SiI, $MeCl_3$ or ACN, RT
	$(Boc)_2O$, $Me_4NOH{\cdot}5H_2O$, ACN	$AlCl_3$, PhOMe, $MeCl_2$, $MeNO_2$, 0-25°C
		Me_3SiOTf, PhSMe, TFA
		H_2SO_4
Fmoc	FmocCl, $NaHCO_3$, aq dioxane	piperidine/DMF, RT
	$FmocN_3$, $NaHCO_3$, aq dioxane	$NH(i\text{-}Pr)_2$/DMF, RT
R^2-dithio carbonyl	R^2Cl, Et_3N, EtOAc, 0°C	mercaptoethanol
		NaOH
		Ph_3P, TsOH
2-$MeSO_2EtOC(O)$	$MeSO_2EtOC(O)Cl$, $NaHCO_3$	NaOH aq
triphenylmethyl (trityl)	TrCl, Et_3N, RT	HCl, acetone, RT
		H_2, Pd black, EtOH, 45°C
		Na, NH_3

[0040] As noted above, the method also includes reacting an N-protected, (*R*,*R*)-4-hydroxy-pyrrolidine-2-carboxylic acid (Formula 2A) or an N-protected, (2*R*,4*S*)-4-hydroxy-pyrrolidine-2-carboxylic acid (Formula 2B), or opposite enantiomers thereof, with an alkylating agent (formula 3) in a solvent and in the presence of a base. In Formula 3, R^2 is as defined above in connection with Formula 1A and Formula 1B, and X is a leaving group. Useful leaving groups include, without limitation, halo

substituents, Cl, Br, and I, and sulfonate substituents, such as toluene-*p*-sulfonate, methylsulfonate, *p*-bromo-benzene-sulfonate, triflate, and the like. Typical alkylating agents thus include, without limitation, alkyl halides, such as MeCl, MeBr, MeI, EtCl, EtBr, EtI, *n*-PrCl, *n*-PrBr, *n*-PrI, *i*-PrCl, *i*-PrBr, *i*-PrI, and the like, and alkylsulfonate esters, such as, MeOTs, MeOMs, MeOBs, MeOTf, EtOTs, EtOMs, EtOBs, EtOTf, *n*-PrOTs, *n*-PrOMs, *n*-PrOBs, *n*-PrOTf, *i*-PrTs, *i*-PrMs, *i*-PrBs, *i*-PrTf, and the like. The alkylating agents may be obtained from commercial sources or may be prepared using methods that are well known in the art.

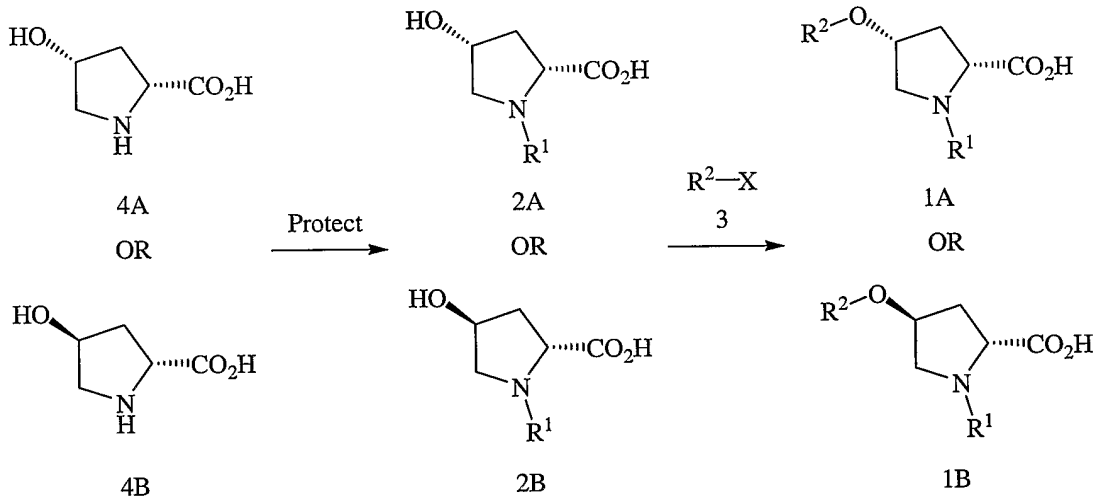
[0041] Useful bases include those that are capable of deprotonating the hydroxy moiety of the N-protected hydroxy proline (formula 2A, 2B, etc.), but do not react appreciably with the alkylating agent (formula 3)—i.e., non-nucleophilic bases whose conjugate acids have pKa's greater than about 16. These include, without limitation, LiH, NaH, LDA, LHMDS, KHMDS, LTMP, *i*-PrONa, *t*-BuOK, and the like, which may be obtained from commercial sources or may be prepared using methods that are well known in the art.

[0042] The alkylation may be carried out in an inert organic solvent. The choice of solvent generally depends on the polarity of the reactants, the nature of the R^2 substituent, and other factors known in the art. Thus, for example, when R^2 is a primary alkyl group, the use of a less polar, aprotic solvent may provide improved yields over a more polar aprotic solvent, whereas the opposite may hold for cases when R^2 is a tertiary alkyl group. Useful solvents include THF, Et_2O, DMSO, DMF, ACN, toluene, 1,4-dioxane, $MeCl_2$, 1,2-dichloroethane, and the like, and are generally used in amounts needed to completely dissolve the reagents.

[0043] The alkylation reaction may employ stoichiometric amounts of the reactants (i.e., molar ratio of the N-protected hydroxy proline to the alkylating agent of 1:1), but to improve conversion, minimize side-products, and so on, the alkylation step may employ an excess of one of the reactants (e.g., molar ratio of 1:1.1 to 1.1:1, 1:1.5 to 1.5:1, 2:1 to 1:2, 3:1 to 1:3, etc.). Similarly, the alkylation reaction may employ stoichiometric amounts of base (i.e., molar ratio of base to N-protected

hydroxy proline of 2:1), but it may also employ an excess of base (e.g., molar ratio of 2.1:1, 2.5:1, 3:1, etc.).

[0044] The alkylation may be run at temperatures of about 0°C to reflux. Typically, the alkylation step is carried out at RT, but the reaction may benefit from higher or lower temperatures. For example, during the addition of reactants, the reaction mixture may be cooled to a temperature of about 0°C to about 5°C and then allowed to react at RT or above.



Scheme I

[0045] Many of the compounds described in this disclosure, including those represented by Formula 1A, Formula 1B, Formula 2A, Formula 2B, Formula 4A, Formula 4B, and Formula 5, are capable of forming pharmaceutically acceptable salts. These salts include, without limitation, acid addition salts (including di-acids) and base salts. Pharmaceutically acceptable acid addition salts include nontoxic salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like, as well nontoxic salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide,

acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, malate, tartrate, methanesulfonate, and the like.

[0046] Pharmaceutically acceptable base salts include nontoxic salts derived from bases, including metal cations, such as an alkali or alkaline earth metal cation, as well as amines. Examples of suitable metal cations include, without limitation, sodium cations (Na^+), potassium cations (K^+), magnesium cations (Mg^{2+}), calcium cations (Ca^{2+}), and the like. Examples of suitable amines include, without limitation, *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, *N*-methylglucamine, and procaine. For a discussion of useful acid addition and base salts, see S. M. Berge et al., "Pharmaceutical Salts," 66 *J. of Pharm. Sci.*, 1-19 (1977); see also Stahl and Wermuth, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* (2002).

[0047] One may prepare an acid addition salt (or base salt) by contacting a compound's free base (or free acid) with a sufficient amount of a desired acid (or base) to produce a nontoxic salt. One may then isolate the salt by filtration if it precipitates from solution, or by evaporation to recover the salt. One may also regenerate the free base (or free acid) by contacting the acid addition salt with a base (or the base salt with an acid). Certain physical properties (e.g., solubility, crystal structure, hygroscopicity, etc.) of a compound's free base, free acid, or zwitterion may differ from its acid or base addition salt. Generally, however, references to the free acid, free base or zwitterion of a compound would include its acid and base addition salts.

[0048] Additionally, certain compounds of this disclosure may exist as an unsolvated form or as a solvated form, including hydrated forms. Pharmaceutically acceptable solvates also include hydrates and solvates in which the crystallization solvent may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO, etc. Generally, for the purposes of this disclosure, references to an unsolvated form of a compound also include the corresponding solvated or hydrated form of the compound.

[0049] The disclosed compounds also include all pharmaceutically acceptable isotopic variations, in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes suitable for inclusion in the disclosed compounds include, without limitation, isotopes of hydrogen, such as ^{2}H and ^{3}H; isotopes of carbon, such as ^{13}C and ^{14}C; isotopes of nitrogen, such as ^{15}N; isotopes of oxygen, such as ^{17}O and ^{18}O; isotopes of phosphorus, such as ^{31}P and ^{32}P; isotopes of sulfur, such as ^{35}S; isotopes of fluorine, such as ^{18}F; and isotopes of chlorine, such as ^{36}Cl. Use of isotopic variations (e.g., deuterium, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements. Additionally, certain isotopic variations of the disclosed compounds may incorporate a radioactive isotope (e.g., tritium, ^{3}H, or ^{14}C), which may be useful in drug and/or substrate tissue distribution studies.

EXAMPLES

[0050] The following examples are intended as illustrative and non-limiting, and represent specific embodiments of the present invention.

EXAMPLE 1. Preparation of (*R*,*R*)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester

[0051] A 5 L, 3-necked flask was charged with (*R*,*R*)-4-hydroxy-pyrrolidine-2-carboxylic acid (300 g, 2.228 mol), di-tert-butyl dicarbonate (499.3 g, 2.228 mol), 50% (w/w) NaOH (118 mL, 2.228 mol), THF (2 L) and H_2O (1 L). The reaction was stirred at RT overnight. To the reaction mixture was added 3N HCl (762 mL, 2.286 mol). The organic and aqueous layers were separated. Brine (1 L) was added to the aqueous layer, which was extracted with THF (1 L). The organic layers were combined, dried over $MgSO_4$ and concentrated to give a wet cake. The wet cake was azeotroped twice with hexane (2 L each) to give the titled compound as a white to off-white solid (469 g, 91% yield).

EXAMPLE 2. Preparation of (*R*,*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester

[0052] A nitrogen-purged, 500 mL, 3-necked flask, which was equipped with a mechanical stirrer and thermocouple, was charged with 60% (w/w) NaH (8 g, 200 mmol) and hexane (250 mL). The mixture was stirred for 1 min, after which the agitation was stopped and the solids were allowed to settle. Hexane was removed with a candle filter. The flask was then charged with THF (250 mL) and MeI (6.51 mL, 105 mmol) and the resulting mixture was cooled to 0°C in an ice bath. (*R*,*R*)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (22 g, 95 mmol) was then added in portions while maintaining a reaction temperature of 5°C or less. The reaction was allowed to warm to RT overnight. To the reaction mixture was added H_2O (100 mL), 1N HCl (100 mL) and NaCl (42 g). The reaction was stirred for 10 min. The layers were separated, and the organic layer was dried over $MgSO_4$, filtered and concentrated to a thick oil. When the solids were just starting to precipitate, hexane (50 mL) was added and a precipitate formed immediately. The mixture was filtered to give the titled compound as a white to yellow-white solid (20.16 g). After sitting for a day, the filtrate was filtered to give a second crop of the titled compound (1.42 g). The two crops were combined to give the titled compound as a white to yellow-white solid (21.58 g, 93% yield; chiral purity via chiral HPLC: 100%).

EXAMPLE 3. Preparation of (*R*,*R*)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester

[0053] (*R*,*R*)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester (7.49 g, 28.2 mmol) was stirred in THF (190 mL) at -60°C. NaH (2.4 g, 59 mmol) was added in one portion, and the reaction mixture was stirred for 30 min. MeI (4.41 g, 31.1 mmol) was added and the reaction mixture was allowed to warm to RT over 5 h, and then heated to reflux for 30 min. The reaction was cooled to RT overnight. To the reaction mixture was added 1N HCl (30 mL), H_2O (100 mL) and NaCl (20 g). The organic and aqueous layers were separated, and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a two-layered oil

(8.39 g), which was partitioned between ACN and hexane. The layers were separated and the lower ACN layer was concentrated under reduce pressure to give the titled compound as an oil (6.97 g, 88% yield).

EXAMPLE 4. Preparation of (4*R*,2*S*)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester

[0054] The titled compound was prepared in a manner similar to Example 1 and Example 2, except that (4*R*,2*S*)-4-hydroxy-pyrrolidine-2-carboxylic acid was used in place of (*R*,*R*)-4-hydroxy-pyrrolidine-2-carboxylic acid, and (4*R*,2*S*)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester was used in place of (*R*,*R*)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester. The titled compound was used as a standard to determine the chiral purity of (*R*,*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester in Example 2. Table III provides the details of the chiral HPLC method.

Table III. Chiral Method

Column	CHIRAPAK OD 4.6 mm x 250 mm 10 μm
Mobile Phase	95:5:0.1 Hexane:EtOH:TFA
Flow Rate	1.0 mL/min
Wavelength	215 nm
Injection Volume	10 mL
Column Temperature	RT
Sample Diluent	80:20 Hexane:EtOH

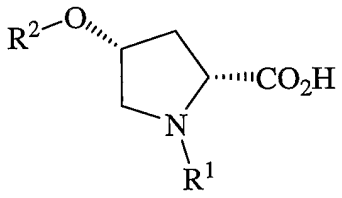
[0055] It should be noted that, as used in this specification and the appended claims, singular articles such as "a," "an," and "the," may refer to one object or to a plurality of objects unless the context clearly indicates otherwise. Thus, for example, reference to a composition containing "a compound" may include a single compound or two or more compounds.

[0056] It is to be understood that the above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those of skill

in the art upon reading the above description. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled. The disclosures of all articles and references, including patent applications, granted patents, and publications, are incorporated herein by reference in their entirety and for all purposes.

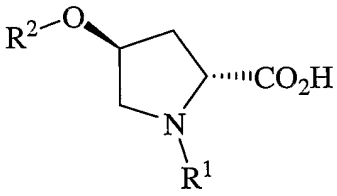
WHAT IS CLAIMED IS:

1. A method of making a compound of Formula 1A,



1A ,

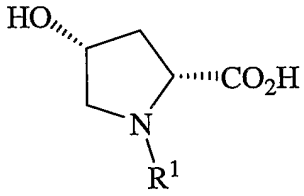
or Formula 1B,



1B ,

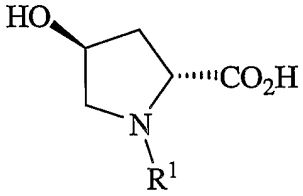
or an opposite enantiomer of the compound of Formula 1A or Formula 1B, or salts thereof, wherein R^1 is an N-protecting group and R^2 is C_{1-6} alkyl, the method comprising:

reacting a compound of Formula 2A,



2A ,

or Formula 2B



2B ,

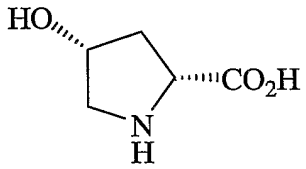
or an opposite enantiomer of the compound of Formula 2A or Formula 2B, or salts thereof, with a compound of Formula 3,

$$R^2—X$$

3 ,

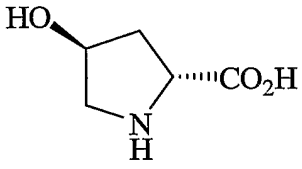
in the presence of a base to give, respectively, the compound of Formula 1A or Formula 1B, or the opposite enantiomer of the compound of Formula 1A or Formula 1B, or salts thereof, wherein R^1 and R^2 in Formula 2A, Formula 2B, and Formula 3 are as defined in Formula 1A and Formula 1B, and X in Formula 3 is a leaving group.

2. The method of claim 1, further comprising installing the N-protecting group on a compound of Formula 4A,



4A ,

or Formula 4B



4B ,

or an opposite enantiomer of the compound of Formula 4A or Formula 4B, or salts thereof, to give, respectively, the compound of Formula 2A, Formula 2B, or the opposite enantiomer of the compound of Formula 2A or Formula 2B, or salts thereof.

3. The method of claim 1, wherein R^1 is benzyl, substituted benzyl, Cbz, Boc, Fmoc, or trityl.

4. The method of claim 1, wherein R^1 is Boc.

5. The method of claim 1, wherein R^2 is C_{1-3} alkyl.

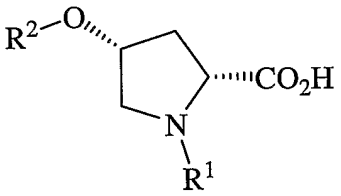
6. The method of claim 1, wherein R^2 is methyl.

7. The method of claim 1, wherein X is Cl, Br, or I.

8. The method of claim 1, wherein the compound of Formula 1A or Formula 1B, or the opposite enantiomer of the compound of Formula 1A or Formula 1B, or salts thereof, is a substantially pure stereoisomer.

9. The method of claim 1, wherein the compound of Formula 1A or Formula 1B, or the opposite enantiomer of the compound of Formula 1A or Formula 1B, or salts thereof, is a pure stereoisomer.

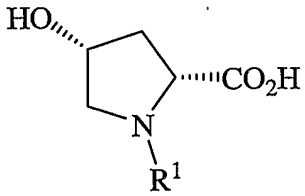
10. A method of making a compound of Formula 1A,



1A ,

or a salt thereof, wherein R^1 is an N-protecting group and R^2 is C_{1-6} alkyl, the method comprising:

reacting a compound of Formula 2A,



2A ,

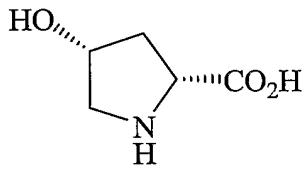
or a salt thereof, with a compound of Formula 3,

R^2—X

3 ,

in the presence of a base to give the compound of Formula 1A or a salt thereof, wherein R^1 and R^2 in Formula 2A and Formula 3, respectively, are as defined in Formula 1A, and X in Formula 3 is a leaving group.

11. The method of claim 10, further comprising installing the N-protecting group on a compound of Formula 4A,



4A ,

or a salt thereof, to give the compound of Formula 2A or a salt thereof.

12. The method of claim 10, wherein R^1 is benzyl, substituted benzyl, Cbz, Boc, Fmoc, or trityl.

13. The method of claim 10, wherein R^1 is Boc.

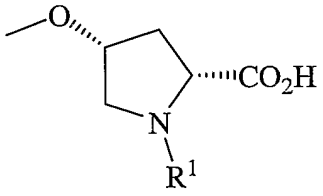
14. The method of claim 10, wherein R^2 is C_{1-3} alkyl.

15. The method of claim 10, wherein R^2 is methyl.

16. The method of claim 10, wherein X is Cl, Br, or I.

17. The method of claim 10, wherein the compound of Formula 1A or a salt thereof, has an ee of at least 95 %.

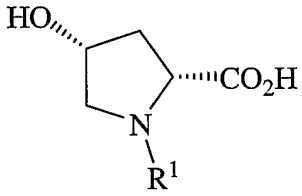
18. A method of making a compound of Formula 5,



5 ,

or a salt thereof, wherein R^1 is an N-protecting group, the method comprising:

reacting a compound of Formula 2A,



2A ,

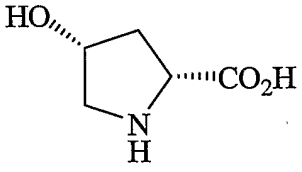
or a salt thereof, with a compound of Formula 6,

Me—X

6 ,

in the presence of a base to give the compound of Formula 1A or a salt thereof, wherein R^1 in Formula 2A is as defined in Formula 5 and X in Formula 6 is a leaving group.

19. The method of claim 18, further comprising installing the N-protecting group on a compound of Formula 4A,



4A ,

or a salt thereof, to give the compound of Formula 2A or a salt thereof.

20. The method of claim 18, wherein R^1 is benzyl, substituted benzyl, Cbz, Boc, Fmoc, or trityl.

21. The method of claim 18, wherein R^1 is Boc.

22. The method of claim 18, wherein X is Cl, Br, or I.

23. The method of claim 18, wherein the compound of Formula 5 or a salt thereof, is a substantially pure stereoisomer.

24. The method of claim 18, wherein the compound of Formula 5 or a salt thereof, is a pure stereoisomer.

INTERNATIONAL SEARCH REPORT

International application No
/IB2005/003205

A. CLASSIFICATION OF SUBJECT MATTER
C07D207/12

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/114683 A1 (ROUX RICHARD ET AL) 19 June 2003 (2003-06-19) scheme 2 paragraphs '0150!, '0151!	1-24
X	US 6 201 006 B1 (KOO BON AM ET AL) 13 March 2001 (2001-03-13) column 192; example 66	1-24
X	BOLDI A M ET AL: "SOLID-PHASE LIBRARY SYNTHESIS OF ALKOXYPROLINES" JOURNAL OF COMBINATORIAL CHEMISTRY, 2001, pages 367-373, XP002363514 ISSN: 0065-7727 scheme 5, preparation of compound 14c	1-24

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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Date of the actual completion of the international search	Date of mailing of the international search report
19 January 2006	13/02/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gregoire, A

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