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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 December 2005 (08.12.2005)

PCT

(10) International Publication Number
WO 2005/116017 A1

(51) International Patent Classification[7]: C07D 413/06

(21) International Application Number: PCT/GB2005/002042

(22) International Filing Date: 24 May 2005 (24.05.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0411596.0 25 May 2004 (25.05.2004) GB

(71) Applicant (*for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BF, BG, BJ, BR, BW, BY, BZ, CA, CF, CG, CH, CI, CM, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GA, GB, GD, GE, GH, GM, GN, GQ, GR, GW, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MC, MD, MK, ML, MN, MR, MW, MX, MZ, NA, NE, NI, NL, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK only*): **ASTRAZENECA AB** [SE/SE]; S-SE-151 85 Södertälje (SE).

(71) Applicant (*for MG only*): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **CHERRYMAN, Janette** [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). **CUTHBERT, Murray, Watson** [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). **DUBIEZ, Jérôme** [FR/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). **HOWELLS, Garnet, Edward** [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). **MULHOLLAND, Keith, Raymond** [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, SE-151 85 Södertälje (SE).

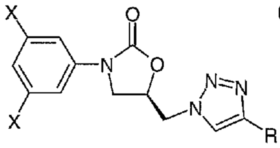
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK,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

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

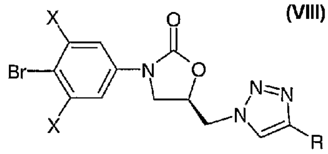
Published:
— *with international search report*

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

(54) **Title:** PROCESS FOR THE PREPARATION OF ARYL SUBSTITUTED OXAZOLIDINONES AS INTERMEDIATES FOR ANTIBACTERIAL AGENTS



(VII)



(VIII)

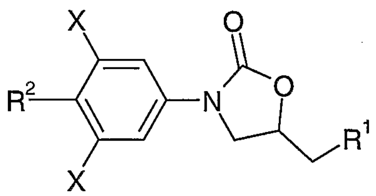
(57) **Abstract:** A compound of the formula (VIII) wherein each X is independently H or F; and R is selected from hydrogen, halogen, cyano, methyl, cyanomethyl, fluoromethyl, difluoromethyl, trifluoromethyl and -Si[(1-4C)alkyl]$_3$; and processes for preparing a compound of formula (VIII) by bromination of a compound of the formula (VII),

WO 2005/116017 A1

PROCESS FOR THE PREPARATION OF ARYL SUBSTITUTED OXAZOLIDINONES AS INTERMEDIATES FOR ANTIBACTERIAL AGENTS

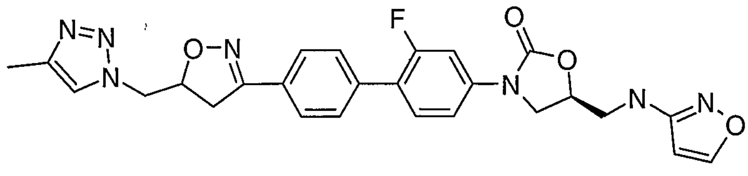
Oxazolidinone containing antibacterial agents have been known for over twenty years. A core feature of the majority of these agents comprises a (substituted) phenyl group attached to the nitrogen of the oxazolidinone ring. Many of these phenyl groups have one or two halo substituents, particularly fluoro, in the meta position(s) relative to the point of attachment to the oxazolidinone ring.

An example of such a structure is a compound of formula (I),where each X is H or halo, for example fluoro; R^1 is often a group such as acetamide, or a C- or N-linked heterocycle (such as triazolyl) and R^2 may be a wide range of substituents, as described for example in WO 01/81350.



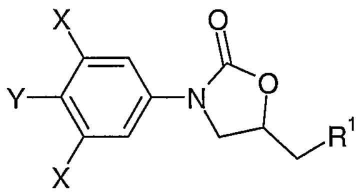
(I)

Subsequently, our patent application WO 03/022824 disclosed compounds containing a bi-aryl group (where each aryl group could be phenyl or one of a selection of heteroaryl rings) and two oxazolidinone and/or isoxazoline rings, such as (II) below:



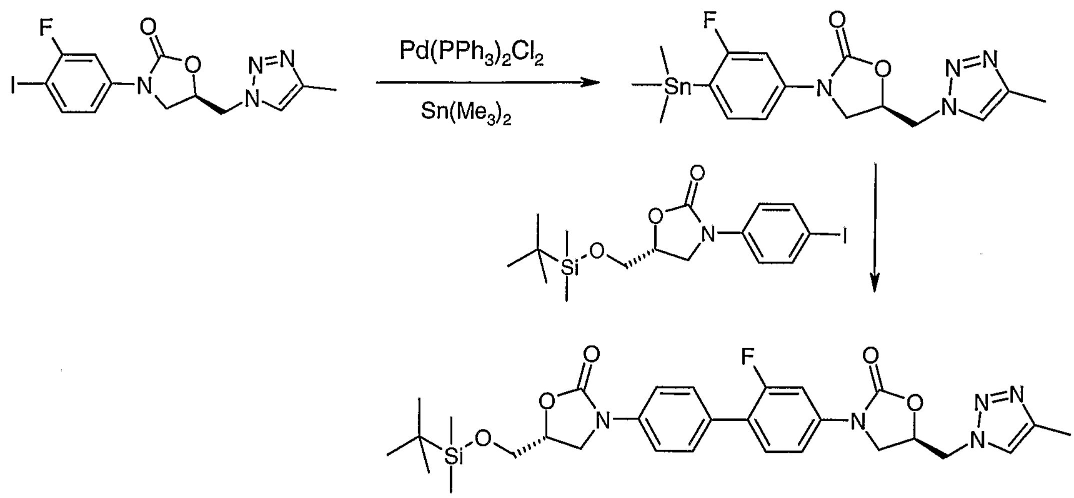
(II)

An efficient, convergent approach to the synthesis of such bi-aryl compounds utilises formation of the aryl-aryl bond as a key synthetic step. For this approach, an intermediate of formula (III) (wherein Y is a group suitable to allow further reaction to form the rest of the target compound) is required.



(III)

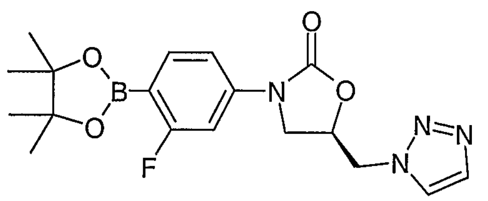
In our patent application, WO 03/022824, halo derivatives of formula (III) above, where R^1 is for example a triazole ring, were converted into corresponding tin derivatives and then coupled as shown in Scheme 1 below.



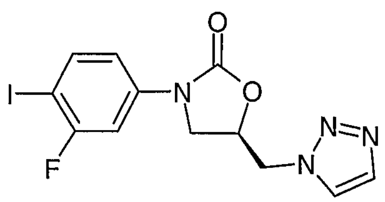
Scheme 1

Other suitable derivatives for such coupling reactions are compounds of the formula (III) wherein Y is a boron derivative such as a boronate ester, which are themselves obtainable from halo compounds.

Our co-pending applications PCT/GB2003/005087 and PCT/GB2004/000730 describe further examples of bi-aryl antibacterial agents, the majority of which have a triazole or substituted triazole ring attached to the oxazolidinone ring. The most common coupling reaction in these applications uses a boronate ester such as (IV), which is made from an iodo derivative such as (V):



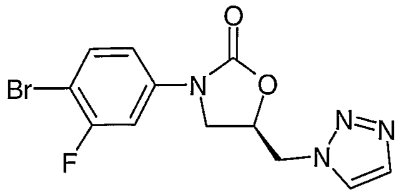
(IV)



(V)

However, the use of iodine-containing compounds on a manufacturing scale is generally considered undesirable, for example for environmental reasons, and therefore it would be preferable to use an alternative halo substituent, such as a bromo substituent.

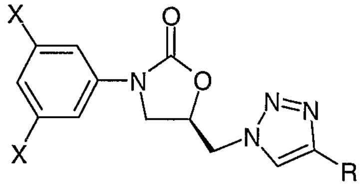
Therefore an efficient approach to intermediates such as (VI) (and the difluoro, des-fluoro and substituted triazole analogues thereof) is required.



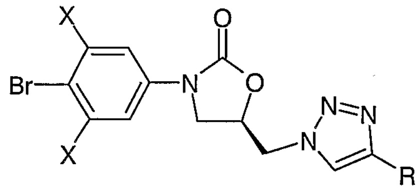
(VI)

Surprisingly we have found that it is possible to introduce a bromine substituent, required for making the tin or boron reagents, after formation of the triazole ring, without causing side reactions such as bromination of the triazole ring.

According to a first aspect of the invention there is provided a process for forming a compound of the formula (VIII) from a compound of the formula (VII), wherein each X is independently H or F and R is selected from hydrogen, halogen, cyano, methyl, cyanomethyl, fluoromethyl, difluoromethyl, trifluoromethyl and –Si[(1-4C)alkyl]$_3$;



(VII)



(VIII)

said process comprising treatment of a solution of the compound of formula (VII) with bromine.

It will be appreciated that solutions of bromine convenient for use in such reactions will tend to degrade with time, such that the concentration of bromine present will decrease and render the reagent unsuitable for use. It will be appreciated that for large scale manufacturing, for example in the manufacture of pharmaceutical agents, quality control procedures demand that the concentration of regents is known and controlled within a specified range. Therefore, a more convenient way to provide bromine for such a reaction is to produce bromine in the reaction medium, for example by the reaction between a bromate, a bromide and acid, according to the reaction:

$BrO_3^- + 6H^+ + 5Br^- \rightarrow 3Br_2 + 3H_2O$

According to a further aspect of the invention, there is provided a process for forming a compound of the formula (VIII) from a compound of the formula (VII) as hereinbefore defined, wherein the bromine is generated in situ from a bromate, a bromide and acid.

According to a further aspect of the invention, there is provided a process for forming a compound of the formula (VIII) from a compound of the formula (VII) as hereinbefore defined, said process comprising treatment of a solution of the compound of formula (VII) with a bromate, a bromide and acid.

Conveniently, the acid and bromide may be provided together by use of hydrobromic acid. Suitably the bromide is added as a solution in water, for example an aqueous solution of hydrobromic acid, such as a 48% w/w aqueous hydrobromic acid solution. Any convenient concentration of such a solution may be used.

Conveniently the bromate is an alkali metal bromate, such as potassium bromate or sodium bromate. Suitably the bromate is added as a solution in water.

The compound of formula (VII) may be dissolved in any suitable organic solvent. In this context, suitable means that the organic solvent must be be miscible with water and must not react with the other reagents.

A suitable solvent is acetic acid. The compound of formula (VII) may be dissolved in a mixture of said suitable organic solvent, such as acetic acid, and water.

Conveniently, the aqueous solution of bromide is added to the solution of the compound of formula (VII), then the solution of bromate is added.

The reaction between bromate and bromide in the presence of acid is exothermic. Conveniently, a vessel containing the reaction mixture may be cooled, for instance in an ice-bath, but maintenance at a particular temperature is not essential for the yield or quality of the product produced. Conveniently a vessel containing the reaction mixture is cooled in an ice-bath such that the temperature of the reaction ranges between 10 and 30°C during the addition of bromate.

Suitably slight molar excesses of bromate and bromide are used in comparison to the quantity of the compound of formula (VII) used. Suitable amounts of bromate and bromide are those used in the accompanying Examples.

The rate of addition of the bromate solution is not critical. Conveniently, it is added at a rate such that the temperature of the reaction is maintained between 10 and 30°C during the addition of bromate.

The reaction mixture may be stirred, for example at about ambient temperature, until the reaction is complete. Typically, the reaction may take 3-4 hours to complete, including the time required for addition of bromate.

After the reaction is complete, it is desirable to remove any excess bromine generated before isolation of the product. Conveniently this may be achieved by addition of a solution of metabisulfite, for example a solution of sodium metabisulfite in water. Sufficient metabisulfite is added to react with any residual bromine.

The product may be isolated by any convenient means, for example by filtration from the reaction mixture, or by dissolution into another organic solvent and appropriate washing and evaporation. If the product solidifies from the reaction mixture, it may be convenient to re-dissolve it (for example by heating the solution, for example to about 80-85 °C) and allow crystallisation in a controlled manner.

According to a further aspect of the invention, there is provided a process for forming a compound of the formula (VIII) from a compound of the formula (VII) as hereinbefore defined, said process comprising treatment of a solution of the compound of formula (VII) with an alkali metal bromate, and hydrobromic acid.

According to a further aspect of the invention, there is provided a process for forming a compound of the formula (VIII) from a compound of the formula (VII) as hereinbefore defined, said process comprising:

a) treatment of a solution of the compound of formula (VII) in a mixture of water and a suitable organic solvent with aqueous hydrobromic acid; and

b) addition of an aqueous solution of an alkali metal bromate.

According to a further aspect of the invention, there is provided a process for forming a compound of the formula (VIII) from a compound of the formula (VII) as hereinbefore defined, said process comprising:

a) treatment of a solution of the compound of formula (VII) in a mixture of water and a suitable organic solvent with aqueous hydrobromic acid;

b) addition of an aqueous solution of an alkali metal bromate; and

c) addition of a solution of sodium metabisulfite to react with any excess bromine.

According to a further aspect of the invention, there is provided a process for forming a compound of the formula (VIII) from a compound of the formula (VII) as hereinbefore defined, said process comprising:

a) treatment of a solution of the compound of formula (VII) in a mixture of water and a suitable organic solvent with aqueous hydrobromic acid;

b) addition of an aqueous solution of an alkali metal bromate;

c) addition of a solution of sodium metabisulfite to react with any excess bromine;

d) isolation of the product compound of the formula (VIII).

According to a further aspect of the invention, there is provided a process for forming a compound of the formula (VIII) from a compound of the formula (VII) as hereinbefore defined, said process comprising:

a) treatment of a solution of the compound of formula (VII) in a mixture of water and a suitable organic solvent with aqueous hydrobromic acid;

b) addition of an aqueous solution of an alkali metal bromate;

c) addition of a solution of sodium metabisulfite to react with any excess bromine;

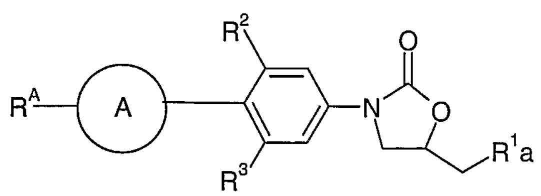
d) isolation of the product compound of the formula (VIII) by heating the mixture resulting from step c) until any solid has dissolved and then cooling the solution until the compound of the formula (VIII) crystallises.

Compounds of the formula (VIII), wherein X and R are as hereinbefore defined are novel, and comprise an independent aspect of the invention. Particular such compounds are those wherein R is hydrogen, halogen or methyl; further particular compounds are those wherein R is hydrogen or methyl, most particularly hydrogen. A preferred compound of the invention is the compound of formula (VI).

In one aspect of the invention, in the compound of formula (VII) at least one X is F. In another aspect, both X are F.

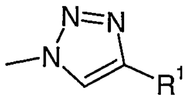
In one aspect, of the invention, in the compound of formula (VII), R is selected from hydrogen, halogen, cyano, methyl, cyanomethyl, fluoromethyl, difluoromethyl, trifluoromethyl and –Si](1-4C)alkyl]$_3$. Suitable values for R as –Si[(1-4C)alkyl]$_3$ are trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl and triisopropylsilyl. Further suitable values for R as –Si[(1-4C)alkyl]$_3$ are trimethylsilyl, triethylsilyl and triisopropylsilyl. In a further aspect, R is hydrogen or methyl. In a still further aspect, R is hydrogen.

The process of the invention is useful in the preparation of compounds of the formula (A),



(A)

wherein

R^1a is  ;

R^2 and R^3 are independently selected from hydrogen and fluorine;

R^1 is selected from hydrogen, halogen, cyano, methyl, cyanomethyl, fluoromethyl, difluoromethyl, trifluoromethyl and –Si[(1-4C)alkyl]$_3$;

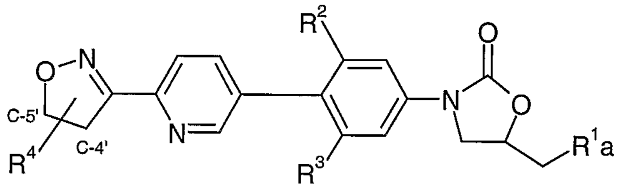
A is an aryl or heteroaryl ring; and

R^A is any group commonplace in the antibacterial oxazolidinone art.

Preferably, A is phenyl, pyridyl, pyrimidinyl or thienyl. More preferaby A is phenyl, pyridyl or pyrimidinyl. Even more preferably A is phenyl or pyridyl. In one embodiment A is phenyl. In another embodiment A is pyridyl.

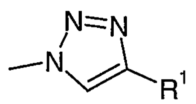
By way of non-limiting examples for group R^A we refer to our applications WO 01/81350 and WO 03/022824 and references therein.

A compound of formula (IX)



(IX)

wherein:

R^1a is  ;

R^2 and R^3 are independently selected from hydrogen and fluorine;

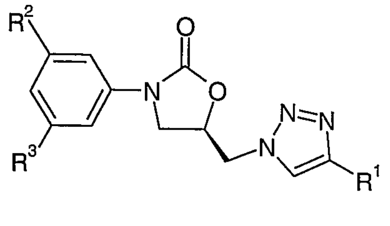
R^1 is selected from hydrogen, halogen, cyano, methyl, cyanomethyl, fluoromethyl, difluoromethyl, trifluoromethyl and –Si[(1-4C)alkyl]$_3$;

wherein R^4 is either a hydroxymethyl substituent on C-4' of the isoxazoline ring; or R^4 is a hydroxymethyl substituent on C-5' of the isoxazoline ring and the stereochemistry at C-5' of the isoxazoline ring and at C-5 of the oxazolidinone ring is selected, such that the compound of formula (I) is a single diastereomer;

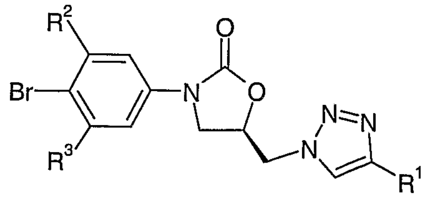
or pharmaceutically-acceptable salts or pro-drugs thereof;

may be prepared by a process comprising the steps of:-

a) conversion of compound of formula (VIIa) to a compound of a formula (VIIIa)



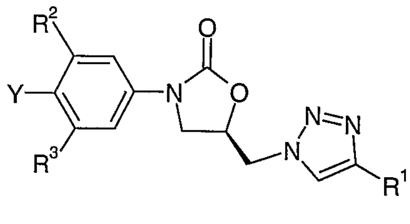
(VIIa)



(VIIIa)

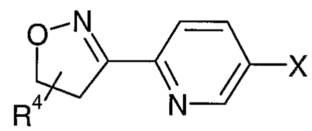
by reaction with an alkali metal bromate, a bromide and acid as described in any aspect or embodiment hereinbefore;

b) formation of a tin or boron derivative of formula (X), wherein Y is a trialkyltin or boronate acid or ester substituent;



(X)

c) coupling with a compound of formula (XI) wherein R^4 is hydroxymethyl or a protected version thereof and X is bromo or iodo;



(XI)

d) optionally deprotecting the hydroxymethyl substituent R^4;

and thereafter if necessary forming a pharmaceutically-acceptable salt or pro-drug thereof.

Suitable conditions for c) (when Y is a boronic acid or ester) include coupling (X) and (XI) in the presence of a palladium (0) compound, for example tetrakis(triphenylphosphine)palladium(0). Other suitable reaction conditions are those in teh presence of a palladium (II) compound, for example 1,1'-[bis(phenylphosphino)ferrocene] dichloropalladium(II) dichloromethane complex. For further information on suitable reaction conditions and catalysts for this type of coupling reaction see, for example, Kotha S. et al, Tetrahedron 2002, **58**, 9633-9695.

Suitable conditions for c) (when Y is a tin derivative such as trimethyltin) include coupling (XI) and (XII) in the presence of a palladium (0) compound, for example tetrakis(triphenylphosphine)palladium(0), or triphenylphosphine and tris (dibenzylideneacetone)dipalladium (0) chloroform adduct. Further suitable reaction conditions for this process are well known in the art.

Suitable trialkyltin derivatives are any such derivative known to be useful in palladium (0) couping reactions, such as trimethyltin.

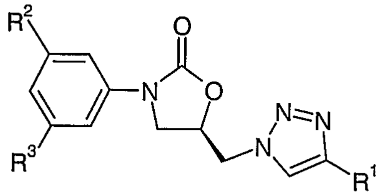
It will be understood that by "Y is a boronic acid or ester" means Y is the group $-B(OR^A)(OR^B)$, wherein R^A and R^B are independently selected from hydrogen and a (1-4C)alkyl group (such as methyl, ethyl and isopropyl), or R^A and R^B together form a 2 or 3 carbon bridge between the two oxygen atoms attached to the boron atom to form a 5- or 6-membered ring respectively (wherein the 2 or 3 carbon bridge is optionally substituted by 1 to 4 methyl groups, for example to form a 1,1,2,2-tetramethylethylene bridge), or R^A and R^B together form a 1,2-phenyl group (thereby giving a catechol ester). This definition of boronic acid ester is similarly applicable wherever the term is applied.

For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Greene & Peter Wuts (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

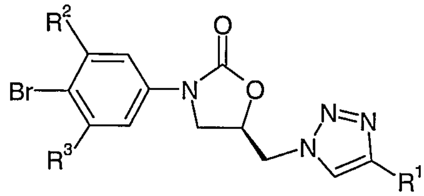
The removal of any protecting groups, the formation of a pharmaceutically-acceptable salt and/or the formation of an in-vivo hydrolysable ester or other pro-drug are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details on the these processes and examples of suitable salts and/or pro-drugs have been given in for example our patent application WO 03/022824.

Compounds of the formula (X) may also be prepared by a process comprising:

a) conversion of compound of formula (VIIa) to a compound of a formula (VIIIa)



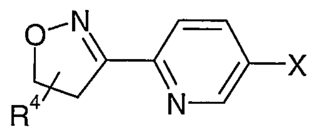
(VIIa)



(VIIIa)

by reaction with an alkali metal bromate, a bromide and acid as described in any aspect or embodiment hereinbefore;

b') coupling with a compound of formula (XI) wherein R^4 is hydroxymethyl or a protected version thereof and X is a trialkyltin or boronate acid or ester substituent;



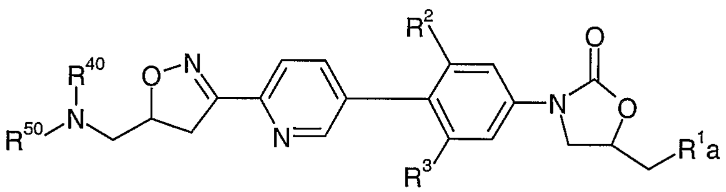
(XI)

c') optionally deprotecting the hydroxymethyl substituent R^4;

and thereafter if necessary forming a pharmaceutically-acceptable salt or pro-drug thereof.

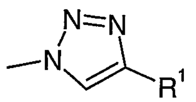
It will be understood that conditions for such a coupling in step b') are directly analogous to those described hereinbefore for process step c).

The process of the invention is also useful in the preparation of a compound of formula (XII)



(XII)

wherein:

R^1a is  ;

R^2 and R^3 are independently selected from hydrogen and fluorine;

R^1 is selected from hydrogen, halogen, cyano, methyl, cyanomethyl, fluoromethyl, difluoromethyl, trifluoromethyl and $-Si[(1\text{-}4C)alkyl]_3$;

R^{40} and R^{50} are independently selected from hydrogen, allyl (optionally substituted on the carbon-carbon double bond by 1, 2 or 3 (1-4C)alkyl groups), methyl, cyanomethyl, carboxymethyl, $-CH_2C(O)OR^{60}$, $-CH_2C(O)NR^{60}R^{70}$, (2-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(2-4C)alkoxy, azido, cyano, $-C(O)OR^{60}$, $-OC(O)R^{60}$, carboxy, $-C(O)NR^{60}R^{70}$, $-S(O)_2R^{60}$, $-S(O)_2NR^{60}R^{70}$, $-NR^{60}R^{70}$, $-NHC(O)R^{60}$ and $-NHS(O)_2R^{60}$],

$-C(O)R^{60}$, $-C(O)CH_2NR^{60}R^{70}$, $-C(O)OR^{60}$, $-C(O)NHR^{60}$, $-C(O)NR^{60}R^{70}$ and $-SO_2NHR^{60}$; or R^{40} and R^{50} together with the nitrogen to which they are attached form a 5 or 6 membered, saturated or partially unsaturated heterocyclyl ring and optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group may optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom (providing the nitrogen is not thereby quaternised) by 1 or 2 (1-4C)alkyl groups;

R^{60} and R^{70} are independently selected from hydrogen, methyl, cyclopropyl (optionally substituted with methyl), carboxymethyl and (2-4C)alkyl (optionally substituted by 1 or 2 substituents independently selected from amino, (1-4C)alkylamino, di-(1-4C)alkylamino, carboxy, (1-4C)alkoxy and hydroxy; wherein a (1-4C)alkylamino or di-(1-4C)alkylamino group may optionally be substitued on the (1-4C)alkyl chain with carboxy);

or R^{60} or R^{70} may form a 4, 5 or 6 membered, carbon-linked saturated heterocyclyl ring, containing 1 or 2 heteroatoms independently selected from O, N and S, wherein a $-CH_2-$ group may optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom by 1 or 2 (1-4C)alkyl;

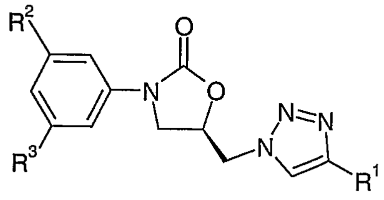
or R^{60} and R^{70} together with a nitrogen to which they are attached form a 4, 5 or 6 membered, saturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group may optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom (providing the nitrogen to which R^{60} and R^{70} are attached is not thereby quaternised) by 1 or 2 (1-4C)alkyl groups;

provided that R^{40} and R^{50} are not both hydrogen.

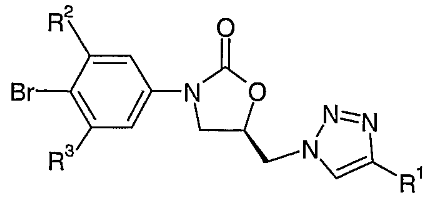
or pharmaceutically-acceptable salts or pro-drugs thereof;

by a process comprising

a) conversion of compound of formula (VIIa) to a compound of a formula (VIIIa)



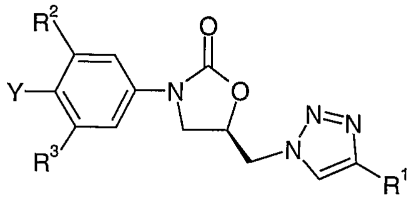
(VIIa)



(VIIIa)

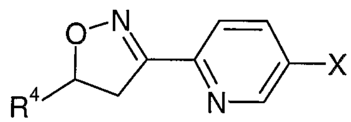
by reaction with an alkali metal bromate, a bromide and acid as described in any aspect or embodiment hereinbefore;

b) formation of a tin or boron derivative of formula (X), wherein Y is a trialkyltin or boronate acid or ester substituent;



(X)

c) coupling with a compound of formula (XIa) wherein R^4 is $–CH_2NR^{40}R^{50}$ or a protected version, or pre-cursor thereof and X is bromo or iodo;



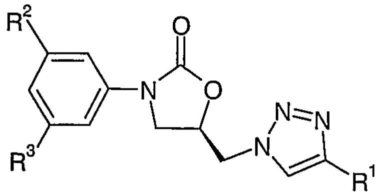
(XIa)

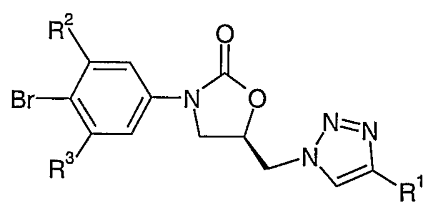
d) optionally deprotecting or converting the substituent R^4 to give a compound of the formula (XII);

and thereafter if necessary forming a pharmaceutically-acceptable salt or pro-drug thereof.

Alternatively, a compound of the formula (XII) may be formed by a process comprising the steps of:

a) conversion of compound of formula (VIIa) to a compound of a formula (VIIIa)

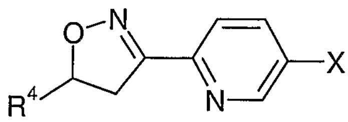




(VIIa) (VIIIa)

by reaction with an alkali metal bromate, a bromide and acid as described in any aspect or embodiment hereinbefore;

b') coupling with a compound of formula (XIa) wherein R^4 is $-CH_2NR^{40}R^{50}$ or a protected version, or pre-cursor thereof and X is a trialkyltin or boronate acid or ester substituent; and



(XIa)

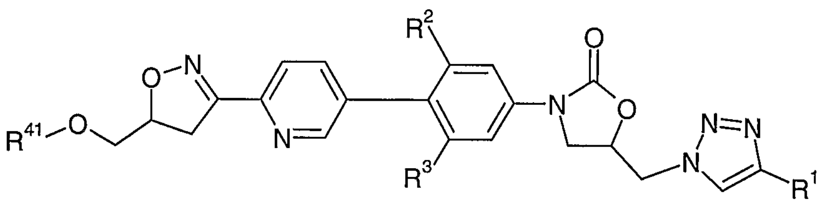
c') optionally deprotecting or converting the substituent R^4 to give a compound of the formula (XII);

and thereafter if necessary forming a pharmaceutically-acceptable salt or pro-drug thereof.

It will be understood that a 4, 5 or 6 membered, saturated or partially unsaturated heterocyclyl ring containing 1 or 2 heteroatoms independently selected from O, N and S (whether or not one of those heteroatoms is a linking N atom), as defined in any definition herein, does not contain any O-O, O-S or S-S bonds.

Examples of conversions of group R^4 in step d) include for example conversion of a compound wherein R^4 is $-CH_2NHR^{40}$ by alkylation or acylation of the remaining NH to give a compound of wherein R^4 is $-CH_2NR^{40}R^{50}$ and R^{50} is an alkyl or acyl group.

A compound of formula (XIII)



(XIII)

wherein:

R_2 and R_3 are independently selected from hydrogen and fluorine;

R^1 is selected from hydrogen, halogen, cyano, methyl, cyanomethyl, fluoromethyl, difluoromethyl, trifluoromethyl and $-Si[(1\text{-}4C)alkyl]_3$;

R^{41} is selected from methyl, cyanomethyl, carboxymethyl, $-CH_2C(O)NR^{51}R^{61}$ and

(2-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(2-4C)alkoxy, cyano, -OC(O)R^{51}, carboxy, -C(O)N$R^{51}R^{61}$, -S$(O)_2R^{51}$, -S$(O)_2$N$R^{51}R^{61}$, -N$R^{51}R^{61}$, -NHC(O)$R^{51}$and -NHS$(O)_2R^{51}$];

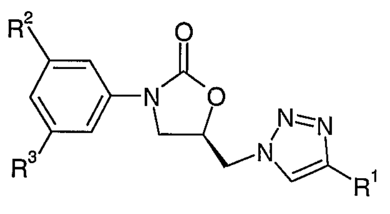
R^{51} and R^{61} are independently selected from hydrogen, methyl, cyclopropyl (optionally substituted with methyl), carboxymethyl and (2-4C)alkyl (optionally substituted by 1 or 2 substituents independently selected from amino, (1-4C)alkylamino, di-(1-4C)alkylamino, carboxy, (1-4C)alkoxy and hydroxy; wherein a (1-4C)alkylamino or di-(1-4C)alkylamino group may optionally be substitued on the (1-4C)alkyl chain with carboxy);

or R^{51} and R^{61} together with a nitrogen to which they are attached form a 4, 5 or 6 membered, saturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, N and S, wherein a -CH_2- group may optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or S$(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom (providing the nitrogen to which R^{51} and R^{61} are attached is not thereby quaternised) by 1 or 2 (1-4C)alkyl groups;

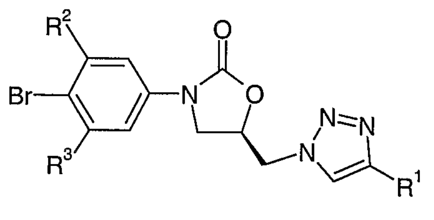
or pharmaceutically-acceptable salts or pro-drugs thereof;

may be prepared by a process comprising

a) conversion of compound of formula (VIIa) to a compound of a formula (VIIIa)



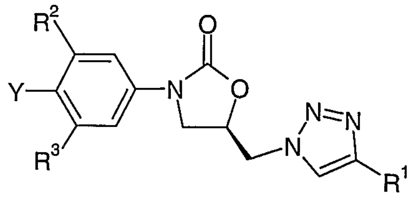
(VIIa)



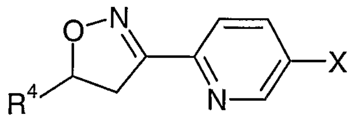
(VIIIa)

by reaction with an alkali metal bromate, a bromide and acid as described in any aspect or embodiment hereinbefore;

b) formation of a tin or boron derivative of formula (X), wherein Y is a trialkyltin or boronate acid or ester substituent;



(X)

c) coupling with a compound of formula (XIa) wherein R^4 is $-CH_2OR^{41}$ or a protected version, or pre-cursor thereof and X is bromo or iodo; 

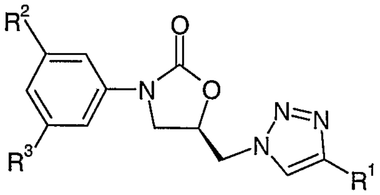
(XIa)

d) optionally deprotecting or converting the substituent R^4 to give a compound of the formula (XIII);

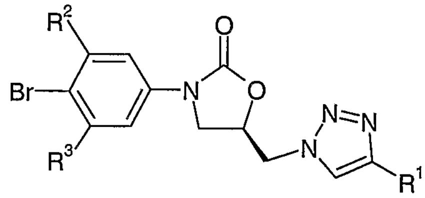
and thereafter if necessary forming a pharmaceutically-acceptable salt or pro-drug thereof.

Alternatively a compound of the formula (XIII) may be prepared by a process comprising:

a) conversion of compound of formula (VIIa) to a compound of a formula (VIIIa)



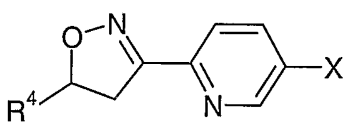
(VIIa)



(VIIIa)

by reaction with an alkali metal bromate, a bromide and acid as described in any aspect or embodiment hereinbefore;

b') coupling with a compound of formula (XIa) wherein R^4 is $-CH_2OR^{41}$ or a protected version, or pre-cursor thereof and X is a trialkyltin or boronate acid or ester substituent; and

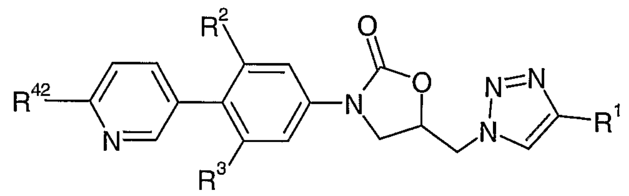


(XIa)

c') optionally deprotecting or converting the substituent R^4 to give a compound of the formula (XIII);

and thereafter if necessary forming a pharmaceutically-acceptable salt or pro-drug thereof.

The process of the invention is also useful in the synthesis of compounds of the formula (XIV):



(XIV)

wherein R^1, R^2 and R^3 are as hereinbefore defined;

R^{42} is (1-4C)alkyl [substituted by 1 or 2 substituents independently selected from hydroxy, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(2-4C)alkoxy, -C(O)OR^{53}, -C(O)R^{53}, -OC(O)R^{53}, carboxy, -C(O)NR^{53}R^{63}, -OC(O)NR^{53}R^{63}, -S(O)$_2$R^{53}, -S(O)$_2$NR^{53}R^{63}, -NR^{53}R^{63}, -NHC(O)R^{53}and -NHS(O)$_2$R^{53}; and optionally additionally substituted by cyclopropyl]; or

R^{53} and R^{63} are independently selected from hydrogen, methyl, cyclopropyl (optionally substituted with methyl), carboxymethyl and (2-4C)alkyl (optionally substituted by one or two substituents independently selected from amino, (1-4C)alkylamino, di-(1-4C)alkylamino, carboxy, (1-4C)alkoxy and hydroxy);

or R^{53} and R^{63} together with a nitrogen to which they are attached form a 4, 5 or 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, N and S, wherein a -CH$_2$- group may optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or S(O)$_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom (providing the nitrogen to which R^{53} and R^{63} are attached is not thereby quaternised) by 1 or 2 (1-4C)alkyl groups;

or R^{53} and R^{63} together with a nitrogen to which they are attached form an imidazole ring, which ring is optionally substituted on an available carbon atom by 1 or 2 (1-4C)alkyl;

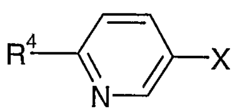
or

R^{42} is –C(O)R^{54}; or

R^{42} is selected from –C(H)=N-OR^{84}, –C(R^{54})=N-OH and –C(R^{54})=N-OR^{84};

R^{54} is (1-6C)alkyl (substituted with 1 or 2 substituents independently selected from hydroxy, carboxy, (1-4C)alkoxy, HET-1 and $NR^{64}R^{74}$);
or R^{54} is (3-6C)cycloalkyl (optionally substituted with 1 substituent selected from hydroxy, carboxy, (1-4C)alkoxy and $NR^{64}R^{74}$);
or R^{54} is HET-1;
R^{64} and R^{74} are independently selected from hydrogen, methyl, cyclopropyl (optionally substituted with methyl), carboxymethyl and (2-4C)alkyl (optionally substituted by a substituent selected from amino, (1-4C)alkylamino, di-(1-4C)alkylamino, carboxy, (1-4C)alkoxy and hydroxy);
or R^{64} and R^{74} together with a nitrogen to which they are attached form a 4, 5 or 6 membered, saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further heteroatom (in addition to the linking N atom) independently selected from O, N and S, wherein a -CH_2- group may optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom (providing the nitrogen to which R^{64} and R^{74} are attached is not thereby quaternised) by 1 or 2 (1-4C)alkyl groups;
or R^{64} and R^{74} together with a nitrogen to which they are attached form an imidazole ring, which ring is optionally substituted on an available carbon atom by 1 or 2 (1-4C)alkyl;
R^{84} is (1-6C)alkyl (optionally substituted with 1 or 2 substituents independently selected from hydroxy, carboxy, (1-4C)alkoxy and $NR^{64}R^{74}$);
HET-1 is a 5 or 6 membered saturated or partially unsaturated heterocyclyl ring, containing 1 or 2 heteroatoms independently selected from O, N and S, wherein a -CH_2- group may optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon or nitrogen atom (providing the nitrogen is not thereby quaternised) by 1 or 2 (1-4C)alkyl.

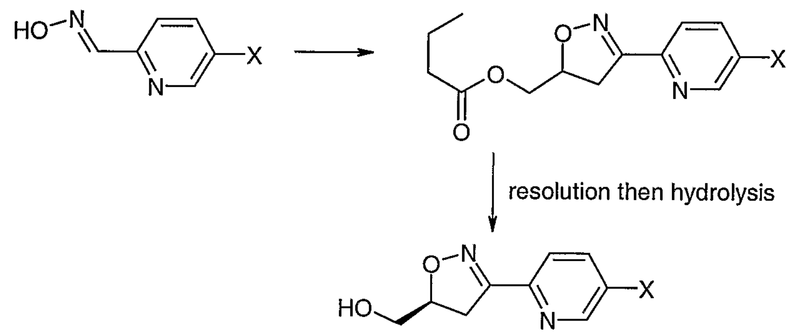
It will be appreciated that in this last aspect, the compound of formula (VIIIa) will be coupled with a compound of formula (XV), wherein X is halo, such as bromo or iodo:



(XV)

It will be appreciated that a compound of the formula (VIIa), (VIIIa), (X), (XII), (XIII) or (IX) wherein R^1 is $-Si[(1\text{-}4C)alkyl]_3$ may be converted to another compound of the formula (VIIa), (VIIIa), (X), (XII), (XIII) or (IX) respectively wherein R^1 is selected from hydrogen, halogen, cyano, methyl, cyanomethyl, fluoromethyl, difluoromethyl and trifluoromethyl, as a separate process step at any appropriate point.

Compounds of the formula (XI) may be derived from an oxime substituted pyridine derivative as shown below, wherein X is Br or I. The oxime derivative itself may be derived from simple halo-pyridine derivatives via aldehydo-halopyridines. The chiral centre on the isoxazole ring may be introduced by any means known in the art, for example by resolution of an ester group, for instance using an enzyme such as a lipase to achieve selectivity. This process is illustrated below for a butyrate ester, however it will be appreciated that other alkyl or alkenyl esters may be used, and that resolution and hydrolysis may be achieved in a single step by enzyme catalysed selective ester hydrolysis. It will be appreciated that X in formula (XI) as shown in the scheme below may be the same throughout the assembly of the 2 ring system, or may be altered at an appropriate point prior to coupling with the compound of formula (X):



(XI) .

The hydroxymethyl substituent in (XI) above may then be elaborated by using standard chemistry to form a compound of the formula (XIa) wherein R^4 is $-CH_2OR^{41}$, or converted using standard chemistry to a compound of formula (XIa) wherein R^4 is $-CH_2NR^{40}R^{50}$.

Compounds of the formula (XV) may be made for example by functionalisation of a di-halopyridine derivative, for example by alkylation using a Grignard reagent.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter. For the avoidance of doubt each stated species represents a particular and independent aspect of this invention.

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl, isopropyl and t-butyl; examples of **(2-4C)alkyl** include ethyl, propyl, isopropyl and t-butyl; examples of **(1-**

6C)alkyl include methyl, ethyl, propyl, isopropyl, t-butyl, pentyl and hexyl; examples of **hydroxy(1-4C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl; examples of **hydroxy(2-4C)alkyl** include 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl and 2-hydroxyisopropyl; examples of **(1-4C)alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; examples of **(2-4C)alkenyl** include allyl and vinyl; examples of **(2-4C)alkynyl** include ethynyl and 2-propynyl; examples of **(1-4C)alkanoyl** include formyl, acetyl and propionyl; examples of **(1-4C)alkoxy** include methoxy, ethoxy and propoxy; examples of **(1-6C)alkoxy** and **(1-10C)alkoxy** include methoxy, ethoxy, propoxy and pentoxy; examples of **(1-4C)alkylthio** include methylthio and ethylthio; examples of **(1-4C)alkylamino** include methylamino, ethylamino and propylamino; examples of **di-((1-4C)alkyl)amino** include dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino and dipropylamino; examples of **halo** groups include fluoro, chloro and bromo; examples of **(1-4C)alkoxy-(1-4C)alkoxy** and **(1-6C)alkoxy-(1-6C)alkoxy** include methoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy and 3-methoxypropoxy; examples of **(1-4C)alkanoylamino** and **(1-6C)alkanoylamino** include formamido, acetamido and propionylamino; examples of **(1-4C)alkylS(O)$_q$-** wherein q is 0, 1 or 2 include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of **hydroxy-(2-4C)alkoxy** include 2-hydroxyethoxy and 3-hydroxypropoxy; examples of **(1-6C)alkoxy-(1-6C)alkyl** and **(1-4C)alkoxy(1-4C)alkyl** include methoxymethyl, ethoxymethyl and propoxyethyl; examples of **(1-4C)alkylcarbamoyl** include methylcarbamoyl and ethylcarbamoyl; examples of **di((1-4C)alkyl)carbamoyl** include di(methyl)carbamoyl and di(ethyl)carbamoyl; examples of **halo** groups include fluoro, chloro and bromo; examples of **halo(1-4C)alkyl** include, halomethyl, 1-haloethyl, 2-haloethyl, and 3-halopropyl; examples of **dihalo(1-4C)alkyl** include difluoromethyl and dichloromethyl; examples of **trihalo(1-4C)alkyl** include trifluoromethyl; examples of **amino(1-4C)alkyl** include aminomethyl, 1-aminoethyl, 2-aminoethyl and 3-aminopropyl; examples of **cyano(1-4C)alkyl** include cyanomethyl, 1-cyanoethyl, 2-cyanoethyl and 3-cyanopropyl; examples of **(1-4C)alkanoyloxy** include acetoxy, propanoyloxy; examples of **(1-6C)alkanoyloxy** include acetoxy, propanoyloxy and tert-butanoyloxy; examples of **(1-4C)alkylaminocarbonyl** include methylaminocarbonyl and ethylaminocarbonyl; examples of **di((1-4C)alkyl)aminocarbonyl** include dimethylaminocarbonyl and diethylaminocarbonyl.

In the formation of a compound of formula (IX), (XII), (XIII), or (XIV) described above, steps b) and c) may be carried out without isolation of the intervening tin or boron compound of formula (X), as illustrated by Example 2 hereinafter.

A further aspect of the invention comprises the use of a compound of formula (VIII) in a process to make a compound of formula (IX), (XII), (XIII) or (XIV).

Examples

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is typically in the range 18-26°C and without exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the invention were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were generally determined in DMSO-d_6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz, or a Bruker DPX400 spectrometer operating at a field strnth of 400MHz; chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad. Time of flight (TOF) mass spectral data were obtained using a Micromass LCT mass spectrometer; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected]; optical rotations were determined at 589nm at 20°C for 0.1M solutions in methanol using a Perkin Elmer Polarimeter 341;

(vi) each intermediate was purified to the standard required for the subsequent stage and was characterised in sufficient detail to confirm that the assigned structure was correct; purity was assessed by HPLC, TLC, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate;

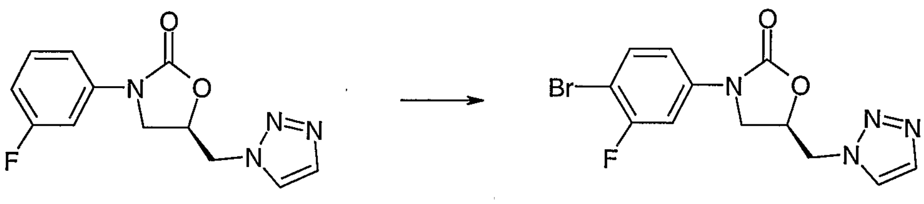
(vii) in which the following abbreviations may be used :-

DMF is N,N-dimethylformamide; DMA is N,N-dimethylacetamide; TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; MPLC is medium pressure liquid chromatography; DMSO is dimethylsulfoxide; $CDCl_3$ is deuterated chloroform; MS is mass spectroscopy; TOF is time of flight; ESP is electrospray; EI is electron impact; CI is chemical ionisation; APCI is atmospheric pressure chemical ionisation; EtOAc is ethyl acetate; MeOH is methanol; phosphoryl is $(HO)_2$-P(O)-O-; phosphiryl is $(HO)_2$-P-O-; Bleach is "Clorox" 6.15% sodium hypochlorite; EDAC is 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide; THF is tetrahydrofuran; TFA is trifluoroacetic acid; RT is room temperature; cf. = compare

(viii) temperatures are quoted as °C.

(ix) MP carbonate resin is a solid phase resin for use in acid Scavenging, available from Argonaut Technologies, chemical structure is PS-$CH_2N(CH_2CH_3)_3^+$ $(CO_3^{2-})_{0.5}$

Example 1: (5R)-3-(4-Bromo-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



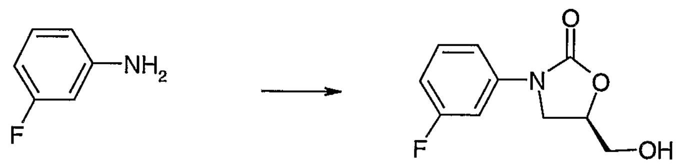
To a stirred solution of (5R)-3-(3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one **(Intermediate 3)** (2.0g, 7.63mmol) in acetic acid (6.0mL) and water (4.0mL) at 14°C was added 48%w/w aqueous hydrobromic acid solution (1.0mL) followed by dropwise addition of a solution of sodium bromate (580mg, 3.81mmol) in water (3.0mL) over 2.5 hours. After stirring the mixture at 26°C for a further 1.5 hours, a solution of sodium metabisulfite (0.435g, 2.29mmol) in water (1.0mL) was added over about 10 minutes. The mixture was heated to 83°C to give a clear solution, which was then cooled to 5°C. The resultant slurry was stirred for a further 1 hour before the solid product was isolated by filtration, washed thrice with water (4.0mL), and dried *in vacuo* at up to 50°C to yield the title compound (2.4g).

MS (TOF): 341.0043 (M+1) for $C_{12}H_{10}N_4O_2FBr^{79}$; calc., 341.0049

^{1}H NMR (400MHz, DMSO-d_6) δ: 3.9 (dd, 1H), 4.2 (t, 1H), 4.8 (d, 2H), 5.2 (m, 1H), 7.3 (ddd, 1H), 7.6 (dd, 1H), 7.7 (dd, 1H), 7.8 (d, 1H), 8.2 (d, 1H).

The intermediates for Example 1 were prepared as follows:

Intermediate 1: (5R)-5-(Hydroxymethyl)-3-(3-fluorophenyl)-1,3-oxazolidin-2-one



Intermediate 1

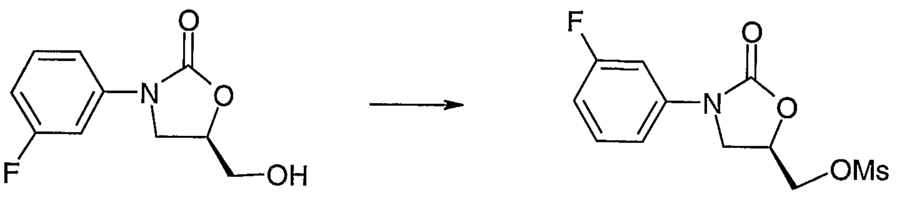
A stirred solution of 3-fluoroaniline (45.68g, 0.41mol) in toluene (447mL) was heated to 30°C and treated with pyridine (39.1mL, 0.48mol). iso-Butyl chloroformate (62mL, 0.48mol) was added over about 0.5hour and the mixture was stirred for about 3 hours at 30°C. Water (134mL) was added and the mixture was stirred at 30°C before the layers were separated. The organic layer was further washed with water (134mL) and then distilled under reduced pressure until about 210mL of distillate was collected.

The stirred residue was diluted with toluene (376mL) and tetrahydrofuran (376mL) and then cooled to –10°C. A solution of n-butyl lithium in toluene (24.5%w/w, 3.3M, 113.6mL, 0.377mol) was added over 50 minutes, followed by addition of R-glycidyl butyrate (57.3mL, 0.40mol). The mixture was warmed to 40°C over about 3 hours and this temperature was maintained for a further 1.5 hour before methanol (192.6mL) was added. The resultant clear solution was added to a mixture of acetic acid (24.5mL) and water (170mL) and the layers were allowed to separate. The organic extracts were stirred overnight with water (250mL), separated, and washed again with water (100mL), before distilling under reduced pressure to leave about 400mL of concentrate, which was cooled to 0°C over a period of about 16 hours and stirred for a further 4 hours at this temperature to give a suspension. The solid was isolated by filtration, washed with toluene (50mL) and dried *in vacuo* at up to 40°C to give the title compound (61.97g).

MS (TOF): 212.0729 (M+1) for $C_{10}H_{10}NO_3F$; calc., 212.0723

^{1}H NMR (400MHz, DMSO-d$_6$) δ: 3.6 (ddd, 1H), 3.7 (ddd, 1H), 3.8 (dd, 1 H), 4.1 (t, 1H), 4.7 (m, 1H), 5.2 (t, 1H), 6.9 (m, 1H), 7.3 (ddd, 1H), 7.4 (td, 1H), 7.5 (dt, 1H).

Intermediate 2: [(5R)-3-(3-Fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl methanesulfonate



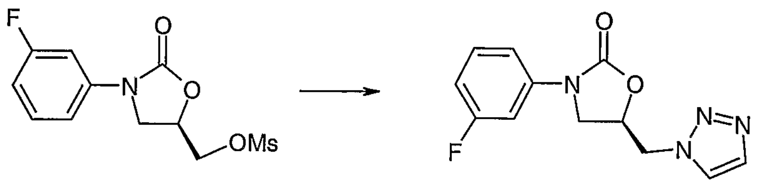
Intermediate 2

A stirred suspension of (5R)-5-(Hydroxymethyl)-3-(3-fluorophenyl)-1,3-oxazolidin-2-one (20.0g, 0.095mol) in toluene (300mL) was heated to 85°C to give a solution, and triethylamine (20.17mL, 0.142mol) was added. The solution was cooled to 68°C, and methanesulfonyl chloride (9.2mL, 0.118mol) was added over 10 minutes. Water (200mL) was added to the mixture and the mixture was stirred at 75°C for 0.5 hour. The mixture was then cooled to 15°C over about 2 hours giving a slurry of the product. The solid was isolated by filtration, washed with water (200mL), and dried to give the title compound (27.3g).

MS (TOF): 290.0506 (M+1) for $C_{11}H_{12}NO_5FS$; calc., 290.0498

^{1}H NMR (400MHz, DMSO-d$_6$) δ: 3.3 (s, 3 H), 3.8 (dd, 1H), 4.2 (t, 1H), 4.5 (dd, 1H), 4.5 (dd, 1H), 5.0 (m, 1H), 7.0 (m, 1H), 7.3 (ddd, 1H), 7.4 (td, 1H), 7.5 (dt, 1H).

Intermediate 3: (5R)-3-(3-Fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



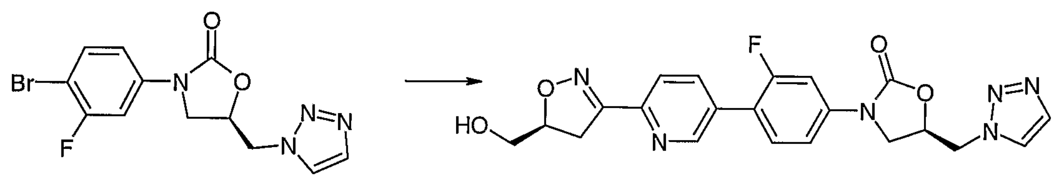
Intermediate 3

A stirred suspension of [(5R)-3-(3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl methanesulfonate (25g, 0.086mol) and sodium azide (6.18g, 0.095mol) in N-methyl-pyrrolidinone (250mL) was heated to 95°C for about 3 hours and then cooled to 20°C. The mixture was filtered and to the filtrates was added (trimethylsilyl)acetylene (24.9mL, 0.172mol). The mixture was heated to 135°C and this temperature was maintained for 5 hours. During this time, two further portions of (trimethylsilyl)acetylene (2.0mL) were added after 2.5 hours and 3.5 hours. Water (10mL) was added and heating was continued for 0.5 hour. The reaction mixture was cooled to 125°C, water (10mL) and (trimethylsilyl)acetylene (2.0mL) were added before heating at 125°C was continued for a further 2 hours. The reaction was cooled to 25°C and evaporated under reduced pressure to give an oily residue. The residue was diluted with acetic acid (95mL) and water (25mL) and heated with stirring to 91°C for 5.5 hours, before cooling to 30°C. The mixture was heated to 61°C and water (300mL) was added over 1 hour, before cooling to 15°C over abut 2.5 hours, to give a suspension of the product. The crude product was isolated by filtration, washed thrice with water (50mL) and recrystallised from a mixture of acetic acid (95mL) and water (245mL). The product was isolated by filtration, washed thrice with water (50mL), and dried *in vacuo* at up to 40°C to give the title compound (5.53g).

MS (TOF): 263.0939 (M+1) for $C_{12}H_{11}N_4O_2F$; calc., 263.0944

^{1}H NMR (400MHz, DMSO-d_6) δ: 3.9 (dd,1H), 4.2 (t, 1H), 4.8 (d, 2H), 5.2 (m, 1H), 7.0 (m, 1H), 7.3 (ddd, 1H), 7.4 (m, 2H), 7.8 (d, 1H), 8.2 (d, 1H).

Example 2: Conversion to (5*R*)-3-[3-Fluoro-4-[((5S)-5-hydroxymethyl-4,5-dihydroisoxazol-3-yl)-3-pyridinyl]phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)oxazolidin-2-one



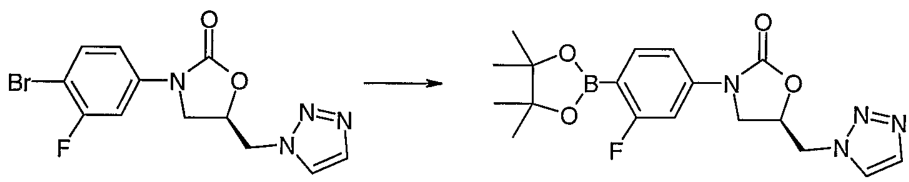
To a stirred mixture of (5R)-3-(4-Bromo-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one **(Example 1)** (60.0g, 0.175mol), potassium acetate (49.41g, 0.498mol) and bis(pinacolato)diboron (51.11g, 0.199mol) in 1,4-dioxan (750mL) was added 1,1'-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (2.74g, 0.0033mol), and the resultant mixture was heated to 82°C. This temperature was maintained for 21 hours and the mixture was then cooled to 25°C before filtration. The solids were washed with 1,4-dioxan (180mL) and to the combined filtrates and washings were added [(5*S*)-3-(5-Bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methanol (**Intermediate 5,** 42.7g, 0.166mol) and 1,1'-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (0.68g, 0.00083mol), followed by a solution of potassium carbonate (45.9g, 0.332mol) in water (300mL). The resulting biphasic mixture was stirred and heated at 80°C for 1.5 hours. After cooling to 50°C the lower, aqueous layer was removed, and the organic layer was further cooled to 30°C, giving a suspension of the product, which was isolate by filtration, washed with a mixture of 1,4-dioxan (180mL) and water (60mL), water (60mL), and methanol (120mL), and then dried *in vacuo* at up to 40°C to give the title compound (56.23g).

MS (TOF): 439.1535 (M+1) for $C_{21}H_{19}N_6O_4F$; calc., 439.1530

^{1}H NMR (400MHz, DMSO-d$_6$) δ: 3.3 (dd, 1H), 3.5 (dd, 1H), 3.6 (m, 2H), 4.0 (dd, 1H), 4.3 (t, 1H), 4.8 (m, 1H), 4.9 (d, 2H), 5.0 (t, 1H), 5.2 (m, 1H), 7.4 (dd, 1H), 7.6 (dd, 1H), 7.7 (t, 1H), 7.8 (d, 1H), 8.0 (broad d, 1H), 8.1 (broad d, 1H), 8.2 (d, 1H), 8.8 (broad s, 1H).

Example 3 – Stepwise Conversion to (5*R*)-3-[3-Fluoro-4-[((5S)-5-hydroxymethyl-4,5-dihydroisoxazol-3-yl)-3-pyridinyl]phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)oxazolidin-2-one

(i) (5*R*)-3-[3-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



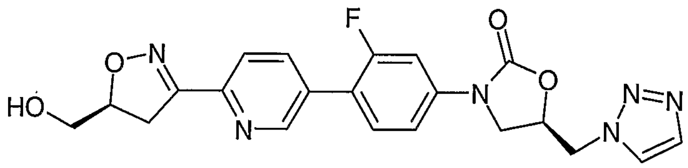
Intermediate 4

Charcoal (6.0g) was added to a stirred solution of (5R)-3-(4-Bromo-3-fluorophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one **(Example 1)** (60.0g, 0.175mol) in 1,4-dioxan (600mL) and the mixture was heated to 60°C for 0.5 hour. The mixture was cooled to 30°C and filtered, the filter cake was washed with further 1,4-dioxan (150mL). Potassium acetate (65.88g, 0.66mol), bis(pinacolato)diboron (51.11g, 0.199mol) and 1,1'-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (2.74g, 0.0033mol) were added to the combined filtrates and washings, and the resultant mixture was heated to 82°C. After 18 hours, the reaction mixture was cooled to 25°C and filtered and the filtered solids were washed with a further portion of 1,4-dioxan (180mL). The combined filtrates and washings were evaporated to dryness under reduced pressure. The residue was dissolved in n-butyl acetate (400mL) by heating to 110°C and cooled to 40°C before charcoal (6.0g) was added. The mixture was heated to 90°C and whilst still hot, solids were removed by filtration. The filtrates were cooled to ambient temperature, the solid product was isolated by filtration, washed with n-butyl acetate (200mL) and iso-hexane (400mL), and air dried to give the title compound (35.77g) **(Intermediate 4)**

MS (TOF): 389.1800 (M+1) for $C_{18}H_{22}B^{11}N_4O_4F$; calc., 389.1796

^{1}H NMR (400MHz, DMSO-d$_6$) δ: 1.3 (s, 12 H), 3.9 (dd, 1 H), 4.2 (t, 1 H), 4.8 (d, 2H), 5.2 (ddd, 1H), 7.3 (dd, 1H), 7.4 (dd, 1H), 7.6 (dd, 1H), 7.8 (d, 1H), 8.2 (d, 1H).

(ii)(5*R*)-3-(3-Fluoro-4-{6-[(5*S*)-5-(hydroxymethyl)-4,5-dihydroisoxazol-3-yl]pyridin-3-yl}phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



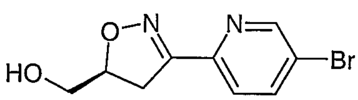
[(5*S*)-3-(5-Bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methanol (**Intermediate 5,** 0.277 g, 1.08 mmol), (5*R*)-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one **(Intermediate 4)**(0.35 g, 0.9 mmol), potassium carbonate (0.622 g, 4.5 mmol), and tetrakis(triphenylphosphino)palladium(0) (0.1 g, 0.09 mmol) were combined and suspended in DMF (7 ml) and water (1 ml). The mixture was heated at 75 °C for 2 hours, then was poured into cold water(30ml). The solids formed were collected, rinsed with water and washed with dichloromethane(2x10ml), the solids were then dissolved in warm trifluoroethanol(2ml), and further purified by column chromatography, eluting with 8% methanol in dichloromethane to give the title compound as a white solid (0.193g).

MS (ESP): 439.22 (M+1) for $C_{21}H_{19}FN_6O_4$

NMR(300Mz)(DMSO-d$_6$) δ: 3.36 – 3.58 (m, 4H); 3.95 (dd, 1H); 4.29 (t, 1H); 4.78 (m, 1H); 4.86 (d, 2H); 5.02 (t, 1H); 5.18 (m, 1H); 7.41 (dd, 1H); 7.58 (dd, 1H); 7.69 (t, 1H); 7.77 (s, 1H); 7.98 (d, 1H); 8.05 (dd, 1H); 8.18 (s, 1H); 8.78 (s, 1H).

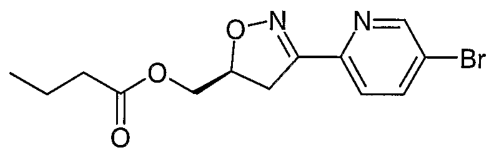
The intermediates for Examples 2 and 3 were prepared as follows:-

Intermediate 5: [(5*S*)-3-(5-Bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methanol



[(5*S*)-3-(5-Bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methyl butyrate (**Intermediate 6,** 16.88 g, 0.051 mol) was dissolved in methanol (110 ml). 50% Aqueous sodium hydroxide (3.6 ml, 0.068 mol) was added. The solution was stirred at RT for 15 minutes, 1M HCl (75 ml) was added, followed by concentration *in vacuo* to ~100 ml total volume. Water (~50 ml) was added, and the white precipitate was collected and rinsed with water. The filtrate was extracted twice with ethyl acetate, the organic layers were pooled, dried over sodium sulfate and evaporated. The solid residue was collected and rinsed with 10: 1 hexane: ethyl acetate, then combined with the initial precipitate before drying in vacuo to give the title compound as a white crystalline solid, 12.3 g (93%). Chiral HPLC analysis indicated < 0.5 % of the (-) isomer was present. $[\alpha]_D = + 139$ (c = 0.01 g/ml in methanol).

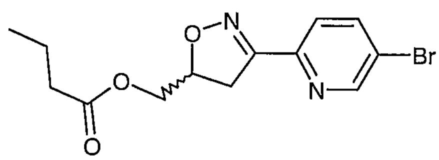
Intermediate 6: (5*S*)-3-(5-Bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methyl butyrate



(+) Isomer assigned as (5*S*) based on comparison with Chem. Lett. 1993 p.1847.

Racemic [3-(5-bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methyl butyrate (**Intermediate 7,** 80 g, 0.244 mol) was dissolved in acetone (4 L), and 0.1 M potassium phosphate buffer (pH~7) (4 L) was added with vigorous stirring to give a clear yellow solution. PS-lipase (1.45 g, Sigma cat no L-9156) was added and the mixture was gently stirred at ambient temp. for 42 hrs. The solution was divided into 3 equal volumes of ~2.6 L and each was extracted with dichloromethane (2 x 1 L), the pooled organic phases were dried over sodium sulfate and evaporated. The unreacted [(5*S*)-3-(5-bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methyl butyrate was isolated via flash column chromatography (9:1 hexane: ethyl acetate) as a clear yellow oil, 36.4 g (45.5%).

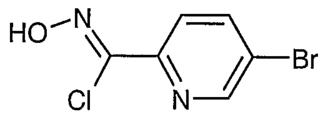
Intermediate 7: [3-(5-Bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methyl butyrate



5-Bromo-*N*-hydroxypyridine-2-carboximidoyl chloride (**Intermediate 8,** 46 g, 195.7 mmol) was added to EtOAc (200 ml) followed by addition of allyl butyrate (145 ml, 1020.4 mmol) and the solution was cooled to 0 °C. Triethylamine (30 ml, 215.8 mmol) in EtOAc (100 ml) was then added dropwise over 1 hour. The reaction was then allowed to stir for 1 hour at 0 °C and then EtOAc (1 L) was added. The precipitate was removed by vacuum filtration and the filtrate was concentrated *in vacuo* to yield the product (65 g).

^{1}H-NMR(DMSO-d_6) δ: 0.81 (t, 3H); 1.43 (m, 2H); 2.24 (t, 2H); 3.21 (dd, 1H); 3.54 (dd, 1H); 4.13 (dd, 1H); 4.23 (dd, 1H); 5.01 (m,1H); 7.85 (dd, 1H); 8.12 (dd, 1H); 8.81 (d, 1H).

Intermediate 8: 5-Bromo-*N*-hydroxypyridine-2-carboximidoyl chloride

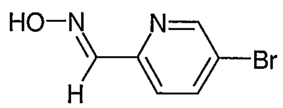


5-Bromopyridine-2-carbaldehyde oxime (**Intermediate 9,** 49.5 g, 246.3 mmol) was dissolved in DMF (150 ml) followed by addition of *N*-chlorosuccinimide (39.5 g, 295.5 mmol). HCl gas was then bubbled in the solution for 20 seconds to initiate the reaction, which was then allowed to stir for 1 hr. The reaction was poured into distilled water (1 L) and the precipitate was collected by vacuum filtration. The filter cake was washed with distilled water (2 x 500 ml) and then dried overnight in a vacuum oven at 60 °C (–30 inches Hg) to yield the product as a white powder (55 g).

^{1}H-NMR(300Mz)($CDCl_3$) δ: 7.73 (d, 1H); 8.09 (d, 1H); 8.73 (s, 1H); 12.74 (s, 1H).

NOTE: *Lachrymator.*

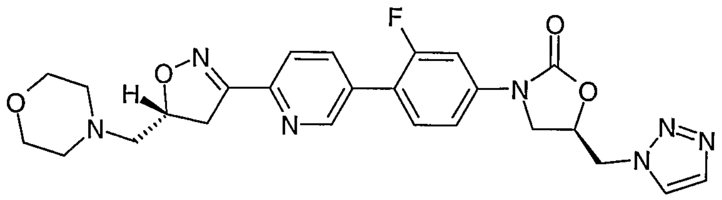
Intermediate 9: 5-Bromopyridine-2-carbaldehyde oxime



5-Bromo-pyridine-2-carbaldehyde (X. Wang et al, Tetrahedron Letters 41 (2000), 4335-4338) (60 g, 322 mmol) was added to methanol (700 ml) and then water was added (700 ml) followed by addition of hydroxylamine hydrochloride (28 g, 403 mmol). Sodium carbonate (20.5 g, 193.2 mmol) in water (200 ml) was added and the reaction was stirred for 30 minutes. Water (500 ml) was then added and the precipitate was filtered and washed with water (2 x 300 ml) to give the desired product (60 g).

NMR (DMSO-d_6) δ: 7.75 (d, 1H); 8.09 (t, 2H), 8.72 (s, 1H); 11.84 (s, 1H).

Example 4: Stepwise conversion to (5*R*)-3-(3-Fluoro-4-{6-[(5*R*)-5-(morpholin-4-ylmethyl)-4,5-dihydroisoxazol-3-yl]pyridin-3-yl}phenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



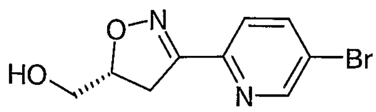
4-{[(5*R*)-3-(5-Bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methyl}morpholine (**Intermediate 12,** 320 mg, 0.98 mmol), (5*R*)-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (400 mg, 1.03 mmol), potassium carbonate (**Intermediate 4,** 450 mg, 3.26 mmol), and tetrakis(triphenylphosphino)palladium(0) (120 mg, 0.10 mmol) were suspended in DMF (5 ml) and water (0.5 ml). The mixture was heated at 80 °C for 60 minutes, allowed to cool, and filtered. The solids were rinsed with acetonitrile and the combined filtrate was adsorbed on silica gel. The adsorbed material was purified by column chromatography (silica gel, 1 to 10 % methanol in dichloromethane). The off-white solid thus obtained (430 mg) was dissolved in hot dioxane (30 ml) and treated with HCl (4M solution in dioxane, 0.25 ml, 1 mmol) to give a suspension, which was diluted with diethyl ether (50 ml) followed by filtration and rinsing with diethyl ether. The hydrochloride salt of the title compound was thus obtained as an off-white solid (400 mg): melting point: 239 - 245 °C.

MS (electrospray): 508 (M+1) for $C_{25}H_{26}FN_7O_4$

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.18 (bm, 2H); 3.37 (dd, 1H); 3.49 (bm, 3H); 3.77 (m, 4H); 3.96 (m, 3H); 4.30 (t, 1H); 4.86 (d, 2H); 5.19 (m, 1H); 5.32 (m, 1H); 7.42 (dd, 1H); 7.59 (dd, 1H); 7.69 (t, 1H); 7.76 (s, 1H); 8.02 (d, 1H); 8.09 (d, 1H); 8.18 (s, 1H); 8.81 (s, 1H); 10.55 (bs, 1H).

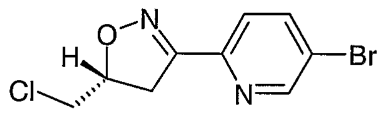
The intermediates for Example 4 were prepared as follows:-

Intermediate 10: [(5*R*)-3-(5-bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methanol



(*R*,*S*)-[3-(5-Bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methanol (prepared by hydrolysis of **Intermediate 7,** 3.1g) was dissolved in hot methanol (25ml), it was then separated by chiral column (Chiral Pak AS) eluting with 30% isopropanol in hexanes. The title compound [(-) isomer, 1.5g)] which eluted first from the column was collected along with the (+) isomer (second peak, 1.18g). Chiral HPLC analysis indicated < 2 % of the (+) isomer was present. $[\alpha]_D$ = -125° (c = 0.0076 g/ml in methanol).

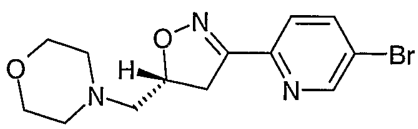
Intermediate 11: 5-Bromo-2-[(5*R*)-5-(chloromethyl)-4,5-dihydroisoxazol-3-yl]pyridine



[(5*R*)-3-(5-Bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methanol (**Intermediate 10,** 0.274 g, 1.06 mmol) was dissolved in dichloromethane (5 ml). Triphenylphosphine (0.8 g, 3.05 mmol) and carbon tetrachloride (0.6 ml, 6.2 mmol) were added and the mixture was stirred at room temperature for 2 hours. Methanol (0.5 ml) was added, and the solution was concentrated and purified by flash chromatography (silica gel, 5 to 20% ethyl acetate in hexane) to yield the title compound as a white solid (280 mg).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.42 – 3.73 (m, 4H); 4.98 – 5.08 (m, 1H); 7.84 (dd, 1H); 7.90 (d, 1H); 8.65 (d, 1H).

Intermediate 12: 4-{[(5*R*)-3-(5-Bromopyridin-2-yl)-4,5-dihydroisoxazol-5-yl]methyl}morpholine

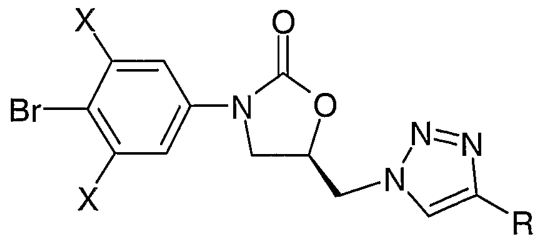


5-Bromo-2-[(5*R*)-5-(chloromethyl)-4,5-dihydroisoxazol-3-yl]pyridine (**Intermediate 11,** 0.276 g, 1.0 mmol), morpholine (0.9 ml, 10.3 mmol), tetrabutyl ammonium iodide (2 mg, catalytic amount) and DMSO (0.9 ml) were combined and warmed to 115 °C for 4 hours. The solution was diluted with water and extracted twice with ethyl acetate. The pooled organic layers were dried over sodium sulfate and evaporated to give crude title compound as a waxy yellow solid (320 mg).

MS (electrospray): 327 (M+1) for $C_{13}H_{16}BrN_3O_2$

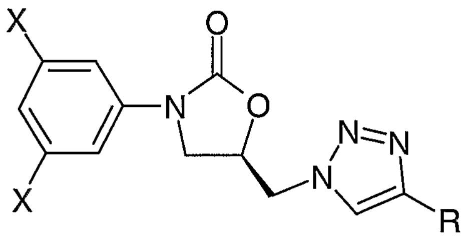
CLAIMS

1. A process for forming a compound of the formula (VIII)



(VIII)

from a compound of the formula (VII),



(VII)

wherein each X is independently H or F and R is selected from hydrogen, halogen, cyano, methyl, cyanomethyl, fluoromethyl, difluoromethyl, trifluoromethyl and –Si[(1-4C)alkyl]$_3$;

said process comprising treatment of a solution of the compound of formula (VII) with bromine.

2. A process as claimed in Claim 1, wherein the bromine is generated in situ from a bromate, a bromide and acid.

3. A process for preparing a compound of the formula (VIII) as defined in claim 1 from a compound of the formula (VII) as defined in claim 1, said process comprising treatment of a solution of the compound of formula (VII) with a bromate, a bromide and acid.

4. A process as claimed in Claim 2 or Claim 3, wherein the bromate is an alkali metal bromate.

5. A process as claimed in any one of Claims 2 to 4, wherein the bromide is provided by hydrobromic acid.

6.A process as claimed in any of Claims 2 to 5, wherein hydrobromic acid provides the bromide and the acid.

7. A process for forming a compound of the formula (VIII) as defined in claim 1 from a compound of the formula (VII) as defined in claim 1, said process comprising treatment of a solution of the compound of formula (VII) with an alkali metal bromate, and hydrobromic acid.

8. A process according to claim 7 comprising:

a) treatment of a solution of the compound of formula (VII) in a mixture of water and a suitable organic solvent with aqueous hydrobromic acid; and

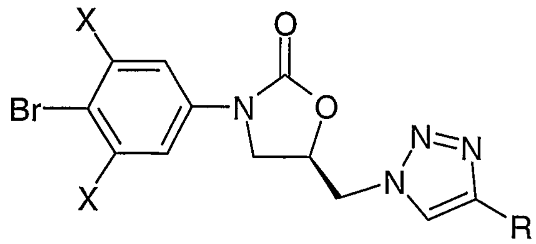
b) addition of an aqueous solution of an alkali metal bromate.

9. A process according to claim 8 comprising the additional step (c) of addition of a solution of sodium metabisulfite to react with any excess bromine.

10. A process according to claim 9 comprising the additional step (d) of isolation of the product compound of the formula (VIII).

11. A process according to claim 10 wherein the step of isolating the product compound of formula (VIII) is performed by heating the mixture resulting from step c) of Claim 9 until any solid has dissolved and then cooling the solution until the compound of the formula (VIII) crystallises.

12. A compound of the formula (VIII)



(VIII)

wherein each X is independently H or F ;and R is selected from hydrogen, halogen, cyano, methyl, cyanomethyl, fluoromethyl, difluoromethyl, trifluoromethyl and –Si[(1-4C)alkyl]$_3$.

13. A compound according to Claim 12, wherein R is selected from hydrogen, halogen or methyl.

14. A compound according to Claim 12 or Claim 13 wherein R is hydrogen.

15. A compound according to any one of Claims 12 to 14 wherein at least one X is F.

16. A compound according to Claim 15 wherein both X are F.

17. A compound according to Claim 12 wherein one X is H and the other is F; and R is hydrogen.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/002042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/06

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)
IPC 7 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, WPI Data, 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.
Y	WO 03/035648 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; GRAVESTOCK, MICHAEL, BARRY) 1 May 2003 (2003-05-01) page 42 - page 44	12-17
Y	WO 03/022824 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; GRAVESTOCK, MICHAEL, BARRY; HA) 20 March 2003 (2003-03-20) page 45 - page 47; examples 58,59	12-17
P,X	WO 2004/078753 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; GRAVESTOCK, MICHAEL, BARRY; HA) 16 September 2004 (2004-09-16) page 29 - page 30	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2005	31/08/2005

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	Menegaki, F

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/002042

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 03035648	A	01-05-2003	EP	1446403	A1	18-08-2004
			WO	03035648	A1	01-05-2003
			GB	2396350	A	23-06-2004
			JP	2005519870	T	07-07-2005
			US	2005043374	A1	24-02-2005
WO 03022824	A	20-03-2003	AT	299502	T	15-07-2005
			BR	0212458	A	19-10-2004
			CA	2459766	A1	20-03-2003
			EP	1427711	A1	16-06-2004
			WO	03022824	A1	20-03-2003
			HU	0401005	A2	30-08-2004
			JP	2005507386	T	17-03-2005
			MX	PA04002303	A	29-06-2004
			NZ	531621	A	24-06-2005
			US	2005107435	A1	19-05-2005
WO 2004078753	A	16-09-2004	WO	2004078753	A1	16-09-2004