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(57) Abstract: The present invention is related to the stereospecific preparation of 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one, and the intermediates thereof. Another aspect of the invention relates to 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one, wherein the carbon atoms having the 1,2-dihydroxy substituents are any of the four diastereomers selected from (R,R), (R,S), (S,R), and (S,S), wherein the carbon three of the pyrrolidin-2-one is (R) or (S), pharmaceutically acceptable salts thereof, solvates thereof, pharmaceutical compositions containing them, and methods using them for in treating or preventing depression, anxiety, obsessive compulsive disorder (OCD) and other disorders for which a 5-HT₁ agonist or antagonist is indicated.



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STEREOSELECTIVE SYNTHESIS OF 1-[6-(1-ETHYL-1,2-DIHYDROXY-PROPYL)-PYRIDIN-3-YL]-3-[2-(4-METHYL-PIPERAZIN-1-YL)-BENZYL]-PYRROLIDIN-2-ONE

Field of the Invention

The present invention is related to the preparation of 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one (referred herein as compound of formula (I)), the intermediates thereof, and the synthesized 1,2-dihydroxy compounds, wherein the 1,2-dihydroxy substituents are any of the four diastereomers selected from (*R,R*), (*R,S*), (*S,R*), and (*S,S*), wherein the C-3 of the pyrrolidin-2-one is (*R*) or (*S*), pharmaceutically acceptable salts thereof, solvates thereof, and pharmaceutical compositions containing them. The synthesized compounds of the present invention bind at one or both of the 5-HT_{1A} and 5-HT_{1B} (formerly classified 5-HT_{1D}) receptors. Said compounds are metabolites of 1-[6-(1-Ethyl-1-hydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one, a selective 5HT_{1B} antagonist. The active metabolites are useful in treating depression, anxiety, obsessive compulsive disorder (OCD) and other disorders for which a 5-HT₁ agonist or antagonist is indicated and have reduced potential for cardiac side effects, in particular, QTc prolongation.

Background of the Invention

Antagonists of serotonin 1 (5-HT₁) receptors, specifically, of one or both of the 5-HT_{1A} and 5-HT_{1B} receptors are useful in treating hypertension, all forms of depression (e.g., depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, pediatric depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, post partum depression, dysthymia; mild, moderate, or severe depressions with or without atypical features, melancholic features, psychotic features, catatonic features; seasonal affective disorder, geriatric depression, chronic depression; adjustment disorder with depressed mood or with anxiety and depressed mood; mixed anxiety and depression; substance induced mood disorder; and mood disorder secondary to a general medical condition), bipolar disorder (including in the depressed phase),

generalized anxiety disorder, social anxiety, separation anxiety disorder, phobias (e.g., agoraphobia, social phobia and simple phobias), posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders (e.g., binge eating disorder, anorexia nervosa and bulimia nervosa), obesity, chemical dependencies (e.g., addictions to alcohol, cocaine, heroin, phenobarbital, marijuana, nicotine and benzodiazepines), cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder; panic disorder with and without agoraphobia; memory disorders (e.g., dementia, amnesic disorders, and age-related cognitive decline (ARCD)), Parkinson's diseases (e.g., dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias), endocrine disorders (e.g., hyperprolactinaemia), vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, gastrointestinal tract disorders (involving changes in motility and secretion), negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, cancer (e.g., small cell lung carcinoma), chronic paroxysmal hemicrania, headache (associated with vascular disorders) autism, pervasive developmental disorder NOS, Asperger's disorder, selective mutism, chronic motor or vocal tic disorder, somatization disorder, insomnia, intermittent explosive disorder, pyromania, pathological gambling, impulse-control disorder, premenstrual dysphoric disorder, and attention-deficit/hyperactivity disorder (ADHD), and other disorders for which a 5-HT₁ agonist or antagonist is indicated.

European Patent Publication 434,561, published on June 26, 1991, refers to 7-alkyl, alkoxy, and hydroxy substituted-1-(4-substituted-1-piperazinyl)-naphthalenes. The compounds are referred to as 5-HT₁ agonists and antagonists useful for the treatment of migraine, depression, anxiety, schizophrenia, stress and pain.

European Patent Publication 343,050, published on November 23, 1989, refers to 7-unsubstituted, halogenated, and methoxy substituted-1-(4-substituted-1-piperazinyl)-naphthalenes as useful 5-HT_{1A} ligand therapeutics.

PCT publication WO 94/21619, published September 29, 1994, refers to naphthalene derivatives as 5-HT₁ agonists and antagonists.

PCT publication WO97/36867, published Oct. 9, 1997, and WO 98/14433, published Apr. 9, 1998, refer to related benzyl(idene)-lactam derivatives having utility as psychotherapeutic agents.

PCT publication WO 96/00720, published January 11, 1996, refers to naphthyl
5 ethers as useful 5-HT₁ agonists and antagonists.

PCT publication WO97/36867, published Oct. 9, 1997, and WO 98/14433, published Apr. 9, 1998, refer to related benzyl(idene)-lactam derivatives having utility as psychotherapeutic agents.

European Patent Publication 701,819, published March 20, 1996, refers to the
10 use of 5-HT₁ agonists and antagonists in combination with a 5-HT re-uptake inhibitor.

Glennon et al., refers to 7-methoxy-1-(1-piperazinyl)-naphthalene as a useful 5-HT₁ ligand in their article "5-HT_{1D} Serotonin Receptors", Drug Dev. Res., 22, 25-36 (1991).

Glennon's article "Serotonin Receptors: Clinical Implications", Neuroscience
15 and Behavioral Reviews, 14, 35-47 (1990), refers to the pharmacological effects associated with serotonin receptors including appetite suppression, thermoregulation, cardiovascular/hypotensive effects, sleep, psychosis, anxiety, depression, nausea, emesis, Alzheimer's disease, Parkinson's disease and Huntington's disease.

World Patent Application WO 95/31988, published November 30, 1995, refers
20 to the use of a 5-HT_{1D} antagonist in combination with a 5-HT_{1A} antagonist to treat CNS disorders such as depression, generalized anxiety, panic disorder, agoraphobia, social phobias, obsessive-compulsive disorder, post-traumatic stress disorder, memory disorders, anorexia nervosa and bulimia nervosa, Parkinson's disease, tardive dyskinesias, endocrine disorders such as hyperprolactinaemia, vasospasm
25 (particularly in the cerebral vasculature) and hypertension, disorders of the gastrointestinal tract where changes in motility and secretion are involved, as well as sexual dysfunction.

G. Maura et al., J. Neurochem, 66 (1), 203-209 (1996), have stated that
30 administration of agonists selective for 5-HT_{1A} receptors or for both 5-HT_{1A} and 5-HT_{1D} receptors might represent a great improvement in the treatment of human cerebellar ataxias, a multifaceted syndrome for which no established therapy is available.

European Patent Publication 666,261, published August 9, 1995, refers to thiazine and thiomorpholine derivatives which are claimed to be useful for the treatment of cataracts.

PCT publication WO 2006/011030, published February 2, 2006, refers to the
5 preparation of novel substituted haloarene compounds.

US Published App. No. 2005-0245521A1, published November 3, 2005 refers to novel benzyl(idene)-lactam derivatives. The compounds are referred to as selective antagonists, inverse agonists and partial agonists of serotonin 1 (5-HT₁) receptors and as being useful in treating depression, anxiety, obsessive compulsive
10 disorder (OCD) and other disorders.

Klapars, et al discuss a general and efficient copper catalyst for the amidation of aryl halides and the N-arylation of nitrogen heterocycles in *J. Am. Chem. Soc.*, 2001, 123, 7727-7729.

Klapars, et al discuss a general and efficient copper catalyst for the amidation
15 of aryl halides in *J. Am. Chem. Soc.*, 2002, 124, 7421-7428.

US Patent No. 6,420,565, issued July 16, 2002, which discusses a process for making 2, 5-substituted pyridine.

Wang, et al. discuss selective monolithiation of 2,5-dibromopyridine with butyllithium in *Tetrahedron Letters*, 41 (2000) 4335-4338.

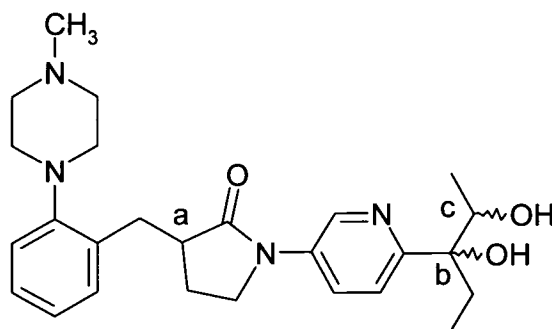
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Summary of the Invention

The present invention is related to the stereospecific preparation of 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one:

25 formula (I):

-5-



(I)

wherein the stereochemistry of a and b and c, where the given definition defines (a) and then (b, c), respectively, is

- 5 (R) and (R, S);
 (R) and (R, R);
 (S) and (R, S);
 (S) and (R, R);
 (R) and (S, S);
 10 (R) and (S, R);
 (S) and (S, S); and
 (S) and (S, R);

prodrugs (e.g., esters) and pharmaceutically acceptable salts thereof.

The invention also concerns the intermediates thereof of the compound of
 15 formula (I). Another aspect of the invention relates to 1-[6-(1-ethyl-1,2-dihydroxypropyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one, wherein the carbon atoms having the 1,2-dihydroxy substituents are any of the four diastereomers selected from (R,R), (R,S), (S,R), and (S,S), wherein the C-3 of the pyrrolidin-2-one (identified as "a" herein) is (R) or (S), pharmaceutically acceptable
 20 salts thereof, solvates thereof, and pharmaceutical compositions containing them.

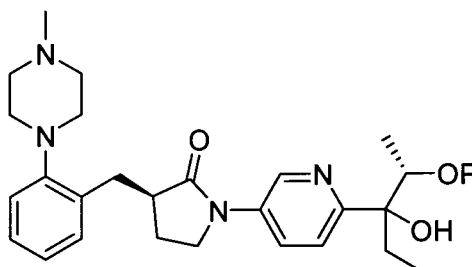
Another aspect of the present invention includes the preparation of (2S)-2-((2-(trimethylsilyl)ethoxy)methoxy)-3-(5-bromopyridin-2-yl)pentan-3-ol from (S)-methyl lactate. Another aspect of the present invention includes the preparation of (2S)-3-(5-bromopyridin-2-yl)-2-(tetrahydro-2H-pyran-2-yloxy)-pentan-3-ol from (S)-methyl
 25 lactate. Another aspect of the present invention includes the preparation of 2(S)-3-(5-

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Bromopyridin-2-yl)-2-(*tert*-butyl-diphenylsilyloxy)pentan-3-ol from (*S*)-methyl lactate. Yet another aspect of the present invention includes the preparation of (2*S*)-3-(5-bromopyridin-2-yl)-2-(*tert*-butyldimethylsilyloxy)pentan-3-ol, (2*S*)-2-(benzyloxy)-3-(5-bromopyridin-2-yl)pentan-3-ol, and (2*S*)-2-(benzyloxymethoxy)-3-(5-bromopyridin-2-yl)pentan-3-ol from (*S*)-methyl lactate.

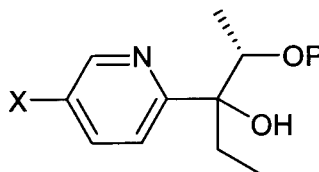
Another aspect of the present invention includes the stereospecific preparation or 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one starting with (*S*)-ethyl lactate rather than (*S*)-methyl lactate to obtain the respective intermediates using procedures discussed herein, making non-critical changes.

Another aspect of the present invention includes the intermediates that are compounds of formula 1-ia:



formula 1-ia

wherein P is an appropriate protecting group;
and formula 1-ib:



formula 1-ib

wherein X is a halogen with atomic number less than or equal to Br or I, preferably Br; and

P is as described for formula 1-ia,
and the processes to prepare them. Appropriate protecting groups are known to those in the art. See, e.g., Green and Wuts, "Protective Groups in Organic

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Synthesis", Third Ed., Wiley & Sons, 1999. Non-limiting examples of appropriate protecting groups include any one of the following:

C₁-C₄ alkyl optionally substituted as valency allows with -oxyC₁-C₄alkyl, nitro, -oxybenzyl optionally substituted on phenyl of the benzyl with up to 3 substituents
5 independently selected from -oxyC₁-C₄alkyl further substituted with silyl further substituted with C₁-C₄alkyl as valency allows;

C₃-C₅alkenyl;

C₅-C₆ heterocycloalkyl optionally substituted with C₁-C₄alkyl;

benzyl optionally substituted on phenyl of the benzyl with up to 3 substituents
10 independently selected from C₁-C₃alkyl, -oxyC₁-C₄alkyl, or nitro; or

silyl substituted as valency allows with substituents independently selected from the group consisting of C₁-C₄alkyl, phenyl, and -oxyC₁-C₄alkyl.

Non-limiting, specific examples of appropriate protecting groups include: methoxymethyl, 1-ethoxyethyl, *tert*-butyl, *tert*-butoxymethyl, 2-methoxyethoxymethyl,
15 allyl, triethylsilyl, triisopropylsilyl, tetrahydro-2H-pyran, tetrahydro-2H-furan, 4-methoxybenzyl, 4-nitrobenzyl, (2-(trimethylsilyl)ethoxy)methyl, *tert*-butyldiphenylsilyl, *tert*-butyldimethylsilyl, benzyl, benzyloxymethyl, 1-[2-(trimethylsilyl)ethoxy]ethyl, and *tert*-butoxydiphenylsilyl.

The present invention includes any one step individually or any combination of
20 any of the individual steps discussed herein.

The present invention includes all intermediates discussed herein and final compounds discussed herein and processes to prepare them.

Detailed Description of the Invention

25 In one practice, and without limitation, the invention relates to 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one having formula (I) as discussed herein. The compound of formula I can, without specifying stereochemistry, be named 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one. It can also be named as 3-(2-
30 (4-methylpiperazin-1-yl)benzyl)-1-(6-(2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one. The two names are used interchangeably. Preferably, the compound of

formula I is (3*R*) 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one. More preferably, the compound of formula I is (3*R*) 1-[6-(1-ethyl-2(*S*)-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one. Also more preferably, the compound of formula I is (3*R*) 1-[6-(1-ethyl-(1(*R*),2(*S*))-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one or (3*R*) 1-[6-(1-ethyl-(1(*S*),2(*S*))-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one. Most preferably, the compound of formula I is (3*R*) 1-[6-(1-ethyl-(1(*R*),2(*S*))-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one. When a compound of formula I is named with specific stereochemistry assigned, it is substantially free of any other isomer, meaning that the compound is at least at least 98% pure, preferably at least 99%. The degree of purity is for the compound after preparation and purification but before preparing any pharmaceutically acceptable formulation for administration, which could include excipients and other pharmaceutically acceptable material.

In another aspect, the invention includes the preparation of compounds of formula I. The following schemes discuss the routes by which the stereospecific synthesis of 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one can be completed. In the schemes, the stereochemistry of carbon-3 of pyrrolidin-one is presented as (*R*) for presentation purposes only and is not meant to limit the scope of the invention.

The preparation of the 1,2-dihydroxy compounds required much work to discover an acceptable synthetic route. 1,2-Diols are generally prepared from epoxides, starting from olefins. Unfortunately, attempts to make the epoxide from the corresponding olefin were unsuccessful. However, a stereoselective synthesis was ultimately discovered.

For the following discussions, the initial starting material is (*S*)-methyl 2-hydroxypropanoate (also known as (*S*)-methyl lactate). By using the (*S*)-methyl lactate, the stereochemistry is fixed for that respective carbon. To obtain the (*R*) isomer, the (*R*)-methyl lactate would be used as the starting material. Alternatively, (*R*)- and (*S*)-ethyl lactates can be used. For exemplification, and not limitation of the

scope of this invention, the (S) methyl lactate is used for discussion purposes. Unless otherwise indicated, reactions conducted at room temperature (RT) are conducted between about 18 to about 25°C. Alkyl and alkoxy groups, containing the requisite number of carbon atoms, can be unbranched or branched.

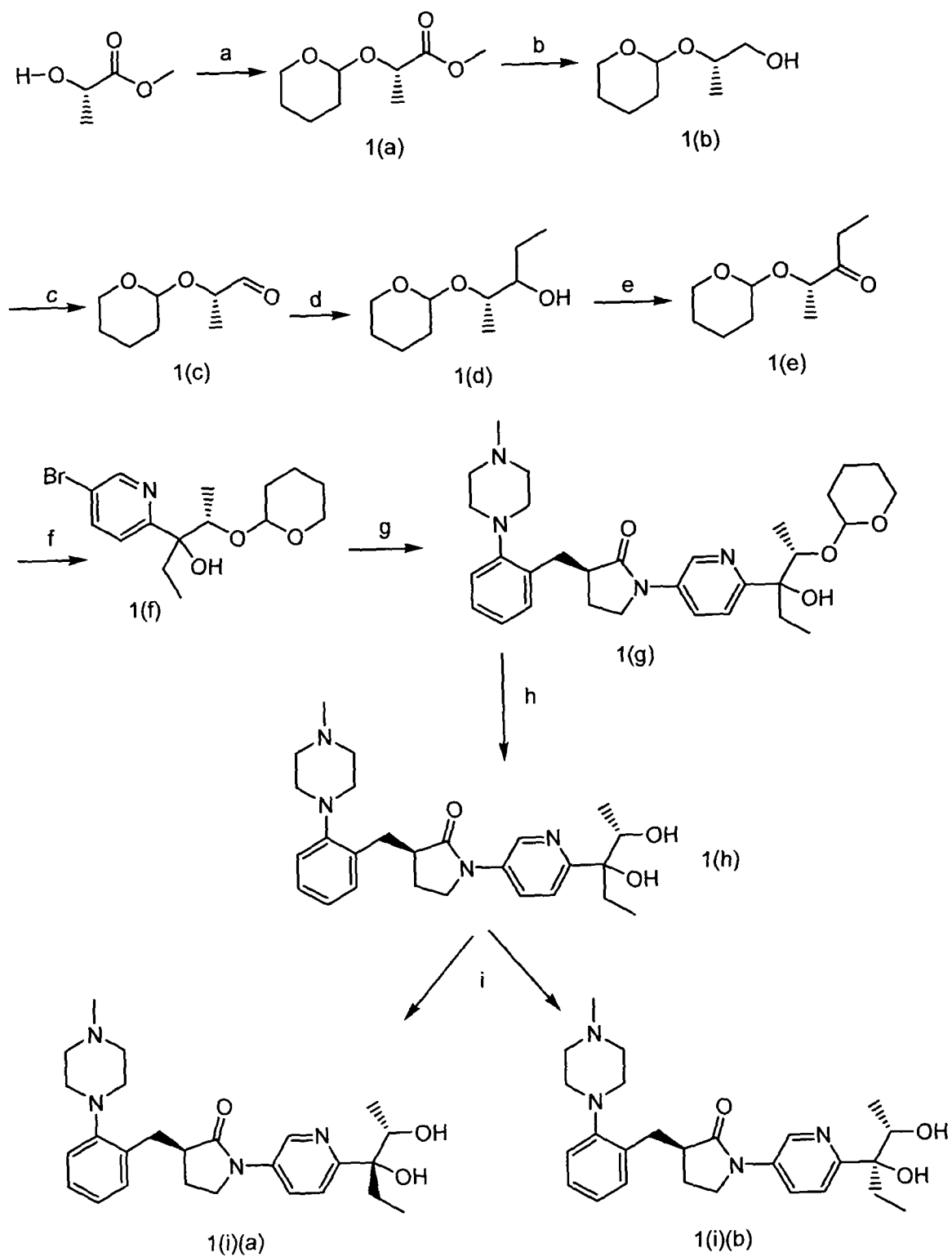
5 The term "halo" and "halogen" are used interchangeably and include fluoro, chloro, bromo and iodo.

 The term "heteroaryl" is intended to include 5- to 7-membered aromatic heterocyclic groups and includes the non-limiting examples thiophenyl, pyridyl, pyrimidyl, pyridazyl, oxazolyl, isooxazolyl, thiazolyl and isothiazolyl, among others.

10 In Scheme 1, the preparation of the 1,2-dihydroxy compounds is presented using a tetrahydropyran protecting group, starting from (S)-methyl lactate and 3,4-dihydro-2*H*-pyran.

-10-

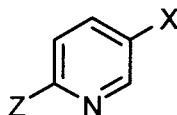
Scheme 1



In Scheme 1, (S)-methyl lactate is protected with a suitable protecting group (Green and Wuts, *supra*), then the ester is reduced to the corresponding primary alcohol by methods known to those skilled in the art, for example, with LAH. The alcohol is then oxidized to the aldehyde by known methods, such as the Swern or
5 Moffatt oxidation, use of TEMPO or Martin's reagent, sodium periodate or chromic acid. The aldehyde 1(c) is reacted with ethyl Grignard affording the secondary alcohol of formula 1(d). The alcohol is oxidized to the ketone 1(e) by known methods such as the Swern or Moffatt oxidation, use of TEMPO or Martin's reagent, sodium periodate or chromic acid or other oxidative conditions.

10 The ketone is coupled with 5-halo-2-metalopyridine to form a compound of the formula 1(f), preferably in an aprotic organic solvent. For example, see US published Patent Application US 2006-0030714, incorporated herein by reference. For example, the reaction can be conducted as follows:

(a) forming a mixture in a non-coordinating reaction inert solvent, optionally
15 toluene, of a dihalopyridine:



wherein Z is Br or I; and X is a halogen with atomic number less than or equal to the selected Z;

with (2S)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-one;

20 (b) treating the mixture formed in step (a) with an (C₁-C₈)alkyl lithium compound, preferably n-butyllithium; and

(c) quenching the mixture formed in (b) with a proton donor so as to form (2S)-3-(5-bromopyridin-2-yl)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-ol.

25 1(g) is obtained using known procedures. For example, see US published Patent Application 2005-0245521, incorporated herein by reference. For example, the pyrrolidinone and 1(f) are stirred together in a non-coordinating reaction inert solvent, optionally toluene. CuI (about 0.05 to 0.2 eq, e.g., about 0.1 eq) is first added and then potassium carbonate (about 1.5 to 2.5 eq., e.g., about 2 eq.), N,N'-

dimethylethylenediamine (about 0.05 to 0.5 eq., e.g., about 0.2 eq), and then water (about 1% to about 10% w/w, e.g., about 5%). The reaction mixture is refluxed until analytical methods, e.g., HPLC, indicates that the reaction is complete. The product is isolated using standard procedures.

5 1(h) is obtained using standard procedures to cleave the protecting group. See, e.g., Green and Wuts, supra. For example 1(g) could be treated with an acid, e.g., glacial acetic acid (about 30 to 300 eq., e.g., about 155 eq) in water (about 1:2 v/v for water:acetic acid), and the process can optionally be heated. Standard isolation/purification procedures are also optional if needed.

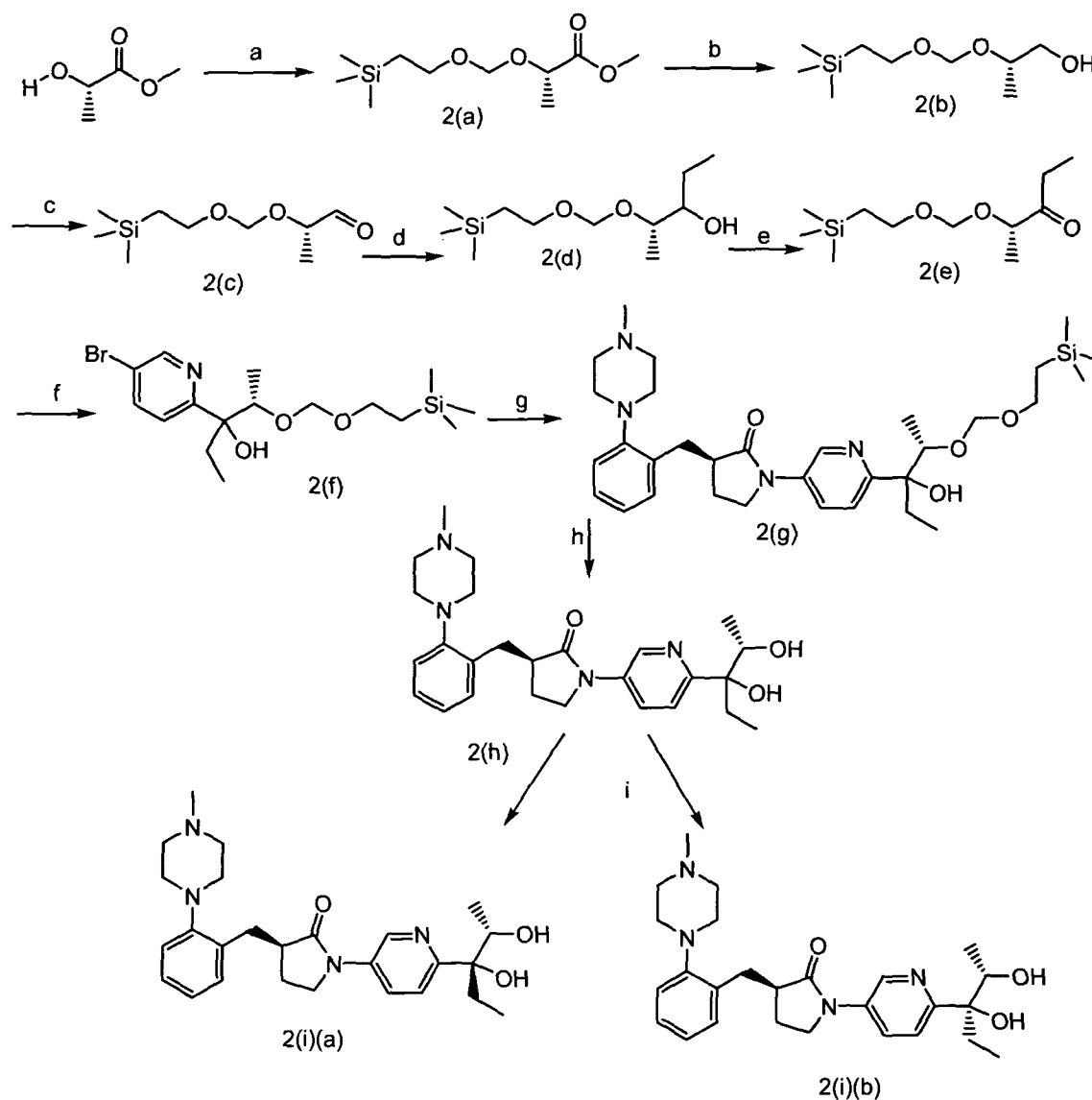
10 1(i) is obtained by isolating the single enantiomers. The four diastereomers can be separated by reverse phase HPLC-chromatography. One type of column that separates all of the four diastereomers is Cosmosil PYE 110Å, 5µm, 4.6x150mm, (Phenomenex Inc.). The experimental conditions for the separation were: mobile phase 20% acetonitrile in 80% aqueous buffer (0.5%(v/v) HClO₄ in water), flow rate
15 2.00mL/min, and UV detection at 210nm. The separation of 1(i)(a) and 1(i)(b) was obtained using a Chiralpack AD, 10x50cm column eluting with 60% heptane in 40% ethanol with the flow rate of 300 ml/min. The approximate elution times were 40min for 1(i)(a) and 85min for 1(i)(b). The isolated material exhibited higher than 98% diastereomeric purity.

20 To determine the absolute stereochemistry of the diastereomers 1(i)(a) and 1(i)(b), the resolved diastereomers are derivatized to carbonates using 1,1'-carbonyldiimidazole. Once the carbonates are isolated, the compounds are analyzed using numerous NMR techniques, including 1D proton, 1D carbon, ¹H-¹H gradient DQFCOSY (Double Quantum-Filtered COrrelation SpectroscopY), ¹H-¹H NOESY
25 (Nuclear Overhauser Enhancement SpectroscopY), ¹H-¹³C multiplicity edited HSQC (Heteronuclear Single Quantum Coherence) and ¹H-¹³C BIRDHMBC (Bilinear Rotation Decoupling-filtered Heteronuclear Multiple Bond Correlation) or ¹H-¹³C multiplicity edited HSQC (Heteronuclear Single Quantum Coherence) and ¹H-¹³C HMBC (Heteronuclear Multiple Bond Correlation).

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In Scheme 2, the preparation of the 1,2-dihydroxy compounds is obtained from (S)-methyl lactate using the (2-(trimethylsilyl)ethoxy)methyl protecting group.

Scheme 2

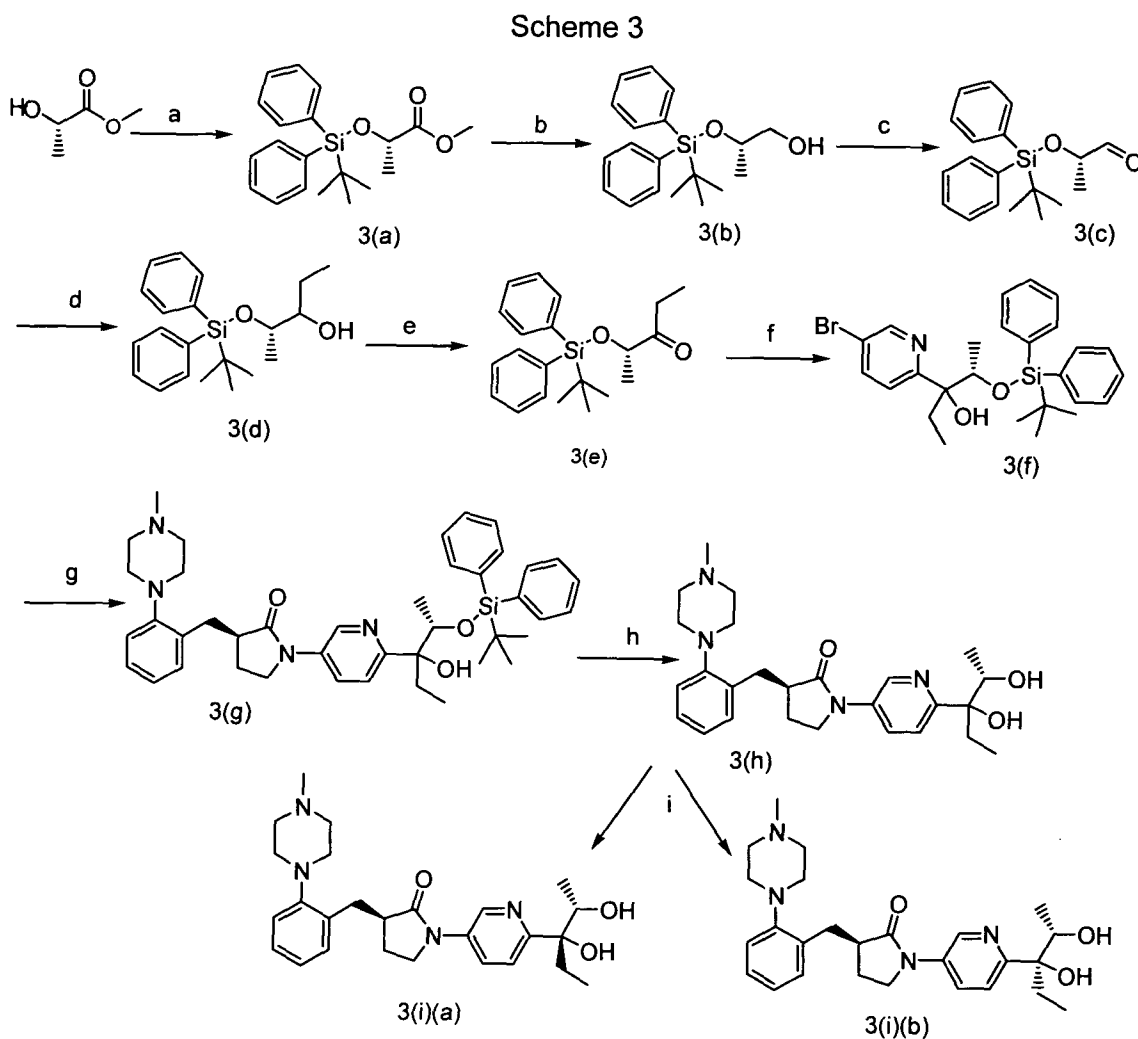


5 Steps a through g of Scheme 2 are conducted using the general procedures discussed for Scheme 1.

2(h) is obtained using standard procedures to cleave the protecting group. See, e.g., Green and Wuts, *supra*. For example 2(g) could be treated with fluoride, e.g., tetrabutylammonium fluoride or pyridine–hydrogen fluoride complex (about 1 to
 10 10 eq., e.g., about 4 eq) in tetrahydrofuran or other aprotic solvent and the process

can optionally be heated. Standard isolation/purification procedures are also optional if needed.

In Scheme 3, the preparation of the 1,2-dihydroxy compounds is presented using a *tert*-butyldiphenylsilyl protecting group, starting from (*S*)-methyl lactate using *tert*-butyldiphenylsilyl chloride.



Steps a through h of Scheme 3 are conducted using the general procedures discussed for Scheme 2.

Alternatively, the propanal can be obtained directly from the propanoate. For example, (*S*)-methyl lactate can be protected with about 1 to 2 eq of, for example, *tert*-butyldimethylsilyl chloride in an acceptable solvent, e.g., *N,N*-dimethylformamide, or 1-methyl-2-pyrrolidinone sufficient to give about a 1 to 3M solution at RT under nitrogen.

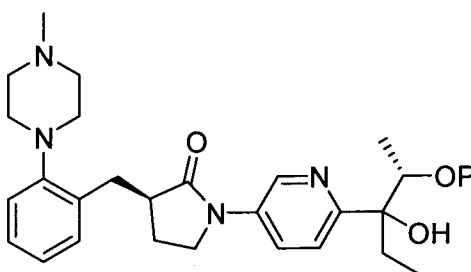
Imidazole (about 1 to 2 eq) is added and the reaction mixture is stirred at RT for about 1 to 8 hours, e.g., 4.5 hours. Diisopropyl ether, hexanes, isopropyl acetate, ethyl acetate (about 1 to 10 volumes) is added and the product is isolated using an acidic work up, e.g., aqueous hydrochloric acid. The propanoate is then mixed with hexanes
5 or with THF, or 2-methyltetrahydrofuran to give a concentration of about 1 to 3 M, cooled below at least -10°C, preferably about -72°C under nitrogen. Diisobutylaluminium hydride (about 1 to 2eq, e.g., 1.3 eq as a 1M solution in hexanes) is added, the reaction stirred for about 30 min to about 4 hours, and allowed to warm up between -10°C and RT before saturated aqueous ammonium chloride (e.g., about
10 6 to 7M) is added. The crude product was isolated and purified by distillation, e.g., the propanal can be collected when boiling at 98-102°C/42mbar. The diol is then obtained following procedures discussed herein starting with the propanal.

Another alternative route to the diol compounds is by obtaining the protected pentan-3-one from the lactate by first making 2-hydroxy-1-morpholinopropan-1-one
15 from the lactate. (S)-Methyl lactate and morpholine (about 1 to 6eq, e.g., about 4eq.) are heated for about 5 to 48h, e.g., about 24 h at about 80 to 120°C, e.g., 110°C under nitrogen. Excess morpholine is evaporated and the crude product can be isolated by distillation, e.g., collecting fractions boiling at 115 –125°C at <1mbar to give (S)-2-hydroxy-1-morpholinopropan-1-one. This intermediate and *N,N*-
20 diisopropylethyl-amine, triethylamine, or sodium carbonate (about 1 to 3 eq., e.g., 1.2 eq) are added to a solvent selected from CH₂Cl₂, THF, or 2-methyltetrahydrofuran to give a concentration of about 0.5 to 3M (relative to the intermediate) and cooled to about 0°C to about RT under nitrogen. (2-(Chloromethoxy)ethyl)-trimethylsilane (from about 1 to 1.5 eq, e.g., about 1.2eq.) is added, the reaction is then stirred at RT for
25 about 12 to 36 hr, e.g., about 20 hr. (S)-1-Morpholino-2-((2-(trimethylsilyl)ethoxy)methoxy)-propan-1-one is isolated using an acidic work up, e.g., quenching with aqueous HCl. The (S)-1-Morpholino-2-((2-(trimethylsilyl)ethoxy)methoxy)-propan-1-one is mixed in THF, 2-methyltetrahydrofuran (from about 0.5 to 3 M, e.g., about 1 M) and cooled to about -72
30 to 0°C. Ethylmagnesium chloride (e.g., about 1 to 3eq., e.g., about 2 eq, it can be used as a 2M solution in THF) is added, the reaction is stirred for about 15 minutes to

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about 3h and then allowed to warm-up to -10 to about 0°C. Saturated aqueous ammonium chloride solution (about 1 to 3 volumes) is added, the reaction mixture warms to RT and (S)-2-((2-(trimethylsilyl)ethoxy)methoxy)-pentan-3-one is isolated using standard work-up procedures. The diol compounds are then obtained using
 5 procedures discussed herein.

The present invention includes intermediates that are compounds of formula 1-ia and formula 1-ib and the processes to prepare them. The process to make a compound of formula 1-ia:

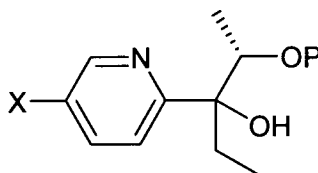


10

formula 1-ia

wherein P is an appropriate protecting group;

comprising the coupling of (R)-3-(2-(4-methylpiperazin-1-yl)benzyl)pyrrolidin-2-one and a compound of formula 1-ib



15

formula 1-ib

wherein X is a halogen with atomic number less than or equal to Br or I, preferably Br; and

P is as described for formula 1-ia;

20 preferably in an aprotic organic solvent. Non-limiting examples of appropriate protecting groups for P are discussed herein.

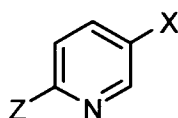
For example, the pyrrolidinone and 1-ib are stirred together in a non-coordinating reaction inert solvent, optionally toluene. Cul (about 0.05 to 0.2 eq, e.g., about 0.1 eq) is first added and then potassium carbonate (about 1.5 to 2.5 eq, e.g.,

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about 2 eq.), N,N'-dimethylethylenediamine (about 0.05 to 0.5 eq., e.g., about 0.2 eq), and then water (about 1% to about 10% w/w, e.g., about 5%). The reaction mixture is refluxed until analytical methods, e.g., HPLC, indicate that the reaction is complete. The compound of formula 1-ia is isolated using standard procedures.

5 The compound of formula 1-ib can be prepared using known procedures. For example, see US published Patent Application US 2006-0030714, incorporated herein by reference. A non-limiting example of preparing the compound of formula 1-ib is as follows:

10 (a) forming a mixture in a non-coordinating reaction inert solvent, optionally toluene, of a dihalopyridine:



wherein Z is Br or I; and X is a halogen with atomic number less than or equal to the selected Z;

with an appropriate reactive species to give a compound of formula 1-ia;

15 (b) treating the mixture formed in step (a) with an (C₁-C₈)alkyl lithium compound; and

(c) quenching the mixture formed in (b) with a proton donor so as to form the compound of formula 1-ib.

20 An appropriate reactive species is a ketone, that when reacted with the dihalopyridine will provide a compound of formula 1-ib. Non-limiting examples include (2S)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-one, (S)-2-((2-(trimethylsilyl)ethoxy)-methoxy)pentan-3-one, or (S)-2-(*tert*-butyldiphenylsilyloxy)pentan-3-one.

25 For example, 2,5-dibromopyridine and the appropriate reactive species are dissolved in toluene and the resulting solution cooled, e.g., to about 0°C, under nitrogen. n-Butyllithium in hexanes is then added and the resulting mixture stirred and the reaction is subsequently quenched by addition of methanol. The intermediate compound of formula 1-ib is obtained using standard procedures.

The present invention includes all compounds made herein, including intermediates.

The following schemes and non-limiting examples are offered in illustration of the present invention; they are not to constrain the scope of the same in any way.

Examples

Example 1(a) - (2S)-Methyl 2-(tetrahydro-2H-pyran-2-yloxy)propanoate:

5 (S)-Methyl lactate (65.4g, 628mmol) was mixed with 1200mL of anhydrous CH₂Cl₂ and cooled to 3°C under nitrogen. *p*-Toluenesulfonic acid monohydrate (1.20g, 0.01eq.) was added, followed by dropwise addition of 3,4-dihydro-2H-pyran (79.22g, 1.5eq. 942mmol). The mixture was warmed to room temperature (RT) and stirred for 3 hours at which point 1200mL of saturated aqueous sodium bicarbonate
10 solution was added and the layers separated. The organic layer was washed with 1200mL brine, dried with magnesium sulfate (MgSO₄), filtered through a Celite® bed and after solvent evaporation 136.6g of **1(a)** was obtained as a tan liquid, which was used without further purification.

Diastereomer 1 (Major): ¹H NMR (400 MHz, CDCl₃) δ 4.65 (t, 1H), 4.38 (q, 1H),
15 3.8 (m, 1H), 3.69 (s, 3H), 3.45 (m, 1H), 1.85-1.45 (m, 6H), 1.40 (d, J=7.05Hz, 3H).

Diastereomer 2 (Minor): ¹H NMR (400 MHz, CDCl₃) δ 4.66 (t, 1H), 4.16 (q, 1H),
3.8 (m, 1H), 3.69 (s, 3H), 3.45 (m, 1H), 1.85-1.45 (m, 6H), 1.35 (d, J=6.64Hz, 3H).

Example 1(b) - (2S)-2-(Tetrahydro-2H-pyran-2-yloxy)propan-1-ol:

Under a nitrogen atmosphere and with ice water cooling, a solution of **1(a)**
20 (136.6g, 726mmol) in 400mL of diethyl ether was added to a mixture of 1M lithium aluminum hydride (871mL, 1.2eq. 871mmol) in THF and 500mL of diethyl ether. This mixture was refluxed 2 hours and allowed to stir and cool to RT overnight. After cooling to 5°C, 27mL of water was slowly added, followed by 500mL of diethyl ether, then 27mL of 15% (w/w) aqueous sodium hydroxide. This thick suspension was then
25 filtered through a sintered glass funnel, dried with MgSO₄ and concentrated to 54.8g of yellow liquid. The crude product was distilled under high vacuum (<1mbar), collecting fractions boiling at 50-65°C yielding to 53.8g of **1(b)**.

Diastereomer 1 (Major): ¹H NMR (400 MHz, DMSO-d₆) δ 4.68 (m, 1H), 4.54 (t, 1H), 3.78 (m, 1H), 3.62 (m, 1H), 3.39 (m, 1H), 3.31 (m, 1H) 3.25 (m, 1H), 1.75 – 1.32
30 (m, 6H), 1.04 (d, J=6.64Hz, 3H).

Diastereomer 2 (Minor): ^1H NMR (400 MHz, DMSO-d_6) δ 4.62 (m, 1H), 4.51 (t, 1H), 3.78 (m, 1H), 3.62 (m, 1H), 3.39 (m, 1H), 3.31 (m, 1H) 3.25 (m, 1H), 1.75 – 1.32 (m, 6H), 0.99 (d, $J=6.23\text{Hz}$, 3H).

Example 1(c) - (2S)-2-(Tetrahydro-2H-pyran-2-yloxy)propanal:

5 A 2 M solution of oxalyl chloride in CH_2Cl_2 (249mL, 1.5eq) was combined with 745mL of anhydrous CH_2Cl_2 and cooled under nitrogen atmosphere to -72°C . A solution of anhydrous dimethyl sulfoxide (70.7mL, 3eq. 77.8g, 996mmol) in 141mL of anhydrous CH_2Cl_2 was added dropwise. After stirring 15 minutes, a solution of **1(b)** (53.2g, 1eq. 332mmol) in 190mL anhydrous CH_2Cl_2 was added dropwise and the
10 suspension stirred for 1 hour. Triethylamine (139mL, 3eq., with about 1 to about 5 eq being an acceptable range) was added dropwise, the cooling bath removed and the reaction mixture allowed to warm to $+2^\circ\text{C}$. The solids were removed by filtration, the filtrate washed with 1200mL water, 1200mL brine, dried with MgSO_4 and concentrated to a brown oil. The crude aldehyde was vacuum distilled and the material boiling at
15 $70-78^\circ\text{C}/12\text{mbar}$ was collected yielding to 42.8g of **1(c)** as a yellowish liquid.

Diastereomer 1 (Major): ^1H NMR (400 MHz, CDCl_3) δ 9.63(s, 1H), 4.69 (m, 1H), 4.23 (q, 1H), 3.85 (m, 1H), 3.47 (m, 1H), 1.85-1.45 (m, 6H), 1.33 (d, $J=7.05\text{Hz}$, 3H).

Diastereomer 2 (Minor): ^1H NMR (400 MHz, CDCl_3) δ 9.63(s, 1H), 4.61 (m, 1H), 3.96 (q, 1H), 3.85 (m, 1H), 3.47 (m, 1H), 1.85-1.45 (m, 6H), 1.25 (d, $J=7.05\text{Hz}$, 3H).

20 **Example 1(d) - (2S)-2-(Tetrahydro-2H-pyran-2-yloxy)pentan-3-ol:**

Working under N_2 -atm, 30.3mL (1.2eq. 60.7mmol) of 2M ethylmagnesium chloride in THF was combined with 70mL of diethyl ether and cooled to -72°C . A solution of **1(c)** (8.0g, 1eq. 50.6mmol) in 10mL of diethyl ether was added dropwise. The resulting suspension was allowed to warm to $+3^\circ\text{C}$. After cooling to -15°C , 40ml
25 saturated aqueous ammonium chloride solution was added and the reaction mixture was allowed to warm-up to RT. The layers were separated, and the aqueous phase was extracted with 40mL diethyl ether. The organic layers were combined, washed with 40mL brine, dried with MgSO_4 and concentrated yielding 9.05g of crude product. The crude product was distilled under a high vacuum ($<1\text{mbar}$), collecting fractions
30 boiling at 66 to 78°C yielding 7.23g of **1(d)** as a clear liquid.

Diastereomer 1 (Major): ^1H NMR (400 MHz, DMSO- d_6) δ 4.61 (m, 1H), 4.38 (m, 1H), 3.75 (m, 1H), 3.44 (m, 1H), 3.39 (m, 1H), 3.20 (m, 1H), 1.68 (m, 1H) 1.57 (m, 1H), 1.41 (m, 5H), 1.21 (m, 1H), 1.06 (d, $J=6.64\text{Hz}$, 3H), 0.85 (t, 3H).

Diastereomer 2 (Minor): ^1H NMR (400 MHz, DMSO- d_6) δ 4.61 (m, 1H), 4.38 (m, 1H), 3.75 (m, 1H), 3.44 (m, 1H), 3.39 (m, 1H), 3.20 (m, 1H), 1.68 (m, 1H) 1.57 (m, 1H), 1.41 (m, 5H), 1.21 (m, 1H), 1.01 (d, $J=6.64\text{Hz}$, 3H), 0.85 (t, 3H).

Diastereomer 3 (Minor): ^1H NMR (400 MHz, DMSO- d_6) δ 4.61 (m, 1H), 4.35 (m, 1H), 3.75 (m, 1H), 3.52 (m, 1H), 3.39 (m, 1H), 3.20 (m, 1H), 1.68 (m, 1H) 1.57 (m, 1H), 1.41 (m, 5H), 1.21 (m, 1H), 1.03 (d, $J=6.64\text{Hz}$, 3H), 0.85 (t, 3H).

Diastereomer 4 (Minor): ^1H NMR (400 MHz, DMSO- d_6) δ 4.61 (m, 1H), 4.33 (m, 1H), 3.75 (m, 1H), 3.60 (m, 1H), 3.39 (m, 1H), 3.28 (m, 1H), 1.68 (m, 1H) 1.57 (m, 1H), 1.41 (m, 5H), 1.21 (m, 1H), 0.97 (d, $J=6.22\text{Hz}$, 3H), 0.85 (t, 3H).

Example 1(e) - (2S)-2-(Tetrahydro-2H-pyran-2-yloxy)pentan-3-one:

A 2 M solution of oxalyl chloride in CH_2Cl_2 (29mL, 1.5 eq. 76.8mmol) was combined with 87mL of anhydrous CH_2Cl_2 and cooled under a nitrogen atmosphere to -72°C . A solution of anhydrous dimethyl sulfoxide (8.18mL, 3eq. 115mmol) in 18.6mL of anhydrous CH_2Cl_2 was added dropwise. After stirring 15 minutes, a solution of **1(d)** (7.23g, 1eq., 38.4mmol) in 22mL anhydrous CH_2Cl_2 was added dropwise and the suspension stirred for 1 hour. Triethylamine (16mL, 3 eq. 115mmol) was added dropwise, the cooling bath removed and the reaction mixture allowed to warm to RT. The solids were removed by filtration, the filtrate washed with 140mL water, 140mL brine, dried with MgSO_4 and concentrated to a brown oil. The crude product was distilled under high vacuum ($<1\text{mbar}$), collecting fractions boiling at $50\text{-}100^\circ\text{C}$ yielding to 6.81g of **1(e)** as a yellowish liquid.

Diastereomer 1 (Major): ^1H NMR (400 MHz, DMSO- d_6) δ 4.59 (m, 1H), 4.20 (q, 1H), 3.77 (m, 1H), 3.44 (m, 1H), 2.7-2.4 (m, 2H), 1.71 (m, 2H), 1.48 (m, 4H), 1.26 (d, $J=6.85\text{Hz}$, 3H), 0.93 (t, 3H).

Diastereomer 2 (Minor): ^1H NMR (400 MHz, DMSO- d_6) δ 4.64 (m, 1H), 4.05 (q, 1H), 3.77 (m, 1H), 3.44 (m, 1H), 2.7-2.4 (m, 2H), 1.71 (m, 2H), 1.48 (m, 4H), 1.18 (d, $J=6.54\text{Hz}$, 3H), 0.93 (t, 3H).

Example 1(f) - (2S)-3-(5-Bromopyridin-2-yl)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-ol:

2,5-Dibromopyridine (127mg, 0.537mmol, 1eq.) and **1(e)** (100mg, 0.537mmol, 1eq.) were dissolved in 610µL of toluene and the resulting solution cooled to 0°C under nitrogen. 2.5 M n-Butyllithium in hexanes (228µL, 1.06eq.) was then added dropwise and the resulting mixture was stirred for 5 min until the reaction was quenched by addition of 37µL methanol. The reaction solution was extracted with water (1mL), the organic layer was separated and dried with MgSO₄. After solvent evaporation 175mg **1(f)** was obtained as brown oil.

10 Diastereomer 1 (Major): LC-MS (ESI): m/z=344.2 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 8.61 (s, 1H), 7.98 (d, 1H), 7.54 (d, 1H), 4.85 (s, 1H), 4.63 (m, 1H), 3.92 (q, 1H), 3.85 (m, 1H), 3.38 (m, 1H), 1.96(m, 1H), 1.85-1.15 (m, 7H), 0.81 (d, J=6.22Hz, 3H), 0.50 (t, 3H).

Diastereomer 2 (Minor): LC-MS (ESI): m/z=344.2 [M+H]⁺

15 ¹H NMR (400 MHz, DMSO-d₆) δ 8.61 (s, 1H), 7.96 (d, 1H), 7.52 (d, 1H), 4.92 (s, 1H), 4.63 (m, 1H), 3.92 (q, 1H), 3.85 (m, 1H), 3.38 (m, 1H), 1.96(m, 1H), 1.85-1.15 (m, 7H), 1.06 (d, J=6.22Hz, 3H), 0.50 (t, 3H).

Diastereomer 3 (Minor): LC-MS (ESI): m/z=344.2 [M+H]⁺

20 ¹H NMR (400 MHz, DMSO-d₆) δ 8.61 (s, 1H), 8.00 (d, 1H), 7.57 (d, 1H), 4.88 (s, 1H), 4.63 (m, 1H), 3.92 (q, 1H), 3.85 (m, 1H), 3.38 (m, 1H), 1.96(m, 1H), 1.85-1.15 (m, 7H), 0.97 (d, J=6.22Hz, 3H), 0.50 (t, 3H).

Diastereomer 4 (Minor): LC-MS (ESI): m/z=344.2 [M+H]⁺

25 ¹H NMR (400 MHz, DMSO-d₆) δ 8.61 (s, 1H), 7.97 (d, 1H), 7.54 (d, 1H), 4.79 (s, 1H), 4.63 (m, 1H), 3.92 (q, 1H), 3.85 (m, 1H), 3.38 (m, 1H), 1.96(m, 1H), 1.85-1.15 (m, 7H), 0.71 (d, J=6.22Hz, 3H), 0.50 (t, 3H).

Example 1(g) - (R)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2S)-3-hydroxy-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-yl)pyridin-3-yl)pyrrolidin-2-one:

30 **1(f)** (3.66g, 1.eq. 10.6mmol) and (R)-3-(2-(4-methylpiperazin-1-yl)benzyl)pyrrolidin-2-one (3.48g, 1.2eq. 12.8mmol) were combined and stirred in 14.6mL of dry toluene. For the preparation of the pyrrolidin-2-one, see, e.g., WO

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2005-090300, incorporated herein by reference. CuI (202mg, 0.1eq 1.06mmol) was added followed by potassium carbonate (2.93g, 2.0eq.), *N,N'*-dimethylethylenediamine (226μL, 187mg, 0.20eq. 2.12mmol), and finally, 183μL of water. The thick suspension was refluxed for 2 days, at which point HPLC indicated the reaction to be complete. The mixture was filtered through a Celite® bed, the filtrate was washed 2 times with an equal amount of water then brine, dried with MgSO₄ and concentrated to 6.5g of dark oil. The crude material was chromatographed on a silica gel column, eluting with 95:5 = acetonitrile:28-30% aqueous ammonium hydroxide to yield 4.8g of **1(g)**.

10 Diastereomer 1: LC-MS (ESI): $m/z=537.5$ $[M+H]^+$

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (d, 1H), 8.09 (dd, 1H), 7.55 (d, 1H), 7.22 (d, 1H), 7.17 (dd, 1H), 7.12 (d, 1H), 7.00 (dd, 1H), 4.76 (s, 1H), 4.64 (m, 1H), 3.88 (q, 1H), 3.71 (m, 3H), 3.39 (m, 1H), 3.18 (m, 1H), 3.00 (dd, 1H), 2.79 (m, 4H), 2.64 (dd, 1H), 2.42 (bs, 4H), 2.17 (s, 3H), 2.00 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.62 (m, 1H), 1.38 (m, 6H), 0.82 (d, *J*=6.23Hz, 3H), 0.49 (t, 3H).

15 Diastereomer 2: LC-MS (ESI): $m/z=537.5$ $[M+H]^+$

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 (d, 1H), 8.09 (dd, 1H), 7.57 (d, 1H), 7.22 (d, 1H), 7.17 (dd, 1H), 7.12 (d, 1H), 7.00 (dd, 1H), 5.01 (s, 1H), 4.60 (m, 1H), 3.88 (q, 1H), 3.71 (m, 3H), 3.39 (m, 1H), 3.18 (m, 1H), 3.00 (dd, 1H), 2.79 (m, 4H), 2.64 (dd, 1H), 2.42 (bs, 4H), 2.17 (s, 3H), 2.00 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.62 (m, 1H), 1.38 (m, 6H), 0.90 (d, *J*=6.23Hz, 3H), 0.49 (t, 3H).

20 Diastereomer 3: LC-MS (ESI): $m/z=537.5$ $[M+H]^+$

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (d, 1H), 8.09 (dd, 1H), 7.55 (d, 1H), 7.22 (d, 1H), 7.17 (dd, 1H), 7.12 (d, 1H), 7.00 (dd, 1H), 4.95 (s, 1H), 4.64 (m, 1H), 3.88 (q, 1H), 3.71 (m, 3H), 3.39 (m, 1H), 3.18 (m, 1H), 3.00 (dd, 1H), 2.79 (m, 4H), 2.64 (dd, 1H), 2.42 (bs, 4H), 2.17 (s, 3H), 2.00 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.62 (m, 1H), 1.38 (m, 6H), 1.03 (d, *J*=6.23Hz, 3H), 0.49 (t, 3H).

25 Diastereomer 4: LC-MS (ESI): $m/z=537.5$ $[M+H]^+$

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 (d, 1H), 8.09 (dd, 1H), 7.57 (d, 1H), 7.22 (d, 1H), 7.17 (dd, 1H), 7.12 (d, 1H), 7.00 (dd, 1H), 4.69 (s, 1H), 4.60 (m, 1H), 3.88 (q, 1H), 3.71 (m, 3H), 3.39 (m, 1H), 3.18 (m, 1H), 3.00 (dd, 1H), 2.79 (m, 4H), 2.64 (dd, 1H), 2.42 (bs, 4H), 2.17 (s, 3H), 2.00 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.62 (m, 1H), 1.38 (m, 6H), 0.90 (d, *J*=6.23Hz, 3H), 0.49 (t, 3H).

1H), 2.42 (bs, 4H), 2.17 (s, 3H), 2.00 (m, 1H), 1.90 (m, 1H), 1.74 (m, 1H), 1.62 (m, 1H), 1.38 (m, 6H), 0.71 (d, J=6.23Hz, 3H), 0.49 (t, 3H).

Example 1(h) - (R)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2S)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one:

5 **1(g)** (230mg, 0.429mmol) was dissolved in 2mL water / 4mL glacial acetic acid and heated in an oil bath at 45 °C. After 2 h the solvent was evaporated and the residue chromatographed on silica gel using 97.5:2.5 = acetonitrile: 28-30% aqueous ammonium hydroxide as eluent. After solvent evaporation, an oil was obtained. This was co-evaporated with 2ml diethyl ether leading to 92mg of **1(h)** as yellowish solids.

10 Diastereomer 1: LC-MS (ESI): m/z=453.5 [M+H]⁺

¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, 1H), 8.33 (dd, 1H), 7.44 (d, 1H), 7.21 (d, 2H), 7.15 (d, 1H), 7.05 (dd, 1H), 3.95 (q, 1H), 3.73 (m, 2H), 3.36 (dd, 1H), 3.08 (m, 1H), 2.94 (m, 4H), 2.78(dd, 1H), 2.59 (bs, 4H), 2.35 (s, 3H), 2.13 (m, 1H), 1.89 (m, 3H), 1.24 (s, 1H), 1.19 (s, 1H), 1.47 (d, J=6.64Hz, 3H), 0.65 (t, 3H).

15 Diastereomer 2: LC-MS (ESI): m/z=453.5 [M+H]⁺

¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, 1H), 8.33 (dd, 1H), 7.30 (d, 1H), 7.21 (d, 2H), 7.15 (d, 1H), 7.05 (dd, 1H), 3.87 (q, 1H), 3.73 (m, 2H), 3.40 (dd, 1H), 3.08 (m, 1H), 2.94 (m, 4H), 2.78(dd, 1H), 2.59 (bs, 4H), 2.35 (s, 3H), 2.13 (m, 1H), 1.89 (m, 3H), 1.24 (s, 1H), 1.19 (s, 1H), 0.90 (d, J=6.64Hz, 3H), 0.65 (t, 3H).

20 **Example 1(i) - (R)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2S,3R)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one, 1(i)(a), and (R)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2S,3S)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one, 1(i)(b):**

25 **1(h)** was resolved into **1(i)** by chiral chromatography on a Chiralpak AD 10cm x 50cm column (Chiral Technologies Inc., Exton, PA). **1(h)** (1.95g) in methanol (15mL) was injected onto the column and eluted with heptane:ethanol = 60:40 at a flow rate of 300mL/min to give **1(i)(a)** and **1(i)(b)** essentially free of the other enantiomer.

30 (R)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2S,3R)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one: Retention time 40 min, LC-MS (ESI): m/z=453.5 [M+H]⁺

¹H NMR (600 MHz, DMSO-d₆) δ 8.81 (d, 1H), 8.11 (dd, 1H), 7.57 (d, 1H), 7.26 (d, 1H), 7.20 (dd, 1H), 7.15 (d, 1H), 7.04 (dd, 1H), 4.59 (s, 1H), 4.58 (s, 1H), 3.90 (m, 1H), 3.75 (m, 2H), 3.25 (dd, 1H), 3.03 (m, 1H), 2.82 (m, 4H), 2.68 (dd, 1H), 2.45 (bs, 4H), 2.21 (s, 3H), 2.04 (m, 1H), 1.94 (q, 2H), 1.78 (m, 1H), 0.77 (d, 3H), 0.53 (t, 3H).

5 ¹³C NMR (150 MHz, DMSO-d₆) δ 175.6, 158.8, 151.8, 138.6, 134.7, 134.0, 130.1, 127.2, 126.1, 123.9, 120.7, 120.3, 79.1, 72.1, 55.2, 52.2, 45.8, 45.4, 43.5, 31.6, 29.6, 17.6, 7.7.

(*R*)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2*S*,3*S*)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one: Retention time 85 min, LC-MS (ESI): m/z=453.5
10 [M+H]⁺

¹H NMR (300 MHz, DMSO-d₆) δ 8.85 (d, 1H), 8.14 (dd, 1H), 7.60 (d, 1H), 7.30 (d, 1H), 7.24 (dd, 1H), 7.18 (d, 1H), 7.10 (dd, 1H), 4.95 (bs, 1H), 4.59 (bs, 1H), 3.82 (m, 1H), 3.78 (m, 2H), 3.25 (dd, 1H), 3.03 (m, 1H), 2.82 (bs, 4H), 2.68 (dd, 1H), 2.45 (bs, 4H), 2.21 (s, 3H), 2.00 (m, 2H), 1.87 (m, 2H), 0.93 (d, 3H), 0.53 (t, 3H).

15 To verify the absolute stereochemistry of the diastereomers Examples 1(i)(a) and 1(i)(b), the resolved diastereomers were derivatized to carbonates using 1,1'-carbonyldiimidazole as derivatizing agent.

(*R*)-3-(2-(4-methylpiperazin-1-yl)benzyl)-1-(6-((4*R*,5*S*)-4-ethyl-5-methyl-2-oxo-1,3-dioxolan-4-yl)pyridin-3-yl)pyrrolidin-2-one:

20 1(i)(a) (100mg, 0.22mmol) was dissolved 1mL anhydrous CH₂Cl₂ under nitrogen and 1,1'-carbonyldiimidazole (43mg, 1.2eq. 0.27mmol) was added. The reaction mixture was stirred 16h, 1ml water was added and the organic phase was separated, dried with MgSO₄, filtered and after solvent evaporation, 100mg of (*R*)-3-(2-(4-methylpiperazin-1-yl)benzyl)-1-(6-((4*R*,5*S*)-4-ethyl-5-methyl-2-oxo-1,3-dioxolan-
25 4-yl)pyridin-3-yl)pyrrolidin-2-one was obtained as oil.

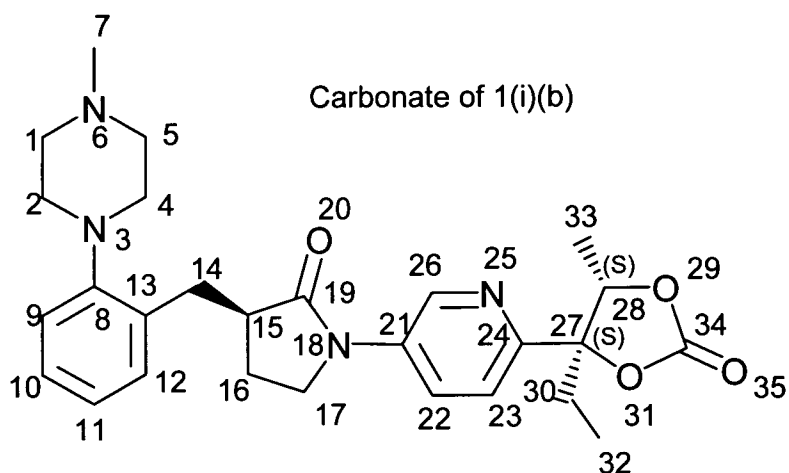
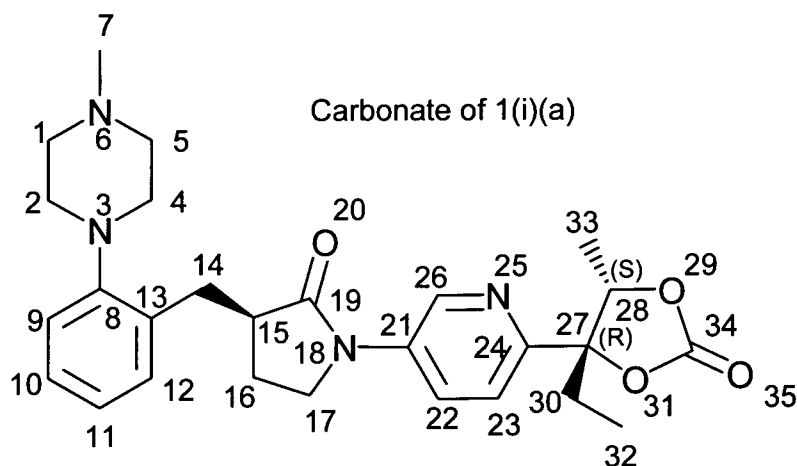
(*R*)-3-(2-(4-methylpiperazin-1-yl)benzyl)-1-(6-((4*S*,5*S*)-4-ethyl-5-methyl-2-oxo-1,3-dioxolan-4-yl)pyridin-3-yl)pyrrolidin-2-one:

30 1(i)(b) (100mg, 0.22mmol) was dissolved 1mL anhydrous CH₂Cl₂ under nitrogen and 43mg (1.2eq. 0.27mmol) of 1,1'-carbonyldiimidazole was added. The reaction mixture was stirred 16h, 1ml water was added and the organic phase was separated, dried with MgSO₄, filtered and after solvent evaporation, the crude

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products was obtained. This was chromatographed on silica gel using 25% isopropanol in 75% acetonitrile as eluent. After combining the appropriate fractions 50mg of (*R*)-3-(2-(4-methylpiperazin-1-yl)benzyl)-1-(6-((4*S*,5*S*)-4-ethyl-5-methyl-2-oxo-1,3-dioxolan-4-yl)pyridin-3-yl)pyrrolidin-2-one was obtained as oil.

5 For the discussions of the data, the following numbering was used:



NMR Sample Preparation

Approximately 10 mg of each sample were dissolved in 0.8 mL of 99.8% chloroform-*d* (CDCl₃) containing 0.05% w/w tetramethylsilane (TMS). The 1D proton spectrum for 1(i)(b) was referenced using the internal standard, TMS, and set equal to 0.00 ppm. The 1D proton spectrum for 1(i)(a) was referenced using the residual protonated solvent, and set equal to 7.27 ppm. The 1D carbon spectrum for 1(i)(b)

was referenced using the solvent and set equal to 77.2 ppm. The 1D carbon spectrum for 1(i)(a) was referenced using the internal standard, TMS, and set equal to 0.00 ppm.

Instrumentation

5 All 1D and 2D data for 1(i)(b) were collected at 298K using a Bruker-Biospin 5mm gradient broadband inverse probe on a Bruker-Biospin DRX NMR spectrometer operating at 500 MHz. All 1D and 2D data for 1(i)(a) were collected at 298K using a Bruker-Biospin 5mm gradient broadband observe probe on a Bruker-Biospin AV NMR spectrometer operating at 600 MHz.

10 1D Data for the carbonate derivative of Example 1(i)(a)*:

Carbon #	Carbon (PPM)	No. of H atoms Attached	Proton (PPM)	Proton Multiplicity
1	55.2	2	2.88	m
2	51.6	2	3.14	m
4	51.6	2	3.14	m
5	55.2	2	2.88	m
7	45.2	3	2.55	s
8	150.0	0		
9	124.9 (121.1)	1	7.10 (7.23)	m
10	127.9	1	7.26	m
11	121.1 (124.9)	1	7.23 (7.10)	m
12	130.4	1	7.24	m
13	134.6	0		
14	32.7	2	3.45 2.73	d dd
15	44.4	1	3.07	m

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16	24.8	2	1.94 2.20	m m
17	46.0	2	3.76	dd
19	176.3	0		
21	135.5	0		
22	126.6	1	8.16	d
23	120.7	1	7.58	d
24	151.6	0		
26	140.1	1	8.93	s
27	89.7	0		
28	82.2	1	4.81	q
30	32.2	2	2.16 2.42	m m
32	7.4	3	0.84	t
33	17.2	3	1.00	d
34	154.1	0		

1D Data for the carbonate derivative of Example (i)(b)*:

Carbon #	Carbon (PPM)	No. of H atoms Attached	Proton (PPM)	Proton Multiplicity
1	55.5	2	2.83	m
2	52.0	2	3.10	m
4	52.0	2	3.10	m
5	55.5	2	2.83	m
7	45.6	3	2.51	s
8	151.3	0		
9	125.1 (121.3)	1	7.09 (7.20)	m
10	128.0	1	7.24	m
11	121.3 (125.1)	1	7.20 (7.09)	m
12	130.6	1	7.21	m
13	134.8	0		
14	32.8	2	3.43 2.74	dd dd
15	44.5	1	3.06	m
16	24.9	2	2.19 2.08	m m
17	46.2	2	3.74	dd
19	176.5	0		
21	135.9	0		
22	127.0	1	8.13	dd
23	120.1	1	7.56	d
24	154.4 (154.2)	0		
26	140.7	1	8.88	d
27	89.2	0		

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28	82.0	1	4.90	q
30	27.1	2	2.10	m
32	7.7	3	0.78	t
33	15.2	3	1.61	d
34	154.2 (154.4)	0		

*s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet, m=multiplet

The values in parenthesis indicate alternative peak assignments of these nuclei.

5 The 1D proton and carbon spectra were consistent with the structures of 1(i)(a) and 1(i)(b). The 2D spectra showed the expected vicinal and geminal ^1H - ^{13}C and ^1H - ^1H correlations for 1(i)(a) and 1(i)(b).

The stereochemistry at C27, relative to C28, of these two compounds was investigated using the ^1H - ^1H NOESY data for each compound. The reduced degrees of rotational freedom of the carbonate, compared to the free diol, allowed the ^1H - ^1H NOESY data to be used to determine the relative stereochemistry at C27. When starting with (S)-methyl lactate, the stereochemistry at C28 has the "S" configuration. For 1(i)(a), the ^1H - ^1H NOESY data shows key correlations of H28 to H30 and H32, respectively. For 1(i)(b), the ^1H - ^1H NOESY data shows a key correlation between H30 and H33. These data, and the reported configuration at C28, allow the determination of the relative stereochemistry at C27 as shown in structures for 1(i)(a) and 1(i)(b).

Example 2(a) - (S)-Methyl 2-((2-(trimethylsilyl)ethoxy)methoxy)propanoate:

(S)-Methyl lactate (10.9g, 105mmol) was mixed with *N,N*-diisopropylethylamine (16.2g, 1.2eq. 126mmol) in 100mL of anhydrous CH_2Cl_2 and cooled to 3°C under N_2 -atm. (2-(Chloromethoxy)ethyl)trimethylsilane (20.9g, 1.2eq. 126mmol) was added dropwise and the cooling bath was removed and stirred for 16h at RT. The mixture was quenched with 100mL of 1M aqueous HCl, the organic layer was separated, washed with 100mL water, 100mL brine, dried with MgSO_4 , filtered through a paper filter and after solvent evaporation 26.6g of **2(a)** was obtained as a yellowish liquid, which was used without further purification.

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^1H NMR (400 MHz, DMSO- d_6) δ 4.61 (dd, 2H), 4.12 (q, 1H), 3.60 (s, 3H), 3.51 (m, 2H), 1.25 (d, $J=7.07\text{Hz}$, 3H), 0.81 (m, 2H), -0.03 (s, 9H).

Example 2(b) - (S)-2-((2-(Trimethylsilyl)ethoxy)methoxy)propan-1-ol

2(a) (5.10g) was mixed with 20mL anhydrous THF and 20mL (40mmol) borane – dimethylsulfide complex, 2M solution in THF, was added dropwise. The reaction solution was refluxed 2 h, allowed to cool to RT and 10mL water was added. The solvent was evaporated and the residue partitioned between 50mL CH_2Cl_2 – 50mL water, the organic phase was separated and washed with 50mL water, 50mL brine, dried with MgSO_4 and filtered through a paper filter. After solvent evaporation, 4.41g **2(b)** was obtained as a colourless liquid.

^1H NMR (400 MHz, CDCl_3) δ 4.75 (ddd, $J = 2.08, 7.06, 18.43$, 2H), 3.72 (m, 2H), 3.55 (m, 2H), 3.46 (m, 1H), 2.78 (bs, 1H), 1.14 (dd, $J = 2.08, 6.23\text{Hz}$, 3H), 0.93 (m, 2H), 0.00 (s, 9H).

Example 2(c) - (S)-2-((2-(Trimethylsilyl)ethoxy)methoxy)propanal:

A 2 M solution of oxalyl chloride in CH_2Cl_2 (15.6mL, 1.5eq. 31.2mmol) was combined with 50mL of anhydrous CH_2Cl_2 and cooled under nitrogen atmosphere to -72°C . A solution of anhydrous dimethyl sulfoxide (4.44mL, 3eq. 62.5mmol, 4.88g) in 10mL of anhydrous CH_2Cl_2 was added dropwise. After stirring 15 minutes, a solution of **2(b)** (4.30g, 20.8mmol) in 12mL anhydrous CH_2Cl_2 was added dropwise and the suspension was stirred for 1 hour. Triethylamine (14.5mL, 5eq. 104mmol) was added dropwise, the cooling bath removed and the reaction mixture allowed to warm to RT. The solids were removed by filtration, the filtrate washed with 150mL water, 150mL brine, dried with MgSO_4 and concentrated to oil. The crude aldehyde was distilled under high vacuum ($<1\text{mbar}$), and the material boiling at 67 to 92°C was collected yielding 1.54g of **2(c)** as a colourless liquid.

^1H NMR (400 MHz, CDCl_3) δ 9.62 (s, 1H), 4.75 (dd, $J = 7.06$, 2H), 4.01 (q, 1H), 3.69 (m, 1H), 3.62 (m, 1H), 3.46 (m, 1H), 1.29 (d, $J = 7.01\text{Hz}$, 3H), 0.91 (m, 2H), -0.03 (s, 9H).

Example 2(d) - (2S)-2-((2-(Trimethylsilyl)ethoxy)methoxy)pentan-3-ol:

Working under N_2 -atm, 6.64mL (1.2eq. 13.3mmol) of 2M ethylmagnesium chloride in THF was combined with 15mL of diethyl ether and cooled to -72°C . A

solution of 2.26g (1eq. 11.1mmol) of **2(c)** in 2mL of diethyl ether was added dropwise. The resulting suspension was allowed to warm to +0°C. After cooling to -25°C, 9ml saturated aqueous ammonium chloride solution was added and the reaction mixture was allowed to warm-up to RT. The layers were separated, the organic phase was washed with 15mL brine, dried with MgSO₄ and concentrated yielding 2.71g of **2(d)** as a slightly yellowish liquid.

Diastereomer 1: ¹H NMR (400 MHz, CDCl₃) δ 4.70 (m, 2H), 3.68 (m, 1H), 3.65 (m, 2H), 3.32 (m, 1H), 2.32 (bs, 1H), 1.54 (m, 1H) 1.41 (m, 1H), 1.15 (dd, J = 1.66, 6.23Hz, 3H), 0.97 (t, 3H), 0.92 (m, 2H), -0.03 (s, 9H).

Diastereomer 2: ¹H NMR (400 MHz, CDCl₃) δ 4.75 (m, 2H), 3.68 (m, 1H), 3.65 (m, 2H), 3.52 (m, 1H), 2.32 (bs, 1H), 1.41 (m, 2H), 1.11 (dd, J = 1.66, 6.22Hz, 3H), 0.97 (t, 3H), 0.92 (m, 2H), -0.03 (s, 9H).

Example 2(e) - (S)-2-((2-(Trimethylsilyl)ethoxy)methoxy)pentan-3-one:

A 2 M solution of oxalyl chloride in CH₂Cl₂ (8.61mL, 1.5eq. 17.2mmol) was combined with 25mL of anhydrous CH₂Cl₂ and cooled under a nitrogen atmosphere to -72°C. A solution of anhydrous dimethyl sulfoxide (2.44mL, 3eq. 34.4mmol, 2.69g) in 5.5mL of anhydrous CH₂Cl₂ was added dropwise. After stirring 15 minutes, a solution of **2(d)** (2.69g, 1eq. 11.5mmol) in 6.5mL anhydrous CH₂Cl₂ was added dropwise and the suspension was stirred for 1 hour. Triethylamine (4.8mL, 3eq. 34.2mmol, 3.48 g) was added dropwise, the cooling bath removed and the reaction mixture allowed to warm to RT. The solids were removed by filtration, the filtrate washed with 80mL water, 80mL brine, dried with MgSO₄ and concentrated to a brown liquid. The crude product was distilled under high vacuum (<1mbar), collecting fractions boiling at 80-93°C yielding to 1.54g of **2(e)** as a yellowish liquid.

¹H NMR (400 MHz, CDCl₃) δ 4.71 (d, 1H), 4.65 (d, 1H), 4.13 (q, 1H), 3.58 (dd, 2H), 2.54 (m, 2H), 1.30 (dd, J = 1.24, 6.64Hz, 3H), 1.04 (t, 3H), 0.91 (m, 2H), -0.03 (s, 9H).

Example 2(f) - (2S)-3-(5-Bromopyridin-2-yl)-2-((2-(trimethylsilyl)ethoxy)methoxy)pentan-3-ol:

2,5-Dibromopyridine (102mg, 0.435mmol, 1eq.) and **2(e)** (101mg, 0.435mmol, 1eq.) were dissolved in 495μL of toluene and the resulting solution cooled to - 0°C

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under nitrogen. 2.5 M n-Butyllithium (184 μ L, 1.06eq.) in hexanes was then added dropwise and the resulting mixture was stirred for 5 min until the reaction was quenched by addition of 30 μ L methanol. The reaction solution was extracted with water (1mL), the organic layer was separated and dried with MgSO₄. After solvent

5 evaporation 137mg **2(f)** was obtained as a brown oil.

Diastereomer 1: LC-MS (ESI): m/z=390.2 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 8.60 (d, 1H), 7.96 (m, 1H), 7.54 (d, 1H), 4.93 (s, 1H), 4.40 (d, J = 6.64, 1H), 4.26 (d, J = 6.64, 1H), 3.95 (q, 1H), 3.54 (m, 2H), 1.86 (m, 1H), 1.59 (m, 1H), 1.05 (d, J = 6.23, 3H), 0.82 (m, 1H), 0.65 (m, 1H), 0.45 (t, 3H), -

10 0.05 (s, 9H).

Diastereomer 2: LC-MS (ESI): m/z=390.2 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 8.60 (d, 1H), 7.96 (m, 1H), 7.51 (d, 1H), 4.89 (s, 1H), 4.65 (d, J = 7.06, 1H), 4.60 (d, J = 7.06, 1H), 3.95 (q, 1H), 3.05 (m, 1H), 2.97 (m, 1H), 1.87 (m, 2H), 0.82 (m, 1H), 0.75 (d, J = 6.23, 3H), 0.65 (m, 1H), 0.45 (t, 3H), -

15 0.09 (s, 9H).

Example 2(g) - (R)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2S)-3-hydroxy-2-((2-(trimethylsilyl)ethoxy)methoxy)pentan-3-yl)pyridin-3-yl)pyrrolidin-2-one:

2(f) (60mg, 1eq. 0.92mmol) and (R)-3-(2-(4-methylpiperazin-1-yl)benzyl)pyrrolidin-2-one (303mg, 1.2eq. 1.11mmol) were combined and stirred in 935 μ L of dry toluene. Cul (18mg, 0.1eq 0.092mmol) was added followed by potassium carbonate (255mg, 2.0eq. 1.84mmol), N,N'-dimethylethylenediamine (20 μ L, 16 mg, 0.20eq. 0.184mmol), and 47 μ L of water. The thick suspension was refluxed for 22 h, at which point HPLC indicated the reaction to be complete. The

20 mixture was filtered through a Celite® bed, the filtrate was washed with 1mL water, 1mL brine, dried with MgSO₄ and concentrated to 632mg of a dark oil. The crude material was chromatographed on a silica gel column, eluting with 95:5 = acetonitrile:28-30% aqueous ammonium hydroxide to yield 446mg of **2(g)** as a clear oil.

Diastereomer 1: LC-MS (ESI): m/z=583.5 [M+H]⁺

30

¹H NMR (400 MHz, CDCl₃) δ 8.84 (d, J = 2.49, 1H), 8.07 (t, 1H), 7.55 (d, J = 4.15, 1H), 7.22 (d, 1H), 7.17 (dd, 1H), 7.11 (d, 1H), 7.00 (dd, 1H), 4.94 (s, 1H), 4.43 (d, J = 7.06, 1H), 4.29 (d, J = 7.06, 1H), 3.94 (d, J = 6.23, 1H), 3.71 (m, 2H), 3.20 (m, 1H), 3.09 (m, 1H), 3.00 (m, 2H), 2.79 (bs, 4H), 2.63, (dd, 1H), 2.44 (bs, 4H), 2.18 (s, 3H), 1.99 (m, 1H), 1.90 (m, 1H), 1.82 (m, 1H), 1.61 (m, 1H), 1.02 (d, J = 6.23Hz, 3H), 0.82 (m, 1H), 0.69 (m, 1H), 0.46, (q, 3H), -0.12 (s, 9H).

Diastereomer 2: LC-MS (ESI): m/z=583.5 [M+H]⁺

¹H NMR (400 MHz, CDCl₃) δ 8.80 (d, J = 2.49, 1H), 8.10 (t, 1H), 7.54 (d, J = 4.15, 1H), 7.22 (d, 1H), 7.17 (dd, 1H), 7.11 (d, 1H), 7.00 (dd, 1H), 4.79 (s, 1H), 4.66 (d, J = 7.06, 1H), 4.60 (d, J = 7.06, 1H), 3.94 (d, J = 6.23, 1H), 3.71 (m, 2H), 3.20 (m, 1H), 3.09 (m, 1H), 3.00 (m, 2H), 2.79 (bs, 4H), 2.63, (dd, 1H), 2.44 (bs, 4H), 2.18 (s, 3H), 1.99 (m, 1H), 1.90 (m, 1H), 1.82 (m, 1H), 1.61 (m, 1H), 0.82 (m, 1H), 0.76 (d, J = 6.23Hz, 3H), 0.69 (m, 1H), 0.46, (q, 3H), -0.02 (s, 9H).

Example 2(h) - (R)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2S)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one:

2(g) (31mg, 0.053mmol) was dissolved to 300μL THF, 55mg (4eq. 0.212mmol) tetrabutylammonium fluoride hydrate was added and heated for 24h at 50°C. Solvent was evaporated and the residue was chromatographed on silica gel using 97.5:2.5 = acetonitrile:28-30% aqueous ammonium hydroxide as eluent. After solvent evaporation, 19mg of **2(h)** was obtained as a colourless oil.

Diastereomer 1: LC-MS (ESI): m/z=453.5 [M+H]⁺

¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, 1H), 8.33 (dd, 1H), 7.44 (d, 1H), 7.21 (d, 2H), 7.15 (d, 1H), 7.05 (dd, 1H), 3.95 (q, 1H), 3.73 (m, 2H), 3.36 (dd, 1H), 3.08 (m, 1H), 2.94 (m, 4H), 2.78(dd, 1H), 2.59 (bs, 4H), 2.35 (s, 3H), 2.13 (m, 1H), 1.89 (m, 3H), 1.24 (s, 1H), 1.19 (s, 1H), 1.47 (d, J=6.64Hz, 3H), 0.65 (t, 3H).

Diastereomer 2: LC-MS (ESI): m/z=453.5 [M+H]⁺

¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, 1H), 8.33 (dd, 1H), 7.30 (d, 1H), 7.21 (d, 2H), 7.15 (d, 1H), 7.05 (dd, 1H), 3.87 (q, 1H), 3.73 (m, 2H), 3.40 (dd, 1H), 3.08 (m, 1H), 2.94 (m, 4H), 2.78(dd, 1H), 2.59 (bs, 4H), 2.35 (s, 3H), 2.13 (m, 1H), 1.89 (m, 3H), 1.24 (s, 1H), 1.19 (s, 1H), 0.90 (d, J=6.64Hz, 3H), 0.65 (t, 3H).

2(h) was resolved into **2(i)** by chiral chromatography as discussed for Example **1(i)**.

Example 3(a) - (S)-Methyl 2-(tert-butyldiphenylsilyloxy)propanoate:

(S)-Methyl lactate (3.27g, 31.4mmol) was mixed with imidazole (2.63g, 1.25eq. 39.3mmol) in 25mL of anhydrous *N,N*-dimethylformamide at RT under N₂-atm. *tert*-Butyldiphenylsilyl chloride (10.36g, 1.2eq. 37.7mmol) was added dropwise and stirred for 16 h at RT. 150mL Diisopropyl ether was added and the mixture was extracted with 100mL of 1M aqueous HCl, 100mL water, 100mL brine, dried with MgSO₄, filtered through a paper filter and after solvent evaporation 13.37g of crude product was obtained, which was chromatographed on Silica gel using hexanes: ethyl acetate = 95:5 as eluent returning 9.20g of **3(a)** as a colorless oil.

¹H NMR (400 MHz, DMSO-d₆) δ 7.55 (d, 4H), 7.40 (m, 6H), 4.20 (q, 1H), 3.46 (s, 3H), 1.26 (d, J=6.64Hz, 3H), 0.99 (s, 9H).

Example 3(b) - (S)-2-(tert-Butyldiphenylsilyloxy)propan-1-ol:

3(a) (4.20g, 12.3 mmol) was mixed with 25mL anhydrous THF and 12.5mL (2 eq. 25mmol) borane–dimethylsulfide complex, 2 M solution in THF, was added dropwise. The reaction solution was refluxed 2h, let cool down to RT and 10mL water was added. The solvent was evaporated and the residue partitioned between 50mL CH₂Cl₂ – 50mL water, the organic phase was separated and washed with 50mL water, 50mL brine, dried with MgSO₄ and filtered through a paper filter. After solvent evaporation, 4.30g of crude product was obtained, which was chromatographed on Silica gel using hexanes: ethyl acetate = 9:1 as eluent returning 3.16g of **3(b)** as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.66 (m, 4H), 7.37 (m, 6H), 3.93 (m, 1H), 3.49 (dd, J = 3.32, 11.21Hz, 1H), 3.49 (dd, J = 5.40, 10.79Hz, 1H), 1.26 (d, J=6.64Hz, 3H), 1.89 (bs, 1H), 1.05 (s, 9H), 1.03 (d, J = 6.23Hz, 3H).

Example 3(c) - (S)-2-(tert-Butyldiphenylsilyloxy)propanal:

A 2 M solution of oxalyl chloride in CH₂Cl₂ (7.5mL, 1.5eq. 15mmol) was combined with 25mL of anhydrous CH₂Cl₂ and cooled under a nitrogen atmosphere to -72°C. A solution of 2.13mL (3eq. 30mmol, 2.35g) of anhydrous dimethyl sulfoxide in 4.8mL of anhydrous CH₂Cl₂ was added dropwise. After stirring 15 minutes, a solution

of 3.15g (10.0mmol) of **3(b)** in 5.8mL anhydrous CH₂Cl₂ was added dropwise and the suspension was stirred for 1 hour. Triethylamine (6.98mL, 5 eq. 50mmol, 5.07g) was added dropwise, the cooling bath removed and the reaction mixture allowed to warm to RT. The reaction mixture was washed with 150mL water, 150mL brine, dried with
5 MgSO₄ and concentrated to an oil. The crude aldehyde was stirred for 15 min in 10mL hexanes, the solids were removed by filtration and after solvent evaporation, 2.99 g of **3(c)** was obtained as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 9.62 (d, J = 5.40Hz, 1H), 7.63 (m, 4H), 7.37 (m, 6H), 4.07 (m, 1H), 1.20 (t, 3H), 1.08 (s, 9H).

10 **Example 3(d) - (2S)-2-(tert-Butyldiphenylsilyloxy)pentan-3-ol:**

Working under N₂-atm, 5.94mL (1.25eq. 11.9mmol) of 2M ethylmagnesium chloride in THF was combined with 13.5mL of diethyl ether and cooled to -72°C. A solution of **3(c)** (2.97g, 1eq. 9.5mmol) in 2.5mL of diethyl ether was added dropwise. The resulting suspension was allowed to warm to +0°C. After cooling to -25°C, 8mL
15 saturated aqueous ammonium chloride solution was added and the reaction mixture was allowed to warm-up to RT. The layers were separated, the organic phase was washed with 10mL brine, dried with MgSO₄ and concentrated yielding 3.07g of **3(d)** as a tan oil.

Diastereomer 1: ¹H NMR (400 MHz, CDCl₃) δ 7.66 (m, 4H), 7.37 (m, 6H), 3.72
20 (m, 1H), 3.48 (m, 1H), 1.90 (bs, 1H), 1.36 (m, 1H), 1.23 (m, 1H), 1.06 (s, 9H), 0.97 (d, 3H), 0.83 (t, 3H).

Diastereomer 2: ¹H NMR (400 MHz, CDCl₃) δ 7.66 (m, 4H), 7.37 (m, 6H), 3.80 (m, 1H), 3.27 (m, 1H), 1.90 (bs, 1H), 1.45 (m, 1H), 1.36 (m, 1H), 1.06 (s, 9H), 0.97 (d, 3H), 0.89 (t, 3H).

25 **Example 3(e) - (S)-2-(tert-Butyldiphenylsilyloxy)pentan-3-one:**

A 2 M solution of oxalyl chloride in CH₂Cl₂ (6.7mL, 1.5eq. 13.4mmol) was combined with 20mL of anhydrous CH₂Cl₂ and cooled under a nitrogen atmosphere to -72°C. A solution of anhydrous dimethyl sulfoxide (1.90mL, 3eq. 26.8mmol, 2.09g) in 4.3mL of anhydrous CH₂Cl₂ was added dropwise. After stirring 15 minutes, a solution
30 of **3(d)** (3.06g, 1eq. 8.93mmol) in 5mL anhydrous CH₂Cl₂ was added dropwise and the suspension was stirred for 1 hour. Triethylamine (3.74mL, 3eq. 26.8mmol, 2.71g) was

added dropwise, the cooling bath removed and the reaction mixture allowed to warm to RT. The solids were removed by filtration, the filtrate washed with 50mL water, 50mL brine, dried with MgSO₄ and concentrated to a tan oil. The crude product was chromatographed on Silica gel by using hexanes:ethyl acetate = 95:5 as eluent
5 yielding to 2.12g of **3(e)** as a slightly yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ 7.64 (m, 4H), 7.37 (m, 6H), 4.19 (q, 1H), 2.56 (q, 2H), 1.16 (d, J = 7.06Hz, 3H), 1.08 (s, 9H), 0.95 (t, 3H).

Example 3(f) - (2S)-3-(5-Bromopyridin-2-yl)-2-(tert-butyldiphenylsilyloxy)-pentan-3-ol:

10 2,5-Dibromopyridine (385mg, 1.62mmol, 1.1eq.) and **3(e)** (500mg, 1.47mmol, 1eq.) were dissolved in 1.67mL of toluene and the resulting solution cooled to – 0°C under N₂-atm. 2.5 M n-Butyllithium (622μL, 1.06eq.) in hexanes was then added dropwise and the resulting mixture was stirred for 5 min until the reaction was quenched by addition of 100μL methanol. The reaction solution was extracted with
15 water (3.5mL), the organic layer was separated and dried with MgSO₄. After solvent evaporation 729mg crude product was obtained as a brown oil. The crude product was chromatographed on Silica gel by using hexanes:ethyl acetate:triethylamine = 92:8:0.1 as eluent yielding to 473mg of **3(f)**.

Diastereomer 1 (Major): LC-MS (ESI): m/z=498.3 [M+H]⁺

20 ¹H NMR (400 MHz, DMSO-d₆) δ 8.55 (d, J = 2.49Hz, 1H), 7.93 (dd, J = 2.49, 8.30Hz, 1H), 7.54 (m, 4H), 7.50, (d, 1H), 7.40 (m, 6H), 4.87 (s, 1H), 4.15 (m, 1H), 2.26 (m, 1H), 1.95 (m, 1H), 1.11 (d, J = 6.64Hz, 3H), 1.00 (s, 9H), 0.79 (t, 3H).

Diastereomer 2 (Minor): LC-MS (ESI): m/z=498.3 [M+H]⁺

25 ¹H NMR (400 MHz, DMSO-d₆) δ 8.58 (d, J = 2.49Hz, 1H), 8.01 (dd, J = 2.49, 8.30Hz, 1H), 7.54 (m, 4H), 7.50, (d, 1H), 7.40 (m, 6H), 4.87 (s, 1H), 4.15 (m, 1H), 1.78 (m, 1H), 1.55 (m, 1H), 1.00 (s, 9H), 0.85 (d, J = 6.23Hz, 3H), 0.46 (t, 3H).

Example 3(g) - (R)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2S)-2-(tert-butyldiphenylsilyloxy)-3-hydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one:

30 **3(f)** (137mg, 1eq. 0.274mmol) and (R)-3-(2-(4-methylpiperazin-1-yl)benzyl)-pyrrolidin-2-one (90mg, 1.2eq. 0.329mmol) were combined and stirred in 250μL of dry toluene. CuI (5 mg, 0.1eq 0.027mmol) was added followed by potassium carbonate

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(76mg, 2.0eq. 0.547mmol), *N,N'*-dimethylethylenediamine (5.8μL, 4.8mg, 0.20eq. 0.055mmol), and finally, 12.5μL of water. The thick suspension was refluxed for 2 days, at which point HPLC indicated the reaction to be complete. The mixture was filtered through a Celite® bed, the filtrate was washed 2 times with equal amount of water then brine, dried with MgSO₄ and concentrated to 310mg of dark oil. The crude material was chromatographed on a silica gel column, eluting with 95:5 = acetonitrile:28-30% aqueous ammonium hydroxide to yield 64mg of **3(g)**.

Diastereomer 1 (Major): LC-MS (ESI): *m/z*=691.5 [M+H]⁺

¹H NMR (700 MHz, CDCl₃) δ 8.66 (d, *J* = 2.54Hz, 1H), 8.17 (dd, *J* = 2.62, 8.72Hz, 1H), 7.65 (dd, 4H), 7.42 (m, 3H), 7.37 (m, 4H), 7.24 (d, 1H), 7.23 (d, 1H), 7.17 (d, 1H), 7.00 (dd, 1H), 4.13 (q, 1H), 3.73 (m, 3H), 3.45 (dd, *J* = 3.67, 13.67Hz, 1H), 3.12 (bs, 4H), 3.08 (bs, 4H), 3.00 (m, 1H), 2.68 (m, 1H), 2.60 (s, 3H), 2.18 (m, 1H), 2.14 (m, 1H), 1.98 (m, 1H), 1.89 (m, 1H), 1.05 (s, 9H), 0.76 (d, *J* = 6.29Hz, 3H), 0.65 (t, 3H).

Diastereomer 2 (Minor): LC-MS (ESI): *m/z*=691.5 [M+H]⁺

Example 3(h) - (*R*)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2*S*)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one:

3(g) (6mg, 8.7μmol) was dissolved to 100μL THF, tetrabutylammonium fluoride hydrate (9mg, 4eq. 34.8μmol) was added and heated for 12h at 50°C. Solvent was evaporated and the residue was chromatographed on silica gel using 97.5:2.5 = acetonitrile:28-30% aqueous ammonium hydroxide as eluent. After solvent evaporation, 2mg of **3(h)** was obtained as a colourless oil.

Diastereomer 1: LC-MS (ESI): *m/z*=453.4 [M+H]⁺

¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, 1H), 8.33 (dd, 1H), 7.44 (d, 1H), 7.21 (d, 2H), 7.15 (d, 1H), 7.05 (dd, 1H), 3.95 (q, 1H), 3.73 (m, 2H), 3.36 (dd, 1H), 3.08 (m, 1H), 2.94 (m, 4H), 2.78(dd, 1H), 2.59 (bs, 4H), 2.35 (s, 3H), 2.13 (m, 1H), 1.89 (m, 3H), 1.24 (s, 1H), 1.19 (s, 1H), 1.47 (d, *J*=6.64Hz, 3H), 0.65 (t, 3H).

Diastereomer 2: LC-MS (ESI): *m/z*=453.4 [M+H]⁺

¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, 1H), 8.33 (dd, 1H), 7.30 (d, 1H), 7.21 (d, 2H), 7.15 (d, 1H), 7.05 (dd, 1H), 3.87 (q, 1H), 3.73 (m, 2H), 3.40 (dd, 1H), 3.08 (m,

1H), 2.94 (m, 4H), 2.78(dd, 1H), 2.59 (bs, 4H), 2.35 (s, 3H), 2.13 (m, 1H), 1.89 (m, 3H), 1.24 (s, 1H), 1.19 (s, 1H), 0.90 (d, J=6.64Hz, 3H), 0.65 (t, 3H).

3(h) was resolved into **3(i)** by chiral chromatography as discussed for Example **1(i)**.

5 **Example 4(a) - (S)-Methyl 2-(tert-butyldimethylsilyloxy)propanoate:**

(S)-Methyl lactate (5.45g, 52.4mmol) was mixed with of *tert*-butyldimethylsilyl chloride (9.47g, 1.2eq. 62.8mmol) in 35mL of anhydrous *N,N*-dimethylformamide at RT under N₂-atm. Imidazole (4.39g, 1.25eq. 65.4mmol) was added and the reaction mixture was stirred for 4.5 h at RT. Diisopropyl ether (150mL) was added and the mixture was extracted with 150mL of 1M aqueous HCl, 150mL water, 150mL brine, dried with MgSO₄, filtered through a paper filter and after solvent evaporation 12.33g of **4(a)** was obtained as a colorless oil.

¹H NMR (400 MHz, DMSO-d₆) δ 4.33 (q, 1H), 3.60 (s, 3H), 1.25 (d, J=6.64Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H).

15 **Example 4(b) (S)-2-(tert-Butyldimethylsilyloxy)propanal:**

4(a) (5.00g, 22.9 mmol) was mixed with 20mL hexanes and cooled to -72°C under N₂-atm. Diisobutylaluminium hydride (29.8ml, 1.3eq. 29.8mmol), 1M solution in hexanes, was added and stirred for 1 h. 3mL of saturated aqueous ammonium chloride solution was added and the reaction mixture was allowed to warm-up to RT. 100mL Hexanes was added and the solids were removed by filtration. After solvent evaporation 3.31g of crude product was obtained, which was vacuum distilled and the material boiling at 98-102°C/42mbar was collected yielding 1.50g of **4(b)** as a colourless liquid.

25 ¹H NMR (400 MHz, CDCl₃) δ 9.60 (s, 1H), 4.07 (m, 1H), 1.26 (d, J = 7.06Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

Example 5(a) - (S)-2-Hydroxy-1-morpholinopropan-1-one:

(S)-Methyl lactate (10.9g, 105mmol) and morpholine (36.5g, 4eq. 419mmol) were heated 24 h at 110 °C under N₂-atm. Excess morpholine was evaporated and the crude product was distilled under high vacuum (<1mbar), collecting fractions boiling at 115 –125°C yielding to 10.7g of **5(a)** as a colorless liquid.

30 LC-MS (ESI): m/z=160.2 [M+H]⁺

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^1H NMR (400 MHz, CDCl_3) δ 4.42 (q, 1H), 3.92 (bs, 1H), 3.69 (m, 6H), 3.40 (m, 2H), 1.30 (d, $J = 6.64\text{Hz}$, 3H).

Example 5(b) - (S)-1-Morpholino-2-((2-(trimethylsilyl)ethoxy)methoxy)-propan-1-one:

5 **5(a)** (1.99g, 12.5mmol) was mixed with *N,N*-diisopropylethylamine (2.02g, 1.25eq. 15.6mmol) in 12mL of anhydrous CH_2Cl_2 and cooled in an ice-bath under N_2 -atm. (2-(Chloromethoxy)ethyl)trimethylsilane (2.50g, 1.2eq. 15.0mmol) was added dropwise, the cooling bath was removed and stirred for 19h at RT. The reaction mixture was quenched with 12mL of 1M aqueous HCl, the organic layer was separated, washed with 12mL water, 12mL brine, dried with MgSO_4 , filtered through a paper filter and after solvent evaporation 3.82g of **5(b)** was obtained as a yellow liquid, which was used without further purification.

LC-MS (ESI): $m/z=290.3$ $[\text{M}+\text{H}]^+$

15 ^1H NMR (400 MHz, CDCl_3) δ 4.71 (d, $J = 7.06\text{Hz}$, 1H), 4.64 (d, $J = 7.06\text{Hz}$, 1H), 4.51 (q, 1H), 3.62 (m, 10H), 1.38 (d, $J = 7.06\text{Hz}$, 3H), 0.92 (m, 2H), 0.05 (s, 9H).

Example 5(c) - (S)-2-((2-(Trimethylsilyl)ethoxy)methoxy)pentan-3-one:

Working under N_2 -atm, **5(b)** (706mg, 2.44mmol) was mixed with 20mL anhydrous THF and cooled in an ice bath. 2 M Ethylmagnesium chloride (2.44mL, 2.0eq. 4.78mmol) in THF was added dropwise and stirred for 20 min. Saturated aqueous ammonium chloride solution (0.5mL) was added and the reaction mixture was allowed to warm-up to RT. The solvent was evaporated and the residue partitioned between 20mL CH_2Cl_2 and 20mL 1 M aqueous HCl. The layers were separated, the organic phase was washed with 20mL water, 20mL brine, dried with MgSO_4 , filtered and concentrated yielding to 682mg of **5(c)** as a yellowish liquid.

25 ^1H NMR (400 MHz, CDCl_3) δ 4.71 (d, 1H), 4.65 (d, 1H), 4.13 (q, 1H), 3.58 (dd, 2H), 2.54 (m, 2H), 1.30 (dd, $J = 1.24, 6.64\text{Hz}$, 3H), 1.04 (t, 3H), 0.91 (m, 2H), -0.03 (s, 9H).

1-[6-(1-Ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one (formula I) was biosynthesized by incubating 1-[6-(1-ethyl-1-hydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one (10 μM) with human hepatocytes (ca 1.0×10^6 cells/mL) for 4 hr at 37°C under an

atmosphere of O₂/CO₂ (95/5). At the end of the incubation, 0.05M carbonate buffer pH10 was added and the mixture was extracted with methyl-t-butyl ether. Comparing the extract to the diastereomers made, it was discovered that the main metabolite is essentially (R)-3-(2-(4-methylpiperazin-1-yl)benzyl)-1-(6-((2S,3R)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one. By "essentially", it is meant that HPLC analysis showed a measurable peak for that co-eluted with only (R)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2S,3R)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one.

The subject invention also includes isotopically-labeled compounds, which are identical to those shown in formula I among other compounds encompassed by the invention, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen and sulfur, such as ²H, ³H, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³⁵S, respectively.

Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example, those into which radioactive isotopes such as ³H and ¹⁴C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ³H, and carbon-14, i.e., ¹⁴C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ²H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, can be preferred in some circumstances. Isotopically labeled compounds of formula I, II, and II' of this invention and prodrugs thereof can generally be prepared by carrying out the procedures exemplified below or those known in the art. ¹⁴C-1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one can be prepared by the methods outlined and exemplified in U.S. Pat.

No. 5,552,412 by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The present invention also relates to a method to treat or the preparation of a pharmaceutical composition for treating a disorder or condition in a mammal, including a human, selected from depression, anxiety, depression with concomitant anxiety, dysthymia, post traumatic stress disorder, panic phobias, obsessive compulsive disorder (OCD), OCD with comorbid Tourette's Syndrome, borderline personality disorder, sleep disorder, psychosis, seizures, dyskinesia, symptoms of Huntington's or Parkinson's diseases, spasticity, suppression of seizures resulting from epilepsy, cerebral ischemia, anorexia, faintness attacks, hypokinesia, cranial traumas, chemical dependencies, premature ejaculation, premenstrual syndrome (PMS) associated mood and appetite disorder, inflammatory bowel disease, modification of feeding behavior, blocking carbohydrate cravings, late luteal phase dysphoric disorder, tobacco withdrawal-associated symptoms, panic disorder, bipolar disorder, sleep disorders, jet lag, cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, chemical dependencies and addictions selected from dependencies on, or addictions to nicotine or tobacco products, alcohol, benzodiazepines, barbiturates, opioids or cocaine; pathological gambling; trichotilomania; headache, stroke, traumatic brain injury (TBI), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome, comprising an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. Said method may also include the administration of 5-HT re-uptake inhibitors, preferably sertraline, or a pharmaceutically acceptable salt thereof, for said treatment.

The present invention also relates to a method of treating a disorder or condition referred to hereinabove in a mammal, including a human, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

The present invention also relates to a pharmaceutical composition for use in treating a disorder or condition referred to hereinabove in a mammal, comprising an amount of a compound of formula I that is effective to provide activity as an antagonist, inverse agonist or partial agonist of 5-HT_{1B} receptors and a
5 pharmaceutically acceptable carrier.

The present invention also relates to a method of treating a disorder or condition referred to herein in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I that is effective to provide activity as an antagonist, inverse agonist or partial agonist of 5-HT_{1B}
10 receptors.

As used herein, the term "depression" includes depressive disorders, for example, single episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression; melancholic depression including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite,
15 hypersomnia, psychomotor agitation or irritability, anxiety and phobias, seasonal affective disorder, or bipolar disorders or manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder.

Other mood disorders encompassed within the term "depression" include
20 dysthymic disorder with early or late onset and with or without atypical features; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood, disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed
25 type; and adjustment disorder with depressed mood.

As used herein, the term "anxiety" includes anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and
30 acute stress disorder, and generalized anxiety disorders.

"Generalized anxiety" is typically defined as an extended period (e.g., at least six months) of excessive anxiety or worry with symptoms on most days of that period. The anxiety and worry is difficult to control and may be accompanied by restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and disturbed sleep.

"Panic disorder" is defined as the presence of recurrent panic attacks followed by at least one month of persistent concern about having another panic attack. A "panic attack" is a discrete period in which there is a sudden onset of intense apprehension, fearfulness or terror. During a panic attack, the individual may experience a variety of symptoms including palpitations, sweating, trembling, shortness of breath, chest pain, nausea and dizziness. Panic disorder may occur with or without agoraphobia.

"Phobias" includes agoraphobia, specific phobias and social phobias. "Agoraphobia" is characterized by an anxiety about being in places or situations from which escape might be difficult or embarrassing or in which help may not be available in the event of a panic attack. Agoraphobia may occur without history of a panic attack. A "specific phobia" is characterized by clinically significant anxiety provoked by feared object or situation. Specific phobias include the following subtypes: animal type, cued by animals or insects; natural environment type, cued by objects in the natural environment, for example storms, heights or water; blood-injection-injury type, cued by the sight of blood or an injury or by seeing or receiving an injection or other invasive medical procedure; situational type, cued by a specific situation such as public transportation, tunnels, bridges, elevators, flying, driving or enclosed spaces; and other type where fear is cued by other stimuli. Specific phobias may also be referred to as simple phobias. A "social phobia" is characterized by clinically significant anxiety provoked by exposure to certain types of social or performance circumstances. Social phobia may also be referred to as social anxiety disorder.

Other anxiety disorders encompassed within the term "anxiety" include anxiety disorders induced by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, phencyclidine, sedatives, hypnotics, anxiolytics and other

substances, and adjustment disorders with anxiety or with mixed anxiety and depression.

In another practice, the invention relates to a pharmaceutical composition for treating a condition or disorder that can be treated by enhancing serotonergic neurotransmission in a mammal, preferably a human, comprising:

- a) a pharmaceutically acceptable carrier;
- b) a compound of formula I; and
- c) one or more 5-HT re-uptake inhibitors, preferably sertraline, or a pharmaceutically acceptable salt thereof;

wherein the amount of the active compounds (i.e., the compounds of formula I and the 5-HT re-uptake inhibitor) are such that the combination is effective in treating such disorder or condition.

In another practice, the invention relates to a method for treating a disorder or condition that can be treated by enhancing serotonergic neurotransmission in a mammal, preferably a human, comprising administering to a mammal requiring such treatment:

- a) a compound of formula I, or a pharmaceutically acceptable salt thereof; and
- b) one or more 5-HT re-uptake inhibitors, preferably sertraline, or a pharmaceutically acceptable salt thereof;

wherein the amounts of the active compounds (i.e., the compound of formula I and the 5-HT re-uptake inhibitor) are such that the combination is effective in treating such disorder or condition.

In another practice, the invention relates to a method for treating a disorder or condition that can be treated by enhancing serotonergic neurotransmission in a mammal, preferably a human, comprising administering to said mammal requiring such treatment:

- a) one or more 5-HT_{1A} antagonists or a pharmaceutically acceptable salt thereof; and
- b) a compound of formula I, or a pharmaceutically acceptable salt thereof;

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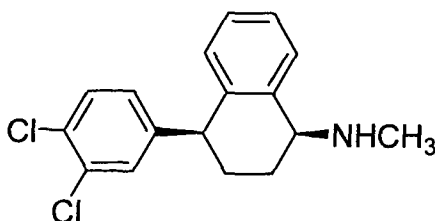
wherein the amounts of each active compound are such that the combination is effective in treating such disorder or condition.

In another practice, the invention relates to a pharmaceutical composition for treating a disorder or condition that can be treated by enhancing serotonergic neurotransmission in a mammal, preferably a human, comprising:

a) one or more 5-HT_{1A} antagonists or a pharmaceutically acceptable salt thereof; and

b) a compound of formula I, or a pharmaceutically acceptable salt thereof; wherein the amounts of each active compound are such that the combination is effective in treating such disorder or condition.

Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine, as used herein has the following structural formula



and ordinarily used in the form of its hydrochloride salt. The synthesis of sertraline is described in U.S. Patent No. 4,536,518, assigned to Pfizer Inc. Sertraline hydrochloride is useful as an antidepressant and anorectic agent, and is also useful in the treatment of depression, chemical dependencies, anxiety, obsessive compulsive disorders, phobias, panic disorder, post traumatic stress disorder, and premature ejaculation.

When used for the treatment of one or more of the above conditions, 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one can be used (either co-administered separately or within the same pharmaceutical composition) in combination with one or more other agents as described hereinabove.

The pharmaceutically acceptable acid addition salts of the compounds of this invention can be formed of the compound itself, or of any of its esters, and include the pharmaceutically acceptable salts which are often used in pharmaceutical chemistry.

For example, salts can be formed with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfonic acids including such agents as naphthalenesulfonic, methanesulfonic and toluenesulfonic acids, fumaric acid, citric acid, salicylic acid, oxalic acid, methanesulfonic acid, maleic acid, di-p-toluoyl acid, tartaric acid, sulfuric acid, nitric acid, phosphoric acid, tartaric acid, pyrosulfuric acid, metaphosphoric acid, succinic acid, formic acid, phthalic acid, lactic acid and the like.

The compounds of this invention, as discussed above, can be administered in the form of pharmaceutically acceptable salts. The salts are conveniently formed, as is usual in organic chemistry, by reacting a compound of this invention, when basic, with a suitable acid, such as have been described above. The salts are quickly formed in high yields at moderate temperatures, and often are prepared by merely isolating the compound from a suitable acidic wash as the final step of the synthesis. The salt-forming acid is dissolved in an appropriate organic solvent, or aqueous organic solvent, such as an alkanol, ketone or ester. On the other hand, if a compound of this invention is desired in the free base form, it is isolated from a basic final wash step, according to the usual practice. A preferred technique for preparing hydrochlorides is to dissolve the free base in a suitable solvent and dry the solution thoroughly, as over molecular sieves, before bubbling hydrogen chloride gas through it.

When used as a medicament, the dose of a compound of formula I to be administered to a human is rather widely variable and subject to the judgment of the attending physician. It should be noted that it can be desirable to adjust the dose of a compound when it is administered in the form of a salt, such as a laureate, the salt forming moiety of which has an appreciable molecular weight. These compounds are, most desirably, administered in dosages ranging from about 0.25 mg up to about 1500 mg per day, preferably from about 0.25 to about 300 mg per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.01 mg to about 10 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the weight and condition of the persons being treated and their

individual responses to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval during which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day. In any given case, the amount of compound administered will depend on such factors as the solubility of the active component, the formulation used and the route of administration.

10 The route of administration of the compounds of this invention is not critical. The compounds can be absorbed from the alimentary tract, however, the compounds can be administered percutaneously, or as suppositories for absorption by the rectum, if desired in a given instance. All of the usual types of compositions can be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, troches, 15 suppositories and suspensions. Compositions are formulated to contain a daily dose, or a convenient fraction of daily dose, in a dosage unit, which can be a single tablet or capsule or convenient volume of a liquid. Transdermal and oral administration are preferred.

Methods of formulation are well known in the art and are disclosed, for example, in Remington: The Science and Practice of Pharmacy, Mack Publishing 20 Company, Easton, Pa., 19th Edition (1995). Pharmaceutical compositions for use within the present invention can be in the form of sterile, non-pyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art.

25 Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

30 Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and

disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars
5 such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidone and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant can be added in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as
10 talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which facilitate the disintegration of a tablet to release a compound when the tablet becomes wet. They include starches, clays, celluloses, alginates and gums, more particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-
15 exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, can be used as well as sodium lauryl sulfate.

Tablets are often coated with sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds can also be formulated as chewable tablets, by using large amounts of pleasant-
20 tasting substances such as mannitol in the formulation, as is now well-established in the art.

When it is desired to administer a compound as a suppository, the typical bases can be used. Cocoa butter is a traditional suppository base, which can be modified by addition of waxes to raise its melting point slightly. Water-miscible
25 suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use.

The effect of the compounds can be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the compound can be prepared and incorporated in a tablet or capsule. The technique can be improved by making
30 pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules can be coated with a film which resists dissolution for a

predictable period of time. Even the parenteral preparations can be made long-acting, by dissolving or suspending the compound in oily or emulsified vehicles which allow it to disperse only slowly in the serum.

Unless otherwise indicated:

5 "Treating" refers to, and includes, reversing, alleviating, inhibiting the progress of, or preventing, a disease, disorder or condition, or one or more symptoms thereof; and, "treatment" and "therapeutically" refer to the act of treating, as defined above.

"Enhanced serotonergic neurotransmission," as used herein, refers to increasing or improving the neuronal process whereby serotonin is released by a pre-synaptic cell
10 upon excitation and crosses the synapse to stimulate or inhibit the post-synaptic cell.

"Chemical dependency," as used herein, means an abnormal craving or desire for, or an addiction to a drug. Such drugs are generally administered to the affected individual by any of a variety of means of administration, including oral, parenteral, nasal or by inhalation. Examples of chemical dependencies treatable by the methods of
15 the present invention are dependencies on alcohol, nicotine, cocaine, heroin, phenobarbital, and benzodiazepines (e.g., Valium (trademark)). "Treating a chemical dependency," as used herein, means reducing or alleviating such dependency.

"Subject" is an animal, including mammals, and including human beings.

The invention includes isotopically-labeled compounds identical to those of
20 formula (I) and other compounds of the invention save for one or more atoms being replaced by one of atomic mass or mass number different from that usually found in nature as understood by the artisan.

"Co-administration" of a combination of a 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one and an additional
25 compound or additional compounds means that these components can be administered together as a composition or as part of the same, unitary dosage form. "Co-administration" also includes administering a 1-[6-(1-ethyl-1,2-dihydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one and an additional compound or additional compounds separately but as part of the same therapeutic
30 treatment program or regimen. The components need not necessarily be administered at essentially the same time, although they can if so desired. Thus "co-

administration" includes, for example, administering a 1-[6-(1-ethyl-1,2-dihydroxypropyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one and an additional compound as separate dosages or dosage forms, but at the same time. "Co-administration" also includes separate administration at different times and in any order. For example, where appropriate a patient can take one or more component(s) of the treatment in the morning and one or more of the other component(s) at night.

The term "prodrug" means compounds that are transformed *in vivo* to yield a compound of the present invention. The transformation can occur by various mechanisms, such as through hydrolysis in blood. A good discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of the present invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C₁-C₈)alkyl, (C₂-C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-((C₁-C₂))alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₁-C₃)alkyl.

Similarly, if a compound of the present invention comprises an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxy-methyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-C₄)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacylα-aminoacyl, where

each α -aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

As used herein, the term "effective amount" means an amount of compound of the methods of the present invention that is capable of treating the specific diseases and pathological conditions. The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the subject, and the severity of the pathological condition being treated.

Advantageously, the present invention also provides kits for use by a consumer for treating disease. The kits comprise a) a pharmaceutical composition comprising an $5HT_{1B}$ agonist/antagonist and a pharmaceutically acceptable carrier, vehicle or diluent; and, optionally, b) instructions describing a method of using the pharmaceutical composition for treating the specific disease. The instructions can also indicate that the kit is for treating disease while substantially reducing the concomitant liability of adverse effects associated with estrogen administration.

A "kit" as used in the instant application includes a container for containing the separate unit dosage forms such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets can be contained in a bottle which is in turn contained within a box.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of

pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or can have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It can be desirable to provide a written memory aid, where the written memory aid is of the type containing information and/or instructions for the physician, pharmacist or subject, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested or a card which contains the same type of information. Another example of such a memory aid is a calendar printed on the card e.g., as follows "First Week, Monday, Tuesday," . . . etc "Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day.

Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter, which indicates the number of daily doses that, has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal

which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The compounds of formula I that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

Compounds of formula I and their pharmaceutically acceptable salts (hereinafter also referred to, collectively, as "the active compounds") are useful psychotherapeutics and are potent agonists and/or antagonists of the serotonin 1A (5-HT_{1A}) and/or serotonin 1B (5-HT_{1B}) receptors.

Biological Assay

The affinities of the compounds of formula I for the various serotonin-1 receptors can be determined using standard radioligand binding assays as described in the literature. The 5-HT_{1A} affinity can be measured using the procedure of Hoyer et al. (*Brain Res.*, 376, 85 (1986)). The 5-HT_{1B} affinity can be measured using the procedure of Heuring and Peroutka (*J. Neurosci.*, 7, 894 (1987)).

The *in vitro* activity of the compounds of the present invention at the 5-HT_{1B} binding site can be determined according to the following procedure. Bovine caudate tissue is homogenized and suspended in 20 volumes of a buffer containing 50 mM TRIS•hydrochloride (tris[hydroxymethyl]aminomethane hydrochloride) at a pH of 7.7.

5 The homogenate is then centrifuged at 45,000G for 10 minutes. The supernatant is then discarded and the resulting pellet resuspended in approximately 20 volumes of 50 mM TRIS•hydrochloride buffer at pH 7.7. This suspension is then pre-incubated for 15 minutes at 37°C, after which the suspension is centrifuged again at 45,000G for 10 minutes and the supernatant discarded. The resulting pellet (approximately 1

10 gram) is resuspended in 150 mL of a buffer of 15 mM TRIS•hydrochloride containing 0.01 percent ascorbic acid with a final pH of 7.7 and also containing 10 µM pargyline and 4 mM calcium chloride (CaCl₂). The suspension is kept on ice at least 30 minutes prior to use.

The inhibitor, control or vehicle is then incubated according to the following

15 procedure. To 50 µL of a 20 percent dimethylsulfoxide (DMSO)/80 percent distilled water solution is added 200 µL of tritiated 5-hydroxytryptamine (2 nM) in a buffer of 50 mM TRIS•hydrochloride containing 0.01 percent ascorbic acid at pH 7.7 and also containing 10 µM pargyline and 4 µM calcium chloride, plus 100 nM of 8-hydroxy-DPAT (dipropylaminotetraline) and 100 nM of mesulergine. To this mixture is added

20 750 µL of bovine caudate tissue, and the resulting suspension is vortexed to ensure a homogenous suspension. The suspension is then incubated in a shaking water bath for 30 minutes at 25°C. After incubation is complete, the suspension is filtered using glass fiber filters (e.g., Whatman GF/B-filters™). The pellet is then washed three times with 4 mL of a buffer of 50 mM TRIS•hydrochloride at pH 7.7. The pellet is then

25 placed in a scintillation vial with 5 mL of scintillation fluid (aquasol 2™) and allowed to sit overnight. The percent inhibition can be calculated for each dose of the compound. An IC₅₀ value can then be calculated from the percent inhibition values.

The activity of the compounds of formula I for 5-HT_{1A} binding ability can be determined according to the following procedure. Rat brain cortex tissue is

30 homogenized and divided into samples of 1 gram lots and diluted with 10 volumes of 0.32 M sucrose solution. The suspension is then centrifuged at 900G for 10 minutes

and the supernate separated and recentrifuged at 70,000G for 15 minutes. The supernate is discarded and the pellet re-suspended in 10 volumes of 15 mM TRIS•hydrochloride at pH 7.5. The suspension is allowed to incubate for 15 minutes at 37°C. After pre-incubation is complete, the suspension is centrifuged at 70,000G
5 for 15 minutes and the supernate discarded. The resulting tissue pellet is resuspended in a buffer of 50 mM TRIS•hydrochloride at pH 7.7 containing 4 mM of calcium chloride and 0.01 percent ascorbic acid. The tissue is stored at -70°C until ready for an experiment. The tissue can be thawed immediately prior to use, diluted with 10 µm pargyline and kept on ice.

10 The tissue is then incubated according to the following procedure. Fifty microliters of control, inhibitor, or vehicle (1 percent DMSO final concentration) is prepared at various dosages. To this solution is added 200 µL of tritiated DPAT at a concentration of 1.5 nM in a buffer of 50 mM TRIS•hydrochloride at pH 7.7 containing 4 mM calcium chloride, 0.01 percent ascorbic acid and pargyline. To this solution is
15 then added 750 µL of tissue and the resulting suspension is vortexed to ensure homogeneity. The suspension is then incubated in a shaking water bath for 30 minutes at 37°C. The solution is then filtered, washed twice with 4 mL of 10 mM TRIS•hydrochloride at pH 7.5 containing 154 mM of sodium chloride. The percent inhibition is calculated for each dose of the compound, control or vehicle. IC₅₀ values
20 are calculated from the percent inhibition values.

The agonist and antagonist activities of the compounds of the invention at 5-HT_{1A} and 5-HT_{1B} receptors can be determined using a single saturating concentration according to the following procedure. Male Hartley guinea pigs are sacrificed and 5-HT_{1A} receptors are dissected out of the hippocampus, while 5-HT_{1B} receptors are
25 obtained by slicing at 350 mM on a McIlwain tissue chopper and dissecting out the substantia nigra from the appropriate slices. The individual tissues are homogenized in 5 mM HEPES buffer containing 1 mM EGTA (pH 7.5) using a hand-held glass-Teflon® homogenizer and centrifuged at 35,000 x g for 10 minutes at 4°C. The pellets are resuspended in 100 mM HEPES buffer containing 1 mM EGTA (pH 7.5) to a final
30 protein concentration of 20 mg (hippocampus) or 5 mg (substantia nigra) of protein per tube. The following agents are added so that the reaction mix in each tube

contained 2.0 mM MgCl₂, 0.5 mM ATP, 1.0 mM cAMP, 0.5 mM IBMX, 10 mM phosphocreatine, 0.31 mg/mL creatine phosphokinase, 100 μM GTP and 0.5-1 microcuries of [³²P]-ATP (30 Ci/mmol: NEG-003 - New England Nuclear). Incubation is initiated by the addition of tissue to siliconized microfuge tubes (in triplicate) at 30°C for 15 minutes. Each tube receives 20 μL tissue, 10 μL drug or buffer (at 10X final concentration), 10 μL 32 nM agonist or buffer (at 10X final concentration), 20 μL forskolin (3 μM final concentration) and 40 μL of the preceding reaction mix. Incubation is terminated by the addition of 100 μL 2% SDS, 1.3 mM cAMP, 45 mM ATP solution containing 40,000 dpm [³H]-cAMP (30 Ci/mmol: NET-275- New England Nuclear) to monitor the recovery of cAMP from the columns. The separation of [³²P]-ATP and [³²P]-cAMP is accomplished using the method of Salomon et al., Analytical Biochemistry, 1974, 58, 541-548. Radioactivity is quantified by liquid scintillation counting. Maximal inhibition is defined by 10 μM (*R*)-8-OH-DPAT for 5-HT_{1A} receptors, and 320 nM 5-HT for 5-HT_{1B} receptors. Percent inhibitions by the test compounds are then calculated in relation to the inhibitory effect of (*R*)-8-OH-DPAT for 5-HT_{1A} receptors or 5-HT for 5-HT_{1B} receptors. The reversal of agonist induced inhibition of forskolin-stimulated adenylate cyclase activity is calculated in relation to the 32 nM agonist effect.

The compounds of formula I can be tested for *in vivo* activity for antagonism of 5-HT_{1B} agonist-induced hypothermia in guinea pigs according to the following procedure.

The *in vitro* activity of the compounds in the present invention at the human ether-a-go-go-related gene potassium channel (hERG) can be determined according to the following procedure. HEK-293 cells expressing the human ERG channel are grown according to standard cell culture techniques. Cells are collected, spun down and the resulting pellet is frozen for future use. On the day of the experiment, frozen cell pellet is weighed (100 mg per 96 well assay plate) and homogenized in 20 volumes of cold 50 mM Tris base containing 10 mM KCl and 1 mM MgCl₂ (pH to 7.4 at 4°C). The homogenate is then centrifuged at 45,000 G for 10 minutes. The supernatant is decanted and the membrane pellet resuspended by Polytron in cold 50 mM Tris base containing 10 mM KCl and 1 mM MgCl₂ (pH to 7.4 at 4°C) to a 20

mg/mL concentration. PVT WGA SPA beads (PEI treated type A) are weighed out and added to diluted tissue, also to concentration of 20 mg/mL. The membrane / bead solution is then gently rotated (speed 2, high) in a cold room (4°C) for 2 hours on a Roto-Torque (Cole-Palmer Model 7637). Following this preincubation, the bead
5 slurry is then centrifuged at 1000 rpm for 5 min at 4°C. The supernatant is decanted and the pellet is resuspended to 5 mg/mL membrane and bead concentration in 50 mM Tris base containing 10 mM KCl and 1 mM MgCl₂ (pH to 7.4 at 22°C)). The resuspended SPA beads / membrane mixture is immediately used in the assay. Beads and membranes are used at a final concentration of 1 mg/well and 25
10 microgram protein/well, respectively. Dilutions of compounds are made in 10% DMSO / 50 mM Tris buffer (pH 7.4) (at 10 x final concentration – so that the final DMSO concentration is 1%). To 96 well SPA plates containing drug dilutions, radioligand is added (5 nM final concentration 3H-dofetilide). The incubation is initiated by the addition of tissue/bead slurry. Assay plates incubate for one hour and then
15 radioactivity is quantified using a MicroBeta scintillation counter. The percent inhibition of specific binding can then be calculated.

The compounds of the invention can be tested for *in vivo* activity for antagonism of 5HT_{1B} agonist-induced by hypothermia in guinea pigs according to the following procedure.

20 Male Hartley guinea pigs from Charles River, weighing 250-275 grams on arrival and 300-600 grams at testing, serve as subjects in the experiment. The guinea pigs are housed under standard laboratory conditions on a 7 a.m. to 7 p.m. lighting schedule for at least seven days prior to experimentation. Food and water are available ad libitum until the time of testing.

25 The compounds of the invention can be administered as solutions in a volume of 1 mL/kg. The vehicle used is varied depending on compound solubility. Test compounds are typically administered either sixty minutes orally (p.o.) or 0 minutes subcutaneously (s.c.) prior to a 5-HT_{1B} agonist, such as [3-(1-methylpyrrolidin-2-ylmethyl)-1H-indol-5-yl]-(3-nitropyridin-3-yl)-amine, which can be prepared as
30 described in PCT publication WO93/11106, published June 10, 1993 which is administered at a dose of 5.6 mg/kg, s.c. Before a first temperature reading is taken,

each guinea pig is placed in a clear plastic shoe box containing wood chips and a metal grid floor and allowed to acclimate to the surroundings for 30 minutes. Animals are then returned to the same shoe box after each temperature reading. Prior to each temperature measurement each animal is firmly held with one hand for a 30-second period. A digital thermometer with a small animal probe is used for temperature measurements. The probe is made of semi-flexible nylon with an epoxy tip. The temperature probe is inserted 6 cm. into the rectum and held there for 30 seconds or until a stable recording is obtained. Temperatures are then recorded.

In p.o. screening experiments, a "pre-drug" baseline temperature reading is made at -90 minutes, the test compound is given at -60 minutes and an additional -30 minute reading is taken. The 5-HT_{1B} agonist is then administered at 0 minutes and temperatures are taken 30, 60, 120 and 240 minutes later.

In subcutaneous screening experiments, a pre-drug baseline temperature reading is made at -30 minutes. The test compound and 5-HT_{1B} agonists are given concurrently and temperatures are taken at 30, 60, 120 and 240 minutes later.

Data are analyzed with two-way analysis of variants with repeated measures in Newman-Keuls post hoc analysis.

The active compounds of the invention can be evaluated as anti-migraine agents by testing the extent to which they mimic sumatriptan in contracting the dog isolated saphenous vein strip (P.P.A. Humphrey et al., Br. J. Pharmacol., 94, 1128 (1988)). This effect can be blocked by methiothepin, a known serotonin antagonist. Sumatriptan is known to be useful in the treatment of migraine and produces a selective increase in carotid vascular resistance in the anesthetized dog. The pharmacological basis of sumatriptan efficacy has been discussed in W. Fenwick et al., Br. J. Pharmacol., 96, 83 (1989).

The serotonin 5-HT₁ agonist activity can be determined by the *in vitro* receptor binding assays, as described for the 5-HT_{1A} receptor using rat cortex as the receptor source and [³H]-8-OH-DPAT as the radioligand (D. Hoyer et al. Eur. J. Pharm., 118, 13 (1985)) and as described for the 5-HT_{1B} receptor using bovine caudate as the receptor source and [³H]serotonin as the radioligand (R.E. Heuring and S.J. Peroutka, J. Neuroscience, 7, 894 (1987)).

The compounds of formula I can advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents such as tricyclic antidepressants (e.g., amitriptyline, dothiepin, doxepin, trimipramine, butriptyline, clomipramine, desipramine, imipramine, iprindole, lofepramine, nortriptyline or protriptyline), monoamine oxidase inhibitors (e.g., isocarboxazid, phenelzine or tranylcyclopramine) or 5-HT re-uptake inhibitors (e.g., fluvoxamine, sertraline, fluoxetine or paroxetine), and/or with antiparkinsonian agents such as dopaminergic antiparkinsonian agents (e.g., levodopa, preferably in combination with a peripheral decarboxylase inhibitor e.g., benserazide or carbidopa, or with a dopamine agonist e.g., bromocriptine, lysuride or pergolide) or with a noradrenaline re-uptake inhibitor (NRI) such as reboxetine. It is to be understood that the present invention covers the use of a compounds of formula (I) or a physiologically acceptable salt or solvate thereof in combination with one or more other therapeutic agents.

Compounds of formula I and the pharmaceutically acceptable salts thereof, in combination with a 5-HT re-uptake inhibitor (e.g., fluvoxamine, sertraline, fluoxetine or paroxetine), preferably sertraline, or a pharmaceutically acceptable salt or polymorph thereof (the combination of a compound of formula I with a 5-HT re-uptake inhibitor is referred herein to as "the active combination"), are useful psychotherapeutics and can be used in the treatment of disorders the treatment of which is facilitated by enhanced serotonergic neurotransmission (e.g., hypertension, all forms of depression (e.g., depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, pediatric depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, post partum depression, dysthymia; mild, moderate, or severe depressions with or without atypical features, melancholic features, psychotic features, catatonic features; seasonal affective disorder, geriatric depression, chronic depression; adjustment disorder with depressed mood or with anxiety and depressed mood; mixed anxiety and depression; substance induced mood disorder; and mood disorder secondary to a general medical condition), bipolar disorder (including in the depressed phase), generalized anxiety disorder, social anxiety, separation anxiety disorder, phobias (e.g., agoraphobia, social phobia and

simple phobias), posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders (e.g., binge eating disorder, anorexia nervosa and bulimia nervosa), obesity, chemical dependencies (e.g., addictions to alcohol, cocaine, heroin, phenobarbital, marijuana, nicotine and benzodiazepines), cluster
5 headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder; panic disorder with and without agoraphobia; memory disorders (e.g., dementia, amnesic disorders, and age-related cognitive decline (ARCD)), Parkinson's diseases (e.g., dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias), endocrine disorders (e.g., hyperprolactinaemia), vasospasm (particularly
10 in the cerebral vasculature), cerebellar ataxia, gastrointestinal tract disorders (involving changes in motility and secretion), negative symptoms of schizophrenia, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, cancer (e.g. small cell lung carcinoma), chronic paroxysmal hemicrania, headache (associated with vascular disorders) autism,
15 pervasive developmental disorder NOS, Asperger's disorder, selective mutism, chronic motor or vocal tic disorder, somatization disorder, insomnia, intermittent explosive disorder, pyromania, pathological gambling, impulse-control disorder, premenstrual dysphoric disorder, and attention-deficit/hyperactivity disorder (ADHD)).

Serotonin (5-HT) re-uptake inhibitors, preferably sertraline, exhibit positive
20 activity against depression; chemical dependencies; anxiety disorders including panic disorder, generalized anxiety disorder, agoraphobia, simple phobias, social phobia, and post-traumatic stress disorder; obsessive-compulsive disorder; avoidant personality disorder and premature ejaculation in mammals, including humans, due in part to their ability to block the synaptosomal uptake of serotonin.

25 United States Patent 4,536,518 describes the synthesis, pharmaceutical composition and use of sertraline for depression and is hereby incorporated by reference in its entirety.

Activity of the active combination as antidepressants and related pharmacological properties can be determined by methods (1)-(4) below, which are
30 described in Koe, B. et al., *Journal of Pharmacology and Experimental Therapeutics*, 226 (3), 686-700 (1983). Specifically, activity can be determined by studying (1) their

ability to affect the efforts of mice to escape from a swim-tank (Porsolt mouse "behavior despair" test), (2) their ability to potentiate 5-hydroxytryptophan-induced behavioral symptoms in mice *in vivo*, (3) their ability to antagonize the serotonin-depleting activity of p-chloroamphetamine hydrochloride in rat brain *in vivo*, and
5 (4) their ability to block the uptake of serotonin, norepinephrine and dopamine by synaptosomal rat brain cells *in vitro*. The ability of the active combination to counteract reserpine hypothermia in mice *in vivo* can be determined according to the methods described in U.S. Pat. No. 4,029,731.

The compositions of the present invention can be formulated in a conventional
10 manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention can be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions can take the form of,
15 for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate);
20 or wetting agents (e.g., sodium lauryl sulfate). The tablets can be coated by methods well known in the art. Liquid preparations for oral administration can take the form of, for example, solutions, syrups or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically
25 acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition can take the form of tablets or
30 lozenges formulated in conventional manner.

The active compounds of the invention can be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions
5 can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the invention can also be formulated in rectal
10 compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or
15 as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer can contain a solution or
20 suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator can be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral
25 or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., depression) is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g., migraine) in the average adult human are preferably arranged so that each metered
30 dose or "puff" of aerosol contains 20 µg to 1000 µg of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 µg to 10 mg.

Administration can be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

In connection with the use of an active compound of this invention with a 5-HT re-uptake inhibitor, preferably sertraline, for the treatment of subjects possessing any
5 of the above conditions, it is to be noted that these compounds can be administered either alone or in combination with pharmaceutically acceptable carriers by either of the routes previously indicated, and that such administration can be carried out in both single and multiple dosages. More particularly, the active combination can be administered in a wide variety of different dosage forms, i.e., they can be combined
10 with various pharmaceutically-acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspension, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes. In general, the compounds of formula I are present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage and a 5-HT re-uptake inhibitor, preferably sertraline, is present in such dosage forms at concentration levels
15 ranging from about 0.5% to about 90% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage.
20

A proposed daily dose of an active compound of this invention in the combination formulation (a formulation containing an active compound of this invention and a 5-HT re-uptake inhibitor) for oral, parenteral, rectal or buccal
25 administration to the average adult human for the treatment of the conditions referred to above is from about 0.01 mg to about 2000 mg, preferably from about 0.1 mg to about 200 mg of the active ingredient of formula I per unit dose which could be administered, for example, 1 to 4 times per day.

A proposed daily dose of a 5-HT re-uptake inhibitor, preferably sertraline, in the
30 combination formulation for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above is from about 0.1 mg

to about 2000 mg, preferably from about 1 mg to about 200 mg of the 5-HT re-uptake inhibitor per unit dose which could be administered, for example, 1 to 4 times per day.

A preferred dose ratio of sertraline to an active compound of this invention in the combination formulation for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above is from
5 about 0.00005 to about 20,000, preferably from about 0.25 to about 2,000.

Aerosol combination formulations for treatment of the conditions referred to above in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains from about 0.01 µg to about 100 mg of the active
10 compound of this invention, preferably from about 1 µg to about 10 mg of such compound. Administration can be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

Aerosol formulations for treatment of the conditions referred to above in the average adult human are preferably arranged so that each metered dose or "puff" of
15 aerosol contains from about 0.01 mg to about 2000 mg of a 5-HT re-uptake inhibitor, preferably sertraline, preferably from about 1 mg to about 200 mg of sertraline. Administration can be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

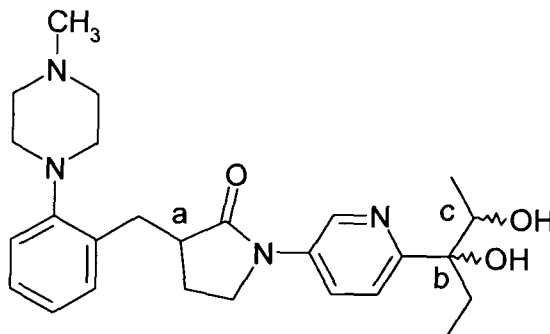
As previously indicated, a 5-HT re-uptake inhibitor, preferably sertraline, in
20 combination with compounds of formula I are readily adapted to therapeutic use as antidepressant agents. In general, these antidepressant compositions containing a 5-HT re-uptake inhibitor, preferably sertraline, and a compound of formula I are normally administered in dosages ranging from about 0.01 mg to about 100 mg per kg of body weight per day of a 5-HT re-uptake inhibitor, preferably sertraline, preferably
25 30mg per kg of body weight per day, more preferably from about 0.1 mg. to about 10 mg per kg of body weight per day of sertraline; with from about 0.001 mg to about 100 mg per kg of body weight per day of a compound of formula I, preferably 30mg per kg of body weight per day, more preferably from about 0.01 mg to about 10 mg per kg of body weight per day of a compound of formula I, although variations will
30 necessarily occur depending upon the conditions of the subject being treated and the particular route of administration chosen.

All references and patents cited herein are incorporated by reference.

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CLAIMS

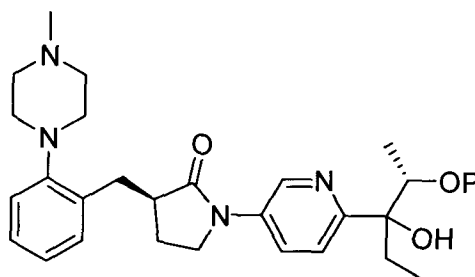
1. A compound of formula (I):



(I)

- 5 wherein the stereochemistry of a and b and c, where the given definition defines (a) and then (b, c), respectively, is
- (R) and (R, S);
 - (R) and (R, R);
 - (S) and (R, S);
 - 10 (S) and (R, R);
 - (R) and (S, S);
 - (R) and (S, R);
 - (S) and (S, S); and
 - (S) and (S, R);
- 15 prodrugs and pharmaceutically acceptable salts thereof.
2. The compound of claim 1, wherein (a) and (b, c) are respectively
- (R) and (S, S); and
 - (S) and (S, S);
- prodrugs and pharmaceutically acceptable salts thereof.
- 20 3. The compound of claim 2, wherein the compound is at least 98% pure.
4. A compound of formula 1-ia:

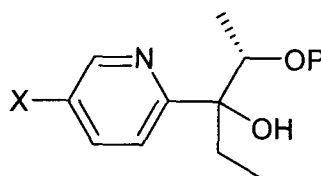
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formula 1-ia

wherein P is an appropriate protecting group.

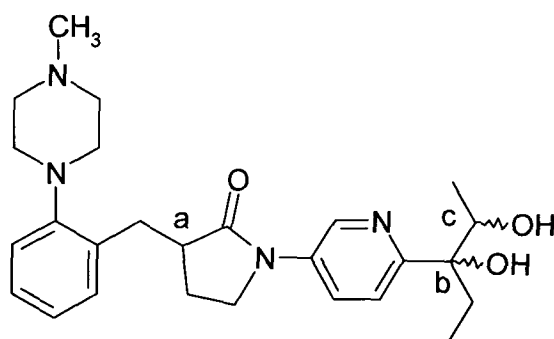
- 5 5. A compound of formula 1-ib:



formula 1-ib

wherein X is a halogen with atomic number less than or equal to Br or I; and
P is an appropriate protecting group.

- 10 6. The process of preparing a compound of formula (I):



(I)

wherein the stereochemistry of a and b and c, where the given definition defines (a)
and then (b, c), respectively, is

- 15 (R) and (R, S);
(R) and (R, R);
(S) and (R, S);
(S) and (R, R);

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(R) and (S, S);

(R) and (S, R);

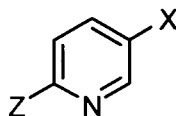
(S) and (S, S); and

(S) and (S, R);

5 and pharmaceutically acceptable salts thereof,

comprising preparing (2S)-3-(5-bromopyridin-2-yl)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-ol from (2S)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-one:

(a) forming a mixture in a non-coordinating reaction inert solvent, optionally toluene, of a dihalopyridine:



10

wherein Z is Br or I; and X is a halogen with atomic number less than or equal to the selected Z;

with (2S)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-one;

(b) treating the mixture formed in step (a) with an (C₁-C₈)alkyl lithium compound; and

15

(c) quenching the mixture formed in (b) with a proton donor so as to form (2S)-3-(5-bromopyridin-2-yl)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-ol;

further comprising preparing (R)-3-(2-(4-methylpiperazin-1-yl)benzyl)-1-(6-((2S)-3-hydroxy-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-yl)pyridin-3-yl)pyrrolidin-2-one from (2S)-3-(5-bromopyridin-2-yl)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-ol:

20

(2S)-3-(5-bromopyridin-2-yl)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-ol and (R)-3-(2-(4-methylpiperazin-1-yl)benzyl)pyrrolidin-2-one are mixed in a non-coordinating reaction inert solvent, optionally toluene,

CuI (about 0.05 to 0.2 eq) is added, potassium carbonate (about 1.5 to 2.5 eq) is then added, N,N'-dimethylethylenediamine (about 0.05 to 0.5 eq) is then added, and then water (about 1% to about 10% w/w) is added; and refluxed until (2S)-3-(5-bromopyridin-2-yl)-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-ol is consumed;

25

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(*R*)-3-(2-(4-methylpiperazin-1-yl)benzyl)-1-(6-((2*S*)-3-hydroxy-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-yl)pyridin-3-yl)pyrrolidin-2-one is isolated using standard procedures, optionally purified; and

further comprising preparing (*R*)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2*S*)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one from (*R*)-3-(2-(4-methylpiperazin-1-yl)benzyl)-1-(6-((2*S*)-3-hydroxy-2-(tetrahydro-2H-pyran-2-yloxy)pentan-3-yl)pyridin-3-yl)pyrrolidin-2-one by cleaving the protecting group with an acid, optionally glacial acetic acid, and optionally purifying.

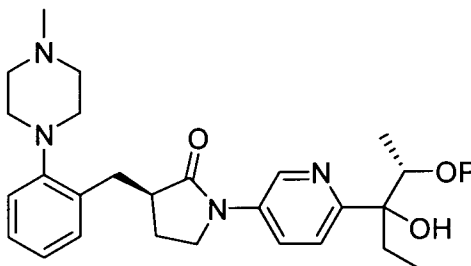
7. The process of claim 6, further comprising the resolution of the diastereomers.

8. The processes of either claim 6 or 7, for the preparation of (*R*)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2*S*,3*R*)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one; and

(*R*)-3-(2-(4-Methylpiperazin-1-yl)benzyl)-1-(6-((2*S*,3*S*)-2,3-dihydroxypentan-3-yl)pyridin-3-yl)pyrrolidin-2-one.

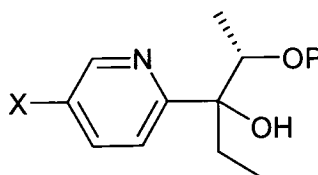
9. The processes of any of claims 6 to 8, wherein the prepared compound is at least 98% pure.

10. The process to prepare a compound of formula 1-ia:



formula 1-ia

wherein P is an appropriate protecting group; comprising the coupling of (*R*)-3-(2-(4-methylpiperazin-1-yl)benzyl)pyrrolidin-2-one and a compound of formula 1-ib



formula 1-ib

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wherein X is a halogen with atomic number less than or equal to Br or I, and P is an appropriate protecting group.

11. The process of claim 10, wherein P is

C₁-C₄ alkyl optionally substituted as valency allows with -oxyC₁-C₄alkyl, nitro,
5 -oxybenzyl optionally substituted on phenyl of the benzyl with up to 3 substituents independently selected from -oxyC₁-C₄alkyl further substituted with silyl further substituted with C₁-C₄alkyl as valency allows;

C₃-C₅alkenyl;

C₅-C₆ heterocycloalkyl optionally substituted with C₁-C₄alkyl;

10 benzyl optionally substituted on phenyl of the benzyl with up to 3 substituents independently selected from C₁-C₃alkyl, -oxyC₁-C₄alkyl, or nitro; or

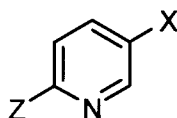
silyl substituted as valency allows with substituents independently selected from the group consisting of C₁-C₄alkyl, phenyl, and -oxyC₁-C₄alkyl.

12. The process of claim 10, wherein P is methoxymethyl, 1-ethoxyethyl, *tert*-butyl, 15 *tert*-butoxymethyl, 2-methoxyethoxymethyl, allyl, triethylsilyl, triisopropylsilyl, tetrahydro-2H-pyran, tetrahydro-2H-furan, 4-methoxybenzyl, 4-nitrobenzyl, (2-(trimethylsilyl)ethoxy)methyl, *tert*-butyldiphenylsilyl, *tert*-butyldimethylsilyl, benzyl, benzyloxymethyl, 1-[2-(trimethylsilyl)ethoxy]ethyl, and *tert*-butoxydiphenylsilyl.

13. The process of any of claims 10 to 12, wherein the reaction is conducted in an
20 aprotic organic solvent.

14. The processes of any of claims 10 to 13, further comprising the process to prepare a compound of formula 1-ib comprising:

(a) forming a mixture in a non-coordinating reaction inert solvent of a
25 dihalopyridine:



wherein Z is Br or I; and X is a halogen with atomic number less than or equal to the selected Z;

with an appropriate reactive species to give a compound of formula 1-ia;

(b) treating the mixture formed in step (a) with an (C₁-C₈)alkyl lithium compound; and

(c) quenching the mixture formed in (b) with a proton donor so as to form the compound of formula 1-ib.

- 5 15. The process of claim 14, wherein the appropriate reactive species is (2S)-2-(tetrahydro-2*H*-pyran-2-yloxy)pentan-3-one, (S)-2-((2-(trimethylsilyl)ethoxy)methoxy)-pentan-3-one, or (S)-2-(*tert*-butyldiphenylsilyloxy)pentan-3-one.