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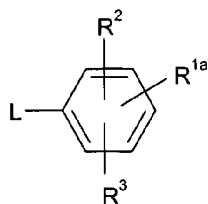
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(54) Title: PROCESS



(III)

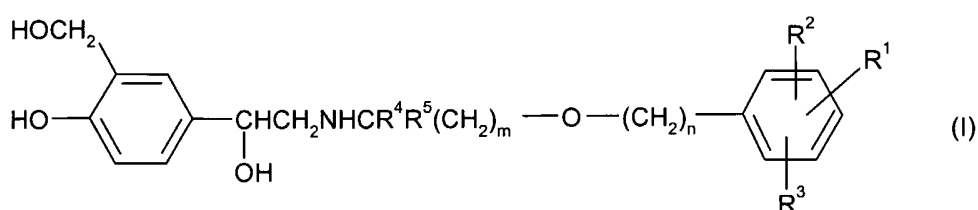
(57) Abstract: The present invention relates to a novel process for the preparation of phenethanolamine derivatives, which process comprises the step of reacting a compound of formula $\text{RO}(\text{CH}_2)_n\text{BR}^a\text{R}^b$ with a compound of formula (III).

Process

The present invention is concerned with a novel process for the preparation of phenethanolamine derivatives.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2 -adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders.

Thus, for example, International Application WO 02/066422 describes compounds of formula (I):



and salts, solvates, and physiologically functional derivatives thereof, wherein:

m is an integer of from 2 to 8;
 n is an integer of from 3 to 11, preferably from 3 to 7;
 with the proviso that m + n is 5 to 19, preferably 5 to 12;

R^1 is $-XSO_2NR^6R^7$

wherein X is $-(CH_2)_p-$ or C_{2-6} alkenylene;
 R^6 and R^7 are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, $C(O)NR^8R^9$, phenyl, and phenyl (C_{1-4} alkyl)-, or R^6 and R^7 , together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and R^6 and R^7 are each optionally substituted by one or two groups selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy-substituted C_{1-6} alkoxy, $-CO_2R^8$, $-SO_2NR^8R^9$, $-CONR^8R^9$, $-NR^8C(O)R^9$, or a 5-, 6- or 7-membered heterocyclic ring;
 R^8 and R^9 are independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and phenyl (C_{1-4} alkyl)-; and
 p is an integer of from 0 to 6, preferably from 0 to 4;

R^2 and R^3 are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo, phenyl, and C_{1-6} haloalkyl; and

R⁴ and R⁵ are independently selected from hydrogen and C₁₋₄alkyl with the proviso that the total number of carbon atoms in R⁴ and R⁵ is not more than 4.

5 In the compounds of formula (I) the group R¹ is preferably attached to the meta-position relative to the -O-(CH₂)_n- link.

R¹ preferably represents -SO₂NR⁶R⁷ wherein R⁶ and R⁷ are independently selected from hydrogen and C₁₋₆alkyl, more preferably R¹ is -SO₂NH₂.

10 R⁴ and R⁵ are preferably independently selected from hydrogen and methyl, more preferably R⁴ and R⁵ are both hydrogen.

m is suitably 4, 5, or 6, and n is suitably 3, 4, 5 or 6. Preferably m is 5 or 6 and n is 3 or 4, such that m + n is 8, 9 or 10, preferably 9.

15

Particularly preferred compounds of the invention include:

3-(4-[[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl)amino)hexyl]oxy}butyl)benzenesulfonamide; and

20 3-(3-[[7-((2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl]phenyl]ethyl)-amino]heptyl]oxy}propyl)benzenesulfonamide.

and salts, solvates, and physiologically functional derivatives thereof.

25 The compounds of formula (I) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents may be used, for example, as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

Salts of formula (I) include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballic, cinnamic, substituted cinnamic (for example, phenyl, methyl, methoxy or halo substituted cinnamic, including 4-phenyl, 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic,

4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

Particularly preferred salts of compounds of formula (I) include the cinnamate, 4-methoxycinnamate, 4-methylcinnamate, naphthalenepropenoate and 4-phenylcinnamate salts.

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the parent compound of formula (I) for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Pharmaceutically acceptable esters of the compounds of formula (I) may have a hydroxyl group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid ester.

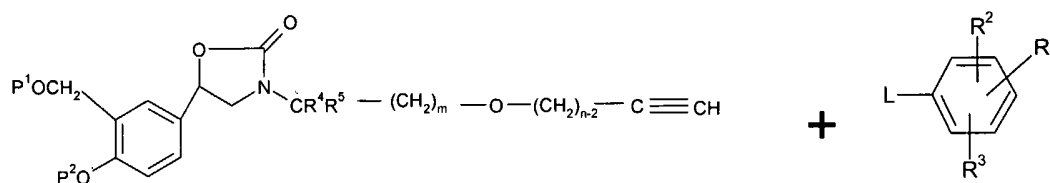
The compounds of formula (I) are selective β_2 -adrenoreceptor agonists. Compounds of formula (I) also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have shown an improved therapeutic index in animal models relative to existing long-acting β_2 -agonist bronchodilators. As such, they may be suitable for once-daily administration.

Compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2 -adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, including seasonal and allergic rhinitis).

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

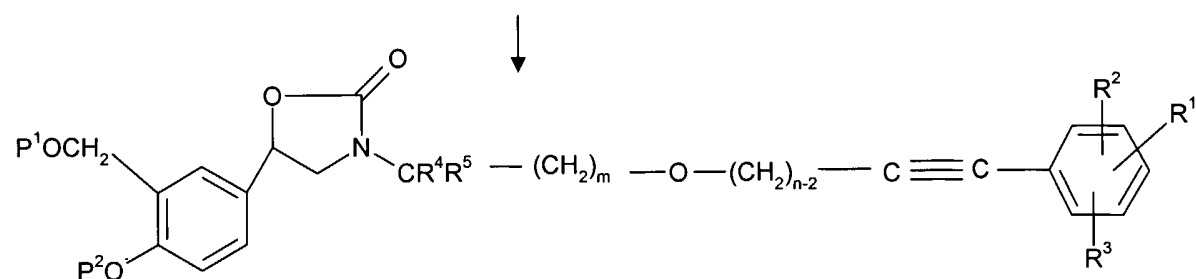
WO 02/066422 describes processes (a) – (d) for preparing compounds of formula (I). The relevant stages of processes (a) and (b) described in WO 02/066422 may be represented schematically, as follows:

5 Process (a):



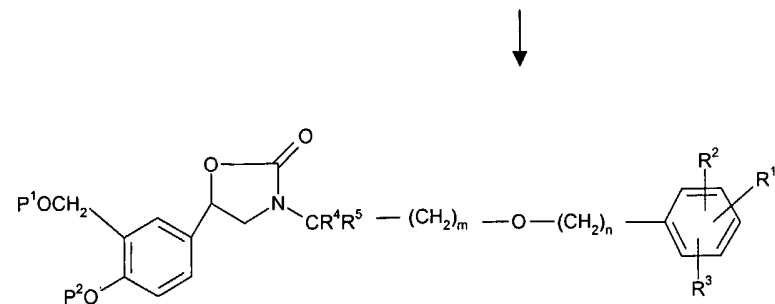
Intermediate 1

Intermediate 2

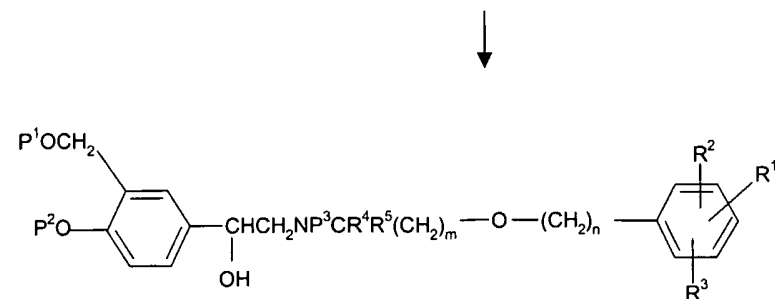


Intermediate 3

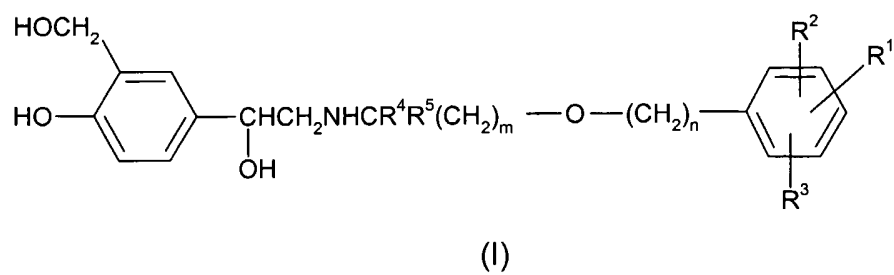
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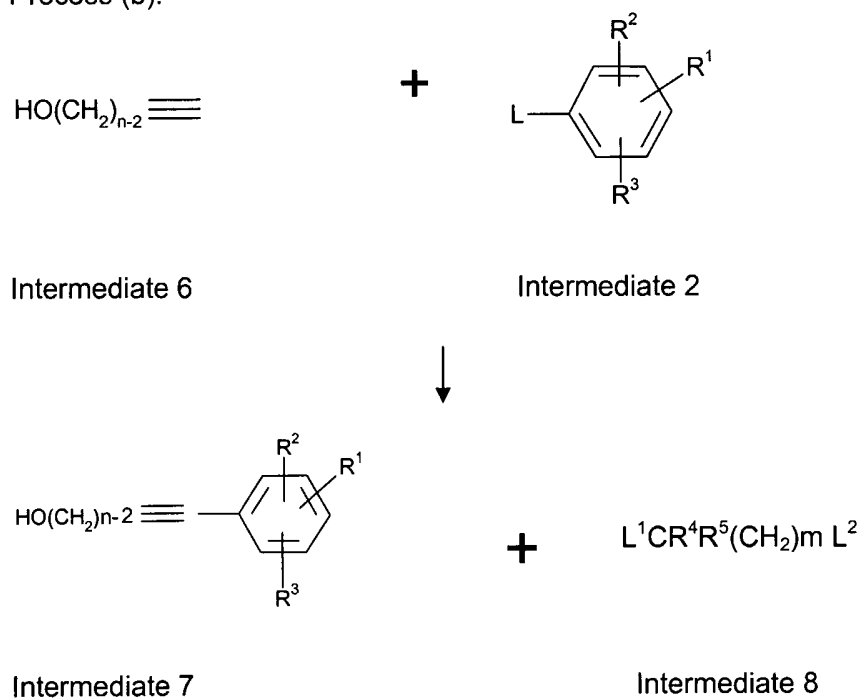
15 Intermediate 4

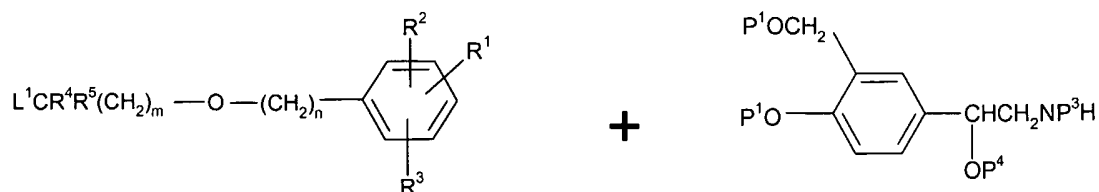


20 Intermediate 5



5 Process (b):

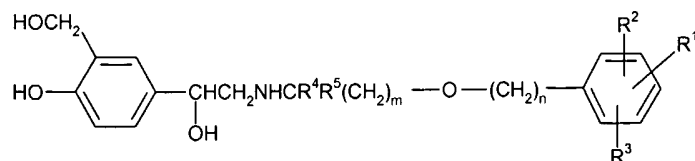




Intermediate 10

Intermediate 11

5



Formula (I)

10 In the above reaction schemes R^1 , R^2 , R^3 , R^4 , R^5 , m and n are as defined hereinabove for formula (I), P^1 , P^2 , P^3 and P^4 each represent hydrogen or a protecting group, as defined in more detail hereinafter, and L , L^1 and L^2 each represent a leaving group, for example a halo group (typically bromo or iodo) or a sulphonate such as an alkyl sulphonate (typically, methanesulphonate), an arylsulphonate (typically, toluenesulphonate), or a haloalkyl sulphonate (typically, trifluoromethanesulphonate).

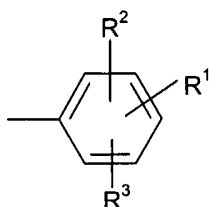
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Process (c) described in WO 02/066422 also proceeds via Intermediate 7 as described above.

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Process (d) described in WO 02/066422 proceeds via an intermediate which corresponds to Intermediate 5, but wherein P^3 represents a chiral auxiliary, such as the S-isomer and/or R-isomer of phenyl glycinol or a substituted derivative thereof.

Thus, in order to introduce the aryl moiety



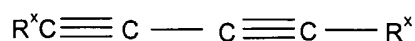
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each of the processes described proceeds at some stage of the synthesis via a reaction between an alkyne (eg. Intermediate 1 or Intermediate 6 described above) and an aryl compound (Intermediate 2 above). This coupling, known as the Sonogashira reaction, is

conveniently effected in the presence of a catalyst system such as bis (triphenylphosphine) palladium dichloride and a cuprous, Cu(I), species such as cuprous iodide, with an organic base such as a trialkylamine, for example, triethylamine, in a suitable solvent, for example acetonitrile or dimethylformamide. The resulting alkyne may then be reduced, either with or without being isolated to convert the triple bond to a single bond. The reduction may be effected by any suitable method such as hydrogenation in the presence of a catalyst, for example, palladium/charcoal or platinum oxide.

However, the Sonogashira coupling and subsequent reduction have certain disadvantages which tend to complicate the overall process.

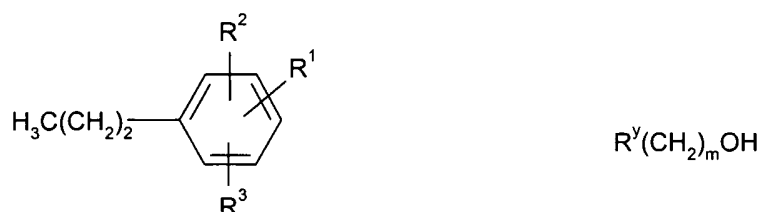
Thus, under the conditions of the coupling reaction, the alkyne intermediate eg. Intermediate 1 (or a variant thereof) has a tendency to form dimers, trimers or higher oligomers, for example of the formula:



wherein R^x represents the side chain of the relevant alkyne intermediate eg. Intermediate 1 above.

Therefore, the alkyne intermediate eg. Intermediate 1 (or a variant thereof) must be used in excess in order that the reaction proceeds to completion. This is of course economically undesirable, especially where chiral intermediates are employed. Furthermore the presence of the oligomerised intermediate introduces additional impurities into the reaction mixture. On a laboratory scale chromatography can be utilised to effect purification, but this is not suitable for larger scale preparations.

In addition, hydrogenation of the alkyne intermediate in the routes shown above, eg. Intermediate 3 or Intermediate 9, may in some circumstances also give rise to unwanted by-products. Thus, when n is 3, hydrogenation, for example using a palladium or platinum catalyst may result in cleavage of the chain to give the hydrogenolysis products, namely the corresponding alcohol and aralkyl compounds:



where R^y is the appropriate moiety corresponding to Intermediate 3 or Intermediate 9.

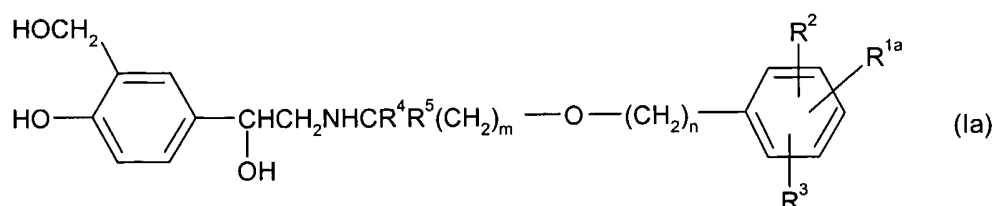
We have now found that in the synthesis of compounds of formula (I) use of an alkyne intermediate (and its associated disadvantages) may be avoided by utilising in its place a boron compound of formula (II):



5 as defined hereinafter.

In a first aspect therefore the present invention provides a process for the preparation of a compound of formula (Ia)

10



or a salt, solvate, or physiologically functional derivatives thereof, wherein:

- 15 m is an integer of from 2 to 8;
 n is an integer of from 3 to 11, preferably from 3 to 7;
 with the proviso that m + n is 5 to 19, preferably 5 to 12;

20 R^{1a} is hydrogen or $-\text{XSO}_2\text{NR}^6\text{R}^7$

20

wherein X is $-(\text{CH}_2)_p-$ or C_{2-6} alkenylene;

R^6 and R^7 are independently selected from hydrogen, C_{1-6} alkyl,

C_{3-7} cycloalkyl, $\text{C}(\text{O})\text{NR}^8\text{R}^9$, phenyl, and phenyl (C_{1-4} alkyl)-,

or R^6 and R^7 , together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring,

25 and R^6 and R^7 are each optionally substituted by one or two groups selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy-substituted C_{1-6} alkoxy, $-\text{CO}_2\text{R}^8$, $-\text{SO}_2\text{NR}^8\text{R}^9$, $-\text{CONR}^8\text{R}^9$, $-\text{NR}^8\text{C}(\text{O})\text{R}^9$, or a 5-, 6- or 7-membered heterocyclic ring;

R^8 and R^9 are independently selected from hydrogen, C_{1-6} alkyl,

30 C_{3-6} cycloalkyl, phenyl, and phenyl (C_{1-4} alkyl)-; and

p is an integer of from 0 to 6, preferably from 0 to 4;

R^2 and R^3 are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo, phenyl, and C_{1-6} haloalkyl; and

35

R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4,

which process comprises the step of reacting a compound of formula (II):

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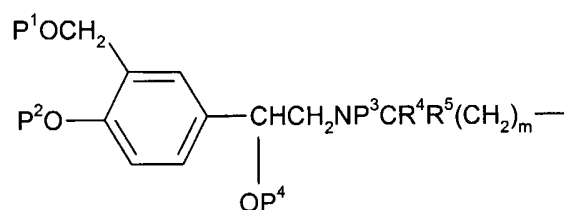
wherein n is as defined for formula (Ia);

R^a and R^b are each independently selected from hydrogen, alkyl, cycloalkyl, or aryloxy or together with the boron atom to which they are attached correspond to a cyclic boron compound such as 9-borabicyclo[3.3.1]nonane; and

10

R is hydrogen or a moiety selected from:

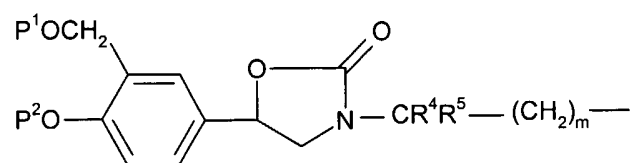
15 (i)



wherein R^4 , R^5 and m are as hereinbefore defined for compounds of formula (Ia) and P^1 , P^2 , P^3 and P^4 each independently represent hydrogen or a protecting group or P^3 represents a chiral auxiliary;

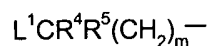
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(ii)



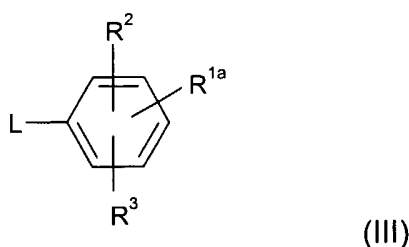
wherein P^1 , P^2 , R^4 and R^5 and m are as hereinbefore defined; and

25 (iii)



wherein L^1 is a leaving group, eg. as defined above;

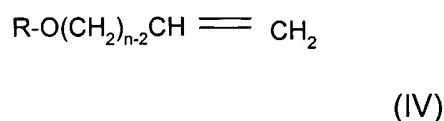
with a compound of formula (III)



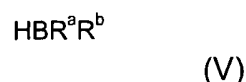
wherein R^{1a} , R^2 , R^3 and L are as hereinbefore defined.

- 5 In the process of the present invention reaction of a compound (II) with a compound (III) may be effected in the presence of a catalyst such as palladium acetate, $PdCl_2$, $Pd(PPh_3)_4$, or $Pd(dba)_2$; and a phosphine such as triphenylphosphine, (di-tert-butylphosphino)biphenyl, tricyclohexylphosphine, triisopropylphosphine, tricyclopentylphosphine, or tri-tert-butylphosphine; and a base such as aqueous
 10 potassium or sodium phosphate, potassium or sodium carbonate, or sodium acetate.

The boron compound of formula (II) may be prepared by reacting an olefin of formula (IV):



- 15 with a boron compound serving to introduce the group $-BR^aR^b$, which may be for example a compound of formula (V):



- 20 wherein R^a and R^b are as hereinbefore defined; or with a cyclic boron compound such as 9-borabicyclo[3.3.1]nonane.

In the compound of formula (V) R^a and R^b preferably represent bulky groups. Examples of the compound (V) include thexylborane, catchecolborane and disiamylborane.

- 25 The compound of formula (II) is preferably prepared in situ.

For optimum efficiency in subsequent stages it is preferred that the compound of formula (IV) is completely converted into a compound of formula (II).

30

Compounds of formula (IV) may be prepared by standard methods well known to those skilled in the art. Thus for example a compound of formula (IV) may be prepared from the corresponding dihaloalkane and hydroxyalkene by conventional chemistry, typically in the presence of an inorganic base such as aqueous sodium hydroxide, under phase transfer conditions, in the presence of a salt such as a tetraalkylammonium bromide. Alternatively a compound of formula (IV) may be prepared by selective mono-bromination of the corresponding diol, e.g. by reaction with aqueous hydrobromic acid in a solvent such as toluene, followed by reaction with an alkenyl halide, e.g. allyl bromide. The reaction may be effected under basic conditions e.g. using aqueous sodium hydroxide and in the presence of a tetraalkylammonium bromide.

In a second aspect the present invention provides a process for preparing a compound of formula (Ia) which comprises the step of reacting an olefin of formula (IV) with a boron compound of formula (V) and, without isolation of the resulting product, further reacting with a compound of formula (III).

The process of the present invention avoids the use of an alkyne intermediate, such as Intermediate 1, 3 or 9 above, and hence avoids the problems associated with such intermediates, in particular formation of dimers or higher oligomers, and those associated with the hydrogenation step, such as the cleavage reaction described hereinabove.

The process of the present invention provides a shorter and cleaner route to intermediate in the synthesis of compounds of formula (Ia), and ultimately to compounds of formula (Ia) themselves.

Depending on the nature of the group R, the product of the reaction of (II) and (III) may then be subject to one or more further reactions to provide compound of formula (Ia).

It will be appreciated that when R is a moiety (i) and P¹, P², P³ and P⁴ each represent hydrogen, then the product of the reaction of (II) and (III) will be a compound of formula (Ia).

When R is a moiety (i) wherein at least one of P¹, P², P³ or P⁴ is a protecting group, or when R is a moiety (ii), it will be appreciated that one or more deprotection steps will be required to obtain a compound of formula (Ia).

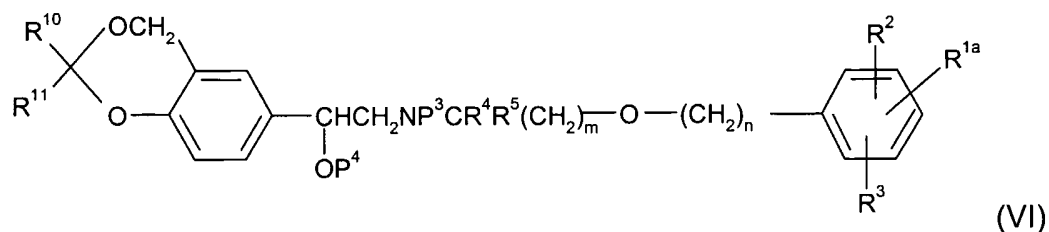
Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by P¹, P² and P⁴ are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by P³ include benzyl,

α -methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino or hydroxyl function. For example, the $-\text{CH}(\text{OH})$ group may be orthogonally protected as $-\text{CHOP}^4$ using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene and Peter G M Wuts (see above).

The deprotection to yield a compound of formula (Ia), may be effected using conventional techniques. Thus, for example, when P^1 , P^2 , and/or P^3 is an aralkyl group, this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

When P^1 and/or P^2 is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by P^3 may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene and Peter G M Wuts (see above). In a particular embodiment, P^1 and P^2 may together represent a protecting group as in the compound of formula (VI):



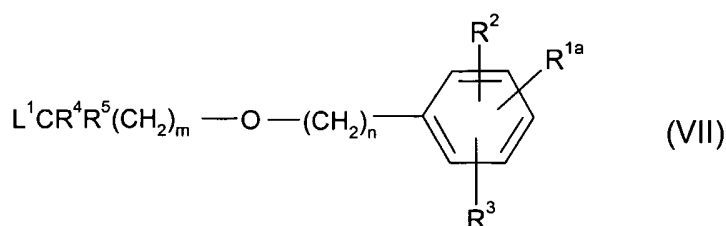
or a salt or solvate thereof, wherein R^{1a} , R^2 , R^3 , R^4 , R^5 , P^3 , P^4 , m , and n are as defined for the compound of formula (Ia) and R^{10} and R^{11} are independently selected from hydrogen, C_{1-6} alkyl, or aryl or R^{10} and R^{11} together form a C_{3-7} cycloalkyl ring. In a preferred aspect, both R^{10} and R^{11} are methyl.

A compound of formula (VI) may be converted to a compound of formula (Ia) by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketalisation in an alcohol, for example ethanol, in the presence of a catalyst such as an acid (for example, toluenesulphonic acid or a sulphonic acid ion

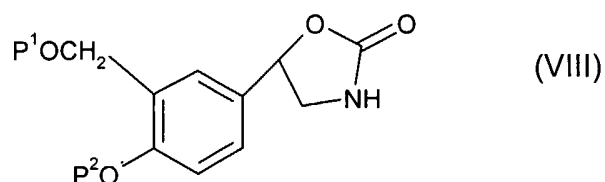
exchange column such as SCX-2) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

When P^3 represents a chiral auxilliary it may typically be removed by hydrogenolysis, using for example a palladium or carbon catalyst, or palladium hydroxide (Pearlman's catalyst).

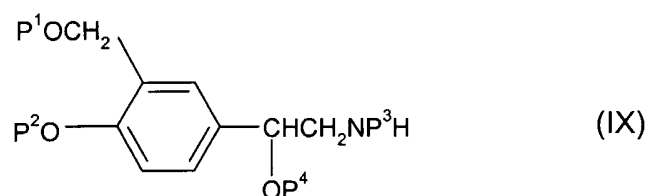
It will further be appreciated that where R is a moiety (iii) the reaction of (II) and (III) will initially provide a compound of formula (VII):



which may be reacted with a compound of formula (VIII):



or formula (IX):



wherein P^1 , P^2 , P^3 and P^4 are as defined above, to give a compound corresponding to Intermediate 4 or Intermediate 5 above, followed if necessary by removal of any protecting groups or functions.

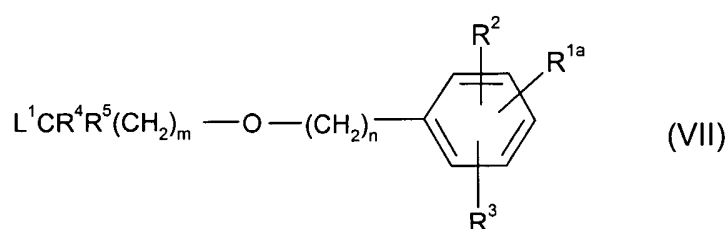
The reaction of compounds of formulae (VII) and (VIII) is optionally effected in the presence of an organic base such as a trialkylamine, for example diisopropylethylamine, and in a suitable solvent, for example an alcohol, eg. ethanol, an ester eg. ethyl acetate; or an amide, eg. dimethyl formamide.

The coupling of a compound of formula (VII) with a compound of formula (IX) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, an inorganic base such as cesium carbonate, or an alkoxide eg. butoxide, in an aprotic solvent, for example, dimethyl formamide.

Compounds of formulae (VIII) and (IX) may be prepared for example as described in WO 02/066422.

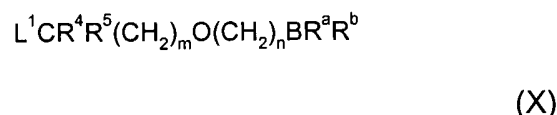
10

In a third aspect, the present invention provides a process for the preparation of a compound of formula (VII):



15

which comprises reacting a compound of formula (X):

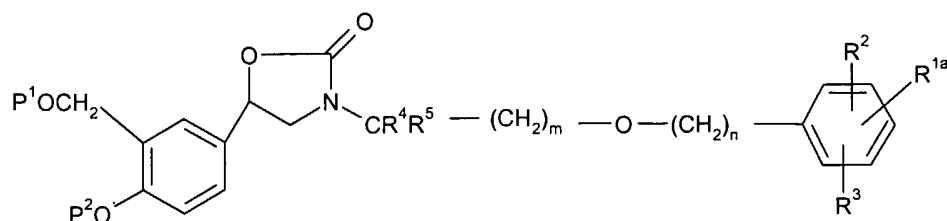


20 wherein R^a , R^b , R^4 , R^5 , L^1 , m and n are as defined hereinabove;

with a compound of formula (III) as defined hereinabove.

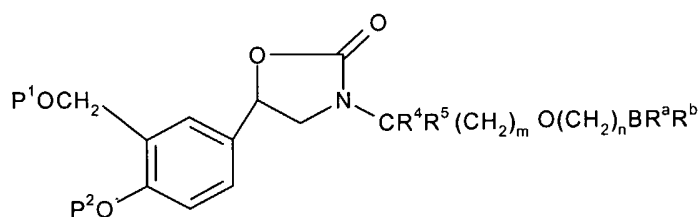
25 In a fourth aspect the present invention provides a process for the preparation of a compound of formula (VII) as defined hereinabove which comprises reacting a compound of formula (IV) with a boron compound of formula (V) and without isolation of the product further reacting with a compound of formula (III).

30 In a fifth aspect the present invention provides a process for the preparation of a compound of formula (XI):



which comprises reacting a compound of formula (XII):

5

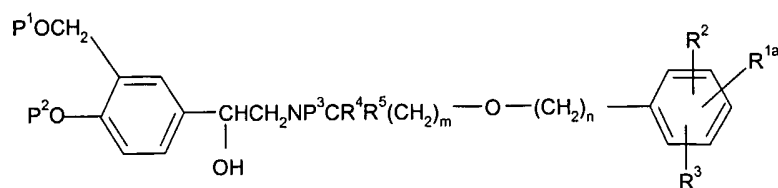


(XII)

10 with a compound of formula (III) as defined hereinabove.

In a sixth aspect the present invention provides a process for the preparation of a compound of formula (XI) which comprises reacting a compound of formula (IV) wherein R represents a moiety (ii) with a compound of formula (V) and without isolation of the product further reacting with a compound of formula (III).

In a seventh aspect the present invention provides a process for the preparation of a compound of formula (XIII):



20

(XIII)

which comprises reacting a compound of formula (II) wherein R represents a moiety (i) with a compound of formula (III) as defined hereinabove.

25

In an eighth aspect the present invention provides a process for the preparation of a compound of formula (XIII) which comprises reacting a compound of formula (IV) wherein

R represents a moiety (i) with a compound of formula (V) and without isolation of the product further reacting with a compound of formula (III).

- 5 For a better understanding of the present invention, the following non-limiting Examples are given by way of illustration.

Synthetic Examples

- 10 Throughout the examples, the following abbreviations are used:

LC: Liquid Chromatography

RT : retention time

THF : tetrahydrofuran

TBAB: tetrabutylammonium bromide

- 15 BBN : 9-borabicyclo[3.3.1]nonane

bp : boiling point

ca : circa

h : hour(s)

min : minute(s)

- 20 All temperatures are given in degrees centigrade.

GC system for Example 1(i) and (ii):

- | | | |
|----|--------------|--|
| | Column | 30 M x 0.25mm x 0.5 micron HP-5 |
| 25 | Temp Program | 50 C for 5 minutes
50 C to 290 C @ 10 C/min.
Hold @ 290 C for 5 min. |
| | Flow | 25 psi (~ 2.8 ml/min) , split 120ml/min |
| | Injector | 150 C |
| 30 | Detector | 300 C |

Example 1

3-{3-[(7-Bromoheptyl)oxy]propyl}benzenesulfonamide

35

(i) 7-bromoheptan-1-ol

To a solution of 1,7- heptanediol (104g, 0.79 mole) in toluene (1250ml) was added aq. HBr (48%, 105ml). The mixture was stirred vigorously and heated at 90°C for 30hr.

A further aliquot of aq HBr (25ml) was added and heating and stirring was continued.

- 40 After a total reaction time of 3 days, the reaction was cooled to room temperature. The lower, aqueous layer was discarded. The organic layer was washed with aq. NaOH (1M, 300ml) followed by water (300ml). The turbid organic extract was concentrated to give the *title compound* as a clear, yellow oil (143g) RT 14.60mins

(ii) 7-Bromoheptyl prop-2-enyl ether

A mixture of 7-bromoheptan-1-ol (100g, 0.49mol) and allyl bromide (92g, 0.76mol) was added at ca. 30 °C to a well stirred solution of 25% NaOH (1L) containing TBAB (8g, 5 mol%). The resulting bi-phasic mixture was stirred at ambient temperature for 7 hrs. The layers were left to settle and the lower aqueous layer then removed. The remaining organic layer was washed with water to give a cloudy yellow oil, which was distilled (0.23 mbar, 80-82 °C) to give the *title compound* as a clear, colourless oil (94g). RT 16.19mins

(iii) 3-{3-[(7-Bromoheptyl)oxy]propyl}benzenesulfonamide

To a solution of 9-BBN (0.5M in THF, 8.9vol, 1.05equiv) was added 7-bromoheptyl prop-2-enyl ether (1equiv). Following complete reaction the hydroborated olefin was added to a solution of 3-bromobenzenesulfonamide (1equiv), Pd(OAc)₂ (0.01equiv), and triphenylphosphine (0.02equiv) in aqueous sodium phosphate (2.5M, 3.4vol).

The mixture was then heated to ca 60°C until the reaction was complete. The mixture was cooled and the aqueous layer removed. Isopropyl acetate (4vol) was added to the mixture and solvent distilled out at atmospheric pressure (10vols). Petrol (6vol) was then added at 60°C followed by charcoal. Solids were filtered off and the mixture cooled to room temperature. The product was filtered off and washed with petrol/isopropyl acetate (2:1 – 2 vols) and dried *in vacuo* at 50°C to give an off white solid (ca 1.1 wts – 60 – 70% theory)

Retention time 5.95 min by HPLC (8 min run time)

¹H NMR (CDCl₃, 400MHz, ppm)

1.34-1.46 (m, 6H), 1.56-1.60 (m, 2H), 1.83-1.94 (m, 4H), 2.75-2.79 (m, 2H), 3.38-3.43 (m, 6H), 4.95 (s, 2H), 7.40-7.46 (m 2H), 7.74-7.77 (m, 2H)

Example 2

3-{3-[(7-Bromoheptyl)oxy]propyl}benzenesulfonamide

9-BBN (0.5M in THF) solution (9.4ml) was added at room temperature under nitrogen with stirring to 7-bromoheptyl prop-2-enyl ether (1g, 4.3mmol) and left for 3hrs. A solution of potassium phosphate (1.8g) in water (3ml) was added to the clear solution followed by 3-bromobenzenesulfonamide (1g 4.24mmol), Pd(OAc)₂ (10mg) and 2-(di-tert-butylphosphino)biphenyl (25mg). The biphasic mixture was stirred at ambient temperature for 1.5hrs at which point LC showed <0.5% a/a 3-bromobenzenesulfonamide and >88% a/a *title compound*. (The reaction mixture was used for experimental isolation methods so a yield of isolated material is not available.)

The product of Examples 1 and 2 may be further reacted to give 3-(3-[[7-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)heptyl]oxy}propyl)benzenesulfonamide and salts thereof such as the (E)-3-(naphthalen-2-yl)-2-propenoate salt, using for example
5 methods described in WO 02/066422

Example 3

3-{4-[(6-Bromohexyl)oxy]butyl}benzenesulfonamide

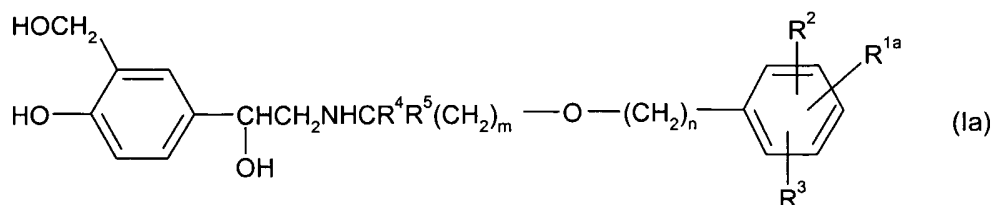
10

6-Bromohexylbut-3-enyl ether (0.8g, 3.4mmol) was added to 9-BBN (0.5M in THF) solution (10ml) at room temperature under nitrogen. After 1.5hrs the solution was added to a stirred mixture potassium phosphate (1.8g) in water (3ml) containing 3-bromobenzenesulfonamide (0.8g, 3.4mmol), Pd(OAc)₂ (10mg) and 2-(di-tert-butylphosphino)biphenyl (25mg). The biphasic mixture was stirred at ambient
15 temperature for 60hrs at which point LC showed 23% a/a of the unreacted 3-bromobenzenesulfonamide and 52% of the *title compound*.

3-{4-[(6-Bromohexyl)oxy]butyl}benzenesulfonamide may be further reacted to give 3-(4-
20 {6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl)amino)hexyl]oxy}butyl)benzenesulfonamide and salts thereof using for example methods described in WO 02/066422.

CLAIMS

1. A process for the preparation of a compound of formula (Ia)



or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;

n is an integer of from 3 to 11, preferably from 3 to 7;

with the proviso that m + n is 5 to 19, preferably 5 to 12;

R^{1a} is hydrogen or -XSO₂NR⁶R⁷

wherein X is -(CH₂)_p- or C₂₋₆ alkenylene;

R⁶ and R⁷ are independently selected from hydrogen, C₁₋₆alkyl,

C₃₋₇cycloalkyl, C(O)NR⁸R⁹, phenyl, and phenyl (C₁₋₄alkyl)-,

or R⁶ and R⁷, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring,

and R⁶ and R⁷ are each optionally substituted by one or two groups selected from halo,

C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, hydroxy-substituted C₁₋₆alkoxy, -CO₂R⁸, -SO₂NR⁸R⁹,

-CONR⁸R⁹, -NR⁸C(O)R⁹, or a 5-, 6- or 7-membered heterocyclic ring;

R⁸ and R⁹ are independently selected from hydrogen, C₁₋₆alkyl,

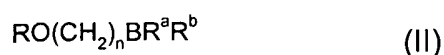
C₃₋₆cycloalkyl, phenyl, and phenyl (C₁₋₄alkyl)-; and

p is an integer of from 0 to 6, preferably from 0 to 4;

R² and R³ are independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo, phenyl, and C₁₋₆haloalkyl; and

R⁴ and R⁵ are independently selected from hydrogen and C₁₋₄alkyl with the proviso that the total number of carbon atoms in R⁴ and R⁵ is not more than 4;

which process comprises the step of reacting a compound of formula (II):

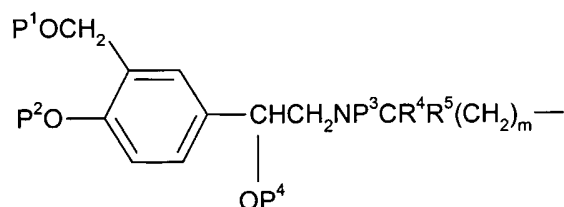


wherein n is as defined for formula (Ia);

R^a and R^b are each independently selected from hydrogen, alkyl, cycloalkyl, or aryloxy or together with the boron atom to which they are attached correspond to a cyclic boron compound such as 9-borabicyclo[3.3.1]nonane; and

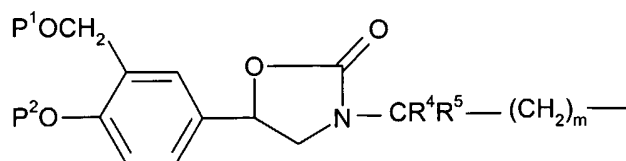
R is hydrogen or a moiety selected from:

(i)



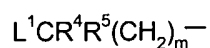
wherein R^4 , R^5 and m are as hereinbefore defined for compounds of formula (I) and P^1 , P^2 , P^3 and P^4 each independently represent hydrogen or a protecting group or P^3 represents a chiral auxiliary;

(ii)



wherein P^1 , P^2 , R^4 and R^5 and m are as hereinbefore defined; and

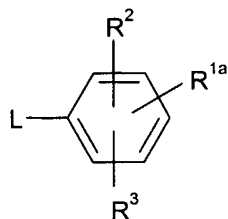
(iii)



wherein L^1 is a leaving group, eg. a halo group or a sulphonate;

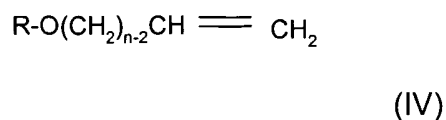
and R^a and R^b are each independently selected from hydrogen, alkyl, cycloalkyl or aryloxy;

with a compound of formula (III)



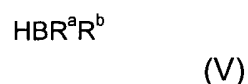
wherein R^{1a} , R^2 , and R^3 are as hereinbefore defined and L is a leaving group, eg. a halo group or a sulphonate.

2. A process according to claim 1 wherein the boron compound of formula (II) is prepared by reacting an olefin of formula (IV):



with a boron compound serving to introduce the group $-BR^aR^b$.

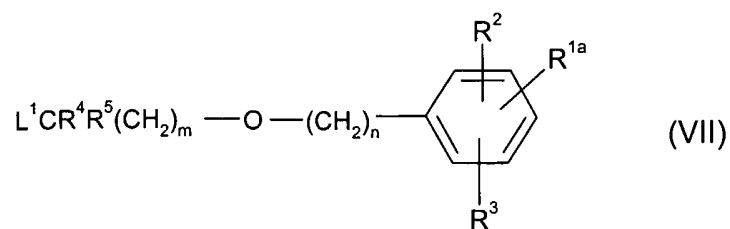
3. A process according to claim 2 wherein said boron compound is a compound of formula (V):



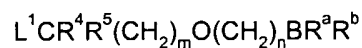
wherein R^a and R^b are as hereinbefore defined or is a cyclic boron compound such as 9-borabicyclo[3.3.1]nonane.

4. A process according to claim 2 or claim 3 which comprises the step of reacting an olefin of formula (IV) with a boron compound of formula (V) and, without isolation of the resulting product, further reacting with a compound of formula (III).

5. A process for the preparation of a compound of formula (VII):



which comprises reacting a compound of formula (X):

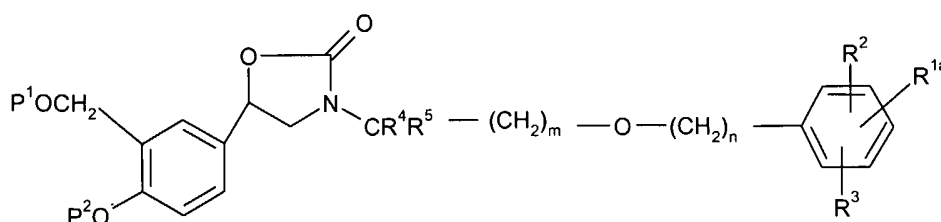


wherein R^a , R^b , R^4 , R^5 , L^1 , m and n are as defined hereinabove;

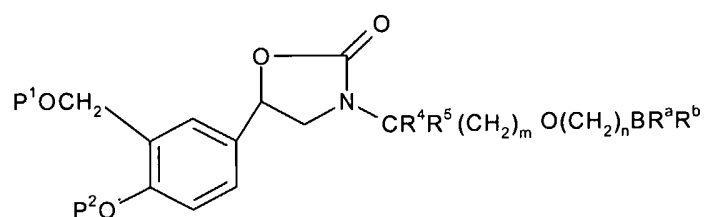
with a compound of formula (III) as defined in claim 1.

6. A process for the preparation of a compound of formula (VII) as defined hereinabove which comprises reacting a compound of formula (IV) with a boron compound of formula (V) and without isolation of the product further reacting with a compound of formula (III).

7. A process for the preparation of a compound of formula (XI):



which comprises reacting a compound of formula (XII):

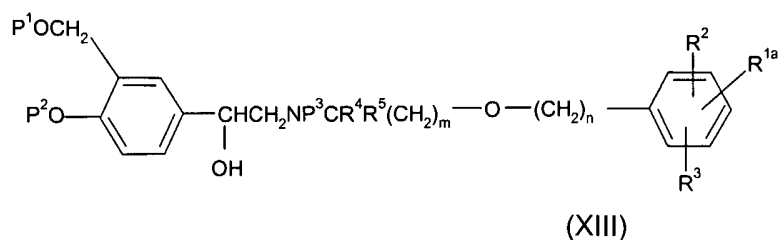


(XII)

with a compound of formula (III) as defined in claim 1.

8. A process for the preparation of a compound of formula (XI) which comprises reacting a compound of formula (IV) wherein R represents a moiety (ii) with a compound of formula (V) and without isolation of the product further reacting with a compound of formula (III).

9. A process for the preparation of a compound of formula (XIII):



which comprises reacting a compound of formula (II) wherein R represents a moiety (i) with a compound of formula (III) as defined in claim 1.

10. A process for the preparation of a compound of formula (XIII) which comprises reacting a compound of formula (IV) wherein R represents a moiety (i) with a compound of formula (V) and without isolation of the product further reacting with a compound of formula (III).

11. A process according to any of claims 1 to 10 wherein in the compound of formula (Ia) m is 6 and n is 4.

12. A process according to any of claims 1 to 10 wherein in the compound of formula (Ia) m is 7 and n is 3.

13. A process according to any of claims 1 to 12 wherein in the compound of formula (Ia) R¹ is -SONHR⁶R⁷.

14. A process according to claim 13 wherein R⁶ and R⁷ each represent hydrogen.

15. A process according to any of claims 1 to 14 wherein in the compound of formula (Ia) R², R³, R⁴ and R⁵ each represent hydrogen.