

Process for the Preparation of Amino Acids Useful in the
Preparation of Peptide Receptor Modulators

FIELD OF THE INVENTION

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The present invention provides process useful for the preparation of intermediates which are useful in the preparation of amino acids useful in preparing peptide receptor modulators, for example agonists or partial
10 agonists of such peptide receptors. Such peptide receptor modulators include, for example glucagon like peptide-1 receptor modulators which are useful for the amelioration of the diabetic condition.

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BACKGROUND OF THE INVENTION

It is desirable to develop peptide receptor modulators which may be useful for affecting the native activity of such a receptor and thus for affecting the
20 biological pathways in which such a receptor is involved.

For example, GLP-1 is an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism, and has been identified as a very potent and efficacious stimulator
25 for insulin release. Therefore, it is desirable to develop modulators of peptide receptors, for example the GLP-1 receptor, which will affect the native activity of the receptor to effect a desired biological response.

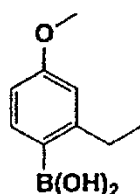
The present invention therefore provides a novel
30 process for the preparation of intermediates useful in the preparation of amino acid which may be used in

preparing peptide receptor modulators, for example GLP-1 receptor modulators, including agonists or partial agonists.

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SUMMARY OF THE INVENTION

In one aspect, the present invention is directed to a process for the preparation of a compound of Formula I:



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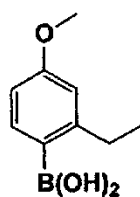
the process comprising the steps of:

methylation of 3-ethylphenol to produce 3-ethylanisole;

15 bromination of the 3-ethylanisole at a position para to a methoxy group to produce 4-bromo-3-ethyl anisole;

conversion of the 4-bromo-3-ethyl anisole, the conversion comprising (a) reacting the 4-bromo-3-ethyl anisole with n-butyl lithium to produce the lithium salt of the corresponding anion of the 4-bromo-3-ethyl anisole; (b) reacting the lithium salt of the anion of the 4-bromo-3-ethyl anisole with triethyl borate; and (c) quenching with aqueous acid.

20 In another aspect, the present invention is directed to a process for the preparation of a compound of Formula I:

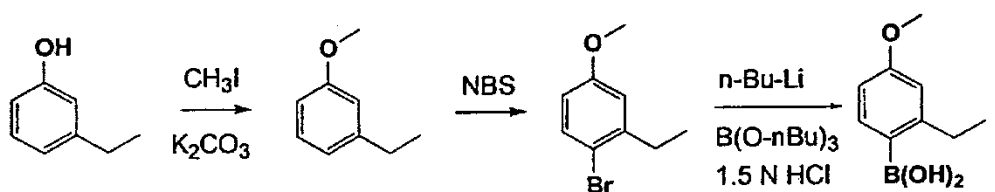


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according to Scheme 1, as follows:

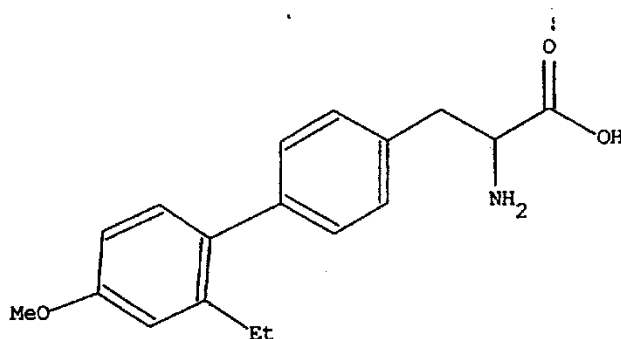
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Scheme 1



In another aspect, the present invention is directed to a process for the preparation of a compound of Formula

10 II:



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the process comprising the steps of:

methylation of 3-ethylphenol to produce 3-ethylanisole;

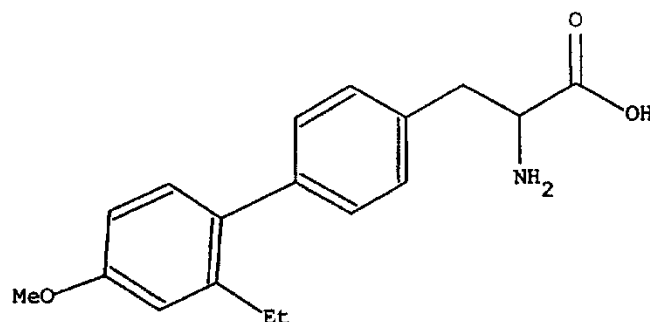
bromination of the 3-ethylanisole at a position para to a methoxy group to produce 4-bromo-3-ethyl anisole;

conversion of the 4-bromo-3-ethyl anisole, the conversion comprising (a) reacting the 4-bromo-3-ethyl anisole with n-butyl lithium to produce the lithium salt of the corresponding anion of the 4-bromo-3-ethyl anisole; (b) reacting the lithium salt of the anion of the 4-bromo-3-ethyl anisole with tri-n-butyl borate; (c) quenching with aqueous acid;

10 reacting the resultant 2-ethyl-4-methoxy-phenylboronic acid with the triflic anhydride of a suitably protected tyrosine amino acid in the presence of a Palladium catalyst (Suzuki coupling); and

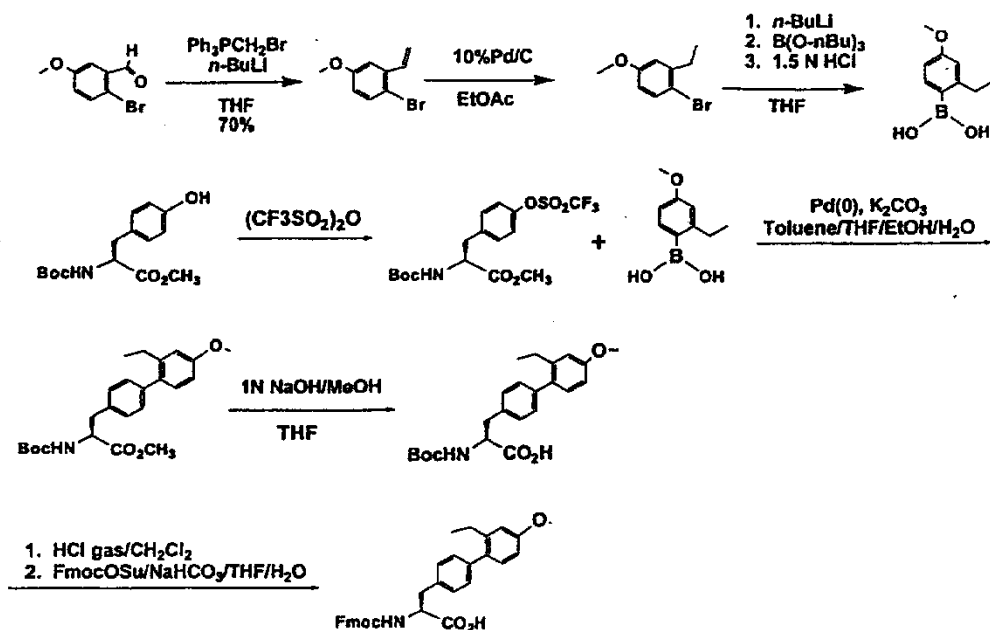
removing the carboxyl protecting group from the resulting biphenyl amino acid to yield the amino-protected amino acid useful for incorporation into a peptide receptor modulator.

In another aspect, the present invention is directed to a process for the preparation of a compound of Formula II:



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according to Scheme 2, as follows:



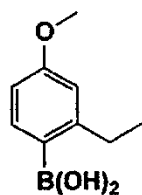
DETAILED DESCRIPTION OF THE INVENTION

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The present invention is directed to processes for the preparation of intermediates useful in the preparation of amino acids useful in preparing peptide receptor modulators, for example GLP-1 receptor modulators, including agonists or partial agonists.

Such peptide receptor modulators may be useful for affecting the native activity of such a receptor and thus for affecting biological pathways in which such a receptor is involved. For example, GLP-1 is an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism, and has been identified as a very potent and efficacious stimulator for insulin release.

Processes of the present invention are useful for preparing compounds of Formula I:

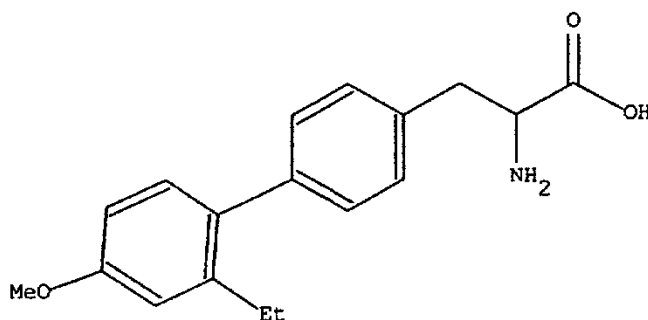


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which are useful in the preparation of amino acids of
Formula II:

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Compounds of Formula II are useful in the preparation of
peptide receptor modulators.

Example 1

Synthesis of (2-Ethyl-4-methoxy)phenyl boronic acid

(2-Ethyl-4-methoxy)phenyl boronic acid (Formula I)
was prepared as follows, and as shown in Scheme 1: (1)
methylation of 3-ethylphenol to produce 3-ethylanisole;
(2) bromination of the 3-ethylanisole at a position *para*

to a methoxy group to produce 4-bromo-3-ethyl anisole;
(3) conversion of the 4-bromo-3-ethyl anisole, the
conversion comprising (a) reacting the 4-bromo-3-ethyl
anisole with n-butyl lithium to produce the lithium salt
5 of the corresponding anion of the 4-bromo-3-ethyl
anisole; (b) reacting the lithium salt of the anion of
the 4-bromo-3-ethyl anisole with tri-n-butyl borate; and
(c) quenching with aqueous acid.

Specifically, To a mixture of 3-Ethylphenol (50 g, 0.4
10 mol, 98 % pure, Fluka) and K_2CO_3 (283 g, 2.05 mol) in dry
acetone (500 ml) was added methyliodide (290 g, 2.05
mol). The reaction mixture was transferred to an
autoclave and refluxed at 70 oC overnight. The reaction
mixture was filtered through a Celite pad. The pad was
15 washed with acetone and the combined filtrate and washes
were concentrated. The product was dissolved in DCM,
filtered and evaporated to dryness. Yield: 50 g, 90 %, as
a brown liquid.

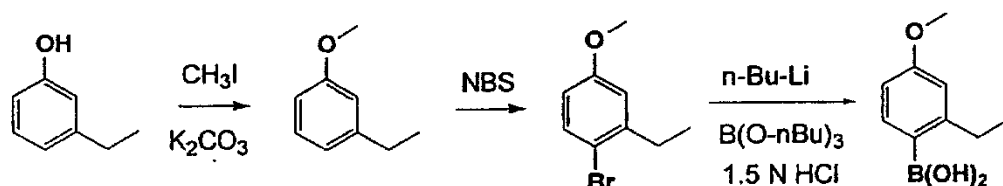
3-Ethylanisole (50 g, 0.3676 mol) and N-
20 bromosuccinimide (72 g, 0.4 mol) in acetonitrile (1 L)
were stirred for 8 hr under dark at RT. The reaction
mixture was concentrated below 40 oC and the residue
obtained was redissolved in CCl_4 and filtered. The
filtrate was concentrated and the product was purified by
25 fractional distillation. Yield: 35 g, 43 %, as pale
yellow liquid.

A solution of 4-bromo-3-ethyl anisole (94 g, 0.437
mol) in THF (900 ml) was cooled to -78 oC. n-Butyl
lithium (249 ml, 0.55 mol) was added dropwise at the same
30 temperature. Stirring was continued for 1 hr at -78 oC.
Tri-n-butyl borate (177 ml, 0.655 mol) was added slowly

at -78 oC. The cooling bath was removed, the reaction mixture was allowed to warm to 0 oC and was quenched with 1.5 N hydrochloric acid at 0 oC. The organic layer was separated. The aqueous layer was extracted with ethylacetate and the combined organic layers were washed with brine and concentrated. The residue obtained was stirred in pet-ether for 30 min. The solid obtained was filtered and dried under vacuum. Yield: 65 g, 82 %, as a white solid.

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Scheme 1



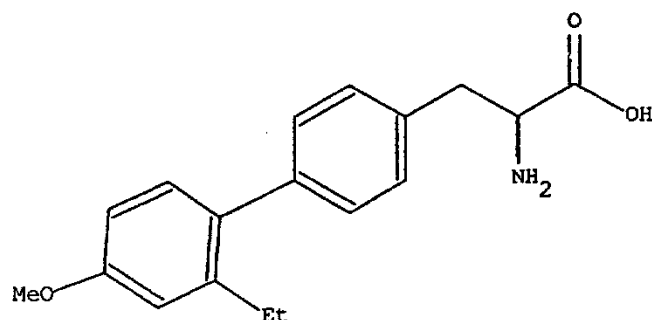
Example 2

Amino Acid Synthesis

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The resultant (2-Ethyl-4-methoxy)phenyl boronic acid was used to prepare the amino acid of Formula II, according to Scheme 2:

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X_{aa2} is Aib;
X_{aa3} is E;
X_{aa4} is G;
X_{aa5} is a T;
5 X_{aa6} is L- α -Me-Phe(2-Fluoro);
X_{aa7} is T;
X_{aa8} is S;
X_{aa9} is D;
X_{aa10} is a compound of Formula II; and
10 X_{aa11} is 4-(2'-methylphenyl)-3-pyridylalanine-NH₂.

Where the above amino acid abbreviations refer to those commonly understood in the art.

Peptide receptor modulators produced from
15 intermediate prepared by processes of the present invention may be prepared by any suitable manner recognized by one of skill in the art of peptide chemistry. For example, the peptides can be synthesized in a stepwise manner on an insoluble polymer support
20 (also referred to as "resin") starting from the C-terminus of the peptide. A synthesis is begun by appending the C-terminal amino acid of the peptide to the resin through formation of an amide or ester linkage. This allows the eventual release of the resulting peptide
25 as a C-terminal amide or carboxylic acid, respectively. Alternatively, in cases where a C-terminal amino alcohol is present, the C-terminal residue may be attached to 2-Methoxy-4-alkoxybenzyl alcohol resin (SASRINTM, Bachem Bioscience, Inc., King of Prussia, PA) as described
30 herein and, after completion of the peptide sequence assembly, the resulting peptide alcohol is released with

LiBH₄ in THF (see J. M. Stewart and J. D. Young, *supra*, p. 92). Also, a peptide synthesizer may be used, for example an Advanced Chemtech Multiple Peptide Synthesizer (MPS396) or an Applied Biosystems Inc. peptide
 5 synthesizer (ABI 433A).

The following abbreviations may be used herein:

Ph = phenyl	DCM = dichloromethane
Bn = benzyl	30 n-BuLi = n-butyllithium
10 i-Bu = iso-butyl	Pd/C = palladium on carbon
i-Pr = iso-propyl	TEA = triethylamine
Me = methyl	min = minute(s)
Et = ethyl	h or hr = hour(s)
Pr = n-propyl	35 L = liter
15 Bu = n-butyl	mL or ml = milliliter
TMS = trimethylsilyl	μL = microliter
Et ₂ O = diethyl ether	g = gram(s)
HOAc or AcOH = acetic acid	mg = milligram(s)
20 MeCN = acetonitrile	40 mol = mole(s)
DMF = N,N-dimethylformamide	mmol = millimole(s)
EtOAc = ethyl acetate	meq = milliequivalent
THF = tetrahydrofuran	rt = room temperature
25 TFA = trifluoroacetic acid	sat or sat'd = saturated
NMP = N-methylpyrrolidone	45 aq. = aqueous
LiBH ₄ = lithium borohydride	mp = melting point
DIEA = Diisopropylethylamine	Bip = biphenylalanine
50 Fmoc = fluorenylmethoxycarbonyl	

Boc or BOC = tert-butoxycarbonyl

NBS = N-Bromosuccinimide

TLC = thin layer chromatography

HPLC = high performance liquid chromatography

5 LC/MS = high performance liquid chromatography/mass
spectrometry

MS or Mass Spec = mass spectrometry

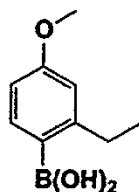
NMR = nuclear magnetic resonance

10 One of skill in the art of peptide chemistry is aware
that amino acid residues occur as both D and L isomers, and
that the present invention includes the use of either or a
mixture of isomers for amino acid residues incorporated in the
synthesis of the peptides described herein.

15 The present invention is not to be limited in scope
by the specific embodiments described that are intended
as single illustrations of individual aspects of the
invention. Functionally equivalent methods and
components in addition to those shown and described
20 herein will become apparent to those skilled in the art
from the foregoing description and accompanying drawings.
Such modifications are intended to fall within the scope
of the appended claims.

WHAT IS CLAIMED IS:

1. A process for the preparation of a compound of
5 Formula I:

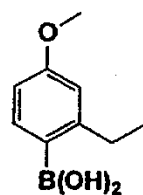


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- said process comprising the steps of:
- 10 methylation of 3-ethylphenol to produce 3-ethylanisole;
- bromination of said 3-ethylanisole at a position para to a methoxy group to produce 4-bromo-3-ethyl anisole;
- 15 conversion of said 4-bromo-3-ethyl anisole, said conversion comprising (a) reacting said 4-bromo-3-ethyl anisole with n-butyl lithium to produce the lithium salt of the corresponding anion of said 4-bromo-3-ethyl anisole; (b) reacting said lithium salt of the anion of
- 20 said 4-bromo-3-ethyl anisole with tri-n-butyl borate; and (c) quenching with aqueous acid.

2. A process for the preparation of a compound of
Formula I:

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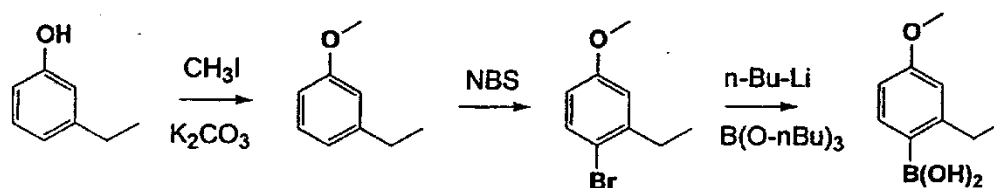


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according to Scheme 1, as follows:

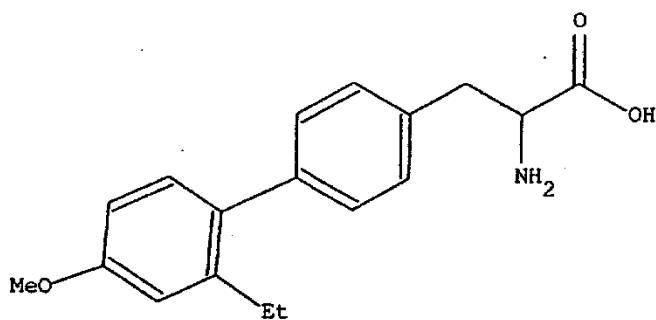
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Scheme 1



3. A process for the preparation of a compound of Formula II:

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said process comprising the steps of:

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methylation of 3-ethylphenol to produce 3-ethylanisole;

bromination of said 3-ethylanisole at a position para to a methoxy group to produce 4-bromo-3-ethyl anisole;

conversion of said 4-bromo-3-ethyl anisole, said
conversion comprising (a) reacting said 4-bromo-3-ethyl
anisole with n-butyl lithium to produce the lithium salt
of the corresponding anion of said 4-bromo-3-ethyl
5 anisole; (b) reacting said lithium salt of the anion of
said 4-bromo-3-ethyl anisole with tri-n-butyl borate; (c)
quenching with aqueous acid;

reacting the resultant 2-ethyl-4-methoxy-
phenylboronic acid with the triflic anhydride of a
10 suitably protected tyrosine amino acid in the presence of
a Palladium catalyst (Suzuki coupling); and

removing the carboxyl protecting group from the
resulting biphenyl amino acid to yield the amino-
protected amino acid useful for incorporation into a
15 peptide receptor modulator.