

TITLE OF THE INVENTION

PROCESS FOR SYNTHESIZING A SUBSTITUTED PYRAZOLE

BACKGROUND OF THE INVENTION

5 The present invention relates to a process for synthesizing a substituted pyrazole. The compound is particularly useful as an anti-diabetic compound. In particular, the compound has demonstrated activity as a glucagon receptor antagonist.

10 Glucagon serves as the major regulatory hormone attenuating the effect of insulin in its inhibition of liver gluconeogenesis and is normally secreted by α -cells in pancreatic islets in response to falling blood glucose levels. The hormone binds to specific receptors in liver cells that triggers glycogenolysis and an increase in gluconeogenesis through cAMP-mediated events. These responses generate glucose (e.g. hepatic glucose production) to help maintain euglycemia by preventing blood glucose levels from falling significantly.

15 In addition to elevated levels of circulating insulin, type II diabetics have elevated levels of plasma glucagon and increased rates of hepatic glucose production. The compound that is the subject of the process described herein is an antagonist of glucagon, and thus useful in improving insulin responsiveness in the liver, decreasing the rate of gluconeogenesis and lowering the rate of hepatic glucose output resulting in a decrease in the levels of plasma glucose.

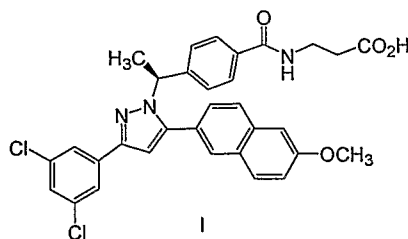
20 One object of the present invention is to provide a process wherein the protecting groups are easily removed without resort to harsh deprotection conditions.

 Another object of the present invention is to provide a process which facilitates selective deprotection.

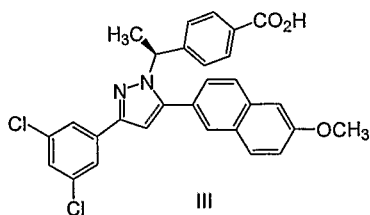
 These and other objects will be apparent from the teachings contained herein.

25 SUMMARY OF THE INVENTION

 The present invention involves a process of synthesizing a compound of formula I:



or a pharmaceutically acceptable salt or solvate thereof, comprising reacting a compound of formula III:



with 1,1'-carbonyldiimidazole and a beta alanine ester or a salt or solvate thereof, and hydrolyzing with a base to provide a compound of formula I.

5 DETAILED DESCRIPTION OF THE INVENTION

The invention is described in connection with the following abbreviations and definitions.

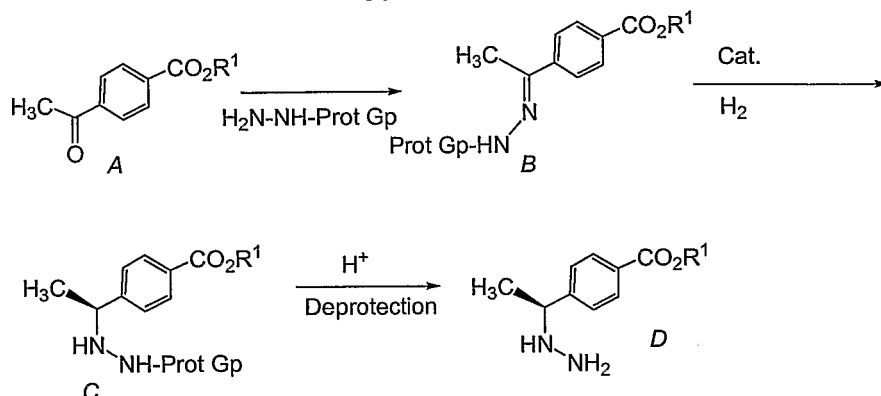
Bu = butyl, t-Bu = t-butyl	Bn and Bn ₂ l = benzyl
BOC, Boc = t-butyloxycarbonyl	CBZ, Cbz = Benzyloxycarbonyl
CDI = carbonyldiimidazole	
COD = cyclooctadiene	C ₆ H ₁₁ = cyclohexyl
DCC = Dicyclohexylcarbodiimide	DCM = dichloromethane
DMAC = dimethylacetamide	DMF = N,N-dimethylformamide
DMAP = 4-Dimethylaminopyridine	Et = ethyl
EtOAc = ethyl acetate	EtOH = ethanol
Fc = ferrocenyl	IPA = isopropanol
HOAc = acetic acid	TFA = Trifluoroacetic acid
Me = methyl	Py, Pyr = pyridyl
Ph = phenyl	IPAc = isopropylacetamide
THF = Tetrahydrofuran	NMP = N-methyl pyrrolidone

Ph ₂ -Fc-P-(tBu) ₂	Xyl-P-Phos	Me-f-Ketalphos

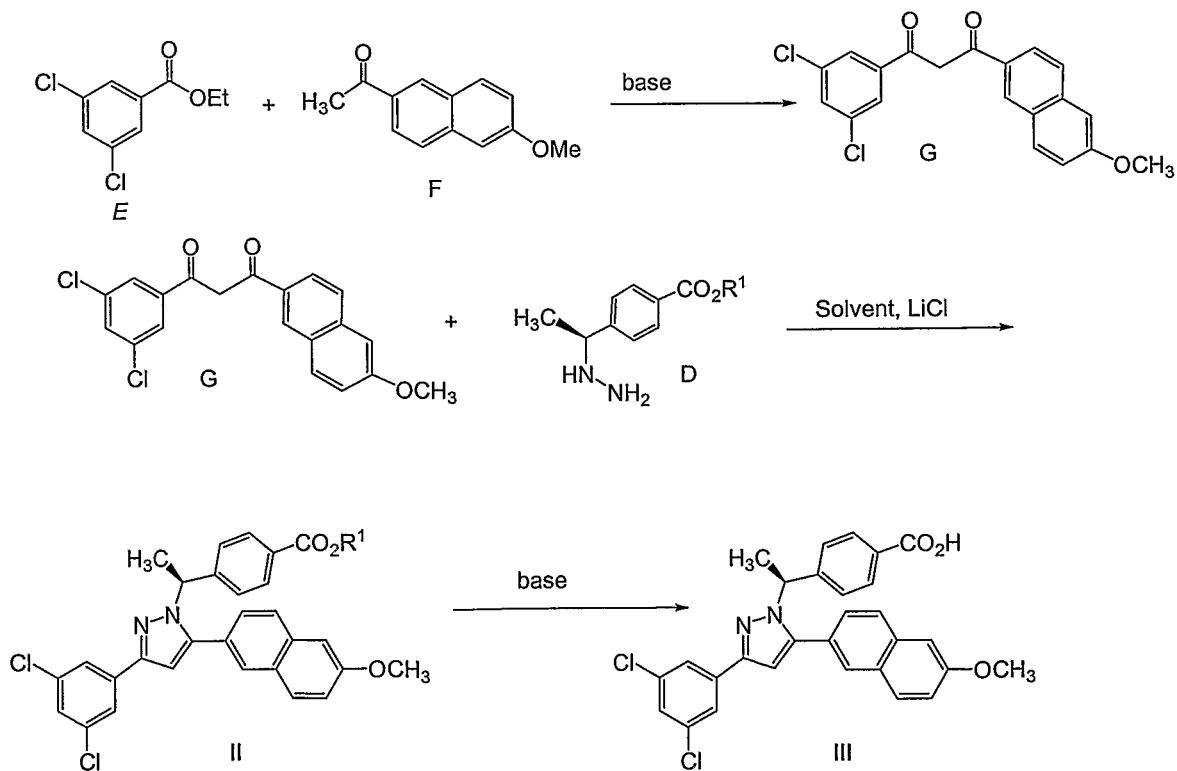
$\text{Ph}_2\text{-Fc-P-(tBu)}_2$ is a Josiphos ligand which is disclosed in U. S. Pat. No. 6,777,567B2 (Solvias) and commercially available from Strem. Xyl-P-Phos is disclosed in U.S. Pat No. 5,886,182 (Syntex) and commercially available from Strem. Me-f-Ketal phos is similarly commercially available from Chiral Quest. A variety of Rh based catalysts may be used as well.

5 The compound described herein may be prepared according to the methodology outlined in the following general synthetic schemes.

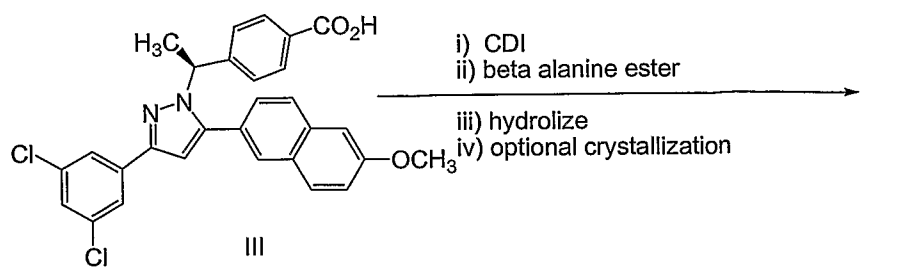
SCHEME I



SCHEME 2



SCHEME 3



Within the schemes above, R^1 represents a suitable ester forming group. Examples include C_{1-10} alkyl, such as ethyl, isopropyl, t-butyl, t-butylcyclohexyl and the like, and benzyl. Preferred is ethyl.

Similarly, the notation Prot Gp-hydrazine refers to a protected hydrazine, protected with a suitable protecting group, designated Prot Gp, which represents the protecting group. Examples include t-butoxycarbonyl, methoxycarbonyl, carboxybenzoyl, benzyl and the like.

Many of the intermediates contain an asymmetric center and thus occur as racemates and mixtures thereof. The present invention therefore includes all such isomeric forms of the compounds, in pure form as well as in mixtures.

The process described herein is generally considered a stereospecific synthesis. Ketone *A* is condensed with a protected hydrazine to produce a protected hydrazone *B*. This condensation reaction is conducted in a suitable solvent, such as toluene, under acidic conditions, with for example, acetic acid, at about 60 degrees C.

The protected hydrazone *B* is asymmetrically hydrogenated using a hydrogen source, such as hydrogen gas, and a catalyst to produce a chiral N-protected-hydrazine *C*. This hydrazine is produced in enantiomeric excess (approximately 86%ee). A suitable catalyst for this conversion is a precatalyst, such as $Rh(COD)BF_4$ mixed with a suitable ligand, such as Josiphos.

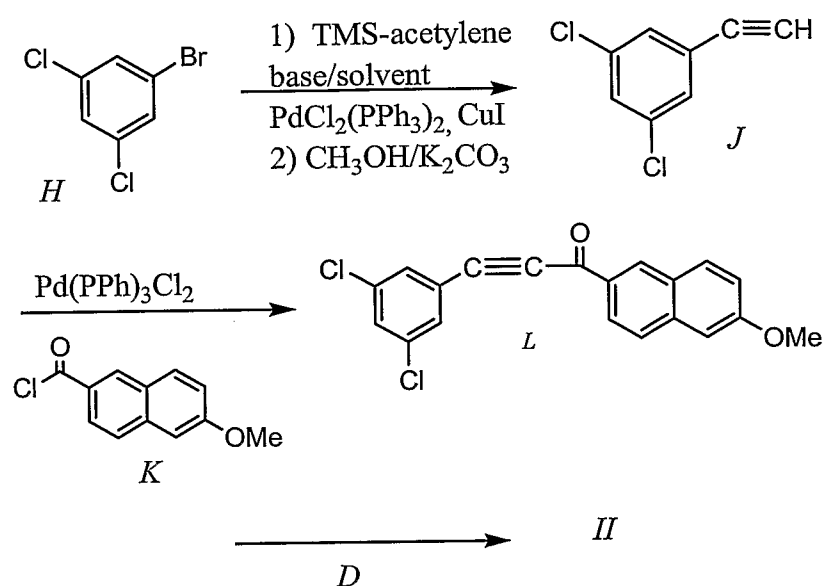
Deprotection of the protecting group in *C* and subsequent enantiomeric excess upgrade using benzene sulfonic acid in ethanol provides a crystalline hydrazine *D* as the benzenesulfonate salt (not shown), with greater than 99% enantiomeric excess.

With reference to Scheme 2, the 1,3-dione *G* is prepared by condensation of ester *E* and ketone *F* in the presence of a base, such as potassium t-butoxide. Cyclization between *D* and *G* can then be undertaken in a suitable solvent, such as DMAc, NMP and the like, in the presence of an additive. Suitable examples of additives include LiCl, LiBr, $MgBr_2$ and other Lewis acids. Alternatively, tetrabutyl ammonium chloride can be used. The additive provides high regioselectivity, as high as about 17:1. The ester forming moiety of compound *II* is thereafter hydrolyzed with a suitable base, for example, NaOH, to produce acid *III*.

As shown with reference to Scheme 3, acid *III* can then be combined with a beta alanine ester, or a salt or solvate thereof, preferably the HCl salt, to form the beta alanyl ester of *III* (not shown). This ester may then be hydrolyzed, such as with additional base, for example, NaOH, and optionally crystallized, such as from acetonitrile and water, to produce the title compound *I* as a free acid.

An alternative process for the synthesis of compounds of formula *II* is shown below in Scheme 4.

Scheme 4



Briefly, 3,5-dichlorophenylacetylene *J* is produced by displacing bromine from bromo-3,5-dichlorobenzene *H*. Such reactions are typically conducted under an inert atmosphere, in base, e.g., triethylamine in a suitable solvent. This intermediate is reacted with 6-methoxy-2-naphthoic acid chloride *K* to produce an acetylenic ketone *L*. The acetylenic ketone *L* is thereafter reacted with the chiral hydrazine *D* to produce the chiral intermediate *II*. Compound *II* is thereafter incorporated into the synthesis described above with respect to Scheme 3, reacting with a beta alanyl ester and then hydrolyzing to produce the target compound *I*.

Dose Ranges

The daily dosage range for the compound of formula *I* is within the general range of from about 0.001 mg to about 1000 mg, in single or divided doses. It may be necessary to use dosages outside of these limits in some cases.

Representative dosages for adults thus range from about 0.1 mg to about 1.0 g per day, preferably about 1 mg to about 200 mg, in single or divided doses.

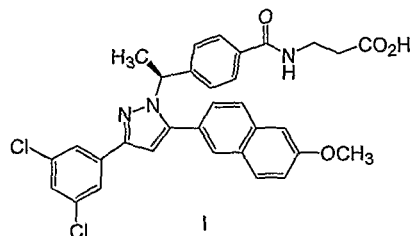
Pharmaceutical Compositions

Pharmaceutical compositions comprise a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier. This encompasses a product comprising the active compound and one or more inert ingredient(s), (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from the combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions between ingredients.

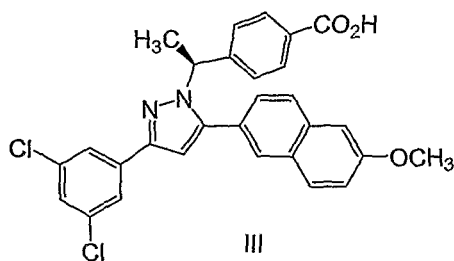
While the invention has been described and illustrated with reference to specific embodiments, numerous changes, modifications, and substitutions can be made therein without departing from the spirit and scope of the invention. It is intended therefore that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A process for the synthesis of a compound of formula *I*:

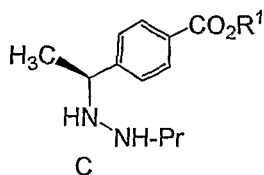


- 5 comprising reacting a compound of formula *III*:

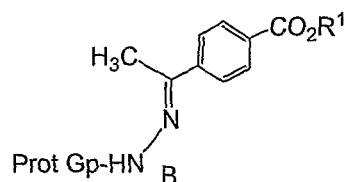


in the presence of 1,1'-carbonyldiimidazole with an ester of beta-alanine or a salt or solvate thereof to produce an ester of formula *II*, and hydrolyzing with a base to provide a compound of formula *I*.

- 10 2. A process for the synthesis of a compound of formula *C*:

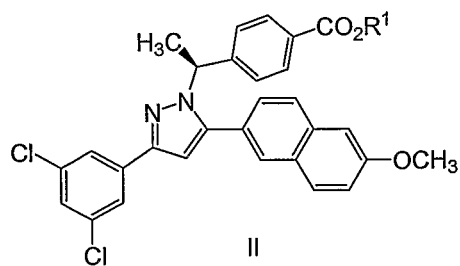


comprising reacting a compound of formula *B*:



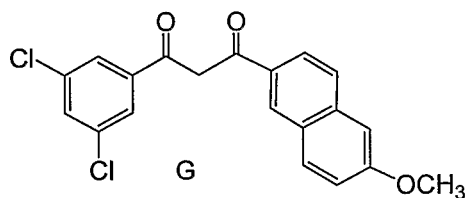
wherein R^1 represents an ester forming group with a catalyst and a hydrogen source to produce a compound of formula *C*.

3. A process for the synthesis of a compound of formula *II*:

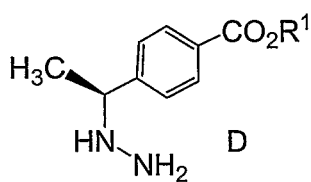


wherein R^1 represents an ester forming group, comprising reacting a compound of formula *G*:

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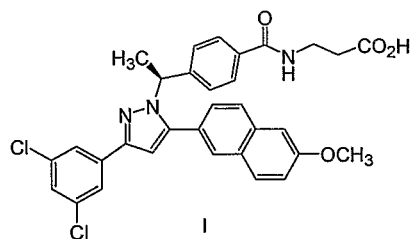
and a compound of formula *D*:



to produce a compound of formula *II*.

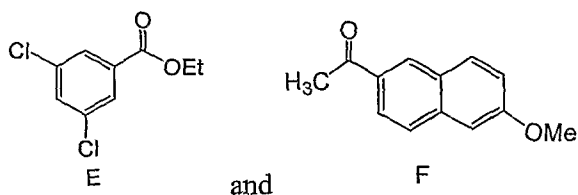
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4. A process for the synthesis of a compound of formula *I*:

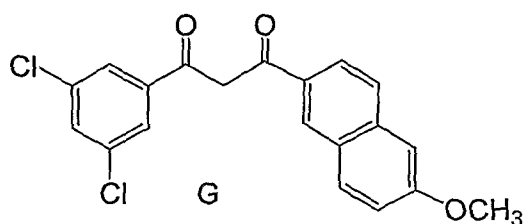


comprising:

- (a) reacting compounds of formulas *E* and *F*:

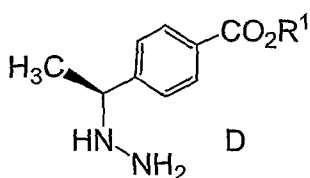


in the presence of potassium *t*-butoxide to produce a compound of formula G:

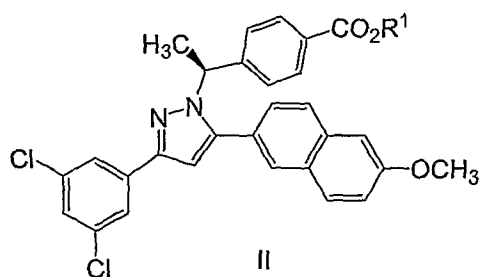


(b) reacting compound G with a compound of formula D:

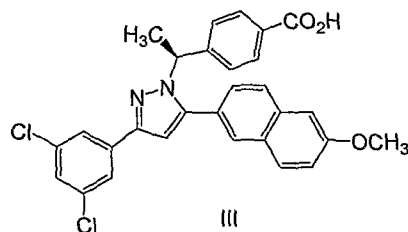
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wherein R¹ represents an ester forming group, to produce a compound of formula II:



(c) hydrolyzing the ester of compound II with a base to produce a compound of formula III:



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(d) reacting compound III with a beta alanine ester or a salt or solvate thereof to produce a beta alanyl ester of III, and

(e) hydrolyzing the beta alanyl ester of III to produce a compound of formula I.