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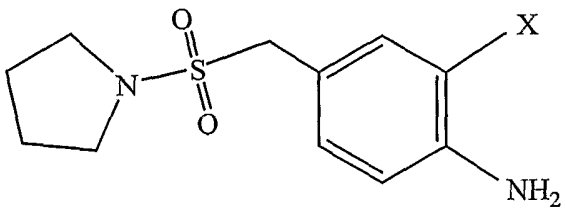
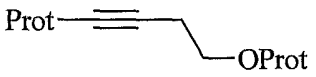
(54) Title: PROCESS FOR THE PREPARATION OF ALMOTRIPTAN



(I)



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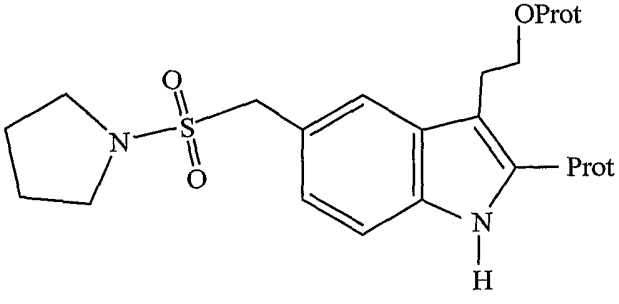

(II)

(57) Abstract: A process for preparing an intermediate of almotriptan is disclosed, the process comprising the step of Heck coupling a 2-halo aniline derivative of Formula (I): wherein X is a halogen with a protected butynol compound of the general formula (III) wherein Prot can be the same or different and is a suitable protecting group, to provide a protected indole derivative of Formula (II).

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ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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PROCESS FOR THE PREPARATION OF ALMOTRIPTAN

PRIORITY

[0001] This application claims the benefit under 35 U.S.C. §119 to U.S. Provisional Application No. 60/691,498, filed June 17, 2005, and entitled "PROCESS FOR THE PREPARATION OF ALMOTRIPTAN"; and Indian Provisional Application No. 666/MUM/2005, filed June 3, 2005, and entitled "PROCESS FOR THE PREPARATION OF ALMOTRIPTAN", the contents of each of which are incorporated by reference herein.

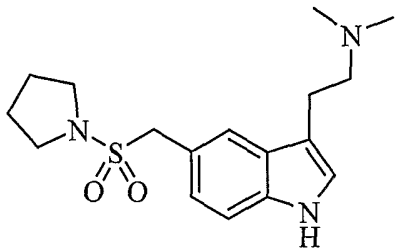
BACKGROUND OF THE INVENTION

1. Technical Field

[0002] The present invention generally relates to an improved process for the preparation of almotriptan or a free base or a pharmaceutically acceptable salt, ester or derivative thereof.

2. Description of the Related Art

[0003] Almotriptan, also known as 1-[[[3-[2-(dimethylamino)ethyl]indol-5-yl]methyl]sulfonyl]pyrrolidine, is represented by the following structure.



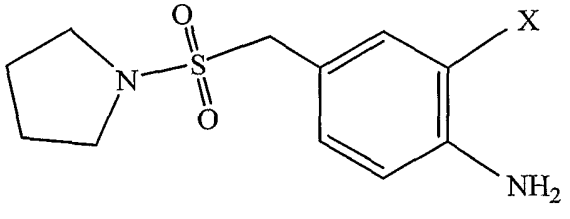
Generally, almotriptan binds with high affinity to 5-HT_{1D}, 5-HT_{1B} and 5-HT_{1F} receptors. Almotriptan has weak affinity for 5-HT_{1A} and 5-HT_7 receptors. The malate salt of almotriptan is indicated for the acute treatment of migraine with or without aura in adults. Almotriptan malate is sold under the trade names AXERT® and ALMOGRAN®. See, e.g., The Merck Index, Thirteenth Edition, 2001, pp. 56, monograph 301; and Physician's Desk Reference, "Axert," 60th Edition, pp. 2430-2434 (2005).

[0004] U.S. Patent No. 5,565,447 ("the '447 patent") discloses 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]pyrrolidine. The '447 patent further discloses that 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]pyrrolidine can be obtained by decarboxylation of 1-[[2-carboxy-3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]pyrrolidine. The '447 patent further discloses that almotriptan base was purified by column chromatography (See Example 1) to obtain a white foam.

[0005] Bosch et al., Tetrahedron 57 pp. 1041-1048 (2001) discloses the synthesis of a tryptophol intermediate of almotriptan by the Heck approach in which aniline nitrogen is protected with a trifluoroacetyl group after iodination of the aniline using $I(C_5H_5N).BF_4$. The iodoaniline is, in turn, reacted with lithium diisopropylamide and methyl 4-bromo crotonate to provide an allylated derivative. The allylated derivative undergoes palladium-catalyzed Heck cyclisation leading to the indole ester which is subsequently converted to tryptophol in three steps. The tryptophol intermediate is then converted to almotriptan.

SUMMARY OF THE INVENTION

[0006] In accordance with one embodiment of the present invention, a process for preparing an intermediate of almotriptan or a free base or a pharmaceutically acceptable salt, ester or derivative thereof is provided comprising the step of Heck coupling a 2-halo aniline derivative of Formula I:

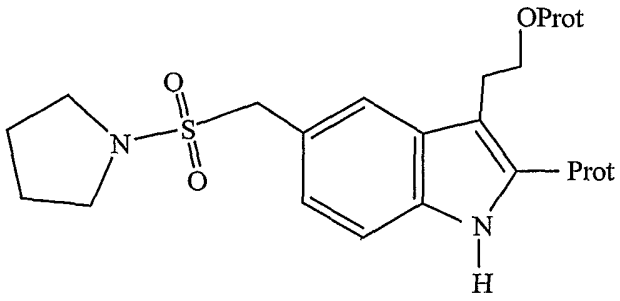


(I)

wherein X is a halogen with a protected butynol compound of the general formula:



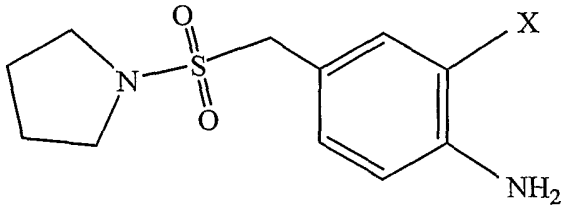
wherein Prot can be the same or different and is a suitable protecting group, to provide a protected indole derivative of Formula II.



(II)

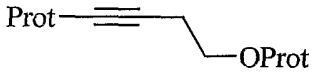
[0007] In accordance with a second embodiment of the present invention, a process for preparing an intermediate of almotriptan or a free base or a pharmaceutically acceptable salt, ester or derivative thereof is provided comprising the steps of:

(a) Heck coupling a 2-halo aniline derivative of Formula I:

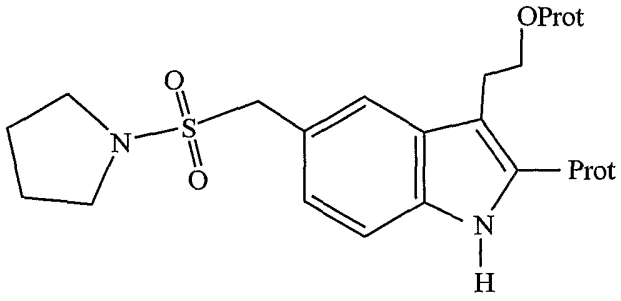


(I)

wherein X is a halogen with a protected butynol compound of the general formula:



wherein Prot can be the same or different and is a suitable protecting group, to provide a protected indole derivative of Formula II:

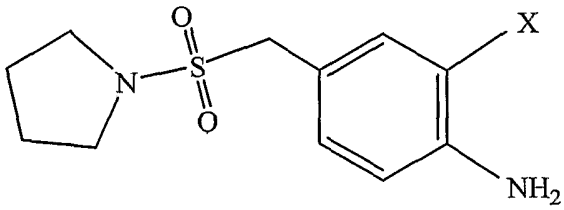


(II); and

(b) deprotecting the protected indole to provide a tryptophol-containing compound.

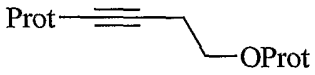
[0008] In accordance with a third embodiment of the present invention, a process for preparing almotriptan or a free base or a pharmaceutically acceptable salt, ester or derivative thereof is provided comprising the steps of:

(a) Heck coupling a 2-halo aniline derivative of Formula I:

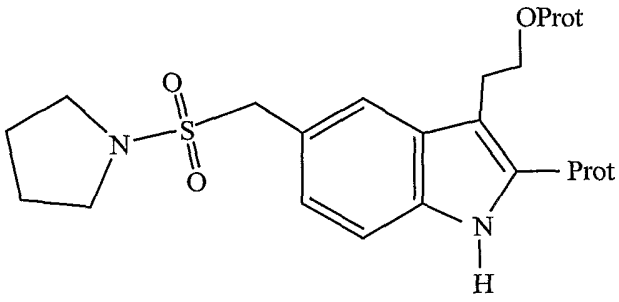


(I)

wherein X is a halogen with a protected butynol compound of the general formula:



wherein Prot can be the same or different and is a suitable protecting group, to provide a protected indole derivative of Formula II:

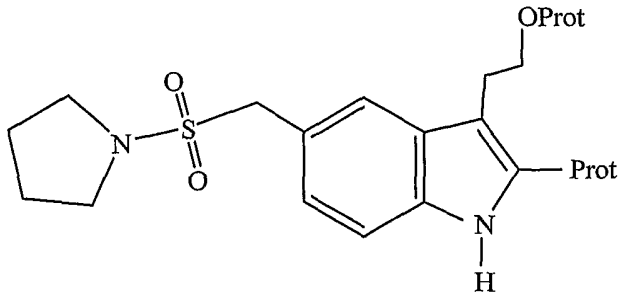


(II);

(b) deprotecting the protected indole of Formula II to provide a tryptophol-containing compound; and

(c) converting the tryptophol to almotriptan or a free base or a pharmaceutically acceptable salt, ester or derivative thereof.

[0009] In accordance with a fourth embodiment of the present invention, an indole compound of Formula II is provided



wherein Prot can be the same or different and is a suitable protecting group.

[0010] In accordance with a fifth embodiment of the present invention, substantially pure almotriptan or a free base or a pharmaceutically acceptable salt, ester or derivative thereof is provided.

[0011] In accordance with a sixth embodiment of the present invention, a pharmaceutical composition comprising a therapeutically effective amount of substantially pure almotriptan or a free base or a pharmaceutically acceptable salt, ester or derivative thereof is provided.

[0012] The advantages of the process of the present invention include at least:

1. The process is an industrially viable process utilizing a reduced number of steps.
2. The yield of the compound obtained from the process is relatively higher compared to other available processes.

DEFINITIONS

[0013] The term "treating" or "treatment" of a state, disorder or condition as used herein means: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof, or (3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical

symptoms. The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician.

[0014] The term "therapeutically effective amount" as used herein means the amount of a compound or crystalline form thereof that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound or crystalline form thereof, the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated. Determining the therapeutically effective amount of a given compound or crystalline form thereof is within the ordinary skill of the art and requires no more than routine experimentation.

[0015] The term "delivering" as used herein means providing a therapeutically effective amount of an active ingredient to a particular location within a host means causing a therapeutically effective blood concentration of the active ingredient at the particular location. This can be accomplished, e.g., by topical, local or by systemic administration of the active ingredient to the host.

[0016] The term "buffering agent" as used herein is intended to mean a compound used to resist a change in pH upon dilution or addition of acid of alkali. Such compounds include, by way of example and without limitation, potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate and other such material known to those of ordinary skill in the art.

[0017] The term "sweetening agent" as used herein is intended to mean a compound used to impart sweetness to a preparation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol, sucrose, fructose and other such materials known to those of ordinary skill in the art.

[0018] The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in tablet granulations. Such compounds include, by way of example and without limitation, acacia alginic acid, tragacanth, carboxymethylcellulose sodium, poly (vinylpyrrolidone), compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and

pregelatinized starch, combinations thereof and other material known to those of ordinary skill in the art.

[0019] When needed, other binders may also be included in the present invention. Exemplary binders include starch, poly(ethylene glycol), guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC™ F68, PLURONIC™ F127), collagen, albumin, celluloses in nonaqueous solvents, combinations thereof and the like. Other binders include, for example, poly(propylene glycol), polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, poly(ethylene oxide), microcrystalline cellulose, poly(vinylpyrrolidone), combinations thereof and other such materials known to those of ordinary skill in the art.

[0020] The term "diluent" or "filler" as used herein is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, sucrose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, starch, combinations thereof and other such materials known to those of ordinary skill in the art.

[0021] The term "glidant" as used herein is intended to mean agents used in tablet and capsule formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Such compounds include, by way of example and without limitation, colloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, cornstarch, talc, combinations thereof and other such materials known to those of ordinary skill in the art.

[0022] The term "lubricant" as used herein is intended to mean substances used in tablet formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate, combinations thereof and other such materials known to those of ordinary skill in the art.

[0023] The term "disintegrant" as used herein is intended to mean a compound used in solid dosage forms to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved. Exemplary disintegrants include,

by way of example and without limitation, starches such as corn starch, potato starch, pre-gelatinized and modified starched thereof, sweeteners, clays, such as bentonite, microcrystalline cellulose (e.g. Avicel™), carsium (e.g. Amberlite™), alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, combinations thereof and other such materials known to those of ordinary skill in the art.

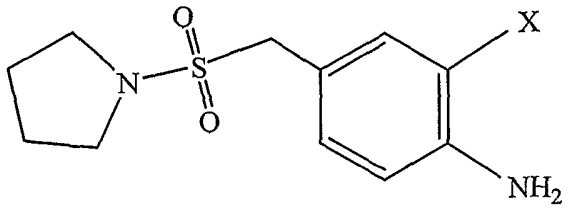
[0024] The term "wetting agent" as used herein is intended to mean a compound used to aid in attaining intimate contact between solid particles and liquids. Exemplary wetting agents include, by way of example and without limitation, gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, (e.g., TWEEN™s), polyethylene glycols, polyoxyethylene stearates colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxyl propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton) is another useful wetting agent, combinations thereof and other such materials known to those of ordinary skill in the art.

[0025] Most of these excipients are described in detail in, e.g., Howard C. Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, (7th Ed. 1999); Alfonso R. Gennaro et al., Remington: The Science and Practice of Pharmacy, (20th Ed. 2000); and A. Kibbe, Handbook of Pharmaceutical Excipients, (3rd Ed. 2000), which are incorporated by reference herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

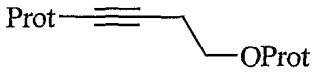
[0026] The present invention involves a process for preparing intermediates of almotriptan or a free base or a pharmaceutically acceptable salt, ester or derivative thereof. In one embodiment of the present invention, a process for preparing almotriptan or a free

base or a pharmaceutically acceptable salt, ester or derivative thereof includes the steps of (a) Heck coupling a 2-halo aniline derivative of Formula I:

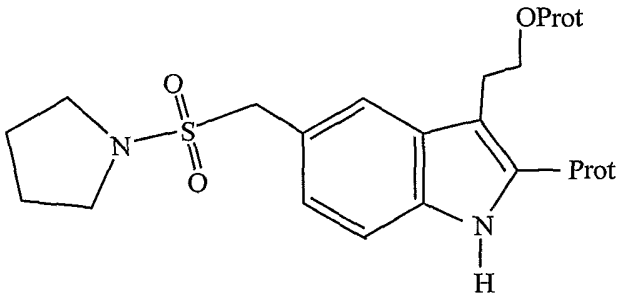


(I)

wherein X is a halogen, e.g., Cl, Br, I and the like, with a protected butynol compound of the general formula



wherein Prot can be the same or different and is a suitable protecting group, to provide a protected indole derivative of Formula II:



(II);

(b) deprotecting the protected indole of Formula II to provide a tryptophol-containing compound; and

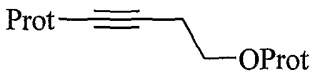
(c) converting the tryptophol to almotriptan or a free base or a pharmaceutically acceptable salt, ester or derivative thereof.

[0027] Representative of a 2-halo aniline derivative of Formula I is disclosed in, e.g., Bosch et al., Tetrahedron 57 pp. 1041-1048 (2001), the contents of which are incorporated by reference therein. In general, a 2-halo aniline derivative of Formula I can be obtained by reacting 4-(pyrrolidinyl–sulfonylmethyl) aniline with a suitable halogenating agent in a solvent to halogenate the 2-position to form the corresponding 2-halo aniline derivative of Formula I. Suitable halogenating agents include, but are not limited to, iodine monochloride, $I(C_5H_5N).BF_4$, N-chlorosuccinimide/HI/KI (i.e., N-chlorosuccinimide/hydrogen iodide/potassium iodide), N-iodosuccinimide, iodine

monobromide and the like and mixtures thereof. Useful solvents include, but are not limited to, alcohols, e.g., methanol, aqueous methanol, ethanol and the like, ethers, e.g., tetrahydrofuran (THF) and the like, halogenated hydrocarbons, e.g., methylene chloride and the like, and mixtures thereof, e.g., THF-water. Preferably, the solvent is an organic solvent such as 95% aqueous methanol.

[0028] If desired, the reaction of the 4-(pyrrolidinyl–sulfonylmethyl) aniline with a suitable halogenating agent can be carried out in the presence of a proton acceptor. Suitable proton acceptors include, but not limited to, carbonates such as calcium carbonate, potassium carbonate, sodium carbonate, lithium carbonate, magnesium carbonate, sodium bicarbonate and the like, hydroxides such as potassium hydroxide, sodium hydroxide, lithium hydroxide and the like and mixtures thereof. The reaction of the 4-(pyrrolidinyl–sulfonylmethyl) aniline with a suitable halogenating agent can be carried out under inert conditions at a temperature ordinarily ranging from about -10°C to about 10°C, and preferably at a temperature of about 0°C.

[0029] The protected butynol compound of the general formula



wherein Prot can be the same or different protecting group can be obtained, for example, by protecting 3-butyn-1-ol with a protecting group such as a silane-containing protecting agent in a suitable solvent using a lithiated base, e.g., n-butyl lithium. Suitable solvents include, but are not limited to, ethers, e.g., tetrahydrofuran, diethyl ether, dioxane, and the like, alkoxy groups, e.g., 2-dimethoxy ethane and the like, and mixtures thereof. Suitable silane-containing protecting agents include, but are not limited to, halogenated hydrocarbyl silanes such as trimethyl chlorosilane, triethyl chlorosilane, and the like, and t-butyldimethylsilane (TBDMS) and the like and mixtures thereof. The protected butynol compound thus obtained can be, for example, a trialkylsilyl butynol, e.g., a bis(trialkylsilyl) butynol such as bis (trimethylsilyl) butynol, bis (triethylsilyl) butynol and the like; t-butyldimethyl silylchloride butynol and the like and mixtures thereof.

[0030] The Heck coupling reaction can be carried out in a dry inert organic solvent which is capable of dissolving the reactants and in the presence of a palladium catalyst and base. A suitable base includes an inorganic base, an organic base and the like and

mixtures thereof. Useful inorganic bases include, but are not limited to, common inorganic bases, such as the hydroxides, oxides or carbonates of Groups I or II of The Periodic Table Of The Elements, e.g., the alkali metal or alkaline earth metal bases such as lithium, sodium, potassium, barium, magnesium or calcium hydroxide; sodium, magnesium or calcium oxide; sodium or potassium carbonate; ammonia solutions and the like and mixtures thereof. Useful organic bases include, but are not limited to, organic amines, such as trimethylamine, triethylamine, piperidine, 3-methylpyridine, piperazine, triethanolamine and the like and mixtures thereof. Suitable solvents include, but are not limited to, amides, e.g., dimethylformamide, dimethylacetamide, and the like, ethers, e.g., diethyl ether, dipropyl ether, tetrahydrofuran (THF), dioxane and the like, alkoxy solvents, e.g., 1,2-dimethoxy ethane and the like, nitriles, e.g., acetonitrile and the like, hydrocarbons, e.g., toluene, xylene and the like and mixtures thereof.

[0031] The palladium catalyst may be in the form of a salt or a complex with organic ligands. Particularly suitable palladium catalysts are, for example, the Group VIII metals, such as Pd(0) complexes or a Pd(II) salt. However, the palladium catalyst used is not particularly limited provided that it is usually used for a Heck coupling reaction. The ligands may be selected from, for example, phosphorus-containing ligands, such as triphenylphosphine (PPh_3), 1,2-bis(diphenylphosphino)ethane and the like. Non-limiting examples of suitable palladium catalysts include, but are not limited to, palladium (II) acetate, palladium (II) bromide, palladium (II) chloride, palladium (II) iodide, palladium tetrakis triphenyl phosphine and the like and mixtures thereof.

[0032] The temperature of the Heck coupling reaction can range from about 70°C to about 120°C. If desired, the reaction can also be carried out in the presence of a suitable proton acceptor such as, for example, alkyl amines, aromatic amines, heterocyclic amines, Group I alkali metal carbonates and bicarbonates, Group II alkaline earth carbonates and bicarbonates and the like and mixtures thereof.

[0033] In step (b) of a process of the present invention, the protected indole is then deprotected to provide a tryptophol-containing compound. Deprotection of the protected indole, e.g., desilylation of the indole, may be achieved using suitable deprotecting agent, for example, MeOH-HCl, tetrabutylammonium fluoride, and the like, to obtain a tryptophol-containing compound. The temperature for deprotection can range of about

0°C to about 35°C. When using an acid to deprotect the protected indole, it may be necessary to basify the reaction mixture. Suitable basifying agents include the inorganic and organic bases discussed above such as sodium carbonate and ammonia. Following basifying of the reaction mixture, the tryptophol-containing compound can be extracted by conventional techniques.

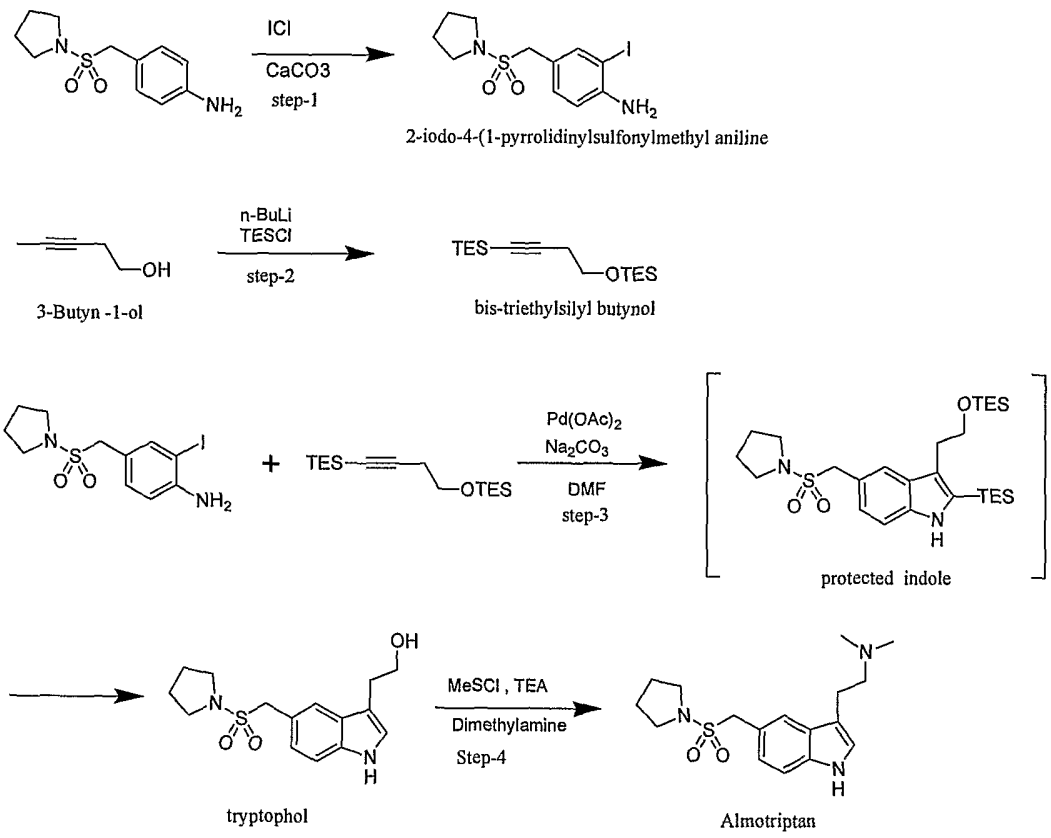
[0034] Next, the tryptophol-containing compound thus obtained is thereafter converted to almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof by techniques well known in the art. The expression "pharmaceutically acceptable salt, ester or derivative thereof" is meant those salts, esters and derivatives which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use. Representative acid additions salts include the hydrochloride, hydrobromide, sulphate, bisulphate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, mesylate, citrate, malate, maleate, fumarare, succinate, tartrate, ascorbate, glucoheptonate, lactobionate, lauryl sulphate salts and the like. Representative alkali or alkaline earth metal salts include the sodium, calcium, potassium and magnesium salts, and the like. For example, almotriptan can be obtained by first forming a mesylate compound from tryptophol followed by displacement with dimethylamine. The salt formation can be carried out in a solvent, for example diethyl ether, THF and the like.

[0035] In one embodiment, conversion of the tryptophol-containing compound to almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof can be carried out by reacting tryptophol with mesyl chloride in a dry inert organic solvent, e.g., THF, dioxane, diethyl ether, 1,2-dimethoxy ethane, and methylene dichloride. The reaction can be carried out at a temperature of about -30°C to about -10°C under nitrogen atmosphere and in the presence of a suitable proton acceptor such as triethylamine (TEA), pyridine, diisopropyl ethylamine, dimethylaminopyridine (DMAP) and the like and mixtures thereof. In another embodiment, the tryptophol-containing compound can be tosylated and the tosyl group can be displaced with a N, N-dimethylamino group, e.g., $N(CH_3)_2$. The N, N-dimethylamino group can be added as is

or part of a solution, e.g., as a 40% aqueous solution or dimethylamine in an alcohol such as methanol, ethanol and isopropanol, or as gaseous dimethylamine which can be spurged directly or as a salt of dimethylamine hydrochloride or any other salt of dimethylamine.

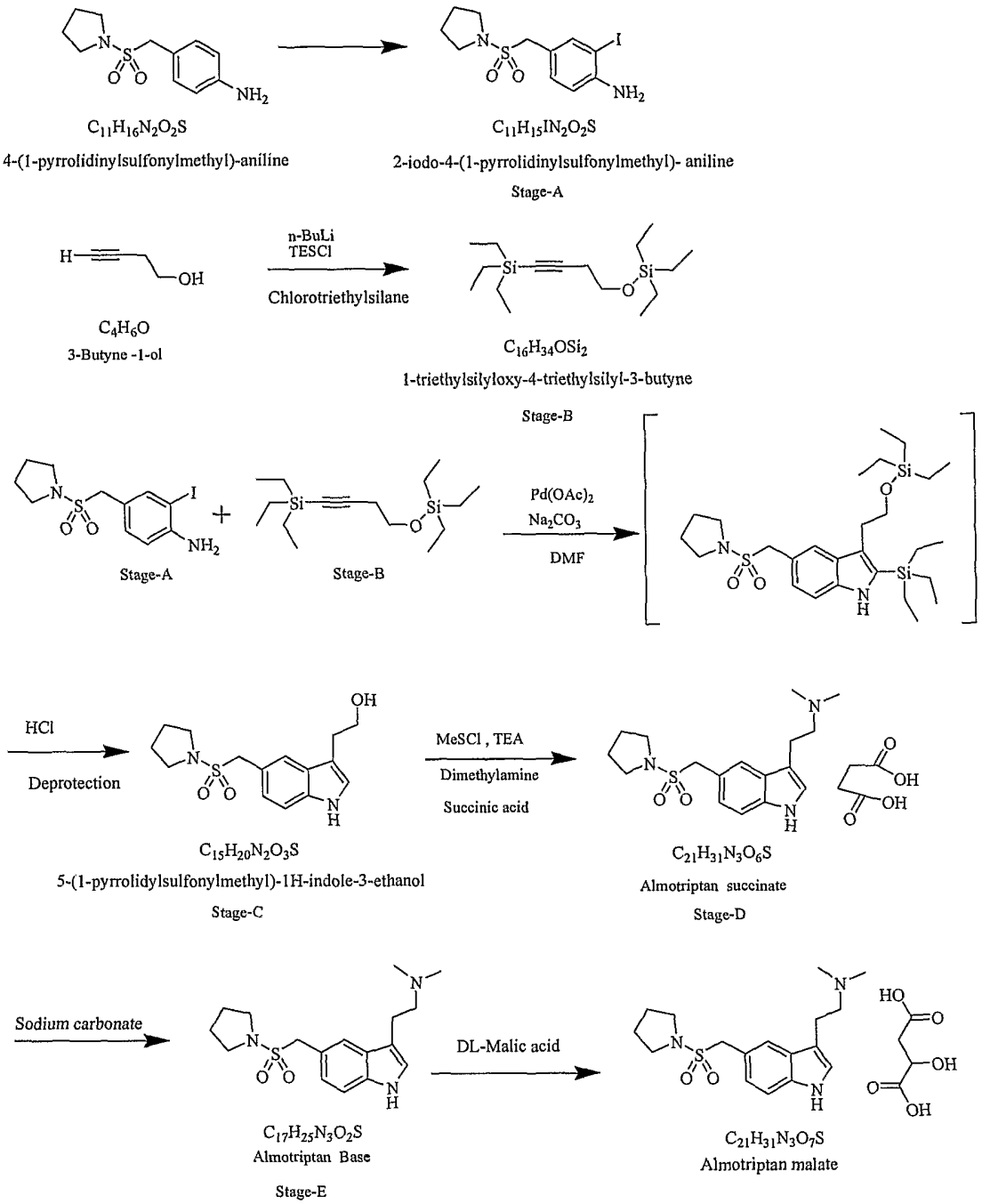
[0036] In another embodiment of the present invention, a process for preparing almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof includes the steps of at least (a) iodination of 4-(pyrrolidinyl–sulfonylmethyl) aniline to provide the corresponding 2-iodo aniline derivative; (b) triethyl silyl protection of 3-butyn-1-ol to provide bis-triethyl silyl butynol; (c) Heck coupling of the 2-iodo aniline derivative with the bis-triethyl silyl butynol followed by its deprotection to provide a tryptophol-containing compound; and (d) converting the tryptophol-containing compound to almotriptan by mesylation followed by displacement with N,N-dimethylamine. This reaction is generally set forth below in Scheme I.

SCHEME I



[0037] The processes of the present invention can also be shown generally below in Scheme II.

SCHEME II



[0038] The almotriptan or free base or pharmaceutically acceptable salt, ester or derivative thereof thus obtained can then be purified to provide a substantially pure compound. By "substantially pure" is meant almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof having a purity greater than or equal to about 98%, and preferably greater than or equal to about 99%. For example, the almotriptan or free base or pharmaceutically acceptable salt, ester or derivative thereof can be purified by column chromatography, e.g., silica gel column chromatography using isopropyl acetate.

[0039] The almotriptan or free base or pharmaceutically acceptable salt, ester or derivative thereof of the present invention may then be formulated into a pharmaceutical composition or dosage form. Such pharmaceutical compositions may be administered to a mammalian patient in any dosage form, e.g., liquid, powder, elixir, injectable solution, etc. Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes. Oral dosage forms include, but are not limited to, tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The almotriptan or free base or pharmaceutically acceptable salt, ester or derivative thereof of the present invention also may be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes. The dosage forms may contain the almotriptan or free base or pharmaceutically acceptable salt, ester or derivative thereof of the present invention as is or, alternatively, as part of a composition. The pharmaceutical compositions may further contain one or more pharmaceutically acceptable excipients as described herein.

[0040] Capsule dosages will contain the almotriptan or free base or pharmaceutically acceptable salt, ester or derivative thereof of the present invention within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated

capsule or tablet may have a coating on the surface thereof or may be a capsule or tablet comprising a powder or granules with an enteric-coating.

[0041] Tableting compositions may have few or many components depending upon the tableting method used, the release rate desired and other factors. For example, the compositions of the present invention may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents such calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

[0042] Other excipients contemplated herein may include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

[0043] Actual dosage levels of the almotriptan or free base or pharmaceutically acceptable salt, ester or derivative thereof of the present invention in the compositions of the invention may be varied to obtain an amount of almotriptan or free base or pharmaceutically acceptable salt, ester or derivative thereof that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon such factors as, for example, the desired therapeutic effect, the route of administration, the desired duration of treatment, and other factors. The total daily dose of the compounds of this invention administered to a host in single or divided dose and can vary widely depending upon a variety of factors including, for example, the body weight, general health, sex, diet, time and route of administration,

rates of absorption and excretion, combination with other drugs, the severity of the particular condition being treated, etc.

[0044] The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention.

Experimental

[0045] The purity was measured by high performance liquid chromatography under the following conditions:

Column: Inertsil ODS 3V (manufactured by GL sciences inc. Japan)

Moving phase: Buffer: 0.1% TEA PH 7.5 with Orthophosphoric acid

Gradient:

Time	Buffer	Acetonitrile
0	10	90
20	50	50
30	75	25
45	10	90
50	10	90

Detector: UV, 227 nm

Flow rate: 1 ml/min.

Retention time: 13 to 15 min

EXAMPLE 1

[0046] Step I: Preparation of 2-iodo-4-(1-pyrrolidinyl methane sulfonyl) aniline

[0047] An iodine monochloride solution (18.9 g in 20 ml of methanol) was added to a mixture of 4-(1-pyrrolidinyl sulfonyl methyl) aniline (25 g), methanol (200 ml) and calcium carbonate (31.2 g) at 0°C over a period of about 30 minutes. The temperature was allowed to rise to room temperature (a temperature ranging from about 25°C to about 30°C). The reaction mixture was stirred for a period of 4 hours at room temperature. The reaction was monitored by thin layer chromatography ("TLC"). After completion of the reaction as determined by TLC, the reaction mass was quenched with a 5% w/v aqueous sodium thiosulphate solution (500 ml). The reaction mass was stirred for 30 minutes at room temperature. The cake was filtered and washed with ethyl acetate until a colorless

cake was obtained. The ethyl acetate layer was charcoalized and filtered on a celite bed. The filtrate was concentrated completely and N-hexane was added to the residue. The slurry was stirred for a period of 30 minutes and the product was filtered and dried to a constant weight. Weight: 30 g.

[0048] Step II: Purification

[0049] The crude material obtained in step I was suspended in 6N hydrochloric acid (65ml) and stirred for a period of 30 minutes. The product was filtered and washed with water. The solid was suspended in a 6N ammonia solution (75 ml) and stirred for a period of 30 minutes. The solid was filtered and washed with water. The product was dried to a constant weight. Weight: 29 g.

EXAMPLE 2

[0050] Preparation of bis-triethylsilyl 3-butynol

[0051] N-butyl lithium (1.6 M, 267 ml) was added to a mixture of 3-butynol (15 g) and tetrahydrofuran (250 ml) at a temperature below -20°C. The reaction mixture was stirred for a period of 1 hour at -20°C. Triethylchlorosilane (66.12 g) was added at a temperature below -15°C. After completion of the addition, the reaction mass was allowed to warm to room temperature. The reaction mass was stirred at room temperature for a period of 2 hours. After completion of the reaction as determined by TLC, the reaction mass was cooled to a temperature of -10°C. Sodium carbonate solution and n-Hexane (150 ml) were added to the reaction mass. The reaction mass was stirred at room temperature for a period of about 20-25 minutes. The layers were separated. The aqueous layer was extracted with n-hexane (150 ml). The organic layers were combined and washed with water. The organic layer was concentrated under vacuum to obtain the bis-triethylsilyl 3-butynol product. Weight: 55 g

EXAMPLE 3

[0052] Preparation of 5-(1-pyrrolidinyl methane sulfonyl)-1H-indole-3-ethanol

[0053] Into a round bottom flask, 2-iodo-4-(1-pyrrolidinyl methane sulfonyl)-aniline (10 g) of Example 1, bis triethyl silyl 3-butynol (8.55 g) of Example 2, sodium carbonate (14.47 g), palladium (II) acetate (90 mg) and dimethylformamide (50 ml) were

added. The reaction mixture was heated to a temperature between 65 to 95°C for a period of 4 hours. After completion of the reaction as determined by TLC, the reaction mass was cooled to room temperature and water (250 ml) was added. The reaction mass was extracted with isopropyl acetate (2x200 ml). The combined organic layer was washed with water and brine. The organic layer was filtered over a celite bed and then concentrated under vacuum to isolate the product. Weight: 14.6 g.

[0054] 2N hydrochloric acid solution (34 ml) was added to the crude product obtained above (14.6 g dissolved in 40 ml of methanol) at room temperature. The reaction mass was stirred at room temperature for a period of 2 hours. After completion of the reaction as determined by TLC, a 5% w/v sodium carbonate solution (100 ml) was added to the reaction mass at a temperature below 20°C. The compound was extracted with isopropyl acetate (3x50 ml). The extracts were combined and washed with water followed by brine. The organic layer was concentrated under vacuum to isolate the product 5-(1-pyrrolidinyl methane sulfonyl)-1H-indole-3-ethanol. Weight: 7.6 g.

EXAMPLE 4

[0055] Preparation of Almotriptan

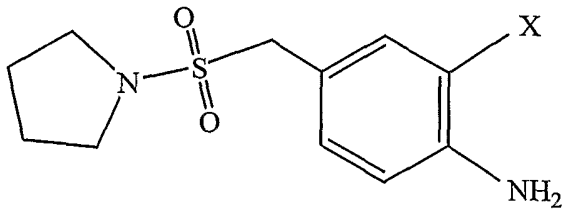
[0056] Methanesulfonyl chloride was added to a solution of 5-(1-pyrrolidinyl methane sulfonyl)-1H-indole-3-ethanol (7 g) of Example 3 in tetrahydrofuran (140 ml) and triethylamine (6 g) at a temperature below -20°C. The reaction mass was stirred at a temperature of about -20°C for a period of 30 minutes. After completion of the reaction as determined by TLC, a dimethyl amine solution (40%, 55 ml) was added at a temperature of about -20°C. After the addition, the reaction mass was allowed to rise to room temperature. The reaction mass was stirred at room temperature. After completion of the reaction as determined by TLC, the tetrahydrofuran was distilled off under vacuum at a temperature below 40°C. The compound was extracted with isopropyl acetate (2x75 ml). The organic layer was combined and concentrated under vacuum to isolate the crude almotriptan. Weight: 5.6 g. Purity: 80 to 88% as determined by HPLC.

[0057] The crude product was purified by silica gel column chromatography using isopropyl acetate to provide pure almotriptan. Purity: 98 to 99% as determined by HPLC.

[0058] It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention.

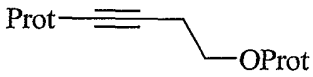
WHAT IS CLAIMED IS:

1. A process for preparing an intermediate of almotriptan, the process comprising the step of Heck coupling a 2-halo aniline derivative of Formula I:

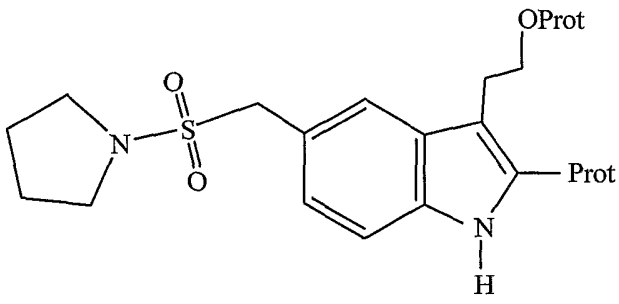


(I)

wherein X is a halogen with a protected butynol compound of the general formula



wherein Prot can be the same or different and are a suitable protecting group, to provide a protected indole derivative of Formula II.



(II)

2. The process of Claim 1, wherein the 2-halo aniline derivative of Formula I is obtained by reacting 4-(pyrrolidinyl–sulfonylmethyl) aniline with a halogenating agent for halogenation of the 2-position.

3. The process of Claim 2, wherein the reaction is carried out in a solvent selected from the group consisting of methanol, water, ethanol, tetrahydrofuran, methylene chloride and mixtures thereof.

4. The process of Claim 2, wherein the reaction is carried out in the presence of a proton acceptor selected from the group consisting of calcium carbonate, potassium carbonate, sodium carbonate, lithium carbonate, magnesium carbonate, sodium bicarbonate, potassium hydroxide, sodium hydroxide, lithium hydroxide and mixtures thereof.

5. The process of Claims 1-4, wherein the protected butynol compound is a bis(trialkylsilyl) butynol.

6. The process of Claims 1-4, wherein the protected butynol compound is selected from the group consisting of bis(trimethylsilyl) butynol and bis(triethylsilyl) butynol.

7. The process of Claims 1-6, wherein the Heck coupling is carried out in an inert solvent and in the presence of a palladium catalyst and a base.

8. The process of Claim 7, wherein the palladium catalyst is selected from the group consisting of palladium (II) acetate, palladium (II) bromide, palladium (II) chloride, palladium (II) iodide, palladium tetrakis triphenyl phosphine and mixtures thereof.

9. The process of Claim 7, wherein the inert solvent is selected from the group consisting of dimethylformamide, dimethylacetamide, diethyl ether, isopropyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxy ethane, acetonitrile, toluene, xylene and mixtures thereof.

10. The process of Claim 7, wherein the base is selected from the group consisting of an alkyl amine, aromatic amine, heterocyclic amine, Group I alkali metal carbonate, Group I alkali metal bicarbonate, Group II alkaline earth carbonate, Group II alkaline earth bicarbonate and mixtures thereof.

11. The process of Claims 1-10, further comprising the step of deprotecting the protected indole of Formula II to provide a tryptophol-containing compound.

12. The process of Claim 11, wherein the deprotection step comprises adding a MeOH-HCl solution or tetrabutylammonium fluoride to obtain a tryptophol-containing compound.

13. The process of Claim 11, further comprising the step of basifying the tryptophol-containing compound.

14. The process of Claim 1, wherein the protecting group Prot is a silane-containing protecting group and the process further comprises the step of desilylating the protected indole of Formula II to obtain a tryptophol-containing compound.

15. The process of Claim 1, further comprising the step of converting the protected indole of Formula II to almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof.

16. The process of Claim 11, further comprising the step of converting the tryptophol-containing compound to almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof.

17. The process of Claim 13, further comprising the step of converting the tryptophol-containing compound to almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof.

18. The process of Claim 16, comprising mesylating the tryptophol-containing compound with a mesylating agent in a dry inert organic solvent in the presence of a proton acceptor followed by N,N-dimethylamine displacement to provide almotriptan.

19. The process of Claim 18, wherein the mesylating agent is mesyl chloride.

20. The process of Claim 18, wherein the organic solvent is selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, 1,2-dimethoxy ethane, methylene dichloride and mixtures thereof.

21. The process of Claim 16, comprising tosylating the tryptophol-containing compound and displacing the tosyl group with a N,N-dimethylamino group to provide almotriptan.

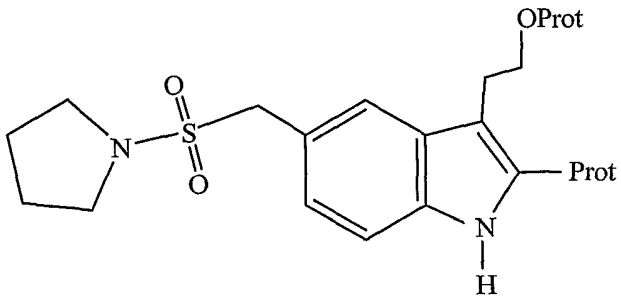
22. The process of Claim 16, further comprising the step of purifying almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof.

23. The process of Claim 17, further comprising the step of purifying almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof.

24. The process of Claims 22 and 23, wherein the step of purifying is performed by column chromatography.

25. The process of Claim 24, wherein the column chromatography is silica gel column chromatography.

26. An indole compound of Formula II



(II)

wherein Prot can be the same or different and are a suitable protecting group.

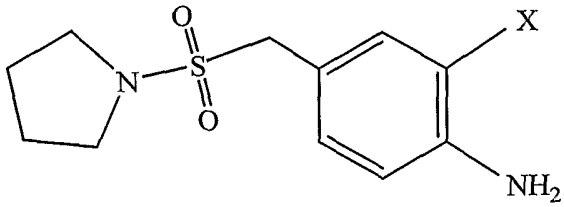
27. The indole compound of Claim 26, wherein the Prot group is a silane-containing protecting group.

28. The indole compound of Claim 26, wherein the Prot group is a trialkylsilyl.

29. The indole compound of Claim 26, wherein each of the Prot group is a trimethylsilyl group or a triethylsilyl group.

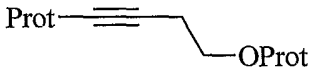
30. A process for preparing almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof, the process comprising the steps of:

(a) Heck coupling a 2-halo aniline derivative of Formula I:

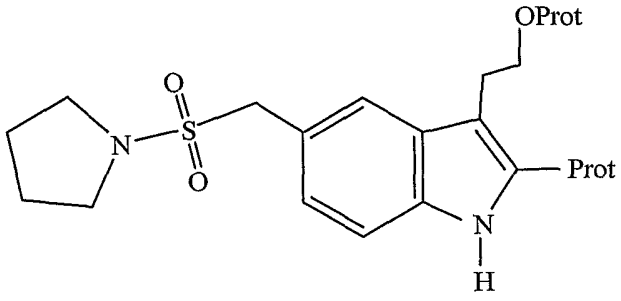


(I)

wherein X is a halogen with a protected butynol compound of the general formula



wherein Prot can be the same or different and are a suitable protecting group, to provide a protected indole derivative of Formula II:



(II);

(b) deprotecting the protected indole of Formula II to provide a tryptophol-containing compound; and

(c) converting the tryptophol to almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof.

31. The process of Claim 30, wherein the 2-halo aniline derivative of Formula I is obtained by reacting 4-(pyrrolidinyl–sulfonylmethyl) aniline with a halogenating agent for halogenation of the 2-position.

32. The process of Claim 31, wherein the reaction is carried out in a solvent selected from the group consisting of methanol, water, ethanol, tetrahydrofuran, methylene chloride and mixtures thereof.

33. The process of Claim 31, wherein the reaction is carried out in the presence of a proton acceptor selected from the group consisting of calcium carbonate, potassium carbonate, sodium carbonate, lithium carbonate, magnesium carbonate, sodium bicarbonate, potassium hydroxide, sodium hydroxide, lithium hydroxide and mixtures thereof.

34. The process of Claims 30-33, wherein the protected butynol compound is selected from the group consisting of bis(trimethylsilyl) butynol and bis(triethylsilyl) butynol.

35. The process of Claims 30-33, wherein the Heck coupling in step (a) is carried out in an inert solvent and in the presence of a palladium catalyst and a base.

36. The process of Claim 35, wherein the palladium catalyst is selected from the group consisting of palladium (II) acetate, palladium (II) bromide, palladium (II) chloride, palladium (II) iodide, palladium tetrakis triphenyl phosphine and mixtures thereof.

37. The process of Claim 35, wherein the inert solvent is selected from the group consisting of dimethylformamide, dimethylacetamide, diethyl ether, isopropyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxy ethane, acetonitrile, toluene, xylene and mixtures thereof.

38. The process of Claim 35, wherein the base is selected from the group consisting of an alkyl amine, aromatic amine, heterocyclic amine, Group I alkali metal carbonate, Group I alkali metal bicarbonate, Group II alkaline earth carbonate, Group II alkaline earth bicarbonate and mixtures thereof.

39. The process of Claim 30, wherein step (b) comprises adding a MeOH-HCl solution or tetrabutylammonium fluoride to the product of step (a) to obtain a tryptophol-containing compound.

40. The process of Claim 30, wherein step (c) comprises mesylating the tryptophol-containing compound with a mesylating agent in a dry inert organic solvent in the presence of a proton acceptor followed by N,N-dimethylamine displacement to provide almotriptan.

41. The process of Claim 40, wherein the mesylating agent is mesyl chloride.

42. The process of Claim 40, wherein the organic solvent is selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, 1,2-dimethoxy ethane, methylene dichloride and mixtures thereof.

43. The process of Claim 30, wherein step (c) comprises tosylating the tryptophol-containing compound and displacing the tosyl group with a N,N-dimethylamino group to provide almotriptan.

44. The process of Claim 39, further comprising basifying the tryptophol-containing compound.

45. The process of Claims 30-44, further comprising the step of purifying almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof.

46. The process of Claim 45, wherein the step of purifying is performed by column chromatography.

47. The process of Claim 46, wherein the column chromatography is silica gel column chromatography.

48. Almotriptan or a pharmaceutically acceptable salt, ester or derivative thereof prepared in accordance with the process of Claims 1-25.

49. Almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof prepared in accordance with the process of Claims 30-47.

50. Substantially pure almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof.

51. The substantially pure almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof of Claim 50, having a purity of greater than or equal to about 98%.

52. The substantially pure almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof of Claim 50, having a purity of greater than or equal to about 99%.

53. A pharmaceutical composition comprising a therapeutically effective amount of substantially pure almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof.

54. The pharmaceutical composition of Claim 53, wherein the substantially pure almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof has a purity of greater than or equal to about 98%.

55. The pharmaceutical composition of Claim 53, wherein the substantially pure almotriptan or a free base or pharmaceutically acceptable salt, ester or derivative thereof has a purity of greater than or equal to about 99%.

56. The pharmaceutical composition of Claims 53-55, further comprising at least one pharmaceutically acceptable carrier, diluent or excipient.

57. The pharmaceutical composition of Claims 53-56, which is in a solid form.

58. The pharmaceutical composition of Claim 57, which is a tablet or capsule.

59. The pharmaceutical composition of Claims 53-56, in the form of a powder suspension in a liquid.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/001471

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/16 C07F7/08 A61K31/4045 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEN C-Y ET AL: "SYNTHESIS OF THE 5-HT1D RECEPTOR AGONIST MK-0462 VIA A PD-CATALYZED COUPLING REACTION" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 35, no. 38, 19 September 1994 (1994-09-19), pages 6981-6984, XP000608320 ISSN: 0040-4039 Scheme 1 page 6982 page 6983; table 1 -----	1-47
Y	EP 0 548 813 A (BRISTOL-MYERS SQUIBB COMPANY) 30 June 1993 (1993-06-30) Scheme 2, page 8 ----- -/--	1-47

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2006	02/10/2006

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/001471

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