PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
C07C 233/14, 233/23	A1	WO 93/01161
		(43) International Publication Date: 21 January 1993 (21.01.93)

(21) International Application Number: PCT/EP92/01496

(22) International Filing Date: 3 July 1992 (03.07.92)

(30) Priority data:
9114948.4 11 July 1991 (11.07.91) GB

(71) Applicant *(for GB only):* PFIZER LIMITED [GB/GB]; Ramgsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant *(for all designated States except GB US):* PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

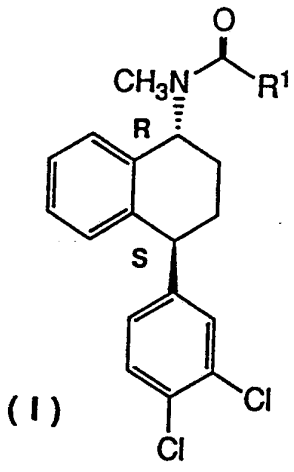
(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* WILLIAMS, Michael, Trevelyan [GB/GB]; WELCH, Willard, McKowan, Jr. [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: WOOD, David, John et al.; Pfizer Limited, Patents Department, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(81) Designated States: CA, FI, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).

Published
With international search report.

(54) Title: PROCESS FOR PREPARING SERTRALINE INTERMEDIATES



(I)

(57) Abstract

The invention provides the substantially geometrically and optically pure trans-steroisomeric form of a compound of formula (I), wherein R^1 is H or C_1-C_4 alkyl, together with processes for its preparation. The compounds are intermediates for the preparation of the antidepressant agent known as sertraline.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		
ES	Spain	MG	Madagascar		

PROCESS FOR PREPARING SERTRALINE INTERMEDIATES

This invention relates to novel trans-N-alkanoyl-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine analogues, which are intermediates in a new process for preparing sertraline, together with intermediates thereto and processes for the preparation thereof.

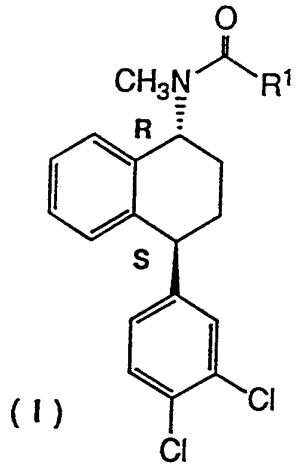
More specifically the invention relates to the (1R,4S)-stereoisomeric form of the said trans-1,4-disubstituted tetrahydronaphthylamines which, upon N-deacylation, afford trans-(1R,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine. The latter, which is disclosed in US 4,556,676 and in the Journal of Medicinal Chemistry, 1984, 27, 1508, is isomeric with the antidepressant agent known as sertraline, or cis-(1S,4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine, which in turn is disclosed in US 4,536,518 and in the Journal of Medicinal Chemistry, 1984, 27, 1508. The trans-(1R,4S)-isomer may be converted to the cis-(1S,4S)-isomer (sertraline) by the conventional procedures subsequently summarised.

The novel compounds of the present invention have been made available by the unexpected discovery that the required trans-isomer may be generated stereoselectively, in high yield, by ionic hydrogenation of the appropriate (1R,4S)-N-alkanoyl-N-methyl-4-(3,4-dichlorophenyl)-4-hydroxy-1,2,3,4-tetrahydro-1-naphthylamine precursor, allowing ready removal of the unwanted (1R,4R)-isomer. Importantly, since the said precursor possesses the 1-(N-alkanoyl)methylamino substituent in the R-configuration, ionic

hydrogenation thereof affords the trans-(1R,4S)-enantiomer in high yield and with high stereoselectivity, thus obviating the need for a subsequent optical resolution to remove the unwanted trans-(1S,4R)-enantiomer.

Thus the present invention provides:-

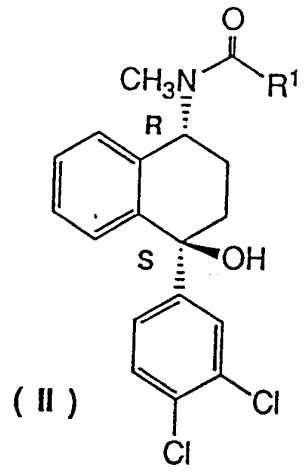
a) the substantially geometrically and optically pure trans-stereoisomeric form, consisting of the trans-(1R,4S)-enantiomer, of a compound of formula:



(I)

wherein R^1 is H or C_1-C_4 alkyl, and R and S represent the absolute configurations of the asymmetric centres;

b) a process for preparing the substantially geometrically and optically pure trans-stereoisomeric form of a compound of formula (I) by subjecting a compound of formula:



(II)

wherein R^1, R and S are as previously defined for formula (I), in a suitable solvent, to ionic hydrogenation conditions.

Alkyl groups containing three or four carbon atoms may be straight or branched chain.

The term "substantially geometrically and optically pure" means that the compounds of the formula (I) contain less than 4%, and preferably less than 2%, of the undesired cis-(1R,4R)-enantiomer.

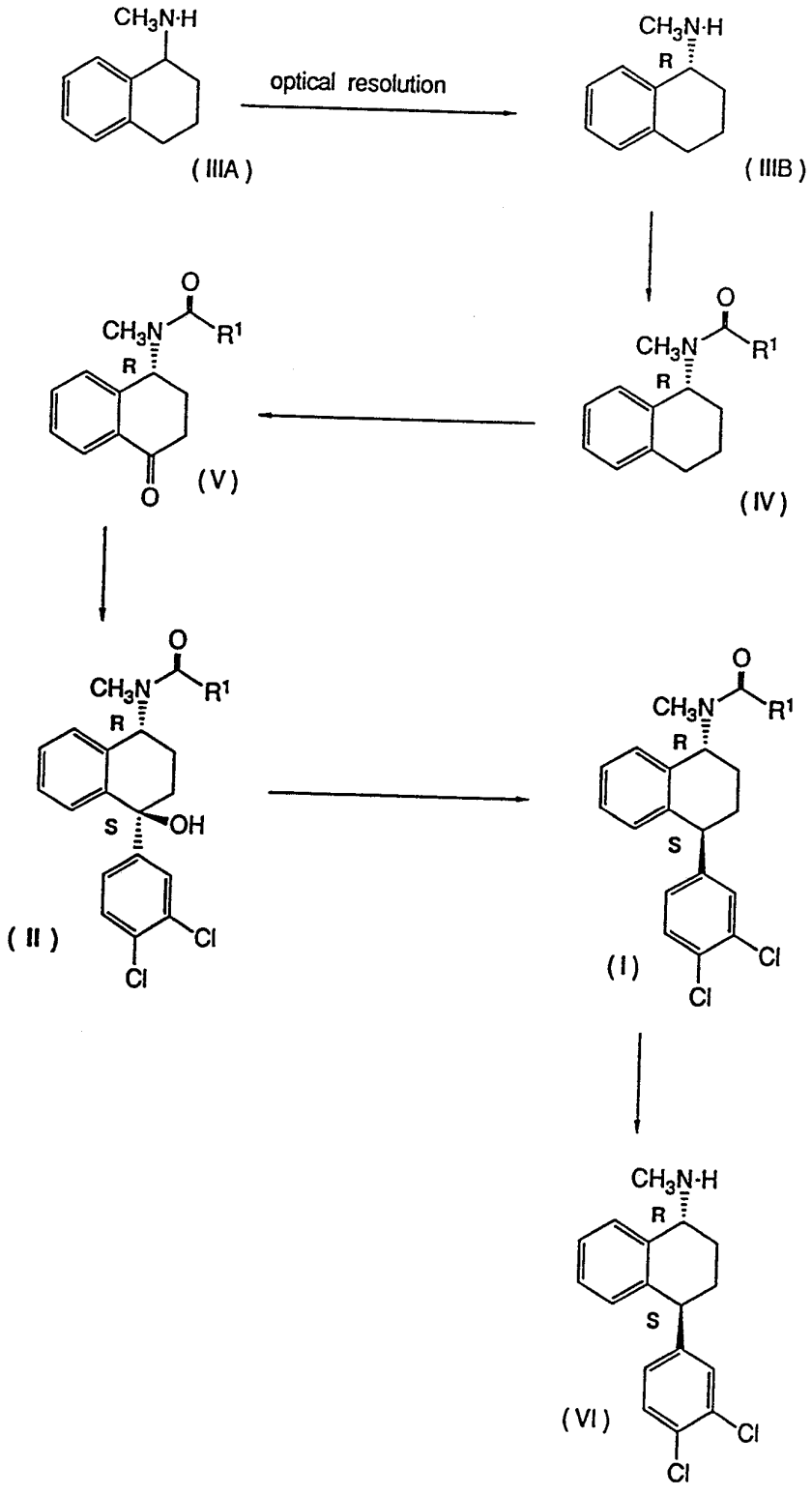
In the above definitions of the compounds of formulae (I) and (II), preferably R^1 is H.

The compounds provided by the present invention may be prepared as follows.

A compound of formula (I) is obtained by ionic hydrogenation of a compound of formula (II) in a suitable solvent, such as dichloromethane, using a combination of either a protic acid, e.g. trifluoroacetic acid, or preferably a Lewis acid, e.g. boron

trifluoride, with a hydride donor, e.g. triethylsilane. Typically the reaction is conducted at from -40 to +25°C for up to to 40 hours, preferably about 20 hours. The product of formula (I) may then be isolated and purified by conventional techniques, e.g. by extractive work-up, followed by chromatographic purification and/or crystallisation of the crude product, to remove any recovered starting material and minor amounts of the unwanted cis-(1R,4R)-isomer. Alternatively, the separation of trans- and cis-isomers can be effected after removal of the N-alkanoyl group, to furnish a compound of formula (VI), wherein R and S are as previously defined, in the next stage of the synthetic sequence depicted in the following Scheme.

Scheme


CH3N·H
optical resolution
(IIIA)
(IIIB)
R
O
CH3N
R1
(V)
(IV)
S
OH
Cl
(II)
(I)
(VI)

The N-alkanoyl group of a compound of formula (I), the major isomer of the aforementioned crude product, is removed by hydrolysis using an aqueous inorganic base such as an alkali metal hydroxide salt, preferably potassium hydroxide, as a 10 molar solution in water. Typically the hydrolysis is carried out in ethylene glycol at the reflux temperature of the reaction medium for from 2 hours to 4 days. For a compound of formula (I) wherein R^1 is H, the N-alkanoyl group is preferably removed by acidic hydrolysis using a mineral acid, e.g. hydrochloric acid, in a suitable solvent such as 2-propanol, 1,4-dioxan or ethyl acetate, at the reflux temperature of the reaction medium for from 2 to 8 hours. The product (VI) is then isolated and purified by conventional procedures, e.g. extractive work-up, optional column chromatography to remove minor amounts of the unwanted cis-(1R,4R)-isomer, and conversion to the hydrochloride salt. The purified free amine may then be transformed to the cis-(1S,4S)-enantiomer (sertraline), as summarised on page 9 et seq.

A compound of formula (II) required for the preparation of a compound of formula (I) may be obtained by the route depicted in the Scheme, wherein R^1, R and S are as previously defined, using routine procedures.

Initially, resolution of the amine (IIIA) is effected to provide the optically pure R-enantiomer (IIIB). The resolution is carried out in a conventional manner by fractional crystallisation of a salt of the amine (IIIA), formed with an optically pure acid such as a sulphonic or carboxylic acid, preferably (2R,3R) (+) tartaric acid, from an appropriate solvent, e.g. water. The free

amine (IIIB) is then liberated by treatment of the resolved amine salt with a base, typically an aqueous solution of sodium or potassium hydroxide.

The amine (IIIB) may also be obtained by asymmetric reduction of the imine precursor, which is directly accessible from α-tetralone and methylamine, by methods well known to persons skilled in the art.

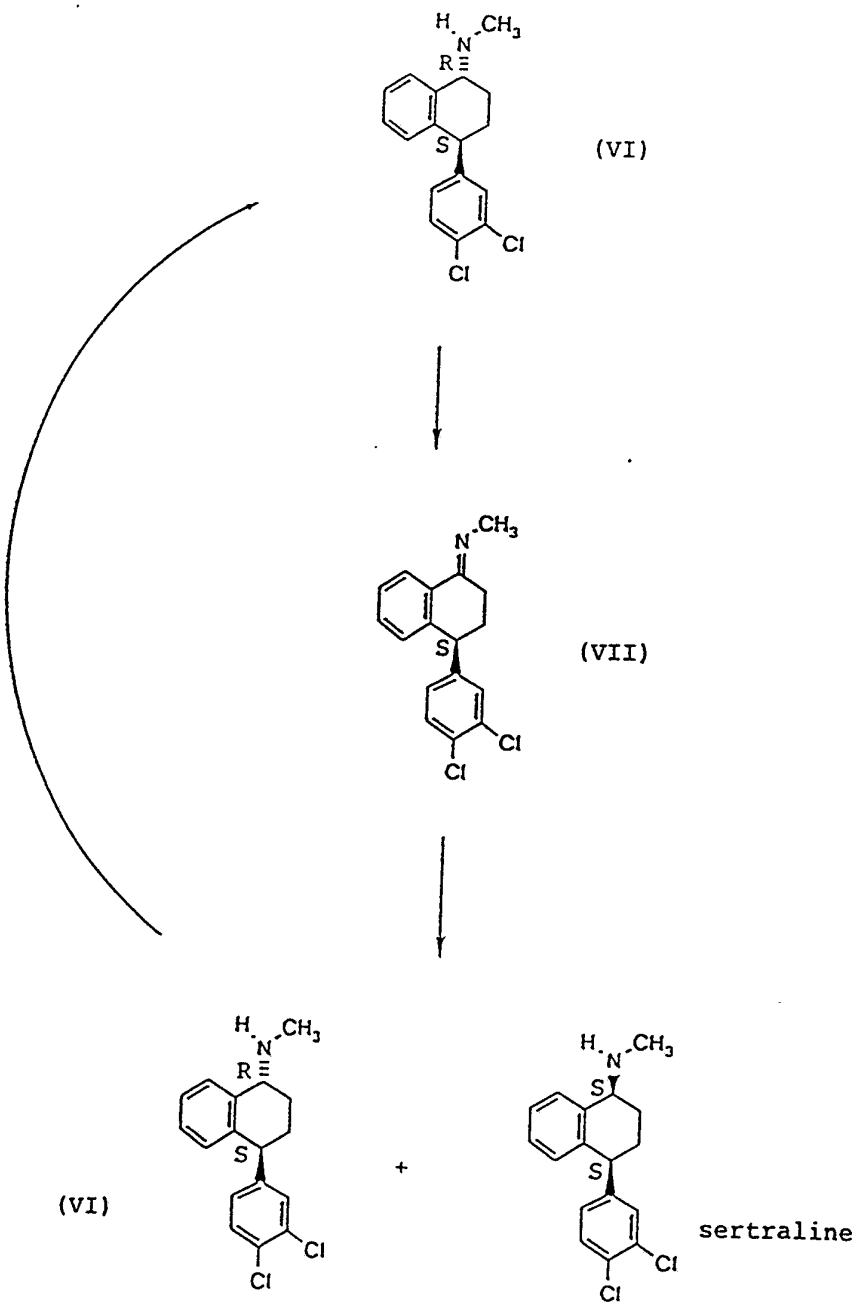
A compound of formula (IV) wherein R^1 is C_1-C_4 alkyl can be prepared by acylating a compound of the formula (IIIB) with either an acyl halide of formula (C_1-C_4 alkyl)CO(Cl or Br) or with an acid anhydride of formula [(C_1-C_4 alkyl)CO]$_2$O. When an acyl halide is employed the reaction may be carried out at from 0 to 25°C, preferably at from 5 to 10°C, in a suitable organic solvent, e.g. dichloromethane, and in the presence of an acid acceptor, e.g. triethylamine. When an acid anhydride is used the reaction may be conducted at up to the reflux temperature of the reaction medium, preferably at 100°C, in a suitably compatible solvent, e.g. a carboxylic acid of formula (C_1-C_4 alkyl)CO_2H. To obtain a compound of formula (IV) wherein R^1 is H, compound (IIIB) is formylated using acetic-formic anhydride which may be generated by the addition of 98% formic acid to stirred acetic anhydride, typically between 0 and 10°C. The freshly prepared mixed anhydride is then reacted with compound (IIIB) in an appropriate solvent, e.g. 98% formic acid, at from 5 to 25°C.

Conversion of a compound of formula (IV) to a ketone of formula (V), via a benzylic oxidation reaction, can be effected with a variety of oxidising agents such as an inorganic

permanganate salt, ammonium cerium(IV) nitrate, cobalt(III) acetate or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, in a suitable solvent. Preferably the reaction is carried out using 3-5 molecular equivalents of potassium permanganate in aqueous acetone in the presence of a buffering reagent such as an alkali, or alkaline earth, metal salt, e.g. magnesium sulphate. The oxidant may be added in portions in a controlled manner, in order to moderate the potentially vigorous reaction, to a solution of the substrate (IV) at from 5 to 30°C. Subsequent to this addition, warming of the reaction mixture at from 30 to 50°C may be required in order to complete the oxidation.

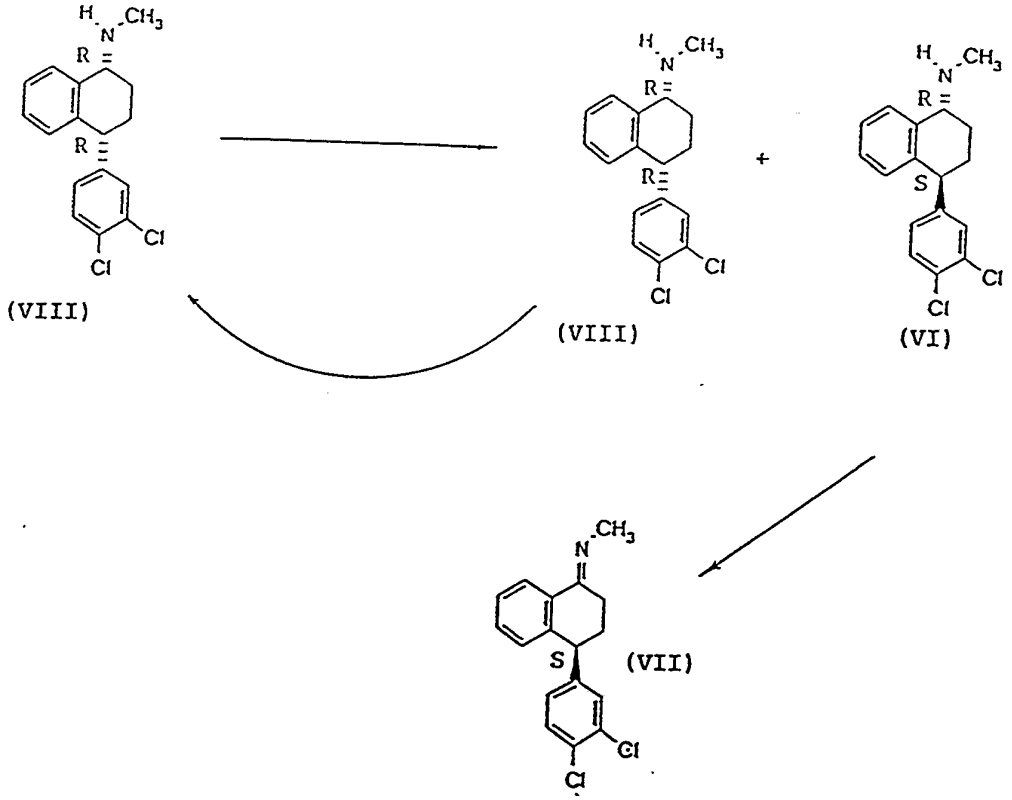
A compound of formula (II) can be prepared stereoselectively from a compound of formula (V) using a 3,4-dichlorophenylmagnesium halide, preferably the iodide, under standard Grignard reaction conditions. Thus, typically, a solution of the ketonic substrate (V) in a suitably compatible solvent, e.g. dry toluene or dry tetrahydrofuran, is added to a freshly prepared solution of the Grignard reagent in an appropriate solvent such as dry diethyl ether, at a temperature of from 5 to 25°C, under anhydrous conditions. The reaction is allowed to proceed at from 20-25°C for from 4 to 24 hours and the mixture may be heated under reflux for up to 1 hour, if necessary, to promote a better conversion of (V) to (II). Minor amounts of the (1R,4R)-alcohol may be removed by column chromatography and/or crystallisation.

The trans-(1R,4S)-amine (VI) may be converted to sertraline by the following process.

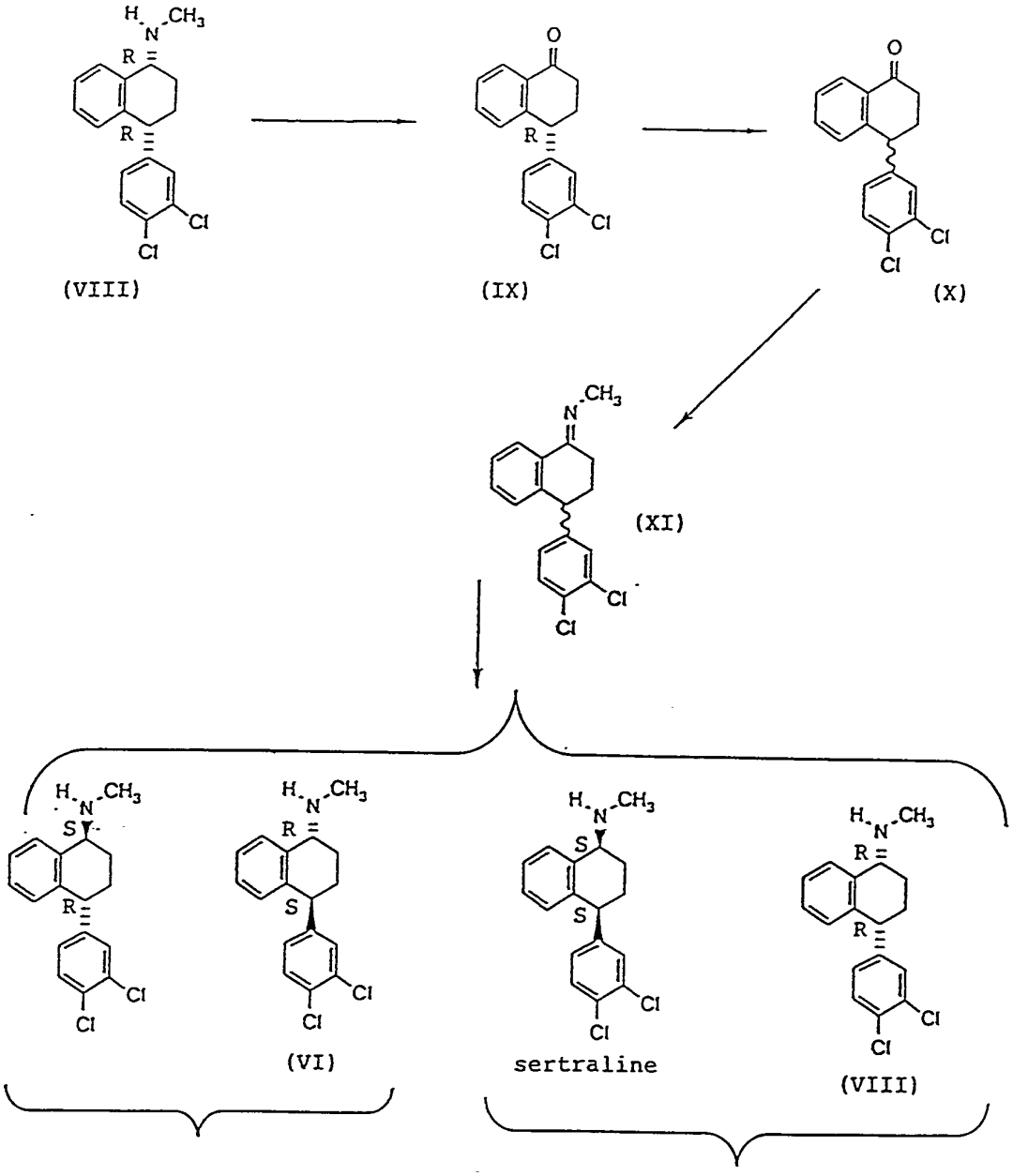


The process involves controlled oxidation of the trans-enantiomer (VI) to afford the imine (VII) which is subsequently reduced, for example by catalytic hydrogenation using 10% palladium on charcoal as catalyst as described in US 4,536,518, to provide a mixture (approximately 7:3 ratio) of sertraline and regenerated (VI); the latter can be separated from sertraline by conventional means and recycled to provide further batches of sertraline. Alternatively, nickel based catalysts may be used in the hydrogenation step to afford a mixture (approximately 8:1 ratio) of sertraline and (VI).

In an alternative process optimisation procedure illustrated below, the cis-(1R,4R)-enantiomer (VIII), which in common with (VI) is an unwanted by-product of processes in which sertraline is produced by resolution of a mixture of all four stereoisomers, may also be recycled to sertraline via the imine (VII). Firstly, however, (VIII) is isomerised by base treatment to a mixture (approximately 2:1 ratio) of (VIII) and the trans-(1R,4S)-enantiomer (VI); the latter is then separated, and converted to imine (VII) as in the first recycle process disclosed above. Clearly, the remaining cis-(1R,4R)-enantiomer (VIII) can re-enter this base equilibration process as required.



Alternatively, in a related process, the unwanted cis-(1R,4R)-enantiomer (VIII) may be oxidised to the α-tetralone (IX) which, in turn, can be isomerised to furnish the known, racemic 4-(3,4-dichlorophenyl)-α-tetralone (X), disclosed in US 4,536,518 and the Journal of Medicinal Chemistry, 1984, 27, 1508. (X) is then transformed to sertraline via racemic imine (XI), preferably by catalytic hydrogenation of (XI) using a palladium or nickel catalyst as mentioned above, followed by separation of the cis-racemate and its subsequent resolution as described in US 4,536,518. This process is depicted overleaf.


(VIII)
(IX)
(X)
(XI)
(VI)
sertraline
(VIII)

The invention will now be more particularly illustrated by the following experimental Examples. The purity of the compounds was monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F_{254} plates. Routine ^{1}H-nuclear magnetic resonance (nmr) spectra were recorded using a Nicolet QE-300 spectrometer and ^{13}C nmr spectra were recorded using a Bruker 250 spectrometer; they were in all cases consistent with the proposed structures. Nuclear Overhauser effect (nOe) experiments were conducted using a Bruker 250 spectrometer.

EXAMPLE 1

(R)(-)-N-Methyl-1,2,3,4-tetrahydro-1-naphthylamine

A solution of (2R,3R)(+) tartaric acid (160.3 g) in water (500 ml) was treated with N-methyl-1,2,3,4-tetrahydro-1-naphthylamine (172.2 g). The resulting solution was cooled from 33°C to room temperature, seeded and stirred for 16 hours. The slurry was refrigerated for 4 hours, filtered and the solid was washed with water (3 x 50 ml). The crude salt (196.2 g) was fractionally recrystallised from water giving the purified (+) tartaric acid salt of the title compound (42 g, 25.3% based on available enantiomer) as white crystals, m.p. 107-109°C, $[\alpha]_D$+12.3° (c=4.2, water). Found: C,54.85; H,7.06; N,4.22. $C_{15}H_{21}NO_6$; H_2O requires C,54.70; H,7.04; N,4.25%.

The salt (38.9 g) was dissolved in water (150 ml), with warming to 40°C, and then basified by the addition of 5N aqueous sodium hydroxide solution (100 ml). The cooled mixture was extracted with dichloromethane (2 x 150 ml). Evaporation under vacuum of the extracts gave the title compound as a colourless oil (19.1 g, 97.2% from salt), $[\alpha]_D$-10.3° (c=5, EtOH). ^{1}H-nmr assay of the (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl derivative using the method of Mosher (J. Org. Chem., 1969 34, 2543) showed the title compound to be a 95.5:4.5 mixture of the (R) and (S) enantiomers, respectively.

EXAMPLE 2

(R)(+)-N-(1,2,3,4-Tetrahydro-1-naphthyl)-N-methylformamide

Acetic anhydride (54.1 g) was chilled to 0°C and stirred as 98% formic acid (33.1 g) was added over 30 minutes, keeping the

temperature below 5°C. The solution was warmed to 50°C, held at this temperature for 15 minutes, and chilled to 5°C. The resulting solution of acetic-formic anhydride was added over 5 minutes to a stirred, chilled solution of (R)(-)-N-methyl-1,2,3,4-tetrahydro-1-naphthylamine (19.08 g) in 98% formic acid (19.08 ml), keeping the tempeature below 10°C. The reaction solution was warmed to room temperature, stirred for 1 hour, poured into an ice-water mixture (200 g) and stirred for 30 minutes. The mixture was basified to pH 9 with 10N aqueous sodium hydroxide solution (about 230 ml) and extracted with dichloromethane (3 x 200 ml). The combined extracts were back-washed with 1N aqueous hydrochloric acid (100 ml), then water (100 ml), and evaporated under vacuum to give the title compound (21.63 g, 96.6%) as a solid, m.p. 53-55°C; Rf 0.80 (silica; chloroform, methanol; 95:5).

A sample of the product (1.5 g) was crystallised from a mixture of ethyl acetate (1.5 ml) and hexane (15 ml) to give a purified sample of the title compound (0.92 g, 61.3% recovery) as white crystals, m.p. 55-56°C, $[\alpha]_D$+19.4° (c=0.5, EtOH). A chiral HPLC assay on an acetylated ß-cyclodextrin column showed this material to contain less than 1% of the (S)-enantiomer. Found: C,76.04; H,7.94; N,7.43. $C_{12}H_{15}NO$ requires C,76.16; H,7.98; N,7.40%.

^{1}H-nmr (300 MHz, $CDCl_3$):

δ = 1.80 - 2.13 (m,4H), 2.70 and 2.73 (2 NMe rotamer singlets, 3H), 2.78 - 2.93 (m,2H), 4.73 - 4.81 and 5.71 - 5.79 (2 rotamer multiplets, 1H), 7.02 - 7.25 (m,4H), 8.30 and 8.34 (2 formyl CH rotamer singlets, 1H) p.p.m.

EXAMPLE 3

(R)(+)-N-(1,2,3,4-Tetrahydro-4-keto-1-naphthyl)-N-methylformamide

To a chilled solution of (R)(+)-N-(1,2,3,4-tetrahydro-1-naphthyl)-N-methylformamide (19.1 g) in acetone (430 ml) was added magnesium sulphate heptahydrate (57 g), water (143 ml) and then, portionwise over 1 hour, potassium permanganate (76 g). The mixture was stirred for 5.5 hours with water bath cooling to keep the reaction temperature below 34°C, filtered and the cake washed with acetone (2 x 100 ml). The filtrate and washes were combined and treated with 10% aqueous sodium metabisulphate solution (140 ml), then the mixture refiltered and extracted with dichloromethane (400 ml and then 200 ml). The combined extracts were evaporated under vacuum to an oil (14.7 g) which was chromatographed on silica (274 g), eluting with a dichloromethane/methanol mixture (98:2) to give the product as an oil (8.2 g, 40%); Rf 0.18 (silica; ethyl acetate) and 0.58 (silica; chloroform, methanol; 95:5).

A sample of the product (1.1 g) was triturated with diethyl ether (20 ml) to induce crystallisation giving a purified sample of the title compound (0.72 g), m.p. 92-93°C; $[\alpha]_D$ + 54.9° (c = 0.5, EtOH). Found: C,70.68; H,6.41; N,6.86. $C_{12}H_{13}NO_2$ requires C,70.92; H,6.45; N,6.64%.

^{1}H-nmr (300 MHz, $CDCl_3$):

δ = 2.17 - 2.56 (m,2H), 2.68 - 2.99 (m,2H), 2.79 and 2.83 (2 NMe rotamer singlets, 3H), 4.96 - 5.04 and 5.92 - 6.01 (2 rotamer

quartets, 1H), 7.10 - 7.24 (q,1H), 7.40 - 7.53 (m,1H), 7.55 - 7.68 (m,1H), 8.07 - 8.16 (t,1H), 8.38 and 8.40 (2 formyl CH rotamer singlets, 1H) p.p.m.

EXAMPLE 4

(1R,4S)(-)-N-[4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-4-hydroxy-1-naphthyl]-N-methylformamide

Magnesium turnings (0.89 g) and a crystal of iodine were stirred in dry diethyl ether (25 ml) as a solution of 1,2-dichloro-4-iodobenzene (10.07 g) in dry diethyl ether (25 ml) was added over 20 minutes. After the exotherm subsided the mixture was heated under reflux for a further 25 minutes to complete the consumption of the magnesium metal. The mixture was then chilled to 5°C, blanketed with nitrogen gas and a solution of (R)(+)-N-(1,2,3,4-tetrahydro-4-keto-1-naphthyl)-N-methylformamide (5 g) in dry toluene (100 ml) was added over 15 minutes. After being stirred for 20 hours the resulting mixture was poured into 10% aqueous ammonium chloride solution (200 ml). The phases were separated, the aqueous layer was washed with toluene (25 ml) and the combined organic layers were evaporated under vacuum to give a mixture of (1R,4S)- and (1R,4R)-isomers (ratio 87:13 respectively by nmr spectroscopy techniques) as a dark oil (10.17 g) which was chromatographed on silica (320 g). Elution with hexane-ethyl acetate mixtures (1:1 to 1:4) gave the title compound as a foam (3.94 g, 45.7%), Rf 0.34 (silica; ethyl acetate) and 0.50 (silica; chloroform, methanol; 95:5) which was sufficiently pure for use in the next step.

A sample of the product (0.92 g) was purified by slow crystallisation from di-2-propyl ether giving the title compound (0.46 g, 50% recovery) as white crystals, m.p. 123-125°C, $[\alpha]_D$ -31.6° (c = 0.5, EtOH). Found: C,61.79; H,5.07; N,3.90. $C_{18}H_{17}Cl_2NO_2$ requires C,61.72; H,4.89; N,4.00%.

^{1}H-nmr (300 MHz, $CDCl_3$):

δ = 1.60 - 2.01 (m,2H), 2.12 - 2.37 (m,2H), 2.38 (s,1H), 2.69 and 2.73 (2 NMe rotamer singlets, 3H), 4.78 - 4.86 and 5.75 - 5.83 (2 rotamer quartets, 1H), 6.89 - 7.04 (m,1H), 7.05 - 7.42 (m,6H), 8.25 and 8.30 (2 formyl CH rotamer singlets, 1H) p.p.m.

EXAMPLE 5

trans-(1R,4S)(+)-N-[4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthyl]-N-methylformamide

To a solution of (1R,4S)(+)-N-[4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-4-hydroxy-1-naphthyl]-N-methylformamide (0.175 g) in dichloromethane (10 ml) was added triethylsilane (0.13 g) in dichloromethane (1 ml). The resulting solution was cooled to -40°C and stirred as boron trifluoride (0.08 g) in dichloromethane (6.5 ml) was added over 30 minutes. The solution was allowed to warm to room temperature over 90 minutes and then treated with further triethylsilane (0.13 g) in dichloromethane (1 ml) followed by further boron trifluoride (0.54 g) in dichloromethane (43.5 g). After overnight stirring at room temperature a third addition of triethylsilane (0.13 g) was made and the solution was gassed with boron trifluoride for about 1 minute. The resulting solution was washed with 2M aqueous sodium carbonate solution (22 ml) and then

saturated brine (25 ml), and the aqueous phases were combined and back-washed with diethyl ether (2 x 25 ml). The combined organic extracts were dried over magnesium sulphate and evaporated under vacuum to give an oil (0.17 g) which was percolated through a column of silica (16 g) eluting with 1:1 ethyl acetate-hexane to remove the low level of recovered starting material. Evaporation under vacuum of the requisite fractions gave the crude product as an oil (154 mg, 92%). A ^{1}H-nmr assay of this material showed it to be an 86:14 mixture of the required (1R,4S) trans-isomer (δ = 4.04 - 4.14 p.p.m., m, for the H_4 proton) and the (1R,4R) cis-isomer (δ = 4.18 - 4.27 p.p.m., m, for the H_4 proton), respectively.

The separation of trans and cis-isomers is most efficiently achieved after removal of the formyl group. However, crystallisation of a sample of the crude product from 1:3 dichloromethane-hexane provided a reference sample of the title compound as white crystals, m.p. 110 - 112°C; Rf 0.62 (silica; chloroform, methanol; 95:5); $[\alpha]_D$+100.8° (c = 1.03, EtOH). Found: C,64.66; H,5.37; N,4.12. $C_{18}H_{17}Cl_2NO$ requires C,64.67; H,5.13; N,4.19%.

^{1}H-nmr (300 MHz, $CDCl_3$):

δ = 1.88 - 2.18 (m,3H), 2.21 - 2.37 (m,1H), 2.73 and 2.78 (2 NMe rotamer singlets, 3H), 4.04 - 4.14 (m,1H), 4.90 - 4.98 and 5.84 - 5.96 (2 rotamer multiplets, 1H), 6.77 - 6.85 (t,1H), 6.91 -7.03 (m,1H), 7.05 - 7.34 (m,4H), 7.36 - 7.47 (m,1H), 8.34 and 8.38 (2 formyl CH rotamer singlets, 1H) p.p.m.

EXAMPLE 6

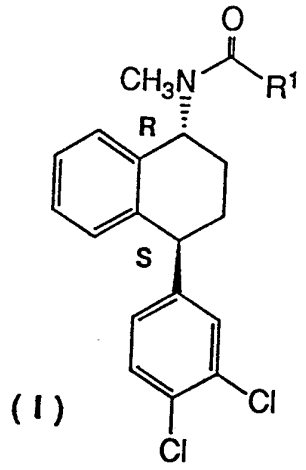
trans-(1R,4S)(+)-N-Methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine hydrochloride

A solution of trans-(1R,4S)(+)-N-[4-(3,4- dichlorophenyl)-1,-2,3,4-tetrahydro-1-naphthyl]-N-methylformamide (0.15g of 86:14 trans-cis mixture from Example 5) in 2-propanol (1.5ml) was treated with concentrated aqueous hydrochloric acid (0.45ml) and heated under reflux for 12.5 hours. The solution was refrigerated overnight, then the resulting mixture granulated at 0°C for several hours. Filtration gave the product (0.110g, 71.4%) as white crystals, m.p. 253-255°C; Rf 0.09 (silica; chloroform, methanol; 90:10); $[\alpha]_D$+41.4°(c=1, MeOH).

N.B. N-Methyl-1,2,3,4-tetrahydro-1-naphthylamine (compound IIIA) is obtainable according to Coll. Czech. Chem. Commun., 1973, 38, 1159.

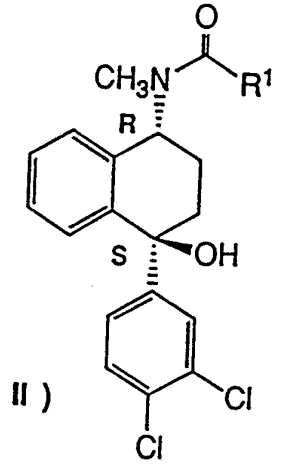
CLAIMS

1. A process for the preparation of the substantially geometrically and optically pure trans-stereoisomeric form of a compound of formula:



(I)

wherein R^1 is H or C_1-C_4 alkyl, and R and S represent the absolute configurations of the asymmetric centres, which comprises ionic hydrogenation of a compound of formula:



(II)

wherein R^1, R and S are as defined for formula (I).

2. A process as claimed in claim 1 wherein the ionic hydrogenation is achieved using a combination of a Lewis acid with

a hydride donor.

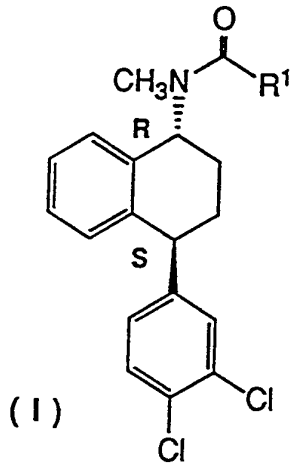
3. A process as claimed in claim 1 wherein the ionic hydrogenation is achieved using a combination of a protic acid with a hydride donor.

4. A process as claimed in claim 2 wherein the Lewis acid is boron trifluoride.

5. A process as claimed in claim 3 wherein the protic acid is trifluoroacetic acid.

6. A process as claimed in any one of claims 2 to 5 wherein the hydride donor is triethylsilane.

7. The substantially geometrically and optically pure trans-stereoisomeric form of a compound of formula:



(I)

wherein R^1 is H or C_1-C_4 alkyl, and R and S represent the absolute configurations of the asymmetric centres.

8. A compound of formula (II) as defined in claim 1.

9. A compound as claimed in claims 7 and 8 or a process as claimed in any one of claims 1 to 6 wherein R^1 is H.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01496

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C233/14; C07C233/23

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	US,A,4 556 676 (W.M. WELCH) 3 December 1985 cited in the application	1-7

° Special categories of cited documents : [10]

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08 OCTOBER 1992	30. 10. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SANCHEZ GARCIA J.M.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9201496 SA 61917

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/10/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4556676	03-12-85	AT-T- 2667	15-03-83
		AU-B- 517842	27-08-81
		AU-A- 6389880	07-05-81
		CA-A- 1130816	31-08-82
		EP-A,B 0028901	20-05-81
		JP-C- 1345886	29-10-86
		JP-A- 58222017	23-12-83
		JP-B- 61010446	29-03-86
		JP-C- 1225987	31-08-84
		JP-A- 56079649	30-06-81
		JP-B- 59000497	07-01-84