

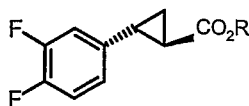
Chemical process for preparation of aromatic cyclopropane esters and amides

The present invention relates to compounds useful as pharmaceutical intermediates, to processes for preparing said intermediates, to intermediates used in said processes, and to the use of said intermediates in the preparation of pharmaceuticals. In particular, the present invention concerns enantiomerically pure trans-cyclopropane carboxylic acid derivatives, processes for preparing said carboxylic acid derivatives and their use in preparing pharmaceuticals.

The compound [1S-(1 α , 2 α , 3 β (1S*,2R*),5 β)]-3-[7-[2-(3,4-difluorophenyl)-cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol (Compound A), and similar such compounds, are disclosed in WO 00/34283 and WO 99/05143. These compounds are disclosed as P_{2T} (which is now usually referred to as P_{2Y12}) receptor antagonists. Such antagonists can be used as, *inter alia*, inhibitors of platelet activation, aggregation or degranulation.

We have now found an advantageous process for preparing enantiomerically pure trans-cyclopropane carboxylic acid derivatives which may be used in the preparation of Compound A. The process offers the following advantages: diastereoselectivity, enantioselectivity, high yield, potential for manufacturing (e.g. reagents and procedures suitable for large scale production, non-hazardous reagents, less waste).

According to a first aspect of the present invention there is provided a compound of formula IV

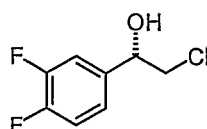


IV

Wherein R is an alkyl group.

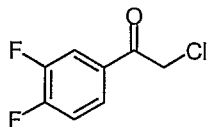
Suitable values of R include, for example, (1-6C)alkyl such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, and tert-butyl. A particular value for R is ethyl.

The compound of formula IV may be prepared from a compound of formula II



II

According to a further aspect of the present invention there is provided a process for preparing a compound of formula II from a compound of formula I.



I

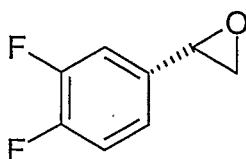
The compound of formula I is reduced to the compound of formula II. The reduction is carried out using a suitable reducing agent. Suitable reducing agents will include those which are able to reduce the carbonyl group in the compound of formula I to the hydroxyl group of formula II and give an enantiometric excess of the compound of formula II with the stereo chemistry shown in formula II.

Examples of suitable conditions include, for example, catalytic reduction or use of a transition metal with chiral ligand.

A particular example of a suitable reducing agent is oxazaborolidine which may be formed by mixing trimethoxy borane and S-diphenylprolinol, followed by addition of borane dimethylsulphide. This is generally carried out in an inert solvent such as toluene. The temperature is conveniently maintained at a temperature in the range 25 to 45⁰ C, for example 35 to 40⁰ C.

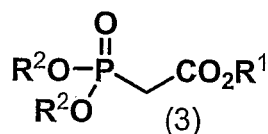
The compound of formula I is treated with the reducing agent so formed. This is generally carried out in an inert solvent such as toluene. The temperature is conveniently maintained at a temperature in the range 25 to 45⁰ C, for example 35 to 40⁰ C.

- 5 The compound of formula IV may be prepared by treating a compound of formula III



III

with a compound of formula :



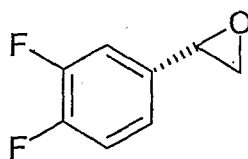
10 Wherein R¹ and R² are independently selected from alkyl such as (C1-6C)alkyl. A preferred agent is triethyl phosphonoacetate.

15 The reaction is generally carried out in an inert solvent such as toluene. The reaction is generally carried out at a temperature in the range 30 to 80⁰C, conveniently 40 to 60⁰ e.g. 40⁰ C. The reaction may conveniently be carried out in the presence of a base. Examples of suitable bases include sodium hydride and alkali metal (for example potassium or sodium) alkoxides (for example t-butoxide). Specific examples are potassium and sodium t-butoxide.

20 The compound of formula III may be prepared by treating the compound of formula II with a base such as an alkali metal hydroxide, for example sodium hydroxide. This is conveniently carried out in a suitable solvent such as water.

25 The compound of formula II may be converted to the compound of formula IV via the compound of formula III, without isolation of the compound of formula III.

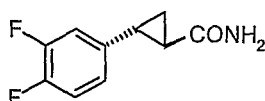
4



III

In a particular embodiment of the present invention, the compound of formula II is converted to the compound of formula IV by treating the compound of formula II with a base such as sodium hydride. This is generally carried out in an inert solvent such as toluene. This is treated with triethyl phosphonoacetate. This is generally carried out at a temperature in the range 30 to 80 °C, conveniently 40 to 60 °C e.g. 40 °C.

The present invention also provides a process for preparing a compound of formula VII which comprises treating the compound of formula IV with ammonia in the presence of a suitable base. Suitable bases include alkali metal alkoxides such as potassium methoxide or sodium methoxide. An agent such as methyl formate may also be present. The reaction is generally carried out in a suitable solvent such as an alcohol in a suitable solvent. In one embodiment, the reaction is carried out in toluene and methanol.



VII

The compound of formula IV may be treated with the base and then treated with ammonia. Preferably, the reaction is under pressure during the treatment with ammonia. An example of a suitable pressure is 2 to 10 bar. The reaction may be carried out at an elevated temperature, such as 40 to 70 °C, for example at about 60 °C.

The present invention is also directed to compounds of formula IV and VII.

The present invention also provides novel intermediates of formula II III or VII.

The invention will now be further illustrated with reference to the following examples.

Example 1

Preparation of 2-chloro-1-(3,4-difluorophenyl)ethanone

- 5 Aluminium trichloride (210.2 g) was added to 1,2-difluorobenzene (200.0 g) at room temperature. The obtained slurry was heated to 50 °C, then chloroacetyl chloride (198.0 g) was added over 50 minutes. The reaction mixture was stirred for an additional 60 minutes, then added slowly to a mixture of ice (786.0 g), water (196.0 g) and 37 wt% hydrochloric acid (297.0 g), during the addition the temperature was kept below 60 °C. After the
- 10 addition the reaction mixture was heated to 60 °C and the layers separated. The organic layer was washed twice with a 20 w/v% sodium chloride solution (200.0 mL). 2-Chloro-1-(3,4-difluorophenyl) ethanone (270.2 g) was obtained by vacuum distillation of the organic layer.

Spectral data:

- 15 ¹H-NMR of 2-chloro-1-(3,4-difluorophenyl)ethanone in CDCl₃, 300 MHz

δ (ppm)	H	Pattern
4.7	ClCH ₂	S
7.3	Ph H-5	dxdxd
7.8	Ph H-6 Ph H-2	M

- ¹³C-NMR of 2-chloro-1-(3,4-difluorophenyl)ethanone in CDCl₃, 75 MHz

δ (ppm)	Assignment
45.7	ClCH ₂ CO
118.4	Ph C-2 and C-5, small J _{F-C} visible
126.2	Ph C-6, small J _{F-C} visible
131.6	Ph C-1, small J _{F-C} visible
149.1-156.3	Ph C-3 and C-4, large J _{F-C} visible
189.3	ClCH ₂ COPh

Example 2**Preparation of 2-chloro-1-S-(3,4-difluorophenyl)ethanol**

5 Trimethoxy borane (2.7 g) was added at room temperature to a stirred solution of S-diphenylprolinol (4.7 g) in toluene (128.6 mL). After stirring this mixture for 90 minutes at 40 °C borane dimethylsulfide (22.3 g) was added over 15 minutes maintaining the temperature between 35 and 45 °C. This mixture was stirred for 60 minutes at 40 °C, then a solution of 2-chloro-1-(3,4-difluorophenyl)ethanone (70.0 g) in toluene (184.1 mL) was
10 dosed over a period of 120 minutes maintaining the temperature between 35 and 45 °C. After the completion of the addition the reaction mixture was stirred for another 60 minutes at 40 °C, then cooled to 10 °C. Methanol (69.7 g) was added over a period of 20 minutes controlling the gas formation and the temperature to a maximum of 35 °C. After the addition the mixture was cooled to 20 °C, then stirred at this temperature for 30
15 minutes. The obtained solution was then distilled, under reduced pressure at maximum 45 °C, till the residual Methanol and trimethoxyborane was less than 2 wt%. The obtained solution in toluene was then washed four times with a 10 wt% aqueous HOAc (280.0 mL) at 45 to 55 °C and the obtained water layer back extracted with toluene (140.0 mL). Both organic layers were combined and washed with water (140.0 mL). The resulting organic
20 layer was azeotroped till less than 0.4 wt% water. After correction with toluene a 33 wt% solution of 2-chloro-1-S-(3,4-difluorophenyl)ethanol was obtained (214.4 g theoretical yield).

The product in solution was characterized by mass spectroscopy (EI):

M/z	Identification
175.6	M ⁺ -H ₂ O
143.6	M ⁺ -CH ₂ Cl

Example 3**Preparation of ethyl (1R,2R)-trans 2-(3,4-difluorophenyl) cyclopropyl carboxylate**

Sodium hydride (13.4 g) was suspended in toluene (119.9 mL) and the resulting slurry

heated to 40 °C, then a solution of triethyl phosphonoacetate (38.4 g) in toluene (60.0 mL) was added over a period of 60 minutes keeping the temperature between 40 and 45 °C. When the addition was complete the reaction mixture was stirred for an additional 60 minutes at 40 °C, then 90.9 g of a 33 wt% solution of 2-chloro-1-S-(3,4-difluorophenyl)ethanol in toluene was added over a period of 35 minutes allowing the temperature to raise to maximum 60 °C. Once the addition was complete the obtained mixture was stirred for an additional 14 hours at 60 °C, then water (155.8 mL) was added and the phases separated at 60 °C. The toluene solution containing ethyl (1R,2R)-trans 2-(3,4-difluorophenyl) cyclopropyl carboxylate was used as such in the next step.

The product in solution was characterized by mass spectroscopy (EI):

m/z	Identification
226.3	M ⁺
198.3	M ⁺ -H ₂ C=CH ₂
180.4	M ⁺ -HOCH ₂ CH ₃
153.7	F ₂ PhCH ₂ CH ₂ CH ₂ ⁺
127.4	F ₂ Ph ⁺

Example 4

Preparation of (1R,2R)-trans 2-(3,4-difluorophenyl) cyclopropyl carboxamide

Starting from 2-chloro-1-S-(3,4-difluorophenyl)ethanol (30.9 g), ethyl (1R,2R)-trans 2-(3,4-difluorophenyl) cyclopropyl carboxylate was prepared as in example 3. The solvent was distilled and to the resulting oil methanol (109.0 mL), methyl formiate (7.2 g) and 30 wt% sodium methoxide in methanol (11.5 g) were added at room temperature. The mixture was heated to 60 °C in a closed reactor, then 2 bar NH₃-pressure was applied. During a period of 4 hours the temperature was maintained at 60 °C and the pressure at 2 bar, then the reactor was cooled to room temperature and vented. The reaction mixture was heated to 60 °C and water (277.2 mL) dosed over 1 hour, the temperature was maintained at 60 °C. The resulting solution was cooled to room temperature, then filtered and washed with 1/1

methanol/water (69.3 mL), then with water (49.5 mL) and finally with DiPE (49.5 mL).

The resulting crystals were dried at 50 °C in a vacuum oven.

After drying (1R,2R)-trans 2-(3,4-difluorophenyl) cyclopropyl carboxamide (22.8 g) was obtained.

Spectral data:

¹H NMR of (1R,2R)-trans 2-(3,4-difluorophenyl) cyclopropyl carboxamide

δ (ppm)	H	Pattern
1.2	CH (from CH ₂)	d×d×d
1.6	CH (from CH ₂) and CH- CONH ₂	d×d×d
2.5	CH-Ph	d×d×d
5.8	NH ₂	
6.8-7.1	3 × Ph-H	M

¹³C NMR of (1R,2R)-trans 2-(3,4-difluorophenyl) cyclopropyl carboxamide

δ (ppm)	Assignment
16.7	CH ₂
25.0	C-CONH ₂ or C-Ph
26.1	C-Ph or C-CONH ₂
115.3	Ph C-2, ² J _{F-C} : 17.6 Hz
117.6	Ph C-5, ² J _{F-C} : 17.4 Hz
122.7	Ph C-6, ³ J _{F-C} : 6.0 Hz and ⁴ J _{F-C} : 3.5
135-155	Ph C-4 and C-3
174.3	CONH ₂

Example 5**Preparation of (1R, 2S)2-(3,4-difluorophenyl)-cyclopropane amine**

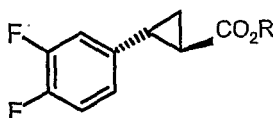
- (1R,2R)-trans 2-(3,4-difluorophenyl) cyclopropyl carboxamide (25.0 g) and 157.4 g of a 5 30 wt% solution of NaOH were mixed and heated to 20-25 °C. A 26 wt% solution of aqueous NaOCl (89.5 g) was dosed over a period of 30 minutes maintaining the temperature below 33 °C. Once the addition was finished the reaction mixture was stirred for an additional 3 hours at 30 to 33 °C. The resulting mixture was then heated to 60 °C and stirred at this temperature for an additional 20 minutes.
- 10 After cooling to 5 °C the pH of the reaction mixture was corrected with HCl 37 wt% (99.1 g) till a pH of 8.5-9.5. iPrOAc (153.3 mL) and MeOH (85.0 mL) were added followed by water (33.8 mL), after stirring and decantation the phases were separated. The obtained water layer was extracted twice with iPrOAc (75.0 and 55.0 mL respectively). And the combined organic phases were diluted till a concentration of 5 wt%. The obtained solution 15 contains (1R, 2S)2-(3,4-difluorophenyl)-cyclopropane amine (18.0 g in 360.4 g solution).

The product in solution was characterized by mass spectroscopy (APCI)

m/z	Identification
210.6	MH ⁺ + CH ₃ CN
169.9	MH ⁺
153.2	MH ⁺ - NH ₃

Claims

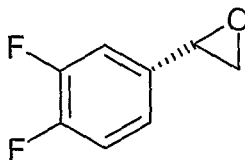
1. A process for preparing a compound of formula IV



IV

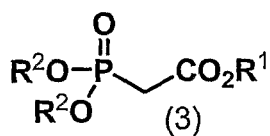
wherein R is an alkyl group,

which comprises treating a compound of formula III



III

with a compound of formula 3

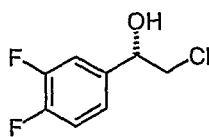


(3)

- wherein R¹ and R² are independently selected from alkyl.

2. A process as claimed in claim 1 wherein the compound of formula 3 is triethyl phosphonoacetate.

3. A process as claimed in claim 1 or 2 which includes the step of preparing the compound of formula III, which step comprises treating a compound of formula II

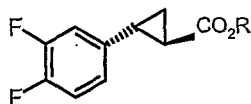


II

11

with a base.

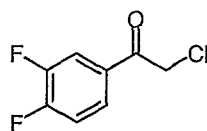
4. A process for preparing a compound of formula IV



IV

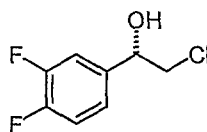
which process comprises

(a) reducing a compound of formula I



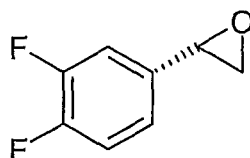
I

to give a compound of formula II



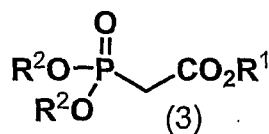
II

(b) treating the compound of formula II with a base to give a compound of formula III



III

(c) treating a compound of formula III with a compound of formula 3

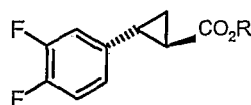


(3)

such as triethyl phosphonoacetate.

5. A process for preparing a compound of formula IV

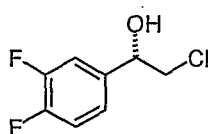
12



IV

comprising

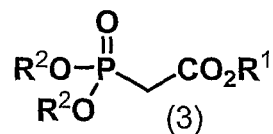
a) the compound of formula II



II

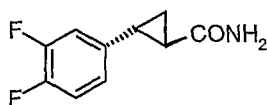
is converted to the compound of formula IV by treating the compound of formula II with a base such as sodium hydride.

b) treating the product of step a) with a compound of formula 3



such as triethyl phosphonoacetate.

6. A process as claimed in any one of the preceeding claims which also includes a step of converting the compound of formula IV to a compound of formula VII



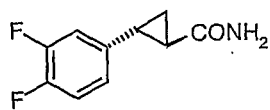
VII

7. A process as claimed in claim 6 wherein the compound of formula IV is treated with ammonia in the presence of a suitable base.

8. A process as claimed in any one of claims 1-6 wherein R, R¹ and R² are independently selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, and tert-butyl.

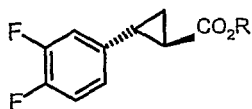
9. A process for preparing a compound of formula VII

13



VII

comprising treating the compound of formula IV



IV

with ammonia in the presence of a suitable base.

10. A process as claimed in claim 9 wherein the base is sodium methoxide.

11. A process as claimed in claim 9 wherein the base is potassium methoxide.

12. A compound of formula II, III or VII.