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(56) Related Art
US 4933477
US 5225602
TOMOSKOZI, I., Tetrahedron, 1963, vol. 19, pages 1969-1979
ARMSTRONG, A. et al., Organic Letters, 2003, vol. 5, pages 2331-2334
BARBIERI, C. et al., Tetrahedron: Asymmetry, 1999, vol. 10, pages 3931-3937
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(54) Title: CHEMICAL PROCESS FOR PREPARATION OF AROMATIC CYCLOPROPANE ESTERS AND AMIDES

(57) Abstract: 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.

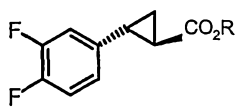
Chemical process for preparation of aromatic cyclopropane esters and amides

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 [1*S*-(1α, 2α, 3β (1*S**,2*R**),5β)]-3-[7-[2-(3,4-difluorophenyl)-cyclopropyl]amino]-5-(propylthio)-3*H*-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_2Y_{12}) 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: diastereoselecivity, 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

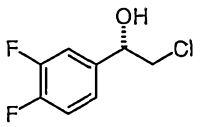


IV

Wherein R is an alkyl group.

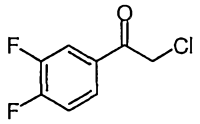
Suitable values of R include, for example, (1-6C)alkyl such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, and tert-butyl. A particular value for R is ethyl.

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.



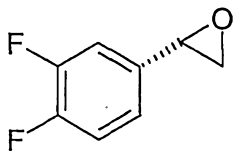
I

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 45^0 C, for example 35 to 40^0 C.

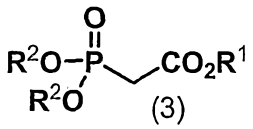
The compound of formula I is treated with the reducing agent so formed. This is generally carried out in an inert solvent such as toluene. The temperature is conveniently maintained at a temperature in the range 25 to 45^0 C, for example 35 to 40^0 C.

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



III

with a compound of formula :



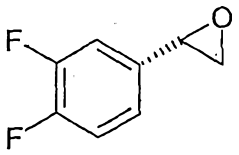
(3)

Wherein R^1 and R^2 are independently selected from alkyl such as (C1-6C)alkyl. A preferred agent is triethyl phosphonoacetate.

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 80^0C, conveniently 40 to 60^0 e.g. 40^0 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.

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.

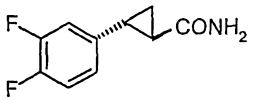
The compound of formula II may be converted to the compound of formula IV via the compound of formula III, without isolation of the compound of formula III.



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 ^{0}C, conveniently 40 to 60 ^{0}C e.g. 40 ^{0}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 formiate 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 70^0 C, for example at about 60^0 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

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 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:

^{1}H-NMR of 2-chloro-1-(3,4-difluorophenyl)ethanone in $CDCl_3$, 300 mHz

δ (ppm)	**H**	**Pattern**
4.7	$ClCH_2$	S
7.3	Ph **H-5**	d×d×d×d
7.8	Ph **H-6** Ph **H-2**	M

^{13}C-NMR of 2-chloro-1-(3,4-difluorophenyl)ethanone in $CDCl_3$, 75 MHz

δ (ppm)	**Assignment**
45.7	$ClCH_2CO$
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	$ClCH_2COPh$

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

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 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 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 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_2O
143.6	M^+-CH_2Cl

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	$M^{+\cdot}$
198.3	$M^{+\cdot}$-$H_2C{=}CH_2$
180.4	$M^{+\cdot}$-$HOCH_2CH_3$
153.7	$F_2PhCH_2CH_2CH_2^{+\cdot}$
127.4	$F_2Ph^{+\cdot}$

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 NH_3-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:

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

δ (ppm)	H	Pattern
1.2	C**H** (from CH_2)	d×d×d
1.6	C**H** (from CH_2) and C**H**-$CONH_2$	d×d×d
2.5	C**H**-Ph	d×d×d
5.8	NH_2	
6.8-7.1	3 × Ph-**H**	M

^{13}C 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**, $^{2}J_{F\text{-}C}$: 17.6 Hz
117.6	Ph **C-5**, $^{2}J_{F\text{-}C}$: 17.4 Hz
122.7	Ph **C-6**, $^{3}J_{F\text{-}C}$: 6.0 Hz and $^{4}J_{F\text{-}C}$: 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 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.

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 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	$MH^+ + CH_3CN$
169.9	MH^+
153.2	$MH^+ - NH_3$

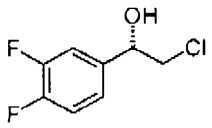
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

2007282181 26 Mar 2012

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

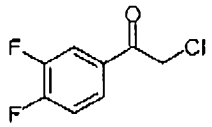
1. A process for preparing a compound of formula II



II

which process comprises

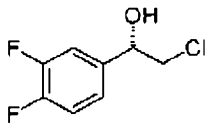
reacting a compound of formula I,



I,

in toluene at a temperature in the range 35 to 45°C, with the reducing agent oxazaborolidine, formed by mixing trimethoxy borane and S-diphenylprolinol followed by addition of borane dimethylsulphide.

2. A compound which is 2-chloro-1-S-(3,4-difluorophenyl)ethanol



II.

3. A process according to claim 1 substantially as hereinbefore described with reference to any one of the examples.