



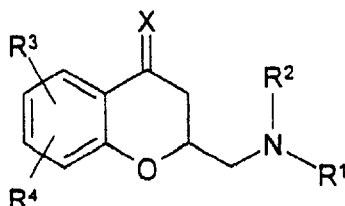
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Chroman derivatives

09 APR 2003

The invention relates to chroman derivatives of the formula I



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in which

- R¹ is acyl having 1-6 C atoms, -CO-R⁵ or an amino protective group,
R² is H or alkyl having 1-6 C atoms,
10 R³, R⁴ in each case independently of one another are H, alkyl having 1-6 C atoms, CN, Hal or COOR²,
R⁵ is phenyl which is unsubstituted or mono- or disubstituted by alkyl having 1-6 C atoms, OR² or Hal,
15 X is H, H or O,
Hal is F, Cl, Br or I,
and their salts.

The invention also relates to the optically active forms, the racemates, the enantiomers and also the hydrates and solvates, e.g. alcoholates, of these compounds.

Similar compounds are disclosed in EP 0 707 007.

25

The invention was based on the object of finding novel compounds which can be used, in particular, as intermediates in the synthesis of medicaments.

30 It has been found that the compounds of the formula I and their salts are important intermediates for the preparation of medicaments, in particular of those which show, for example, actions on the central nervous system.



166166

09 APR 2003

The invention relates to the chroman derivatives of the formula I and their salts.

Above and below, the radicals R^1 , R^2 , R^3 , R^4 , R^5 and X have the meanings indicated in the formulae I to [sic] II, if not expressly stated otherwise.

In the above formulae, alkyl has 1 to 6, preferably 1, 2, 3 or 4, C atoms. Alkyl is preferably methyl or ethyl, furthermore propyl, isopropyl, in addition also butyl, isobutyl, sec-butyl or tert-butyl. Acyl has 1 to 6, preferably 1, 2, 3 or 4, C atoms. Acyl is in particular acetyl, propionyl or butyryl.

R^2 is preferably H, in addition also methyl, ethyl or propyl.

R^3 and R^4 are preferably H.

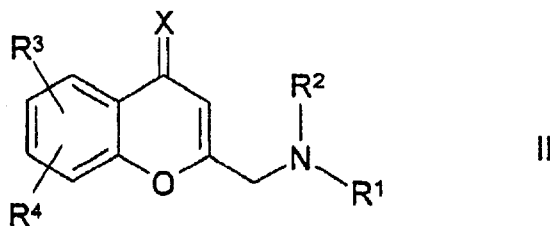
R^5 is preferably, for example, phenyl, o-, m- or p-tolyl, o-, m- or p-hydroxyphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-fluorophenyl. The radical R^1 is acyl, $-CO-R^5$ or else an amino protective group which is known per se; acetyl is particularly preferred.

The expression "amino protective group" is generally known and relates to groups which are suitable for protecting (for blocking) an amino group from chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at other positions in the molecule. Typical groups of this type are, in particular, unsubstituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino protective groups are removed after the desired reaction (or reaction sequence), their nature and size is otherwise uncritical; however, those having 1-20, in particular 1-8, C atoms are preferred. The expression "acyl group" is to be interpreted in the widest sense in connection with the present process and the present compounds. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids and also, in

particular, alkoxycarbonyl, aryloxy carbonyl and especially aralkoxycarbonyl groups. Examples of acyl groups of this type are alkanoyl such as acetyl, propionyl, butyryl; aralkanoyl such as phenylacetyl; aroyl such as benzoyl or toluylyl; aryloxyalkanoyl such as phenoxyacetyl; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC (tert-butoxycarbonyl), 2-iodoethoxycarbonyl; aralkyloxy carbonyl such as CBZ (carbobenzoxycarbonyl, also called "Z"), 4-methoxybenzyloxy carbonyl, FMOC (9-fluorenylmethoxycarbonyl); arylsulfonyl such as Mtr (4-methoxy-2,3,6-trimethylphenylsulfonyl). Preferred amino protective groups are BOC and Mtr, in addition CBZ or FMOC.

The compounds of the formula I can have one or more chiral centres and therefore occur in various stereoisomeric forms. The formula I includes all these forms.

The invention furthermore relates to a process for the preparation of chroman derivatives of the formula I according to Claim 1 and also of their salts, in which X is O, characterized in that a compound of the formula II



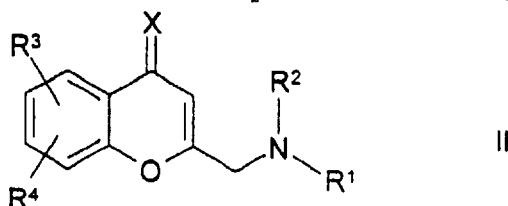
in which R^1 , R^2 , R^3 , R^4 have the meanings indicated in Claim 1 and X is O, is hydrogenated with the aid of an enantiomerically enriched catalyst.

The invention also relates to a process for the preparation of chroman derivatives of the formula I

09 APR 2003

according to Claim 1 and also of their salts, in which X is H, H,

characterized in that a compound of the formula II



5 in which R¹, R², R³, R⁴ have the meanings indicated in Claim 1 and X is O,
is hydrogenated with the aid of an enantiomerically enriched catalyst,
and then reduced in the customary manner.

10

In particular, it has been found that (2-acetylaminomethyl)chromen-4-one can be hydrogenated using various enantiomerically pure rhodium-diphosphane complexes to give enantiomerically enriched
15 (2-acetylaminomethyl)chroman-4-one.

The invention also relates to a process for the preparation of chroman derivatives of the formula I, characterized in that the enantiomerically enriched
20 catalyst is a transition metal complex.

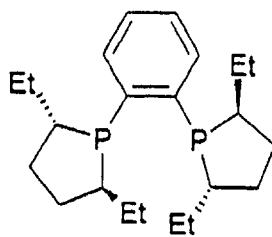
Particularly preferably, the catalyst is a transition metal complex comprising a metal selected from the group rhodium, iridium, ruthenium and palladium.

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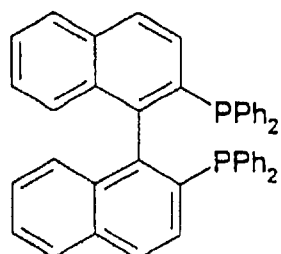
The invention furthermore relates to a process for the preparation of chroman derivatives of the formula I, characterized in that the catalyst is a transition metal complex in which the transition metal is
30 complexed with a chiral diphosphane ligand.

The ligands below may be mentioned by way of example:

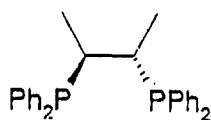
09 APR 2003



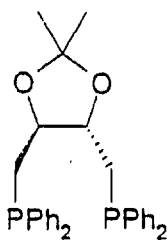
(S) -EtDuphos:



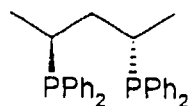
BINAP:



5 (S,S) -Chiraphos:

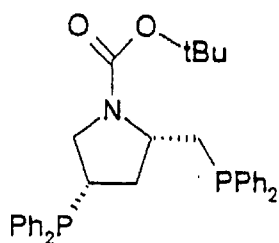


(S,S) -DIOP:



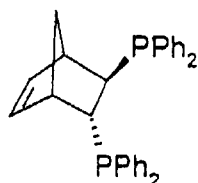
(S,S) -Skewphos (BDPP):

10

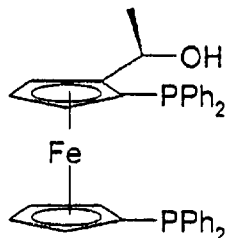


(S,S) -BPPM:

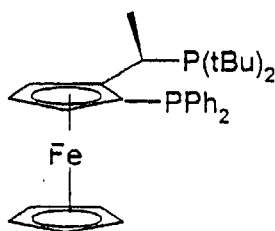
09 APR 2003



(R,R)-Norphos:



(S,R)-BPPFOH:



5 (S,R)-PFctBu:

Depending on the choice of the (R) or (S) enantiomer of the ligand in the catalyst, the (R) or (S) enantiomer is obtained in an excess.

10

Precursors used for the chiral ligands are compounds such as, for example, $\text{Rh}(\text{COD})_2\text{OTf}$ (rhodium-cyclooctadiene triflate), $[\text{Rh}(\text{COD})\text{Cl}]_2$, $\text{Rh}(\text{COD})_2\text{BF}_4$, $[\text{Ir}(\text{COD})\text{Cl}]_2$, $\text{Ir}(\text{COD})_2\text{BF}_4$ or $[\text{Ru}(\text{COD})\text{Cl}_2]_x$.

15

The compounds of the formula I and also the starting substances for their preparation are otherwise prepared by methods known per se, such as are described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), mainly under reaction conditions which are known and suitable for the reactions mentioned. Use can also be made in this case of variants which are known per se, but not mentioned here in greater detail.

25

If desired, the starting substances can also be formed in situ such that they are not isolated from the reaction mixture, but immediately reacted further to
5 give the compounds of the formula I.

The compounds of the formula II are known in some cases; the unknown compounds can easily be prepared analogously to the known compounds.

10 The conversion of a compound of the formula II in which X is O into a compound of the formula I in which X is O is carried out according to the invention using hydrogen gas with the aid of an enantiomerically enriched catalyst in an inert solvent such as, for
15 example, methanol or ethanol.

Suitable inert solvents are furthermore, for example, hydrocarbons such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons such as
20 trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols such as isopropanol, n-propanol, n-butanol or tert-butanol; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers
25 such as ethylene glycol monomethyl or monoethyl ether (methyl glycol or ethyl glycol), ethylene glycol dimethyl ether (diglyme); ketones such as acetone or butanone; amides such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles such as
30 acetonitrile; sulfoxides such as dimethyl sulfoxide (DMSO); carbon disulfide; nitro compounds such as nitromethane or nitrobenzene; esters such as ethyl acetate, and optionally also mixtures of the solvents mentioned with one another or mixtures with water.

35

The reaction time of the enantioselective hydrogenation, depending on the conditions used, is between a few minutes and 14 days; the reaction

temperature is between 0 and 150°, normally between 20 and 130°.

Customarily, the catalyst/substrate ratio is between 1:2000 and 1:50, particularly preferably 1:1000 and 1:100. The reaction time is then, for example, between 3 and 20 hours. The hydrogenation is carried out under 1-200 bar of hydrogen, preferably at 3-100 bar.

The conversion of a compound of the formula II in which X is O into a compound of the formula I in which X is H, H is carried out according to the invention using hydrogen gas with the aid of an enantiomerically enriched catalyst in an inert solvent such as methanol or ethanol, such as described above, followed by a conversion of the 4-oxo group into a methylene group according to known conditions. The reduction is preferably carried out using hydrogen gas under transition metal catalysis (for example by hydrogenation on Raney nickel or Pd-carbon in an inert solvent such as methanol or ethanol).

The conversion of compounds of the formula I in which R³, R⁴ is COOalkyl into compounds of the formula I in which R³, R⁴ is COOH is carried out, for example, using NaOH or KOH in water, water-THF or water-dioxane at temperatures between 0 and 100°.

The removal of a radical R¹ from a compound of the formula I is carried out - depending on the protective group used - for example using strong acids, expediently using TFA (trifluoroacetic acid) or perchloric acid, but also using other strong inorganic acids such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids such as trichloroacetic acid or sulfonic acids such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but not always necessary. Suitable inert solvents are preferably organic solvents, for example carboxylic acids such as acetic

09 APR 2003

can be used, e.g. sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, in addition
5 organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, e.g. formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid,
10 pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid,
15 p-toluenesulfonic acid, naphthalenemono- and disulfonic acids and laurylsulfuric acid. Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of the compounds of the formula I.

20

On the other hand, compounds of the formula I can be converted into the corresponding metal salts, in particular alkali metal or alkaline earth metal salts, using bases (e.g. sodium or potassium hydroxide or
25 carbonate), or into the corresponding ammonium salts.

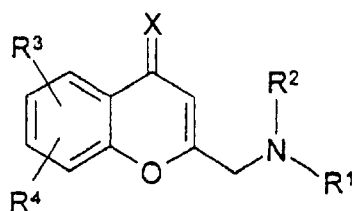
The invention furthermore relates to the use of the compounds of the formula I as intermediates for the synthesis of medicaments. Appropriate medicaments are
30 described, for example, in EP 0 707 007.

The invention accordingly relates in particular to the use of the compounds of the formula I according to Claim 1 in the synthesis of

35 (R)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chroman and its salts, characterized in that

a) a compound of the formula II

09 APR 2003



in which

R¹ has the meaning indicated in Claim 1,

R², R³ and R⁴ are H and X is O,

5 is hydrogenated with the aid of an enantiomerically enriched catalyst,

b) in that, from the enantiomerically enriched mixture of the (R) and (S) compounds of the formula I thus obtained, in which

10 R¹ has the meaning indicated in Claim 1,

R², R³ and R⁴ are H and X is O,

the enantiomerically pure (R) compound of the formula I, in which

R¹ has the meaning indicated in Claim 1,

15 R², R³ and R⁴ are H and X is O,

is obtained by crystallization,

in that

c) the enantiomerically pure (R) compound of the formula I, in which

20 R¹ has the meaning indicated in Claim 1,

R², R³ and R⁴ are H and X is O,

is then reduced in the customary manner, in that

d) the radical R¹ in which

25 R¹ has the meaning indicated in Claim 1,

R², R³ and R⁴ are H and X is H,H,

is removed from the (R) compound of the formula I thus obtained,

in that

30 e) the (R)-(chroman-2-ylmethyl)amine thus obtained is converted into its acid addition salt and this is reacted in a known manner to give (R)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]chroman and, if appropriate, converted into its acid addition salt,

09 APR 2003

where the recovery of the (R) enantiomer can also be carried out by crystallization from the enantiomerically enriched (R,S) mixture after stage c) or after stage d).

5

The invention furthermore relates to the use of the compounds of the formula I as intermediates for the synthesis of medicaments which show actions on the central nervous system.

10

Above and below, all temperatures are indicated in °C. In the following examples, "customary working up" means: if necessary, water is added, the mixture is adjusted, if necessary, depending on the constitution of the final product, to a pH of between 2 and 10 and extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate and evaporated, and the residue is purified by chromatography on silica gel and/or by crystallization.

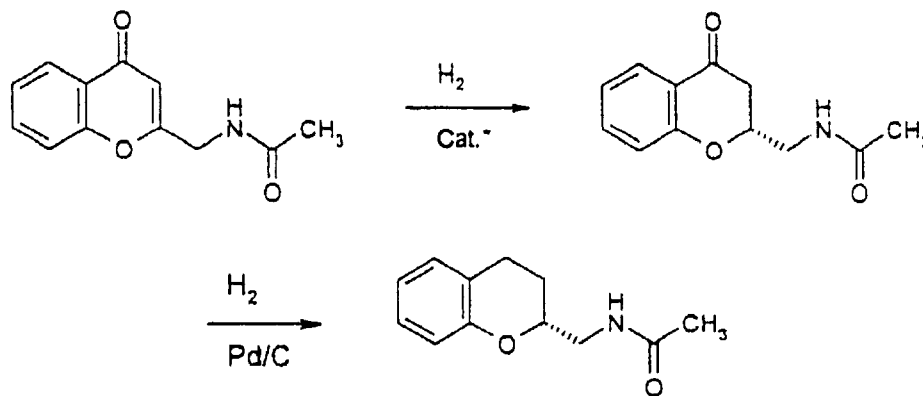
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20 R_f values on silica gel.

Examples

Experimental data (complex preparation, hydrogenation, analytical methods):

25



All reactions were carried out under inert conditions (i.e. anhydrous and oxygen-free reaction conditions).

30 1. Preparation of the catalyst/substrate solution:

09 APR 2003

1.1. Example:

11.2 mg of $\text{Rh}(\text{COD})_2\text{OTf}$ (rhodium-cyclooctadiene triflate) were dissolved in 5 ml of methanol and cooled to 0°C. A cooled solution of 1.1 eq of bisphosphane
5 (e.g. 12.6 mg of (R,R)-Skewphos) in 5 ml of methanol was then added. After stirring at room temperature for 10 min, the complex solution was treated with the substrate solution consisting of 110 mg of (2-acetylaminomethyl)chromen-4-one in 10 ml of methanol.

10

1.2. Example:

51.4 mg of $[\text{Rh}(\text{COD})\text{Cl}]_2$ were dissolved in 4 ml of the solvent mixture toluene/methanol 5:1 and treated with a solution consisting of 5 ml of toluene, 1 ml of
15 methanol and 1.1 eq of bisphosphane (e.g. 130.6 mg of (R)-BINAP). 1 ml of this catalyst complex solution was added to 510.8 mg of (2-acetylaminomethyl)chromen-4-one, dissolved in 15 ml of toluene and 3 ml of methanol.

20

2. Enantioselective hydrogenation

The catalyst/substrate solution to be hydrogenated was filled into an autoclave in a countercurrent of
25 protective gas. The protective gas atmosphere was replaced by flushing several times with hydrogen (1-5 bar H_2 atmosphere). The batches analogous to 1.1. reacted even at room temperature and 5 bar of hydrogen. The catalysts analogous to 1.2. afforded the best
30 results at 50°C and 80 bar of hydrogen. As a rule, the hydrogenation was terminated after 15 hours.

3. Sampling and analytical methods

35 A sample was taken in a countercurrent of protective gas. The complex was separated off by column chromatography on silica gel (eluent: ethyl acetate) before the determination of the enantiomeric excesses.

09 APR 2003

The enantiomeric excess of the hydrogenation product was determined on the chiral HPLC phase:

5 Column: Daicel Chiralcel OJ (I.D. × length/mm:
 4.6 × 250)
 Eluent: n-hexane: i-propanol = 9:1
 Flow: 0.8 ml/min (18 bar, 28°C)
 Detection: UV 250 nm
 Retention: R_t(R) = 27 min; R_t(S) = 29 min
10

 The concentration of the crude hydrogenation solution led to the precipitation of the product. An increase in the enantiomeric excess was detected by means of fractional crystallization.
15

4. Further reduction

 After complete conversion was detected, the reduction of the keto group was carried out by means of
20 palladium-carbon as a one-pot process. The crude ketone solution resulting from the homogeneous hydrogenation was treated with 10% by weight water-moist palladium-carbon (e.g. 100 mg of water-moist Pd/C to 1 g of (2-acetylaminomethyl)chromen-4-one) and 1 ml of glacial
25 acetic acid. Hydrogenation was carried out at a hydrogen pressure of 7 bar and 50°C for 14 h.

5. Work-up and analytical methods

30 The palladium-carbon was removed by filtration. The enantiomeric excess of the hydrogenation product was determined on a chiral HPLC phase:

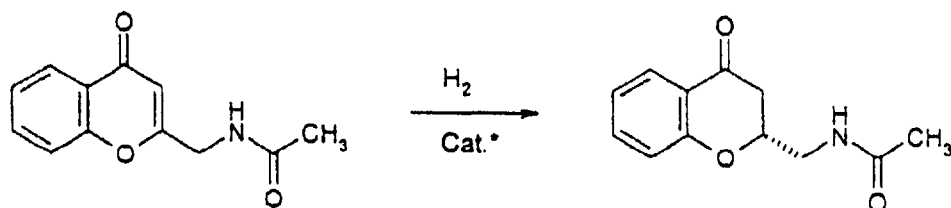
35 Column: Daicel Chiralcel OJ (I.D. × length/mm:
 4.6 × 250)
 Eluent: n-hexane: i-propanol = 9:1
 Flow: 0.8 ml/min (18 bar, 28°C)
 Detection: UV 250 nm
 Retention: R_t(R) = 25 min; R_t(S) = 27 min

09 APR 2003

During the reduction with palladium-carbon, the enantiomeric excess remained unchanged.

5 The concentration of the crude hydrogenation solution led to the precipitation of the product. An increase in the enantiomeric excess was detected by means of fractional crystallization.

Enantioselectivities of the homogeneous hydrogenation:



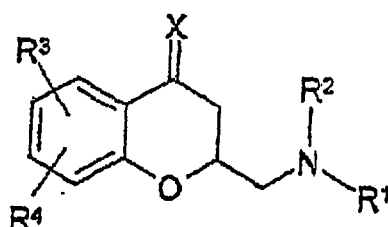
	Elab No.	Complex:metal anion ligand (addition)	Solvent	Pressure	% ee
1.	18	Rh-OTf-(<i>R,R</i>)-EtDuphos	CH ₂ Cl ₂	1	55 S
2.	13	Rh-OTf-(<i>R,R</i>)-EtDuphos	THF	1	44 S
3.	14	Rh-OTf-(<i>R,R</i>)-EtDuphos	MeOH	1	64 S
4.	15	Rh-OTf-(<i>R,R</i>)-EtDuphos	EE	1	33 S
5.	6	Rh-OTf-(<i>R,R</i>)-EtDuphos	<i>i</i> PrOH	1	20 S
6.	23a	Rh-OTf-(<i>R,R</i>)-EtDuphos	MeOH	1	34 S
7.	23b	Rh-OTf-(<i>R,R</i>)-EtDuphos	MeOH	1	36 S
8.	23c	Rh-OTf-(<i>R,R</i>)-EtDuphos	MeOH	5	45 S
9.	23d	Rh-OTf-(<i>R,R</i>)-EtDuphos	MeOH	5	31 S
10.	12	Ru-Cl ₂ -(<i>R</i>)-BINAP (AgOOCFF ₃)	<i>i</i> PrOH	5	50 S
11.	19	Rh-ClO ₄ -(<i>S,S</i>)-Chiraphos	<i>i</i> PrOH	1	-
12.	20	Rh-OTf-(<i>S,S</i>)-DIOP	THF	1	rac.
13.	20	Rh-OTf-(<i>S,S</i>)-DIOP	THF	3	8 R
14.	21	Rh-OTf-(<i>R,R</i>)-Skewphos	THF	1	-
15.	22b	Rh-OTf-(<i>S,S</i>)-BPPM	MeOH	1	7 S
16.	24a	Rh-OTf-(<i>R,S</i>)-BPPFOH	MeOH	1	54 R
17.	24b	Rh-OTf-(<i>R,S</i>)-BPPFOH	MeOH	1	54 R
18.	24c	Rh-OTf-(<i>R,S</i>)-BPPFOH	MeOH	5	63 R
19.	25a	Rh-OTf-(<i>R</i>)-BINAP	MeOH	1	1 R
20.	25b	Rh-OTf-(<i>R</i>)-BINAP	MeOH	5	rac.
21.	26a	Rh-OTf-(<i>S,S</i>)-Norphos	MeOH	1	42 R
22.	26b	Rh-OTf-(<i>S,S</i>)-Norphos	MeOH	5	60 R
23.	26c	Rh-OTf-(<i>S,S</i>)-Norphos	<i>i</i> PrOH	5	12 R
24.	26d	Rh-OTf-(<i>S,S</i>)-Norphos	THF	5	3 R
25.	27a	Rh-OTf-(<i>S,S</i>)-Norphos	MeOH	8	64 R
26.	27b	Rh-Cl-(<i>S,S</i>)-Norphos	MeOH	8	40 R
27.	27c	Rh-OTf-(<i>S,S</i>)-Norphos	MeOH	30	65 R
28.	27d	Rh-OTf-(<i>S,S</i>)-Norphos	MeOH	60	64 R
29.	28a	Rh-OTf-(<i>R,R</i>)-EtDUPhos	MeOH	10	16 S
30.	28b	Rh-OTf-(<i>R,R</i>)-EtDUPhos	MeOH	30	28 S
31.	29a	Rh-OTf-(<i>R,S</i>)-BPPFOH	MeOH	10	55 R
32.	29b	Rh-OTf-(<i>R,S</i>)-BPPFOH	MeOH	30	56 R
33.	37	Rh-ClO ₄ -(<i>S,S</i>)-Chiraphos	MeOH	10	30 R
34.	38	Rh-OTf-(<i>S,S</i>)-DIOP	MeOH	10	rac.
35.	39	Rh-OTf-(<i>R,R</i>)-Skewphos	MeOH	10	46 S
36.	40	Rh-OTf-(<i>S,S</i>)-BPPM	MeOH	10	9 S
37.	41	Ir-Cl-(<i>S,S</i>)-DIOP	MeOH	10	8 R
38.	42	Ir-Cl-(<i>S,S</i>)-DIOP	CH ₂ Cl ₂	10	7 S

0.	43	Ir-Cl-(<i>S,S</i>)-DIOP (+ I)	MeOH	10	-
1.	44	Ir-Cl-(<i>S,S</i>)-DIOP (+ I)	MeOH	30	-
2.	45	Ir-Cl-(<i>S,S</i>)-DIOP (+ I +CH ₃ COOH)	MeOH	10	-
3.	46	Ir-OTf-(<i>S,S</i>)-DIOP	MeOH	10	11R
4.	47	Ir-OTf-(<i>S,S</i>)-DIOP (+ I)	MeOH	10	39 R
5.	49	Rh-OTf-(<i>S,S</i>)-Norphos	MeOH	10, RT	57 R
6.	50	Rh-OTf-(<i>S,S</i>)-Norphos	MeOH	10, 50°C	60 R
7.	52	Rh-BF ₄ -(<i>R,S</i>)-PFctB	MeOH	10, 50°C	33 S
8.	54	Rh-Cl-(<i>R</i>)-BINAP	Tol:MeOH 5:1	80, 50°C	91S
9.	59	Rh-Cl-(<i>S,S</i>)-Norphos	Tol:MeOH 5:1	80, 50°C	19 R
10.	62	crude 59//Pd/C	Tol:MeOH 5:1	7, 50°C	18 R

09 APR 2003

Patent Claims

1. Chroman derivatives of the formula I



in which

R^1 is acyl having 1-6 carbon atoms, $-CO-R^5$, phenylacetyl, phenoxyacetyl, methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, tert-butoxycarbonyl, 2-iodoethoxycarbonyl, carbobenzoxy carbonyl, 4-methoxybenzyloxycarbonyl, 9-fluorenylmethoxycarbonyl or 4-methoxy-2,3,6-trimethylphenylsulfonyl,

R^2 is H or alkyl having 1-6 carbon atoms,

R^3 and R^4 are each, independently of one another, H, alkyl having 1-6 carbon atoms, CN, Hal or $COOR^2$,

R^5 is phenyl which is unsubstituted or monosubstituted or disubstituted by alkyl having 1-6 carbon atoms, OR^2 or Hal,

X is H, H or O,

Hal is F, Cl, Br or I,

and salts thereof,

where N-(chroman-2-ylmethyl)cyclopropanecarboxamide is excluded.

2. Enantiomers of the compounds of the formula I according to Claim 1.

3. Compounds of the formula I according to Claim 1

a) N-(4-oxochroman-2-ylmethyl)acetamide;

b) N-(chroman-2-ylmethyl)acetamide;

c) (S)-N-(4-oxochroman-2-ylmethyl)acetamide;

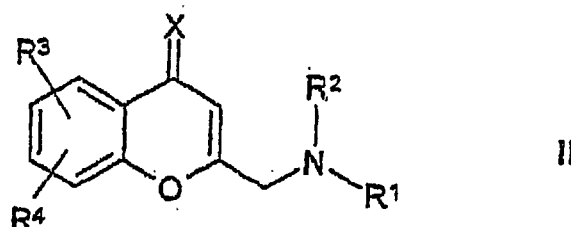
d) (R)-N-(4-oxochroman-2-ylmethyl)acetamide;

e) (S)-N-(chroman-2-ylmethyl)acetamide;

09 APR 2003

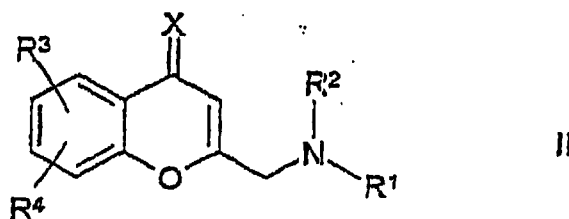
f) (R)-N-(chroman-2-ylmethyl)acetamide;
and salts thereof.

4. Process for the preparation of chroman derivatives of the formula I according to Claim 1 and salts thereof, in which X is O, characterised in that a compound of the formula II



in which R^1 , R^2 , R^3 and R^4 are as defined in Claim 1, and X is O, is hydrogenated with the aid of an enantiomerically enriched catalyst.

5. Process for the preparation of chroman derivatives of the formula I according to Claim 1 and salts thereof, in which X is H,H, characterised in that a compound of the formula II



in which R^1 , R^2 , R^3 and R^4 are as defined in Claim 1, and X is O, is hydrogenated with the aid of an enantiomerically enriched catalyst and subsequently reduced in a conventional manner.

6. Process for the preparation of chroman derivatives of the formula I according to Claim 4 or 5, characterised in that the enantiomerically enriched catalyst is a transition-metal complex.
7. Process for the preparation of chroman derivatives of the formula I according to Claim 4, 5 or 6, characterised in that the catalyst is a transition-metal complex containing a metal selected from the group consisting of rhodium, iridium, ruthenium and palladium.
8. Process for the preparation of chroman derivatives of the formula I according to Claim 4, 5, 6 or 7, characterised in that the catalyst is a

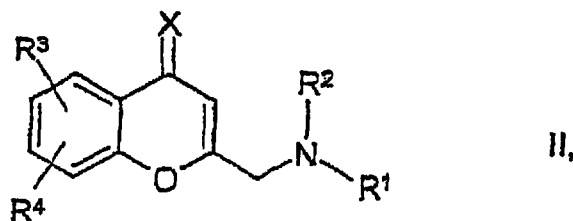
transition-metal complex in which the transition metal is complexed to a chiral diphosphine ligand.

9. Use of the compounds of the formula I according to Claim 1 as intermediates in the synthesis of medicaments.

5 10. Use of the compounds of the formula I according to Claim 1 as intermediates in the synthesis of medicaments which exhibit actions on the central nervous system.

10 11. Use of the compounds of the formula I according to Claim 1 in the synthesis of (R)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chroman and salts thereof, characterised in that

a) a compound of the formula II



in which

R¹ is as defined in Claim 1,

15 R², R³ and R⁴ are H and X is O,

is hydrogenated with the aid of an enantiomerically enriched catalyst,

b) in that the enantiomerically pure (R) compound of the formula I in which

20 R¹ is as defined in Claim 1,

R², R³ and R⁴ are H and X is O,

is isolated from the resultant enantiomerically enriched mixture of the (R) and (S) compounds of the formula I in which

R¹ is as defined in Claim 1,

25 R², R³ and R⁴ are H and X is O,

by crystallisation,

in that

c) the enantiomerically pure (R) compound of the formula I in which

30 R¹ is as defined in Claim 1,

09 APR 2003

R^2 , R^3 and R^4 are H and X is O,
is subsequently reduced in a conventional manner,
in that

5 d) the radical R^1 is cleaved off from the resultant (R) compound
of the formula I in which

R^1 is as defined in Claim 1,
 R^2 , R^3 and R^4 are H and X is H,H,
in that

10 e) the resultant (R)-(chroman-2-ylmethyl)amine is converted into
its acid-addition salt, and the latter is converted in a known manner
into (R)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]chroman
and, if desired, converted into its acid-addition salt,
where the isolation of the (R) enantiomer from the enantiomerically
15 enriched (R,S) mixture by crystallisation can also be carried out after
step c) or after step d).