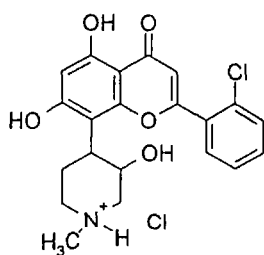


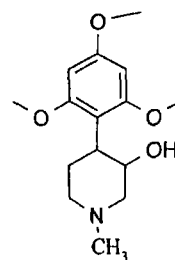
Description

Process for the preparation of (-)-cis-3-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)piperidine

(-)-cis-3-Hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)piperidine (II) is a central building block in the synthesis of flavopiridol (I) (HMR 1275 or L86-8275), the first potent inhibitor of the cyclin-dependent protein kinase (see, for example, Sedlacek, Hans Harald; Czech, Joerg; Naik, Ramachandra; Kaur, Gurmeet; Worland, Peter; Losiewicz, Michael; Parker, Bernard; Carlson, Bradley; Smith, Adaline; et al. Flavopiridol (L86 8275; NSC 649890), a new kinase inhibitor for tumor therapy. Int. J. Oncol. (1996), 9(6), 1143-1168 or Czech, Joerg; Hoffmann, Dieter; Naik, Ramachandra; Sedlacek, Hans-Harald. Antitumoral activity of flavone L 86-8275. Int. J. Oncol. (1995), 6(1), 31-36).



(I)



(II)

20

The process for the preparation of (II) previously described in EP-B 0 241 003 and EP-B 0 366 061 is time-consuming and includes reactions (hydroboration, Swern oxidation, sodium borohydride reduction) which are difficult to handle on the industrial scale. Surprisingly, we have now found a significantly simpler preparation process, which is illustrated in Scheme 1.



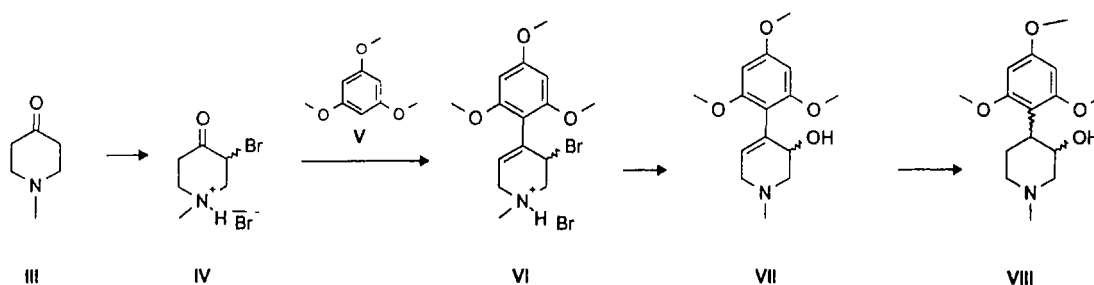
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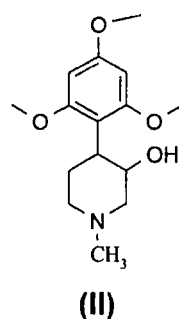
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Scheme 1:

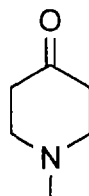


5 The process for the preparation of (-)-cis-3-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)piperidine (II)



10 comprises

a₁) converting 1-methylpiperidin-4-one (III)



III

into the hydrobromide according to known processes, or

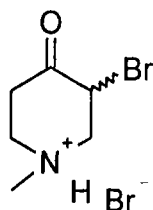
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a₂) converting 1-methylpiperidin-4-one (III) directly into the hydrobromide, prior to the subsequent bromination, by introduction of 1-methylpiperidin-4-one into an HBr/glacial acetic acid solution, and

20

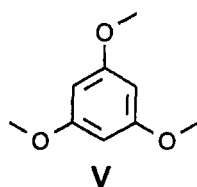
b) reacting 1-methylpiperidin-4-one hydrobromide in a suitable solvent, , acetic acid, in the temperature range from 0°C-30°C with bromine to give 3(R,S)-bromo-1-methyl-4-oxopiperidine hydrobromide (IV)

3



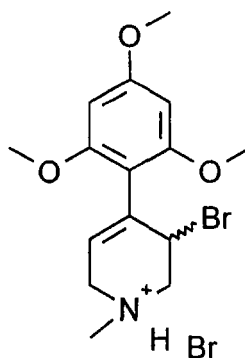
IV

- 5 c) reacting this intermediate (IV) directly by addition of 0.8-1 equivalent of 1,3,5-trimethoxybenzene (V)



V

- 10 to the reaction solution at 0°-30°C to give 3(R,S)-bromo-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrobromide (VI)

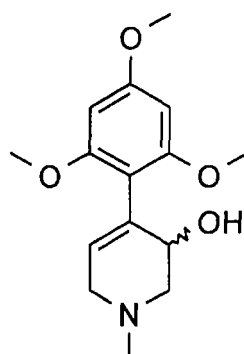


VI

- 15 and, if appropriate, additionally adding acetic anhydride to remove any water of reaction formed

- 20 d₁) first isolating the compound (VI) as a solid by stirring the reaction solution into a suitable organic solvent, , methyl tert-butyl ether, dichloromethane etc., and subsequently reacting the resulting product with water and by stirring at 50°-100°C, preferably at

60°-80°C, to give 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII)

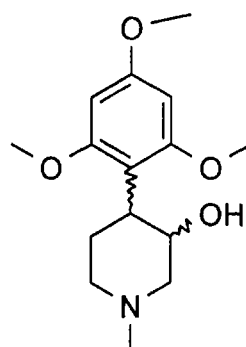


VII

or

- 5 d2) treating the reaction mixture containing the compound (VI) directly with water and reacting by stirring at 50°-100°C, preferably at 60°-80°C, to give 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII), and
- 10 d3) cooling the reaction mixtures obtained according to d1) or d2), if appropriate diluting further with water and adjusting to pH > 12 at 0°-30°C by addition of aqueous alkali, preferably sodium hydroxide, 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII) precipitating, filtering off the resulting crude product with suction and if appropriate, for purification, taking it up again in aqueous hydrochloric acid, filtering and optionally extracting with a water-immiscible solvent, e.g. ethyl acetate, and then adjusting the aqueous phase to pH > 12 by addition of aqueous
- 15 alkali, preferably sodium hydroxide, 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII) precipitating, extracting the precipitated product, if appropriate for further purification, with one or more suitable organic solvents, , acetone, isopropanol, diisopropyl ether or alternatively mixtures of these
- 20 solvents, and
- 25 e1) catalytically hydrogenating the resulting product (VII) in a suitable solvent, e.g. methanol, isopropanol, water or mixtures of these solvents using a suitable catalyst, e.g. palladium/carbon, rhodium/carbon etc., to give the racemic 3,4-cis alcohol (VIII)
- 30

5



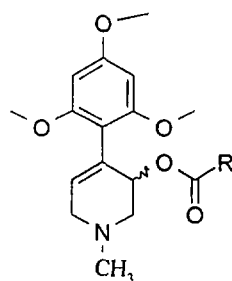
VIII

where the 3,4-trans alcohol, which possibly results in small amounts during the reduction, can be removed by crystallization from suitable solvents, , acetone, or

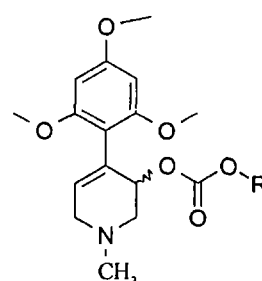
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e₂) for the hydrogenation, employing easily accessible esters (IXa) or carbonates (IXb) of the compound (VII)

10



IXa



IXb

in which R is (C₁-C₁₆)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₁₆)-alkyl or (C₆-C₁₄)-aryl and in the formula (IXa) is further carboxy-(C₂-C₆)-alkyl;

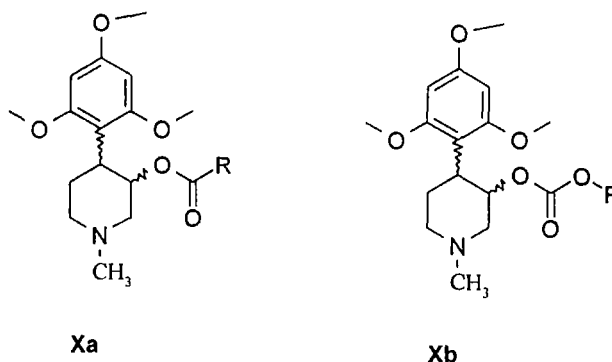
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compounds (Xa) and (Xb) being obtained, from which the compound (VIII) can be liberated by known procedures,

20

f₁) obtaining the enantiomerically pure cis alcohol (II) from the compound (VIII) by a known process by resolution using suitable chiral auxiliary reagents such as, for example, ketopinic acid, or

f₂) carrying out the resolution using the compounds (Xa) or (Xb)



5 where R is (C₁-C₁₆)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₁₆)-alkyl or (C₆-C₁₄)-aryl and in the formula (Xa) is further carboxy-(C₂-C₆)-alkyl,

and then converting these into the compound (II) by known processes,

10

it also being possible to exchange the sequence of the reaction steps e) and f), i.e. also to carry out the resolution as early as at the stage of the allyl alcohol (VII) or of the compounds (IXa) and (IXb) obtained therefrom.

15

In analogy to a process described in the literature (Trost et al., JACS 1994, 116, 10320), the esters (IXa) or carbonates (IXb) are suitable for the deracemization to give the enantiomerically pure esters. After hydrogenation and ester cleavage, (-)-cis-3-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)piperidine (II) is then obtained.

20

3(R,S)-Bromo-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrobromide (VI) and 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII) are valuable intermediates in the preparation of (-)-cis-3-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)piperidine (II).

25

Examples:

30 Example 1:

Preparation of 3(R,S)-bromo-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrobromide (VI)

75.7 ml (0.44 mol) of 33% strength HBr in glacial acetic acid were added to 200 ml of glacial acetic acid, and 50 g (0.44 mol) of 1-methylpiperidin-4-one (III) were then rapidly added dropwise at 20-25°C with ice-cooling. 70.4 g (0.44 mol) of bromine were added dropwise at 20-25°C in the course of 30 min to the suspension of the hydrobromide obtained in this way, a clear, yellowish solution being obtained. This was stirred at 25°C for a further 15 min and 67.2 g (0.40 mol) of 1,3,5-trimethoxybenzene (V) were then added to the reaction solution. It was then stirred at 25°C for 1 h. After this, 300 ml of methyl tert-butyl ether were allowed to run in, the product being deposited in oily form. The supernatant was decanted off, the residue was stirred again with 300 ml of methyl tert-butyl ether and the supernatant was decanted off. The residue was then stirred with 150 ml of dichloromethane, the product crystallizing out. The 3(R,S)-bromo-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrobromide (VI) obtained was filtered off with suction, washed with 50 ml of dichloromethane and dried in vacuo.

Yield: 147 g of almost colorless crystals.

M.p.: 190-192°C

MS(ES^+): 342.2(M+H)⁺

Example 2:

Preparation of 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII)

50 g (0.118 mol) of 3(R,S)-bromo-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrobromide (VI) were heated under reflux for 2 h in 100 ml of water. The reaction mixture was then cooled to 20°C and adjusted to pH 12.5 by dropwise addition of 30 ml of 30% strength sodium hydroxide solution. After a short time, a pale brown precipitate crystallized out. The mixture was stirred at 5-10°C for a further 1 h, and the precipitated product was filtered off with suction and washed with 30 ml of water. The crude product was then stirred with 20 ml of acetone, filtered off with suction and dried in vacuo.

Yield: 25.2 g of colorless crystals

M.p.: 125-127°C

MS(CI^+): 280.3(M+H)⁺

Example 3:

Preparation of 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII)

- 5 75.7 ml (0.44 mol) of 33% strength HBr in glacial acetic acid were added to 100 ml of glacial acetic acid and 50 g (0.44 mol) of 1-methylpiperidin-4-one (III) were then vigorously added dropwise at 20-25°C with ice-cooling. 70.4 g (0.44 mol) of bromine were added dropwise at 20-25°C under nitrogen in the course of 30 min to the suspension of the hydrobromide
10 obtained in this way, a clear, yellowish solution being obtained. This was stirred at 25°C for a further 60 min and 67.2 g (0.40 mol) of 1,3,5-trimethoxybenzene (V) were then added to the reaction solution. It was then stirred at 25°C for 1 h. After this, 400 ml of water were allowed to run in and the mixture was heated to reflux for 3 h. The reaction mixture was
15 allowed to stand at room temperature overnight, diluted with 400 ml of water and then cooled to 10°C, and a total of 320 ml of conc. sodium hydroxide solution were added dropwise at this temperature in the course of 4 h to the well stirred mixture (pH after addition 10.7). In the course of this the allyl alcohol (VII) first precipitated in slightly oily form, but then on
20 longer stirring became solid and could readily be filtered off with suction. The dark yellow precipitate was filtered off with suction, washed with water and dried well. The crude product was then stirred with 80 ml of acetone, filtered off with suction and dried in vacuo.

Yield: 55 g of pale yellow crystals

25 M.p.: 125-127°C

MS(Cl⁺): 280.3(M+H)⁺

¹H-NMR(dmso-d₆): δ (ppm) 6.15(s, 2H); 5.65(dd, 1H); 4.20(m, 1H); 3.80(s, 3H); 3.75(s, 6H); 3.31(dd 1H); 2.89(m, 1H); 2.84(dd, 1H); 2.71(d, 1H); 2.57(dd, 1H); 2.24(s, 3H)

30

Example 4:

Preparation of 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII)

- 35 75.7 ml (0.44 mol) of 33% strength HBr in glacial acetic acid were added to 100 ml of glacial acetic acid and 50 g (0.44 mol) of 1-methylpiperidin-4-one (III) were then rapidly added dropwise at 20-25°C with ice cooling. 70.4 g (0.44 mol) of bromine were added dropwise at 20-25°C under nitrogen in the course of 30 min to the suspension of the hydrobromide obtained in this

way, a clear, yellowish solution being obtained. This was stirred at 25°C for 60 min and 67.2 g (0.40 mol) of 1,3,5-trimethoxybenzene (V) were then added to the reaction solution. After 15 min, a further 40.8 g (0.4 mol) of acetic anhydride were added with cooling and the mixture was stirred at 25°C for 1 h. After this, 750 ml of water were allowed to run in and the mixture was heated at 80°C for 9.5 h. The reaction mixture was then cooled to 5-10°C and adjusted to pH 5.5 by dropwise addition of 200 ml of conc. sodium hydroxide solution in the course of 30 min. In the course of this, unreacted 1,3,5-trimethoxybenzene precipitated. The suspension was filtered and the filtrate was adjusted to pH 14 at 5-10°C using a further 200 ml of conc. sodium hydroxide solution. In the course of this, the allyl alcohol (VII) initially precipitated in slightly oily form, but on longer stirring became solid and could then be readily filtered off with suction. The batch stood overnight at room temperature. The pale yellow precipitate was then filtered off with suction, washed with 300 ml of water to neutral pH and dried well. Crude yield: 87.2 g of pale yellow crystals. The crude product was then stirred with 100 ml of acetone, filtered off with suction and dried in vacuo.

Yield: 73 g of pale yellow crystals

M.p.: 125-127°C

MS(Cl⁺): 280.3(M+H)⁺

Example 5:

Preparation of racemic 3,4-cis alcohol (VIII)

3.5 g (12.5 mmol) of 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII) were dissolved in 100 ml of methanol and treated with 0.35 g of catalyst (5% Pd/C, previously washed with MeOH) and hydrogenated in a Büchi autoclave for 15 h at 50°C and a hydrogen pressure of 50 bar. The catalyst was then filtered off, the filtrate was evaporated in vacuo on a rotary evaporator and the residue was stirred with 4 ml of acetone. The product obtained was filtered off and dried in vacuo.

Yield: 2.7 g of colorless crystals

M.p.: 131-132°C

MS(Cl⁺): 282.3(M+H)⁺

Example 6:

Preparation of racemic 3,4-cis alcohol (VIII)

10.0 g (35.8 mmol) of 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-
5 1,2,3,6-tetrahydropyridine (VII) were dissolved in 100 ml of methanol and
treated with 1.5 g of catalyst (5%Pd/C, previously washed with MeOH) and
hydrogenated in a Büchi autoclave for 39 h at 50°C and a hydrogen
pressure of 50 bar. The catalyst was then filtered off, the filtrate was
evaporated in vacuo on a rotary evaporator and the residue was stirred
10 with 20 ml of acetone. The product obtained was filtered off and dried in
vacuo.

Yield: 9.2 g of colorless crystals

M.p.: 131-132°C

MS(Cl⁺): 282.3(M+H)⁺

15

Example 7:

Preparation of 3(R,S)-acetoxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-
tetrahydropyridine (IXa) [R= methyl]

2.79 g (10 mmol) of 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-
20 1,2,3,6-tetrahydropyridine (VII) were dissolved in 15 ml of acetic anhydride
and stirred at 100°C for 4 h. The solution was then evaporated in vacuo in
a rotary evaporator and the residue was dissolved in 10 ml of water,
adjusted to pH > 12 with sodium hydroxide solution and extracted twice
25 with 20 ml of ethyl acetate each time. The combined organic phases were
washed with 10 ml of saturated sodium chloride solution, then dried over
sodium sulfate and evaporated in vacuo on a rotary evaporator.

Yield: 2.55 g of an oil

MS(ES⁺): 322.2(M+H)⁺

30

Example 8:

Preparation of 3(R,S)-methyloxycarbonyloxy-1-methyl-4-(2,4,6-trimethoxy-
phenyl)-1,2,3,6-tetrahydropyridine (IXb) [R= methyl]

8.37 g (30 mmol) of 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-
35 1,2,3,6-tetrahydropyridine (VII) were dissolved in 83.7 ml of tetrahydrofuran
and treated with 12.4 ml (90 mmol) of triethylamine. The mixture was
cooled to 5°C, 2.55 ml (33 mmol) of methyl chloroformate were added
dropwise in the course of 15 min and the mixture was stirred at 5-10°C for

a further 3 h. Since TLC checking still showed starting material, a further 1.0 ml (12.9 mmol) of methyl chloroformate were added and the mixture was stirred again for 1 h. 50 ml of water were then added and the mixture was extracted twice with 50 ml of ethyl acetate each time. The combined organic phases were washed with 30 ml of saturated sodium chloride solution, then dried over sodium sulfate and evaporated in vacuo on a rotary evaporator.

Yield: 8.7 g of an oil which becomes solid on allowing to stand

MS(ES^+): 338.2($\text{M}+\text{H}$)⁺

Example 9:

Preparation of racemic cis ester (Xa) [R= methyl]

15.33 g of toluenesulfonic acid salt of 3(R,S)-acetoxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (IXa) [R= methyl] were dissolved in 153 ml of methanol, filtered through active carbon and the filtrate was treated with 1.53 g of catalyst (5% Rh/C) and hydrogenated in a Büchi autoclave for 24 h at 50°C and a hydrogen pressure of 18 bar. The catalyst was then filtered off and the filtrate was evaporated in vacuo on a rotary evaporator. The residue was dissolved in 50 ml of water and adjusted to a pH of > 12 using conc. sodium hydroxide solution. After a short time, the base precipitated. The product obtained was filtered off, washed with water and dried in vacuo.

Yield: 8.5 g of colorless crystals

M.p.: 115-117°C

MS(Cl^+): 324.2($\text{M}+\text{H}$)⁺

Example 10:

Preparation of racemic 3,4-cis alcohol (VIII) from (Xa) [R= methyl]

1.61 g (5 mmol) of racemic cis ester (Xa) [R = methyl] were heated under reflux for 8 h in 20 ml of methanol and with 5 ml of conc. hydrochloric acid. The methanol was then removed in vacuo, the residue was treated with 10 ml of water and a pH of > 12 was set using conc. sodium hydroxide solution. In the course of this the product precipitated. The product obtained was filtered off, washed with water and dried in vacuo.

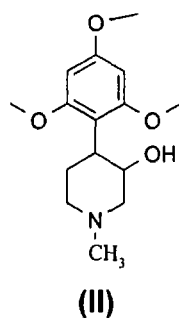
Yield: 1.1 g of colorless crystals

M.p.: 131-132°C

MS(Cl^+): 282.4($\text{M}+\text{H}$)⁺

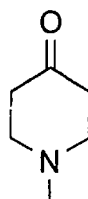
Patent claims:

1. A process for the preparation of (-)-cis-3-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)piperidine (II)



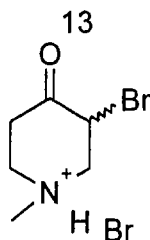
comprises

- a₁) converting 1-methylpiperidin-4-one (III)

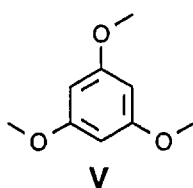


into the hydrobromide according to known processes, or

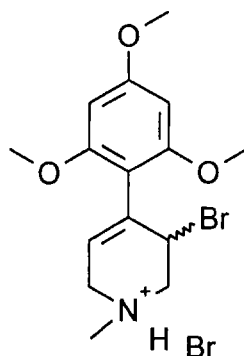
- a₂) converting 1-methylpiperidin-4-one (III) directly into the hydrobromide, prior to the subsequent bromination, by introduction of 1-methylpiperidin-4-one into an HBr glacial acetic acid solution, and
- b) reacting 1-methylpiperidin-4-one hydrobromide in a suitable solvent in the temperature range from 0°C-30°C with bromine to give 3(R,S)-bromo-1-methyl-4-oxopiperidine hydrobromide (IV)

**IV**

- c) reacting this intermediate (IV) directly by addition of 0.8-1 equivalent of 1,3,5-trimethoxybenzene (V)

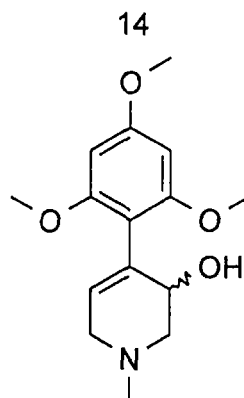
**V**

to the reaction solution at 0°-30°C to give 3(R,S)-bromo-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrobromide (VI)

**VI**

and, if appropriate, additionally adding acetic anhydride to remove any water of reaction formed

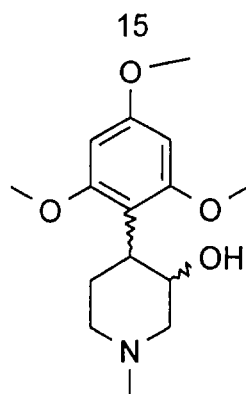
- d₁) first isolating the compound (VI) as a solid by stirring the reaction solution into a suitable organic solvent, and subsequently reacting the resulting product with water and by stirring at 50°-100°C to give 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII)



VII

or

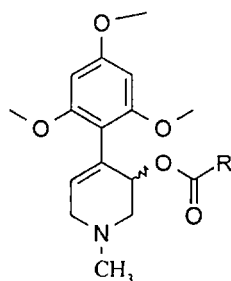
- d₂) treating the reaction mixture containing the compound (VI) directly with water and reacting by stirring at 50°-100°C to give 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII), and
- d₃) cooling the reaction mixtures obtained according to d₁) or d₂), if appropriate diluting further with water and adjusting to pH > 12 at 0°-30°C by addition of aqueous alkali, 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII) precipitating, filtering off the resulting crude product with suction and if appropriate, for purification, taking it up again in aqueous hydrochloric acid, filtering and optionally extracting with a water-immiscible solvent, and then adjusting the aqueous phase to pH > 12 by addition of aqueous alkali, 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII) precipitating, extracting the precipitated product, if appropriate for further purification, by stirring with one or more suitable organic solvents or alternatively mixtures of these solvents, and
- e₁) catalytically hydrogenating the resulting product (VII) in a suitable solvent or mixtures of these solvents using a suitable catalyst to give the racemic 3,4-cis alcohol (VIII)



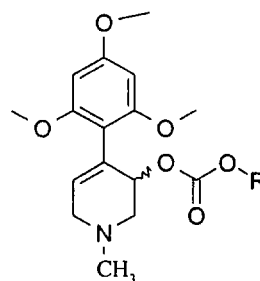
VIII

where the 3,4-trans alcohol, which possibly results in small amounts during the reduction, can be removed by crystallization from suitable solvents, or

- e₂) for the hydrogenation, employing easily accessible esters (IXa) or carbonates (IXb) of the compound (VII)



IXa



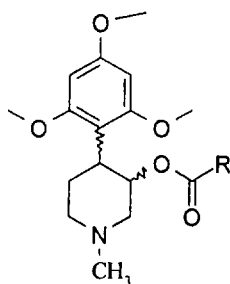
IXb

in which R is (C₁-C₁₆)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₁₆)-alkyl or (C₆-C₁₄)-aryl and in the formula (IXa) is further carboxy-(C₂-C₆)-alkyl,

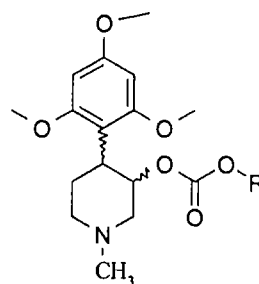
compounds (Xa) and (Xb) being obtained, from which the compound (VIII) can be liberated by known procedures,

- f₁) obtaining the enantiomerically pure cis alcohol (II) from the compound (VIII) by a known process by resolution using suitable chiral auxiliary reagents, or

f₂) carrying out the resolution using the compounds (Xa) or (Xb)



Xa



Xb

where R is (C₁-C₁₆)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₁₆)-alkyl or (C₆-C₁₄)-aryl and in the formula (Xa) is further carboxy-(C₂-C₆)-alkyl,

and then converting these into the compound (II) by known processes,

it also being possible to exchange the sequence of the reaction steps e) and f), i.e. also to carry out the resolution as early as at the stage of the allyl alcohol (VII) or of the compounds (IXa) and (IXb) obtained therefrom.

2. 3(R,S)-Bromo-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrobromide (VI).
3. 3(R,S)-Hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine (VII).
4. The use of (-)-cis-3-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-piperidine (II) for the preparation of flavopiridol (I).