

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International patent classification⁶: C07D 211/42, 211/74, 211/72, 405/04	A1	(11) International publication number: WO 99/37615 (43) International publication date: 29 July 1999 (29.07.99)
(21) International application number: PCT/EP98/08327 (22) International filing date: 18 December 1998 (18.12.98) (30) Data relating to the priority: 198 02 449.5 23 January 1998 (23.01.98) DE (71) Applicant (for all designated States except US): HOECHST MARION ROUSSEL DEUTSCHLAND GMBH [DE/DE]; Brüningstrasse 50, D-65929 Frankfurt am Main (DE). (72) Inventors; and (75) Inventors/Applicants (US only): Insert representative(s)/ attorney(s) here		(81) Designated states: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With the International Search Report. Before expiry of the period provided for amending the claims, will be republished if such amendments are received.

As printed

(54) Title: METHOD FOR PRODUCING (-)CIS-3-HYDROXY-1-METHYL-4-(2,4,6-TRIMETHOXYPHENYL)-PIPERIDINE**(54) Bezeichnung:** VERFAHREN ZUR HERSTELLUNG VON (-)CIS-3-HYDROXY-1-METHYL-4-(2,4,6-TRIMETHOXYPHENYL)-PIPERIDIN**(57) Abstract**

Disclosed is a method for producing (-)cis-3-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-piperidine characterised in that 1-methyl-piperidine-4-one is converted into hydrobromide, subsequently transformed with bromine into 3(R,S)-bromine-1-methyl-4-oxo-piperidine-hydrobromide and reacted with 1,3,5-trimethoxybenzol to form 3(R,S)-bromine-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydro-pyridine-hydrobromide. By stirring the reaction solution into an organic solvent, 3(R,S)-bromine-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydro-pyridine-hydrobromide is initially isolated as a solid and subsequently the product is mixed with water and converted into 3(R,S)-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydro-pyridine by means of stirring. The product thus prepared is catalytically hydrogenated into a racemic 3,4-cis-alcohol and subsequently, enantiomerically pure (-)cis-3-hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-piperidine is obtained by separation of racemic mixtures with chiral auxiliary reagents from racemic 3,4-cis alcohol.

(57) Zusammenfassung

Es ist ein Verfahren zur Herstellung von (-)cis-3-Hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-piperidin beschrieben, das dadurch gekennzeichnet ist, daß man 1-Methyl-piperidin-4-on in das Hydrobromid überführt, anschließend mit Brom zum 3(R,S)-Brom-1-methyl-4-oxo-piperidin-hydrobromid und weiter mit 1,3,5-Trimethoxybenzol zum 3(R,S)-Brom-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydro-pyridin-hydrobromid umsetzt. Durch Einrühren der Reaktionslösung in ein organisches Lösungsmittel wird zunächst 3(R,S)-Brom-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydro-pyridin-hydrobromid als Feststoff isoliert und nachfolgend das Produkt mit Wasser versetzt und durch Rühren zu 3(R,S)-Hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydro-pyridin umgesetzt. Das dann aufgearbeitete Produkt wird zum racemischen 3,4-cis-Alkohol katalytisch hydriert und anschließend durch Racematspaltung mit chiralen Hilfsreagenzien aus dem racemischen 3,4-cis-Alkohol das enantiomerenreine (-)cis-3-Hydroxy-1-methyl-4-(2,4,6-trimethoxyphenyl)-piperidin erhalten.



G00002



162162