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E. S. D.

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Asunto : Solicitud de patente para **"PROCEDIMIENTO PARA LA PREPARACIÓN DE HIDROCLORURO DE L-FENILEFRINA"**

Solicitante : **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG**

Fecha de Solicitud : 20 de Enero de 2000

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al oficio número 9287, notificado por fijación en lista el 7 de Octubre de 2004.

2. Mediante el oficio número 9287 se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

2.1. Atentamente presento junto con este escrito el artículo de SAKURABA S ET AL: "Efficient Asymmetric Hydrogenation of Alpha-Amino Ketone Derivatives a Higly Enantioselective Synthesis of Phenylephrine, Levamisole, Carnitine and Propanolol". Chemical and Pharmaceutical Bulletin, JP, Pharmaceutical Society of Japan. Tokio. Vol. 43, no. 5, 1 May 1995 (1995-05-01). Pages 738-747, XP000571426. ISSN: 0009-2363.

3. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito a ustedes que se continúe su tramitación.

Bogotá, 29 DIC. 2004
Señora Jefe

EMILIO FERRERO
T.P.A No. 31.929

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PRP/PRP/ID-000403/WPC13736

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Efficient Asymmetric Hydrogenation of α-Amino Ketone Derivatives. A Highly Enantioselective Synthesis of Phenylephrine, Levamisole, Carnitine and Propranolol [1]

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The complexes of pyrrolidine bisphosphine ligands (CPMs) with rhodium (I) were found to be efficient catalysts for asymmetric hydrogenation of α-amino ketone hydrochloride derivatives. Utilizing this methodology, we have developed efficient asymmetric syntheses of the optically active β-amino alcohols, phenylephrine, levamisole, carnitine and propranolol.

Key words catalytic asymmetric hydrogenation; rhodium complex; chiral bisphosphine; α-amino ketone

Optically active secondary amino alcohols are important intermediates for chiral synthesis of biologically active substances such as adrenergic agents, anthelmintics, β-blockers and antidepressants. One of the most efficient methods for the synthesis of optically active amino alcohols is a catalytic asymmetric hydrogenation of prochiral amino ketone catalyzed by a chiral phosphine ligand–rhodium(I) complex. Although several attempts have been made to achieve homogeneous asymmetric hydrogenation of α-aminoacetophenone derivatives with chiral bisphosphine–rhodium catalysts, no practical catalyst has been developed.[2,3] In our recent studies on the development of efficient chiral bisphosphine ligands for asymmetric hydrogenations, we prepared several efficient ligands on the basis of our design concept. Among them, *N*-substituted 4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidines (CPMs) (3—6) showed high enantioselectivity in the rhodium(I)-catalyzed asymmetric hydrogenations of a variety of α-amino ketone derivatives, and the hydrogenation products could be easily purified as optically pure forms. In this paper we report the development of *N*-substituted CPMs and their use in asymmetric hydrogenation of α-amino ketone derivatives, leading to practical synthesis of (*S*)-(−)-levamisole (27), (*R*)-(−)-phenylephrine hydrochloride (28), (*R*)-(−)-carnitine (32) and (*S*)-propranolol hydrochloride (37a).

We have proposed a design concept, named the "respective control concept," for developing chiral bisphosphine catalysts that are highly efficient in terms of both enantioselectivity and catalytic activity. This concept is based on the idea that one phosphino group of the bisphosphine ligands oriented *cis* to the prochiral group of the substrates controls the enantioselectivity and the other oriented *trans* controls the catalytic activity.[4] On the basis of this concept, we designed and synthesized *N*-substituted pyrrolidinebisphosphines (3—6)[5] bearing a dicyclohexylphosphino group at C_4 of the pyrrolidine ring and a diphenylphosphino group at C_2-methylene. *N*-Substituted pyrrolidine bisphosphines (3—6) were prepared by the reaction of the pyrrolidine bisphosphine (2) with the corresponding chloroformate or dicarbonate, isocyanate or acyl chloride, respectively (Fig. 1). Further, we synthesized (2*S*,4*S*)-*N*-(methylcarbamoyl)-4-(dicyclo-

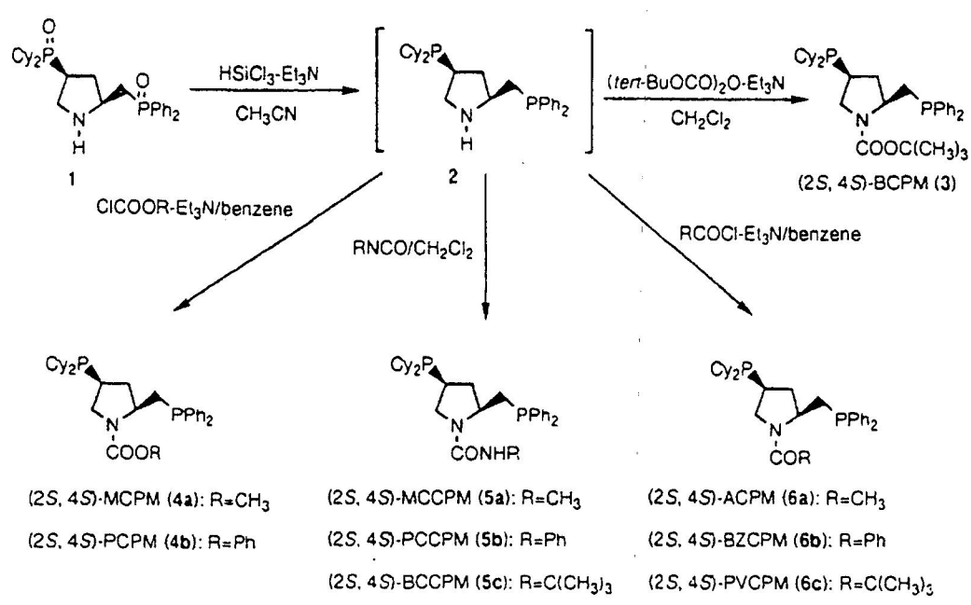
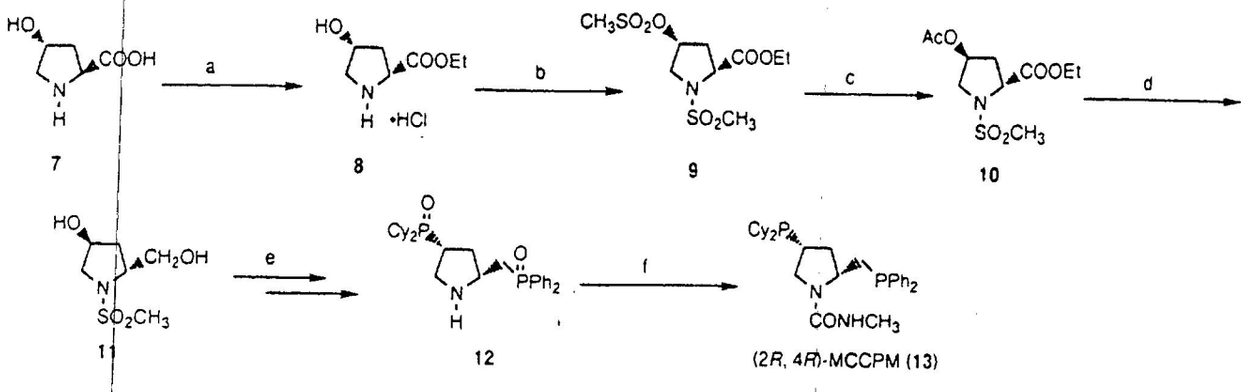


Fig. 1

* To whom correspondence should be addressed.

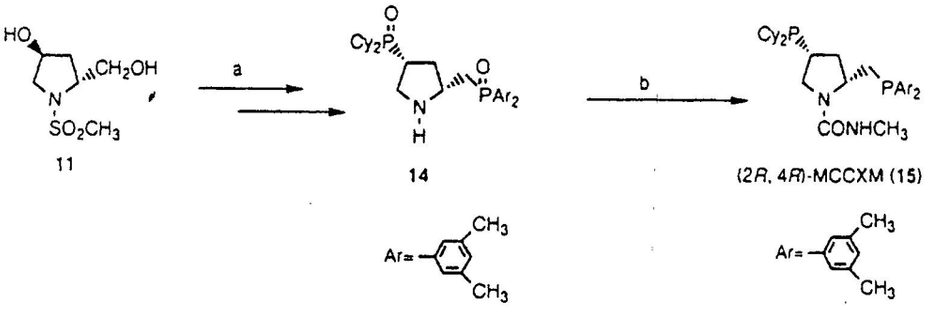
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reagents,
a) i)AcOH-Ac_2O / HCl, ii)AcCl, EtOH b) methanesulfonyl chloride, pyridine c) tetramethylammonium acetate, benzene d) $LiAlH_4$, THF e) ref. 5c. f) $HSiCl_3$-Et_3N, CH_3CN, then CH_3NCO, CH_2Cl_2

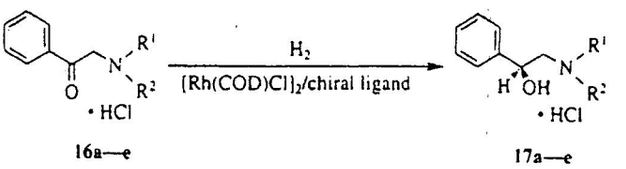
Chart 1



reagents,
a) ref. 5c b) $HSiCl_3$-Et_3N, CH_3CN, then CH_3NCO, CH_2Cl_2

Chart 2

Table 1. Asymmetric Hydrogenations of α-Aminoacetophenone Hydrochloride Derivatives Catalyzed by Neutral Rhodium Complexes of (2*S*,4*S*)-*N*-Substituted CPM[a]



16a—e 17a—e

Entry	Substrate			Ligand	Conditions[a]		Product[b]		
		R^1	R^2		[S]/[C]	H_2 (atm)		$[\alpha]_D^{23}$	%ee[c] (confign.)
1	**16a**	H	H	3	1000	20	**17a**	+35.5°	81 (*S*)
2	**16b**	Me	H	3	1000	20	**17b**	+42.7°	81 (*S*)
3	**16c**	Me	Bn	3	1000	20	**17c**	+50.9°	85 (*S*)
4	**16c**	Me	Bn	**5a**	1000	20	**17c**	+54.2°	90 (*S*)
5	**16c**	Me	Bn	**5a**	1000	5	**17c**	+54.8°	91 (*S*)
6	**16c**	Me	Bn	**5a**	10000	20	**17c**	+53.0°	88 (*S*)
7	**16d**	H	Bn	3	1000	20	**17d**	+24.1°	87 (*S*)
8	**16d**	H	Bn	**5a**	1000	20	**17d**	+25.9°	93 (*S*)
9	**16d**	H	Bn	**5a**	10000	20	**17d**	+25.2°	91 (*S*)
10	**16e**	Et	Et	3	1000	20	**17e**	+60.2°	93 (*S*)
11	**16e**	Et	Et	**5a**	1000	20	**17e**	+62.5°	97 (*S*)
12	**16e**	Et	Et	**5a**	10000	20	**17e**	+61.8°	96 (*S*)

a) All hydrogenations were carried out with substrate (5.0 mmol) and triethylamine (0.025 mmol) in methanol (10 ml) at 50 °C for 20 h. *b*) The chemical yields were quantitative. The conversions were 100%, as determined by TLC analysis. *c*) Calculated on the basis of the maximum optical rotations of pure enantiomers (*S*)-(+)-**17a—e**: [R^1, R^2, $[\alpha]_D^{23}$ (*c* = 5.0, H_2O)]: H, H, +43.7°; Me, H, +52.7°; H, Bn, +27.8°; Me, Bn, +60.1°; Et, Et, +64.6°]

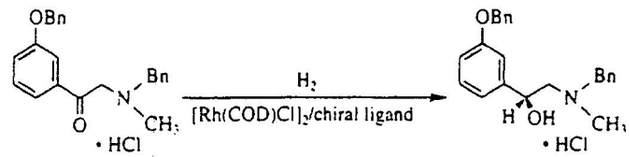
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hexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine ((2*S*,4*S*)-MCCPM) (**13**), the antipode of **5a**, and (2*R*,4*R*)-*N*-(methylcarbamoyl)-4-(dicyclohexylphosphino)-2-[(di-3,5-xylylphosphino)methyl]pyrrolidine ((2*R*,4*R*)-MCCXM) (**15**). The synthetic routes to **13** and **15** from *N*-(methylsulfonyl)-4-hydroxy-D-prolinol (**11**)[6] are illustrated in Charts 1 and 2.

Phenylephrine (**28**) and a precursor of levamisole (**25**) have a β-amino-α-arylethanol skeleton. Initially we examined the asymmetric hydrogenation of α-aminoacetophenone hydrochloride derivatives (**16** and **18**) with neutral (2*S*,4*S*)-*N*-substituted CPM–rhodium catalysts (Tables 1 and 2).[7] All asymmetric hydrogenations of **16** and **18** proceeded smoothly in the presence of 0.1—0.001 mol% of a neutral rhodium catalyst and triethylamine in methanol at 50 °C for 20 h under an initial hydrogen pressure of 20 atm. In Table 1, (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine ((2*S*,4*S*)-BCPM) (**3**)– and MCCPM (**5a**)–rhodium(I) complexes were found to give β-amino-α-phenylethanol derivatives with high enantioselectivity (81—97% ee) as well as high catalytic activities. In Table 2, the *N*-substituent effects of CPM ligands on the enantioselectivity are summarized. The highest enantioselectivity favoring (*S*)-(+)-**19** (85% ee) was achieved by using (2*S*,4*S*)-MCPM (**4a**)- or (2*S*,4*S*)-MCCPM (**5a**) as a ligand (entries 7 and 8). The synthesis of the substrate (**18**) is shown in Chart 3.

The asymmetric synthesis of (*S*)-(−)-levamisole (**27**)[8] is shown in Chart 4. 2-Bromoacetophenone (**23**) was converted to 2-[*N*-(2-chloroethyl)]aminoacetophenone hydrochloride (**24**) with 2-chloroethylamine. (*S*)-β-Amino alcohol hydrochloride (**25**) was obtained by the asymmetric hydrogenation of **24** carried out in methanol at

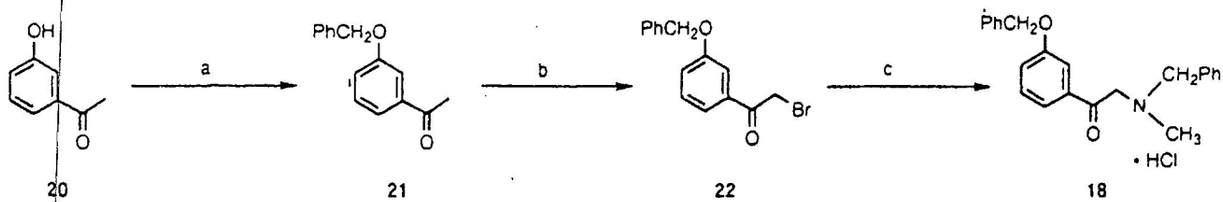
Table 2. Asymmetric Hydrogenation of 3'-Benzyloxy-2-(*N*-benzyl-*N*-methyl)aminoacetophenone Hydrochloride Catalyzed by (2*S*,4*S*)-*N*-Substituted CPM–Rhodium Complexes[a]



18 19

Entry	Ligand	Product[b]		
		$[\alpha]_D^{23}$ (c = 2.0, H_2O)[c]	%ee[d]	Confign.
1	**3**	+33.8°	75	*S*
2	**5c**	+34.5°	76	*S*
3	**6c**	+34.1°	75	*S*
4	**4b**	+32.4°	72	*S*
5	**5b**	+33.6°	74	*S*
6	**6b**	+34.1°	75	*S*
7	**4a**	+38.2°	85	*S*
8	**5a**	+38.5°	85	*S*
9	**6a**	+35.5°	79	*S*

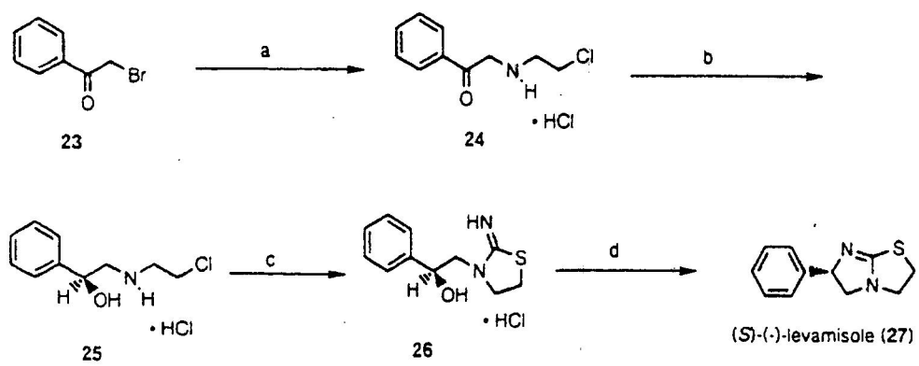
a) All asymmetric hydrogenations were carried out with substrate (3.0 mmol), triethylamine (0.03 mmol), $[Rh(COD)Cl]_2$ (0.0015 mmol) and ligand (0.0039 mmol) in methanol (10 ml) at 50 °C for 20 h under an initial hydrogen pressure of 20 atm. *b*) The chemical yields were quantitative. The conversions were 100%. *c*) Measured after debenzylation. *d*) Calculated on the basis of the maximum optical rotation of pure (*R*)-(−)-phenylephrine hydrochloride: $[\alpha]_D^{23}$ −45.2° (c = 2.0, H_2O).



20 21 22 18

reagent,
a) $PhCH_2Cl$, NaOEt b) Br_2, $CaCO_3$ c) i) $PhCH_2NH(Me)$ ii) HCl gas

Chart 3



23 24 25 26 (*S*)-(-)-levamisole (27)

reagents and conditions,
a) 2-chloroethylamine hydrochloride, sodium hydroxide, benzene, 20 °C, 22 h, 43%. b) (2*S*, 4*S*)-MCCPM-Rh(I) complex, triethylamine, H_2, methanol, 96%. c) potassium thiocyanate, ethanol, H_2O, reflux, 30 h, 90%. d) ref. 8a.

Chart 4

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50 °C for 20 h under 20 atm of hydrogen pressure in the presence of triethylamine using the neutral rhodium complex of (2*S*,4*S*)-MCCPM. The β-amino alcohol (**25**) was allowed to react with potassium thiocyanate, affording 3-(2-hydroxy-2-phenylethyl)-2-iminothiazolidine hydrochloride (**26**) in 90% ee. Thus, a formal synthesis of (*S*)-(−)-levamisole (**27**) has been achieved by using **25** as the key intermediate.

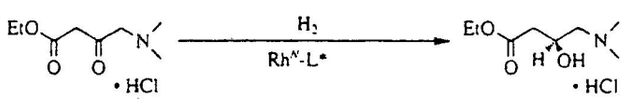
The asymmetric synthesis of phenylephrine hydrochloride (**28**)[9] is shown in Chart 5. For the synthesis of biologically active (*R*)-(−)-phenylephrine hydrochloride [*vs.* (*R*)-(−)-**19**, we used (2*R*,4*R*)-MCCPM (**13**), the antipode of **5a**. The (*R*)-β-amino alcohol hydrochloride (**19**) was readily available by the asymmetric hydrogenation of **18**[10] in a quantitative yield. Debenzylation of **19** gave **28** as crystals. Optically pure **28** was obtained by a single recrystallization from 2-propanol.

(*R*)-Carnitine (**32**)[11-14] is known to be abundant in the human body and to be involved in the human metabolism and transport of long-chain fatty acids. The asymmetric hydrogenation of ethyl 4-(dimethylamino)-3-oxobutanone (**30**) gave (*R*)-(−)-norcarnitine (**31**). By reaction with methyl iodide, **31** was readily converted into (*R*)-(−)-carnitine (**32**) (3-hydroxy-4-(trimethylammonio)butyrate) (Chart 6). The results of asymmetric hydrogenation of **30** are summarized in Table 3.[15] (2*S*,4*S*)-MCCPM (**5a**) and (2*S*,4*S*)-MCCXM–rhodium complexes were found to have not only higher catalytic activity, but also higher enantioselectivity than (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine ((2*S*,4*S*)-BPPM) (**41**)–rhodium complex.

When the MCCXM–rhodium complex was used, 82–85% ee was obtained with quantitative chemical yield.

The synthesis of (*S*)-propranolol hydrochloride (**37a**)[16-18] is shown in Chart 7. After conversion of 1-naphthol (**33**) to the allyl naphthyl ether (**34**), oxidative bromination of the olefinic part of **34** with excess sodium bromite in aqueous acetic acid[19] gave the α-bromo ketone (**35**). Amination of **35** with isopropylamine was followed by treatment with hydrogen chloride gas[20] to give *N*-isopropyl-3-(naphthyloxy)-2-oxo-1-propylamine hydrochloride (**36a**). Asymmetric hydrogenation of **36a** proceeded smoothly in the presence of 0.01 mol% of (2*S*,4*S*)-MCCPM–rhodium(I) complex and 0.25 mmol of triethylamine in methanol at 50 °C for 20 h under an initial hydrogen pressure of 20 atm.[21] Usual work-up gave colorless crystals of (*S*)-propranolol hydrochloride (**37a**). Optically pure **37a** was obtained by single recrystallization from methanol–ether. Asymmetric hydrogenation of a series of 3-(aryloxy)-2-oxo-1-propylamine derivatives (**36a**—**e**) catalyzed by (2*S*,4*S*)-MCCPM–rhodium(I) complex smoothly gave (*S*)-methoprorol hydrochloride (**37b**) and the synthetic intermediates **37d** and **37e** for 5-[(aryloxy)-methyl]-2-oxazolidinones (centrally acting muscle relaxants) such as (*S*)-mephenoxalone and (*S*)-metaxalone (Table 4).[22] The synthesis of the substrates **36a**—**e** is

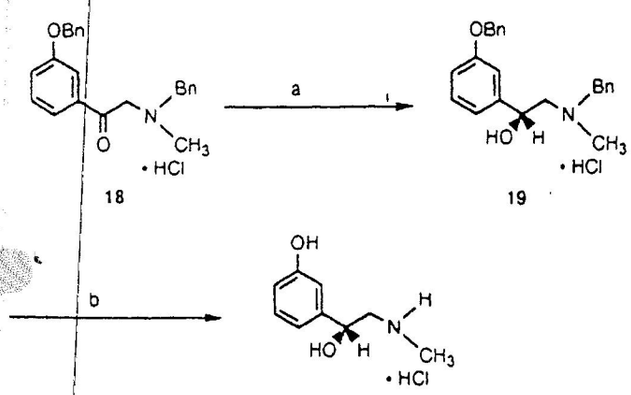
Table 3. Asymmetric Hydrogenation of Ethyl 4-(Dimethylamino)-3-oxobutanoate[a]



30 **31**

Ligand	[S]/[C]	Convn. (%)[b]	ee%[c]	Confign.
(2*S*,4*S*)-MCCXM	100	100	85.0	*S*
	1000	100	82.0	*S*
(2*S*,4*S*)-MCCPM	100	100	82.7	*S*
	1000	100	78.6	*S*
(2*S*,4*S*)-BPPM (**41**)	100	100	41.4	*S*
	1000	0	—	

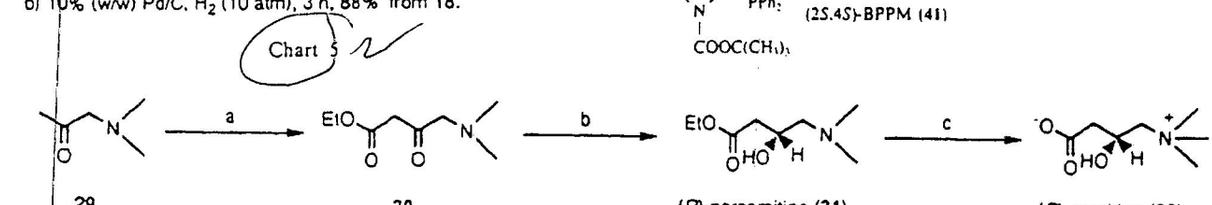
a) All asymmetric hydrogenations were carried out in the presence of 1–0.1 mol% of a neutral rhodium catalyst prepared *in situ* by mixing $[Rh(COD)Cl]_2$ and the chiral ligand in a ratio of 1:2.4, H_2 20 atm, 50 °C, 20 h, 0.5 M in ethanol. [Subst.]/[Et_3N] = 200. b) Determined by ^1H-NMR analysis. c) The hydrogenation product was converted into **32** and then its ee% was calculated on the basis of the maximum rotation of pure L-carnitine hydrochloride: $[\alpha]_D$ −22.0° (*c* = 1.0, H_2O).



(*R*)-phenylephrine hydrochloride (**28**)

reagents and conditions,
a) (2*R*, 4*R*)-MCCPM-Rh(I) complex, triethylamine, H_2, methanol.
b) 10% (w/w) Pd/C, H_2 (10 atm), 3 h, 88% from **18**.

Chart 5



reagents,
a) i) NaH, $(EtO)_2CO$. b) (2*R*, 4*R*)-MCCXM-Rh (I) complex, triethylamine, H_2, methanol.
c) CH_3I; HCl.

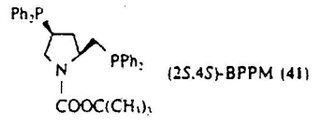
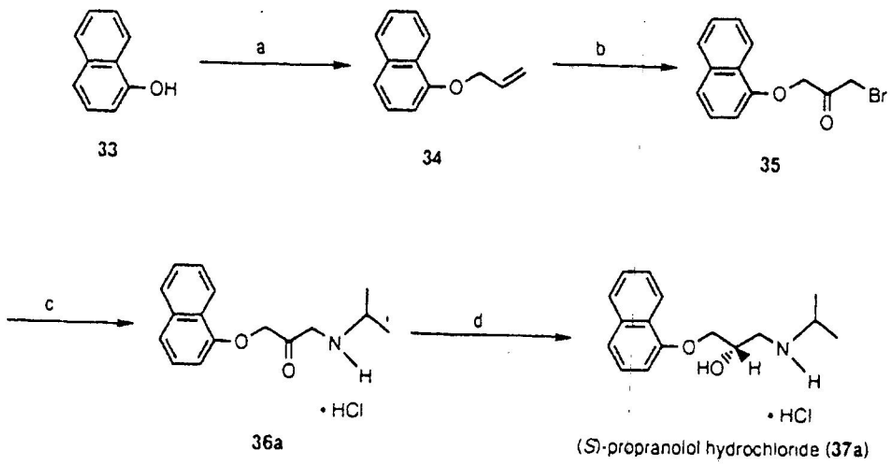


Chart 6

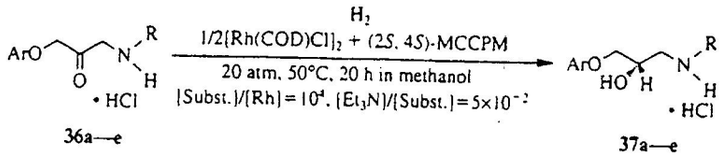
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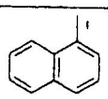
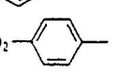
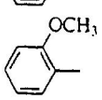
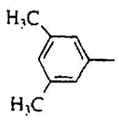
reagents and conditions,
a) NaH, KI, allyl bromide, *N*, *N*-dimethylformamide, 0–25 °C, 6 h, 91%. b) 5 equiv. of sodium bromite, AcOH-H_2O, 0–25 °C, argon, 6 h, 62%. c) $(CH_3)_2CHNH_2$, $(CH_3)_2CHOH$-H_2O, 40 °C, 1 h; then HCl gas, 0°C, 51%. d) H_2 (20 atm), $[Rh(COD)Cl]_2$, (2*S*, 4*S*)-MCCPM, Et_3N, methanol, 50°C, 20 h, 98% (90.8%ee); then recrystallization from methanol-ether, 92% (*ca.* 100%ee).

Chart 7

Table 4. Asymmetric Hydrogenation of 3-(Aryloxy)-2-oxo-1-propylamine Derivatives Catalyzed by the (2*S*,4*S*)-MCCPM–Rhodium (I) Complex[a]



36a—e 37a—e

Entry	Substrate			Product			
		Ar-	R-	Convn. (%)[b]	$[\alpha]_D^{21}$ (c = 1.1, ethanol)	%ee[c]	Confign.[d]
1	36a		$(CH_3)_2CH$-	100	−23.2°	90.8	*S*
2	36b	$CH_3O(CH_2)_2$- 	$(CH_3)_2CH$-	100	−19.0°	93.1	*S*
3	36c		$(CH_3)_2CH$-	100	−23.5°	86.6	*S*
4	36d		Bn-	100	−14.1°	97.4	*S*
5	36e		Bn-	100	−19.2°	94.9	*S*

a) The reaction was carried out by using 0.01 mol% rhodium catalyst. The chemical yields were quantitative. b) Determined by ^{1}H-NMR analysis. c) Determined by HPLC analysis of the free amines with a chiral column (Chiralcel OD). d) Assignment based on the optical rotations of authentic samples prepared from (2*S*)-glycidyl tosylate: M. Klunder J., Ko S. Y., Sharpless K. B., *J. Org. Chem.*, 51, 3710 (1986).

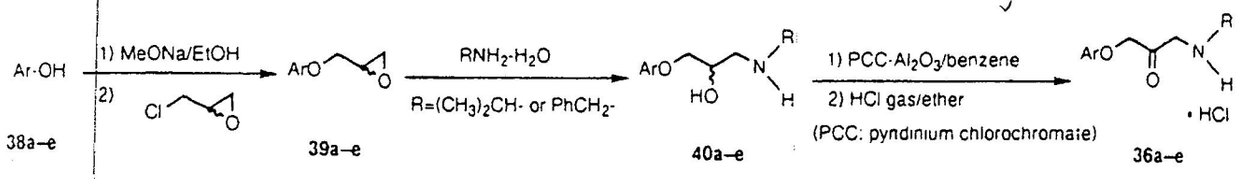
shown in Chart 8.

Efficient asymmetric syntheses of biologically active substances which have a β-amino alcohol skeleton, such as (*S*)-levamisole, (*R*)-phenylephrine hydrochloride, (*R*)-carnitine and (*S*)-propranolol hydrochloride, were achieved using the catalytic asymmetric hydrogenation of α-amino ketone derivatives with the rhodium(I) complex of a chiral bisphosphine, *N*-substituted CPM, as the key step. Our method has provided a new efficient procedure for synthesizing several types of optically pure β-amino alcohols.

Experimental

General Procedures All melting points were determined with a micro-melting point apparatus (Yazawa) and are uncorrected. Optical

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38a–e 39a–e 40a–e 36a–e

a: Ar=1-naphthyl
b: Ar=$CH_3O(CH_2)_2C_6H_4$
c: Ar=C_6H_5
d: Ar=2-$CH_3OC_6H_4$
e: Ar=3, 5-$(CH_3)_2C_6H_3$

a: Ar=1-naphthyl, R=$(CH_3)_2CH$
b: Ar=$CH_3O(CH_2)_2C_6H_4$, R=$(CH_3)_2CH$
c: Ar=C_6H_5, R=$(CH_3)_2CH$
d: Ar=2-$CH_3OC_6H_4$, R=Bn
e: Ar=3, 5-$(CH_3)_2C_6H_3$, R=Bn

Chart 8

rotations were measured on a JASCO DIP-140 digital polarimeter. Infrared (IR) spectra were measured on a JASCO A-202 or IR-810 IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on JEOL JNM-FX 90Q, JNM-GX 270 spectrometers using tetramethylsilane (TMS) as an internal standard, and the chemical shifts are given in δ values. Column chromatography was carried out on Silica gel 60 (70—230 mesh, Merck).

(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine; (2*S*,4*S*)-BCPM (3) (2*S*,4*S*)-4-(Dicyclohexylphosphinyl)-2-[(diphenylphosphinyl)methyl]pyrrolidine (1) was prepared from 4-hydroxy-L-proline ethyl ester hydrochloride according to the reported procedure (ref. 5*c*). Under an argon atmosphere, trichlorosilane (42.7 g, 0.294 mol) was added dropwise to a stirred mixture of 1 (43.8 g, 0.084 mol), triethylamine (34.0 g, 0.336 mol) and degassed acetonitrile (2200 ml) at 0 °C. The mixture was refluxed for 3 h, then cooled with ice, and degassed benzene (2000 ml) and degassed 30% NaOH (890 ml) were added. The whole was heated to 60 °C with stirring under an argon atmosphere for 30 min. The organic layer was separated and washed with degassed H_2O, degassed saturated aqueous $NaHCO_3$ and degassed saturated aqueous NaCl, then dried over anhydrous $MgSO_4$ and evaporated. The residue and triethylamine (8.5 g, 0.084 mol) were dissolved in degassed CH_2Cl_2 (400 ml). To this solution, di-*tert*-butyl dicarbonate (20.1 g, 0.092 mol) was added dropwise at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 2 h under an argon atmosphere, then concentrated under reduced pressure, and the solid residue was recrystallized from degassed ethanol to give 3 as white crystals (39.4 g, 83%), mp 180—183 °C, $[\alpha]_D^{25}$ −39.7° (*c* = 1.00, benzene). IR (KBr): 1685 (C=O) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 1.02—1.89 (22H, m, $P(C_6H_{11})_2$), 1.43 (9H, s, $C(CH_3)_3$), 1.98—2.35 (3H, m, CCH_2C. H_a of CH_2P), 2.88—3.20 (2H, m, H_b of CH_2P, PCH), 3.61—3.98 (3H, m, CH_2NCH), 7.26—7.61 (10H, m, $P(C_6H_5)_2$). *Anal.* Calcd for $C_{34}H_{46}NO_2P_2$: C, 72.19; H, 8.73; N, 2.48. Found: C, 72.09; H, 8.71; N, 2.43.

(2*S*,4*S*)-*N*-(Alkoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (4a—b) A Typical Procedure is Given for the Preparation of (2*S*,4*S*)-*N*-(Methoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine; (2*S*,4*S*)-MCPM (4a): Phosphine oxide reducing product (2) was prepared by means of the same procedure as for the preparation of (2*S*,4*S*)-BCPM (3) using 1 (300 mg, 0.60 mmol), triethylamine (268 mg, 2.47 mmol), trichlorosilane (326 mg, 2.41 mmol) and acetonitrile (30 ml). The reaction product and triethylamine (146 mg, 1.39 mmol) were dissolved in degassed benzene (8 ml). To this solution, methyl chloroformate (68 mg, 0.66 mmol) was added dropwise at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 2 h under an argon atmosphere, washed with degassed saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and evaporated. The residue was recrystallized from degassed methanol, affording 4a as white crystals (285 mg, 91%), mp 149—151 °C, $[\alpha]_D^{24}$ −52.8° (*c* = 0.50, benzene). IR (KBr): 1694 (C=O) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 0.84—2.53 (25H, m, $P(C_6H_{11})_2$, CCH_2C. H_a of CH_2P), 2.72—3.36 (2H, m, H_b of CH_2P, PCH), 3.64 (3H, s, OCH_3), 3.45—4.14 (3H, m, CH_2NCH), 7.15—7.60 (10H, m, $P(C_6H_5)_2$). *Anal.* Calcd for $C_{31}H_{43}NO_2P_2$: C, 71.11; H, 8.28; N, 2.67. Found: C, 70.84; H, 8.38; N, 2.67.

(2*S*,4*S*)-*N*-(Phenoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine; (2*S*,4*S*)-PCPM (4b): 72% yield, mp 120 °C (dec.) $[\alpha]_D^{24}$ −44.5° (*c* = 0.82, benzene). IR (KBr): 1719 (C=O) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 0.81—2.58 (25H, m, $P(C_6H_{11})_2$, CCH_2C. H_a of CH_2P), 2.80—3.51 (2H, m, H_b of CH_2P, PCH), 3.54—4.26 (3H, m, CH_2NCH), 6.76—7.72 (15H, m, $P(C_6H_5)_2$, OC_6H_5). *Anal.* Calcd for $C_{36}H_{45}NO_2P_2$: C, 77.82; H, 7.74; N, 2.39. Found: C, 77.99; H, 7.73; N, 2.31.

(2*S*,4*S*)-*N*-(Carbamoyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (5a—c) A Typical Procedure is Given for the Preparation of (2*S*,4*S*)-*N*-(Methylcarbamoyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine; (2*S*,4*S*)-MCCPM (5a): Phosphine oxide reducing product (2) was prepared by means of the same procedure as for the preparation of (2*S*,4*S*)-BCPM (3) using 1 (300 mg, 0.60 mmol), triethylamine (268 mg, 2.47 mmol), trichlorosilane (326 mg, 2.41 mmol) and acetonitrile (30 ml). The reaction product was dissolved in degassed CH_2Cl_2 (8 ml). To this solution, methyl isocyanate (38 mg, 0.66 mmol) was added dropwise at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 2 h under an argon atmosphere, then concentrated *in vacuo*, and the residue was recrystallized from degassed methanol, affording 5a as white crystals (292 mg, 96%), mp 142—144 °C, $[\alpha]_D^{20}$ −19.8° (*c* = 0.60, benzene). IR (KBr): 3320 (NH), 1625 (C=O) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 0.75—2.47 (25H, m, $P(C_6H_{11})_2$, CCH_2C. H_a of CH_2P), 2.72 (3H, d, *J* = 4.2 Hz, CH_3), 2.77 (1H, s, NH), 2.90—3.31 (2H, m, H_b of CH_2P, PCH), 3.46—4.09 (3H, m, CH_2NCH), 7.15—7.70 (10H, m, $P(C_6H_5)_2$). *Anal.* Calcd for $C_{31}H_{44}N_2OP_2$: C, 71.24; H, 8.49; N, 5.36. Found: C, 71.02; H, 8.45; N, 5.30.

(2*S*,4*S*)-*N*-(Phenylcarbamoyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine; (2*S*,4*S*)-PCCPM (5b): 82% yield, mp 183—184 °C, $[\alpha]_D^{21}$ −30.8° (*c* = 1.00, benzene). IR (KBr): 3280 (NH), 1643 (C=O) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 0.84—1.98 (22H, m, $P(C_6H_{11})_2$), 2.00—2.25 (3H, m, CCH_2C. H_a of CH_2P), 2.82—3.01 (1H, m, PCH), 3.03—4.29 (4H, m, H_b of CH_2P, CH_2NCH), 5.79—6.00 (1H, m, NH), 6.90—7.68 (15H, m, $P(C_6H_5)_2$, NC_6H_5). *Anal.* Calcd for $C_{37}H_{45}N_2OP_2$: C, 73.95; H, 7.93; N, 4.79. Found: C, 73.86; H, 7.95; N, 4.69.

(2*S*,4*S*)-*N*-(*tert*-Butylcarbamoyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine; (2*S*,4*S*)-BCCPM (5c): 71% yield, mp 160—161 °C, $[\alpha]_D^{20}$ −15.6° (*c* = 1.00, benzene). IR (KBr): 3450 (NH), 1643 (C=O) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 0.93—2.48 (25H, m, $P(C_6H_{11})_2$, CCH_2C. H_a of CH_2P), 1.28 (9H, s, $C(CH_3)_3$), 2.69—3.41 (2H, m, H_b of CH_2P, PCH), 3.48 (1H, br s, NH), 3.59—4.67 (3H, m, CH_2NCH), 7.15—7.60 (10H, m, $P(C_6H_5)_2$). *Anal.* Calcd for $C_{34}H_{49}N_2OP_2$: C, 72.31; H, 8.92; N, 4.96. Found: C, 72.58; H, 8.94; N, 4.80.

(2*S*,4*S*)-*N*-(Acyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (6a—c) A Typical Procedure is Given for the Preparation of (2*S*,4*S*)-*N*-(Acetyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine; (2*S*,4*S*)-ACPM (6a): Phosphine oxide reducing product (2) was prepared by means of the same procedure as for the preparation of (2*S*,4*S*)-BCPM (3) using 1 (300 mg, 0.60 mmol), triethylamine (268 mg, 2.65 mmol), trichlorosilane (326 mg, 2.41 mmol) and acetonitrile (30 ml). The reaction product was dissolved in degassed benzene (8 ml). To this solution, acetyl chloride (52 mg, 0.66 mmol) was added dropwise at 0 °C under an argon atmosphere. The mixture was stirred at room temperature under an argon atmosphere for 2 h, washed with degassed saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and evaporated. The residue was recrystallized from degassed methanol, affording 6a as needles (265 mg, 87%), mp 169—172 °C, $[\alpha]_D^{23}$ −16.3° (*c* = 0.40, benzene). IR (KBr): 1642 (C=O) cm^{-1}. ^{1}H-

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NMR δ ($CDCl_3$): 0.80—2.66 (25H, m, $P(C_6H_{11})_2$, CCH_2C, H_a of CH_2P), 1.95 (3H, s, CH_3), 3.00—3.43 (2H, m, H_b of CH_2P, PCH), 3.47—4.35 (3H, m, CH_2NCH), 7.20—7.77 (10H, m, $P(C_6H_5)_2$). *Anal.* Calcd for $C_{31}H_{43}NOP_2$: C, 73.35; H, 8.54; N, 2.76. Found: C, 73.00; H, 8.53; N, 2.81.

(2*S*,4*S*)-*N*-(Benzoyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine; (2*S*,4*S*)-BZCPM (6b): 82% yield, mp 223—224 °C, $[\alpha]_D^{23}$ −74.5° (c = 0.50, benzene). IR (KBr): 1620 (C=O) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 0.78—2.55 (25H, m, $P(C_6H_{11})_2$, CCH_2C, H_a of CH_2P), 2.94—4.66 (5H, m, H_b of CH_2P, PCH, CH_2NCH), 7.20—7.84 (15H, m, $P(C_6H_5)_2$, CC_6H_5). *Anal.* Calcd for $C_{36}H_{45}NOP_2$: C, 75.35; H, 7.96; N, 2.46. Found: C, 75.64; H, 8.05; N, 2.44. **(2*S*,4*S*)-*N*-(Pivaloyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]-pyrrolidine; (2*S*,4*S*)-PVCPM (6c)**: 82% yield, mp 201—203 °C, $[\alpha]_D^{22}$ −5.5 (c = 0.62, benzene). IR (KBr): 1617 (C=O) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 0.78—2.48 (25H, m, $P(C_6H_{11})_2$, CCH_2C, H_a of CH_2P), 1.17 (9H, s, $C(CH_3)_3$), 2.78—3.78 (2H, m, H_b of CH_2P, PCH), 3.87—4.52 (3H, m, CH_2NCH), 7.23—7.72 (10H, m, $P(C_6H_5)_2$). *Anal.* Calcd for $C_{34}H_{49}NOP_2$: C, 74.29; H, 8.98; N, 2.55. Found: C, 73.81; H, 9.01; N, 2.59.

(2*R*,4*R*)-4-Hydroxyproline Ethyl Ester Hydrochloride (8) A solution of 4-hydroxy-L-proline (7) (26.2 g, 0.2 mol) in glacial acetic acid (300 ml) and acetic anhydride (102 g, 2 mol) was refluxed for 6 h. After evaporation, the residue was dissolved in 2 N HCl (400 ml) and refluxed for 3 h. The mixture was decolorized with activated carbon powder and evaporated to give a crystalline residue. The residue was added to a solution of acetyl chloride (31.4 g, 0.4 mol) in ethanol (200 ml), and the mixture was stirred at 50 °C for 30 min and then refluxed for 2 h. After cooling to 5 °C, the precipitate was separated by filtration and washed with ice-cold ethanol. Vacuum drying of the precipitate gave **8** as white crystals (26.1 g, 78%), mp 160—163 °C, $[\alpha]_D^{20}$ + 59.8° (Free amine, c = 1.0, H_2O).

(2*R*,4*S*)-*N*-(Methylsulfonyl)-4-(acetoxy)pyrrolidinecarboxylic Acid Ethyl Ester (10) Methanesulfonyl chloride (42.96 g, 0.375 mol) was added dropwise to a solution of **8** (29.35 g, 0.15 mol) in pyridine (225 ml) at 5 °C, and the mixture was stirred at room temperature for 5 h. After standing at room temperature for a day, the reaction mixture was evaporated. The residue was acidified to pH 2 by addition of 2 N HCl and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave **9**, which was used without further purification (47.5 g). A solution of tetraethylammonium acetate tetrahydrate (41 g, 0.157 mol) in benzene (350 ml) was refluxed with azeotropic removal of water in a Dean-Stark trap for 4 h. After cooling of the mixture to room temperature, a solution of **9** (47.5 g) in benzene (50 ml) was added and the whole was refluxed for 1 h. H_2O (80 ml) and ethyl acetate (150 ml) were added to the mixture, then the organic layer was separated and washed with saturated aqueous NaCl. After evaporation of the solvent, the residue was purified by column chromatography on silica gel with ethyl acetate–benzene (1 : 4) as the eluent to give **10** (34.4 g, 74%).

(2*R*,4*S*)-*N*-(Methylsulfonyl)-4-(hydroxy)-2-[(hydroxy)methyl]pyrrolidine (11) A solution of **10** (11.74 g, 42 mmol) in anhydrous tetrahydrofuran (THF) (150 ml) was added dropwise to a stirred and ice-cooled suspension of lithium aluminum hydride (4.0 g, 105 mmol) in THF (300 ml). The mixture was stirred at 0 °C for 1 h and at room temperature for 3 h, and then a small amount of water was added with cooling in an ice bath. Filtration through Celite and evaporation of the filtrate under reduced pressure gave **11** (7.72 g, 94%), which was used without further purification. ^{1}H-NMR δ ($CDCl_3$): 1.57—2.33 (1H, br, OH), 1.87—2.16 (2H, m, CCH_2C), 2.96 (3H, s, CH_3), 3.52 (1H, br, OH), 2.43—4.11 (5H, m, CH_2NCHCH_2O), 4.45 (1H, br, OCH).

(2*R*,4*R*)-4-(Dicyclohexylphosphinyl)-2-[(diphenylphosphinyl)methyl]-pyrrolidine (12) The title compound was prepared from **11** by using the same procedure as for the preparation of (2*S*,4*S*)-BCPM (ref. 5*c*). ^{1}H-NMR δ ($CDCl_3$): 0.96—3.63 (31H, m, $P(C_6H_{11})_2$, CCH_2C, CH_2P, PCH, CH_2NCH, CH_3CH_2OH), 1.23 (3H, t, J = 7.08 Hz, CH_3CH_2OH), 2.14 (1H, s, NH), 3.82 (2H, q, J = 7.08 Hz, CH_3CH_2OH), 7.36—7.97 (10H, m, Ar-H).

(2*R*,4*R*)-*N*-(Methylcarbamoyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine; (2*R*,4*R*)-MCCPM (13) The title compound was prepared from **12** by using the same procedure as for the preparation of (2*S*,4*S*)-MCCPM (**5a**), mp 144—146 °C, $[\alpha]_D^{22}$ +27.8° (c = 0.6, benzene).

(2*R*,4*R*)-4-(Dicyclohexylphosphinyl)-2-[(di-3,5-xylphosphinyl)methyl]-pyrrolidine (14) The title compound was prepared from **11** according to the reported procedure (ref. 5*c*). ^{1}H-NMR δ (DMSO-d_6): 0.92—2.64 (26H, m, $P(C_6H_{11})_2$, CCH_2C, CH_2P), 2.36 (12H, s, $CH_3 \times 4$), 3.04—4.43 (4H, m, CH_2NCH, PCH), 7.10—7.60 (6H, m, Ar-H).

(2*R*,4*R*)-*N*-(Methylcarbamoyl)-4-(dicyclohexylphosphino)-2-[(di-3,5-xylphosphino)methyl]pyrrolidine; (2*R*,4*R*)-MCCXM (15) The title compound was prepared from **14** by using the same procedure as for the preparation of (2*S*,4*S*)-MCCPM (**5a**), $[\alpha]_D^{24}$ −10.5° (c = 0.5, benzene). ^{1}H-NMR δ ($CDCl_3$): 0.88—2.51 (25H, m, $P(C_6H_{11})_2$, CCH_2C, H_a of CH_2P), 2.28 (6H, s, $PhCH_3 \times 2$), 2.72 (3H, d, $NHCH_3$), 2.77 (1H, s, NH), 2.90—3.32 (2H, m, H_b of CH_2P, PCH), 3.56—4.00 (3H, m, CH_2NCH), 6.92—7.52 (6H, m, Ar-H).

3′-Benzyloxyacetophenone (21) *m*-Hydroxy acetophenone (**20**) (25 g, 0.184 mol) was added to a solution of sodium (4.3 g, 0.19 mol) in ethanol (66 ml). Then benzyl chloride (23.15 g, 0.184 mol) was added, and the mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated and distilled under reduced pressure to give **21** (32.8 g, 79%), bp 152—154 °C (0.27 mm Hg). ^{1}H-NMR δ ($CDCl_3$): 2.58 (3H, s, CH_3), 5.12 (2H, s, $PhCH_2$), 7.10—7.65 (9H, m, Ar-H).

3′-Benzyloxy-2-bromoacetophenone (22) Br_2 (16 g, 0.1 mol) was added to a mixture of **21** (22.6 g, 0.1 mol), $CaCO_3$ (10 g, 0.1 mol) and $CHCl_3$ (100 ml) at 5 °C. The mixture was stirred at 10 °C for 1 h, then poured into ice water (100 ml), and the organic layer was separated. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was crystallized from ethanol to give **22** as white crystals (21.0 g, 69%), mp 59—63 °C. ^{1}H-NMR δ ($CDCl_3$): 4.46 (2H, s, CH_2Br), 5.17 (2H, s, CH_2Ph), 7.28—7.70 (9H, m, Ar-H).

3′-Benzyloxy-2-(*N*-benzyl-*N*-methyl)aminoacetophenone Hydrochloride (18) A solution of **22** (21.0 g, 68.8 mmol) in benzene (450 ml) was added to a solution of *N*-benzylmethylamine (16.7 g, 138 mmol) in benzene (50 ml) at 40 °C, and the mixture was stirred at 50 °C for 4 h, then cooled in an ice bath. The precipitate was filtered off. The filtrate was washed with H_2O (200 ml) and the organic layer was acidified with 4 N HCl (138 ml). The acid layer was separated and further extraction of the organic layer with 4 N HCl was carried out. The combined acid layer was made alkaline with 4 N NaOH (70 ml), and extracted with benzene. The combined extracts were washed with H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel with benzene–ethanol (50 : 1) as the eluent to give an oil. This oil was dissolved in ether and acidified with hydrogen chloride gas. The precipitate was collected to give **18** (12.7 g, 47%). ^{1}H-NMR δ ($CDCl_3$): 3.12 (3H, d, J = 5 Hz, NCH_3), 4.50 (2H, d, J = 5 Hz, NCH_2Ph), 4.64 (2H, d, J = 5 Hz, $C(O)CH_2N$), 5.14 (2H, s, OCH_2Ph), 7.32—7.84 (14H, m, Ar-H).

(*R*)-1-(*m*-Hydroxyphenyl)-2-methylaminoethanol Hydrochloride; (*R*)-(−)-Phenylephrine Hydrochloride (28) A mixture of $[Rh(COD)Cl]_2$ (1.5 mg, 3×10^{-3} mmol), (2*R*,4*R*)-MCCPM (2.04 mg, 3.9×10^{-3} mmol) and degassed methanol (10 ml) was stirred at room temperature for 5 min. This catalytic solution was added to a solution of **18** (2.3 g, 6 mmol) and triethylamine (3 mg, 0.03 mmol) in degassed methanol (total 15 ml). The mixture was placed in an autoclave, pressurized with hydrogen to 20 atm and stirred for 20 h at 50 °C. To this solution, a mixture of 10% Pd–C (0.7 g) and ethanol (10 ml) was added. This mixture was placed in an autoclave, and stirred at 50 °C for 3 h under an initial hydrogen pressure of 10 atm. H_2O (20 ml) and active carbon powder (1 g) were added, then the whole was stirred at room temperature for 30 min. After filtration and evaporation, the residue was crystallized from benzene to give **28** as white crystals (1.07 g, 88%), $[\alpha]_D^{20}$ −38.3° (c = 2.0, H_2O). Optically pure **28** was obtained by recrystallization from 2-propanol, $[\alpha]_D^{22}$ −45.2° (c = 2.0, H_2O). ^{1}H-NMR δ (DMSO-d_6): 2.60 (3H, s, NCH_3), 3.04 (2H, m, CH_2N), 4.82 (1H, m, $CH(OH)$), 6.60—7.30 (4H, m, Ar-H).

2-[*N*-(2-Chloroethyl)]aminoacetophenone Hydrochloride (24) 2-Chloroethylamine hydrochloride (6.05 g, 52.2 mmol) and 28% NaOH (11.4 ml, 105 mmol) were added to a solution of 2-bromoacetophenone (**23**) (9.44 g, 0.05 mol) in benzene (140 ml) at 0 °C, then the mixture was stirred at room temperature for 18 h. It was diluted with benzene (100 ml), and the organic layer was washed with 1 N NaOH and extracted with 1 N HCl. The acid layer was made alkaline to pH 14 by addition of 1 N NaOH and extracted with benzene. The organic layer was washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. After extraction with 1 N HCl, the acid layer was concentrated *in vacuo*. The residue was crystallized from ethanol to give **24** as white crystals (4.79 g, 43%), mp 187—189 °C, IR (KBr): 1700 (C=O) cm^{-1}, ^{1}H-NMR δ

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(DMSO-d_6): 3.45 (2H, t, $NHCC\underline{H}_2Cl$), 4.02 (2H, t, NCH_2CCl), 4.86 (2H, s, CCH_2N), 7.50—8.20 (5H, m, Ar-H), 9.80 (1H, br s, NH).

(*S*)-1-Phenyl-2-[*N*-(2-chloroethyl)]aminoethanol Hydrochloride (25) A mixture of $[Rh(COD)Cl]_2$ (4.93 mg, 0.01 mmol), (2*S*,4*S*)-MCCPM (12.5 mg, 0.024 mmol) and degassed methanol (15 ml) was stirred at room temperature for 5 min. This catalytic solution was added to a solution of **24** (4.68 g, 20 mmol) and triethylamine (4.9 mg, 0.048 mmol) in degassed methanol (total 30 ml). The mixture was placed in an autoclave, pressurized with hydrogen to 20 atm and stirred for 20 h at 50 °C. The reaction mixture was evaporated and the residue was dissolved in H_2O. Active carbon powder (1 g) was added to this solution, then the mixture was stirred at room temperature for 20 min. After filtration, the filtrate was evaporated and the residue was crystallized from benzene (50 ml) to give **25** as white crystals (4.51 g, 96%), mp 145—147 °C, $[\alpha]_D^{25}$ +37.2° (c = 1.0, H_2O). ^{1}H-NMR δ (DMSO-d_6): 3.12 (2H, d, CCH_2N), 3.41 (2H, t, NCH_2Cl), 3.97 (2H, t, NCH_2CCl), 5.05 (1H, dd, $\underline{CH}(OH)$), 6.23 (1H, br s, $CH(\underline{OH})$), 7.38 (5H, s, Ar-H), 9.46 (1H, br s, NH).

(*S*)-3-(2-Hydroxy-2-phenylethyl)-2-iminothiazolidine Hydrochloride (26) A solution of potassium thiocyanate (1.69 g, 17.4 mmol) in H_2O (20 ml) was added to a solution of **26** (2.74 g, 11.6 mmol) in ethanol (100 ml), then the mixture was refluxed for 30 min. It was cooled in an ice bath, 2 N HCl (15 ml) was added, and the whole was stirred at room temperature for 2 h, then evaporated. The residue was decolorized by stirring in a mixture of active carbon powder and ethanol. The mixture was filtered and the filtrate was evaporated. The residue was crystallized from acetone to give **26** as white crystals (2.50 g, 83%), mp 198—201 °C, $[\alpha]_D^{25}$ −47.8° (c = 2.0, H_2O). ^{1}H-NMR δ (DMSO-d_6): 3.45 (2H, t, $NCCH_2S$), 3.73 (2H, d, CCH_2N), 4.06 (2H, t, NCH_2CS), 4.93 (1H, d, $\underline{CH}(OH)$), 6.07 (1H, br s, $CH(\underline{OH})$), 7.26—7.60 (5H, m, Ar-H), 9.88 (1H, br s, NH).

(*S*)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*]-thiazole; Levamisole (27) Thionyl chloride (510 mg, 4.3 mmol) was added to a suspension of **27** (1.04 g, 4 mmol) in CH_2Cl_2 (5 ml), then the mixture was stirred at room temperature for 2 h and evaporated. The residue was crystallized from ethanol to give white crystals (1.03 g) hydrochloride salt. After desalting with saturated aqueous K_2CO_3, a solution of the HCl-free product in ethanol was refluxed for 1 h and then evaporated. The residue was dissolved in H_2O and to this solution was added a solution of K_2CO_3 (0.69 g, 5 mmol) in H_2O (5 ml). The aqueous layer was extracted with CH_2Cl_2 and the organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel with ethyl acetate as the eluent to give **27** as white crystals (637 mg, 78%), mp 55.5—56.5 °C, $[\alpha]_D^{25}$ −49.0° (c = 1.0, $CHCl_3$). ^{1}H-NMR δ ($CDCl_3$): 2.88—3.76 (6H, m, SCH_2CH_2N, $PhCCH_2N$), 5.45 (1H, t, PhCHCN), 7.28—7.39 (5H, m, Ar-H).

Ethyl 4-(Dimethylamino)-3-oxobutanone (30) A solution of dimethylaminoacetone (29) (2.01 g, 19.9 mmol) in 1,2-dimethoxyethane (10 ml) was added dropwise to a mixture of 1, 2-dimethoxyethane (10 ml), sodium hydride (2.11 g of a 50% dispersion in oil, 44 mmol) and diethylcarbonate (4.81 g, 40.8 mmol) at 85 °C. The mixture was refluxed for 2 h, then allowed to cool to room temperature and a mixture of acetic acid (2.63 g, 43.8 mmol) and H_2O (20 ml) was added to it. After evaporation of the 1, 2-dimethoxyethane, the residue was acidified to pH 5.5 by addition of acetic acid and extracted with hexane. The acid layer was made alkaline to pH 8.0 by addition of 2 N NaOH and extracted with ethyl acetate. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was distilled to give **30** as an oil (2.53 g, 73%), bp 55—65 °C (0.6 mmHg). ^{1}H-NMR δ ($CDCl_3$): 1.27 (3H, t, $OCH_2\underline{CH}_3$), 2.3 (6H, s, $N(CH_3)_2$), 3.23 (2H, s, $C(O)CH_2N$), 3.47 (2H, s, $C(O)CH_2C(O)$), 4.18 (2H, q, $O\underline{CH}_2CH_3$).

(*R*)-4-Dimethylamino-3-hydroxybutyric Acid Ethyl Ester; Norcarnitine (31) A mixture of $[Rh(COD)Cl]_2$ (1.7 mg, 3.5×10^{-3} mmol), (2*R*,4*R*)-MCCPM (4.86 mg, 8.4×10^{-3} mmol) and degassed ethanol (5 ml) was stirred at room temperature for 5 min. This catalytic solution was added to a mixture of **30** (1.45 g, 8.4 mmol), ethanol (10 ml), *p*-toluenesulfonic acid (1.59 g, 8.4 mmol) and triethylamine (3.5 mg, 0.035 mmol). The mixture was placed in an autoclave, pressurized with hydrogen to 20 atm and stirred for 20 h at 50 °C. The reaction mixture was brought to ambient temperature, and evaporated. The residue was dissolved in H_2O (20 ml) and the solution was neutralized to pH 8—9 by addition of 2 N NaOH, then extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, evaporated and distilled to give **31** as an oil (1.4 g, 96%), bp 73 °C (0.4 mmHg). ^{1}H-NMR δ ($CDCl_3$): 1.28 (3H, t, $OCH_2\underline{CH}_3$), 2.30 (6H, s, $N(CH_3)_2$), 2.20—2.55 (4H, $C(O)CH_2\underline{CH}_2N$), 3.50 (1H, s, OH), 4.16 (2H, q, $O\underline{CH}_2CH_3$).

(*R*)-3-Hydroxy-4-(trimethylammonio)butyrate; (*R*)-Carnitine (32) Iodomethane (950 mg, 6.7 mmol) was added to a solution of **31** (500 mg, 2.85 mmol) in acetone (10 ml), and the mixture was stirred at room temperature for 18 h. After evaporation under reduced pressure, 15% methanol/H_2O and silver(I) oxide (632 mg, 2.85 mg) were added to the residue and the mixture was stirred at room temperature for 18 h. It was filtered and the filtrate was evaporated, then 6 N HCl (4 ml) and H_2O (10 ml) were added to the residue and the mixture was stirred at 60 °C for 30 min, cooled to room temperature and filtered. The filtrate was evaporated to give **32** as crystals (540 mg, 100%). These crystals (500 mg) were recrystallized from ethanol to give **32** as white crystals (340 mg), mp 142 °C (dec.), IR (KBr): 3300 (OH), 1730 (C=O) cm^{-1}, $[\alpha]_D^{22}$ −22.0 (c = 1.0, H_2O). ^{1}H-NMR δ (DMSO-d_6): 2.50 (2H, d, J = 6 Hz, CH_2CO_2), 3.23 (9H, s, $CH_3 \times 3$), 3.45 (2H, d, J = 6 Hz, CH_2N), 4.12—4.67 (1H, m, $\underline{CH}(OH)$).

3-(Aryloxy)-2-oxo-1-propylamine Hydrochloride Derivatives (36a—e) A Typical Procedure is Given for the Preparation of *N*-Isopropyl-3-naphthyloxy-2-oxo-1-propylamine Hydrochloride (**36a**): 1-Naphthol (**38a**) (4.33 g, 30 mmol) was added to a solution of sodium methoxide (1.78 g, 33 mmol) in methanol (60 ml) and the mixture was stirred at room temperature for 30 min under an argon atmosphere. Epichlorohydrine (2.78 g, 3.0 mmol) was added, and the whole was refluxed for 8 h, then concentrated *in vacuo*. The residue was treated with H_2O (30 ml) and extracted with ether. The combined organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and evaporated to give **39a**. Isopropylamine (15 ml) and H_2O (1 ml) were added to **39a**, and the mixture was refluxed in a sealed tube for 3 h, then evaporated to give **40a** as a slightly yellow solid. PCC–Al_2O_3 (50 g) was added to a solution of **40a** in benzene (100 ml), and the mixture was vigorously stirred at 40 °C for 18 h under an argon atmosphere. PCC–Al_2O_3 was filtered off and the filtrate was evaporated. The residue was dissolved in ether (100 ml) and acidified with hydrogen chloride gas under ice cooling. The precipitate was separated by filtration and dissolved in ice-cold 1 N NaOH. Extraction with ether was carried out, then the organic layer was washed with saturated aqueous NaCl and dried over anhydrous K_2CO_3. After filtration, the filtrate was acidified with hydrogen chloride gas at 0 °C. The precipitate was separated by filtration and recrystallized from methanol–ether three times to give **36a** as white crystals (1.35 g, 15%), mp 250 °C (dec.), IR (KBr): 3350 (NH), 1710 (C=O) cm^{-1}, ^{1}H-NMR δ (CD_3OD): 1.05 (3H, d, J = 6.5 Hz, CH_3), 1.14 (3H, d, J = 6.5 Hz, CH_3), 2.78—3.00 (1H, m, CH), 4.29 (2H, s, NH, HCl), 4.68 (2H, s, CH_2N), 4.89 (2H, s, OCH_2), 6.61—6.84, 7.00—7.74, 8.01—8.34 (7H, m, Ar-H). *Anal.* Calcd for $C_{16}H_{19}NO_2 \cdot HCl$: C, 65.41; H, 6.68; N, 4.77. Found: C, 65.15; H, 6.66; N, 4.56.

N-Isopropyl-3-[[4'-(2''-methoxyethyl)phenyl]oxy]-2-oxo-1-propylamine Hydrochloride (**36b**): 25% yield, mp 257—260 °C (dec.), IR (KBr): 3340 (NH), 1720 (C=O) cm^{-1}, ^{1}H-NMR δ (CD_3OD): 1.04 (3H, d, J = 6.5 Hz, CH_3), 1.14 (3H, d, J = 6.5 Hz, CH_3), 2.80—3.12 (3H, m, CH, CH_2-Ar), 4.55 (3H, s, OCH_3), 4.70 (2H, s, CH_2N), 4.93 (2H, s, OCH_2), 4.89—5.11 (2H, m, $O\underline{CH}_2CH_2$), 5.89 (2H, br s, NH, HCl), 6.80 (2H, d, J = 8.3 Hz, Ar-H), 7.25 (2H, d, J = 8.3 Hz, Ar-H). *Anal.* Calcd for $C_{15}H_{23}NO_3 \cdot HCl$: C, 59.69; H, 7.68; N, 4.64. Found: C, 59.39; H, 7.56; N, 4.58.

N-Isopropyl-2-oxo-3-phenyloxy-1-propylamine Hydrochloride (**36c**): 14% yield, mp 228 °C (dec.), IR (KBr): 3340 (NH), 1724 (C=O) cm^{-1}, ^{1}H-NMR δ (CD_3OD): 1.05 (3H, d, J = 6.5 Hz, CH_3), 1.15 (3H, d, J = 6.5 Hz, CH_3), 2.81—3.01 (1H, m, CH), 4.60 (2H, s, CH_2N), 5.00 (2H, s, OCH_2), 6.12 (2H, br s, NH, HCl), 6.65—7.21 (5H, m, Ar-H). *Anal.* Calcd for $C_{12}H_{17}NO_2 \cdot HCl$: C, 59.14; H, 7.44; N, 5.75. Found: C, 59.33; H, 7.39; N, 5.61.

N-Benzyl-3-(2'-methoxyphenyloxy)-2-oxo-1-propylamine Hydrochloride (**36d**): 24% yield, IR (KBr): 3300 (NH), 1705 (C=O) cm^{-1}, ^{1}H-NMR δ (CD_3OD): 3.80 (3H, s, CH_3), 4.20 (2H, s, CH_2-Ar), 4.30 (2H, s, CH_2N), 4.74 (2H, s, OCH_2), 4.89 (2H, s, NH, HCl), 6.83 (4H, br s, Ar-H), 7.39 (5H, br s, Ar-H). *Anal.* Calcd for $C_{17}H_{19}NO_3 \cdot HCl$: C, 63.45; H, 6.25; N, 4.35. Found: C, 63.07; H, 6.11; N, 4.29.

N-Benzyl-3-(3',5'-dimethylphenyloxy)-2-oxo-1-propylamine Hydrochloride (**36e**): 24% yield, IR (KBr): 3340 (NH), 1710 (C=O) cm^{-1}, ^{1}H-NMR δ (CD_3OD): 2.25 (3H, s, Ar-CH_3), 2.38 (3H, s, Ar-CH_3), 4.00 (2H, s, CH_2-Ar), 4.29 (2H, s, CH_2N), 4.78 (2H, s, OCH_2), 5.01 (2H, s, NH, HCl), 6.56 (3H, br s, Ar-H), 7.41 (5H, br s, Ar-H). *Anal.* Calcd for $C_{19}H_{23}NO_2 \cdot HCl$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.21; H, 6.74;

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N, 4.33.

Asymmetric Hydrogenation of 3-Aryloxy-2-oxo-1-propylamine Hydrochloride (36a—e) (General Procedure) A mixture of $[Rh(COD)Cl]_2$ (4.9 mg, 1.0×10^{-2} mmol), (2*S*,4*S*)-MCCPM (12.5 mg, 2.4×10^{-2} mmol) and degassed methanol (10 ml) was stirred at room temperature under an argon atmosphere for 5 min. Triethylamine (10.1 mg, 10 mmol) was dissolved in degassed methanol (10 ml). The catalytic solution (1.0 ml) and triethylamine solution (1.0 ml) were added to a solution of 3-aryloxy-2-oxo-1-propylamine hydrochloride (**36a—e**) (20.0 mmol) in degassed methanol (total 20 ml). The mixture was placed in an autoclave, pressurized with hydrogen to 20 atm and stirred for 20 h at 50 °C. The reaction mixture was evaporated, then H_2O (20 ml) and active carbon powder (0.5 g) were added to the residue. After stirring at room temperature for 30 min and filtration through Celite, the filtrate was evaporated as the benzene azeotrope to give **37a—e** quantitatively. Part of the product was dissolved in 0.5 N NaOH at 0 °C and extracted with ether. The combined extracts were washed with saturated aqueous NaCl, and dried over anhydrous K_2CO_3. This ether solution was analyzed by HPLC to determine the enantiomeric purity (Daicel Chiralcel OD, *n*-hexane : 2-propanol = 9 : 1).

Allyl 1-Naphthyl Ether (34) Under an argon atmosphere, 1-naphthol (**33**) (7.57 g, 52.5 mmol) was added to a suspension of sodium hydride (2.20 g of a 60% dispersion in oil; 55 mmol; oil removed with *n*-hexane) in dimethylformamide (DMF) (80 ml) at 0 °C, then the mixture was stirred at room temperature for 15 min. A solution of allyl bromide (6.65 g, 50 mmol) in DMF (80 ml) and potassium iodide (8.3 g, 50 mmol) were added, and the whole was stirred at room temperature for 6 h, then evaporated. The residue was taken up in H_2O (200 ml) and extracted with ether. The organic layer was washed with 0.5 N NaOH and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated to give **34** as a viscous oil (8.38 g, 91%), which was confirmed to be almost pure by GLC, and was used without further purification. ^{1}H-NMR δ ($CDCl_3$): 3.92 (2H, dd, OCH_2), 4.93—5.43, 5.57—6.22 (3H, m, $CH=CH_2$), 6.59—6.84, 7.01—7.72, 7.99—8.32 (7H, m, Ar-H).

3-Naphthyloxy-2-oxo-1-propyl Bromide (35) Sodium bromite (20.23 g, 150 mmol) was added to a solution of **35** (5.53 g, 30 mmol) in 80% acetic acid (150 ml) at 0 °C and the mixture was stirred at room temperature under an argon atmosphere for 6 h, poured into ice-cold H_2O (500 ml) and neutralized with sodium hydrogen carbonate. After filtration through Celite, the filtrate was extracted with CH_2Cl_2, and the combined extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel with $CHCl_3$–*n*-hexane (2 : 1) as the eluent to give **35** (5.19 g, 62%). IR (neat): 1710 (C=O) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 4.78 (2H, s, CH_2), 4.91 (2H, s, CH_2), 6.63—6.88, 6.99—7.67, 7.89—8.30 (7H, m, Ar-H). *Anal.* Calcd for $C_{13}H_{11}BrO_2$: C, 55.94; H, 3.97. Found: C, 56.37; H, 3.71.

***N*-Isopropyl-3-naphthyloxy-2-oxo-1-propylamine Hydrochloride (36a)** A solution of **35** (4.19 g, 15 mmol) in 2-propanol (20 ml) was added to a mixture of 40% isopropylamine (3 ml) and 2-propanol (20 ml) at 0 °C, and the mixture was stirred at 40 °C under an argon atmosphere for 1 h. The reaction mixture was acidified with hydrogen chloride gas under ice cooling, and acetone (80 ml) was added. The whole was allowed to stand under an argon atmosphere at room temperature for a day. The precipitate was separated by filtration and recrystallized from ethanol–ether to give **36a** as white needles (2.25 g, 51%).

(*S*)-(−)-Propranolol Hydrochloride (37a) Asymmetric hydrogenation was carried out by means of the same procedure as for the preparation of **37a—e** using **36a** (2.00 g, 6.8 mmol). Work-up gave **37a** as white crystals (1.97 g, 98%). $[\alpha]_D^{22}$ −23.2° (*c* = 1.08, ethanol). Optically pure **37a** was obtained by recrystallization from methanol–ether. mp 199—202 °C. $[\alpha]_D^{22}$ −25.9° (*c* = 1.06, ethanol). IR (KBr): 3400 (NH), 3240 (OH) cm^{-1}. ^{1}H-NMR δ (CD_3OD): 1.12 (3H, d, *J* = 6.5 Hz, CH_3), 1.23 (3H, d, *J* = 6.5 Hz, CH_3), 3.13 (2H, dd, *J* = 4, 13 Hz, CH_2N), 3.10—3.34 (2H, m, NCH, OCH), 4.05 (2H, dd, *J* = 4, 11 Hz, OCH_2), 4.67 (3H, br s, NH, OH, HCl), 6.70—6.82, 6.98—7.70, 7.75—8.10 (7H, m, Ar-H). *Anal.* Calcd for $C_{16}H_{22}ClNO_2$: C, 64.95; H, 7.50; N, 4.74. Found: C, 64.98; H, 7.43; N, 4.74.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, D.C., 21 de enero de 2005

Apoderado: Emilio Ferrero Oficio: 11927

REFERENCIA: Radicación No. 0-3108
Tramite 002
Evento 001
Actuación 430
Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

- Capítulo descriptivo, folios 2 a 67;
- Capitulo reivindicatorio, folios 87 a 89;
- 1° examen de forma folios 34 y 35;
- Respuesta técnica al primer examen de forma, folios 75 a 77;
- Solicitud de la cual se reivindica prioridad, folios 38 a 73;
- 2° examen de forma folio 92;
- Solicitud del examen de patentabilidad, folios 94 y 95;
- Examen de patentabilidad Art-46, folios 150 a 152;
- Respuesta al examen de patentabilidad, folios 153 a 163.

2. Objeto de la invención:

La presente solicitud cuyo título es "PROCEDIMIENTO PARA LA PREPARACIÓN DE HIDROCLORURO DE FENILEFRINA"

El objeto de la solicitud es un proceso de obtención de clorhidrato de fenilefrina.

El objeto de la invención se puede clasificar según la clasificación internacional como A61K 31/13

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: "*El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*
Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

No	Documento No.	Título	Fecha de Publicación
D1	Chemical and Pharmaceutical Bulletin, JP, Pharmaceutical Society of Japan.	Efficient asymmetric hidrogenation of alpha-amino ketone derivatives a highly enantioselectivo, synthsis of phenylefrine, levamisol, carnitine and propanolol.	01-may-1995

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.*"

En cumplimiento de este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

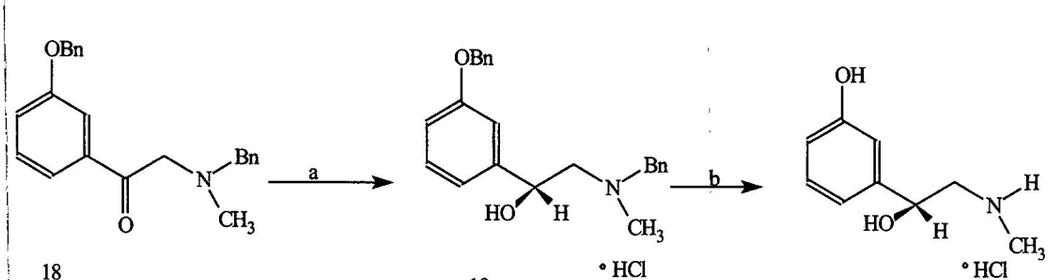
Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece:

"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica." "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida".

La solicitud en estudio se refiere a diferentes objetos, tales como un método para preparar una amina de la fórmulaVIIa; un método para preparar un epoxido de fórmula (Ia), un método para preparar un compuesto IIIa, un método para elaborar un compuesto de formula VI a , un metodo para elaborar un derivado morfolino, un cpmpuesto de fórmula IIIa, un compuesto de fórmula IV a, un compuesto de fórmula IV, un compuesto de fórmula Va un compuesto de fórmula V.

-La anterioridad D1 describe un proceso par ala obtención del clorhidrato de L-fnilefrina el cual cumple los pasos de:



18 19 • HCl • HCl

(R)clorhidrato de fenilefrina.

Parte de un compuesto β ceto amino, sobre el cual se hace una hidrogenación asimetrica selctiva, luego se hace una desbencilación reductiva con paladio he hidrógeno, para obtener la correspondiente (R) clorhidrato de fenilefrina. Esta explicitamente descrito en el folio 157 (pag 741), columna de la izquierda, y folio 160 (pag 744) penultimo parrafo, de D1. Cuando se comparan los dos proceso son iguales entre sí, porque parten de los mismos derivados β ceto amino, con las mismas etapas y los mismos catalizadores, para obtener el (R)clorhidrato de fenilefrina , por lo tanto se considera que la solicitud en estudio no tiene novedad.

No.	Documento	Reivindicaciones Afectadas	Requisito que afecta
D1	Chemical and Pharmaceutical Bulletin, JP, Pharmaceutical Society of Japan.	1 a 23	Novedad

En cumplimiento del artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese conforme a lo dispuesto en el numeral 5.2, literal e), del capitulo 5° del titulo 1° de la Circular Única n°. 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL.
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 27 ENE 2005

CONCEPTO TÉCNICO No. 90	EXAMINADOR TÉCNICO Código: 202012