Preparation and Properties of Some Prochiral and Chiral Precursors of S-3-(3-Hydroxyphenyl)-1-propylpiperidine (S-3-PPP)

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Various synthetic approaches to 2,3-dehydro- and 3,4-dehydro-1-propio-nylpiperidines **12,13** and to their 1-propyl congeners **14,15**,-two pairs of unsaturated, regioisomeric precursor of S-(-)-3-PPP [S-(-)-3-(3-hydroxyphe-nyl)-1-propylpyperidine, **20**] were investigated. Compounds **12** and **13** were prepared by regioselective elimination of water in **11**. Preparation of **14** and **15** by two different methods is described. The ratio of the E/Z isomers at the C(O)-N bond in **11–13** was determined by ^{13}C-NMR, and separation of the enantiotopic ^{1}H-NMR signals in the enantiomers of **18** and **19** was investigated with chiral shift reagent Eu(tfc)$_3$. Hydrogenation of **15** was performed with five different Rh(l) catalytic complexes, affording the O-methyl-conge-ner of 3-PPP **19**. Complete conversion of **15** into **19** was only achieved at elevated temperature and/or pressure to give the R- or S-isomer with low enantioselectivity (7–18% e.e.).

INTRODUCTION

Since Hjorth et al.[1] showed for (±) 3-(3 hydroxyphenyl)-1-propylpiperidine (3-PPP, **20**) to be a selective presynaptic agonist at central dopamine D2 receptors, several synthetic routes to a series of 3-aryl-piperidines were elaborated. Loozen and Brands[2] described the synthesis of various 3-arylpiperidines starting from 3-methoxyphenylacetonitrile. Langham *et al.*[3] condensed lithiated 2-propylpiperidone with 2-bromo-3-methoxycyclohexen-1-one, and in a few additional steps converted the resulting bromo-enone into 3-PPP. Nickel(II) catalyzed cross coupling of aryl magnesium bromides with 3-bromo-pyridine, followed by quaternization and hydrogenation of the pyridine ring, was used in preparation of 3- PPP and some congeners[4,5]. After demonstration that a more interesting biological activity is contained in the (-)-enantiomer

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of 3-PPP[6], much attention has been paid to the preparation of pure enantiomers and determination of their absolute configuration. All cited preparations, however, were either non-enantioselective, and racemic 3-PPP was separated by the traditional methods[4,5,7,8], or started from the chiral, optically active materials and led stereoselectively to the pure enantiomers of 3-PPP[5].

There is only a brief note in the literature that an achiral rhodium(I) complex with triphenylphosphine (Wilkinson's catalyst) gave sluggish hydrogenation of an unsaturated precursor of 3-PPP[9]; not a single example of the application of chiral homogeneous catalysts[10] is reported, however. Related to our recent project on the synthesis and evaluation of new catalytic complexes for hydrogenation, with chiral ligands derived either from the most widespread monosaccharides[11-14] or alpha-aminoacids[15], we have undertaken preparation of **12–15**, structurally isomeric, prochiral precursors of (-)-3-PPP in order to evaluate them as substrates for enantioselective hydrogenation.
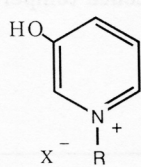
RESULTS AND DISCUSSION

Two isomeric 1-propionyl-tetrahydropyridine derivatives, **12** and **13**, were our first synthetic goal. Compound **12**, although N-acylenamine, cannot be expected to behave, on complexation, as a bidentate substrate because of the forced transoid relation around N(1)–C(2)-bond between the amide carbonyl group and the double C=C bond in the ring[16]. Moreover, steric impediment of the endocyclic double bond could make it unaccessible to coordination, as already noticed for similar structures[17]. Due to the absence of extended conjugation, present in **12**, regioisomer **13** seemed a more reactive substrate for hydrogenation. With similar argumentation in mind, preparation of the second pair of isomeric substrates **14/15** was undertaken.

Preparation of **8–11** started from the commercially available 3-hydroxypyridine **1**, or 3-hidroxypiperidine hydrochloride **3**. N-Alkylated and saturated derivatives **4** and **5** were oxidized into **6** and **7**. Compounds **8** and **9** were obtained via Grignard reaction of **6** and **7** with 3-methoxyphenyl-magnesium bromide. To obtain **11**, common intermediate for **12,13** and **14**, N-benzyl group in **9** was hydrogenolyzed and the resulting **10** was acylated. Some transformations outlined above were found superficially described, and the intermediates incompletely (or not at all) characterized in the literature and patents.
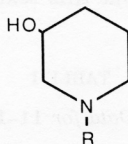
From the structurally isomeric compounds **12** and **13**, only **12** was previously described[9]. It was isolated in 35% yield as the only product of elimination of water from **11** with P_2O_5. We tried elimination of water with various dehydrating agents in order to obtain both isomers **12/13** from the common precursor **11**. In all experiments, formation of both isomers was observed; their ratio depended on the reaction conditions. With P_2O_5 in xylene, **12** prevailed over **13** (ca. 4:1, 50–55% yield). Acetylchloride in acetic acid afforded **13** prevalently (2:1, 80% yield). In both cases, the optimal reaction time was ca. 30 min. and its extension lowered the yield of both products.

According to the described procedure[9], we prepared, starting from **12**, compound **14** in 5.5% yield only. The reaction mixture contained larger quantities of side products, from which two were isolated, by preparative tlc chromatography, but could not be identified. Repeated reduction with freshly prepared and filtered $LiAlH_4$-solution didn't afford any result.

An interesting feature of N-propionyl derivatives **11–13** and **18** is their low conformational mobility around the amide C–N bond, which allows identification of the
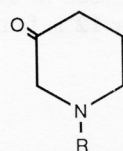
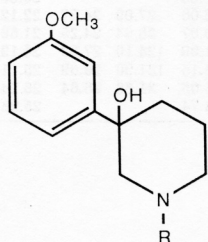|	R	X
1	nill	
2	CH₂CH₂CH₃	Br

Compounds 1–2:

	R	X
1	nill	
2	$CH_2CH_2CH_3$	Br

Compounds 3–5:

	R
3	H
4	$CH_2CH_2CH_3$
5	CH_2Ph

Compounds 6–7:

	R
6	
7	

Compounds 8–11:

	R
8	$CH_2CH_2CH_3$
9	CH_2Ph
10	H
11	$COCH_2CH_3$

12

13

14
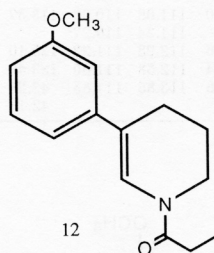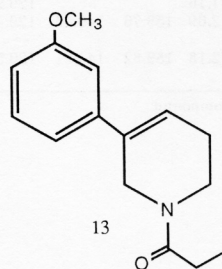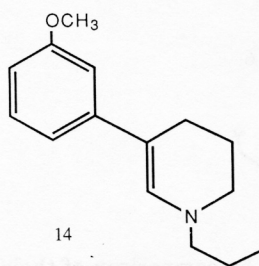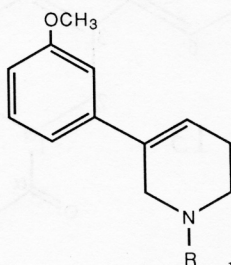
Compounds 15–16:

	R
15	$CH_2CH_2CH_3$
16	CH_2Ph
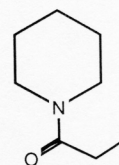
17
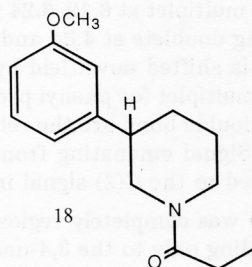
18

19

(-) - 20

E/Z isomers by ^{13}C-NMR spectra. Doubling of some characteristic signals in these compounds is observed at ambient temperature (Table I, in formula **13**, the numbering system used in Table I. and throughout this text is illustrated. Coalescence temperature for **12** is found at ca 50°C.

TABLE I

^{13}C-NMR Data for **11–13** and **18**

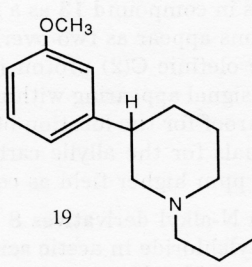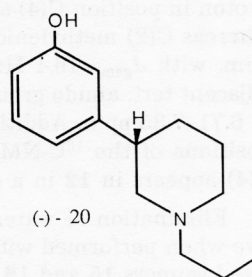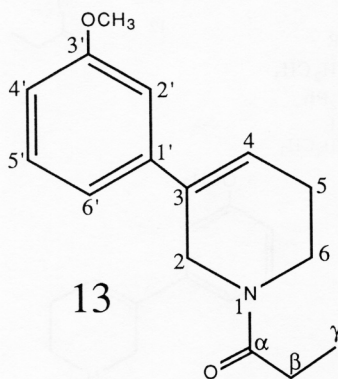|	δ in ppm														
C*	C(α)	C(3')	C(1')	C(5')	C(6')	C(2')	C(4')	C(3)	C(2)	-OCH3	C(6)	C(4)	C(5)	C(β)	C(γ)
11	173.83	159.65	147.69	129.29	117.21	112.42	111.18	71.84	56.49 56.26	55.19	45.99+ 41.99	36.69	26.47	22.12 20.88	9.48
12	171.39 171.16	159.81	141.65	129.40 129.24	117.10	111.68 111.34	110.95 110.27	118.57	122.80 121.84	55.14	43.06 40.07	27.09 26.64	24.77 24.25	22.12 21.56	9.14
13	172.69	159.76	140.46	129.40	117.66 117.44	112.98 112.58	111.23 111.00	135.10 133.46	46.45 43.40	55.19	41.99 38.15	124.10 121.90	27.03 26.69	26.13 25.11	9.14
18	172.18	159.82	144.81	129.57	119.36	113.85	111.85	42.38 42.16	52.43 48.42	55.19	46.05 43.74	31.88	26.64	26.24 25.28	9.59

C* – Compound

The position of the double bond in **13** was determined by comparison of their ^{1}H- and ^{13}C-NMR spectra with those of isomer **12**[9]. The signal arising from the olefinic proton in position C(4) appears in compound **13** as a sharp multiplet at 6.12–6.24 ppm, whereas C(2) methylenic protons appear as two overlapping doublets at 4.34 and 4.36 ppm, with $J_{gem} = 16.1$ Hz. The olefinic C(2) proton in **12** is shifted downfield by the adjacent tert. amido group, its signal appearing within the multiplet for phenyl protons at 6.71–7.35 ppm. Additional proof for the location of the double bond are the relative positions of the ^{13}C-NMR signals for the allylic carbons. Signal emanating from the C(4) appears in **12** in a ca. 18 ppm higher field as compared to the C(2) signal in **13**.

Elimination of water from N-alkyl derivatives **8** and **9** was completely regioselective when performed with acetylchloride in acetic acid, leading only to the 3,4-unsaturated isomers **15** and **16**. The considerable quantity of impurities required purification of crude **15** and **16** by column chromatography. Regioisomers **14** and **15** were also prepared by independent methods[9,5], and the structure of **15** obtained by elimination of water from **8** was confirmed by a comparison of the spectroscopic data.

LIS ^{1}H-NMR Study of Racemic 18 and 19

Since the enantiomerically enriched precursors of (-)-3-PPP, **18** and **19**, were envisaged as products of enantioselective hydrogenation of their respective prochiral precursors **12/13** and **14/15**, respectively, ^{1}H-NMR spectra of racemic **18** and **19** were examined in the presence of the chiral shift reagent Eu(tfc)$_3$.[19,20] Optically pure **18** has not been described, and therefore the chiral LIS method appears as the method of choice for determination of enantiomeric excess[19,20]. In Figures 1–3 the plots of δ values for specific protons in **18** and **19** vs. LSR/substrate ratio are presented.

As expected, amide **18** is the stronger binding ligand, with carbonylic oxygen as the binding site[21,22]. Different sensitivity of the two diastereotopic methylene groups at C(2) and C(6) to the variation of LSR concentration reflects in particular this coordination. Already in the absence of LSR, C(2) and C(6) H_A, H_B, diastereotopic protons in **18** and **19** form two well separated multiplets due to the low conformational mobility of the piperidine ring bearing the 3-(3'-methoxy) phenyl group in equatorial position. Two discrete signals appear also for the enantiotopic protons Ha,Hb in the spectrum of model compound **17**, indicating that N-acylation of piperidine raises nonequivalence of *gem* ring protons at ambient temperature*. Protons H_A and H_B on C(2) in the enantiomers of **18**, enantiotopic through external comparison, are well separated on addition of Eu(tfc)$_3$[23] (Figure 1). Due to the lower coordinating ability of **19**, analogous signals are not separated on addition of chiral LSR. It is also interesting that
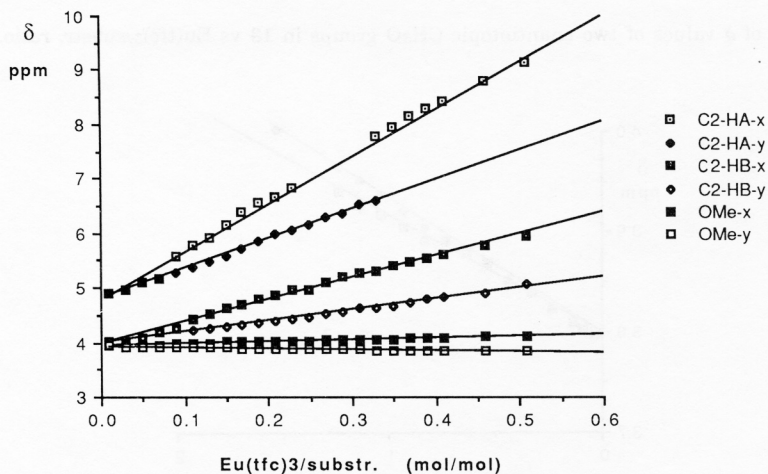
Fig. 1. Plot of δ values for various protons in **18** vs Eu(tfc)$_3$/substr. ratio. x and y denote pairs of enantiotopic protons.

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*Note: According to the referee's suggestion, we assign enantiotopic methylene protons in **3–5** and **12–17** as C$_{Ha,Hb}$, and diastereotopic methylene protons in **8–11** and **18–20** as C$_{HA,HB}$. Both assigments are based on internal comparison[23]. However, C$_{HA,HB}$ protons within one enantiomer of **8–11** and **18–20** are enantiotopic through external comparison to corresponding protons in the other enantiomer.

in the enantiomers of **18** and **19**, Eu(tfc)$_3$ rises splitting of the signal for the two methoxy groups which are also enantiotopic through external comparison[23] (Figures 2 and 3). Their respective singlets exhibit opposite directions of the induced shifts, as already noticed for some lanthanide complexes of racemic compounds[24]. This effect is less pronounced for **19**; the concentrations of the chiral LSR higher than 0.8 M were required to separate the two methoxy signals.
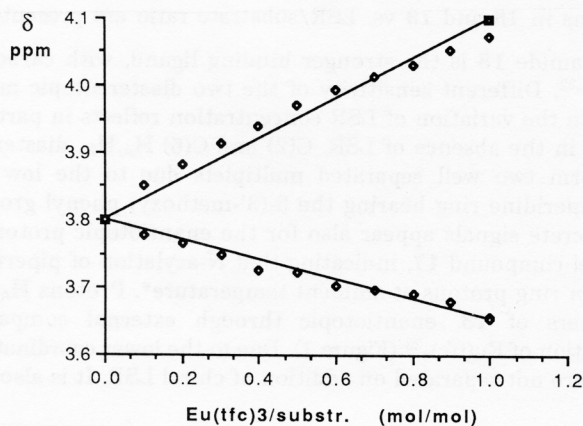
Fig. 2. Plot of δ values of two enantiotopic CH$_3$O groups in **18** vs Eu(tfc)$_3$/substr. ratio.
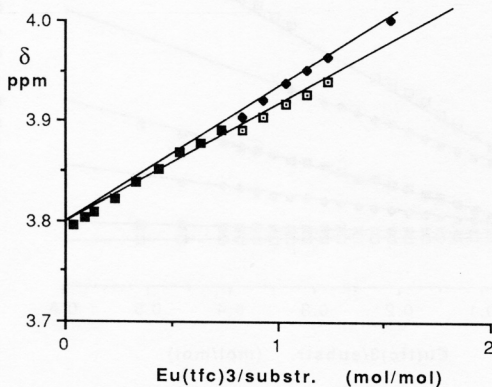

Fig. 3. Plot of δ values of two enantiotopic CH$_3$O groups in **19** vs Eu(tfc)$_3$/substr. ratio.

The large difference in the shifts of C-(2)-H$_A$,H$_B$ and Ar-OCH$_3$ protons in the complex of **18**, and virtually absent separation of C(6)-H$_A$,H$_B$ signals, indicate Z-conformation of the carbonyl group to the 3-substituent in the piperidine ring (Figure 4).
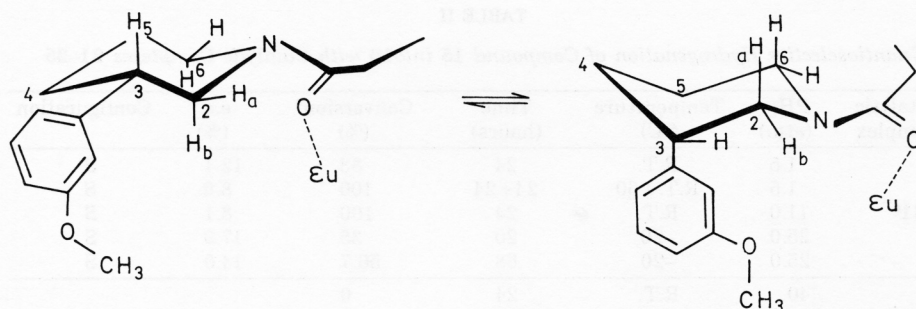
Fig. 4. Conformational equilibrium in **18**.

Different shifts of enantiotopic methoxy groups in the complex of racemic **18** can be explained by their proximity to the lanthanide bound to the carbonyl oxygen. This conformation seems to be preserved in the Eu(tfc)$_3$ complex of its C(α)-deoxo-analogue **19**, since the methoxy group still undergoes small shifts at high LSR/substrate ratios. Observation of the models confirms that the methoxyphenyl group should be in axial position in order to assure spatial proximity of methoxy protons to the bound lanthanide. This leads to inversion of the piperidine ring, which is known to require only ca. 15 kcal/mol[25,26] for N-alkylpiperidines. Generally, conformation of 3-phenyl group and N-propyl side chain in (-)-3-PPP[21] are shown by X-ray crystallography[5], and ^{13}C-NMR[24], to be »soft parameters«. The former method, however, revealed that the 3'-hydroxy group on the equatorially situated phenyl is on the side of the C(2) atom, as we observed for the LIS complex of **18** and **19**.

Enantioselective Hydrogenation

Although the sluggish reactivity of polysubstituted ethene derivatives in catalytic hydrogenation is known[28] and the only example of an effective catalyst for such substrates is reported by Noyori et al[17], we examined in hydrogenation of **12** and **15**. Some Rh(I) catalysts recently prepared in our laboratory. Preliminary experiments revealed that **15** can be reduced easier than **12**, because of the extended conjugation of the double bond in compound **12**. The first results obtained in hydrogenation of isomer **15** are summarized in Table II. The following chiral catalysts were used: Rh(I) [(2R,3R)-3,4-bis(diphenylphosphinoxy)tetrahydropyran, norbornadien]perchlorate (**21**)[11], Rh(I) [(2R,3R)-2-diphenylphosphinomethyl-3-diphenylphosphinotetrahydropyran, norbornadiene]perchlorate (**22**)[13], Rh(I) [7-bromo-1,3-dihydro-3-(S)-methyl-5-(pyrid-2'-yl)-2H-1,4-benzodiazepin-2-one,norbornadiene]perchlorate (**23**)[15], and Rh(I) [7-bromo-1,3-dihydro-3-(s)-benzyl-5-(pyrid-2-yl)-2H-1,4-benzodiazepin-2-one, norbornadien]perchlorate (**24**)[15], all prepared in our laboratory. The well-known Rh(I) complex of DIOP (**25**)[27] was used for comparison.

In some experiments, O-methyl-derivative of 3-PPP **19** was obtained from **15** in good to quantitative yields, but low enantioselectivity. These results can be explained by the forcing conditions of hydrogenation (pressure and temperature), regularly required to achieve reasonable hydrogenation rates (Table II). Our work is now oriented towards searching for new catalysts, based on dinitrogen ligands, more suitable for hydrogenation of various unsaturated substrates.

TABLE II

Enantioselective Hydrogenation of Compound **15** *into* **19** *with Catalytic Complexes* **21–25**

Catalytic Complex	PH_2 (atm)	Temperature (°C)	Time (hours)	Conversion[a] (%)	e.e.[b] (%)	Configuration
21[c]	1.5	R.T.	24	83	12.1	S
	1.5	R.T. + 60	24 + 24	100	8.6	S
	11.0	R.T.	24	100	8.1	S
	25.0	−20	20	35	17.9	S
	25.0	−20	68	56.7	14.0	S
22[d]	40	R.T.	24	0		
	40	40	24	0		
	40	60	24	0		
	60	R.T. + 60	20 + 70	100	0	
23[e]	1.5	R.T. + 60	20 + 48	90	0	
	10.0	R.T. + 40	20 + 24	100	0	
24[e]	10	40	20	100	7.3	R
25[c]	13	R.T.	24	0		
	20	60	24	100	10.0	R
	30	R.T.	20	100	8.5	R

[a] Based on chromatographic separation of **19**; [b]Enantiomeric excess was calculated by $[\alpha]_D^{20} = -6.50$ (c = 2.6, MeOH) for optically pure S-(-)-3-O-Me-PPPxHCl[5]; [c]Ratio catalyst-to-substrate 1:50, solvent: ethanol-benzene (1:1); [d]Ratio catalyst-to-substrate 1:100, solvent: ethanol-benzene (1:1); [e]Ratio catalyst-to-substrate 1:100, solvent: 0.3 M NaOH/MeOH.

EXPERIMENTAL

Melting points were determined on a Buechi mp apparatus (after Tottoli) and are not corrected. IR Spectra were obtained for potassium bromide pellets on a Perkin-Elmer Model 137 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded for solutions in $CDCl_3$ on a Joel FX 90Q Fourrier-transform spectrometer with tetramethylsilane as internal standard, unless otherwise stated. Optical rotations were measured with a Perkin-Elmer M 141 polarimeter at ambient temperature, using 1 dm cells. TLC was performed on Merck's DC-alufolien with silicagel 60 F_{254} and preparative thick layer (2 mm) chromatography on Kemika F_{254} plates. Column chromatography was run over granular silicagel 0.05–0.2 mm (Kemika). Flash column chromatography was performed with air as pressurizing gas, and using silicagel Merck, 0.040–0.063 mm (230–240 mesh ASTM). The spots were visualized by UV-illumination or by spraying with ninhydrin reagent. Eu(tfc)₃ was purchased from Aldrich, and was used without purification.

3-Hydroxy-1-propylpyridinium Bromide (**2**)

3-Hydroxypyridine (**1** 38.04 g, 400 mmol) and bromopropane (52.67 g, 428 mmol) in dry methanol (200 ml) was heated for 24 hours in a high-pressure steel vessel at 105°C. Evaporation of the solvent gave an oil (80 g), which crystallized while kept in refrigerator. IR: 3370 (broad), 2970 (broad), 1620, 1605, 1590, 1400 (broad), 1310, 1260, 1230, 1160, 1030, 810, 760, 680 cm⁻¹. ^{1}H NMR (DMSO): 8.89–8.83 [m, C(2)-H + C(6)-H], 8.26–7.97 [m, C(4)-H + C(5)-H], 4.74 [t, C(α)-2H, $J_{\alpha,\beta} = 7.0$], 2.12–1.80 [m, C(β)-2H], 0.91 [t, C(γ)-3H, $J_{\gamma,\beta} = 7.0$]. ^{13}C NMR (DMSO): 156.54 C(3), 135.50 C(4), 132.56 C(6), 131.15 C(2), 128.73 C(5), 61.68 C(α), 23.87 C(β), 9.87 C(γ).

3-Hydroxy-1-propylpiperidine (**4**)

Compound **2** (12 g, 54.6 mmol) was dissolved in methanol (20 ml) and hydrogenated for 5 hours over 5% Pt /C (720 mg) in a high-pressure steel vessel at 400 psi and 100°C. The catalyst was filtered off and solvent evaporated to give crude hydrobromide. It was dissolved in methanol and the

solution was made alkaline by adding Dowex 2x8, 50/100 mesh (100 g wet). After 1 hour stirring, the ion exchanger was filtered off. Evaporation afforded 6.19 g (78.8%) of yellow oil, which was distilled at 104–105°C/25 mm Hg, to give the analytically pure compound. IR: 3380 (broad), 2940, 2880, 2805, 2780, 1475, 1150, 1070, 975 cm^{-1} ^{1}H NMR: 3.81–3.66 [m, C(3)-H], 3.26 [broad s, shifted to higher field on heating at 50°C, C(3)-OH], 2.59 [dd, C(2)-H, $J_{2,2'}$ = 11.1 Hz, $J_{2,3}$ = 2.9 Hz], 2.37–2.21 [m, C(2')-H + C(6)-2H + C(α)-2H], 1.87–1.29 [m, C(4)-2H + C(5)-2H + C(β)-2H], 0.88 t, C(γ)-3H, $J_{\gamma,\beta}$ = 7.0 Hz]. ^{13}C NMR: 66.31 C(3), 61.06 C(2) or C(α), 60.78 C(α) or C(2), 53.50 C(6), 32.90 C(4), 22.74 C(5), 19.81 C(β), 11.96 C(γ).

1-Benzyl-3-hydroxypiperidine (5)

Compound 5 was prepared by a modified procedure[29], starting from 3(15.04 g, 109 mmol). This was dissolved in acetone (82 ml) and water (2 ml) and crude potassium carbonate (25 g, 230 mmol) and benzyl chloride (18 g, 142 mmol) were added. The resulting suspension was stirred for 22 hours at ambient temperature, the precipitate was filtered off and filtrate concentrated. The residue was dissolved in 10% aqueous HCl, the solution was extracted with ether, the aqueous layer made alkaline and the product extracted with ether. Washed and dried extracts afforded on evaporation 20.11 g (96.2%) of chromatographically pure yellow oil, b.p. 100–105°C/0.1 mm Hg. IR: 3400 (broad), 2940, 2800, 1455, 1155, 1060, 970, 740, 700 cm^{-1}. ^{1}H NMR: 7.29 (s, 5H, phenyl), 3.81 broad s, C(3)-OH], 3.50 (s, CH$_2$Ph), 2.47 [d, C(2)-2H], 2.33 [m, C(6)-2H + C(3)-H], 1.61 [m, C(4)-2H + C(5)-2H] ^{13}C NMR: 137.78, 129.13, 128.16, 127.03 (phenyl), 66.37 C(3), 62.98 (CH$_2$Ph) 60.44 C(2), 53.27 C(6), 32.17 C(4), 22.18 C(5).

1-Propyl-3-piperidone (6)

This compound was prepared following the method already described.[29,30] To a solution of 3-hydroxy-1-propylpiperidine 4 (9.9 g, 69 mmol) in acetone (138 ml) and AcOH (28 ml), a solution of CrO$_3$ (8.7 g, 75 mmol) in water (22ml) was added. The resulting mixture was cooled to 0°C and conc. H$_2$SO$_4$ (29 ml) was added dropwise under stirring and keeping the temperature at 0°C. During addition, the mixture became dark and after 5 hours stirring at 0°C dark green. It was made alkaline (pH 8) under cooling by dropwise addition of conc. aqueous ammonia (ca. 110 ml). The cold aqueous layer was extracted with ether, washed extracts were dried and concentrated in vacuo at room temperature. The resulting oil (6.5 g) darkened rapidly at room temperature and had to be kept in a freezer. It was distilled giving 5.6 g (57.4%) of yellow oil, b.p. 50–70 °C/0.75 mm Hg. IR: 3430 (broad), 2960, 2940, 2880, 2800, 2760, 1725 (C=O) cm^{-1}. ^{1}H NMR: 2.99 [s, C(2)-2H], 2.65 [t, C(6)-2H, $J_{6,5}$ = 5.3 Hz], 2.47–2.30 [C(4)-2H + C(α)-2H], 2.09–1.71 [m, C(5)-2H], 1.62–1.30 [m, C(β)-2H], 0.89 [t, C(γ)-3H, $J_{\gamma,\beta}$ = 7.0 Hz]. ^{13}C NMR: 206.66 C(3), 64.67 C(2) or C(α), 60.10 C(α) or C(2), 51.92 C(6), 38.71 C(4), 24.04 C(5), 19.92 C(β), 11.74 C(γ).

1-Benzyl-3-piperidine (7)

Preparation of ketone 7 by different synthetic routes[31,32] has already been described. It was obtained in 60.5% yield by oxidation of the corresponding aminoalcohol 5 as described for 6 IR: 3060, 3020, 2940, 2795, 2775, 1720 (C=O), 1490, 1450, 1320, 1230, 1120, 1070, 1040, 1000, 740, 695 cm^{-1}. ^{1}H NMR: 7.29 (s, 5H, phenyl), 3.58 (s, CH$_2$Ph), 3.01 [s, C(2)-2H], 2.65 [t, C(6)-2H, $J_{6,5}$ = 5.3 Hz], 2.38 [t, C(4)-2H, $J_{4,5}$ = 8.3 Hz], 1.88 [C(5)-2H]. ^{13}C NMR: 206.21 C(3), 136.85, 128.50, 127.88, 126.87 (phenyl), 64.05 (CH$_2$Ph), 62.02 C(2), 51.07 C(6), 38.26 C(4), 23.53 C(5).

3-Hydroxy-3-(3-methoxyphenyl)-1-propylpiperidine (8)

3-Methoxyphenyl magnesium bromide was prepared from MG (1.7 g, 70 mmol) and 3-bromoanisole (10.8 g, 58 mmol) in dry THF (36 ml) under nitrogen atmosphere at 30–35°C. The resulting solution was stirred at room temperature for 2 hours and then the solution of 1-propyl-3-piperidone 6 (4.1 g, 2.9 mmol) in THF (35 ml) was added dropwise maintaining a gentle reflux. Stirring was continued under nitrogen at room temperature for 16 hours. Saturated solution of ammonium chloride (ca. 25 ml) was added dropwise under cooling and filtered through celite. The filtrate was acidified with 2 M HCL, washed with ethylacetate, basified with conc. NaOH

and the separated base extracted with ethylacetate. The organic extract was dried and evaporated to yield 6.35 g (88%) of the pure oily product. IR: 3370, (broad), 2960, 2930, 2870, 2805, 1610, 1600, 1585, 1485, 1465, 1450, 1430, 1380, 1290, 1255, 1180, 1160, 1085, 1050, 1010, 780, 700 cm^{-1}. ^{1}H NMR: 7.34–6.98 (m, 3H, phenyl), 6.85–6.71 (m, 1H, phenyl), 3.90 [broad s, shifted to higher field on heating at 50 °C, C(3)-OH], 3.80 (s, -OCH$_3$), 2.95-2.77 [m, C(2)-2H], 2.44-1.28 [m, C(4,5,6,α,β)-10H], 0.89 [t, C(γ)-3H, $J_{\gamma,\beta}$= 7.0 Hz]. ^{13}C NMR: 159.53 C(3'), 147.69 C(1'), 128.95 C(5''), 116.93 C(6'), 110.67 C(4'), 70.99 C(3), 65.35 C(2), 59.88 C(6), 54.97 (-OCH$_3$), 53.22 C(α), 36.46 C(4), 22.01 C(5), 19.93 C(β), 11.79 C(γ).

1-Benzyl-3-hydroxy-3-(3-methoxyphenyl)piperidine (**9**)

Crude **9** was prepared using the same method as described for **8**. Purification on a silicagel column with dichlormethane-methanol-conc. ammonia (95 : 4.9 : 0.1) as eluent afforded pure product in 85.5% yield. IR: 3460 (broad), 3000, 2920, 2780, 1600, 1570, 1475, 1440, 1420, 1365, 1280, 1240, 1190, 1150, 1090, 1035, 990, 910, 770, 730, 690 cm^{-1}. ^{1}H NMR: 7.30–6.67 (m, 9H, 2x phenyl), 3.89 [broad s, C(3)-OH], 3.72 (s, -OCH$_3$)], 3.50 (s, CH$_2$Ph), 2.76–2.64 [m, C(2)-2H], 2.32–2.19 [m, C(6)-2H], 1.99–1.74 [m, C(4)-2H + C(5)-2H]. ^{13}C NMR: 159.25, C(3'), 147.18 C(1'), 137.53 + 128.73 + 128.61 + 127.99 + 126.86 [phenyl + C(5)], 116.71 C(6'), 111.85 C(2'), 110.44 C(4'), 70.83 C(3), 64.79 C(2), 62.30 C(6), 54.73 (-OCH$_3$), 52.65 C(1'), 36.06 C(4), 21.56 C(5).

3-Hydroxy-3-(3-methoxyphenyl)piperidine (**10**)

Compound **9** (13.07 g, 43.95 mmol) was dissolved in ethanol (150 ml) and hydrogenated at ambient temperature and atmospheric pressure with 10% Pd/C (1.5 g). After 21 hours, the catalyst was filtered off and the solvent evaporated. quantitative yield of a colourless oil was obtained, which solidified in refrigerator. IR: 3400 (broad), 2940, 1605, 1585, 1485, 1430, 1255, 1045, 780, 700 cm^{-1}. ^{1}H NMR: 7.37–6.76 (m, 4H, phenyl), 3.82 (s, -OCH$_3$), 2.85–2.65 [m, C(2)-2H + C(6)-2H + C(3)-OH + NH], 1.87–1.31 [m, C(4)-2H + C(5)-2H], ^{13}C NMR: 159.37 C(3'), 148.02 C(1'), 120.90 C(5'), 116.82 C(6'), 111.97 C(2'), 110.55 C(4'), 70.35 C(3), 57.56 (-OCH$_3$), 54.97 C(2), 45.83 C(6), 36.51 C(4), 22.18 C(5).

3-Hydroxy-3-(3-methoxyphenyl)-1-propionylpiperidine (**11**)

Compound **10** (10.59 g, 51 mmol) was dissolved in methanol (165 ml), and propionic anhydride (8.44 g, 65 mmol) was added. After stirring at room temperature for 1 hour, the solvent was evaporated and the residue partitioned between chloroform and 2N sodium carbonate. The organic layer was dried, concentrated and crude oil was purified on a silicagel column using dichlormethane-methanol (96 : 4) as eluant to afford a pure product (9.35 g, 62.1%). IR: 3400 (broad), 2940, 1625 (broad), 1460 (broad), 1290, 1260, 1170, 1145, 1080, 1050, 1015, 785, 700 cm^{-1}. ^{1}H NMR: 7.35–6.99 (m, 3H, phenyl), 6.86–6.74 (m, 1H, phenyl), 4.71–4.33 [m, C(2)-H$_A$], 3.90–3.60 [m, C(2)-H$_B$], 3.79 (s, -OCH$_3$), 3.31–2.95 [m, C(3)-OH + C(6)-2H], 2.40 [q, C(β)-2H, $J\beta,\gamma$= 7.3 Hz], 2.08-1.57 [m, C(4)-2H + C(5)-2H], 1.12 [t, C(γ)-3H, $J_{\gamma,\beta}$= 7.3 Hz]. ^{13}C NMR: see Table I.

3-(3-Methoxyphenyl)-1-propionyl-1,4,5,6-tetrahydropyridine (**12**) *and*
3-(3-Methoxyphenyl)-1-propionyl-1,2,5,6-tetrahydropyridine (**13**)

Method A: To a stirred solution of compound **11** (5.05 g, 19.2 mmol) in xylene (106 ml), phosphorus pentoxide (4.03 g, 28,3 mmol) was added in portions. The mixture was refluxed for 30 minutes, the solution was separated by decantation and the precipitate washed with chloroform. The combined, washed, dried and concentrated organic layer left a crude product which was chromatographed on silicagel column with chloroform-ethylacetate-petrolether (5 : 2 : 3) as eluant to afford 1.98 g (42%) of pure compound **12**, R$_f$ 0.5, and 0.52 g (11%) isomer **13**, R$_f$ 0.25 (dichlormethane-ethylacetate 19 : 1).

Compound **12** was crystallized from cyclohexane, m.p. 55–56°C. IR: 2940, 1655, 1645, 1600, 1590, 1500, 1475, 1460, 1430, 1405, 1375, 1310, 1290, 1200, 1185, 1080, 1040, 1015, 975, 895, 860, 840, 820, 795, 750, 690 cm^{-1}. ^{1}H NMR: 7.35–6.71 [m, 5H, phenyl + C(2)-H], 3.82 (s, -OCH$_3$),

3.82–3.56 [m, C(6)-2H], 2.65–2.43 [m, C(4)-2H + C(β)-2H], 2.08–1.89 [m, C(5)-2H], 1.20 [t, C(γ)-3H, $J_{\gamma,\beta}$ = 7.3 Hz]. ^{13}C NMR: see Table I.

Compound **13** was rechromatographed on preparative tlc plates using the same eluant as for column chromatography. Trituration with acetone yielded analytically pure **13** m.p. 56–57 °C. IR: 3479 (broad), 2940, 1650 (broad), 1605, 1585, 1450 (broad), 1380, 1295, 1260, 1205, 1170, 1050, 785, 765, 700 cm^{-1}. ^{1}H NMR: 7.41–6.69 (m, 4H, phenyl), 6.24–6.12 [sharp m, C(4)-H], 4.36 [d, C(2)-H$_a$], 4.34 [d, C(2)-H$_b$, J_{gem} = 16.1 Hz], 3.81 (s, -OCH$_3$), 3.74 [t, C(6)-H$_a$,$J_{a,5}$ = 5.9 Hz], 3.57 [t, C(6)-H$_b$, $J_{b,5}$ = 5.9 Hz], 2.55–2.30 [m, C(5)-2H + C(β)-2H], 1.18 [t, C(γ)-3H, $J_{\gamma,\beta}$ = 7.3 Hz]. ^{13}C NMR: see Table I.

Anal.   Calc'd for $C_{15}H_{19}NO_2$ (245.32):   C 73.44 %, H 7.81 %, N 5.71 %.
    Found: C 73.66 %, H 7.86 %, N 5.88 %.

Method B: Solution of compound **11** (1.96 g, 7.44 mmol) in AcOH (21.5 ml) and acetylchloride (21.5 ml) was refluxed for 30 minutes under nitrogen. The evaporation residue was partitioned between chloroform and conc NaOH. The organic layer was washed, dried and evaporated to a brown oil. Chromatography on silicagel column with dichlormethane-methanol (94 : 4) as eluant yielded 0.51 g (27.8%) of isomers **12** and 1.13 g of the mixture **12 + 13**, which was rechromatographed to afford 0.98 g (53.6%) of pure compound **13**.

3-(3-Methoxyphenyl)-1-propyl-1,2,5,6-tetrahydropyridine (**15**)

3-Hydroxy-3-(3-methoxyphenyl)-1-propylpiperidine **8** (5.25 g, 21.1 mmol) and AcCl (25 ml) were refluxed in AcOH (25 ml) for 2.5 hours under nitrogen. The solvent was evaporated, the residue dissolved in water, basified with conc. NaOH and the crude product extracted with dichlormethane. Organic extracts were washed with water, dried, evaporated and the residual oil (5.12 g) purified on a silicagel column with chloroform-methanol 97 : 3 as eluant affording 2.43 g (50%) of pure product. IR: 2970, 2940, 2840, 2815, 1605, 1585, 1490, 1470, 1290, 1215, 1170, 1140, 1055, 965, 850, 780, 765, 700 cm^{-1}. ^{1}H NMR: 7.31–7.13 [m, C(5')-H], 6.98–6.70 [m, C(6')-H + C(2')-H + C(4')-H], 6.15–6.06 [m, C(4)-H], 3.79 (s, -OCH$_3$), 3.35–3.27 [m, C(2)-2H], 2.68–2.23 [m, C(6)-2H + C(α)-2H + C(5)-2H], 1.74–1.71 [m, C(β)-2H], 0.94 [t, C(γ)-3H, $J_{\gamma,\beta}$ = 7.0 Hz], ^{13}C NMR: 159.59 C(3'), 141.88 C(1'), 135.44 C(3), 129.18 C(5'), 122.75 C(4), 117.61 C(6'), 112.13 C(2'), 111.06 C(4'), 60.55 C(α), 55.14 (-OCH$_3$), 54.95 C(2), 49.60 C(6), 26.47 C(5), 20.32 C(β), 12.02 C(γ).

3-(3-Methoxyphenyl)-1-benzyl-1,2,5,6-tetrahydropyridine (**16**)

This compound was obtained in 73.4% yield starting from **9**, following the method described for **15**. IR: 2940 (broad), 1740, 1605, 1590, 1495, 1430, 1370, 1240, 1045, 780, 740, 700 cm^{-1}. ^{1}H NMR: 7.46–6.72 (m, 9H, 2x phenyl), 6.18–6.08 [m, C(4)-H], 3.79 (s, -OCH$_3$), 3.69 (s, CH$_2$Ph), 3.43 [m, C(2)-2H, J = 2.3 Hz], 2.69–2.58 [m, C(6)-2H], 2.36 [broad s, C(5)-2H]. ^{13}C NMR: 158.97 C(3'), 141.03 C(1'), 137.53 + 128.45 + 127.60 + 126.47 [phenyl + C(5')], 134.65 C(3), 123.07 C(4), 116.87 C(6'), 111.51 C(2'), 110.39 C(4'), 62.02 C(2), 54.35 (-OCH$_3$), 54.01 C(6), 48.42 CH$_2$Ph, 25.68 C(5).

1-Propionylpiperidine (**17**)

A solution of piperidine (0.85 g, 10 mmol) and propionic anhydride (3.0 g, 23 mmol) in methanol (20 ml) was stirred for 20 hours at ambient temperature. The solution was concentrated, excess of propionic anhydride hydrolyzed by stirring in aqueous 2 M K$_2$CO$_3$. Then reaction mixture was neutralized with 2 M HCl and the crude product extracted with chloroform. Organic extract was dried and evaporated to yield 1.22 g (86.5 %) of pure product. IR: 3520 (broad), 2990, 2940, 2860, 1645, 1445, 1255, 1230, 1140, 1080, 1020 cm^{-1}. ^{1}H NMR: 3.60–3.50 [m, C(2), C(6)-2H$_a$], 3.44–3.38 [m, C(2), C(6)-2H$_b$], 2.37 [q, C(β)-2H, $J_{\gamma,\beta}$ = 7.3 Hz], 1.60 [broad s, C(3),C(5)-4H + C(4)-2H], 1.14 [t, C(γ)-3H, $J_{\gamma,\beta}$ = 7.3 Hz]. ^{13}C NMR: 171.39 C(α), 45.88 + 42.04 [C(2),C(6)], 25.90 [C(3), C(5)] 25.06 C(4), 23.98 C(β), 8.97 C(γ).

3-(3-Methoxyphenyl)-1-propionylpiperidine (18)

Compound **11** (150 mg, 0.61 mmol) was hydrogenated over PtO_2 x H_2O (80–85% Pt, 10 mg) in methanol (7 ml) at 60 °C and 40 atm for 18 hours. The catalyst was filtered off, the solvent was removed under reduced pressure , and the product separated by preparative tlc (dichlormethane-methanol 99 : 1, three developments, recovery with acetone). Besides the starting material (46 mg, 30.7%, R_f 0.43, strong UV absorption), product **18** was obtained in 39.3% (62 mg) yield, R_f 0.29 (weak UV absorption). IR: 3440 (broad), 2940, 2860, 1650 (broad), 1620, 1610, 1590, 1500, 1475, 1440,1380, 1330, 1295, 1260, 1200, 1165, 1130, 1080, 1055, 990, 860, 830, 790, 755, 705 cm^{-1}. ^{1}H NMR: 7.29–7.17 (m, 1H, phenyl), 6.85–6.76 (m, 3H, phenyl), 4.80–4.71 [m, C(2)-H_A], 3.97–3.80 [m, C(2)-H_B], 3.80 (s, -OCH_3), 3.04 [t,C(6)-H_A], 2.63 [broad s, C(6)-H_B + C(3)-H], 2.37 [q, C(β)-2H, $J_{\beta,\gamma}$ = 7.9 Hz], 2.10–2.45 [m, C(4)-2H + C(5)-2H], 1.15 [t, C(γ)-3H, $J_{\gamma,\beta}$ = 7.9 Hz]. ^{13}C NMR: see Table I.

3-(3-Methoxyphenyl)-1-propylpiperidine (19)

Compound **15** (168 mg, 0.73 mmol) was hydrogenated over 10% Pt/C (16 mg) in ethanol (15 ml) at 60 °C and 40 atm for 22 hours. The catalyst was filtered off and the solvent evaporated. The yellow oil, obtained in a quantitative yield, afforded by preparative tlc chromatography (methanol-chloroform 19.5 : 0.5) an analytically pure product. IR: 2940 (broad), 2810, 1770, 1620, 1610, 1590, 1495, 1475, 1460, 1440, 1380, 1325, 1290, 1270, 1190, 1170, 1145, 1095, 1055, 875, 780, 700 cm^{-1}. ^{1}H NMR: 7.30–7.12 (m, 1H, phenyl), 6.86–6.67 (m, 3H, phenyl), 3.79 (s, -OCH_3), 3.10–2.80 [m, C(2)-2H + C(3)-H], 2.35–2.20 [m, C(6)-2H], 1.90–1.25 [m, C(α)-2H + C(4)-2H + C(5)-2H + C(β)-2H], 0.89 [t, C(γ)-3H, $J_{\gamma,\beta}$ = 7.3 Hz]. ^{13}C NMR: 159.65 C(3'), 146.56 C(1'), 129.24 C(5'), 119.64 C(6'), 113.26 C(2'), 111.29 C(4'), 61.29 C(2) or C(6), 61.7 C(6) or C(2), 55.08 (-OCH_3), 53.95 C(α), 43.00 C(3), 31.66 C(4), 25.79 C(5), 20.09 C(β), 12.02 C(γ).

Hydrogenation Experiments

The catalytic complex **21** was freshly prepared from [Rh(NBD)$_2$]ClO$_4$ complex and diphenyl-phosphinite[11]. The other four Rh(I) complexes **22–25** were prepared previously[13,15,27]. Deaerated solutions of complexes **21,22** and **25** (Table II) were stirred under nitrogen for 30 minutes, then substrate **12** or **15** was added, and the mixture was repeatedly spilled with hydrogen. Activation of the dissolved catalytic system **23** and **24** was performed before addition of the substrate by stirring under hydrogen for 60 minutes. All experiments were performed in a Parr all-purpose bomb, 25 ml volume.

The solvent was removed *in vacuo*, the residue dissolved in light-petroleum, filtered, concentrated, and submitted to preparative tlc chromatography (chloroform-methanol 19:1) to afford pure **19** (Table II).

REFERENCES

1. S. Hjorth, A. Carlsson, H. Wilstroem, P. Lindberg, D. Sanchez, U. Hacksell, L. E. Arvidsson, U. Svensson, J. L. G. Nilsson, *Life Sciences* **28** (1981) 1225.
2. H. J. J. Loozen, F. T. L. Brands, *J. Roy. Neth. Chem. Soc. (Rec. Tray Chim. Pays-bas)* **100** (1981) 333.
3. B. J. Langham, R. J. Shephend, A.C. White, *Chem. and Ind.* **1983** 168.
4. U. Hacksell, L.-E. Arvidsson, U. Svensson, J.G.L. Nilsson, D. Sanchez, H. Wilstroem, P. Lindberg, S. Hjorth, A. Carlsson, *J. Med. Chem.* **24** (1981) 1475.
5. S. O. Thorberg, L. Gawell, I. Csoeregh, and J. G. L. Nilsson, *Tetrahedron* **41** (1985) 129.

6. S. Hjorth, A. Carlsson, D. Clark, K. Svensson, H. , D. Sanchez, P. Lindberg, U. Hacksell, L. E. Arvidsson, A. J. Johansson, J. G. L. Nilsson, *Psychopharmacology* **81** (1983) 89.
7. H. Wilstroem, D. Sanchez, P. Lindberg, U. Hacksell, L.-E. Arvidsson, A. M. Johansson, S.O. Thorberg, J. L. G. Nilsson, K. Svensson, S. Hjorth, D. Clark, A. Carlsson, *J. Med. Chem.* **27** (1984) 1030.
8. W. Arnold, J. J. Daly, R. Imhof, E. Kyburz, *Tetrahedron Lett.* **24** (1983) 343.
9. S. O. Thorberg, L. Johansson, L. Gawell, C. Stahlberg, *Labeld Compd. and Radiopharm.* **23** (1986) 927.
10. H. B. Kagan, in »*Assymetric Synthesis*«, Vol. **5**, *Chiral Catalysis* (J.D. Morrison Ed.), Academic Press Inc., 1985, pp. 1–35.
11. I. Habuš, Z. Raza, V. Šunjić, *J. Mol. Catal.* **42** (1987) 173.
12. G. Snatzke, Z. Raza, I. Habuš, V. Šunjić, *Carbohydr. Res.* **182** (1988) 172.
13. I. Habuš, Z. Raza, V. Šunjić, *Croat. Chem. Acta* **61** (1988) 857.
14. V. Šunjić, I. Habuš, G. Snatzke, *J. Organomet. Chem.* **370** (1989) 295.
15. a.) V. Šunjić, Z. Raza, D. Šepac, G. Snatzke, *Third International Conference on Circular Dichroism Spectroscopy*, Prague, August 21–25, 1989., b.) P. Čudić, B. Klaić, Z. Raza, D. Šepac, V. Šunjić, *Tetrahedron* **47** (1991), in press.
16. Ref. 10. pp. 44–45.
17. R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, H. Takaya, *J. Am. Chem. Soc.* **108** (1986) 7117.
18. Ger. Offen. DE 3,149703, *Chem. Abstr.* **97** (1982) P 127510 z.
19. A. F. Cockerill, G. L. O. Davis, R. C. Harden, D. M. Rackham, *Chem. Rev.* **73** (1973) 553.
20. M. D. McCreary, D. W. Lewis, D. L. Wernick, G. M. Whitesides, *J. Am. Chem. Soc.* **96** (1974) 1038. '
21. L. R. Isbrandt, M.T. Rogers, *J. C. S. Chem. Commun.* **1971**, 3583.
22. V. Šunjić, A. Lisini, A. Sega, T. Kovač, F. Kajfež, B. Ruščić, *J. Heterocycl. Chem.* **16** (1979) 757.
23. K. Mislow, M. Raban, *Top. Stereochem.* **1** (1967) 1.
24. J. Reuben, *J. C. S. Chem. Commun.* **1979**, 68.
25. T. A. Crabb, A. R. Katritzky, *Adv. Heterocycl. Chem.* **36** (1984) 1.
26. D. A. Forsyth, V. Prapansiri, *J. Am. Chem. Soc.* **111** (1989) 4548.
27. H. B. Kagan, T. P. Dang, *J. Amer. Chem. Soc.* **94** (1972) 6429.
28. K. E. Koenig, in »*Asymmetric Synthesis*«, Vol. **5**, *Chiral Catalysis* (J.D. Morrison Ed.), Academic Press Inc, pp. 73–77.
29. A. Balsamo, A. Lapucci, B. Macchia, F. Macchia, R. Ceserani, D. Longiave, *Eur. J. Med. Chem., Chim. Ther.* **16** (1981) 63.
30. M. A. Iorio, P. Ciuffa, G. Damia, *Tetrahedron* **26** (1970) 178.
31. B. M. Iselin, K. Hoffmann, *Helv. Chem. Acta* **37** (1954) 178.
32. P. Krogsgard-Larsen, H. Hjeds, *Acta Chim. Scand.* **P 30** (1976) 884.

SAŽETAK

Priprava i svojstva nekih prokiralnih i kiralnih prekursora (-)-3-PPP

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Istraživane su razne metode priprave nezasićenih, regioizimernih prekursora (-)-3-PPP [3-(3-hidroksifenil)-1-propionilpiperidina **20**]. 2,3-Dehidro- i 3.4-dehidro-1-propionil-piperidini **12** i **13** dobiveni su regioselektivnom eliminacijom vode iz spoja **11**, dok su odgovarajući 1-propil-spojevi, osim eliminacijom vode iz spoja **8**, dobiveni i drugim sintetskim putem. ^{13}C-NMR spektroskopijom određen je odnos E/Z konformera oko C-N-amidne veze u spojevima **11**–**13** i **18**. Također je istraživano odjeljivanje enantiotopnih ^{1}H-NMR signala u enantiomernim parovima **18** i **19** s pomoću kiralnog reagensa Eu(tfc)$_3$.