Pergamon

Tetrahedron 57 (2001) 1631–1637

TETRAHEDRON

Rhodium catalyzed hydroformylation of 1,1-bis(*p*-fluorophenyl)allyl or propargyl alcohol: a key step in the synthesis of *Fluspirilen* and *Penfluridol*

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Received 14 September 2000; revised 16 November 2000; accepted 7 December 2000

Abstract—*Fluspirilen* (**1**) and *Penfluridol* (**2**), two neuroleptic agents, belong to a wide class of pharmaceuticals that contain in their molecules a 4,4-bis(*p*-fluorophenyl)butyl group bound to a nitrogen atom of a pyrrolidine, piperidine or piperazine moiety. A key intermediate for the synthesis of compounds **1** and **2**, 4,4-bis(*p*-fluorophenyl)butylbromide (**15**), has been prepared starting from commercially available 4,4′-difluorobenzophenone (**7**) following a preparative route involving the rhodium catalyzed hydroformylation in toluene or in the biphasic system toluene/water or cyclohexane/water of 1,1-bis(*p*-fluorophenyl)-2-propenol (**8**) and/or 1,1-bis(*p*-fluorophenyl)-2-propynol (**12**). *Fluspirilen* and *Penfluridol* were obtained in 70–80% yield by reaction of bromide **15** with 1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one (**16**) and 4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol (**17**), respectively. The overall yields of the two pharmaceuticals **1** and **2**, based on starting ketone **7**, were about 35–40%. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Several therapeutically active molecules embody in their framework a 4,4-bis(*p*-fluorophenyl)butyl group bound to a nitrogen atom of a pyrrolidine, piperidine or piperazine moiety: this class of compounds includes neuroleptics such as *Fluspirilen* (**1**), *Penfluridol* (**2**) and *Pimozide* (**3**), vasodilators such as *Lidoflazine* (**4**), antiparkinsonians such as P-608 (**5**) and the hypolipaemic agent (**6**)[1] (Fig. 1).

More recently, many other more structurally complex molecules endowed with interesting therapeutic activity, bearing the 4,4-bis(*p*-fluorophenyl)butyl group, have been synthesized and successfully tested in the treatment of various diseases: the overall number of compounds containing the aforementioned moiety is estimated to account for more than 300.[2] A key intermediate for the synthesis of compounds **1**–**6**, 4,4-bis(*p*-fluorophenyl)butylbromide **15**, is typically obtained through a rather tedious reaction scheme starting from cyclopropane carboxylic acid methyl ester and *p*-fluorophenyl magnesium bromide and involves three steps. The overall yield is 50%.[3] Alternatively, bromide **15** can be obtained by reaction of *p*-fluorophenyl magnesium bromide with 4-bromo-1-(*p*-fluorophenyl)-butanon, followed by dehydroxylation of the intermediate tertiary alcohol with hydriodic acid and acetic acid in the presence of red phosphorus in low overall yield.[4]

Recently, we reported a new synthetic approach to 4,4-bis(*p*-fluorophenyl)butan-1-ol **14**, an immediate precursor of **15**, through the production of 3,3-bis(*p*-fluorophenyl)-propanal by selective rhodium catalyzed hydroformylation of 1,1-bis(*p*-fluorophenyl)ethene followed by homologation of the obtained aldehyde, which is then reduced to alcohol **14**.[1]

We describe here a new and more efficient preparative route to **14**, using 4,4′-difluorobenzophenone (**7**) as starting material and again involving a selective hydroformylation step.

2. Results and discussion

Our synthetic strategy to transform ketone **7** into the key intermediate 4,4′-bis(p-fluorophenyl)butan-1-ol (**14**) is illustrated in Scheme 1. This readily available ketone was converted to diaryl vinyl carbinol **8** by reaction with vinyl magnesium bromide in THF in 85% yield. Then, this alcohol was subjected to rhodium catalyzed hydroformylation at 60°C and 100 atm (CO/H_2=1) using $HRh(CO)(PPh_3)_3$ as the catalyst precursor (substrate to Rh molar ratio=500). The *oxo*-product was obtained as the hemiacetal **10** in about 80% yield. In all the hydroformylation experiments, besides the expected linear aldehyde, about 15% of ketone **7** and

Keywords: *Fluspirilen*; *Penfluridol*; hydroformylation.
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0040–4020/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4020(00)01151-0

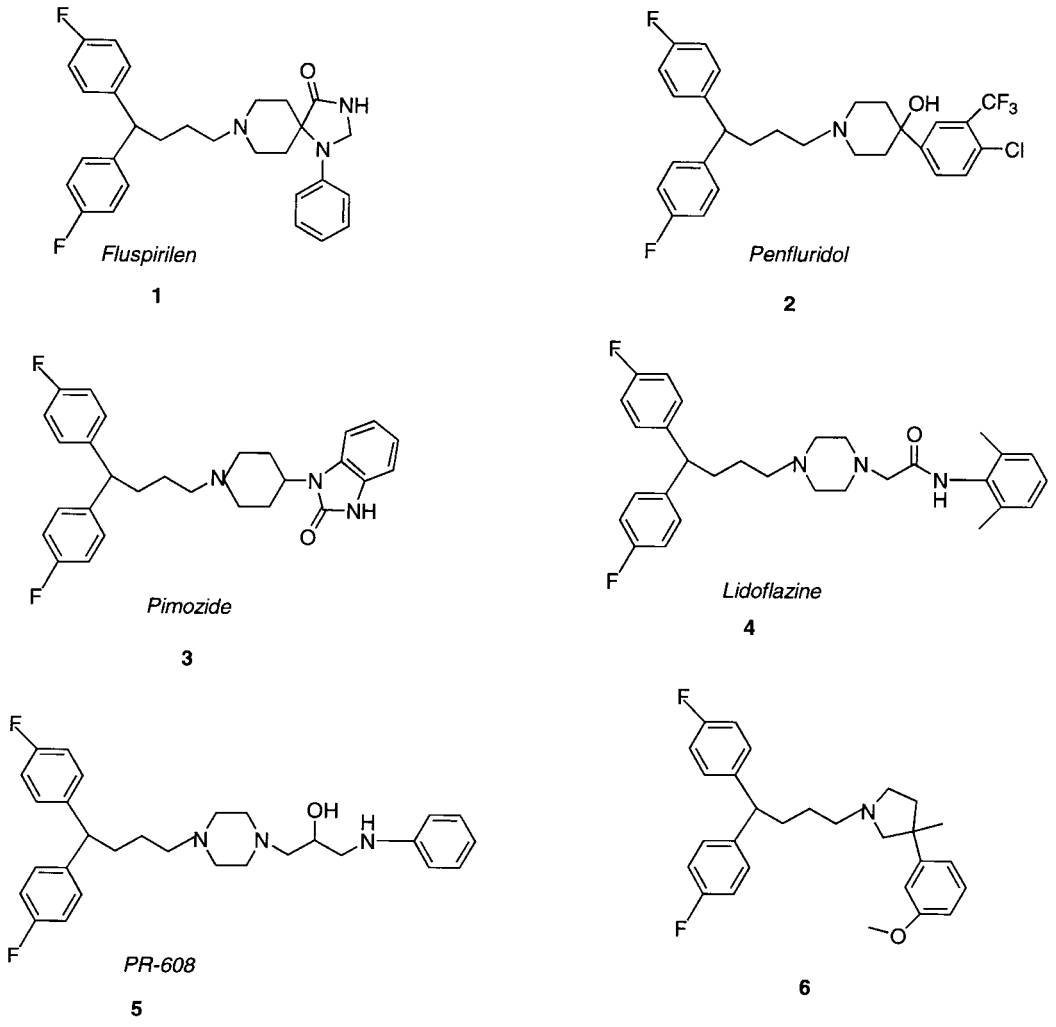
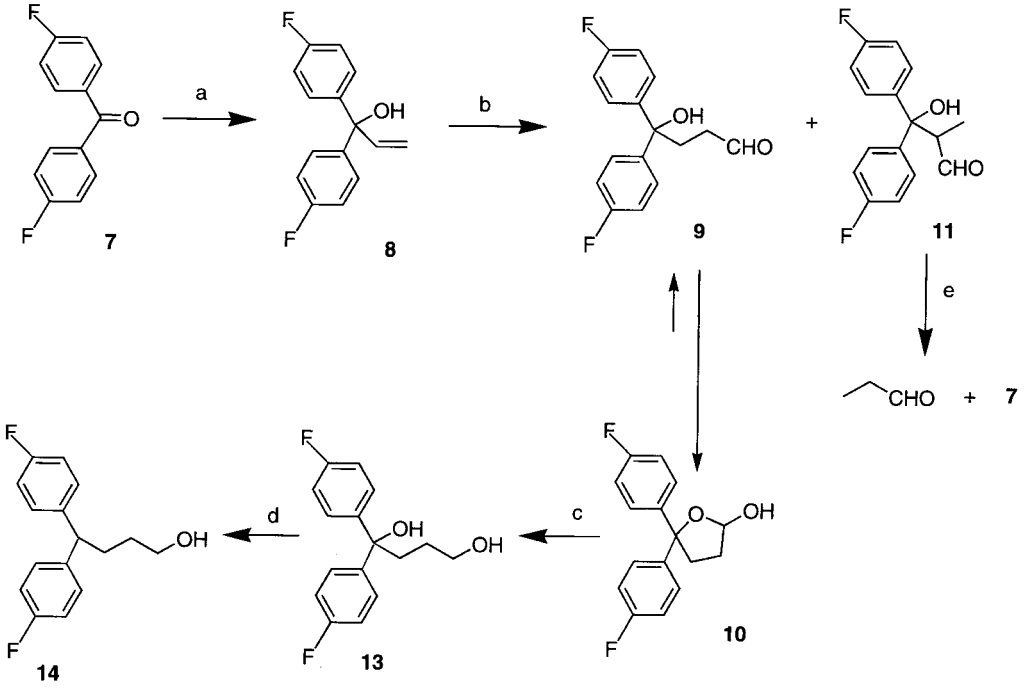


Figure 1.



Scheme 1. (a) CH_2=CHMgBr, THF, 85%. (b) CO, H_2, Rh cat., 80%. (c) $NaBH_4$, NaOH, CH_3OH, 90%. (d) H_2, Pd/C, C_2H_5OH, 85%. (e) Thermal retroaldolization.

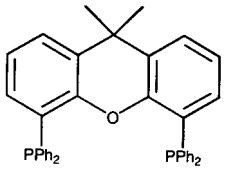


Figure 2. Xantphos (bite angle 109.8°).

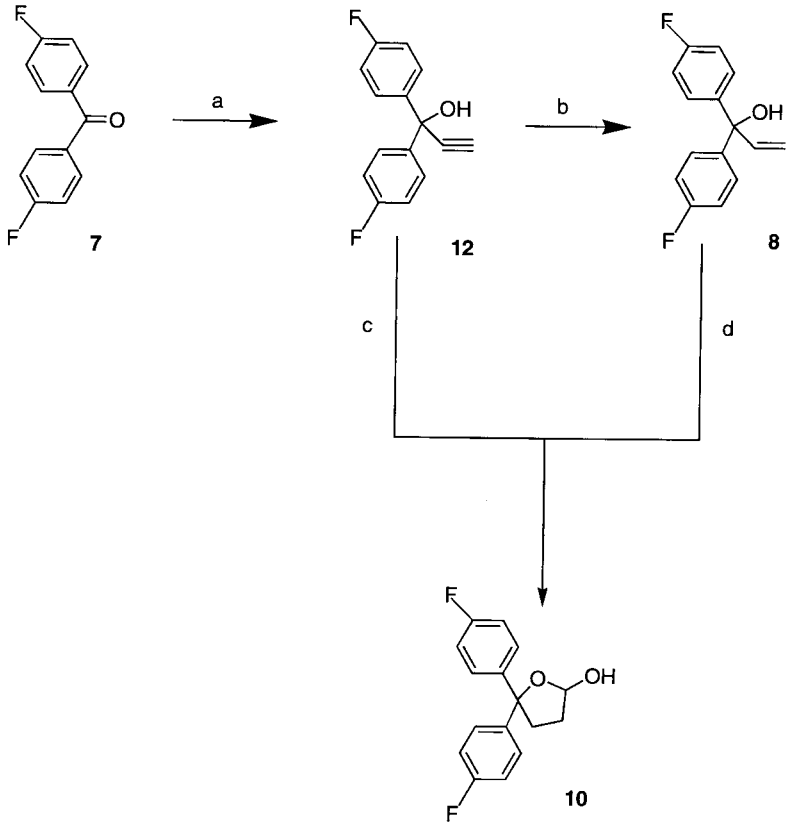
propanal was detected in the reaction mixture. These compounds derive from the cleavage of the branched aldehyde, 2-methyl-3,3-bis(*p*-fluorophenyl)-3-hydroxypropanal **11**, formed in minor amounts in the *oxo*-reaction, that under experimental conditions undergoes a thermal retro-aldolization reaction (Scheme 1).

In 1995, Van Leeuwen and collaborators[5] developed a new class of diphosphines based on xanthene-type backbones such as Xantphos, which promote an exceptionally high regioselectivity towards the formation of linear aldehydes in the rhodium catalyzed hydroformylation of olefins. This particular behavior of Xantphos was ascribed to the large 'natural' bite angle of the ligand[5–7] (Fig. 2).

The allyl alcohol **8** was then hydroformylated under the same conditions using the catalytic system $HRh(CO)(PPh_3)_3$/Xantphos (1/3 molar ratio). After 24 h at 60°C, 90% of the substrate was converted: the proportion of the hemiacetal **10** in the reaction mixture reached about 99%, only 1% of the ketone **7** being present. This result, which was very good, was confirmed by another *oxo*-experiment; preforming the active catalytic species by heating $Rh(CO)_2acac$ with Xantphos in toluene (Rh to ligand molar ratio=2.2) at 60°C and 10 atm (CO/H_2=1) for 2 h. Then the substrate was added (substrate to Rh molar ratio=500/1) and subjected to hydroformylation under the above reaction conditions: after 24 h almost quantitative substrate conversion was achieved and again about 99% of the desired hemiacetal **10** was obtained besides a negligible amount of ketone **7** (<1%).

As vinyl magnesium bromide, employed for the preparation of **8**, is not available on a semi-industrial scale, the following alternative convenient synthetic route was then explored by us: ketone **7** was subjected to ethynylation reaction with lithium acetylide following the procedure described in the literature[8] (Scheme 2). The resulting ethynyl carbinol **12**, obtained in 92% yield, was easily and selectively hydrogenated to **8** using the Lindlar catalyst.[9]

Alternatively, **12** can be converted to the hemiacetal **10** by hydroformylation reaction under the same conditions adopted in the case of **8**, but using a large excess of triphenylphosphine (rhodium to phosphorus molar ratio=30) according to Fell and coworkers' suggestions:[10] the yield of the *oxo*-product **10** however did not exceed 60% (Scheme 2). The hydroformylation of diaryl allyl alcohol **8** was also conveniently carried out in the biphasic system water–toluene or water–cyclohexane, using the water



Scheme 2. (a) Lithium acetylide ethylendiamine, acetylene, benzene, 92%. (b) Lindlar cat., 90%. (c) CO, H_2, Rh cat./PPh_3, toluene, 60%. (d) CO, H_2, Rh cat., 80%.

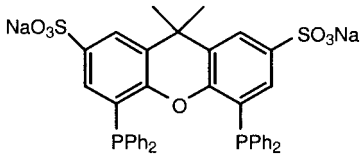
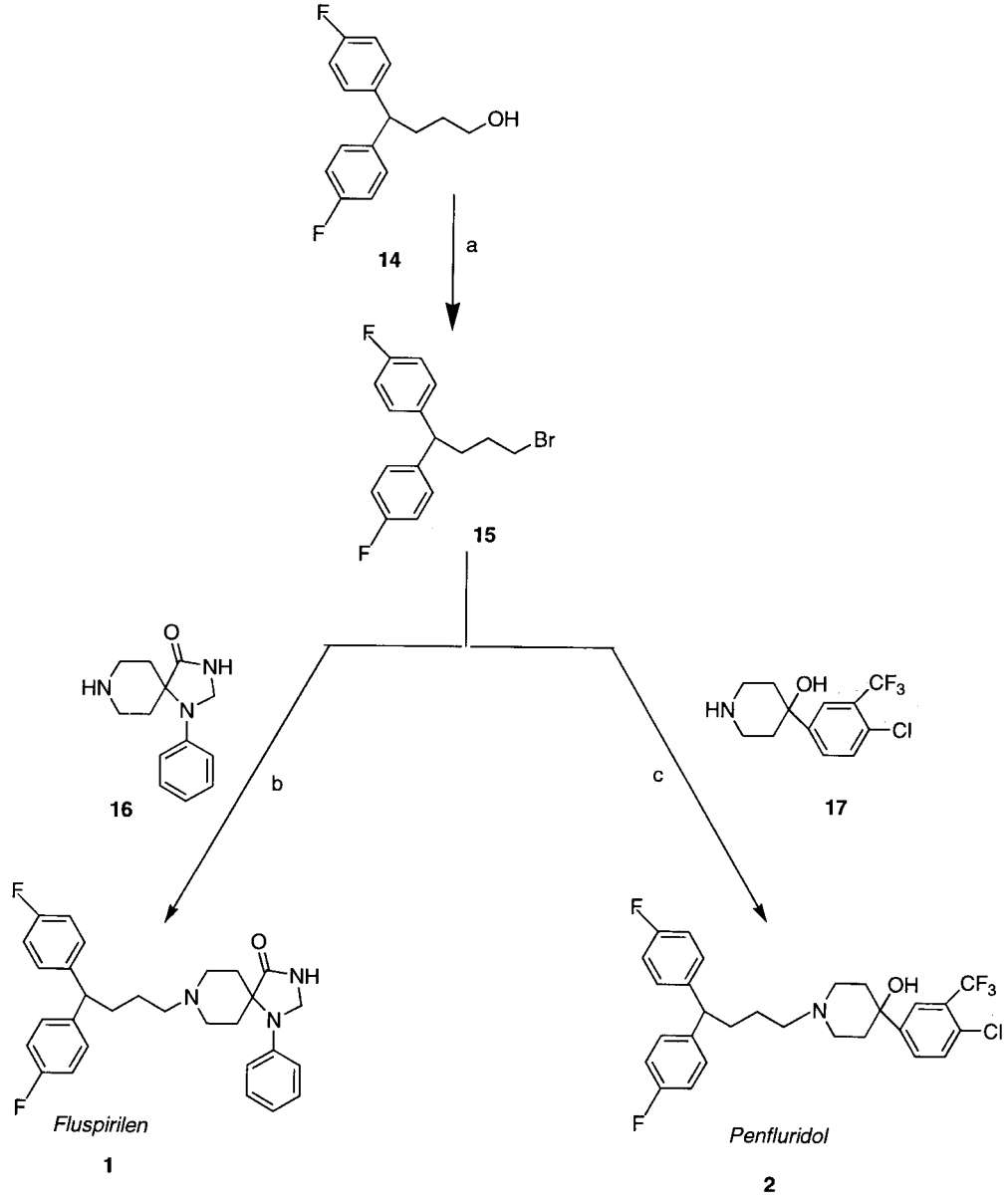


Figure 3. 2,7-Bis($SO_3Na)_2$ Xantphos.

soluble complex formed by $[Rh(COD)Cl]_2$/triphenylphosphine- 3,3′,3″-trisulfonic acid trisodium salt (TPPTS) as the catalyst.[11] In this case, after 24 h at 100°C, the yield of the desired product **10** was more than 95% and only a very low amount of ketone **7** was present in the reaction mixture. Analogous excellent results were achieved in the aqueous biphasic hydroformylation of compound **8** using the water soluble diphosphine 2,7-bis($SO_3Na)_2$Xantphos, which was recently claimed to promote the same exceptionally high regioselectivity to the linear *oxo* aldehyde in the rhodium catalyzed hydroformylation of terminal olefins[12] (Fig. 3).

Thus, the expected hemiacetal **10** was produced in 98–99% yield by hydroformylating **8** in the presence of the catalytic system $Rh(CO)_2$acac/2,7-bis($SO_3Na)_2$Xantphos adopting the same reaction conditions used in the case of rhodium complexes with the ligand TPPTS.

The biphasic catalytic process offers several advantages with respect to that performed in hydrocarbon solvents: (i) much easier separation of the reaction products; (ii) nearly quantitative recovery of the expensive rhodium catalyst; (iii) negligible decrease in the catalytic activity of the rhodium species. As a matter of fact we observed, after five recycles of the catalytic solution, practically no loss in efficiency. Furthermore, it must be pointed out that there are remarkable economic and ecological



Scheme 3. Br_2, PPh_3, CH_3CN, 80%. (b) Na_2CO_3, KI, **16**, toluene, 70%. (c) Na_2CO_3, KI, **17**, toluene, 75%.

advantages for the use of water in a semi-industrial scale hydroformylation.

However, the biphasic *oxo*-reaction on ethynyl carbinol **12**, carried out under the same experimental conditions, did not exceed 60% yield of the hemiacetal **10**. The hemiacetal **10** was converted to 4,4-bis(*p*-fluorophenyl)butan-1-ol (**14**) by $NaBH_4$ reduction[13] to 1,1-bis(*p*-fluorophenyl)-1,4-butandiol (**13**), followed by regioselective hydrogenolysis of the carbon–oxygen bond of the tertiary alcoholic function catalyzed by Pd/C (10%) at 80°C and atmospheric H_2 pressure in hot ethanol.[14] The overall yield of these two steps reached about 75%. Treatment of alcohol **14** with bromine in the presence of triphenylphosphine in acetonitrile at 0–25°C produced the desired bromide **15** in 80% yield[15] (Scheme 3).

Fluspirilen (**1**) and *Penfluridol* (**2**) were finally obtained in 70–80% yield by N alkylation of 1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one (**16**) and 4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol (**17**), respectively, with bromide **15** in hot toluene in the presence of Na_2CO_3 and KI (Scheme 3).[16] The best overall yields of both pharmaceuticals, based on starting ketone **7**, were very close to 40%.

3. Conclusions

The neuroleptic agents *Fluspirilen* and *Penfluridol* were synthesised in good yields employing the diaryl butanol **14** as the key intermediate for the N alkylation of the piperidine derivatives **16** and **17**, respectively, to the final products. An efficient preparative method to compound **14** was set up involving a highly regioselective hydroformylation step to convert the diaryl vinyl carbinol **8** into hemiacetal **10**. Particularly interesting are the results obtained in the biphasic *oxo* reaction on **8** using both the water soluble catalytic systems $[Rh(COD)Cl]_2$/TPPTS and $Rh(CO)_2$acac/2,7-bis$(SO_3Na)_2$Xantphos: in our hands the hemiacetal **10** was obtained in about 90% isolated yield. The preparative route outlined in this work is quite competitive with that proposed by Jansen,[3] taking into account that the starting cyclopropane carboxylic acid methyl ester is much less accessible on a semi-industrial scale[17] than 4,4′-bis(*p*-fluorophenyl)benzophenone[18] used as a starting material in our synthetic scheme.

4. Experimental

4.1. General

The rhodium complexes $[Rh(COD)Cl]_2$ and $HRh(CO)(PPh_3)_3$ were prepared following well-known procedures.[17,18] $Rh(CO)_2$acac, PtO_2, 4,4′-difluorobenzophenon and vinylmagnesium bromide were purchased from Aldrich. Xantphos was prepared as described in the literature.[5] 2,7-bis$(SO_3Na)_2$Xantphos was a generous gift of Professor van Leuween.[19] TPPTS was used as received from Fluka AG. 1-Phenyl-1,3,8-triazaspiro-(4,5)decan-4-one **16** and 4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol **17** were Acros products. Solvents were purified following well-known procedures.[20]

Elemental analyses were performed using a Perkin–Elmer Model 240C elemental analyzer. ^1H NMR spectra of $CDCl_3$ solutions were recorded using a 200 MHz Brucker AC200 spectrometer. GC–MS spectra were recorded using an HP 5971 Series mass spectrometer.

4.1.1. Synthesis of 1,1-bis(*p*-fluorophenyl)-2-propen-1-ol (8). A 1 M solution of vinylmagnesium bromide in THF (25.2 mL) was added dropwise to 5.0 g (22.9 mmol) of ketone **7** dissolved in 50 mL of anhydrous ether. The mixture was stirred at reflux for 5 h, then cooled to rt and poured into a saturated solution of NH_4Cl. The organic phase was separated and the water was extracted three times with ether. The combined ethereal solution was dried over Na_2SO_4, evaporated at reduced pressure and then distilled under vacuum to give pure alcohol **8** as a colorless oil in 85% yield.

Bp 93°C/0.05 mm Hg; ^1H NMR ($CDCl_3$): δ 7.40–7.27 (m, 4H), 7.10–6.92 (m, 4H), 6.53–6.38 (dd, 1H, J=11.0, 17.0 Hz), 5.38–5.23 (dd, 2H, J=11.0, 17.0 Hz), 2.40 (s, 1H). IR (KBr) (cm^{-1}): 3584, 3449, 3072, 2986, 1601, 1508, 1410, 1227, 1159, 835. MS (70 eV) *m/z* (relative intensity): 246 (M^+, 2). Anal. Calcd for $(FC_6H_4)_2C(OH)CH{=}CH_2$: C, 73.16; H, 4.91. Found: C, 73.30; H, 4.93.

4.1.2. Synthesis of 1,1-bis(*p*-fluorophenyl)-2-propyn-1-ol (12). A 50 mL three-necked flask fitted with a septum-capped inlet, magnetic stirring bar and thermometer was charged, under nitrogen atmosphere, with 0.92 g (10.1 mmol) of lithium acetylide ethylendiamine, 12 mL of benzene and 2.0 g (9.2 mmol) of ketone **7**. Acetylene was bubbled by means of a gas syringe and the mixture was heated at 55°C. After 4 h it was cooled to rt and 2.5 mL of water was slowly added. The mixture was heated at gentle reflux for 2 h, then cooled to rt, the organic phase separated and dried on $MgSO_4$. Pure product **12** was obtained as a colorless oil, in 92% yield, by distillation under vacuum.

Bp 98°C/0.05 mm Hg; ^1H NMR ($CDCl_3$) δ 7.62–7.50 (m, 4H), 7.10–6.96 (m, 4H), 2.94 (s, 1H), 2.92 (s, 1H). IR (KBr) (cm^{-1}): 3580, 3445, 3072, 2986, 2120, 1506, 1414, 1230, 1162, 838. MS (70 eV) *m/z* (relative intensity): 244 (M^+, 3). Anal. Calcd for $(FC_6H_4)_2C(OH)CCH$: C, 73.76; H, 4.13. Found: C, 74.02; H, 4.14.

4.1.3. Hydroformylation of substrate 8. A mixture of 1.0 g (4.06 mmol) of allyl alcohol **8**, and 7.4 mg (0.008 mmol) of $HRh(CO)(PPh_3)_3$ in 5 mL of toluene was introduced under a nitrogen purge in a 150 mL stainless steel reaction vessel and pressurized to 100 atm with synthesis gas (CO/H_2=1). After 5 h at 60°C the reactor was cooled to rt, the residual gases released and the reaction mixture analyzed by GLC (95% convn.). The pure aldehyde was obtained, in the form of the hemiacetal **10**, as a white solid, by crystallization from *n*-hexane in 93% yield.

Mp 112–113°C; ^1H NMR ($CDCl_3$): δ 7.45–7.28 (m, 4H),

Table 1. Hydroformylation of **8** catalyzed by rhodium complexes

Entry	Catalytic precursor	Temperature (°C)	Time (h)	Conv.[a] (%)	**7**+propanal Yield[a] (%)	**10** Yield[a] (%)
1	$HRh(CO)(PPh_3)_3$	60	5	95	15	80
2[b]	$HRh(CO)(PPh_3)_3$/Xantphos	60	24	90	1	89
3[c]	$Rh(CO)_2$acac/Xantphos	60	24	99	1	98
4[d]	$[Rh(COD)Cl]_2$/TPPTS	100	24	99	4	90
5[e]	$Rh(CO)_2$acac/ 2,7-bis$(SO_3Na)_2$Xantphos	100	24	99	1	98

Substrate=4.06 mmol; substrate to catalyst (molar ratio)=500; Solvent: toluene (5 mL); TPPTS=triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt.
[a] Determined by GC.
[b] Rh/Xantphos (molar ratio)=1/3.
[c] Rh/Xantphos (molar ratio)=1/2.2.
[d] Rh/TPPTS (molar ratio)=1/3.
[e] Rh/2,7-bis$(SO_3Na)_2$Xantphos=1/5.

7.05–6.92 (m, 4H), 5.78–5.72 (q, 1H, J=3.7 Hz), 2.65–2.52 (m, 2H), 2.08–1.98 (m, 2H). IR (KBr) (cm^{-1}): 3284, 3063, 2959, 1598, 1506, 1227, 827. MS (70 eV) *m/z* (relative intensity): 276 (M^+, 10). Anal. Calcd for $(FC_6H_4)_2CO$-$CH(OH)CH_2CH_2$: C, 69.56; H, 5.11. Found: C, 69.82; H, 5.12.

The same reaction was also carried out in the presence of the catalyst precursor $HRh(CO)(PPh_3)_3$/Xantphos (Rh to ligand molar ratio=1/3) at 60°C for 24 h (see Table 1).

4.1.4. Hydroformylation of substrate 8 catalyzed by $Rh(CO)_2$acac/Xantphos. A mixture of 2.1 mg (0.008 mmol) of $Rh(CO)_2$acac and 10.4 mg (0.018 mmol) of Xantphos in 4 mL of toluene was introduced under a nitrogen purge in a 150 mL stainless steel reaction vessel. The autoclave was pressurized to 10 atm with synthesis gas (CO/H_2=1) and heated at 60°C under stirring for 2 h to form the active catalyst. Then, 1.0 g (4.06 mmol) of allyl alcohol **8** and 6 mL of toluene were placed in the reactor, pressurized to 10 atm (CO/H_2=1) and heated at 60°C for 24 h. After usual work-up the hemiacetal **10** was recovered as described above.

4.1.5. Hydroformylation of substrate 8 catalyzed by $[Rh(COD)Cl]_2$/TPPTS. In a Schlenk tube 4.0 mg (0.008 mmol) of $[Rh(COD)Cl]_2$ and 27.6 mg (0.049 mmol) of TPPTS were dissolved under nitrogen in 1.5 mL of degassed H_2O; then, a solution of 0.5 g (2.03 mmol) of **8** in 2 mL of toluene was added. The two-phase liquid mixture was transferred to a 150 mL stainless steel autoclave under nitrogen, pressurized to 100 atm with synthesis gas (CO/H_2=1) and heated at 100°C for 24 h. The reactor was then cooled to rt, the residual gases released and the reaction mixture analyzed by GLC (>99% convn.). The organic phase was separated, toluene removed under *vacuum* and pure product **10** was recovered as described previously.

4.1.6. Hydroformylation of substrate 8 catalyzed by $Rh(CO)_2$acac/2,7-bis$(SO_3Na)_2$Xantphos. In a Schlenk tube 1.0 mg (0.004 mmol) of $Rh(CO)_2$acac and 15.9 mg (0.02 mmol) of 2,7-bis$(SO_3Na)_2$Xantphos were dissolved under nitrogen in 1.5 mL of degassed H_2O. The Schlenk was transferred into an autoclave, pressurized to 20 atm (CO/H_2=1) and heated at 100°C for 4 h. The autoclave was then cooled to rt, depressurized and a solution of 0.5 g (2.03 mmol) of **8** in 2 mL of toluene was added to the catalytic aqueous solution. The autoclave was then pressurized to 100 atm with synthesis gas (CO/H_2=1) and heated at 100°C for 24 h. After usual work-up, pure product **10** was recovered and characterized as previously described.

4.1.7. Hydroformylation of substrate 12. A mixture of 0.6 g (2.46 mmol) of **12**, 9.0 mg (0.0098 mmol) of $HRh(CO)(PPh_3)_3$ and 77.0 mg of PPh_3 in 5 mL of toluene was introduced under a nitrogen purge in a 150 mL stainless steel reaction vessel and pressurized to 100 atm with synthesis gas (CO/H_2=1). After 24 h at 100°C the reactor was cooled to rt, the residual gases released and the reaction mixture analyzed by GLC (99% convn.). The aldehyde was obtained in the form of the hemiacetal **10**, in 61% yield, besides 38% of unidentified high boiling by-products. Product **10** was obtained in a pure form as previously described.

4.1.8. Synthesis of 1,1-bis(*p*-fluorophenyl)-1,4-butandiol (13). A mixture of 26.7 mg (0.71 mmol) of $NaBH_4$ in 0.04 mL of NaOH 2N diluted with 0.35 mL of H_2O was added to 500 mg (1.8 mmol) of **10** dissolved in 10 mL of CH_3OH and stirred at rt for 3 h. The reaction mixture, after evaporation of methanol at reduced pressure, was diluted with water and extracted three times with ether. After usual work-up, glycol **13** was obtained in a pure form, as a white solid, (90% yield) by flash chromatography on silica gel using a 6:4 hexane/ether mixture as eluent.

Mp 93.5–94°C; ^{1}H NMR ($CDCl_3$): δ 7.48–7.31 (m, 4H), 7.08–6.93 (m, 4H), 3.77–3.62 (t, 2H, J=7.3 Hz), 3.50 (br s, 1H), 2.50–2.35 (t, 2H, J=7.3 Hz), 1.90 (br s, 1H), 1.72–1.52 (m, 2H). IR (KBr) (cm^{-1}): 3320, 3200, 2925, 1603, 1507, 1223, 830. MS (70 eV) *m/z* (relative intensity): 278 (M^+, 1). Anal. Calcd for $(FC_6H_4)_2C(OH)CH_2CH_2CH_2OH$: C, 69.05; H, 5.79. Found: C, 69.27; H, 5.81.

4.1.9. Synthesis of 4,4-bis(*p*-fluorophenyl)butan-1-ol (14). Hydrogen gas was bubbled into a mixture of 500 mg (1.8 mmol) of glycol **13** and 225 mg of 10% Pd/C in 10 mL of 95% C_2H_5OH and heated at reflux overnight; the mixture was cooled to rt, filtered off and the solvent evaporated under *vacuum*. Pure alcohol **14** was obtained as a colorless oil (85% yield) by flash chromatography on silica gel using a 7:3 hexane/ether mixture as eluent.

^{1}H NMR ($CDCl_3$): δ 7.23–7.10 (m, 4H), 7.06–6.92 (m, 4H), 3.96–3.85 (t, 1H, J=0.6 Hz), 3.49–3.38 (t, 2H, J=7.3 Hz),

2.23–2.10 (m, 2H), 1.90–1.73 (m, 2H). IR (KBr) (cm^{-1}): 3360, 3041, 2939, 2868, 1603, 1507, 1223, 1158, 827. MS (70 eV) *m/z* (relative intensity): 262 (M^+, 7). Anal. Calcd for $(FC_6H_4)_2CHCH_2CH_2CH_2OH$: C, 73.27; H, 6.15. Found: C, 73.54; H, 6.17.

4.1.10. Synthesis of 4,4-bis(*p*-fluorophenyl)butylbromide (15). A solution of 1.5 g (5.7 mmol) of PPh_3 in 6 mL of anhydrous CH_3CN was cooled to 0°C under nitrogen and added dropwise with 0.91 g (5.7 mmol) of Br_2 maintaining the temperature below 5°C. The mixture was then warmed to rt and 1.0 g (3.6 mmol) of alcohol **14** dissolved in 2 mL of CH_3CN was added dropwise. The solution was left to react for 2 h at rt and after evaporation of the solvent at reduced pressure the product was diluted with hexane. The solid residue was filtered off, the solvent evaporated and the crude oil was purified by flash chromatography on silica gel using a 7:3 hexane/ether mixture as eluent. Pure bromide **15** was obtained as a pale yellow oil in 80% yield.

^{1}H NMR ($CDCl_3$): δ 7.22–7.12 (m, 4H), 7.07–6.92 (m, 4H), 3.97–3.85 (t, 1H, J=0.6 Hz), 3.48–3.38 (t, 2H, J=7.3 Hz), 2.22–2.10 (m, 2H), 1.94–1.72 (m, 2H). IR (KBr) (cm^{-1}): 3046, 2926, 2863, 1597, 1506, 1221, 823. MS (70 eV) *m/z* (relative intensity): 325 (M^+, 3). Anal. Calcd for $(FC_6H_4)_2CHCH_2CH_2CH_2Br$: C, 73.3; H, 6.1. Found: C, 73.51; H, 6.11.

4.1.11. Synthesis of Fluspirilen (1). A solution of 1.0 g (3.1 mmol) of bromide **15** dissolved in 15 mL of toluene, 625 mg (2.7 mmol) of the piperidino derivative **16**, 497 mg (4.7 mmol) of Na_2CO_3 and a few crystals of KI was heated at reflux for 66 h; after this time the reaction mixture was cooled to rt and 10 mL of H_2O was added. The organic phase was separated, dried over Na_2SO_4 and evaporated at reduced pressure to give a pale yellow oil. After treatment with *n*-hexane the oil afforded a white solid and pure *Fluspirilen* **1** was obtained in 70% yield with respect to **16** by flash chromatography on silica gel using $CHCl_3$ as eluent.

^{1}H NMR ($CDCl_3$): δ 7.30–6.85 (m, 13H), 4.74 (s, 2H), 3.94–3.89 (t, 1H, J=0.6 Hz), 2.77–2.57 (m, 6H), 2.47–2.42 (t, 2H, J=7.3 Hz), 2.09–2.02 (q, 2H, J=7.3 Hz), 1.74–1.70 (d, 2H, J=7.3 Hz), 1.56–1.35 (m, 2H). MS (70 eV) *m/z* (relative intensity): 475 (M^+, 6). Anal. Calcd for $(FC_6H_4)_2CHCH_2CH_2CH_2N(CH_2)_4CCONHCH_2NC_6H_5$: C, 73.24; H, 6.57; N, 8.84. Found: C, 73.52; H, 6.59; N, 8.86.

4.1.12. Synthesis of Penfluridol (2). Following the procedure described for the synthesis of **1**, *Penfluridol* **2** was obtained as a white solid in 75% yield by reacting bromide **15** with the piperidino derivative **17** in boiling toluene and in the presence of Na_2CO_3 and a few crystals of KI.

^{1}H NMR ($CDCl_3$): δ 7.83–6.92 (m, 11H), 3.92–3.82 (t, 1H, J=0.6 Hz), 2.85–2.70 (br d, 4H), 2.52–2.27 (m, 4H), 2.18–1.95 (m, 2H), 1.79–1.40 (m, 5H). MS (70 eV) *m/z* (relative intensity): 523 (M^+, 14). Anal. Calcd for $(FC_6H_4)_2CHCH_2CH_2CH_2N(CH_2)_4C(OH)C_6H_3(Cl)(CF_3)$: C, 63.10; H, 5.69; N, 2.73. Found: C, 62.9; H, 5.67; N, 2.72.

Acknowledgements

We thank Dr Claudete Justina Valduga for the partial experimental assistance.

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