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Rhodium-catalyzed hydroformylation of 1,1-bis(*p*-fluorophenyl)ethene and 3,3-bis(*p*-fluorophenyl)propene

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Abstract

1,1-Bis(*p*-fluorophenyl)ethene and 3,3-bis(*p*-fluorophenyl)propene were hydroformylated using rhodium catalysts: whereas, the chemoselectivity of the reaction is rather high for both olefins, the regioselectivity towards the formation of the linear aldehyde is very high only for the former substrate. In the case of the latter olefin extensive double bond isomerization takes place under oxo conditions. The obtained 3,3-bis(*p*-fluorophenyl)propanal is converted to 4,4-bis(*p*-fluorophenyl) butanal by an improved two-step homologation procedure involving a Wittig reaction. This aldehyde is a valuable building block for some interesting pharmaceuticals.

Keywords: Hydroformylation; Rhodium catalysts; Diarylolefines

1. Introduction

1,1-Diarylethenes have been shown to be very interesting substrates for rhodium-catalyzed hydroformylation [1–3]: the selectivity towards the formation of the linear oxo-aldehydes 3,3-diarylpropanals is generally rather high, reaching in most cases yields up to 90%. These aldehydes are transformed through conventional chemical reactions in a variety of therapeutically active compounds, their activity spanning from choleretic and spasmolitic to antihistaminic and urological.

In particular, 1-(*N*,*N*-dialkylamino)-3,3-diarylpropanes [4,5] are easily available by reductive amination of the 3,3-diarylpropanals in the presence of the appropriate amine partner catalyzed by PtO_2 at 120°C and 60 atm H_2 in nearly quantitative yields [6]. Other methods are, however, available to accomplish the conversion of these aldehydes to the target compounds, namely: (i) a two-step reductive amination involving the formation of the corresponding enamine followed by the double bond reduction with sodium borohydride [6]; (ii) oxidation of the aldehydes to the corresponding acids and their conversion to the appropriate amides followed by reduction with lithium aluminum hy-

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dride/aluminum chloride [7]; (iii) one-pot transformation of 1,1-diarylethenes under oxo-conditions, exploiting the ability of rhodium hydrido carbonyl complexes to reduce the above carbon–carbon double bond of enamines [6].

This class of amino-compounds includes many valuable pharmaceutical agents such as Fenpiprane (spasmolitic), Diisopromine (choleretic), Tolpropamine (antihistaminic) and Milverine (antispasmodic), whose preparation can be effected using the hydroformylation reaction as intermediate step in a competitive way with respect to the traditional reaction methodologies currently employed for their industrial synthesis [8–11].

Some important therapeutically active compounds embody in their molecule a 4,4-bis(*p*-fluorophenyl)butyl moiety as the substituent at the nitrogen atom of a piperidine or pyrrolidine derivative partner (Fig. 1).

In the commercial synthesis this substituent is introduced in these molecules by alkylation of the heterocyclic nitrogen atom with 1-bromo- [12–14] or 1-chloro-4,4-bis(*p*-fluorophenyl)butane [15,16]. The bromide is in turn accessible through a rather laborious experimental proce-

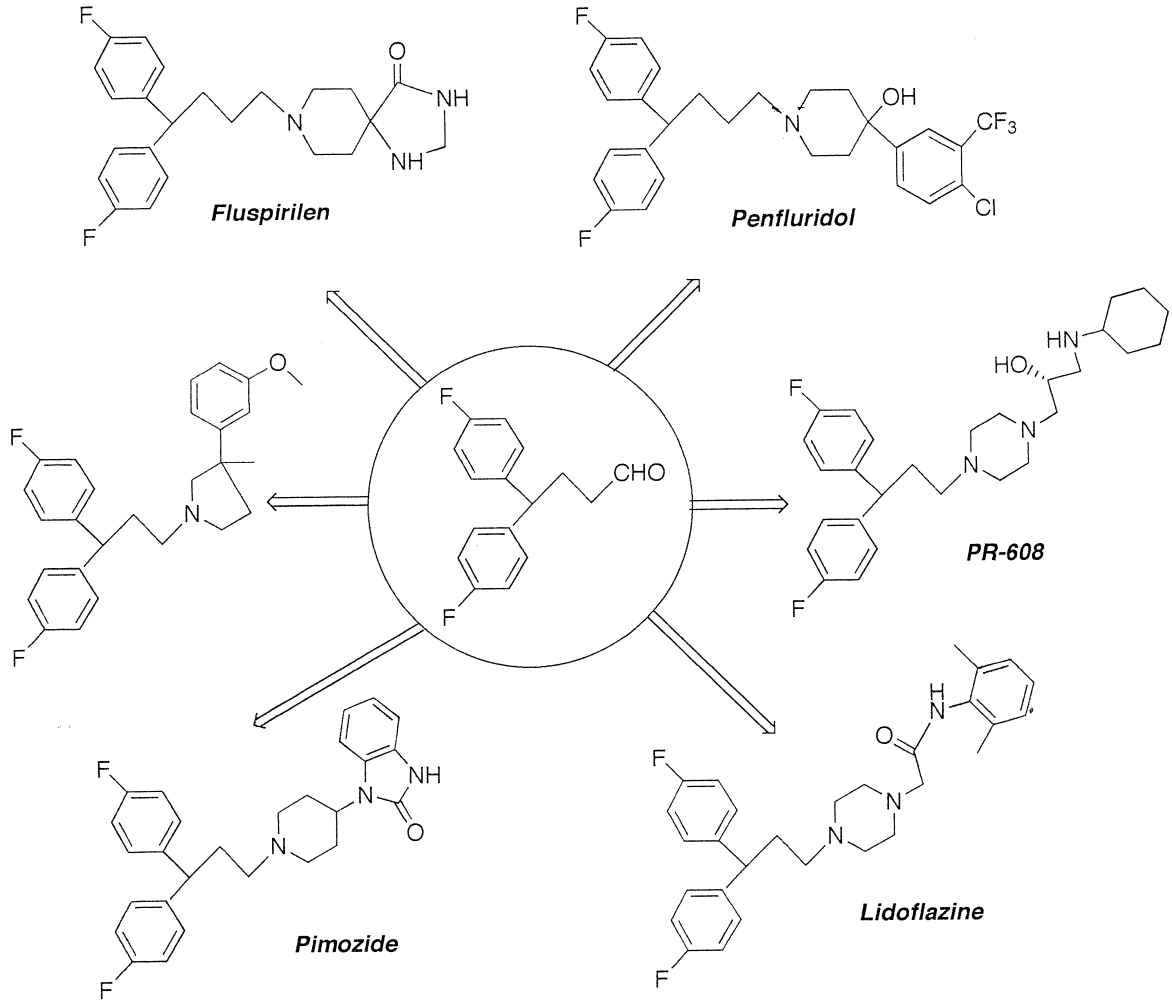


Fig. 1. Some important therapeutically active compounds containing in their molecule a 4,4-bis(*p*-fluorophenyl)butyl moiety.

dure in about 60% overall yield involving a rearrangement reaction of bis(*p*-fluorophenyl) cyclopropyl carbinol promoted by hydrobromic acid followed by catalytic hydrogenation of the resulting 1,1-bis(*p*-fluorophenyl)-4-bromobutene [12–14].

The related chloride can be prepared by addition of 4-fluorophenylmagnesium bromide to 4-chloro-*p*-fluorobutyrophenone followed by dehydration of the formed tertiary carbinol to the corresponding olefin which finally is catalytically reduced to the desired halide [15,16].

Owing to our previous experience in developing new and more convenient routes to valuable intermediates for various pharmacologically active compounds [17,18] and to some recent interesting results obtained in the application of hydroformylation to pursue this aim [19], we planned to employ synthetic strategies involving the hydroformylation to prepare 4,4-bis(*p*-fluorophenyl)butanal **5**, which can represent a key-precursor for the above pharmaceutical compounds.

2. Experimental

2.1. Materials

The rhodium complexes $[RhCl(CO)_2]_2$, $Rh_6(CO)_{16}$ and PtO_2 were Aldrich products. $HRh(CO)(PPh_3)_3$ was prepared following a well-known procedure [20]. Triphenylphosphine, triphenylphosphite, dimethylphenylphosphine, diphenylphosphine oxide, 1,4-bis(diphenylphosphino)butane and tris(2,4-di-*tert*-butylphenyl) phosphite were used as received from Aldrich. 4,4′-Difluorobenzophenone and the instant ylides (methoxymethyl)triphenylphosphonium bromide mixture with sodium amide and methyltriphenylphosphonium bromide mixture with sodium amide were purchased from Aldrich. Solvents were purified following well-known procedures [21].

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. IR spectra were obtained using a Bio-Rad FTS-40 interferometer. GC-MS spectra were recorded using an HP 5971 Series mass spectrometer.

2.2. Synthesis of 4,4′-bis(p-fluorophenyl)-ethene—*2*

Method a. Olefin **2** was prepared by Wittig reaction on 4,4′-difluorobenzophenone **1** with an equimolecular amount of a ready-to-use mixture of methyltriphenylphosphonium bromide and sodium amide in ethyl ether at room temperature [6] and purified by flash chromatography on silica gel using hexane as eluent (88.0% yield). *Method b*. A solution of 10.02 g (45.9 mmol) of ketone **1** in 130 ml of ether was slowly added to 60.0 mmol of an etheral solution of CH_3MgI, previously obtained by adding dropwise 8.52 g (60.0 mmol) of CH_3I dissolved in 15 ml of ether to 1.46 g of Mg, and refluxed for 2 h. After usual work-up, the pure alcohol 4,4-bis(*p*-fluorophenyl)methylcarbinol was obtained in almost quantitative yield by flash chromatography on silica gel using a 7:3 hexane/ether mixture as eluent. This alcohol was then dehydrated to olefin **2** after 2 h reflux in benzene in the presence of a 10% w/w of *p*-toluensulfonic acid. Pure compound **2** was recovered in almost quantitative yield as reported in *method a*.

Compound **2** gave satisfactory analytical data and ^1H NMR pattern was in agreement with its structure.

Compound **2**: IR 1603 (vs) cm^{-1}; m/z 216 $(M)^+$. Anal. Calcd. for $(FC_6H_4)_2C{=}CH_2$: C, 77.77; H, 4.66. Found: C, 78.04; H, 4.67. ^1H NMR($CDCl_3$) δ 7.34–7.27 (dd, 4H), 7.13–7.01 (t, 4H), 5.43 (s, 2H).

2.3. Synthesis of 3,3-bis(p-fluorophenyl)-propene—*8*

(a) Preparation of 1-methoxy-2,2′-(*p*-fluorophenyl)ethene **6**. 4,4′-Difluorobenzophenone **1** was subjected to Wittig reaction with an equimolar amount of a ready-to-use mixture of

(methoxymethyl)triphenylphosphonium bromide and sodium amide in ether at room temperature [6]; pure enol ether **6** was obtained (95% yield) by flash chromatography on silica gel using hexane as eluent.

Compound **6** gave satisfactory analytical data and ^{1}H NMR pattern was in agreement with its structure.

Compound **6**: mp 49.0–49.5°C; IR 1240 (vs) cm^{-1}; *m/z* 246 (M)$^+$. Anal. Calcd. for $(FC_6H_4)_2C{=}CHOCH_3$: C, 73.16; H, 4.91. Found: C,73.45; H, 4.94. ^{1}H NMR ($CDCl_3$) δ 7.40–7.28(dd, 4H), 7.23–6.95 (t, 4H), 6.42 (s, 1H), 3.55 (s, 3H).

(b) Hydrolysis of enol ether **6** to 4,4′-bis(*p*-fluorophenyl)ethanal **7**. A mixture of 0.50 g (2.03 mmol) of enol ether **6**, 2.5 ml of ether, 1 ml of H_2O and 3.5 ml of CF_3SO_3H was deareated by three freeze-pump-thaw cycles and heated at reflux for half an hour; the mixture was then cooled to room temperature, the ether phase washed several times with water and then dried over anhydrous $MgSO_4$. After evaporation of the solvent, aldehyde **7** was obtained in a pure form (90% yield) by flash chromatography on silica gel using a 9:1 hexane/ether mixture as eluent.

Compound **7** gave satisfactory analytical data and ^{1}H NMR pattern was in agreement with its structure.

Compound **7**: IR 1725 (vs) cm^{-1}; *m/z* 232 (M)$^+$. Anal. Calcd. for $(FC_6H_4)_2CHCHO$: C, 72.41; H, 4.34. Found: C, 72.66; H, 4.35. ^{1}H NMR ($CDCl_3$) δ 9.92–9.88 (d, 1H), 7.27–7.12 (dd, 4H), 7.05–6.98 (t, 4H), 4.87–4.84 (d, 1H).

(c) Synthesis of olefin **8** from **7**. Olefin **8** was obtained by Wittig reaction on aldehyde **7** with an equimolar amount of a ready-to-use mixture of methyltriphenylphosphonium bromide and sodium amide in ether at room temperature for 5 h [6]. Pure olefin **8** was obtained (75% yield) by flash chromatography on silica gel using hexane as eluent.

Compound **8** gave satisfactory analytical data and ^{1}H NMR pattern was in agreement with its structure.

Compound **8**: IR 1605 (s) cm^{-1}; *m/z* 230 (M)$^+$. Anal. Calcd. for $(FC_6H_4)_2CHCH{=}CH_2$: C, 78.25; H, 5.25. Found: C, 78.56; H, 5.27. ^{1}H NMR ($CDCl_3$) δ 7.25–7.10 (dd, 4H), 7.07–6.98 (t, 4H), 6.37–6.18 (m, 1H), 5.32–5.22 (dt, 1H), 5.04–4.93 (dt, 1H), 4.77–4.68 (d, 1H).

*2.4. General procedure for the hydroformylation of substrates **2** and **8***

A 150 ml stainless steel reaction vessel was charged under nitrogen purge with 2.3 mmol of the olefin **2** or **8**, 0.009 mmol of rhodium catalyst, 0.018 mmol of the ligand of choice and 5 ml of anhydrous benzene. The reactor was then pressurized to 100 atm with synthesis gas ($CO/H_2 = 1$) and heated at 80–120°C for the due time (see Tables 1 and 2). From the reaction mixture the aldehydes were recovered by flash chromatography on silica gel using a 9:1 hexane/ether mixture as eluent.

Compounds 3,3-bis(*p*-fluorophenyl)propanal **3**, 4,4-bis(*p*-fluorophenyl)butanal **5** and 3,3-bis(*p*-fluorophenyl)-2-methylpropanal **9** gave satisfactory analytical data and ^{1}H NMR patterns were in agreement with their structures.

Compound **3**: IR 1724 (vs) cm^{-1}; *m/z* 246 (M)$^+$. Anal. Calcd. for $(FC_6H_4)_2CHCH_2CHO$: C, 73.16; H, 4.91. Found: C, 73.35; H, 4.93. ^{1}H NMR ($CDCl_3$) δ 9.74–9.73 (t, 1H), 7.34–7.20 (dd, 4H), 7.15–6.94 (t, 4H), 4.66–4.58 (t, 1H), 3.17–3.12 (dd, 2H).

Compound **5**: IR 1725 (vs) cm^{-1}; *m/z* 260 (M)$^+$. Anal. Calcd. for $(FC_6H_4)_2CHCH_2CH_2CHO$: C, 73.83; H, 5.42. Found: C, 74.05; H, 5.44. ^{1}H NMR ($CDCl_3$) δ 9.74–9.73 (t, 1H), 7.28–7.16 (dd, 4H), 7.10–6.92 (t, 4H), 4.0–3.85 (t, 1H), 2.52–2.28 (complex multiplet, 4H).

Compound **9**: IR 1724 (vs) cm^{-1}; *m/z* 260 (M)$^+$. Anal. Calcd. for $(FC_6H_4)_2CHCH(CH_3)CHO$: C, 73.83; H, 5.42. Found: C, 74.0; H, 5.43. ^{1}H NMR ($CDCl_3$) δ 9.57–9.54(d, 1H), 7.26–7.12 (dd, 4H), 7.08–6.94 (t, 4H),4.13–4.05 (d, 1H), 3.33–3.13 (complex multiplet, 1H), 1.08–0.98 (d, 3H).

Table 1
Hydroformylation of 1,1-bis(*p*-fluorophenyl)ethene catalyzed by rhodium complexes[a]

Entry	Catalytic precursor	Reaction time (h)	Temperature (°C)	Convn[b] (%)	Substrate hydrogenation yield[b] (%)	Hydroformylation yield[b] (%)	Alcohol[c] yield[b] (%)	Aldehyde **3** selectivity%
1	$HRh(CO)(PPh_3)_3$	48	80	15.0	8.0	7.0	–	> 99
2	$[RhCl(CO)_2]_2$	48	100	99.0	25.2	73.8	–	> 99
3	$[RhCl(CO)_2]_2$	48	120	99.0	12.8	72.5	13.7	> 99
4	$[RhCl(CO)_2]_2$/DPPB	72	80	19.0	3.0	16.0	–	> 99
5	$[RhCl(CO)_2]_2$/DPPB	64	100	24.0	4.0	20.0	–	> 99
6	$[RhCl(CO)_2]_2$/DMPP	87	100	94.0	48.0	46.0	–	> 99
7	$[RhCl(CO)_2]_2/P(OC_6H_5)_3$	89	100	86.0	4.0	82.0	–	> 99
8	$[RhCl(CO)_2]_2/P(OC_6H_5)_3$	22	120	100.0	10.0	86.0	4.0	> 99
9	$[RhCl(CO)_2]_2/(Ph)_2P(O)H$	24	120	100.0	16.0	74.0	9.0	> 99
10	$[RhCl(CO)_2]_2$/L	15	120	98.0	10.3	87.6	–	> 99
11	$[RhCl(CO)_2]_2$/L	24	120	100.0	5.8	88.3	5.7	> 99

[a]Substrate 2.3 mmol; benzene 5 ml; $p(CO) = p(H_2) = 50$ atm; substrate to catalyst molar ratio 250:1; Rh/P 1:1 molar ratio; Rh/L 1:1 molar ratio.
[b]Determined by GLC analysis.
[c]3,3-bis(*p*-fluorophenyl)propan-1-ol.
DPPB = 1,4-bis(diphenylphosphino)butane; DMPP = dimethylphenylphosphine; L = tris(2,4-di-*tert*-butylphenyl)phosphite.

2.5. Homologation of aldehyde *3* to aldehyde *5*

Concentrated HCl (0.9 ml) was added dropwise, under nitrogen, to an etheral solution (2 ml) of 2.78 g (9.5 mmol) of 1-methoxy-4,4-bis(*p*-fluorophenyl)-1-butene **4**, previously obtained in 83% yield by Wittig reaction on aldehyde **3** with an equimolar amount of a ready-to-use mixture of (methoxymethyl)triphenylphosphonium bromide and sodium amide in ether at room temperature [6]. After 24 h stirring at room temperature the conversion of **4** to **5** resulted almost complete. The reaction mixture was extracted three times with ether, washed several times with water and dried over anhydrous Na_2SO_4. After evaporation of the solvent, pure aldehyde **5** was obtained by flash chromatography on silica gel using a 9:1 hexane/ether mixture as eluent. Aldehyde **5** showed the same analytical data previously described.

Table 2
Hydroformylation of 3,3-bis(*p*-fluorophenyl)propene catalyzed by rhodium complexes[a]

Entry	Catalytic precursor	Reaction time (h)	Temp (°C)	Convn[b] (%)	Substrate hydrogenation yield[b] (%)	Hydroformylation yield,[b] %	Aldehyde **5** selectivity (%)
1	$HRh(CO)(PPh_3)_3$	48	90	89.2	< 1	89.2	55.9
2	$HRh(CO)(PPh_3)_3/PPh_3$	41	90	> 99	–	> 99	53.3
3	$[RhCl(CO)_2]_2$	48	90	84.8	3.7	81.1	51.1
4	$[RhCl(CO)_2]_2$/L	42	90	> 99	–	> 99	54.1
5	$Rh_6(CO)_{16}$	48	90	> 99	–	> 99	50.7

[a]Substrate 2.3 mmol; benzene 5 ml; $p(CO) = p(H_2) = 50$ atm; substrate to catalyst molar ratio 250:1; Rh/PPh_3 1:2 molar ratio; Rh/L = 1:1 molar ratio.
[b]Determined by GLC analysis.
L = tris(2,4-di-*tert*-butylphenyl)phosphite.

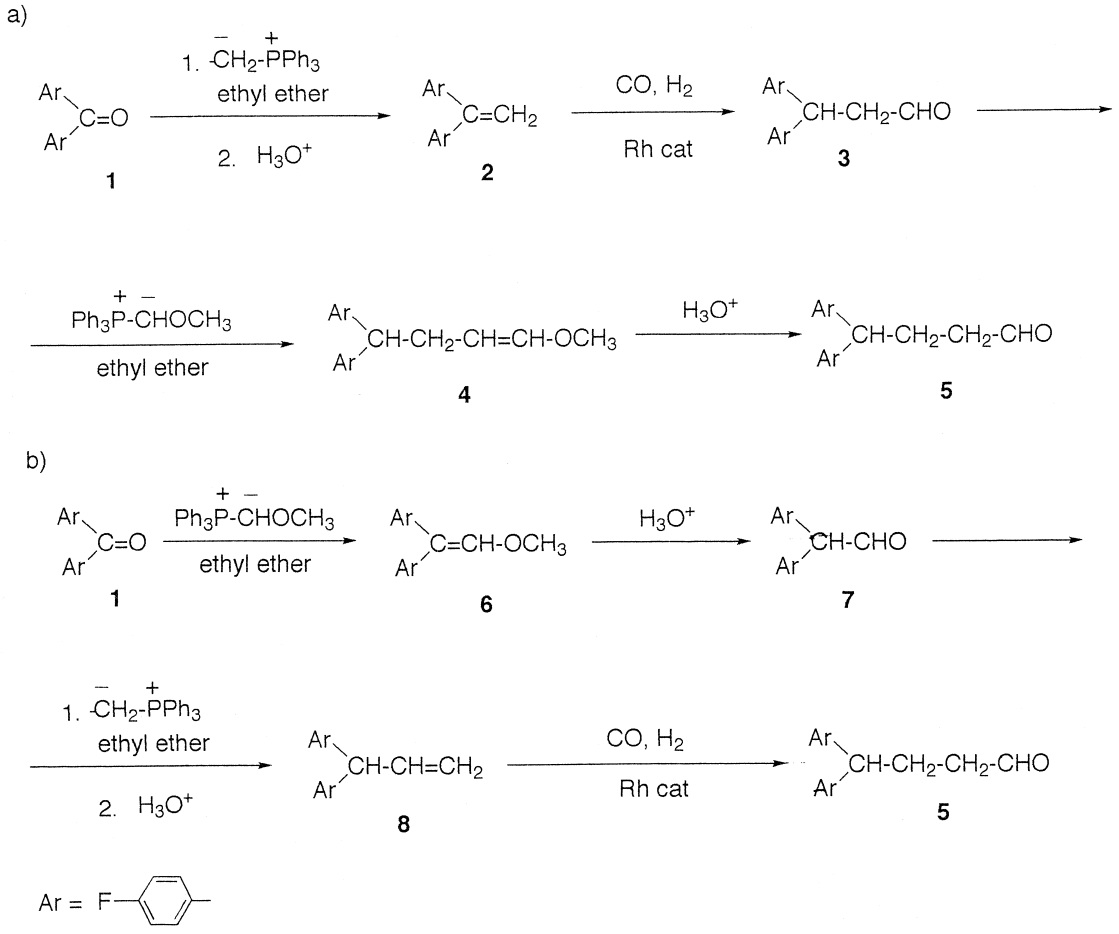
3. Results and discussion

Both preparative pathways depicted in Scheme 1 start from the commercially available 4,4′-difluorobenzophenone **1**.

According to the first route ketone **1** was converted to 1,1-bis (*p*-fluorophenyl)ethene **2** by reaction with the instant ylide CH_3-$PPh_3Br/NaNH_2$ in diethyl ether at room temperature in 88% yield [22]. Olefin **2** can be prepared in high yield also by addition of methylmagnesium iodide to ketone **1** with formation of the corresponding diaryl methylcarbinol, followed by dehydration in boiling toluene in the presence of *p*-toluenesulfonic acid [23].

1,1-Diarylethene **2** should represent a convenient candidate for the rhodium-catalyzed hydroformylation to aldehyde **3** in the light of our recent good outcomes achieved in the same reaction on 1,1-diphenylethene (88% yield of 3,3-diphenylpropanal) [18,19]. Thus, olefin **2** was subjected to a set of oxo experiments using common catalytically active rhodium carbonyl complexes that have the actual possibility to be employed also in semi-industrial scale processes. Experimental conditions and results are reported in Table 1.

From these data the following comments can be drawn: (i) reaction rates are comparable with those found for the related substrate 1,1-diphen-



Scheme 1.

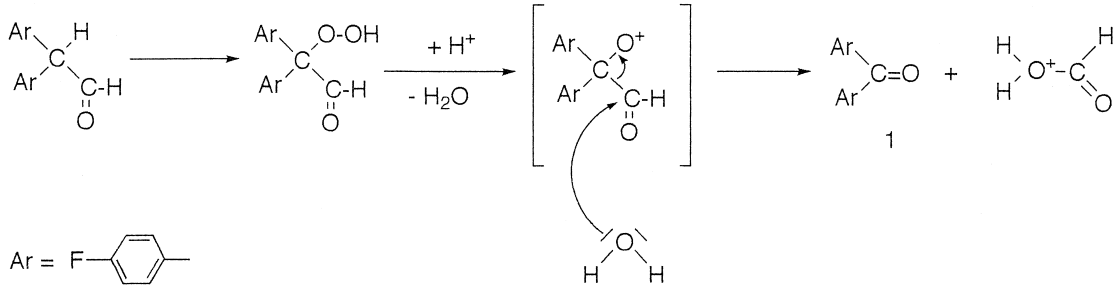
ylethene under the same reaction conditions; (ii) in some cases the chemoselectivity is rather unsatisfactory due to the catalytic reduction of the olefinic double bond that can become the prevailing reaction (entry 6); (iii) the regioselectivity towards the formation of the more useful linear aldehyde **3** is always very high (> 99%); (iv) temperature increase is beneficial for the reaction rate but brought about the partial reduction of the *oxo*-product to the corresponding alcohol (entries 3 and 8-11). The highest yields of aldehyde **3** (82–88%) were achieved with $[Rh(CO)_2Cl]_2$ at 100–120°C and 100 atm ($CO/H_2 = 1$) (entries 7, 8, 9 and 11) or in the presence of $P(OC_6H_5)_3$ or of the bulky ligand tris(2,4-di-*tert*-butylphenyl)phosphite [24].

The homologation reaction of aldehyde **3** to aldehyde **5** was accomplished by Wittig reaction using the instant ylide $CH_3OCH_2PPh_3Br/NaNH_2$ under the above reported conditions in about 83% yield [22], followed by hydrolysis of the intermediate 1-methoxy-4,4-bis(*p*-fluorophenyl)-1-butene **4** with HCl in water–diethyl ether [25]. The overall homologation yield was about 80%.

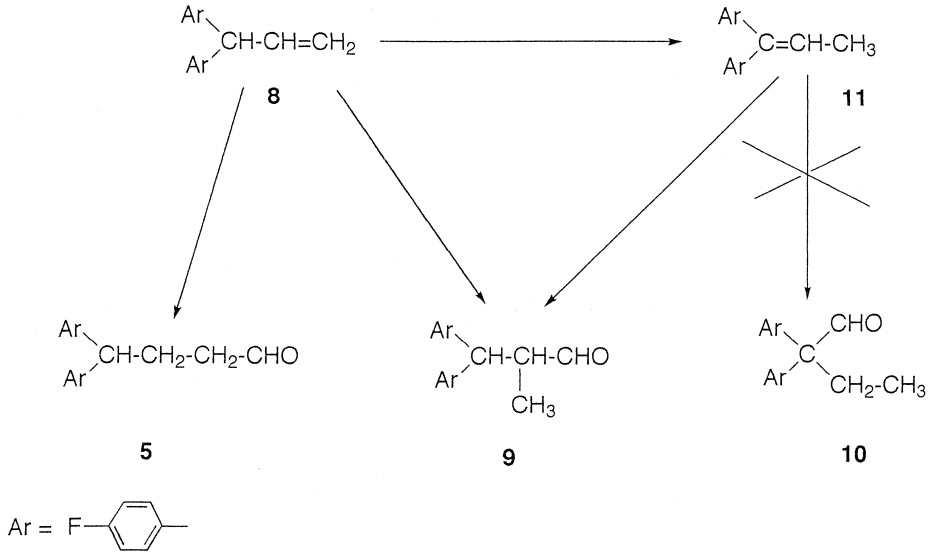
The second synthetic strategy to get aldehyde **5** is based on the preparation of 3,3-bis(*p*-fluorophenyl)propene **8** and its hydroformylation as outlined in Scheme 1b. The homologation of ketone **1** to aldehyde **7** carried out by the above described Wittig method gave the intermediate 1-methoxy-2,2′-(*p*-fluorophenyl)ethene **6** in about 90% yield [22]. The hydrolysis of this compound showed to be very sensitive towards the different acid conditions employed: the rate of formation of aldehyde **7** from its enolether precursor resulted to be rather low (60% conversion after 48 h) under the same conditions used for the preparation of aldehyde **5** from **4**; on the other hand, a longer reaction time promoted the formation of high boiling by-products deriving from aldehyde **7** decomposition. The use of a stronger acid as trifluoromethanesulfonic acid under an inert atmosphere dramatically increased the hydrolysis rate giving 90% aldehyde **7** after half an hour heating in diethyl ether/water solution. Carrying out the reaction in the air and for prolonged times resulted to be very detrimental for the chemoselectivity of the reaction, the main product being the ketone **1** imputable to the tendency of the aldehyde **7** towards air oxidation. Although no investigation was carried out by us to elucidate the mechanism of formation of the starting ketone **1**, we assume that this oxidative cleavage occurs through the steps depicted in Scheme 2: (i) peroxidation of the carbon–hydrogen bond in α-position to the carbonyl group; (ii) decomposition of this peroxide under acidic conditions with the transient formation of an electron-deficient oxygen intermediate; (iii) cleavage of the carbon–carbon bond to give ketone **1** and formic acid [26]. The aldehyde **7** was then transformed into olefin **8** by Wittig reaction with the instant ylide $CH_3PPh_3Br/NaNH_2$ in 80% yield [22].

The hydroformylation of olefin **8** was effected under the reaction conditions employed for olefin **2**: the results are collected in Table 2.

Whereas both reaction rate and chemoselectivity are higher than those found for the oxo-re-



Scheme 2.



Scheme 3.

action of **2**, the regioselectivity is quite unsatisfactory: aldehyde **5** to aldehyde **9** molar ratio resulted close to 1 in all hydroformylation experiments. This fact is to be imputed to the easy isomerization of olefin **8** to olefin **11** promoted by rhodium catalyst occurring during the oxo-reaction (Scheme 3).

Similar isomerization phenomena, by which an olefinic double bond migrates to establish the conjugation with an aromatic system under oxo-conditions, are well documented in the literature [27]. Olefin **8** did not rearrange to olefin **11** thermally at 80°C in benzene, but its isomerization took place smoothly, if a catalytic amount of $HRh(CO)(PPh_3)_3$ was present in the solution. The use of excess PPh_3 is ineffective in preventing the double bond migration (entry 2, Table 2) [28].

These results point out that only the preparative route involving the hydroformylation of 1,1-bis(*p*-fluorophenyl)ethene can be conveniently employed for the synthesis of aldehyde **5**. This intermediate can be easily transformed, for instance, into the bromide by $NaBH_4$ reduction to the corresponding alcohol [29] which in turn gives the desired bromide by reaction with Br_2/PPh_3 [30].

In conclusion, the rhodium catalyzed hydroformylation of 1,1-bis(*p*-fluorophenyl)ethene opens an alternative preparative way to achieve valuable intermediates for the synthesis of several pharmaceutical compounds. In our opinion these methods appear to be more convenient than those currently employed for the production on commercial scale of the class of therapeutically active agents containing the 1,1-bis(*p*-fluorophenyl)butyl moiety.

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