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Application of Organometallic Chemistry on Metal Surfaces to Fine Chemicals: A New Access to Trimegestone by Chemo-, Regio-, and Diastereoselective Hydrogenation of Cetaloxopromegestone on $Pt/Sn/SiO_2$ Catalysts

Valérie Gertosio,* Catherine C. Santini,*,[1] Mostapha Taoufik,* François Bayard,* Jean-Marie Basset,* Jean Buendia,† and Michel Vivat†

*Laboratoire de Chimie Organométallique de Surface, UMR 9986 CNRS-ESCPE-Lyon, 43 Bd du 11 Novembre 1918, 69616 Villeurbanne Cédex, France; and †Hoechst-Marion-Roussel Company (HMR), 102 route de Noisy, 93235 Romainville Cédex, France

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The selective hydrogenation of cetaloxopromegestone (17α-methyl-17β-(1,2-dioxopropyl)-estra-5,9-dien-3-ketal) to the ketal precursor of Trimegestone (17α-methyl-17β-(2(S)-hydroxy-1-oxopropyl)-estra-5,9-dien-3-ketal) was carried out on various silica-supported monometallic catalysts and on bimetallic platinum–tin catalysts prepared by the interaction of $Sn(CH_3)_4$ with reduced Pt/SiO_2 under H_2 at room temperature. The selective hydrogenation must occur stereoselectively at the C_{21} ketone of cetaloxopromegestone, which possesses another ketone at C_{20} and two conjugated olefinic double bonds at C_5–C_{10} and C_9–C_{11}. Of the various supported metals (Pd, Ru, Rh, Pt), the Pt/SiO_2 catalyst exhibited low chemoselectivity (52%), but the diastereoselectivity at C_{21} reached 70%. The chemoselectivity of Pt_xSn_y/SiO_2 catalysts increased from 52 to 100%. At the same time, however, the d.e. at C_{21} decreased from 70 to 30%. This inverse tendency of chemo- and diastereoselectivity upon the addition of tin can be explained by the fact that the multifunctional molecule can be coordinated to the surface either by its C_{21} carbonyl (which leads to high chemoselectivity) or simultaneously by its C=C bonds and C_{21} carbonyl (which leads to high diastereoselectivity). This substrate–catalyst binding, governed by the amount of tin that is added, controls the chemo- and diastereoselectivity via the coordination mode of the chiral cetaloxopromegestone.

Key Words: **diastereoselective; chemoselective hydrogenation; platinum–tin catalyst.**

1. INTRODUCTION

Trimegestone (17α-methyl-17β-(2(S)-hydroxy-1-oxopropyl)-estra-4,9-dien-3-one), a new progestomimetic molecule developed for the treatment of postmenopausal diseases, obtained industrially by a bioreduction process (Scheme 1, route 1) (1, 2), has also been produced by catalytic reduction with supported platinum–tin catalysts (Scheme 1, route 2) of oxopromegestone, **1** (17α-methyl-17β-1,2-dioxopropyl)-estra-4,9 dien-3-one) (3). However, a partial hydrogenation at the C_3 and C_{20} carbonyls and a weak diastereoselectivity at C_{21} were observed with this catalyst (3). This required another strategy for the synthesis of Trimegestone, **2**.

To achieve the selective hydrogenation of **1** to **2**, it was necessary to protect the ketone at C_3 (formation of the cyclic ketal **3**) and to find a new catalyst to achieve the chemo-, regio-, and diastereoselective hydrogenation of **3** to **4** (Scheme 1, route 3). The transformation of **4** to **2** occurs in acidic medium (Scheme 1, route 4) (1).

We report the catalytic results of the selective hydrogenation of **3** with supported group VIII metals, associated or not associated with tin. The method used to prepare bimetallic catalysts by surface organometallic chemistry is of particular interest for determining a structure–activity correlation. Indeed, the selective hydrogenolysis of tin–alkyl complexes on reduced metal particles leads to a new material in which the tin reacts selectively on the particle but not on the support (4–6). The careful control of this very special hydrogenolysis reaction makes it possible to place tin atoms either on the surface of the particle (below 50°C, under H_2) or in the bulk as an alloy (above 350°C, under H_2) (4). If the location of the tin on the platinum and the corresponding chemo-, regio-, and stereoselectivity of the catalytic reaction are known, then it becomes progressively possible to obtain a structure–activity relationship in catalysis on metals (3, 5, 6). This study revealed a number of parameters that can explain the catalytic role of tin additives in the control of the chemo- and diastereoselectivity of the reaction.

2. EXPERIMENTAL

The synthesis and characterization of compounds **3**, **4**, and **5** by HMR are reported in the literature (1, 2). The

[1] To whom correspondence should be addressed. Fax: 0033472431795. E-mail: santini@cpe.fr.

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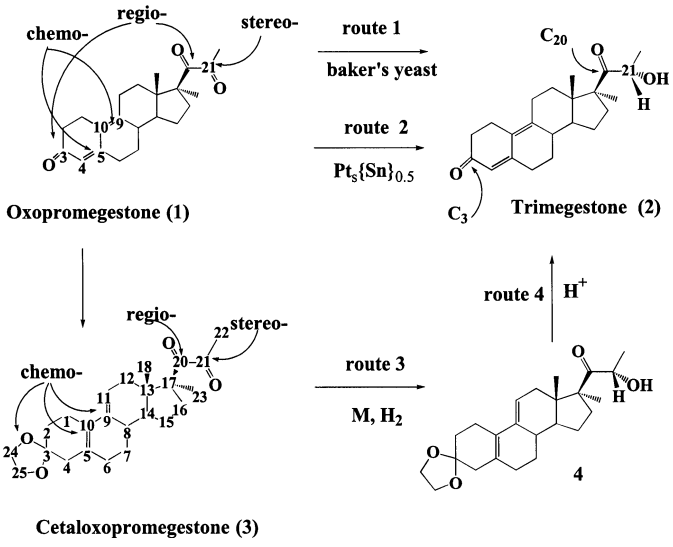


SCHEME 1. Formation of Trimegestone, **2**: route 1, stereospecific bioreduction of oxopromegestone, **1** (1, 2); route 2, reduction of oxopromegestone, **1**, with $Pt(Sn)/SiO_2$ catalyst (3); route 3, first step in the new strategy for synthesizing **2**; route 4, transformation of **4** into **2** by acidic deprotection of ketone at C_3 (1).

commercial compound tetramethylstannane was used without further purification. Ethyl acetate, heptane, cyclohexane, Tetrahydrofuran (THF), and acetic acid were purified by distillation (7).

Silica gel plates ($60F_{254}$) and thin-layer plates of silica gel (precoated silica gel 60; 0.25 mm thick; Merck) were used for thin-layer chromatography (TLC) analyses. The chromatographic chamber was saturated with the eluent vapor: cyclohexane/ethyl acetate (60/40, v/v). Spots were detected by UV or by spraying with a sulfuric acid solution (5% sulfuric acid in ethanol, v/v).

High-performance liquid chromatography (HPLC) analyses were carried out using the following conditions: column Waters, WAT054275; symmetry C_{18}; %C 19; spherical particles; pore size, 100 Å, 5 μm; l = 25 cm; d = 4.6 mm; eluent, acetonitrile–water 70/30 (v/v); flow rate, 1 ml/min; detection, UV 210 nm.

Infrared spectra were recorded with a Nicolet 550 spectrometer.

^{1}H, ^{13}C, and ^{13}C DEPT (Distortionless Enhancement by Polarization Transfer) nuclear magnetic resonance (NMR) spectra were recorded, in $CDCl_3$, using a Brüker AC 300 spectrometer at 300 MHz for proton and 75.48 MHz for carbon. Chemical shifts are given in parts per million with respect to TMS as internal standard.

2.1. Formation and Characterization of Hydrogenated Products of *3*

To identify some of the products of an unselective hydrogenation, the reactions of **3** with $NaBH_4$, which reduces only the C=O bonds (18), and with a Pd/C catalyst, which reduces only the C=C bonds (18), were carried out. All the reduction products were separated and purified by preparative TLC (eluent: cyclohexane/ethyl acetate, 60/40). Each spot was analyzed by infrared (IR) spectroscopy and ^{1}H and ^{13}C NMR spectroscopy. The data for **3**–**5** were compared to original samples (1, 2). The compounds **6**–**13** were identified by ^{13}C NMR. Using HPLC, it was therefore possible to associate a definite product with each retention time as well as with its response factor. In this way, the catalytic hydrogenation of **3** could be monitored by HPLC.

2.1.1. Unsaturated-α-hydroxyketones, ***4***–***7***. $NaBH_4$ (21.10 mg, 55.8 mmol), dissolved in 3 ml THF : H_2O (1 : 1), was added to a solution of **3** (200.8 mg, 52.3 mmol) in 15 ml THF at room temperature. After 5 h at this temperature, the solvents were removed under vacuum and the residue was extracted with dichloromethane. After washing with water, the organic phase was dried and the solvents were distilled under vacuum. Thin-layer chromatography showed that there were four spots, at R_f 0.3, 0.5, 0.63, and 0.8 (with cyclohexane/ethyl acetate (60/40) as eluent), in the crude mixture that were attributed to the following:

α-Dihydroxy-20,21. $R_f = 0.3$; HPLC, $R_f = 5.5$ min; IR ($CDCl_3$): ν(O–H) 3450 cm^{-1}.

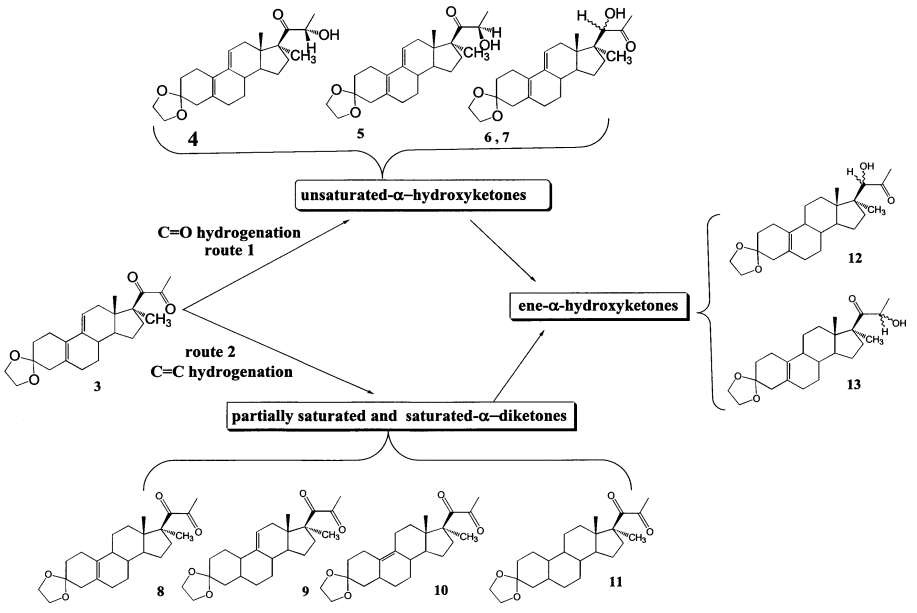
α-Hydroxyketone 21-OH(S), **4**, and α-hydroxyketone 21-OH(R), **5**. (**4**) $R_f = 0.5$; HPLC, $R_f = 8.0$ min; (**5**) $R_f = 0.5$; HPLC, $R_f = 9.0$ min; IR ($CDCl_3$): ν(O–H) 3450 and ν(C=O) 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ_{ppm}): 5.6 (s) C_{11}–H, 4.5 (m) C_{21}–H (**4**), 4.4 (m) C_{21}–H (**5**), 3.9 (s) $C_{24}H_2$, $C_{25}H_2$, 3.75 (d) C_{21}–OH (**4**), 3.1 (d) C_{21}–OH (**5**), 1.4–2.7 (m) CH_2, 1.35 (d) C_{22}–H, 1.15 (s) C_{23}–H, 0.65 C_{18}–H (s); ^{13}C NMR ($CDCl_3$, δ_{ppm}): (**4**) 218.7 C_{20}, 135 C_9, 129.8 C_5C_{10}, 125.2 C_5C_{10}, 118 C_{11}, 108 C_3, 71.4 C_{21}, 64 C_{24}, C_{25}, 60.5 C_{17}; (**5**) 218.5 C_{20}, 135 C_9, 129.8 C_5C_{10}, 126 C_5C_{10}, 118 C_{11}, 108 C_3, 71.3 C_{21}, 64 $C_{24}C_{25}$, 60.2 C_{17}.

α-Hydroxyketone 20-OH(S + R), **6** and **7**. $R_f = 0.63$; HPLC, $R_f = 11.0$ min; IR ($CHCl_3$): ν(O–H) 3450, ν(C=O) 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ_{ppm}): 5.6 (s) C_{11}–H, 4.3 (d) C_{20}–H, 3.9 (s) $C_{24}H_2$,$C_{25}H_2$, 3.7 (d) C_{20}–OH, 1.4–2.7 (m) CH_2, 2.3 (s) C_{22}–H, 1.15 (s) C_{23}–H, 0.7–0.9 (m) C_{18}–H ppm; ^{13}C NMR ($CDCl_3$, δ_{ppm}): (**5**–**6**) 211.2 C_{21}, 135 C_9, 129 C_5C_{10}, 126 C_5C_{10}, 118 C_{11}, 108 C_3, 71.3 C_{20}, 64 C_{24}, C_{25}, 58.3 C_{17}.

3. $R_f = 0.8$; HPLC, $R_f = 10.0$ min; ^{13}C NMR ($CDCl_3$, δ_{ppm}): 206.5, 200.7 $C_{20}C_{21}$, 135 C_9, 129.8 C_5C_{10}, 125.2 C_5C_{10}, 118 C_{11}, 108 C_3, 64 $C_{24}C_{25}$, 56.8 δC_{17}.

The response factor in the HPLC of these compounds was 0.65.

2.1.2. Saturated and partially unsaturated α-diketones, ***8***–***11***. The hydrogenation of **3** (200 mg, 52.1 mmol) in 25 ml ethyl acetate with a Pd/C catalyst (42.6 mg (52×10^{-2} mmol)) at 25°C and under 80 bar of hydrogen resulted in 185 mg of yellow wax. Thin-layer chromatography (eluent: cyclohexane/ethyl acetate, 60/40) indicated that there were four spots in the crude mixture, which were



SCHEME 2. Reaction routes in the hydrogenation of cetaloxopromegestone **3**.

attributed to the compounds **8** to **11**. Their retention times in the HPLC chromatogram were between 23.7 and 30.5 min. The ^{13}C NMR data indicate that only C=C bonds were reduced and that C=C bonds were partially hydrogenated in **8** and **9**, partially hydrogenated and isomerized in **10**, and totally hydrogenated in **11**.

The ^{13}C NMR data of the compounds **8** to **11** in $CDCl_3$ are as follows (δ_{ppm}): 200.7–207.3 C_{21} and C_{20}, 131 C_9, 130 C_5C_{10}, 126 C_5C_{10}, 120 C_{11}, 108.7–108.2 (3 peaks) C_3, 64.4 and 64.3 $C_{24}C_{25}$, 58.7 and 58.5 C_{17}.

The response factor in the HPLC of these compounds was 0.7.

*2.1.3. Saturated and partially unsaturated α-hydroxyketones **12** and **13**.* Under the same experimental conditions as described previously, a mixture of **4** to **7** in 25 ml ethyl acetate was hydrogenated with a Pd/C catalyst (42.6 mg; 52×10^{-2} mmol) at 25°C and under 80 bar of hydrogen to give a yellow residue. This crude mixture was purified using preparative TLC, with cyclohexane/ethyl acetate (60/40) as eluent. It showed two spots corresponding to **12** and **13** respectively, at $R_f = 9.8$ and 12.8 min in HPLC. The ^{13}C NMR data of the compounds **12** and **13** in $CDCl_3$ are as follows (δ_{ppm}): 218.8, 217.4 C_{21} or C_{20} (**12** and **13**), 129.5 (**12**), 129.1 (**13**) C_5C_{10}, 125.6 (**12**), 125.5 (**13**) C_5C_{10}, 109.1, 108.1 C_3, 71.3 C_{21} or C_{20}, 64.7 and 64.3 $C_{24}C_{25}$, 60.2 and 60.1 C_{17}.

The ^{13}C NMR spectra showed only two peaks, in the region of the $\delta_{C=C}$ resonance, for each compound, 129.5 and 125.6 ppm for **12** and 129.1 and 125.5 ppm for **13**, instead of four peaks (135 C_9, 129 C_5C_{10}, 126 C_5C_{10}, 118 C_{11}) for the compounds **4**–**7** which have two C=C bonds (C_5–C_{10} and C_9–C_{11}). ^{13}C DEPT NMR spectra indicated that these resonances for **12** and **13** were due to quaternary carbon. Consequently, only the double bond C_5–C_{10} is present in compounds **12** and **13** and the double bond C_9–C_{11} has been hydrogenated.

All the synthesized compounds **4** to **13** are depicted in Scheme 2.

2.2. Catalyst Preparation and Characterization

2.2.1. Monometallic catalysts. Degussa Aerosil 200 silica with a surface area of about 200 m^2/g was used as the support for Ru, Rh, Pd, and Pt. The support was calcined in an air flow at 500 °C before impregnation.

Pd/C (4.5%, Disp. = 26%), Ru/C (5%, Disp. = 55.7%), and Ru/Al_2O_3 (5%, Disp. = 20%) were purchased from Aldrich. The Ru/SiO_2 (1.4%) catalyst was prepared by treating dehydroxylated silica with $Ru_3(CO)_{12}$ in dichloromethane in an argon atmosphere (8). The Rh/SiO_2 (1.6%), Pt/SiO_2 (1.46 and 1.32%), and Pd/SiO_2 (1.3%) catalysts were obtained by ionic exchange of $[Rh(NH_3)_5Cl_2]^+Cl^-$ and $[M(NH_3)_4]^{2+}(OH^-)_2$ (M = Pt and Pd, respectively) with surface protons of silica (6, 9).

All the precursors were then washed, dried, and decomposed by calcination at 400°C in a stream of nitrogen/oxygen (5/1). All monometallic catalysts, except for Pd/C, were reduced in a flow of H_2 at 350°C overnight before the hydrogenation reaction.

Dispersion of supported metals, expressed as the fraction of the number of surface atoms to the total number of atoms (M_s/M_t), was calculated from H_2 chemisorption data, obtained in a static volumetric apparatus (Table 1). According to transmission electron microscopy, the average sizes of the metal particles in Rh/SiO_2 and Pt/SiO_2 catalysts were

TABLE 1

Characteristics of Monometallic Catalysts

Catalyst	% Metal	H/M values (pressure H_2)	Reference	Dispersion (%)
Pd/SiO_2	2.3	1 (20 mbar)	10, 11	90
Pd/C*	5	1 (20 mbar)	10, 11	25
Pt/SiO_2	1.46	1.8 (150 mbar)	12–15	47
Pt/SiO_2	1.32	1.8 (150 mbar)	12–15	39
Rh/SiO_2	1.26	1.3 (15 mbar)	9	93
Ru/SiO_2	1.37	1 (100 mbar)	16, 17	60
Ru/Al_2O_3*	5	1 (100 mbar)	16, 17	56
Ru/C*	5	1 (100 mbar)	16, 17	20

about 1 and 2 nm, respectively, in good agreement with chemisorption data.

2.2.2. Bimetallic catalyst $Pt(Sn)_n/SiO_2$. The preparation of the bimetallic catalysts has been described elsewhere (3). Pt/SiO_2 was reduced at 350°C in a flow of hydrogen for 4 h. At room temperature, the hydrogen was flushed from the reactor with argon and the catalyst was transferred to a Schlenk tube. The desired amounts of tetramethylstannane and *n*-heptane (10 ml) were added. The mixture was stirred at room temperature for 22 h under hydrogen. At the end of the reaction the gas phase analysis was performed as follows: The Schlenk tube was connected to a calibrated 6-liter flask, itself under vacuum. The stopcock between the Schlenk tube and the 6-liter flask was opened to allow the gases in the sample tube to expand into the calibrated 6-liter flask. A sample of the gas was withdrawn through a septum and analyzed by gas chromatography (GC). The quantity of evolved methane determined by GC analysis (capillary column, KCl/Al_2O_3; 130°C) showed that all the tin–carbon bonds had been hydrogenolyzed. The Schlenk tube was then placed under dry argon, and the solid was washed with *n*-heptane to eliminate physisorbed or unreacted tetramethylstannane (0 to 5% of introduced tetramethylstannane) and dried under vacuum (10^{-4} Torr (1 Torr = 1.33 N/m^2) at 50°C for 1 h).

Elemental analysis (CNRS, Service Central d'Analyse, 69390 Vernaison, France) of the bimetallic catalyst gave the number of grafted tin atoms per surface platinum atom defined as n ($n = Sn/Pt_s$). These catalysts are described as $Pt_s(Sn)_n/SiO_2$. Elemental analysis performed before and after the catalytic run showed no decrease in the Sn content.

2.3. Catalytic Tests of Cetaloxopromegestone Hydrogenation

Hydrogenation was carried out in a Parr 4560 minireactor, fitted with a mechanical stirrer, at 25°C under 80 atm of H_2. The experimental conditions were the same for all catalytic runs: 52.1 mmol of **3**, 25 ml of ethyl acetate, ratio substrate/surface atom = 100. In a typical run, 0.25 g of cetaloxopromegestone, **3**, was dissolved in 25 ml ethyl acetate under argon. The powder of reduced monometallic or dried platinum–tin catalyst was then carefully introduced into the autoclave in a flow of argon. Monitoring and quantification of the reaction were carried out by HPLC. At the end of each catalytic run, ^{13}C NMR analyses of the crude products were performed after filtering the catalyst and evaporating the solvents.

After reaction with acetic acid and perchloric acid, the ketone C_3 was regenerated (1). Thus, **4** produced **2**, which was fully identified by comparison with the data of an authentic sample of **2** (provided by HMR). The diastereoselectivity (d.e) value (100 [*S* (**4**) − *S* (**5**)]/[*S* (**4**) + *S* (**5**)]) was determined by ^1H NMR, either from the ratio of the area of the resonance H–C_{21} (4.5 (m) and 4.4 (m) for **4** and **5**) or from the ratio of the area of the resonance HO–C_{21} (3.75 (d) **4** and 3.1 (d) **5**) and by HPLC from the ratio of the area of the peaks of **4** and **5**.

3. RESULTS

The starting substrate, cetaloxopromegestone **3**, is a multifunctional chiral molecule, which provides a good test for chemo-, regio-, and diastereoselective catalysis. Thus, the hydrogenation of **3** can take place at three different sites: (i) cyclic ketal at C_3, (ii) two carbon–carbon double bonds at $C_{5,10}$ and $C_{9,11}$, and (iii) the two ketones at C_{20} and C_{21} (Scheme 1). When only ketones are reduced (Scheme 2, route 1), the unsaturated α-hydroxyketones, **4** to **7**, are formed. When only carbon–carbon double bonds are reduced (Scheme 2, route 2), saturated and partially saturated diketones, **8** to **11**, are obtained. Both series of compounds can then be reduced further to yield **12** and **13**, saturated alcohols and fully reduced products.

In this work, chemoselectivity refers to the reduction of the ketone at C_{20} and C_{21} vs all possible reduced products, regioselectivity to the reduction of the ketone at C_{21} vs all possible reduced products, and diastereoselectivity to the Si/Re reduction at C_{21}. If $S(\boldsymbol{n})$ is the selectivity in $\boldsymbol{n}$, i.e., the ratio between the amount of desired product and the amount of substrate consumed, $S(\boldsymbol{n}) = (\boldsymbol{n})/(\mathbf{3})_0 - (\mathbf{3})_t$, the chemoselectivity ($S_{C=O}$), regioselectivity (RS), and diastereomeric excess (d.e) are defined by the following equations:

$$S_{C=O} = S(\mathbf{4}) + S(\mathbf{5}) + S(\mathbf{6}) + S(\mathbf{7}) \quad [1]$$

$$RS = S(\mathbf{4}) + S(\mathbf{5}) + S(\mathbf{13}) \quad [2]$$

$$\text{d.e. } C_{21} = 100[S(\mathbf{4}) - S(\mathbf{5})]/[S(\mathbf{4}) + S(\mathbf{5})] \quad [3]$$

3.1. Catalytic Hydrogenation of Cetaloxopromegestone, *3*

Selectivity in heterogeneous catalytic hydrogenation depends on a complex set of factors, such as the nature of the catalyst, the reaction medium, and the reaction

conditions (21). For a selective hydrogenation, the most important parameter is the nature of the metals and their additives.

3.1.1. Monometallic catalysts. Whatever the catalyst, the ketal functionality was not cleaved. The activities of Pd, Ru, Pt, and Rh in the hydrogenation of cetaloxopromegestone **3** are as follows: Pd ≫ Ru > Pt ≫ Rh. With Rh/SiO_2, no reduction was observed at room temperature. These metals can be divided into two groups: with Pd and Rh catalysts, the hydrogenation of the C=C double bonds was favored (Scheme 2, route 2). These results are in good agreement with the literature (21). These metals cannot be used effectively for the selective hydrogenation of carbonyl groups in the presence of carbon–carbon double bonds (21). With Pd/SiO_2 (dispersion of 90%) and Pd/C (dispersion of 25%), the conversion of **3** was rapid and gave the α-diketones **8** to **11**, all these compounds being primary products. With Rh/SiO_2, but at higher temperatures (60 and 160°C), the reduction occurred, but all the products **4** to **11** were obtained. On the other hand, with Ru and Pt the reduction of the keto groups was favored (Scheme 2, route 1).

With Ru/SiO_2, the complete conversion of **3** was obtained after 30 h (Fig. 1). At the beginning, only the ketones were reduced to the unsaturated α-hydroxyketones **4** to **7**. After 14 h, there was hydrogenation of carbon–carbon double bonds and formation of **12** and **13**. Conversion was about 80% and the hydrogenation was fully chemoselective. After 30 h, the chemoselectivity was 86% and the regioselectivity 80%; the diastereoselectivity, however, was only 7%. Modification of the nature of the support (C, SiO_2, Al_2O_3), of the temperature (8, 25, 60°C), and of the nature of the solvent (ethyl acetate, toluene, tetrahydrofuran) had only a small effect on the selectivity of the hydrogenation of **3** (Table 2). The chemoselectivity was always very high

TABLE 2

Hydrogenation of 3 with Ru Catalysts

Experimental conditions	d.e. at C_{21}	$S_{(C=O)}$	Conversion % (h)
Ru/SiO_2, 8°C	9	100	40 (60)
Ru/SiO_2, 25°C	7	85	100 (30)
Ru/SiO_2, 60°C	0	89	100 (20)
Ru/SiO_2, 25°C, toluene[a]	7	100	100 (20)
Ru/SiO_2, 25°C, THF[b]	7	100	60 (60)
Ru/C, 25°C	—	—	N.R.
Ru/Al_2O_3, 25°C	12	100	25 (30)

Note. $P_{H_2} = 80$ atm, (**3**)/[Ru_S] = 100, V (AcOEt) = 25 ml.
[a] Solvent = toluene.
[b] Solvent = THF.

(largely above 80%), but the diastereoselectivity never exceeded 12%.

With Pt/SiO_2, the conversion of **3** was complete after 50 h. At 95% conversion, all the products **4** to **11** (unsaturated α-hydroxyketones and partially and saturated α-diketones) were present in the following proportions: 21-OH (S), **4** (33%); 21-OH (R), **5** (6%); 20-OH (R + S), **6** and **7** (13%); 20-OH (R + S)-(5-10)-ene, **12** (9%); 21-OH (R + S)-(5-10)-ene, **13** (30%), and saturated α-diketones **8**, **9**, **10**, and **11** (9%) (Fig. 2). With the exception of **12** and **13** all these compounds are primary products.

The chemoselectivity increased with conversion from 10 to 52% (Fig. 3). The regioselectivity of the hydrogenation was equal to 69%. The diastereoselectivity (d.e. at C_{21}) for the formation of **4** was equal to 70% and did not vary with conversion (Fig. 3).

It is interesting that with ruthenium and platinum **4** was obtained. As mentioned previously, the reduction of **1** with the same catalysts did not give **2** due to the competitive

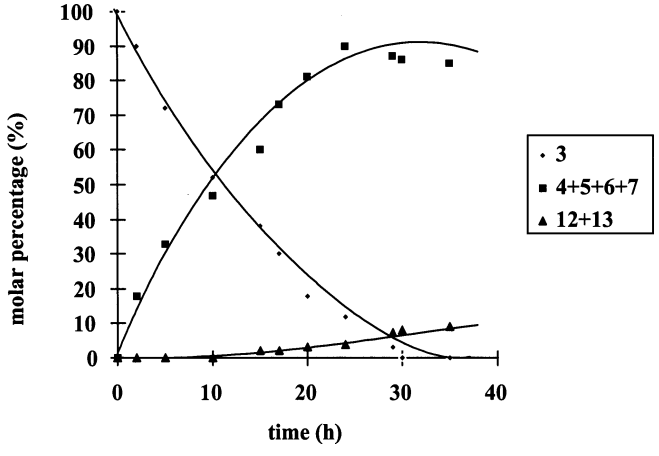


FIG. 1. Conversion of **3** in the presence of Ru/SiO_2 as the catalyst (Ru, 1.37%; dispersion, 60%) [(**3**)] = 2.1 mol/L, m (Ru/SiO_2) = 64 mg (P_{H_2} = 80 atm, 25°C, (**3**)/[Ru_S] = 100, V(AcOEt) = 25 ml).

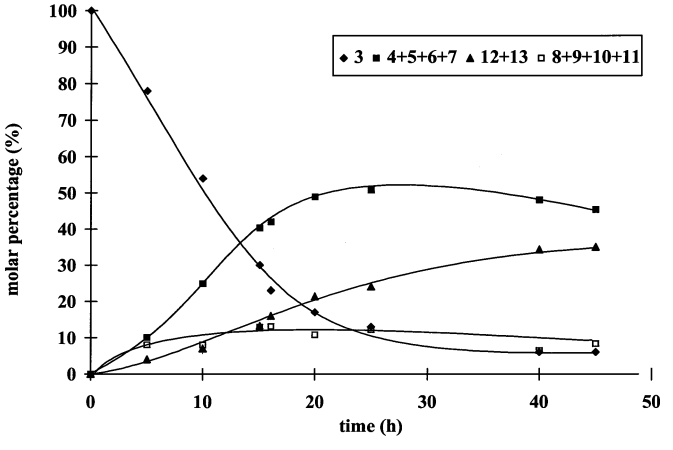


FIG. 2. Evolution of the product composition with time during the reduction of **3** in the presence of Pt/SiO_2 (Pt = 1.46, 1.32% , dispersion = 47%) as catalyst. ([(**3**)] = 2.1 mol/L, m (Pt/ SiO_2) = 152 mg (P_{H_2} = 80 atm, 25°C, (**3**)/[Pt_S] = 100, V(AcOEt) = 25 ml).

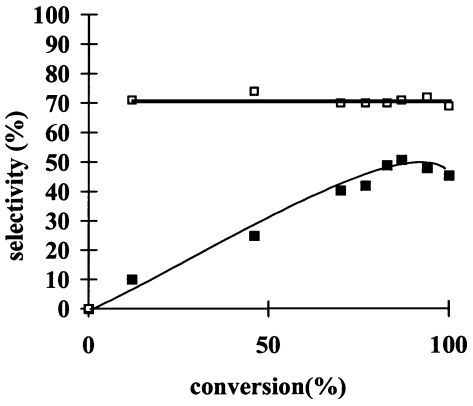


FIG. 3. Evolution of chemoselectivity (■) and diastereoselectivity (□) with conversion during the reduction of **3** in the presence of Pt/SiO_2 (Pt = 1.46, 1.32%, dispersion = 47%) as catalyst ([(**3**)] = 2.1 mol/L, *m* (Pt/SiO_2) = 152 mg (P_{H_2} = 80 atm, 25°C, (**3**)/[Pt_s] = 100, *V*(AcOEt) = 25 ml).

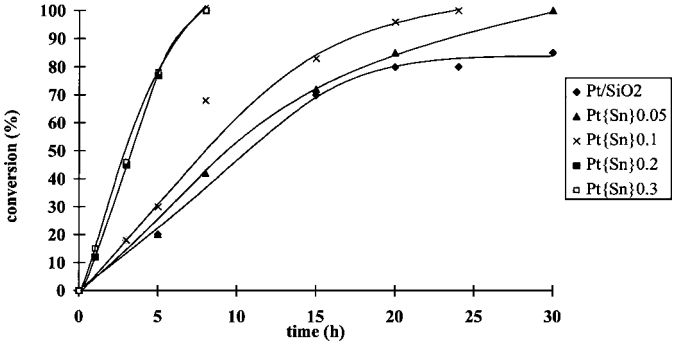


FIG. 4. Evolution of molar percentage of **3** with time during the reduction in the presence of $Pt(Sn)_n/SiO_2$ ($n = 0, 0.05, 0.1, 0.2, 0.3$) as catalyst ($P_{H_2}$ = 80 atm, 25°C, (**3**)/[Pt_S] = 100, *V*(AcOEt) = 25 ml).

reduction of the carbonyl at C_3 (3) (see Scheme 1). This means that the carbonyl at C_3, which is the least hindered, must be protected to enable the regioselective reduction at C_{21}.

3.1.2. Bimetallic catalyst. The catalytic properties of group VIII metals can be strongly modified through interaction with organometallic compounds such as R_4Sn (4–6). In particular, it was found that the presence of Sn alkyl fragments or Sn adatoms on the surface of Rh completely reversed the chemoselectivity of this metal in the hydrogenation of α,β-unsaturated aldehydes (22) or of aromatic ketones (23). In particular, with the platinum–tin catalysts, the chemoselectivity in the reduction of the carbonyl of oxopromegestone **1** increased significantly (3).

The $Pt_s(Sn)_n/SiO_2$ catalysts were prepared by the selective hydrogenolysis of $Sn(CH_3)_4$ in a solution of *n*-heptane with reduced Pt/SiO_2. The number, *n*, of tin atoms grafted onto surface platinum atoms varied from 0 to 0.3. For these values, all the tin–carbon bonds were fully hydrogenolyzed (see Experimental). Therefore, it is assumed that the platinum surface was modified by tin(0) adatoms (4). Elemental analysis performed on catalysts before and after catalytic runs did not reveal a detectable change in the Sn percentage.

The formation of Pt–Sn bonds usually decreases the activity of platinum catalysts (3–6). Interestingly, when the ratio Sn/Pt_s changed from 0 to 0.3, the total conversion of **3** was obtained five times faster (Fig. 4). Different research groups have already observed an increase in the activity of the hydrogenation of α–β unsaturated aldehydes (5, 6, 24) on addition of Sn to Pt catalysts.

The chemoselectivity increased with increasing Sn/Pt_s ratio to reach a value of 100% for an Sn/Pt_s ratio of 0.3. The regioselectivity (80%) did not change with the Sn/Pt_s ratio. In contrast, the diastereoselectivity at C_{21} decreased from 69 to 25% when the Sn/Pt_s ratio varied from 0 to 0.3 (Table 3).

With the Pt/Sn catalyst, as with the Pt catalyst, the cyclic ketal group was not cleaved, and the regio- and diastereoselectivity (80 and 25%, respectively) did not change with the conversion.

4. DISCUSSION

The hydrogenation of **3** on silica-supported Ru, Rh, Pd, and Pt catalysts was investigated under similar

TABLE 3

Hydrogenation of 3 with $Pt(Sn)_n/SiO_2$ ($n = 0$–0.3) Catalysts

$Pt(Sn)_n/SiO_2$	Reaction time (h)	Yield **8**–**13** (%)	Yield **6** and **7** (%)	Yield **5** (%)	Yield **4** (%)	Selectivity Chemo. (%)	Regio. (%)	d.e. C_{21} (%)
Pt/SiO_2	40	48	13	6	33	52	69	69
$Pt(Sn)_{0.05}$	43	20	19	11	50	80	76	63
$Pt(Sn)_{0.1}$	24	14	19	23	44	86	78	31
$Pt(Sn)_{0.2}$	8	6	19	26	49	94	80	31
$Pt(Sn)_{0.3}$	8	0	20	30	50	100	80	25

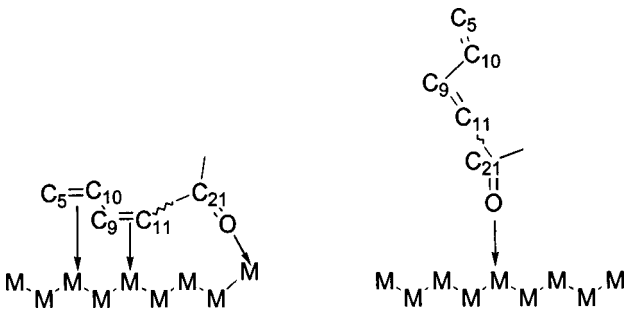


FIG. 5. Different possibilities of adsorption of the keto-α-β unsaturated moiety of **1** on a metallic surface.

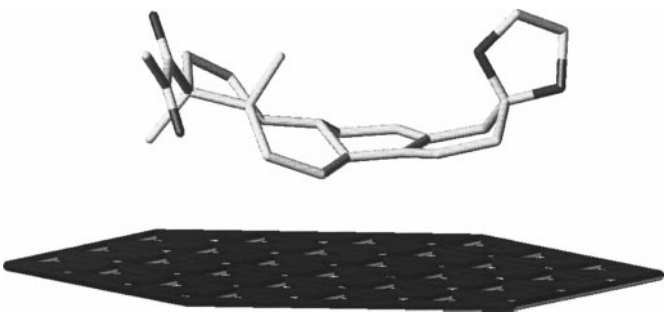


FIG. 6. Selective adsorption of **3**, through its alpha face, on an idealized Pt(111) face.

experimental conditions. This hydrogenation of a multifunctional chiral molecule must occur in a chemo-, regio-, and stereoselective way at the C_{21} ketone of the molecule, which also possesses another ketone at C_{20} and two conjugated olefinic double bonds at C_5–C_{10} and C_9–C_{11}. Of the various supported metals (Pd, Ru, Rh, Pt), Pt is the only metal that exhibits an intrinsic high diastereoselectivity at C_{21} (70%) with good regioselectivity (80%) and moderate chemoselectivity (52%). The other group VIII metals exhibit diastereoselectivity close to zero or none at all with varying degrees of chemoselectivity (100% for Ru and 0% for Pd).

One of the key results of this work is that with Pt_x Sn_n/SiO_2 catalysts (with increasing n values, $n = 0.05$, 0.1, 0.3) the chemoselectivity increased from 52 to 100% and, at the same time, the d.e. at C_{21} decreased from 70 to 30% (Table 3).

These results show the inverse relationship between chemo- and diastereoselectivity upon the addition of tin. This phenomenon can be explained in the following way: the multifunctional molecule can be coordinated to the metallic surface either through the C_{21} carbonyl (Fig. 5, right) or simultaneously through the C=C bonds and the C_{21} carbonyl (Fig. 5, left). This versatile behavior of a ligand, the molecule 3 in our case, is referred to as hapticity.

The most stable conformation of **3** was determined using a semi-empirical method (25, 26). In this low energy conformation, the adsorption of **3** on an idealized Pt(111) surface showed that **3** would be selectively coordinated to the surface, via its alpha face, through the C=C bond and the C_{21} carbonyl simultaneously (Fig. 6). This multiple-center coordination, through several multiple bonds of **3**, will induce the C_{21} carbonyl to be hydrogenated stereoselectively to the right diasteromer **4**. However, the drawback is the partial hydrogenation of the C=C double bond which decreases the chemoselectivity.

This multiple-center coordination, through several multiple bonds, is not allowed in the case of Pt/Sn due to the noncoordinating power of $Sn^{(0)}$ toward C=C double bonds. Only the carbonyl groups are coordinated to platinum in an η_1-mode (28) (Fig. 5, right). This induces high chemoselectivity but low diastereoselectivity, because the molecule can freely rotate around the Pt–O–C_{21} moiety. Thus, the substrate–catalyst binding, governed by the amount of tin, controls the chemo- and the stereoselectivity via the coordination mode of the chiral cetaloxopromegestone.

It is of interest that these results correlate with those already published by us of the diastereoselective hydrogenation of oxopromegestone, **1**, to 3β-OH. In the absence of tin, silica-supported platinum reduces **1** to 3β-OH (Fig. 7; Scheme 3) with a chemoselectivity of 24% but with a d.e. at C_3 of 100%. With the $Pt/Sn_{0.5}$ catalyst, the chemoselectivity reaches 93%, but diastereoselectivity at C_3 decreases to 34% (3). Here also there is a reverse and continuous evolution between chemo- and diastereoselectivity with increasing amounts of tin. Figure 7 shows this reverse tendency for the two substrates **1** and **3**. The explanation proposed for the effect of the hapticity of the substrate in the chemisorbed state on the resulting diastereoselectivity is valid for the diastereosective hydrogenation at both the C_3 and the C_{21} carbonyl.

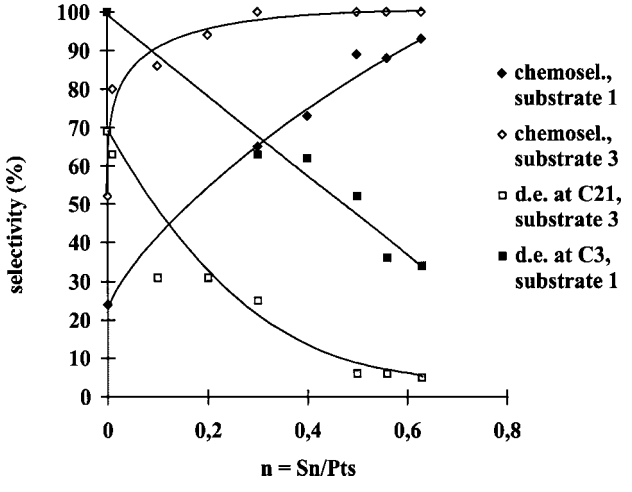
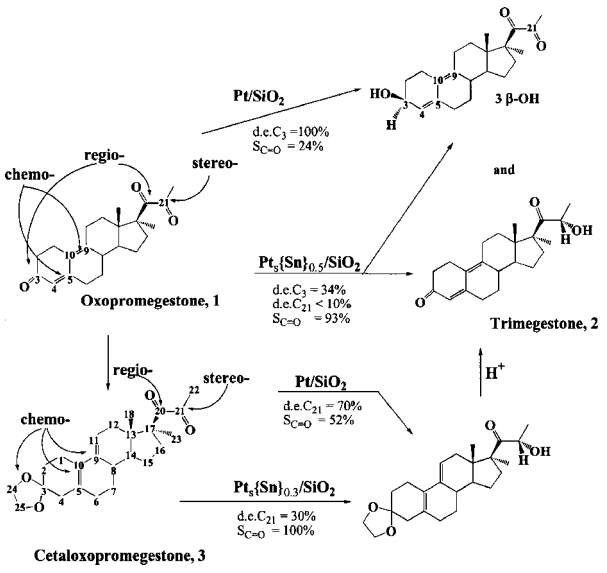


FIG. 7. Comparison of the evolution of chemo- and diastereoselectivity during the reduction of **1** and **3** in the presence of the $Pt(Sn)_n/SiO_2$ ($n = 0$–0.6) catalyst.



SCHEME 3. Chemo-, regio-, and, diastereoselective hydrogenation of oxopromegestone and cetaloxopromegestone on $Pt/Sn/SiO_2$ catalysts: possible new access to Trimegestone, **2**.

5. CONCLUSION

The selective hydrogenation of cetaloxopromegestone (17α-methyl-17β-(1,2-dioxopropyl)-estra-5,9-dien-3-ketal) (**3**) to the ketal precursor of Trimegestone (17α-methyl-17β-(2(*S*)-hydroxy-1-oxopropyl)-estra-4,9-dien-3-one) (**4**) depends on catalysts with a high degree of chemoselectivity (selective hydrogenation of the carbonyl versus the internal carbon–carbon double bond), regioselectivity (hydrogenation of the C_{21} ketone), and stereoselectivity (selective formation of the 21(S)–OH alcohol).

The ruthenium catalyst was found to be highly chemoselective but had almost no diastereoselectivity. Platinum was not chemoselective but the diastereoselectivity reached 70%. For the $Pt_s(Sn)_n/SiO_2$ catalyst with *n* smaller than 0.3 the chemoselectivity reached 100% but the diastereoselectivity decreased sharply to 30%.

These results have been explained by the hapticity of the substrate, i.e., the way in which the substrate is coordinated to the catalyst surface. This substrate–catalyst binding controls the transition state structure, and the chemo- and stereoselectivities occur at this stage. Note that the protection of ketone C_3 has proved to be effective in increasing the selectivity in product **4**.

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