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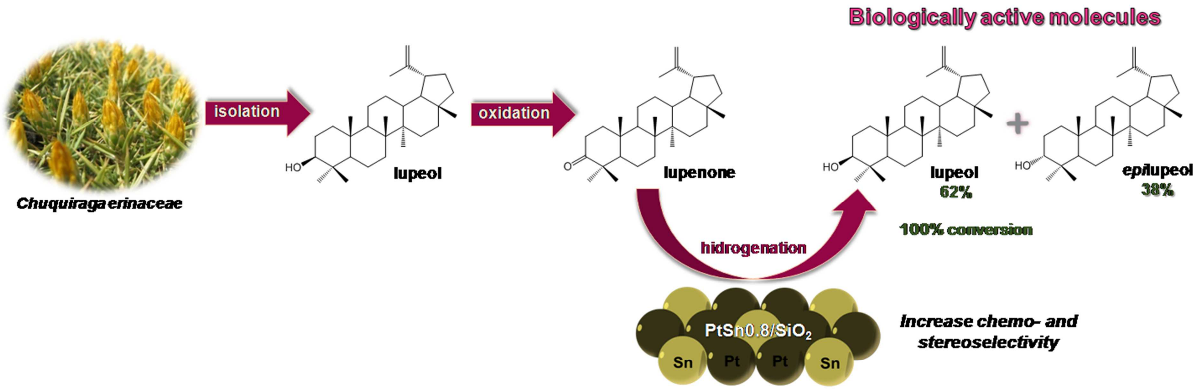

Biologically active molecules
isolation
oxidation
Chuquiraga erinaceae
HO
lupeol
O
lupenone
HO
lupeol
62%
HO
epi-lupeol
38%
100% conversion
hidrogenation
PtSn0.8/SiO2
Sn
Pt
Pt
Sn
Increase chemo- and stereoselectivity

Novel access to *epi*lupeol through chemoselective hydrogenation of lupenone using platinum-based organotin catalysts

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Keywords: hydrogenation of lupenone, PtSn, *epi*lupeol

ABSTRACT

Catalytic hydrogenation of terpenes constitutes one of the most interesting reactions in the transformation of natural products. One of the key goals in this synthesis is the selective hydrogenation of the C=O bond for obtaining biologically active epimeric alcohols. In the present work, the use of Pt and Pt-Sn catalysts supported on silica was studied as an alternative to the chemoselective hydrogenation of lupenone. It was observed that Sn produces geometric and electronic modifications that lead to improvement in the chemo- and stereoselectivity of the desired product.

1. INTRODUCTION

Numerous studies conducted over the last decade have revealed the importance of using natural products as a source of bioactive compounds for the development of new drugs [1]. Among the natural products, terpenes show enormous stereochemical and structural diversity which makes them base molecules for the production of many interesting products for fine chemistry and especially for the pharmaceutical industry. Although some of these substances are accessible from natural sources, in many cases it is necessary to transform them into other less available and/or pharmacologically more active compounds. Since most of the products in the pharmaceutical industry require high purity, the demand for highly chemo- and stereoselective processes is increasing.

The hydrogenation of terpenes and their derivatives constitutes one of the most interesting reactions in the transformation of bioactive natural products [2]. This reaction presents an interesting challenge since this type of compound contains C=O and C=C bonds that can be hydrogenated. One of the key goals in this synthesis is the selective hydrogenation of the C=O bond for obtaining biologically active epimeric alcohols. For example, Symon *et al*. observed that the 3β-hydroxy-, 3-keto-, and 3α-hydroxyl series derived from lupane-type triterpenes increases their activity against human melanoma cells [3]. Moreover, Reyes *et al*. determined that the orientation of the C-3 hydroxyl group can modify the anti-inflammatory activity of this type of triterpenes [4]. In previous studies, these authors reported the isolation of a series of lupane-type triterpenes of the *Maytenus* species. Among the triterpenes involved, they highlighted 3-*epi*betulinic acid for its cytotoxic activity against cell lines of human carcinoma of the larynx (Hep-2) and cervix (HeLa) [5].

To date different methods have been investigated for the synthesis of lupane-type 3α-hydroxy triterpenes (**Figure 1**). From the selective hydrogenation of the corresponding carbonyl derivatives: a) a mixture of epimeric alcohols with high chemo- and diastereoselectivity towards the 3β-epimer was obtained when using inorganic hydrides, such as $NaBH_4$, in the hydrogenation of lupenone (**2**) [6]. b) The use organic hydrides, such as L-Selectride, in the hydrogenation of betulonic acid led to the corresponding epimers of betulinic acid with higher stereoselectivity towards the 3α-epimer [3]. Through bimolecular nucleophilic substitution, lupeol (**1**) and betulin gave products of $\Delta^{2,3}$ elimination and in none of the cases the product of the expected bimolecular nucleophilic substitution was obtained. On the other hand, the catalytic hydrogenation of betulonic acid over Raney Ni resulted only in the reduction of the isopropenyl double bond, while use of 5% Ru-C gave a mixture of epimers of 20,29-dihydrobetulinic acid, products of the hydrogenation of the C=O and C=C bonds [3]. Although the use of L-Selectride leads to 3-*epi*betulinic acid, this method suffers from a variety of disadvantages, such as low yields, requirement of expensive reagents in large excess, dry solvents and inert atmosphere.

Alternatively, terpenes that contain both an isolated C=C bond and another C=C bond conjugated to a carbonyl group, such as citral, can be selectively hydrogenated to the corresponding allylic alcohols (geraniol and nerol) with high chemoselectivity, through bimetallic catalysts [7,8]. For example, when using Pt-Co/C catalysts the citral hydrogenation to geraniol/nerol is favoured. It was proposed that Co improves the catalytic performance of Pt by electron transfer. This electron transfer is favoured by the high interaction of both metals existing in these types of bimetallic compounds [9]. Similar results and conclusions were obtained with other supported catalytic systems, such as Rh-Ge and Pt-Ge [10,11].

In previous works, we studied the hydrogenation reactions of prochiral carbonyl compounds employing Pt catalysts modified with organotin precursors, either chiral or achiral, supported on silica. These systems were obtained using techniques derived from the Organometallic Surface Chemistry on Metals (SOMC/M), and proved to be active and selective in these hydrogenation reactions of interest in fine chemistry [12–16].

To the best of our knowledge, Pt-Sn catalysts have not been used for the chemoselective hydrogenation of lupane-type triterpenes. In the present paper, we propose the use of Pt and Pt-Sn catalysts supported on silica, as an alternative for the chemoselective hydrogenation of lupenone. To this end, Pt-based catalysts modified with Sn with different contents of the second metal were synthesized and characterized. It is expected that the most electropositive metal produces geometric and electronic modifications that lead to improved selectivity of the desired product, as has been reported in the literature for the hydrogenation of other carbonyl compounds [17]. Considering the biological importance of the 3α-hydroxy triterpenes and our experience in the transformation of bioactive natural products extracted from native species into potentially more useful bioactive compounds [18,19], the synthesis from their 3β-epimers more available in nature, is interesting. The aim of this study was to synthesize 3α-lupeol (**3**) by hydrogenation of lupenone (**2**), obtained by oxidation from natural triterpene lupeol (**1**) isolated from the vegetal species *Chuquiraga erinaceae* subsp. *erinaceae* [18], using Pt-based organotin catalysts (**Figure 1**).

2. EXPERIMENTAL

2.1 Preparation of the catalysts

The procedures followed to prepare Pt and Pt-Sn catalysts have been previously published [14–17]. The monometallic catalyst was prepared by ionic exchange, using SiO_2 (Evonik, 180 m^2/g) as support, which had been previously treated with an ammonia solution, under continuous stirring for 30 minutes at room temperature. The solid, properly functionalized, was contacted with an aqueous solution of $Pt(NH_3)_4Cl_2$ (Aldrich), in an appropriate concentration so as to obtain 1 wt.% of Pt in the final catalyst. After 24 h of exchange, the solid was separated by filtration, dried in an oven at 105 °C, calcined in air at 500 °C and subsequently reduced in H_2 at 500 °C for 2 h. The catalyst so obtained was designated Pt.

The bimetallic catalysts were obtained using techniques derived from Surface Organometallic Chemistry of Metals (SOMC/M). These techniques consist of a controlled surface reaction between a reduced monometallic catalyst (Pt) and a solution of an organometallic compound ($SnBu_4$) in a paraffinic solvent. In this work, bimetallic systems with Sn/Pt atomic ratios 0.2 and 0.8 were prepared; these catalysts have been denominated PtSn0.2 and PtSn0.8, respectively. The reaction between the monometallic catalyst and the organotin compound solution was carried out under a H_2 atmosphere for 4 h. The temperature used for the reaction was 90 and 120 °C for the preparation of the PtSn0.2 and PtSn0.8 systems, respectively. For PtSn0.2, n-heptane was used as solvent while for the catalyst PtSn0.8, n-decane was employed. The bimetallic systems obtained were then washed with n-heptane in flowing N_2, dried in an oven at 105 °C and finally reduced at 500 °C in H_2 flow for 2 h.

2.2 Catalysts characterization

The Pt content of the catalysts was determined by atomic absorption spectrometry (Varian Spectra AA55). The amount of Sn present in the catalysts was determined spectroscopically at 530 nm by a complex formed with phenyl fluorone. The results were consistent with those determined by difference between initial and final concentration of $SnBu_4$ paraffinic solution. These last were obtained by gas chromatography, using a Varian CP-3800 gas chromatograph, equipped with a FID detector and a Factor Four (VF-1 ms, 15mx0.25mm ID DF = 0.25) capillary column.

Temperature-programmed reduction (TPR) tests were performed in a Quantachrome apparatus equipped instrument with a thermal conductivity detector. Each sample, previously calcined at 500 °C for 4h, was heated from 20 to 850 °C at a heating rate of 10 °C/min. using a mixture having a composition of 5% H_2 in N_2 at a flow of 25 mL/min. Hydrogen chemisorption measurement was performed in pulse dynamic equipment with catharometric detection, considering a stoichiometry of adsorption H/Pt_s. The specific surface area of the support was measured in equipment Micromeritics ASAP 2020 by N_2 adsorption at 77 K.

The particle size distribution of the solids was determined by transmission electron microscopy (TEM) in a JEOL 100 CX microscope with a resolution of 6 Å and an accelerating voltage of 100 kV. The samples were prepared by its suspension in bidistilled water and subsequent dispersion in an ultrasonic bath.

2.3 Isolation and purification of lupeol (**1**)

The lupeol extraction method from *Chuquiraga erinacea*, reported by us [18], was optimized following this procedure: ground dry leaves (20 g) of *C. erinacea* were refluxed with EtOH (200 mL) for 16 h. The extract was concentrated in a rotary evaporator at 40◦C until an oily residue was obtained. It was further lyophilized yielding 1.1 g of extract which was partitioned between H_2O/MeOH 5:5 (20 mL) and hexane (2 x 35 mL) affording 411.5 mg of hexanic subextract. That subextract was subjected to column chromatography (2 x 45 cm, silica gel 70-230 Mesh, relation 1:75) eluting with mixtures of hexane/AcOEt. Thirty-three fractions were collected and monitored by thin layer chromatography (TLC). The fractions 8-17 (85.2 mg, Rf 0.32), eluted with hexane/AcOEt 9.5:0.5, were collected and analyzed by RMN and CG-MS. It was determined the presence of five monohydroxylated triterpenes: lupeol (44.25 %), pseudotaraxasterol (29.20 %), taraxasterol (6.64 %), α-amyrin (6.65 %) and β-amyrin (13.26 %). Recromatography of those fractions on silica gel (200-425 Mesh, relation 1:60) impregnated with silver nitrate (10%) gave pure lupeol (**1**) as white solid (35.6 mg, 41.8 %), eluting with chloroform. Spectroscopic data of **1** were in agreement with those reported in literature [18].

2.4 Synthesis of lupenone (**2**)

To a solution of **1** (300 mg, 0,7 mmol) in acetone (20 mL) Jones reagent was added dropwise at 0°C, until the solution changed from colorless to orange. The reaction was stirred for 30 min and quenched with i-PrOH (10 mL), filtered through Florisil and washed several times with AcOEt. The solvent was removed and the residue was purified by flash chromatography on silica gel with hexane/AcOEt (9:1) affording 284.5 mg (0.67 mmol, 95.3%) of **2** as a white amorphous solid. Lupenone (**2**) was identified by comparison of their spectroscopic data with those reported in the literature [20].

2.5 Hydrogenation of lupenone (**2**)

Hydrogenation of **2** was carried out in autoclave reactor at 100ºC and a H_2 pressure of 10 atm. In each catalytic assay, 60 mg (0.14 mmol) of lupenone, 200 mg of catalyst and 20 mL of 2-propanol as solvent were used. The reaction evolution was followed by TLC using *epi*lupeol (**3**) as control, obtained from the reduction of **2** with $NaBH_4$ (4.6% yield) [6].

2.6 Spectroscopic data

Compound **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (3H, s, H-24), 0.79 (3H, s, H-28), 0.83 (3H, s, H-25), 0.95 (3H, s, H-27), 0.98 (3H, s, H-23), 1.03 (3H, s, H-26), 1.63-1.25 (25H, m), 1.68 (3H, s, H-30), 2.38 (1H, ddd, *J*= 11.2 Hz, 11.0 Hz, 5.7 Hz, H-19), 3.18 (1H, dd, *J*= 10.6 Hz, 5.6 Hz, H-3), 4.57 (1H, *br* s, H-29b), 4.66 (1H, *br* s, H-29a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1 (C-20), 109.5 (C-29), 79.2 (C-3), 55.5 (C-5), 50.6 (C-9), 48.5 (C-18), 48.1 (C-19), 43.2 (C-17), 43.0 (C-14), 41.0 (C-8), 40.2 (C-22), 39.0 (C-1), 38.9 (C-4), 38.2 (C-13), 37.3 (C-10), 35.7 (C-16), 34.5 (C-7), 30.0 (C-21), 28.1 (C-23), 27.6 (C-2), 27.6 (C-15), 25.3 (C-12), 21.1 (C-11), 19.5 (C-30), 18.5 (C-6), 18.1 (C-28), 16.3 (C-25), 16.1 (C-26), 15.5 (C-24), 14.5 (C-27).

Compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, s, H-28), 0.85 (3H, s, H-25), 0.94 (3H, s, H-27), 0.96 (3H, s, H-24), 1.03 (6H, s, H-23, H-26), 1.63-1.25 (27H, m), 2.41 (1H, m, H-19), 4.54 (1H, *br* s, H-29b), 4.67 (1H, *br* s, H-29a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.0 (C-3), 150.8 (C-20), 109.5 (C-29), 55.0 (C-5), 49.9 (C-9), 48.3 (C-18), 48.0 (C-19), 47.4 (C-4), 43.1 (C-17), 43.1 (C-14), 40.9 (C-8), 40.1 (C-22), 39.7 (C-13), 38.2 (C-1), 36.9 (C-10), 35.7 (C-16), 34.2 (C-2), 33.7 (C-7), 29.9 (C-21), 27.5 (C-15), 26.8 (C-23), 25.2 (C-12), 21.6 (C-24), 21.1 (C-11), 19.8 (C-30), 19.8 (C-6), 18.1 (C-28), 16.0 (C-25), 16.2 (C-26), 15.9 (C-27).

Compound **3**:^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (3H, s, H-24), 0.83 (3H, s, H-28), 0.85 (3H, s, H-25), 0.94 (3H, s, H-27), 0.96 (3H, s, H-23), 1.03 (3H, s, H-26), 1.63-1.25 (27H, m), 2.38 (1H, ddd, *J*= 11.2 Hz, 11.0 Hz, 5.7 Hz, H-19), 3.40 (1H, *br* s, H-3), 4.56 (1H, *br* s, H-29b), 4.69 (1H, *br* s, H-29a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2 (C-20), 109.5 (C-29), 76.4 (C-3), 50.4 (C-9), 48.5 (C-5), 48.2 (C-18), 48.2 (C-19), 43.2 (C-17), 43.1 (C-14), 41.2 (C-8), 40.2 (C-22), 38.2 (C-13), 37.7 (C-4), 37.3 (C-10), 35.8 (C-16), 34.3 (C-7), 31.7 (C-1), 30.0 (C-21), 28.4 (C-23), 27.6 (C-15), 25.4 (C-2), 25.3 (C-12), 22.3 (C-24), 21.0 (C-11), 19.4 (C-30), 18.4 (C-6), 18.2 (C-28), 16.3 (C-25), 16.1 (C-26), 14.8 (C-27).

Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (3H, s, H-24), 0.76 (3H, d, *J*= 5.1 Hz, H-30), 0.84 (3H, d, *J*= 7.1 Hz, H-29), 0.85 (3H, s, H-25), 0.87 (3H, s, H-28), 0.94 (6H, s, H-23, H-27), 1.04 (3H, s, H-26), 1.63-1.25 (27H, m), 2.41 (1H, m, H-19); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.3 (C-3), 55.1 (C-5), 49.6 (C-9), 47.7 (C-18), 47.5 (C-4), 44.8 (C-19), 43.3 (C-17), 43.3 (C-14), 41.0 (C-8), 40.5 (C-22), 39.7 (C-1), 38.1 (C-13), 37.0 (C-10), 35.6 (C-16), 34.3 (C-2), 33.8 (C-7), 29.5 (C-20), 27.5 (C-15), 27.0 (C-12), 26.8 (C-23), 23.1 (C-30), 22.1 (C-21), 21.6 (C-11), 21.2 (C-24), 19.8 (C-6), 18.2 (C-28), 16.1 (C-26), 16.0 (C-25), 15.3 (C-29), 14.5 (C-27).

Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (3H, s, H-24), 0.76 (3H, d, *J*= 5.1 Hz, H-30), 0.83 (3H, s, H-28), 0.84 (3H, d, *J*= 7.1 Hz, H-29), 0.85 (3H, s, H-25), 0.94 (6H, s, H-23, H-27), 1.04 (3H, s, H-26), 1.63-1.25 (28H, m), 3.39 (1H, *br* s, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.4 (C-3), 50.1 (C-9), 49.2 (C-5), 47.8 (C-18), 44.9 (C-19), 43.3 (C-17), 43.3 (C-14), 41.3 (C-8), 40.6 (C-22), 38.0 (C-13), 37.7 (C-4), 37.5 (C-10), 35.7 (C-16), 34.5 (C-7), 33.4 (C-1), 29.5 (C-20), 28.3 (C-23), 27.5 (C-15), 27.0 (C-21), 25.6 (C-2), 23.1 (C-29), 22.3 (C-24), 22.1 (C-12), 21.0 (C-11), 18.5 (C-6), 18.2 (C-28), 16.2 (C-25), 16.0 (C-26), 15.3 (C-30), 14.7 (C-27).

Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (3H, s, H-24), 0.76 (3H, d, *J*= 5.1 Hz, H-30), 0.77 (3H, s, H-28), 0.84 (3H, d, *J*= 7.1 Hz, H-29), 0.85 (3H, s, H-25), 0.94 (6H, s, H-23, H-27), 1.04 (3H, s, H-26), 1.63-1.25 (28H, m), 3.19 (1H, *br* s, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.2 (C-3), 55.4 (C-5), 50.3 (C-9), 47.8 (C-18), 44.9 (C-19), 43.3 (C-17), 43.3 (C-14), 41.0 (C-8), 40.6 (C-22), 39.0 (C-1), 38.9 (C-4), 38.0 (C-13), 37.3 (C-10), 35.7 (C-16), 34.5 (C-7), 29.5 (C-20), 28.1 (C-23), 27.6 (C-15), 27.6 (C-2), 27.0 (C-12), 23.1 (C-30), 22.1 (C-21), 21.1 (C-11), 18.5 (C-6), 18.2 (C-28), 16.2 (C-25), 16.1 (C-26), 15.5 (C-24), 15.3 (C-29), 14.6 (C-27).

3. RESULTS AND DISCUSSION

3.1 Results of catalysts characterization

The chosen method to prepare the monometallic catalyst was ionic exchange. This technique allows obtaining catalysts with high dispersion and good homogeneity of supported metallic phase. These characteristics are fundamental to subsequent preparation of bimetallic catalysts by controlled surface reaction.

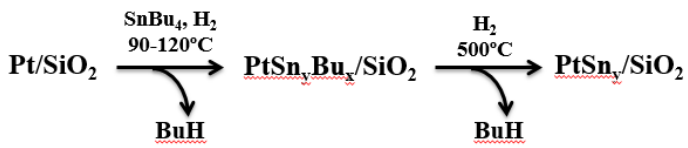
Figure 2 shows the TPR diagram of Pt/SiO_2 catalyst. As can be seen, there are two main peaks to around 250ºC and 450ºC. The first one can be attributed to the reduction to Pt^{4+} to Pt^{2+}. During impregnation, some of the platinum complex can interact with silanol groups of the support to produce Pt-(O-Si≡)y^{2-y} (reaction 1). The peak around to 450ºC can be assigned at this specie. Further, Pt-(O-Si≡)y^{4-y} species could be formed during catalyst preparation. The reduction of Pt-(O-Si≡)y^{4-y} (reaction 2) could be assigned to the shoulder around 500ºC [21].

$Pt(NH_3)_4^{2+} + y\text{HO-Si}\equiv \rightarrow \text{Pt-(O-Si}\equiv)_y^{2-y} + 4NH_4^+$ (reaction 1)

$\text{Pt-(O-Si}\equiv)_y^{4-y} + y/2H_2 \rightarrow \text{Pt} + y\equiv\text{Si-OH}$ (reaction 2)

In **Table 1** are reported the results of the catalysts characterization. The H_2 chemisorption assays indicate a high dispersion of Pt phase in the monometallic catalyst. As already mentioned, a high exposed Pt surface is very important to subsequent preparation of bimetallic systems by the chosen technique. As expected, dispersion of the catalysts decreases with the Sn content. This fact indicates that the second metal interacts selectively with Pt, as has already been reported [17]. In the same way, the TEM results (**Table 1**) show a similar mean particle size. It is consistent with the selective interaction of Sn on Pt.

Bimetallic systems were prepared by controlled surface reaction between $SnBu_4$ and Pt previously reduced, following the reaction in two steps represented below. In the first, the molecules of $SnBu_4$ react with Pt to obtain species like $PtSn_yBu_x$, with some butyl groups attached to the Sn surface. In the second step, above to 150ºC the butyl groups are completely eliminated leading to bimetallic catalysts, PtSn. The Sn/Pt molar relationship reached depends to the temperature of the first step. Thus, to prepare the PtSn0.2 catalyst was necessary 90ºC, while for the PtSn0.8 catalyst 120ºC. The Sn/Pt molar relationship was determined by UV-visible spectrophotometric (**Table 1**). These results are coincident with chromatographic determination from the difference between initial and final concentration in the paraffinic solutions, after of modification with $SnBu_4$.



3.2 Hydrogenation reaction

Figure 1 shows the products of the hydrogenation of lupane-type triterpenes. As can be seen, for betulonic acid, the use of a large excess L-Selectride leads to 3-*epi*betulinic acid with low yields. On the other hand, the catalytic hydrogenation over Raney Ni only results in the reduction of the isopropenyl double bond, and the use 5% of Ru-C gives a mixture of epimers of 20,29-dihydrobetulinic acid, products of the hydrogenation of the C=O and C=C bonds [3]. For lupenone, hydrogenation with $NaBH_4$ leads to the synthesis of α-lupeol, with a yield of 4.6% [6]. This is the only method reported to obtain 3-*epi*lupeol.

The objective of this study was to achieve the selective hydrogenation of lupenone to obtain biologically active epimeric alcohols. For this reason, the use of Pt and Pt-Sn catalysts supported on silica was proposed.

Firstly, hydrogenation of lupenone (**2**) was carried out using the Pt/SiO_2 monometallic catalyst. The TLC showed the presence of three compounds (**Figure 3**) and confirmed the disappearance of the starting material after 14 h of reaction. The crude material was chromatographed over flash silica gel with hexane/AcOEt to give 22.6 mg (38.3%) of 20,29-dihydrolupenone (**4**), the hydrogenation product of the side chain, 4.3 mg (16.6%) of 20,29-dihydro*epi*lupeol (**5**), and 21.6 mg (36.0%) of 20,29-dihydrolupeol (**6**), hydrogenation adducts of both the side chain and the carbonyl group.

The ^1H NMR spectrum of the reaction crude revealed the disappearance of olefinic protons (at δ_H 4.69 and δ_H 4.56 ppm), and the appearance of H-3 resonances, corresponding to epimer alcohols (**5** at δ_H 3.39 ppm, and **6** at δ_H 3.19 ppm). The α:β epimer ratio was 32:68 (**Figure 3**). These results show that the Pt/SiO_2 catalyst was more selective to the C=C bond in all the cases, leading to products of hydrogenation of the side chain. Moreover, the ratio of epimers observed for this system showed selectivity towards the β-epimer, the most stable product (thermodynamic product).

Considering the results obtained with the monometallic catalyst, the design of bimetallic systems was proposed, which have been shown to be selective to the hydrogenation of the carbonyl group in aromatic ketones [14,17]. Therefore, the systems PtSn0.2 and PtSn0.8 were chosen for the selective hydrogenation of lupenone.

Figure 4 shows the products from the hydrogenation of lupenone (**2**) with the PtSn 0.2 system after 14 h of reaction. The formation of four compounds, lupeol (**1**), *epi*lupeol (**3**), 20,29-dihydro*epi*lupeol (**5**) and 20,29-dihydrolupeol (**6**), was confirmed by TLC with the corresponding controls. By TLC, disappearance of the starting material was also confirmed.

The ^1H NMR spectrum of the reaction crude showed the appearance of the H-3 resonances, corresponding to a mixture of epimer alcohols (**3** and **5** at δ_H 3.39 ppm and **1** and **6** at δ_H 3.19 ppm, α:β epimer ratio 23:77) and the presence of olefinic protons (at δ_H 4.69 and δ_H 4.56 ppm). The ratio of the area between these olefinic protons (H-29a or H-29b) and H-3 (α+ β) showed 61% hydrogenation of the C=C bond, therefore this system was not completely chemoselective (**Figure 4**).

The results obtained with the PtSn 0.2 system indicate that although the presence of Sn favoured the hydrogenation of the carbonyl group, the amount of it was not sufficient to achieve total chemoselective hydrogenation of lupenone. This system also showed selectivity towards the β-epimer.

Figure 5 shows the products from the hydrogenation of lupenone with the PtSn0.8 system after 14 h of reaction. The formation of lupeol (**1**) and *epi*lupeol (**3**) and the disappearance of lupenone (**2**) were confirmed by TLC. The crude material was chromatographed over flash silica gel with hexane/AcOEt to give 35.0 mg (59.0%) of lupeol (**1**) and 21.5 mg (36.1%) of *epi*lupeol (**3**).

^{1}H NMR analysis of the reaction crude showed that there was no hydrogenation of the C=C bond, confirming the chemoselectivity of this system. The observed ratio of epimers (α:β=38:62) showed an increase in the proportion of the desired α-epimer (**Figure 5**).

Table 2 shows the composition in mole percent of the reaction mixture after 14 h. As can be seen, the addition of Sn on Pt favours the hydrogenation of the carbonyl group. Bimetallic PtSn systems have been characterized by X-ray photoelectron spectroscopy (XPS), showing that the presence of Sn produces an increase in the electronic density of Pt, leading to the formation of polarized states of $Pt^{\delta-}$ and $Sn^{\delta+}$ [17]. Thus, polarization of C=O is favoured and, consequently, its hydrogenation, increasing selectivity for the desired product. The system with the highest Sn content (PtSn0.8) was 100% chemoselective in the hydrogenation of the carbonyl group of lupenone (compounds **1** and **3**). For these bimetallic systems, it was observed that Sn produces changes in the stereoselectivity of the reaction. A possible explanation for this could be that by accelerating the rate of hydrogenation as a consequence of the increase in the electrophilicity of the carbonyl group, Sn decreases the possibility of obtaining the most stable product (thermodynamic product), leading to a greater proportion of the α-epimer (kinetic product). As observed in the PtSn0.2 and PtSn0.8 systems, the increase of Sn favoured the formation of the desired α-epimer (PtSn 0.2, α:β=23:77; PtSn 0.8, α:β=38:62).

4. CONCLUSIONS

In conclusion, the hydrogenation of lupenone using the PtSn0.8 bimetallic system was 100% chemoselective, leading to a mixture of epimeric alcohols. In addition, the desired epimer (*epi*lupeol) was obtained with a higher stereoselectivity than that obtained in the hydrogenation of these triterpenes with inorganic or organic hydrides.

These facts can be explained due to the presence of Sn, which produces geometric and electronic modifications that lead to improvements in the chemo- and stereoselectivity of the desired product.

Therefore, it could be demonstrated that the use of Pt-Sn heterogeneous catalysts constitutes an attractive alternative for the hydrogenation of lupane-type triterpenes.

5. ACKNOWLEDGEMENTS

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Table 1. Catalysts characterization.

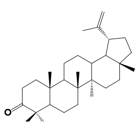
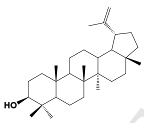
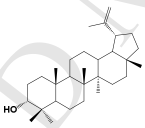
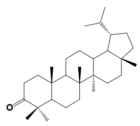
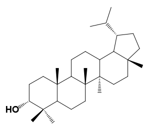
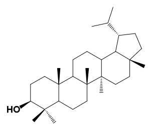
Catalyst	Sn/Pt[1]	H/Pt[2]	d_{TEM} (nm)[3]
Pt	-	0.65	2.2
PtSn0.2	0.2	0.25	2.2
PtSn0.8	0.8	0.20	2.1

[1] The amount of Sn present in the catalysts was determined spectroscopically at 530 nm by a complex formed with phenyl fluorine.

[2] Hydrogen chemisorption measurement was performed in pulse dynamic equipment with catharometric detection, considering a stoichiometry of adsorption H/Pt_s=1.

[3] The particle size distribution of the solids was determined by transmission electron microscopy (TEM) in a JEOL 100 CX microscope with a resolution of 6 Å and an accelerating voltage of 100 kV.

Table 2. Composition in moles of percent of the reaction mixture, after 14 h of reaction.[a]

Catalyst	2 	1 	3 	4 	5 	6 
Pt	-	-	-	42.4	18.4	39.2
PtSn0.2	-	31.0	8.0	-	15.0	46.0
PtSn0.8	-	62.0	38.0	-	-	-

[a] Hydrogenation of **2** was carried out in autoclave reactor at 100ºC and a H_2 pressure of 10 atm. In each catalytic assay, 60 mg (0.14 mmol) of lupenone, 200 mg of catalyst and 20 mL of 2-propanol as solvent were used.

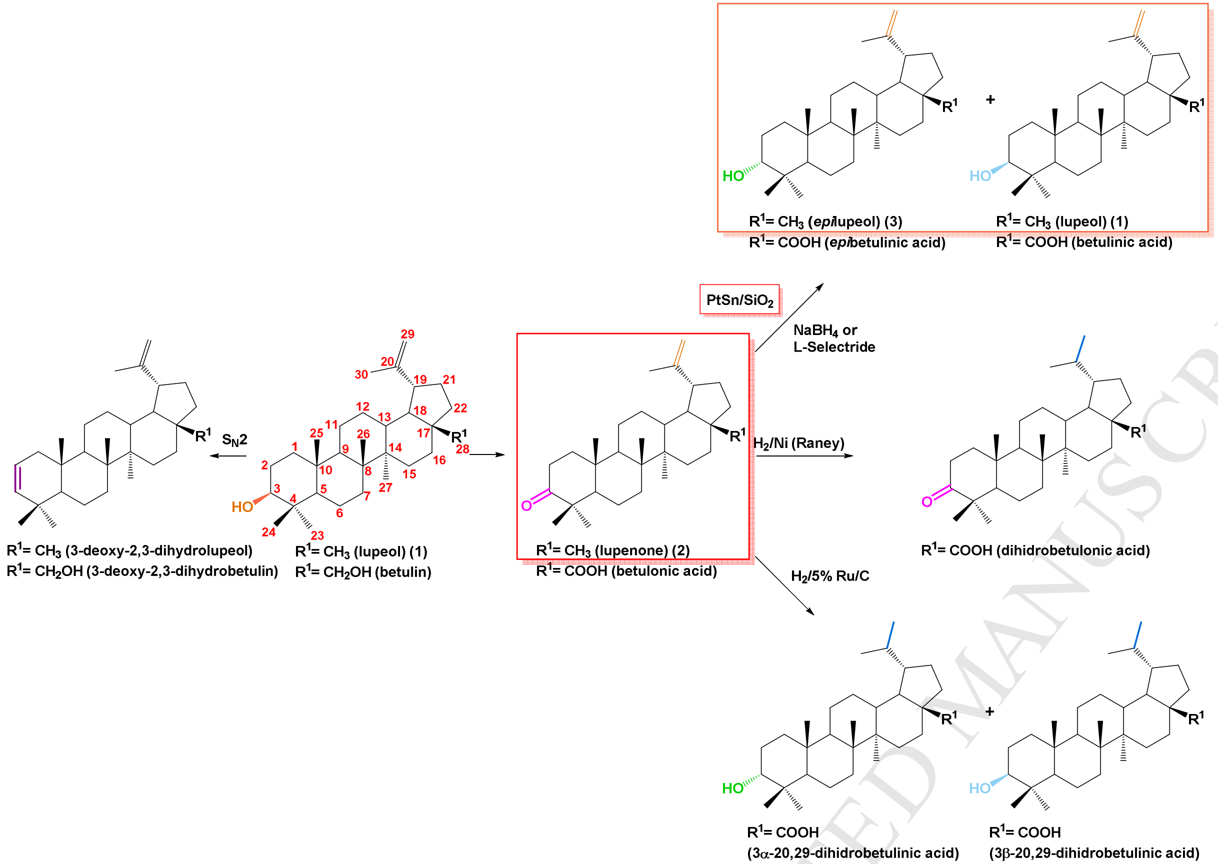


Figure 1. Reaction scheme of the methods reported in literature and proposed in this work for the synthesis of lupane-type 3α-hydroxy triterpenes.

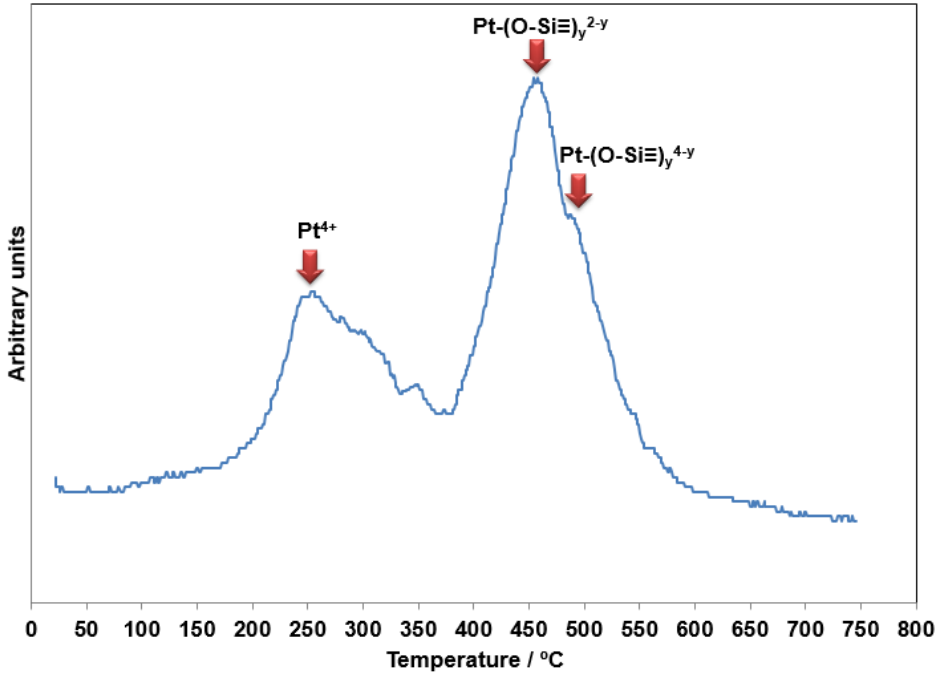


Figure 2. TPR diagram of Pt/SiO_2 (heating rate of 10 °C/min. using a mixture having a composition of 5% H_2 in N_2 at a flow of 25 mL/min).

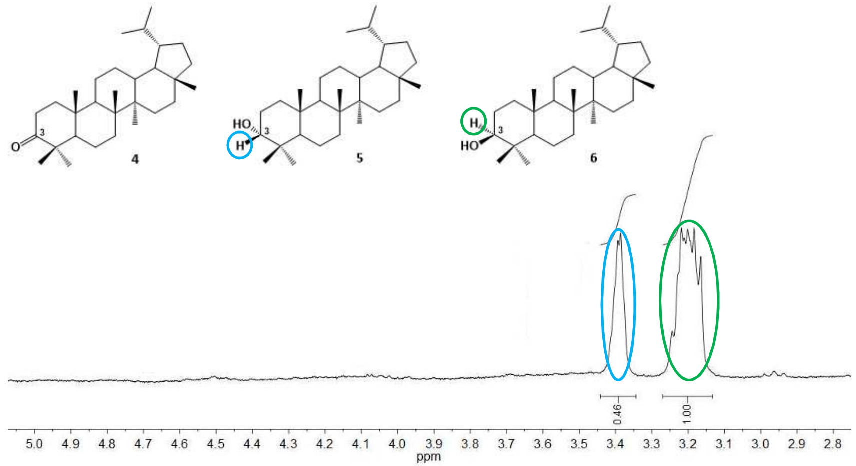


Figure 3. Products from the hydrogenation of lupenone (**2**) on Pt/SiO_2, ^{1}HNMR spectrum and relation of areas of H-3 resonances, corresponding to epimer alcohols **5** and **6**.

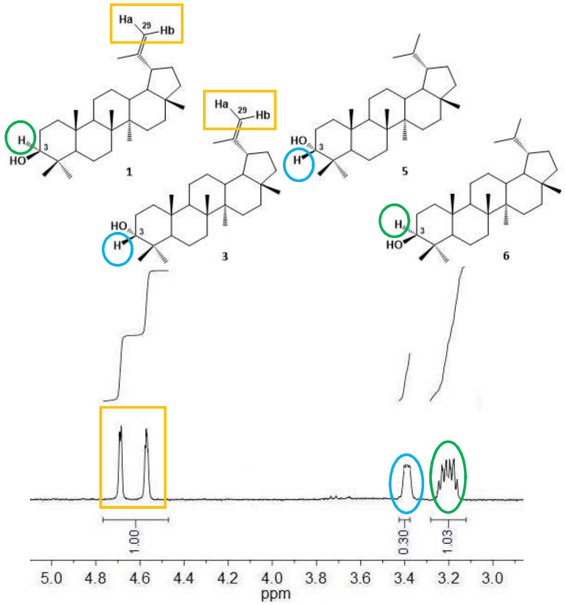


Figure 4. Products from the hydrogenation of lupenone (**2**) on PtSn0.2, [1]HNMR spectrum and relation of areas of H-3 (comp. **1**, **3**, **5** and **6**), H-29a and H-29b (comp. **1** and **3**) resonances.

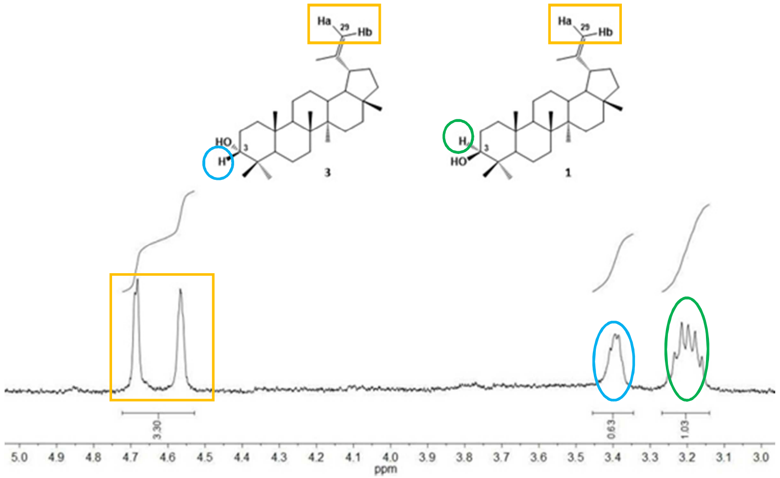


Figure 5. Products from hydrogenation of lupenone (**2**) on PtSn0.8, ^{1}HNMR spectrum and relation of areas of H-3, H-29a and H-29b resonances corresponding to epimer alcohols **1** and **3**.

Highlights

• PtSn0.8 system proved to be chemo- and stereoselectivity in lupenone hydrogenation. This system allowed reaching approximately 38% of diastereoisomeric excess to *epi*lupeol.

• Geometric and electronic effects due to the presence of Sn encouraged the interaction through the carbonyl group of lupenone.

• An average yield towards *epi*lupeol of 36% was achieved.