Artículo original

Catalytic hydrogenation of kaurenoic and grandiflorenic acids methyl esters with $RuCl_2(DMSO)_4$ in homogeneous and biphasic media.

Hidrogenación catalítica de los ésteres metílicos de los ácidos kaurénico y grandiflorénico con $RuCl_2(DMSO)_4$ en medio homogéneo y bifásico.

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ABSTRACT

$RuCl_2(DMSO)_4$ was used in hydrogenation reactions of kaurenoic and grandiflorenic acid methyl ester in homogeneous medium and grandiflorenic acid methyl ester in biphasic toluene/water media. The reaction products were characterized by GC-MS. The catalytic parameters were optimized giving high percent conversion and some stereomeric preference for both acids.

KEY WORDS

Catalysis, hydrogenation, natural products, ruthenium complexes.

RESUMEN

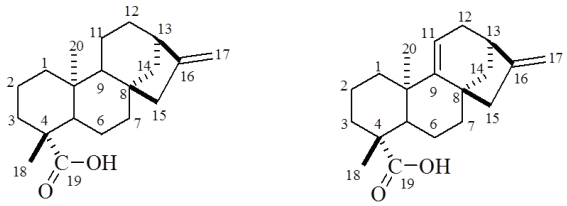
$RuCl_2(DMSO)_4$ fue utilizado en reacciones de hidrogenación de los ésteres metílicos de los ácidos kaurenoico y grandiflorénico en medio homogéneo y el éster metílico del ácido grandiflorénico en medio bifásico tolueno/agua. Los productos de reacción fueron caracterizados por cromatografía de gases acoplado a un espectrómetro de masas (CG-EM). Se optimizaron los parámetros catalíticos obteniéndose altos porcentajes de conversión con preferencia estereomérica para ambos ácidos.

PALABRAS CLAVE

Catálisis, hidrogenación, productos naturales, complejos de rutenio.

INTRODUCTION

Ent-Kaur-16-en-19-oic acid (Kaurenoic acid, 1) and *ent*-kaur-9(11),16-dien-19-oic acid (Grandiflorenic acid, 2), figure 1, are diterpenes with rigid tetracyclic structures, present in *Espeletiinae* species, which are resinous plants that grow above 2500 m of altitude in Colombian and Venezuelan Andes [1]. Kaurenoic acids have antimicrobial, citotoxic [2-5], anti-inflammatory [6], anticonvulsant, antiprotozoarial properties and *in vitro* show anti-carcinogenic biological activity [7].



1 **2**

Fig. 1. Kaurenoic acid (1) and grandiflorenic acid (2) structures.

The *Espeletia schultzii Wedd* and other similar species from the Asteraceae family, contain essential oils with 80.5 % monoterpenes, 15.5 % sesquiterpenes and 0.30 % diterpenes [8]. Natural products hydrogenation compounds are important in pharmaceutical, perfume and flavor´s industry [3]. Kaurenoic and grandiflorenic acids have been hydrogenated using Rh in homogeneous media [9] and

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Ru in homogeneous media [10]. Ruthenium catalyst has been used in homogeneous and biphasic media in hydrogenation reactions of unsaturated substrates, showing high conversion rates [11,12]. The goal in this work is hydrogenation of methyl esters of kaurenoic and grandiflorenic acids, derivatives of $RuCl_2(DMSO)_4$ catalyst in homogeneous and biphasic media.

MATERIAL AND METHODS

$RuCl_2(DMSO)_4$ was prepared by Wilkinson´s method [13]. **1** and **2** (figure 1), were obtained following Usubillaga´s method. These acids were methylated as shown in figure 2. Diazomethane reagent was prepared as reported in the literature [14].

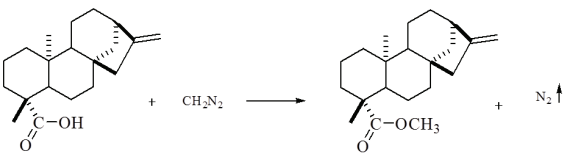

Fig. 2. Methyl esterification of kaurenoic acid. Kaurenoic acid, 1. Methyl kaurenoate, 3.

The differents compounds of esters methylated were separated by flash chromatography (silica gel 60 (70-230 mesh ASTM) and 40 weight % of $AgNO_3$ and analyzed by GC-MS (HP 5973, 70 eV, capillary column, 5 % phenyl-methyl-polyxyloxane, 30 m long, 0.25 mm diameter and 0.25 μm thick stationary phase).The use of the methyl kaurenoate and methyl grandiflorenoate improves the chromatographic and GC separations.

Catalytic trials. All catalytic trials were done in batch reactors (Parr Instruments, model 4768, inner glass liner), the catalyst (0,05 g, 0,1 mmol) and the amount of substrate required for each trial (methyl kaurenoate (**3**) and methyl grandiflorenoate (**4**), as required by the substrate/catalyst ratio), were dissolved in 10 mL of toluene for the homogeneous system; for biphasic system, the catalyst was dissolved in 5 mL of water and the substrate (methyl grandiflorenoate) in 5 mL of toluene. The experimental parameters were varied (pressure: 1000, 500 and 200 psi H_2; substrate/ catalyst ratio: 150:1, 100:1, 50:1; reaction time: 24 h and 6 h; temperature 100 ºC). The products were analyzed by GC-MS (HP 5973, 200 ºC isothermal conditions). **4** was hydrogenated using heterogeneous Pd/C catalyst with the following conditions: substrate in 10 mL dry methanol, 800 psi H_2 pressure, 12 h reaction time, temperature ambient.

RESULTS AND DISCUSSION

Homogeneous hydrogenation of methyl kareunoate. The results changing the substrate/ catalyst ratio are shown in table 1; showing a total conversion of substrate to isomerization and hydrogenation products in both reactions. When the substrate/catalyst ratio increases from 50:1 to 150:1, the amount of isomerization product decreases, it shows that during the process, the isomerization product is also hydrogenated. The retention time for pure substrate was 3.79 min, this time was obtained under similar GC-MS conditions to the run with substrate/catalyst ratio 50:1 (see bottom table 1, a). Retention time corresponding to pure substrate with similar GC-MS conditions run to substrate/catalyst ratio 150:1 was a single peak at 18.9 min (see bottom table 1, b).The GC conditions were changed to improve the peak separation. Three products were obtained for both substrate/catalyst ratios (see figure 3). According to the mass spectrum the first product show a molecular ion in 316 m/z which corresponds to the isomer product of methyl ester kaurenoic acid (see figure 3: product **5**), (methyl *iso*-kaurenoate, IUPAC nomenclature: methyl *ent*-kaur-15-en-19-oate), the second and third products have the same mass spectrum, and shows a molecular ion in 318 m/z which corresponds to the hydrogenation products where the C-16 methylen could be either α or β oriented (see figure 3: products **6** and **7**) In this order, according to Rivas´s [10], who reported similar results (similar GC retention times, and similar peak sequence) using ruthenium clusters as catalyst, the most favored stereoisomer hydrogenation product using NOESY as characterization NMR bi-dimensional technique was the beta-hydrogenation product methyl *ent*-16β-hidro-kaur-19-oate (see figure 3: Product **6**). Also, the mass spectrum of this isomer of the present work corresponds with the reported in the work above mentioned [10]. To explain the favored stereoselectivity to the β methyl position, we speculate that there is a competition for the π Ru complex above or below the plane of the terminal double bond, with a more efficient internal H addition from below giving a sigma alkyl Ru complex with the primary terminal carbon and the reductive elimination to form the final hydrogenated product adding the final hydrogen from the same side of the sigma alkyl complex [9,15].

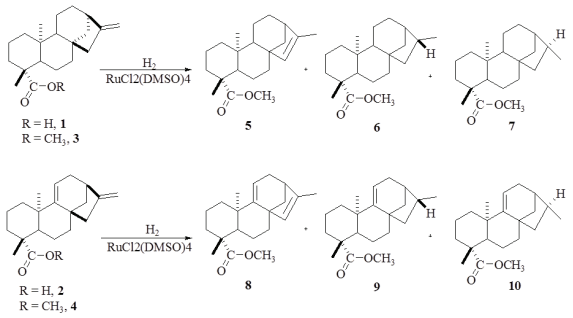

Fig. 3. Scheme of hydrogenation and isomerization products with both substrates.

Molecular structure of kaurenoic acid, **1**; methyl kaurenoate, **3**; grandiflorenic acid, **2**; methyl grandiflorenoate, **4**; methyl *iso*-kaurenoate, **5**; methyl *iso*-grandiflorenoate, **8**; methyl *ent*-kaur-16*β*-hidro-19-oate, **6**; methyl *ent*-kaur-16*β*-hidro-9(11)-en-19-oate, **9**; methyl ent-kaur-16*α*-hidro-19-oate, **7**; methyl *ent*-kaur-16*α*-hidro-19-oate, **10**.

TABLA 1
Reaction products for *ent*-kaurenoic acid methyl ester hydrogenation (homogeneous medium)[a].

Subst/cat ratio	Ret. t.(min.)	% Conv.	Products
50:1[a]	3.52	9.56	5
	3.72	27.28	7
	3.89	63.16	6
150:1 [b]	15.4	1.0	5
	17.2	34.18	7
	19.3	64.82	6

a) P= 1000 psi H2, T= 100 ºC, t = 24 h. GC-MS conditions: 200 ºC to 300 ºC ramp; 5 ºC /min, 20 min total time.
b) GC-MS conditions: 200 ºC isotherm, 22 min total time.

Homogeneous hydrogenation of methyl grandifloreunoate. The results of the variation for the substrate/catalyst ratio, H_2 pressure and reaction time are shown in table 2.

TABLA 2
Reaction products for grandiflorenic acid methyl ester hydrogenation (homogeneous medium)[a] (T= 100 ºC).

Sub/cat. Ratio	Press.(psi H_2)	t (h)	Ret. time (min.)	% Conv.	Products. (See fig.3)
50:1	1000	24	12.4	1.0	8
			13.0	26.33	9
			13.8	72.67	10
50:1	500	24	12.4	1.0	8
			13.0	35.49	9
			13.6	63.51	10
100:1	200	6	12.3	1.0	8
			12.9	12.81	9
			13.7	86.19	8 + 4
50:1	200	6	12.3	1.0	8
			12.9	10.88	9
			13.6	89.12	10 + 4

GC-MS, 200 ºC isotherm, 18 min total time.

The retention time of methyl grandiflorenoate pure to this GC-MS conditions was 13.6 min. Unfortunately, this retention time too corresponding with a hydrogenation product. This is perfectly determinated when compared the peak and their mass spectrum, so, to 24 h reaction, we observed a complete conversion of the substrate. When the reaction time was 6 h, still had substrate without reaction and was impossible obtain favorable conditions in the GC-MS to separate this mixture of substrate and hydrogenation product. The mass spectrum was analyzed with each peak in the chromatogram which showed fragmentation patterns with molecular ion 314 m/z and 316 m/z. Based on the mass spectra of the products, the first one show a molecular ion of 314 m/z which correspond to the isomerization product of the terminal double bond; the second product show a molecular ion of 316 m/z corresponding to hydrogenation product, but it was not possible to assign to which stereoisomer it correspond. The internal double bond is not hydrogenated under this reaction conditions. Both of these results could be explained taking into account the necessary formation of a π Ru complex with the terminal C=C double bond in a catalytic cycle. Strong steric hindrance is expected for the π Ru complex with the internal double bond in the grandiflorenic substrate, leading to no hydrogenation of this internal double bond. The isomerization reaction to the internal double bond, is also expected to be sensitive to steric hindrance, as observed for the low per cent conversion.

Biphasic hydrogenation of methyl grandifloreunoate. The results are presented in table 3. Based on the mass spectra of the products the results are similar to the homogeneous reaction; but, respecting the stereoselectivity, comparing the reactions where parameters were 50:1 substrate/catalyst ratio, 24 h, 500 Psi to homogeneous and biphasic hydrogenation reaction, this last show a high selectivity with a high percent of conversion to one hydrogenation product which was not possible to identify using NMR technique due to the formation of a mixture, even using heterogeneous catalyst. So, the first product correspond to the isomerization of the terminal double bond, the other products are the two stereoisomers of the terminal double bond hydrogenation. To compare the hydrogenation activity, methyl grandiflorenoate was hydrogenated using heterogeneous Pd/C catalyst (Substrate in 10 mL dry methanol, 800 psi H_2 pressure, 12 h reaction time, room temperature). GC-MS shows three products of isomerization and hydrogenation of the terminal double bond, and the three products corresponding to the isomerization and hydrogenation products of methyl grandiflorenoate, showing that the internal double bond gets, is hydrogenated under this reaction conditions. The

heterogeneous hydrogenation reaction is less sensitive to steric requirements than the homogeneous and biphasic metal catalyzed reactions [10].

TABLA 3
Reaction products for methyl grandiflorenoate hydrogenation (biphasic medium)[a] (T= 100 ºC).

Subst./cat.ratio	Pressure (psi H_2)	Time (h)	Ret. Time(min.)	% Conv.	Products
50:1	500	24	12.3	1.0	8
			12.9	12.75	9
			13.7	87.25	10
100:1	200	6	12.4	1.07	8
			12.8	1.83	9
			13.5	97.10	7 + 4
			13.7		
50:1	200	6	12.3	1.06	8
			12.9	1.80	9
			13.5	97.14	7 + 4
			13.7		

a) GC-MS, 200 ºC isotherm, 18 min total time.

CONCLUSIONS

$RuCl_2(DMSO)_4$ complex has shown catalytic hydrogenation activity for kaurenoic and grandiflorenic acids methyl ester. In homogeneous medium, both acids give terminal double bond hydrogenation, producing the α and β methyl position stereoisomers, favoring the β isomer, probably due to less steric hindrance during the Ru metal π complex formation. Some terminal double bond isomerization is observed for both acids, and no internal double bond hydrogenation is observed for grandiflorenic acid methyl ester. In biphasic system, grandiflorenic acid methyl ester gives similar results to the homogeneous reaction. In heterogeneous Pd/C, grandiflorenic acid methyl ester hydrogenation of both the terminal and internal double bond is observed.

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